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Role of Physical Exercise and Antioxidant Nutraceuticals in Aged

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Original Research Article

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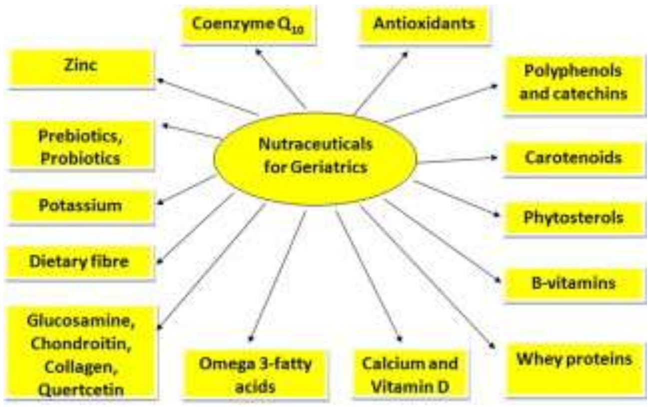
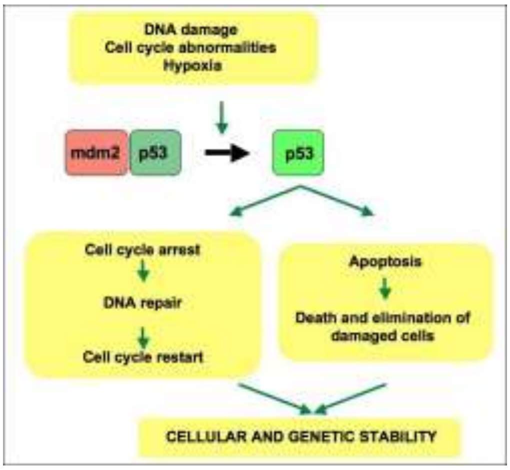
Abstract: Excess free-radical formation has been hypothesized to contribute to cancer, atherosclerosis, aging, and exercise-associated muscle damage. Antioxidant supplements such as vitamin C, vitamin E, and beta-carotene have been touted as beneficial for enhancing exercise performance and for preventing certain diseases. Before physicians routinely recommend supplements to prevent exercise-associated damage, more study will be required. Recommendations for the prevention of cardiovascular disease and cancer are more complex. Because study results have been contradictory, individual supplement recommendations must be offered with caution. Physicians must be cognizant of which supplements patients are taking and be prepared to discuss risks and benefits. The most beneficial prescription is probably a daily diet containing five to seven servings of fruits and vegetables..Muscular exercise promotes the production of radicals and other reactive oxygen species in the working muscle. Growing evidence indicates that reactive oxygen species are responsible for exercise-induced protein oxidation and contribute to muscle fatigue. To protect against exercise-induced oxidative injury, muscle cells contain complex endogenous cellular defence mechanisms (enzymatic and non-enzymatic antioxidants) to eliminate reactive oxygen species. Furthermore, exogenous dietary antioxidants interact with endogenous antioxidants to form a cooperative network of cellular antioxidants. Knowledge that exercise-induced oxidant formation can contribute to muscle fatigue has resulted in numerous investigations examining the effects of antioxidant supplementation on human exercise performance. To date, there is limited evidence that dietary supplementation with antioxidants will improve human performance. Furthermore, it is currently unclear whether regular vigorous exercise increases the need for dietary intake of antioxidants. Clearly, additional research that analyses the antioxidant requirements of individual athletes is needed.

Keywords: antioxidants, exercise, oxidative stress, performance, reactive oxygen species.

