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REVIEW ARTICLE

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Clinical, cellular and molecular approaches to oxidative stress in athletes' bodies: a systematic and integrative review

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Abstract

Introduction: Frequent physical exercises can cause a state of transient fatigue, thus increasing the regenerative capacity of the body and inducing an overcompensation of the biological systems involved. The state resulting from overtraining has negative consequences not only for physical performance but also for health and when this state occurs, reactive oxygen species (ROS) are synthesized in the body. **Objective:** It was to carry out a systematic and integrative review of the main clinical, cellular and molecular approaches to oxidative stress in athletes' bodies, as well as the main functions of antioxidants in mitochondria. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from October to December 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 127 articles were found, and a total of 67 articles were fully evaluated and 57 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 7 studies at high risk of bias and 25 studies that did not meet the GRADE. Studies have shown that free radicals play important roles as regulators in muscle signaling processes. Oxidative stress reflects an imbalance between the production of reactive oxygen species and adequate antioxidant defense. The relationship between exercise and oxidative stress is extremely complex, depending on the mode, intensity, and duration of exercise. High levels of reactive oxygen species produced in skeletal muscle during exercise have been associated with muscle damage and impaired muscle function. Antioxidant supplementation may be warranted under specific conditions when athletes are exposed to high oxidative stress or do not meet dietary antioxidant requirements. Continuous aerobic exercise under moderate-intensity or high-intensity interval training can be recommended to increase the body's ability to maintain redox balance, especially for unhealthy individuals.

Keywords: Physical exercises. Oxigen-reactive species. Oxidative stress. Antioxidants. Mitochondria.

Introduction

Frequent physical exercises can cause a state of transient fatigue, thus increasing the regenerative capacity of the body and inducing an overcompensation of the biological systems involved. Specifically, strenuous exercise, defined as any activity that expends six metabolic equivalents per minute or more, causes structural damage to muscle cells, leading to pain and swelling, increased free radicals, impaired immune function, and removal of proteins from circulation, among others. consequences. These processes have various clinical manifestations, including inflammation and immunosuppression, which increases vulnerability to infection [1,2].

In this context, if the imbalance between the work and recovery phases is prolonged, the body may not be able to adequately adapt to the physical workload. The state resulting from overtraining has negative consequences not only for physical performance but also for health and when this state occurs, reactive oxygen species (ROS) are synthesized in the body [2].

In this sense, free radicals are produced during aerobic cellular metabolism and play important roles as regulatory mediators in signaling processes. Oxidative stress reflects an imbalance between the production of

reactive oxygen species and adequate antioxidant defense [3]. This adverse condition can lead to cell and tissue damage of components and is involved in different pathophysiological states, including aging, exercise, inflammatory, cardiovascular, neurodegenerative diseases, and cancer [3].

In particular, the relationship between exercise and oxidative stress is extremely complex, depending on the mode, intensity, and duration of exercise [4]. Moderate regular training appears to be beneficial for oxidative stress and health. On the other hand, acute exercise leads to increased oxidative stress, although this same stimulus is necessary to allow for upregulation in endogenous antioxidant defenses [5].

Thus, supporting endogenous defenses with additional oral antioxidant supplementation may represent a suitable non-invasive tool to prevent or reduce oxidative stress during training [6]. However, excess exogenous antioxidants can have detrimental effects on health and performance. Whole foods, rather than capsules, contain antioxidants in natural ratios and ratios, which can work synergistically to optimize the antioxidant effect. Thus, an adequate intake of vitamins and minerals through a varied and balanced diet remains the best approach to maintaining an optimal antioxidant status [7-10].

Also, supplementation with antioxidants can be warranted in specific conditions, when athletes are exposed to high oxidative stress or do not meet dietary antioxidant needs [11]. In addition, it is recommended the need to adopt an individualized diet for each athlete who practices a certain sport or in a certain training period, clinically supervised with the inclusion of blood count and physiological tests, in a comprehensive nutritional assessment [2].

In this regard, the present study aimed to carry out a systematic and integrative review of the main clinical, cellular and molecular approaches to oxidative stress in athletes' bodies, as well as the main functions of antioxidants in mitochondria.

Methods

Study Design

The rules of a systematic review of the PRISMA Platform (Transparent reporting of systematic review and meta-analysis-HTTP://www.prisma-statement.org/) were followed.

