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Review

The Role of Exercise-Induced Reactive Oxygen Species (ROS) Hormesis in Aging: Friend or Foe

Ronny Lesmana[a,b,c] Cynthia Parameswari[d] Gabriela Fernanda Mandagi[d] Julianne Fay Wahyudi[d] Noah Jefferson Permana[d] Putri Teesa Radhiyanti[a] Julia Windi Gunadi[e]

[a]Physiology Division, Department of Biomedical Science, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia, [b]Center of Excellence in Highter Education for Pharmaceutical Care Innovation, Universitas Padjadjaran, Bandung, Indonesia, [c]Biological Activity Division, Central Laboratory, Universitas Padjadjaran, Bandung, Indonesia, [d]Undergraduate Medical Program, Faculty of Medicine, Universitas Padjadjaran, Bandung, Indonesia, [e]Physiology Department, Faculty of Medicine, Maranatha Christian University, Bandung, Indonesia

Key Words
Aging • Antioxidant • Exercise • Oxidative stress • ROS

Abstract
Reactive oxygen species (ROS) are oxygen derivatives that arise intrinsically from the oxidative phosphorylation process and extrinsically as a response to xenobiotics and pollution. ROS is involved in various conditions such as exercise, aging, inflammation, and neurodegenerative diseases. In the aging process, increased cellular senescence and decreased endogenous antioxidants also occur. Meanwhile, physical activity, specifically exercise, can modulate ROS. The impact of exercise on ROS varies from harmful to beneficial and depends on the type of exercise as they induce different types of ROS. Long-term exercise regulates signaling pathways that enhance antioxidant defense systems and control ROS production. This review will discuss studies on how exercise can regulate ROS and which type of exercise has a role in delaying the aging process. This review also exposes the impact of nutraceutical antioxidant agents that likely enhance the benefit of exercise. The nutraceutical antioxidants agents that likely enhance the benefit of exercise are creatine, whey, and ascorbic acid. Exercise is rewarding for the aging population concerning increasing their quality of life. Special consideration to exercise needs to be given to the type of exercise, and the exercise must be done continuously.

Ronny Lesmana
Faculty of Medicine, Biomedical Science, Physiology Division, Universitas Padjadjaran
Jalan Ir. Soekarno KM 21 Jatinangor, Sumedang, 45363, Jawa Barat (Indonesia)
Tel.+62 22 84288888, E-Mail ronny@unpad.ac.id

Introduction

The aging process generates a progressive loss of many biological functions, starting from the cellular level. Several cardinal biomarkers of aging are telomere length shortening, DNA damage, and oxidative stress [1–3]. Telomere length shortening, also known as telomere attrition, is hypothesized to trigger cellular aging as its length correlates with many vertebrates' survival [4]. DNA damage elicits activation of DNA damage response (DDR) which includes increasing levels of reactive oxygen species (ROS). Moreover, high levels of ROS could also damage DNA, resulting in a vicious cycle of ROS production [5]. These processes may lead to cellular cycle arrest or cellular senescence. Cellular senescence causes immunosenescence and mitochondrial dysfunction. Immunosenescence is a term used to describe a chronic deterioration of immune function, such as neutrophil dysfunction associated with the pathogenesis of age-related diseases [6]. Cellular senescence attenuates GRSF1, which functions to maintain mitochondrial phosphorylation in complex I, causing impairment of the electron transport chain that leads to mitochondrial dysfunction marked by increased ROS production [7, 8].