INTRODUCTION

Free radicals are generated during normal cellular function and are part of the natural physiological process of all living beings [1, 3]. They normally act as both beneficial and toxic compounds, since they can be either helpful or harmful for the body [4]. When an overload of free radicals cannot gradually be processed or in case of a poor availability of the naturally occurring antioxidant body protection, free radicals accumulation in the body generates a phenomenon called "oxidative damage", also known as "oxidative stress", a term frequently used to imply random, indiscriminate damage to a wide range of biomolecules [6]. Oxidative stress is generally considered the starting point for the onset of several diseases and certainly plays a major role in the development of aging and chronic and degenerative disorders such as arthritis, autoimmune disorders, cardiovascular and neurodegenerative diseases, inflammation and cancer [9]. Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) are the terms collectively describing free radicals and other non-radical reactive derivatives. Indeed, high levels of ROS can be lethal to cells. Modifications in cellular lipids are reported, as well as DNA and proteins degradation. ROS overproduction contributes to cell genomic instability and cancerogenesis, through the promotion of aberrant cell proliferation, apoptosis and uncontrolled cell growth [12].





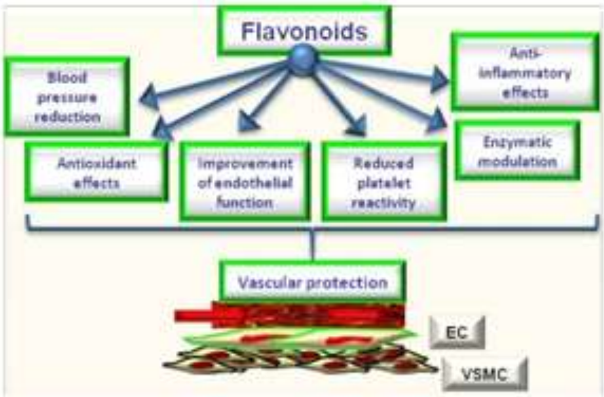
Mechanisms of oxidation

Oxidation and reduction reactions, known as redox reactions, refer to all chemical reactions in which loss or gain of electrons occurs, thus modifying the oxidation number.

In a biological environment, oxidants, that accept electrons, and reductants, that donate electrons, are called pro-oxidants and antioxidants, respectively. A cell's redox state describes the pro-oxidant/antioxidant balance and plays an important role in the modulation of different signaling and metabolic processes. During normal metabolism, oxygen is utilized in mitochondria for energy production. A small percentage of oxygen is not completely reduced, leading to the production of oxygen intermediates known as ROS [1]. At the same time, when reactants are derived from nitrogen, they are called reactive nitrogen species (RNS). Reactive species can be classified into two categories: free radicals and non-radical derivatives. The free radical group includes compounds such as the superoxide anion, nitric oxide or the nitric dioxide radicals. Most typical non radical reactive species relevant to biological systems are singlet oxygen, ozone (O_3), hydrogen peroxide (H_2O_2), peroxynitrite (ONOO–), hypochlorous acid, organic peroxides and aldehydes. Cells and extracellular spaces are exposed to a large variety of reactive stimuli from both exogenous and endogenous sources. The exogenous sources include exposure to oxygen, radiation, air pollutants, drugs, alcohol, heavy metals, bacteria, viruses, sunlight, and food. Nonetheless, exposure to endogenous sources is much more important and extensive, because it is a continuous process during the lifespan. As mentioned before, the most vulnerable targets of reactive species are proteins, lipids and DNA. ROS can oxidize proteins damaging their structure, impairing their functional activity and also affecting gene transcription. Reactive species oxidize polyunsaturated free fatty acids and initiate lipoprotein oxidation, with consequent changes in fluidity and permeability of the cell membrane. One of the major sources of free radicals is immune system and inflammation is the primary immune system reaction to eliminate pathogens or other stimuli in order to restore the cells to normal state or replace destroyed tissue with scar. Indeed, when cells of an organ are damaged, the immune system cells become activated and trigger the production of free radicals to destroy damaged structures. However, the free radicals produced by the immune system against the damaged organ oxidize and damage neighboring healthy cells, generating inflammation.

