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Spirulina platensis Enhances the Beneficial Effect of Exercise on Oxidative Stress and the Lipid Profile in Rats

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ABSTRACT

This study aimed to evaluate the effect of Spirulina platensis *and moderate exercise on oxidative stress and lipid profiles in the rats. Forty male Wistar rats were allocated to the following 10-week treatments, three times a week: exercise (E, 30 min swimming),* S. platensis *(SP, 26 mg/Kg); exercise and* Spirulina *(ES); and control (C). Outcomes were Thiobarbituric Acid Reactive Substances (TBARS) in serum and brain, and cholesterol and triglycerides (TG) in serum. Rats treated with exercise showed lower brain TBARS than the controls, mostly in association with* S. platensis*. In the groups E and ES, serum TBARS decreased after intervention. Compared with the controls, both E and ES prevented an increase in cholesterol and reduced triglycerides. Results demonstrated that* S. platensis *enhanced the beneficial effect of exercise on oxidative stress and lipid profiles in rats, which might be a promising approach for treating metabolic syndrome in humans.*

Key words: Exercise, antioxidant, cholesterol, lipid peroxidation

INTRODUCTION

The aging process has been considered a major epidemiological phenomenon of humanity, given the impressive increase in life expectancy observed in the last century (Blagosklonny 2010; Vaupel 2010, Scott et al. 2015). Consequently, the search for new preventive and therapeutic strategies has received special attention by the scientific community (Farooq et al. 2014; Quirós et al. 2015). Among several mechanisms involved in the process of aging, oxidative stress and hyperlipidemia have been considered as new targets for therapeutic approaches (Wang and Michaelis 2010; Gamba et al. 2015; Hare et al. 2015) because both participate in the pathogenesis of atherosclerosis and metabolic syndrome (Ungvari et al. 2010; Onat et al. 2012). According to Vaziri et al. (2010), the available pharmacological therapies have been largely ineffective in ameliorating oxidative stress, inflammation, HDL deficiency and/or dysfunction, atherosclerosis and cardiovascular disease. In this context, there is need to search for new therapeutic strategies.

Several nutritional components have been tested as antioxidant agents, such as vitamins, flavonoids and ubiquinone (Macedo et al. 2014). Recent studies have described an antioxidant effect of *S. platensis*, a cyanobacterium that contains phycocyanin, which in turn acts by promoting inactivation of free radicals (Bermejo-Bescós et al. 2008; Pabon et al. 2012; Farooq et al. 2014). *S. platensis* has been marketed in many countries

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and utilized as nutraceuticals, demonstrating good safety profiles. It has other potential benefits, including anti-inflammatory, hypolipidemic and antineoplastic activity (Zheng et al. 2013; Farooq et al. 2014). Moderate levels of aerobic exercise have also been demonstrated to reduce oxidative strandess (Venditti and Di 1997; Cakir et al. 2010).

Animal and human studies have indicated that moderate exercise induces liberation of Reactive Oxygen Species (ROS), followed by activation of antioxidant enzymes, resulting in a beneficial balance in favor of antioxidant processes (Gomez-Cabrera et al. 2008). However, it is known that extenuating exercise may result in cellular damage due to excess production of ROS (Vina et al. 2000), suggesting that exercise as a therapeutic approach should be used in moderate levels. Thiobarbituric Acid Reactive Species (TBARS) have been used in the analysis of lipid peroxidation by means of malonaldehyde measurement, which is considered a marker of oxidative stress (Babusikova et al. 2007; Sainz et al. 2010). The combination of hyperlipidemia and oxidative stress has been shown to act synergistically in the process of aging (Babusikova et al. 2007; Zhao et al. 2015), particularly in brain damage (Navarro and Boveris 2010) and atherosclerosis development (Negre-Salvayre et al. 2010), potentially resulting in a variety of chronic diseases (Adibhatla and Hatcher 2008; Navarro and Boveris 2010). Treatments able to interfere in both oxidative stress and hyperlipidemia would have great relevance in clinical practice. It was hypothesized that a combination of *S. platensis* and moderate exercise could potentiate the benefic effects of exercise on oxidative stress and the lipid profile. Thus, this study aimed to answer this question in the rats.