Data Sources and Research Strategy

The search strategies for this systematic review were based on the keywords (MeSH Terms): "Physical exercises. Oxigen-reactive species. Oxidative stress. Antioxidants. Mitochondria". The research was carried out from October to December 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. In addition, a combination of keywords with the Booleans "OR", "AND" and the "NOT" operator were used to target scientific articles of interest.

Study Quality and Risk of Bias

The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument.

Results and discussion

Summary of Literary Findings

A total of 127 articles were found. Initially, article duplication was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing articles that did not include the topic of this article, resulting in 74 articles. A total of 67 articles were fully evaluated and 57 were included and developed in the present systematic review study (**Figure 1**). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 7 studies at high risk of bias and 25 studies that did not meet the GRADE.

Figure 1. Flowchart showing the article selection process.

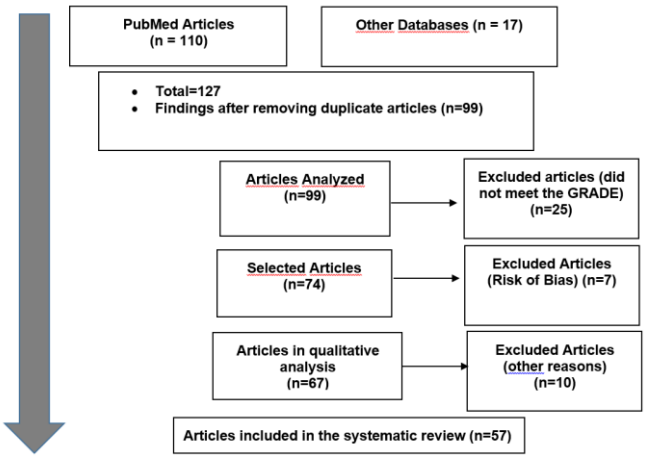
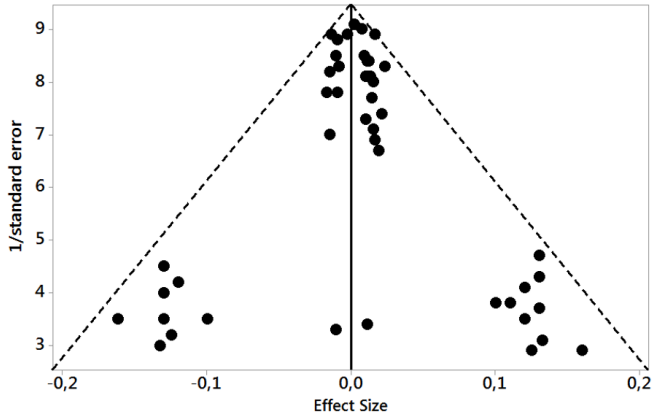


Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size using the Cohen Test (d). The sample size was determined indirectly by the inverse of the standard error (1/Standard Error). This graph showed symmetrical behavior, not suggesting a significant risk of bias, both between studies with small sample sizes (lower precision) that are shown at the bottom of the graph and in studies with large sample sizes that are presented in the upper region.

Figure 2. The symmetrical funnel plot suggests no risk of bias between the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (Ntotal=57 studies evaluated in full in the systematic review).



Source: Own authorship.

Main Evidences – Reactive Oxygen Species

High levels of reactive oxygen species (ROS) produced in skeletal muscle during exercise have been associated with muscle damage and impaired muscle function. Supporting endogenous defense systems with additional oral doses of antioxidants has received much attention as a non-invasive strategy to prevent or reduce oxidative stress, decrease muscle damage and improve exercise performance. The consistent finding is that antioxidant supplementation attenuates exercise-induced oxidative stress **[1,2,12]**.

Furthermore, scientific evidence indicates the harmful effects of high-dose antioxidant supplementation on the health benefits and performance of physical training. Although ROS are associated with harmful biological events, they are also essential for the development and optimal functioning of all cells. In certain situations, high doses of antioxidants may impair the positive effects of physical training and interfere with important physiological processes mediated by ROS, such as vasodilation and insulin signaling. It is recommended that an adequate intake of vitamins and minerals through a varied and balanced diet remains the best approach to maintaining optimal antioxidant status in exercise individuals **[2,12]**.

In this regard, exhaustive exercise can induce the excessive generation of ROS, increasing levels of oxidative stress. While physiological levels are crucial for optimal cell signaling and exercise adaptations, higher concentrations of ROS have been shown to damage macromolecules. In addition to single doses of antioxidants, antioxidant-rich whole-grain diets are gaining increasing attention due to their practicality and multicomponent ingredients **[7,8]**.