Physical exercise as an antioxidant

Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy consume, which may be unstructured, it can be an everyday life activity, an exercise that includes prearranged, deliberate and repetitive activity, grassroots and competitive sports and a regular physical activity of moderate intensity such as walking, cycling or sports that brings significant health benefits .The term “physical activity” should not be confused with the term “exercise”, which is a sub-category of physical activity and is characterized by being planned, structured, constant and aimed at improving or maintaining one or more aspects of physical fitness. Both moderate and vigorous physical activity bring health benefits. Physical efforts and skills can be involved in the common term of “Sport”, a human activity capable of achieving a result requiring physical exertion and/or physical skill, which, by its nature and organization, may be competitive and is generally accepted as being a sport. In order to counteract the negative effects and toxicity of oxidative stress on health, subjects at any age, with particular attention to aging, can benefit from constant, therefore repeated over time, physical activity that can alleviate the harmful effects caused by free radicals. However, although reactive species are associated with harmful biological events, they are essential in cellular development and optimal function. Indeed, cells have evolved strategies to utilize reactive species as biological stimuli. They act as subcellular messengers in important molecular signaling processes and modulate enzyme and gene activation. ROS are involved in the immune response of cells and drug detoxification, they are a requisite for vasodilation, optimal muscular contraction and initiation of apoptosis [2]. Moreover, accumulating evidence suggests that ROS are generated during exercise and modulate the level of muscle contraction. Modest ROS supplementation causes increase to force. However, relevant rise in ROS production that occurs during strenuous exercise contributes to the development of acute muscle fatigue [5]. Physical activity improves antioxidant defenses and lowers lipid peroxidation levels both in adult and in aged individuals [1]. Elderly physically active individuals show antioxidant activity and lipid peroxidation levels similar to young sedentary subjects, emphasizing the importance of regular physical activity to decelerate the aging-associated impairment process. Moderate exercise and an active lifestyle have been demonstrated to be useful not only in the prevention of oxidative stress, but also in the primary and secondary protection from cardiovascular disorders, type II diabetes, metabolic syndrome and neurodegenerative diseases like Alzheimer's disease [2]. The beneficial effects of exercise are also reflected in the release of myokines. These molecules exert auto-, para- and/or endocrine effects and include cytokines, interleukins such as IL-6 and other peptides that are produced, expressed, and released by muscle fibers and have a role in the protection against diseases associated with low-grade inflammation such as atherosclerosis [4]. The extent to which reactive species are or helpful or harmful depends on the exercise duration, intensity, fitness condition and nutritional status of the individual l [8].



The antioxidant defense tools of the body consist of antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase, etc.) and non-enzymatic antioxidants (Coenzyme Q10, glutathione, uric acid, lipoic acid, bilirubin, etc.). The exercise-induced ROS generation results in increased activity of enzymatic antioxidants, which then lead to an increased resistance to oxidative challenges, including a wide variety of oxidative stress-related diseases, including cardiovascular diseases, acquired neurodegenerative disorders (Alzheimer's and Parkinson's disease), asthma, diabetes and mitochondrial myopathies. CoQ10, also known as ubiquinone, is a fat-soluble molecule present in most eukaryotic cells, primarily in mitochondria. It is a component of the electron transport chain and plays a part in the cellular energy production. Its reduced form, ubiquinol, acts as an important antioxidant in the body. CoQ10 is synthesized endogenously, and its dietary uptake is limited.

It has been reported that strenuous exercise, reported as at least thirty minutes of intense and close to the limit muscle contractile activity, increases oxidant production in muscle, limiting performance [13]. Chronic exposure to high levels of ROS can become toxic, exhausting the enzymatic and non-enzymatic antioxidant system and leading to impaired cellular function, macromolecule damage, apoptosis, and necrosis. Therefore, excessive physical exercise is detrimental to untrained individuals, but progressive training allows the cells to more easily detoxify a larger amount of ROS. An excessive physical activity could be detrimental when it induces an altered hormonal activity, changes of the sleep-wake rhythm, of the appetite, alterations of the arterial pressure and of the heart rate. Indeed, those who are over-trained often find an increase in their heartbeats even at rest, struggle to fall asleep, are nervous and/or depressed, can be hypotensive and have a less efficient immune system.