MATERIAL AND METHODS

Animals

A total of 40 male Wistar rats (five months old) were studied. They were categorized in four groups of 10 animals, which were treated for 10 weeks with one of the following interventions: exercise (E); *S. platensis* (S); exercise and *S. platensis* (ES); and control (C).

Interventions

The animals received standard rodent chow, balanced according to the recommendations of the National Research Council and National Institute of Health (USA), the Nuvital make, type Nuvilab CR1. The amount of feed provided was 20 g/day, average intake of an adult mouse (Fiocruz 1994). The rats were fed early at around 10.00 am. The animals were subjected to seven days acclimatization for swimming to receive treatment by gavage (in this period, all the animals received saline by gavage). *S. platensis* used for the experiments was obtained from the Universidade Federal do Rio Grande, Escola de Química e Alimentos, Laboratório de Engenharia Bioquímica, Rio Grande-RS, Brazil in the form of a powder, which was prepared by drying the microalgal biomass, followed by pulverization in the ball mil, and then maintained at -20°C. For aerobic exercise, a pool was designed to allow four animals to swim simultaneously. The experiment was conducted in accordance with Brazilian law 11.794/08 and ethical principles from Brazilian Society of Laboratory Animal Science (SBCAL). The study was approved by the Ethics Committee - Universidade de Passo Fundo (certificate nº 006/2010).

Study protocol

The steps of the study are presented in Figure 1.

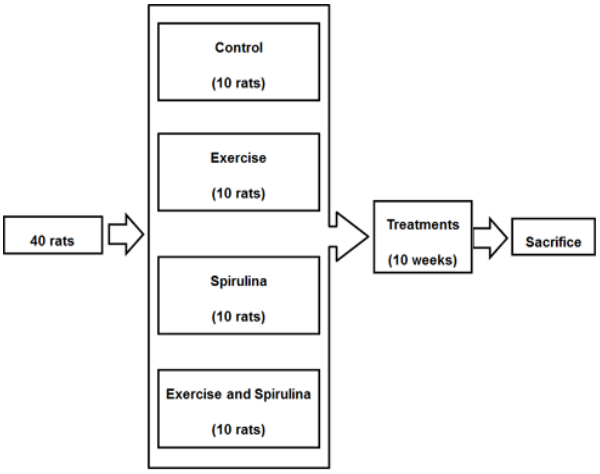

Figure 1 - Experiment flow sheet.

Rats were randomly allocated to one of the four interventions. Rats of group E underwent a 30 min session of swimming in water at 32°C (Fig. 2A), three times a week for ten weeks. They also received oral saline by gavage (Fig. 2B) before exercise. The subgroups S and ES were treated with *S. platensis* (26 mg/kg). This quantity was diluted with 2.00 mL of distilled water and then subjected to the rats for oral gavage three times a

week. This amount was based on the calculation of National Health Surveillance Agency (ANVISA) data as 1.6 g/day for an adult human of 60 kg. Subgroup ES underwent all the steps described above, with exception of oral *S. platensis*, instead of saline. Subgroup C received oral saline three times a week. Blood samples were collected from the retro-orbital vein before starting the interventions and then 10 weeks later. Rats were weighed once a week during the experiment. Between the interventions, the animals were kept in collective cages with free access to food and water and a 12:12-h light-dark cycle. At the end of the experiment, the animals were sacrificed by guillotine, followed by removal of the brains.