Accordingly, a recent narrative review study reviewed the current state of research on this topic and presented recent advances regarding the antioxidant effects of whole dietary strategies on exercise-induced oxidative stress in humans. A total of twenty-eight studies were included in this narrative review and demonstrated the scavenging effects of exercise-induced ROS generation, markers of oxidative stress, inflammatory markers, and antioxidant capacity, with only one study not confirming these positive effects. Although the literature is still scarce on the effects of complete dietary strategies on exercise-induced oxidative stress, most studies have demonstrated favorable effects. However, the protocols are still very heterogeneous, and more systematically designed studies are needed to strengthen the evidence **[1,13]**.

Oxi-Reduction (Redox)

Redox reactions control fundamental processes in human biology. Therefore, it is safe to assume that exercise responses and adaptations are mediated by redox reactions. Several scientific studies show that redox reactions are the basis of exercise physiology, describing the redox signaling pathways that regulate four characteristic acute responses induced by exercise, such as contractile function muscle, muscle contractile function, glucose uptake, blood flow, and bioenergetics and four chronic exercises of induced adaptations, such as mitochondrial biogenesis, muscle hypertrophy, angiogenesis, and redox homeostasis **[14]**.

In this sense, it is well established that exercise stimulates a set of local and systemic stressors that trigger integrated acute responses that, in the long run, long-term, resulting in phenotypic adaptations in all systems of the human body **[15-17]**. An interesting series of studies have been performed on intact mouse fibers (ie fibers along with their entire redox environment consisting of antioxidants and target molecules) **[18]**.

Transient exposure (4 minutes) or low concentration (in the order of nM and pM) of hydrogen peroxide (H_2O_2) or start-butyl hydroperoxide (t-BOOH) increased the submaximal production of muscle force in fast-twitch muscle fibers, while the addition of the antioxidant dithiothreitol (DTT) resulted in a progressive decline in strength. On the other hand, prolonged exposure (8 minutes) or high concentration (in the order of mM) of H_2O_2 decreased submaximal force production muscle, an indication of the development of muscle fatigue, and this was reversed by addition of DTT **[18]**.

In this context, transient exposure of uncontained intact muscle fibers to DTT decreased submaximal force production and this was reversed after the treatment with the opposite redox stimulus, H_2O_2 **[19]**. Thus, an optimal cellular redox state appears be the main determinant for the normal production of muscle force, while a reduced state (e.g., at rest) or oxidized (e.g., during fatigue protocols) negatively regulates this process **[20]**.

Similar studies using skin muscle fiber preparations mechanically showed that H_2O_2, in concentrations of up to 10 mM, does not exert necessarily an effect on force production **[21]**. However, in some cases, comparable or even higher levels of H_2O_2 have been found to negatively affect function contractile due to the oxidation of specific cysteine and methionine residues at the interface actin-myosin **[21]**.

Furthermore, a study by Murphy et al. (2008) **[22]** treated the fibers injured muscles with myoglobin and glutathione, along with low H_2O_2 concentrations (100-300 μM). They found that glutathione prevented partially the decline in muscle force production induced by the H_2O_2-Fe2+ / myoglobin in slow-twitch muscle fibers, while in slow-twitch muscle fibers fast twitch, glutathione increased Ca2+ sensitivity that was later explained by the interaction of glutathione with oxidized cysteine residues in the rapid isoform of troponin, which increased myofibrillar sensitivity to Ca2+ **[21]**.

Therefore, H_2O_2 regulates the production of muscle force positively or negatively mainly by changing myofibrillar sensitivity to Ca^{2+}. Still in this context, in addition to H_2O_2, it was also demonstrated that the radical superoxide affects muscle force production, however, this was facilitated by a different mechanism, i.e., a cross-linked sarcoplasmic Ca2+ change rather than sensitivity to Ca^{2+} **[23]**.

Regarding nitric oxide (NO) and its effects on force production, experiments with intact fast-twitch muscle fibers have shown that NO affects contractile function by altering myofibrillar sensitivity to Ca^{2+}. In addition, a study that used injured muscle fibers treated with S-nitroso-Nacetylpenicillamine and nitrosoglutathione (nitric oxide donors) reported a decrease in Ca^{2+} sensitivity in fast-twitch fibers, but maximum strength was not affected **[24]**.