Thus, since it has been reported that subjects involved in regular exercise, due to an adaptive response, demonstrate higher levels of mitochondrial content and accumulate lower levels of ROS at the given intensity than those who are untrained, the rationale is that both younger and elder population can take advantage of a constant physical activity in order to favor a more rapid recovery of the oxidation generated by strenuous exercise bouts, often referred to a maximal aerobic test, and thus to protect the body from oxidative damage.

The exogenous antioxidants

Besides the endogenous enzymatic and non-enzymatic antioxidant defenses that the human body develops to cope with the excess of free radicals produced upon oxidative stress, and besides the protective mechanisms of scavenging or detoxifying ROS, blocking ROS production or sequestering transition metals, the body exploits also other antioxidants which are normally supplied within the diet and which are called exogenous antioxidants.

Nutritional antioxidants act in different mechanisms and compartments, but are mainly free radical scavengers: 1) they neutralize free radicals, 2) they repair oxidized membranes, 3) they decrease reactive oxygen species production, 4) via lipid metabolism, short-chain free fatty acids and cholesteryl esters neutralize reactive oxygen species [12].

Exogenous antioxidants have generated growing interest in preventing or reducing oxidative stress, in decreasing muscle soreness and physical stress, and in ameliorating sport performance The exogenous antioxidants act in addition to the endogenous ones, and the most known are tocopherols (vitamin E), ascorbic acid (vitamin C), carotenoids (β-carotene), ubiquinone and polyphenols [11].

Vitamin E refers to a group of fat-soluble compounds that include tocopherols and tocotrienols. α-Tocopherol is the most biologically active form, has been shown to protect the cells from lipid peroxidation [6] and has been shown to have a role in the prevention of chronic diseases associated with oxidative stress.

Polyphenols are a group of water-soluble, plant-derived substances, characterized by the presence of more than one phenolic group [6]. Polyphenols are divided into two sub-categories: flavonoids and phenolic acids. Although there may be some evidence to support acute antioxidant supplementation immediately before certain types of intense exercise, where performance is fundamental, it is a much more common practice for athletes to continuously take antioxidants throughout the training period.Among antioxidants, flavonoids, a polyphenol class of pigments generally ubiquitous in the Plant Kingdom usually occurring in flowers, fruits and seeds, has been demonstrated to provide many health benefits and to influence exercise performance for athletes and for subjects non necessarily in constant training, such as elderly people [8]. Flavonoids include flavonols (quercetin), flavones (luteolin), flavanones (naringenin), anthocyanidins (cyanidin) and isoflavones (genistein). The other classes of non-flavonoid compounds involve low-molecular weight phenolic acids, stilbenes, chalcones, lignans and coumarins [9].

In this review we will describe the flavonoid quercetin and the two non-flavonoid polyphenols resveratrol and curcumin. The choice of these three antioxidants is given by the fact that they have excellent antioxidant and anti-inflammatory properties in both *in vitro* and *in vivo* models, are natural substances with promising therapeutic activities and potential health benefits, are easily recoverable from plants, food and other supplements, enter easily in a common daily diet and up to date display no toxicity for the body. We will examine their properties and activity as well as their benefits on sport performance and on aging, which is often associated with decreased vascular function partially due to oxidative stress, muscular weakness, fatigue and cognitive decline and which is expected to increase through the years and can get favorable benefits from a constant exercise activity. Nutritional antioxidants act in different mechanisms and compartments, but are mainly free radical scavengers: 1) they neutralize free radicals, 2) they repair oxidized membranes, 3) they decrease reactive oxygen species production, 4) via lipid metabolism, short-chain free fatty acids and cholesteryl esters neutralize reactive oxygen species [7]. Exogenous antioxidants have generated growing interest in preventing or reducing oxidative stress, in decreasing muscle soreness and physical stress, and in ameliorating sport performance [13]. The exogenous antioxidants act in addition to the endogenous ones, and the most known are tocopherols (vitamin E), ascorbic acid (vitamin C), carotenoids (β-carotene), ubiquinone and polyphenols [12].