ROS are oxygen derivatives that arise intrinsically from the oxidative phosphorylation process as an excess product and extrinsically as a response to xenobiotics and pollution. As a reactive molecule, the generation of ROS is observed as a cascade of transitions from one species to another. The first generation of ROS, such as superoxide radical ($O_2^{\bullet-}$), nitric oxide radical ($NO^{\bullet}$), and hydrogen peroxide (H_2O_2), is mainly crucial for redox signaling [9]. Mitochondria is the primary contributor to this type of ROS, mainly $O_2^{\bullet-}$, via incomplete oxygen reduction at the electron transport chains (ETC). Meanwhile, in the cytoplasm, $O_2^{\bullet-}$ and H_2O_2 are produced by NOX (nicotinamide adenine dinucleotide phosphate [NADPH] oxidases) family. These enzymes contain seven isoforms, NOX1, NOX2, NOX3, NOX4, NOX5, DUOX1, and DUOX2, distributed differently throughout the body [10–14]. Moreover, NOXs are triggered by specific stimuli from the environment. A study by Rathore et al. [15] showed hypoxia induces ROS production, which further causes AMPK (AMP-activated protein kinase) activity. Several fundamental roles that AMPK carried out include modulating cell growth and adjusting metabolism [16]. On the other hand, reactive nitrogen species (RNS) is well known as $NO^{\bullet}$ Derivatives that arise from L-arginine (L-Arg) and catalyzed by nitric oxide synthase (NOS).

The second generation of ROS, including peroxynitrite ($ONOO^-$), peroxynitrous acid (ONOOH), hydroxyl radical ($OH^{\bullet}$), and hypochlorous acid (HOCl), are mostly had high reactivity as well as low selectivity to their molecule target which contributes to oxidative stress. The third generation of ROS, such as nitrogen dioxide radical ($NO_2^{\bullet}$), carbonate radical ($CO_3^{\bullet}$), alkoxyl radical ($RO^{\bullet}$), and peroxyl radical ($ROO^{\bullet}$), is a potent oxidative stress inducer that causes cellular damage [9]. Therefore, ROS is an advantage and disadvantage due to its contribution to physiological and pathological conditions. Based on the analysis and synthesis of several references listed in Supplementary Table 1, we discuss the beneficial and harmful effects of ROS and how exercise can regulate ROS (for all supplementary material see www.cellphysiolbiochem.com).

The living organism must balance ROS production and its elimination rate and magnitude. Endogenous antioxidant enzymes and dietary antioxidants are needed to scavenge the excess ROS, thereby maintaining redox homeostasis. The human body has its antioxidant defense system, which includes superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT). SOD is an essential antioxidant that acts as a first-line defense mechanism against oxidative stress and ROS-mediated disease by catalyzing the conversion of highly reactive $O_2^{\bullet-}$ to H_2O_2, which is relatively stable. These enzymes have three isoforms, SOD1-3, located differently throughout the human body. The primary clearance of $O_2^{\bullet-}$ in the cytosol is SOD1, while SOD2 is mainly within the mitochondrial matrix. On the other hand, SOD3 is the primary protection against extracellular $O_2^{\bullet-}$ as it is secreted in the extracellular [17]. CAT is an enzyme that decomposes H_2O_2 into H_2O. Meanwhile, GPX is a selenium-containing peroxide responsible for reducing H_2O_2 that comes in eight isoforms