Unlike fast-twitch fibers, the same study showed that slow-twitch muscle fibers treated with nitric oxide donors did not exhibit altered myofibrillar Ca^{2+} sensitivity. Other studies have shown that, along with Ca^{2+} sensitivity, reactive nitrogen species can also affect muscle force production and this may result from S-nitrosylation of the myosin heads by peroxynitrite, which is a highly reactive species produced by the reaction of the superoxide radical with nitric oxide **[24]**.

In this sense, nitro-active modifications, along with other redox reactions, of calcium-uptake-release proteins, such as the ryanodine receptor/ Ca^{2+} release channel (RyR1), have also been described. These structural changes also affect muscle contractile function, indicating that oxygen, nitrogen, and sulfur radicals regulate muscle force production and the development of fatigue by altering Ca^{2+} release **[25-27]**.

Antioxidants and Mitochondria

To better understand and improve the detoxification processes of radicals that cause oxidative stress in the human body, it is always necessary to put the spotlight on oxidative stress, which is a phenomenon caused by the imbalance between the production and accumulation of reactive oxygen species (ROS) in cells and tissues and the ability of a biological system to detoxify these reactive products. ROS can play various physiological roles (ie cell signaling) and are normally generated as by-products of oxygen metabolism **[2,28]**.

Furthermore, environmental stressors, that is, UV, ionizing radiation, pollutants and heavy metals and xenobiotics (anticlastic drugs) contribute to significantly increasing the production of ROS, therefore causing the imbalance that leads to cell and tissue damage (oxidative stress). Therefore, several antioxidants have been explored in recent years for their real or supposed beneficial effect against oxidative stress, such as vitamin E, flavonoids, and polyphenols. Although the literature describes oxidative stress as harmful to the human body, it is also true that it is explored as a therapeutic approach to treat clinical conditions such as cancer **[28]**.

In this sense, the maintenance of the mitochondrial genome is essential for proper cell functioning. Thus, mitochondrial DNA (mtDNA) needs to be faithfully replicated, transcribed, translated, and repaired in the face of a constant onslaught from endogenous and environmental agents **[29]**. Although only 13 polypeptides are encoded in mtDNA, the mitochondrial proteome comprises more than 1500 proteins that are encoded by nuclear genes and translocated to mitochondria to maintain mitochondrial function. Regulation of mtDNA and mitochondrial proteins by epigenetic changes (heavy metals and xenobiotics) and post-translational modifications facilitate interference between the nucleus and mitochondria and ultimately lead to the maintenance of cellular health and homeostasis **[29]**.

In this context, DNA methyl-transferase enzymes

were identified in mitochondria, implying that methylation occurs within this organelle; however, until the extent to which mtDNA is methylated has been debated for many years. The mechanisms of demethylation within this organelle have also been postulated, but the exact mechanisms and their results are still an active area of research. Mitochondrial dysfunction in the form of altered gene expression and ATP production, resulting from epigenetic changes, can lead to some conditions, including neurodegenerative diseases related to aging, altered metabolism, changes in circadian rhythm, and cancer **[28,29]**.

An overview of the epigenetic regulation of mtDNA via methylation, long and short non-coding RNAs, and post-translational modifications of nucleoid proteins (such as mitochondria that lack histones), highlighting the influence of xenobiotics and heavy metals on mtDNA methylation **[29]**.

As such, mitochondrial function is critical in regulating all three of the classic physiological factors that limit endurance performance **[30]**. Mitochondria have been overlooked in the age of genomics research, but these organelles are experiencing a renaissance as their importance as signaling modulators, not just energy producers, becomes clear. Although exercise physiologists have constantly studied mitochondria concerning their ability to metabolize substrates **[31]**, new data further elucidate the mechanism of energy generation and delivery within skeletal muscles **[32]**.

Furthermore, subsarcolemmal and intermyofibrillar mitochondria are heterogeneous subpopulations **[33]**. This heterogeneity may be partially due to the need for sub-sarcolemmic mitochondria to regulate sarcolemmal membrane function, whereas mitochondria are the main powerhouses of exercise due to their proximity to contracting sarcomeres **[34]**. However, subsarcolemmal and intermyofibrillar changes are part of a mitochondrial reticulum that provides a conductive pathway for energy distribution **[35]**. Within this mitochondrial reticulum, proteins associated with the proton-mitochondrial motif and force production are preferentially located at the periphery of the cell, and proteins that use the proton-motor force for ATP production within the cell **[32]**.