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Vitamin C or L-ascorbic acid is a co-factor in a range of essential metabolic reactions in humans (e.g. collagen synthesis). This water-soluble vitamin is produced endogenously by almost all organisms, some species of birds and several mammals, excluding humans. L-ascorbate, an ion form of ascorbic acid, is a strong reducing agent and its oxidized form is reduced back by enzymes and glutathione [2]. β-Carotene belongs to a group of red, orange and yellow pigments called carotenoids . Others include α-carotene, β-cryptoxanthin, lycopene, lutein and zeaxanthin. These fat-soluble substances are found in plants and play a role in photosynthesis. β-Carotene is the most active carotenoid; after consumption it is converted to retinol, a readily usable form of vitamin A. β-carotene possesses antioxidant properties, anticancerogenic effects and has positive effects on the immune system. CoQ10 is synthesized endogenously, but it can be taken also as exogenous antioxidant [2, 3] and is well tolerated over a wide dosage range, with minimal side effects [4]. Some authors reported that CoQ10 may have a beneficial effect in the treatment of oxidative phosphorylation disorders [6] and can reduce oxidative stress in glaucoma patients [5].

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This flavonoid is known to exert a valuable antioxidant activity [3]. Antioxidant properties of quercetin are attributed to its chemical structure, particularly to the presence and position of the hydroxyl (-OH) groups, responsible of the protection against free radical injury through a radical scavenging mechanism [4]. It has been reported that quercetin is able to regulate the transcription factor AP-1 [4], involved in the expression of genes associated with cell growth and cellular stress. Recent discoveries have shown that quercetin induces and activates Sirtuin-1 (SIRT1), correlated to skeletal muscle function and mitochondrial formation [9].

Resveratrol

Resveratrol is a polyphenol chemically characterized as 3,5,4′-trihydroxystilbene occurring in the seeds and skins of grapes, red wine, mulberries, blueberries, cranberries, peanuts and, in particular, in the roots of the cultivated knotweed *(Polygonum cuspidatum)* [9]. Red wine and knotweed are the most common natural source of resveratrol. Many *in vivo* and *in vitro* studies reported different important properties of this natural compound. Resveratrol is non-toxic, easily absorbed and well tolerated by humans. The metabolism of resveratrol is high, leading to the production of conjugated sulfates and glucuronides, which retain some biological activity and accumulate in intestinal cells and in the liver [9]. Concerning its antioxidant activities, *in vitro* evidence shows that resveratrol can scavenge hydroxyl radicals and prevent oxidative DNA damage [1] and it induces the upregulation of SOD 1, 2 and 3, catalase and glutathione peroxidase (GPX) protecting the organism from oxidative damage.