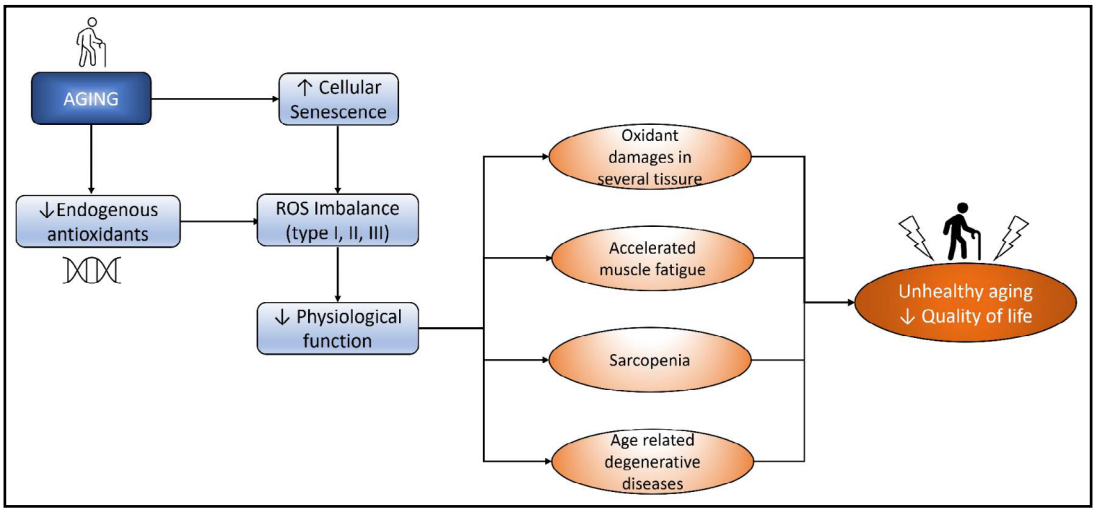


Fig. 1. Aging induces ROS imbalance that decreases physiological function and finally decreases QoL.

GPX1-8 [18]. Exogenous antioxidants, including vitamin C and E supplementation, and other minerals, like selenium (Se) and zinc (Zn), are shown to lower the concentration of ROS, thus preventing inflammation and muscles damages [19, 20]. Besides that, fruit and vegetables are rich sources of antioxidants that keep ROS at a flat rate [21, 22].

Oxidative stress is one of both promising and controversial theories of aging pathomechanism. Briefly, the theory says that the imbalance between pro-oxidants and antioxidants leads to oxidative damage, which results in cellular processes and the development of aging. Pro-oxidants include mitochondrial ROS and ROS-producing enzymes, such as xanthine oxidase (XO) and NOX [1]. To counter these pro-oxidants, there is an involvement of an endogenous antioxidant defense system composed of low molecular weight antioxidants (reduced glutathione [GSH], ascorbic acid tocopherols, etc.) and antioxidant enzymes. Endogenous antioxidants reduce ROS species to their less harmful form [9]. Kozakiewicz, et al. [23] showed a significant decrease in several antioxidant enzymes, such as Zn, Cu-superoxide dismutase (SOD-1), CAT, and glutathione peroxidase (GSH-Px), in older adults. The decreased activity of endogenous antioxidants is shown to cause higher levels of oxidative stress [24, 25]. In addition, some authors said that aging is closely related to increased ROS that scavenges NO. These findings indicate lower activities of primary antioxidant enzymes in older adults, indicating antioxidant defense impairment contributing to aging processes. Moreover, chronic oxidative stress leads to various consequences such as oxidant damage in several tissues, accelerated muscle damage, sarcopenia, and age-related degenerative diseases. The pathomechanism of oxidative stress in the aging process is depicted in Fig. 1.

Oxidant Damages in Several Tissue

Oxidative damage occurs when the capacity of oxidative stress is exceeded due to the generation of ROS and RNS caused by increased oxygen flux. This condition leads to cell damage and cell death. An untrained individual is likelier to have significantly raised oxidative stress resulting in muscle damage, neutrophil activation, inflammation, and muscle soreness. One period of complete exercise may lead to peripheral fatigue, the temporary redox imbalance accumulation, and oxidative DNA damage as reflected in the elevated biomarkers of redox state and oxidative DNA damage based on the C242T polymorphism in the gene encoding NOXs subunit p22phox (CYBA) [26]. Furthermore, Moflehi et al. [27] stated that a single session of aerobic exercise causes significant increases in malondialdehyde (MDA), a marker of oxidative stress, and creatine kinase (CK), a marker of muscle damage.

On the other side, exercise can modulate oxidative stress and may protect against DNA damage. Besides pro-oxidants, exercise also causes an increase in antioxidants in the body, including SOD. Frequency, intensity, time, and type of exercise are the factors influencing whether the exercise cause more pro-oxidants or antioxidants. A study conducted by Cho et al. [26] revealed that a single bout of exhaustive exercise via inducing the increase of both pro-oxidant and antioxidant status, but the increase in antioxidant status is not enough to scavenge oxidant increase, thus leading to oxidative damage. On the other hand, Shin et al. [28] had shown that long-term aerobic exercise training with moderate intensity causes a significant increase in SOD activity and reduces oxidative damage from acute exercise with moderate and high intensity. This finding is in line with the theory from Metin et al. [29], which suggested that the increase of antioxidant status may be caused by the elevation of oxidative stress caused by regular exercise.