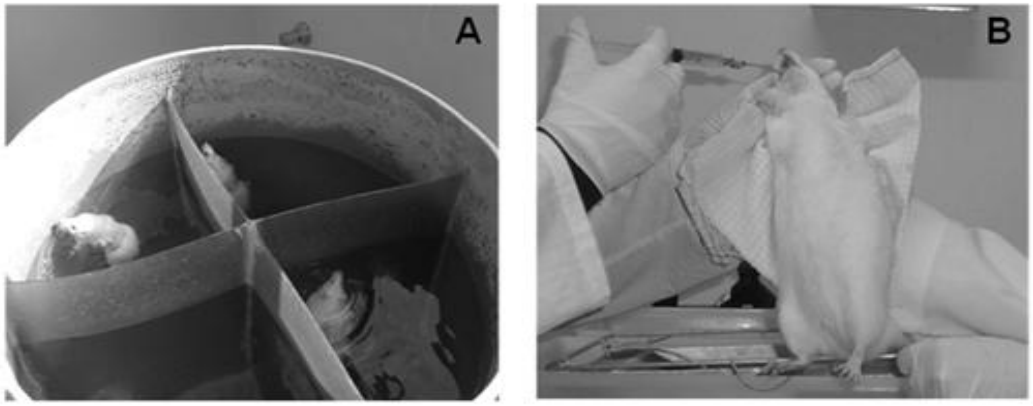

Figure 2 - Experimental procedures**.** (A) Rats exercising in the specially designed swimming pool. (B) A rat receiving oral saline by gavage.

Thiobarbituric acid reactive substances (TBARS)

TBARS were analyzed in serum and brain tissue. Blood samples from the pre- and post-treatment measurements were collected in a heparinized tube and were centrifuged at 3000 rpm for 10 min. The supernatant was removed and stored at -80°C in microtube of 2 mL. Brain tissue from the right hemisphere was homogenized with phosphate buffer, pH 7.4. Determination of TBARS was performed as described elsewhere Steels et al. (1994). TBARS concentration in the serum and brain was determined from the absorbance at 532 nm and expressed in nmol.

Lipid profile

Total cholesterol (TC) and triglycerides (TG) were measured in the serum collected before and after the treatment. The analyses were carried out utilizing the commercially available reagent kits (Labtest, Lagoa Santa - Brazil).

Statistical analysis

Quantitative variables were first tested for Gaussian distribution. Data were expressed as the mean and standard deviation (SD) or when otherwise stated. Student t tests, ANOVA, χ^2 test or Fisher´s exact test were employed when appropriate. The analysis was performed using GraphPad Prism 5 (GraphPad Software, Inc., San Diego, CA, USA). A P value < 0.05 was accepted as indicating significance.

RESULTS

Animals

Out of 40 rats, three died during the procedures: two from the exercise group and one from the control group. Thus, the final study sample was composed of 37 rats. Weight gain after treatment was significantly higher in both the controls (pre 360 ± 17 g vs. post 421 ± 33 g; $P < 0.001$) and S rats (352 ± 23 g vs. 409 ± 15 g; $P < 0.0001$). The E (368 ± 40 g vs. 384 ± 27 g; $P = 0.064$) and ES groups (385 ± 42 g vs. 409 ± 43 g; $P = 0.064$) did not have a significant increase in the weight (Fig. 3A). Inter-treatment comparison revealed that the magnitude of weight increase was significantly higher in the controls than in both the ES group (61.0 ± 20.9 g vs. 23.6 ± 30.4 g; $P < 0.01$) and E group (61.0 ± 20.9 g vs. 16.5 ± 17.0 g; $P < 0.01$). The S group had a significant weight increase when compared with the ES (56.7 ± 14.6 g vs. 23.6 ± 30.4 g; $P < 0.01$) and E groups (56.7 ± 14.6 g vs. 16.5 ± 17.0 g; $P < 0.01$) (Fig. 3B).