Quercetin

Curcumin, also chemically known as diferuloylmethane, is a bright yellow polyphenol found in the rhizome of *Curcuma longa* (turmeric). Quercetin (3,3′,4′,5,7-pentahydroxylflavone) is a natural bioactive flavonoid found in a wide variety of cultivated plants and derived foods, such as nuts, grapes, onions, broccoli, apples and black tea [7]. Its amounts in vegetables was found to be below 10 mg/kg, but it reaches up to 40 mg/kg in beans and apples and up to 100 mg/kg in onions. This flavonoid is known to exert a valuable antioxidant activity [73]. Antioxidant properties of quercetin are attributed to its chemical structure, particularly to the presence and position of the hydroxyl (-OH) groups, responsible of the protection against free radical injury through a radical scavenging mechanism [74]. It has been reported that quercetin is able to regulate the transcription factor AP-1 [75], involved in the expression of genes associated with cell growth and cellular stress. Curcumin is well known to be a natural compound exerting antioxidant effects [4]. Due to its particular chemical structure, curcumin is indeed a scavenger of reactive oxygen and nitrogen species [6]. In addition, curcumin is a lipophilic compound, which makes it an efficient collector of peroxyl radicals. Curcumin can modulate the activity of GSH, catalase, and SOD enzymes active in the neutralization of free radicals and it can inhibit ROS-generating enzymes such as lipoxygenase/cyclooxygenase and xanthine hydrogenase/oxidase [9]. Curcumin is well known to be a natural compound exerting antioxidant effects. Due to its particular chemical structure, curcumin is indeed a scavenger of reactive oxygen and nitrogen species. In addition, curcumin is a lipophilic compound, which makes it an efficient collector of peroxyl radicals. Curcumin can modulate the activity of GSH, catalase, and SOD enzymes active in the neutralization of free radicals and it can inhibit ROS-generating enzymes such as lipoxygenase/cyclooxygenase and xanthine hydrogenase/oxidase [9].

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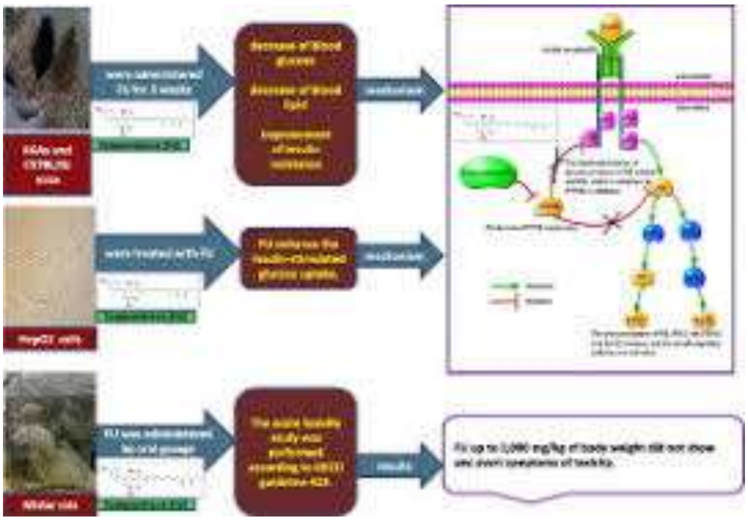

Quercetin, resveratrol and curcumin and their synergism with physical exercise

The role of nutraceutical formulations in improving exercise performance arouses increasing interest for researchers. Literature suggests that polyphenol nutraceuticals and their subclass flavonoids have a protective role against exercise-induced muscle injury, just due to their antioxidant and anti-inflammatory properties [8].

The exercise-induced lipid peroxidation was also reduced by the combination of quercetin and resveratrol in fourteen athletes randomly assigned to take these two compounds the week before exercise. Blood was taken at baseline, pre-exercise, immediately after exercise, and 1 h after exercise. In another study, conducted among 60 healthy subjects non-professional athletes with regular exercise, it was seen that eight-week supplementation with quercetin and vitamin C was effective in reducing oxidative stress and reducing inflammatory biomarkers including IL-6.

In a recent work it was seen that in healthy middle-aged and older adults, who were sedentary or moderately physically active, 12 weeks of curcumin supplementation improves artery endothelial function by increasing vascular nitric oxide bioavailability and reducing oxidative stress . Moreover, it was seen that an active metabolite of curcumin, Tetrahydrocurcumin (THC), possesses extremely strong antioxidant activity compared to other curcuminoids. The antioxidant role of THC has been implicated in recovery from renal injury in mice and in anti-inflammatory responses [7].