In addition, two significant factors affect oxidant and antioxidant balance in the body, including individual fitness level and BMI. A study conducted by Watson et al. [30] showed that antioxidant levels in an athlete are significantly higher compared to a sedentary individual with sex matches. These elevated antioxidant levels are parallel with lower lipid peroxidation, which is proven by lower MDA levels in athletes. Furthermore, BMI is closely related to oxidant production in the body. Obese individuals, compared to non-obese showed significantly higher ROS levels immediately after exercise [31]. Mechanisms regarding this finding remain unclear, but it is suggested that higher ROS levels in an obese individual are related to neurotrophic factors that influence Blood-Brain Barrier (BBB) disruption.

Accelerated Muscle Fatigue

Fatigue is shown to be correlated with oxidative stress. A study held on the non-aging population showed that higher oxidative stress index (OSI) and reactive oxygen metabolites-derived compounds (d-ROMs) with lower biological antioxidant potential (BAP) are found in chronic fatigue syndrome patients (patients) at rest than in healthy individuals. High OSI and d-ROMs are also found in healthy individuals following sub-acute and acute fatigue [32]. Together, ROS accumulation potentially accelerates muscle fatigue in older adults since they showed a significant decrease in antioxidant defense mechanisms.

There are many studies concerning exercise's effect on age-related accelerated muscle fatigue. Several types of resistance training are given to the aging population, and there are positive outcomes regarding muscle activity. In mobility-limited older adults, progressive resistance training (PRT) increases their muscle strength and torque capacity. However, it does not influence the ability to recover from- and the magnitude of fatigue [33]. Drop-set resistance training increases muscle mass, strength, endurance, and functionality tasks. In addition to resistance exercise, different nutraceuticals are given to see if they would improve the gain of training alone. Combining creatine supplementation with training augments muscle mass gains and enables individuals to train to greater capacity over time. Note that this intervention is more effective in aging males than females [34]. The addition of whey to resistance exercise in frail elderly significantly improves muscle function, measured by handgrip strength, chair-stand ability, and walking speed [35]. However, the study conducted by Kirk et al. [36] revealed that a combination of leucine-enriched whey protein did not augment the improvement result of muscle fatigue and health-related quality of life ($_{HR-}$QOL) after exercise alone.

Nutraceuticals and pharmaceuticals can also be used to counteract muscle deterioration during aging. A healthy aging population who given an essential amino acid (EAA)-based multi-ingredient nutritional supplementation containing EAA, creatine, vitamin D, and muscle restores complex gain muscle strength, muscle power, and muscle mass that balance out more than a year of age-related loss of muscle mass and strength [37]. In the average aging population, oxidative stress is lowered from polyphenol-rich nutraceuticals, making them a potential agent. Green tea and sour tea (*Hibiscus sabdariffa L.*), both rich in flavonoid and polyphenols, significantly lessened malondialdehyde (MDA) and significantly

increased total antioxidant capacity (TAC) level with sour tea consumption only [38]. Grape juice consumption also shares the same result as acidic tea consumption and lowers DNA damage, isoprostane, and lower muscle fatigue with higher upper limb strength results [22]. In the middle-aged population, beta-alanine (β-alanine) and phosphodiesterase-5 inhibitors sildenafil supplementation increases exercise endurance and muscle proteome [39, 40]. In summary, exercises, nutraceuticals, and pharmaceuticals can improve muscle performance in the aging population. A combination of nutraceuticals and exercises may add the improvement by exercise only.

Sarcopenia

Sarcopenia is an age-related loss of muscle mass and function caused by factors inherent to skeletal [41]. The pathogenesis of sarcopenia is multifactorial; however, several studies suggest that oxidative stress plays a major role in the development of sarcopenia [42].