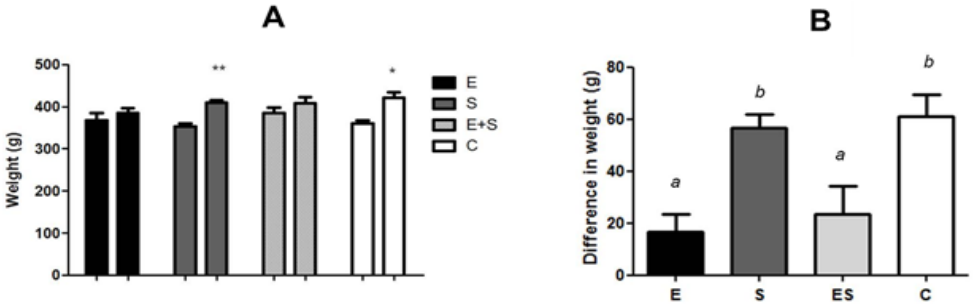

Figure 3 - Exercise and exercise associated with *S. platensis* prevented the increase in weight. (A) Weight before and after treatments. Data are presented as the mean and std. deviation. *P < 0.001; **P < 0.0001 (Student t tests followed by two way ANOVA). (B) Difference in weight after ten-week treatments. Data are presented as the mean and std. deviation. Different letters represent significant differences (P < 0.01) (One way ANOVA).

Thiobarbituric acid reactive substances (TBARS)

Rats in the ES group showed lower levels of brain TBARS (in nmol) than both the controls (mean ± SD: 0.009 ± 0.004 vs. 0.025 ± 0.004; P < 0.0001) and S group rats (0.009 ± 0.004 vs. 0.037 ± 0.003; P < 0.0001). Animals treated with the E also presented lower levels of brain TBARS compared with both the controls (0.014 ± 0.005 vs. 0.025 ± 0.004; P = 0.0014) and S group (0.014 ± 0.005 vs. 0.037 ± 0.003; P < 0.0001). Controls had lower levels of brain TBARS than the S group rats (0.025 ± 0.004 vs. 0.037 ± 0.003; P < 0.0001) (Fig. 4).

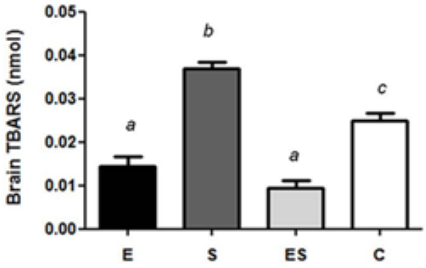

Figure 4 - Brain TBARS after treatments. Data are presented as the mean and std. deviation. Different letters represent significant differences (P < 0.001) (One way ANOVA).

Rats treated with either E or ES showed a significant decrease in serum TBARS (in nmol) after the treatment (E: 0.025 ± 0.002 vs. 0.021 ± 0.002; P < 0.05 / ES: 0.027 ± 0.002 vs. 0.021 ± 0.002; P < 0.001) as presented in Figure 5A. Other groups did not have significant decrease (S: 0.026 ± 0.001 vs. 0.024 ± 0.002; P = 0.35 / C: 0.024 ± 0.001 vs. 0.024 ± 0.001; P = 0.39). Inter-treatment comparison showed that the magnitude of serum TBARS decrease was significantly higher in the ES group than in both the controls (-0.0061 ± 0.0032 vs. -0.0007 ± 0.002; P < 0.01) and S group (-0.0061 ± 0.003 vs. -0.0012 ± 0.002 g; P < 0.01) (Fig. 5B).

Cholesterol

Serum cholesterol levels (mg/dL) increased significantly in both the controls (43.8 ± 8.0 vs. 66.1 ± 8.5; P < 0.0001) and S group rats (50.8 ± 6.2 vs. 62.2 ± 11.9; P < 0.01) following the treatment. Rats treated with either E or ES did not have a significant increase in cholesterol (E: 48.4 ± 6.7 vs. 56.5 ± 6.4; P = 0.1 / ES: 59.2 ± 6.5 vs. 63.5 ± 3.5; P = 0.06) (Fig. 6A). Inter-treatment comparisons (Fig. 6B) revealed that controls had a greater increase in serum cholesterol compared with the E (22.2 ± 7.7 vs. 8.0 ± 7.7; P < 0.001), S (22.2 ± 7.7 vs. 11.4 ± 8.0; P < 0.001) and ES (22.2 ± 7.7 vs. 5.3 ± 5.8; P < 0.001) groups.