CONCLUSION

ROS or free radicals derived from oxidative stress are required at low concentrations for many important physiological functions, such as muscle contraction and drug detoxification. However, the dramatic increase in ROS during strenuous physical exercise can damage cell membranes, having deleterious effects on skeletal muscle performance, macromolecule damage and cellular function impairment. A constant, progressive physical activity allows the cells to better detoxify a large amount of ROS, and this has been demonstrated both in adult subjects and in elderly people, who show antioxidant activity levels similar to young sedentary subjects and who can take advantage of regular physical activity to protect themselves from oxidative damage and prevent from age-related disorders. Besides the endogenous antioxidant systems, several natural compounds which are normally supplied within the diet can act as exogenous antioxidants and are marketed as important ergogenic factors in physical exercise, both in young age and in aging. Therefore, exogenous natural supplements, together with a regular physical activity, are valid and promising molecules able to protect the body from oxidative damage and to alleviate the age-related pathophysiological disturbances. Future researches will further determine appropriate recommendations both in young age, adulthood and in aging especially, since nutrition and exercise are two effective and accessible strategies towards health maintenance in the aging population. Therefore, other natural, non-toxic compounds and innovations in research design may allow the opportunity to better understand the role of exogenous antioxidant supplementation and to give new, promising anticipations for the improvement of human healthcare.

REFERENCES

1. Valko, M., Leibfritz, D., Moncol, J., Cronin, M. T., Mazur, M., & Telser, J. (2007). Free radicals and antioxidants in normal physiological functions and human disease. *The international journal of biochemistry & cell biology*, *39*(1), 44-84.
2. Ye, J., Jiang, Z., Chen, X., Liu, M., Li, J., & Liu, N. (2017). The role of autophagy in pro-inflammatory responses of microglia activation via mitochondrial reactive oxygen species in vitro. *Journal of neurochemistry*.

3. Jiao, Y., Wang, Y., Guo, S., & Wang, G. (2017). Glutathione peroxidases as oncotargets. *Oncotarget*, *8*(45), 80093.
4. Pham-Huy, L. A., He, H., & Pham-Huy, C. (2008). Free radicals, antioxidants in disease and health. *International journal of biomedical science: IJBS*, *4*(2), 89.
5. Halliwell, B. (2007). Biochemistry of oxidative stress.
6. Giampietro, R., Spinelli, F., Contino, M., & Colabufo, N. A. (2018). The pivotal role of copper in neurodegeneration: a new strategy for the therapy of neurodegenerative disorders. *Molecular pharmaceutics*, *15*(3), 808-820.
7. Wu, C., Zhao, W., Yu, J., Li, S., Lin, L., & Chen, X. (2018). Induction of ferroptosis and mitochondrial dysfunction by oxidative stress in PC12 cells. *Scientific reports*, *8*(1), 574.
8. Phull, A. R., Nasir, B., ul Haq, I., & Kim, S. J. (2017). Oxidative stress, consequences and ROS mediated cellular signaling in rheumatoid arthritis. *Chemico-biological interactions*.
9. Kaffe, E. T., Rigopoulou, E. I., Koukoulis, G. K., Dalekos, G. N., & Moulas, A. N. (2015). Oxidative stress and antioxidant status in patients with autoimmune liver diseases. *Redox Report*, *20*(1), 33-41.
10. Carru, C., Da Boit, M., Paliogiannis, P., Zinellu, A., Sotgia, S., Sibson, R., ... & Gray, S. R. (2018). Associations between markers of oxidative stress, skeletal muscle mass and function and to the influence of resistance exercise training, in older adults. *Experimental gerontology*.
11. Lan, J., Huang, Z., Shao, J., & Huang, C. (2018). Redox regulation of microRNAs in cancer. Cancer Lett.
12. Patel, S. N., Sonani, R. R., Jakharia, K., Bhastana, B., Patel, H. M., Chaubey, M. G., ... & Madamwar, D. (2018). Antioxidant activity and associated structural attributes of Halomicronema phycoerythrin. *International journal of biological macromolecules*.
13. Sznarkowska, A., Kostecka, A., Meller, K., & Bielawski, K. P. (2017). Inhibition of cancer antioxidant defense by natural compounds. *Oncotarget*, *8*(9), 15996.