ROS-induced oxidative in skeletal muscles leads to decreased muscle mass and reduced muscle fiber diameter. A proposed mechanism of oxidative-stress-enhanced proteolytic systems is initiated by modulating cysteine proteases, calpain, and caspase-3 that cause protein degradation and the breakdown of the sarcomere [43]. In addition, a study by Bak et al. [44] reported that oxidative stress in muscles stimulated myostatin expression. Interestingly, myostatin functions as a negative muscle regulator; if its concentration increases, sarcomeric protein synthesis will be inhibited [45]. These conclude that excessive ROS results in decreased muscle protein turnover by simultaneously augmenting proteolysis and attenuating protein synthesis.

Accumulation of ROS also induces oxidative damage to proteins involved in the excitation-coupling response, resulting in decreased muscle contractile function [46]. Furthermore, it also causes impairment in the neuromuscular junction and SERCA pump, further impairing muscle function [47]. Thus, a disused muscle would eventually become atrophy and bear mitochondrial dysfunction, leading to further ROS production.

Mitochondria, as a ROS generator, could accumulate ROS that damages the mtDNA and cause defective production of the electron transport chains, resulting in a vicious cycle of continual ROS production [48]. Excessive ROS is also correlated to an altered mitochondria morphology marked by a thickened outer membrane, decreased membrane potential, and increased mitochondrial fission proteins, such as Drp1, that cause mitochondria fragmentation [44].

Age-related Degenerative Disease

It is well known that aging and age-related diseases are the consequences of oxidative stress [5]. Neurodegenerative diseases have been linked with the disturbances in redox homeostasis in the brain with increasing age. ROS production in specific brain regions and lowered antioxidant function cause oxidative damage leading to neuronal death and neurodegeneration associated with Parkinson's disease and Alzheimer's [49–51]. The study showed a progressive age-related rise in protein nitration and oxidation with a gradual decrease in SOD, CAT, and GSH in the postmortem human brain of individuals between 0.01 to 80 years [50]. Moreover, the accumulation of unrepaired damage due to oxidative damage in the aging brain is responsible for neurodegeneration [52]. In addition, interleukin (IL)-1, IL-6, TNF-α, and chemokines are released as ROS production increases, leading to neuroinflammatory processes. A large amount of ROS causes chronic stress, thus leading to cell death and dementia [53].

Excess ROS also contributes to cardiovascular diseases by deteriorating endothelial function. As aging increases ROS, the NO bioavailability is compromised in the systemic circulation and the musculature in older humans, thus further inducing endothelial

dysfunction [54]. Studies have also shown that vascular oxidative stress is mainly caused by $O2^{\bullet-}$ as the inhibition of its main generator (NADPH oxidase) has been shown to reduce arterial oxidative stress and normalize endothelial dysfunction in mice [55].

Respiratory diseases are caused by increased ROS production triggered by environmental exposure, primarily cigarette smoking, various toxicants, and infectious agents resulting in oxidative stress. Oxidative stress causes cellular damage by lipid peroxidation, protein oxidation, and DNA histone modification [56, 57]. Moreover, elevated ROS levels trigger a cascade of events that produce pro-inflammatory mediators that promote inflammation. Inflammation further enhances ROS production and contributes to detrimental pathological characteristics in pulmonary disease. A study demonstrated erdosteine could reduce oxidative stress in patients with severe COPD, thus alleviating the symptoms and highlighting that oxidative stress is one major contributor to the pathogenesis of respiratory disease [58].

Exercise Produces both ROS and Antioxidant

Although it was believed that ROS is pathological, recent studies have also shown that a relative amount of ROS elicits a physiological role. Exercise has increased ROS production [59], producing a ROS signaling response [60]. These findings are further confirmed by exploring exercise markers upon NOX knockout. Even after exercise, the examination of mice skeletal tissue with NOX knockout showed no significant increases in specific antioxidant enzymes (SOD2, catalase) and mitochondrial protein levels (mitochondrial complex I, pyruvate dehydrogenase, OPA1, and mitofusin 2) [61], and no difference in metabolic responses [62, 63]. Investigation of the white adipose tissue also showed impaired exercise adaptation markers (Nrf2, HMOX, SOD1, CAT) upon NOX knockout [64]. These findings suggest that exercise-induced ROS induces beneficial adaptation.