Thus, moderate exercise combined with adequate nutrition is considered a protective factor against cardiovascular diseases and musculoskeletal disorders. However, it is known that physical activity does not only have positive effects. Achieving good performance requires very high oxygen consumption, which leads to the formation of ROS **[35]**.

Besides, a major role is played by antioxidants, in particular natural antioxidants that can be taken in through the diet. Natural antioxidants are molecules capable of neutralizing oxygen free radicals without causing cellular cytotoxicity. In recent years, research has conducted several studies on the identification of natural micronutrients to prevent or mitigate oxidative stress induced by physical activity, helping to support conventional drug therapies against heart failure and muscle damage. In particular, sulfur-containing compounds can protect the body from oxidative stress, including six natural and defined antioxidants such as glutathione, taurine, lipoic acid, sulforaphane, garlic, and methylsulfonylmethane **[35]**.

Moreover, the literature suggests that dietary antioxidants are capable of detoxifying the peroxides produced during exercise, which could result in lipid peroxidation, and that they are capable of scavenging peroxyl radicals and, therefore, can prevent muscle damage. Endogenous antioxidant enzymes also play a protective role in the lipid peroxidation process. The reviewed studies (rodents and humans) showed significant increases in malondialdehyde (a product of lipid peroxidation) following exercise to exhaustion, and also favorable changes in plasma antioxidant levels and antioxidant enzyme activity. In trained subjects and trained rats, enzyme activity antioxidant increases markedly. Thus, the increase in oxidative stress induced by exercise is compromised by the increase in antioxidant activity, preventing lipid peroxidation. Studies in humans have demonstrated that dietary supplementation with antioxidant vitamins has favorable effects on lipid peroxidation after exercise **[36]**.

Also, vitamin C supplementation attenuates oxidative stress (lipid peroxidation) and inflammatory response (IL-6) to a single bout of exercise **[37]**. In this sense, concerning the biotransformation of human molecules and elimination systems, several clinical and in vivo studies were performed to evaluate the effects of food and food-derived components on the activity of detoxification pathways, including phase I cytochrome P450 enzymes, of phase II conjugation, Nrf2 and metallothionein signaling **[38]**.

Additionally, to study the effect of specific dietary components on health and performance in athletes, several groups have used metabolomics. Vitamin E supplementation has been shown to influence phospholipid metabolism and induce lysoPC generation, a general pro-inflammatory response. A diet rich in flavonoids triggered changes in 63 plasma metabolites with 70% belonging to lipids and xenobiotics **[39]**.

Besides, soy protein polyphenol complex supplementation was associated with an increase in the phenolic signature and ketogenesis in runners during

recovery from a 3-day heavy effort [40]. Consumption of fruits such as bananas and pears improved cycling performance by 75 km, reduced fatty acid oxidation, and increased antioxidant capacity [41]. In addition, pistachio ingestion was also associated with improved 75 km cycling time and increased post-exercise plasma levels of raffinose, sucrose, and related metabolites to oxidative stress [42].

In addition, studies have adopted a predictive metabolomics approach examining the effect of macronutrient composition consumed immediately after exercise on the serum metabolic profile in the initial phase of recovery. These studies suggested that pro-anabolic processes were favored with a mixture of carbohydrates and proteins compared to the consumption of water or carbohydrates [43]. In this context, the Wellnessup Diet (WD) was conceived as a healthy diet based on organic plant-based diets, including various vegetables, fruits, whole grains, nuts, and phytonutrients.

Thus, a study evaluated the effects of ingestion of 4 weeks of WD on detoxification of toxic trace elements, body fat reduction, and safety parameters. A total of forty-five women with a body mass index (BMI) of 23.5-30 kg/m2 were recruited. Thirty of these were assigned 1:1 to the test group (WD, 15 subjects) and control group (calorie-restricted diet, CKD, 15 subjects) in a single-blind, randomized, and the remaining 15 subjects were assigned to the control group 2 (maintain a regular diet, MDR). The levels of four toxic trace elements (nickel (Ni), rhodium (Rh), tin (Sn), and gallium (Ga)) in hair decreased in the WD group after the diet compared to before the diet to the CKD or MDR groups ($p<0.05$). At the end of the trial, both WD and CKD groups had lower BMI, Waist Circumference, Hip Circumference, and WHR compared to baseline values ($p < 0.05$). Compared with the WD group, the CKD group had a greater mean change ($p < 0.05$) from baseline for weight loss and fat-free mass [44].