Triglycerides

Serum TG (mg/dl) decreased significantly in the E (131.5 ± 18.0 vs. 57.42 ± 8.9; P < 0.001), S (126.29 ± 14.2 vs. 99.26 ± 19.6; P < 0.0001) and ES (139.73 ± 26.3 vs. 77.00 ± 18.3; P < 0.0001) groups after the treatment (Fig. 7A), whereas the control group demonstrated no change (126.91 ± 31.7 vs. 113.37 ± 17.9; P = 0.335). Inter-treatment comparisons revealed that the magnitude of the decrease in TG was significantly higher in the E group than in both the controls (decrease in mg/dl: 61.7 ± 33.1 vs. 13.5 ± 27.7; P < 0.001) and S group (61.7 ± 33.1 vs. 27.0 ± 7.2; P < 0.001). The ES group had a significant decrease in TG when compared with the control (62.7 ± 16.5 vs. 13.5 ± 27.7; P < 0.001) and S group (62.7 ± 16.5 vs. 27.0 ± 7.2; P < 0.001) (Fig. 7B).

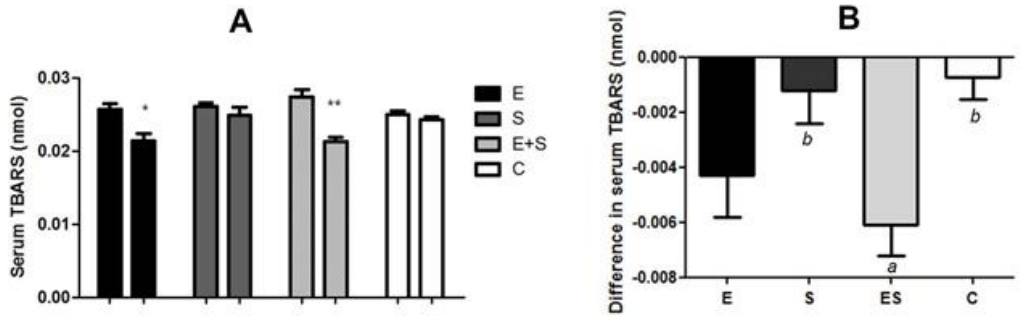

Figure 5 - Exercise alone and combined with *S. platensis* were both efficacious in reducing serum TBARS. (A) Serum TBARS before and after treatments. Data are presented as the mean and std. deviation. *P < 0.05; **P < 0.001 (Student t tests followed by two way ANOVA). (B) Difference in serum TBARS after ten-week treatments. Data are presented as the mean and std. deviation. Different letters represent significant differences (P < 0.01) (One way ANOVA).

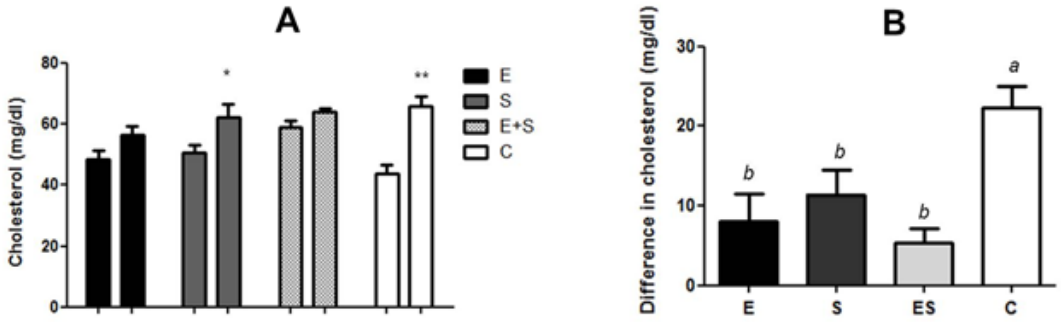

Figure 6 - The combination of exercise and *S. platensis* prevented an increase in serum cholesterol. (A) Cholesterol before and after treatments. Data are presented as the mean and std. deviation. *P < 0.01; **P < 0.0001 (Student t tests followed by two way ANOVA). (B) Difference in cholesterol after ten-week treatments. Data are presented as the mean and std. deviation. Different letters represent significant differences (P < 0.001) (One way ANOVA).

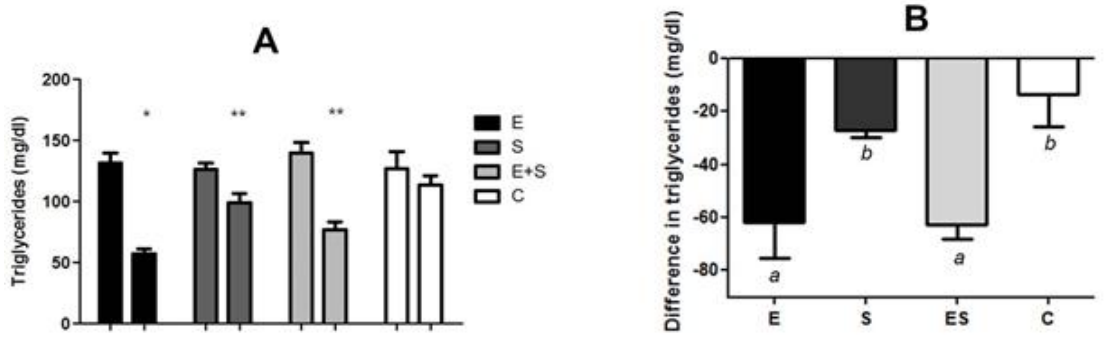

Figure 7 - Exercise, *S. platensis* and its combination decrease the triglycerides. (A) TG before and after treatments. Data are presented as the mean and std. deviation. *P < 0.01; **P < 0.0001 (Student t tests followed by two way ANOVA). (B) Difference in TG after ten-week treatments. Data are presented as the mean and std. deviation. Different letters represent significant differences (P < 0.001) (One way ANOVA).

DISCUSSION

Oxidative stress and dyslipidemia have been the focus of intensive studies given their importance in the aging process and its relation with disease development (Vaziri et al. 2010; Hwang et al. 2011). Oxidative stress predominates in the different pathophysiology, with the emphasis in the cerebral injury (Gomez-Pinilla 2011; Macedo et al. 2014). A greater susceptibility of the brain to oxidative stress is supported by several evidences. The brain accounts for only 2% of the body weight, but it consumes about 20% of the body oxygen, which increases the mitochondrial formation of ROS. The brain contains relatively high concentrations of readily peroxidizable lipids, such as polyunsaturated fatty acids, representing one third of the brain fatty acids (Hwang et al. 2011). As a result, lipid peroxidation is one of the major consequences of the free radical mediated injury to the brain (Hwang et al. 2011; Zheng et al. 2013).

Different investigations have shown significant results in the use of *Spirulina platensis* against oxidative stress and dyslipidemias (Bermejo-Bescós et al. 2008; Hwang et al. 2011; Farooq et al. 2014). Based on this, studies were conducted to assess the oxidative stress and lipid profiles in the rats treated with *S. platensis*, moderate exercise, or both. For the assessment of oxidative stress, brain and serum TBARS were measured, which was a marker of lipid peroxidation, resulting from the process of oxidative stress (Gustav-Rothenberg et al. 2010; Potter et al. 2011). Lipid profiles were evaluated by measuring cholesterol and TG in the serum. The main findings of this study were as follows: (1) rats had lower levels of brain TBARS when treated with exercise, particularly in association with *S. platensis*; (2) exercise alone and exercise combined with *S. platensis* both reduced serum TBARS; and (3) compared with the controls, both exercise alone and exercise plus *S. platensis* prevented the increase in cholesterol levels and diminished serum TG.