Also, to reduce and eliminate the chromium toxin from the human body, the detoxification process through diet could be used. Thus, a descriptive study with 10 workers analyzed the intake of foods containing glutathione to improve chromium detox and calculate the cost of food intake. Intake of foods containing glutathione (avocados, broccoli, carrots, tomatoes, and grapes) considerably increased chromium detoxification [45].

To investigate whether aquatic athletes follow a diet Ideally, 58 athletes, all members of the Greek national swimming teams, were tested. Dietary intake was assessed at nutrient level, food, and food group using the 24-hour recall method and a food frequency questionnaire. Mean energy consumption for men and women was 14.3 and 8.5 MJ, respectively. The mean carbohydrate intake for male and female athletes female was 4.5 g/kg and 3.8 g/kg of body weight, respectively. the ingestion of fat was 153 g for men and 79 g for women. A significant number of athletes (71% of men, and 93% of women) did not reach the Dietary Intake of Reference to at least one of the antioxidant vitamins. The data suggest that athletes of both sexes consumed a lot of fat and little carbohydrate. Therefore, insufficient fruit and vegetable intake was linked to low antioxidant intake [46].

Added to this, a study observed the values of malondialdehyde and antioxidant vitamins to physical performance parameters. A total of eighty-four male athletes performed a maximal incremental test to exhaustion on a treadmill. Plasma malondialdehyde and antioxidant vitamins in plasma and erythrocytes were determined before and after the test. As a result, in the plasma, there was a decrease in malondialdehyde after the test. In erythrocytes, the results showed an increase in vitamin C and a decrease in vitamin E after the test. Maximal oxygen consumption values were positively associated with vitamin C and negatively associated with malondialdehyde levels before the test. On the other hand, the maximum oxygen consumption, the total test time, and the total test distance were positively related to the malondialdehyde values obtained after the test. Therefore, malondialdehyde, vitamin C, and vitamin E levels were related to performance parameters. These results may be linked to the adaptation of antioxidant systems due to regular training [47].

In this regard, cells have their mechanisms for dealing with a variety of stress conditions. In response to stressful conditions, and depending on the nature of the stress, cells activate or deactivate various signaling pathways. Generally, the attempt is to repair damage caused by stress by inducing pro-survival pathways. However, where the extent of damage is high, cells activate cell death pathways (pro-apoptotic pathways). Under conditions of stress, the process of deciding whether to activate pro-survival or pro-apoptotic pathways are collectively called the cellular stress response [48].

In this sense, the toxicity of heavy metals corresponds to the condition of stress, and it has been well established that oxidative stress is a key factor in adverse health toxic induced. Therefore, during the last few decades, the main focus of researchers was on the elucidation of oxidative stress induced by toxic and cellular regulators. As a result, several regulatory molecules have been reported to be activated in

response to oxidative stress induced by toxic heavy metals [48].

In this context, non-coding RNAs (ncRNAs), also called microRNA, are RNA molecules that cannot be translated into proteins [49]. The most common ncRNAs are tRNAs and rRNAs, which are essential for protein synthesis. Other ncRNAs, such as long and short ncRNAs, regulate gene expression through epigenetic mechanisms and may also act as signaling molecules to regulate essential cellular and biological processes [50,51]. The ncRNAs involved in the epigenetic regulation of mitochondrial gene expression can be encoded by the nuclear and mitochondrial genomes, however, it is unclear whether the ncRNAs encoded by mtDNA are derived from mitochondrial genes integrated into the nuclear genome or are transcribed within the mitochondria [52-57].

Conclusion

Studies have shown that free radicals play important roles as regulators in muscle signaling processes. Oxidative stress reflects an imbalance between the production of reactive oxygen species and adequate antioxidant defense. The relationship between exercise and oxidative stress is extremely complex, depending on the mode, intensity, and duration of exercise. High levels of reactive oxygen species produced in skeletal muscle during exercise have been associated with muscle damage and impaired muscle function. Antioxidant supplementation may be warranted under specific conditions when athletes are exposed to high oxidative stress or do not meet dietary antioxidant requirements. Continuous aerobic exercise under moderate-intensity or high-intensity interval training can be recommended to increase the body's ability to maintain redox balance, especially for unhealthy individuals.

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Informed consent

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

It was applied by Ithenticate@.

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