The present results demonstrated that the rats treated with exercise had lower levels of brain TBARS, particularly when exercise was combined with *S. platensis.* This latter regimen also showed benefits in reducing serum TBARS. In the clinical context, these findings indicated that exercise might be useful to prevent the conditions related to oxidative stress such as cardiovascular and neurodegenerative diseases. Furthermore, the combination of exercise and *S. platensis* might potentiate such action. In humans, a study evaluating the acute antioxidant response to exercise plus *S. platensis* found that the supplementation of *S. platensis* significantly decreased carbohydrate oxidation rate and increased glutathione levels in comparison with placebo (Kalafati et al. 2010). These results were in agreement with the present findings, which observed an improvement in lipid peroxidation in serum in the rats treated with exercise and *S. platensis*. Zheng et al. (2013) reported decreased lipid peroxidation in the hippocampus and cortex with the use of *S. platensis* in the rats at a dosage of 50 mg/Kg per day. In the present study, the combination of exercise and *S. platensis* prevented an increase in serum cholesterol after short-term treatment, compared with the controls. Most studies in the literature observed a decrease in cholesterol after exercise alone or exercise combined with nutritional supplements, such as vitamin E and carnitine (Quiles et al. 2003; Kim et al. 2004).

Meilhac et al. (2001) found that exercise combined with vitamin E prevented the increase in cholesterol in mice treated with a hypercholesterolemic diet; mice treated with normal diet showed an increase in cholesterol levels after exercise compared with sedentary animals. Nakaya et al. (1988) reported that individuals with higher levels of serum cholesterol received greater benefits in reducing cholesterol after treatment with *S. platensis*. According to Ramamoorthy and Premakumari, (1996), the greater the amount of *S. platensis* that was offered, the greater was the reduction in cholesterol levels. These data explained the present results observed in the *S. platensis* group, which did not present benefits because the animals were not hypercholesterolemic. In addition, the *S. platensis* dose used in the present study was relatively low compared with that used in other studies (Kim and Park 2003; Khan et al. 2005). The serum TG was reduced after all the interventions, except in the control group. The most pronounced decrease was observed in the rats treated with exercise and exercise plus *S. platensis*. A study with overweight humans demonstrated that exercise associated with supplementation with whey protein, which has antioxidant properties, resulted in a significant decrease in TG in the experimental groups (exercise and exercise plus supplementation) and an increase in the total antioxidant capacity that

was not observed in the control group (Sheikholeslami and Ahmadi 2012). However, the effects of *S. platensis* on TG have been controversial in other studies. Cheong et al. found a decrease in TG after the treatment with *S. platensis* in the rabbits with increased levels of serum lipids (Cheong et al. 2010).

These benefits were potentiated when *S. platensis* was combined with exercise. In this context, there was agreement with Lu et al. (2006), who aimed to assess the effects of *Spirulina* supplementation on preventing skeletal muscle damage on untrained human beings. The results showed that plasma concentrations of malondialdehyde (MDA) were significantly decreased after supplementation with *Spirulina* ($P < 0.05$). These results suggested that the ingestion of *S. platensis* showed preventive effect of the skeletal muscle damage and that probably led to postponement of the time of exhaustion during the all-out exercise. Kalafati et al. (2010) reported the benefits of *S. platensis* combined with physical exercise. The supplementation with *Spirulina* induced a significant increase in exercise performance, fat oxidation, and GSH concentration and attenuated the exercise-induced increase in lipid peroxidation. Pinilla Gomez (2011) showed the importance of physical exercise and dietary supplementation with functional substances with a view to mitigating damage and preventive health care with emphasis on brain health. Several other studied have shown the importance of the choice of preventive strategies for health. The use of *S. platensis* cyanobacteria has been shown with significant attenuation capacity of free radicals, preventing and/or avoiding the installation of different pathologies (Bermejo-Bescós et al. 2008; Bertolin et al. 2009; Pabon et al. 2012; Farooq et al. 2014; Yogianti et al. 2014). Results of these studies and present results matched on the profiles of oxidative stress and lipid levels in mice with the use of therapies moderate exercise and *S. platensis*.

CONCLUSION

In conclusion, the use of *S. platensis* and moderate exercise on showed decreased levels of TBARS, a marker of oxidative stress in the brain and serum. These benefits were potentiated when *S. platensis* was combined with exercise. This combination also prevented an increase in serum cholesterol and decreased TG levels. Therefore, moderate exercise and *S. platensis* might be useful in treating the cardiovascular, neurodegenerative and other diseases related to aging. Further studies are needed to confirm the benefits of these interventions in humans.

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