Considering that ROS could be either pathological or physiological, it is suggested that ROS has a biphasic effect, beneficial up to a certain point and delirious with increasing levels. A study on ischemia/reperfusion injury showed that dosing mitoPQ results in an increase in ROS production. Low doses protect myocytes, but higher doses cause myocyte dysfunction and death [65]. Another study showed the biphasic effect of stimulating ROS production by gelatin treatment to injured skeletal muscle. A low dose of gelatin results in an increased antioxidant response, tissue adaptation to mild stress, myogenesis, and muscle regeneration. A high amount of gelatin causes ROS overproduction, leading to a worse tissue injury [66]. Therefore, ROS has a biphasic effect.

Although ROS has been shown to have a biphasic effect, the cutoff point between physiological and pathological ROS has not been defined. Most studies showed that the level of ROS is a determining factor between physiological and pathological ROS. However, there might also be other parameters for the biphasic cutoff point. A recent review classified ROS into several types based on its structure, compartmentalization, and reactivity [67]. The kind of ROS is potentially crucial in determining the cutoff point. However, current studies have not investigated the importance of ROS type in elucidating this biphasic effect. Therefore, further studies could explore the impact of ROS types in determining the cutoff point of the ROS biphasic effect.

ROS can be modulated by physical activity. There are different impacts of acute and chronic physical activity on oxidative stress. Acute exercise induces reactive oxygen, nitrogen species, and oxidative stress. Still, regular exercise training causes the endogenous antioxidative system and protects the body against adverse effects of oxidative damage [68]. This statement is supported by Nyberg et al.'s study [54], which stated that lifelong physical activity opposes compromised NO in systemic circulation and skeletal muscle of sedentary old individuals. He et al. [69] found that exercise training can alter antioxidant capacity in skeletal muscle. This finding is supported by Powers et al. [70]. They stated that high-intensity exercise training with all kinds of duration and low and moderate-intensity exercise training with an extended period elevate SOD activity in the myocardium. Lots of pathways

suggest mechanisms that lie behind the protective effect of ROS. Research by Yavari et al. [71] showed that mitochondrial ROS produced during regular exercise is needed to activate primary signaling pathways associated with muscle adaptation. Acute exercise stress (AES) will activate signaling of Nrf2/ARE (antioxidant response element) and subsequent enhancement of antioxidant defense pathways in wild-type (WT) mouse hearts [72].

In contrast, oxidative stress and blunted defense mechanisms were observed in Nrf2-/- mice [72]. Furthermore, Nrf2 is found to control neuronal survival in aging. On the other hand, Nrf2 also scavenges and controls ROS production via NADPH oxidase [73].

Besides that, ROS can also be regulated by exogenous antioxidants. Supplementation of antioxidants is reported to attenuate injury from strenuous resistance exercise [74]. Before exercise, acutely elevated antioxidant levels post-exercise, ascorbic acid supplementation–antioxidant protecting cellular components from radical damage. The beneficial effect of ascorbic acid supplementation is that they interfere with glucose utilization or transportation, thus leading to lower production of ROS.

Moderate elevation of mitochondrial oxidants has been shown to enhance systemic defense through adaptive response, termed mitohormesis [75, 76]. However, this does not apply to hydrogen peroxide. Based on a recent review, supraphysiological H_2O_2 level, measured at more than 100 nM, leads to cellular growth arrest and cell death. This state, that is to say, oxidative distress, correlates to pathologies [77]. Bladier et al. [78] showed a senescence-like state response in fibroblast that is given 50-100 μM H_2O_2 and apoptosis on 300-400 μM H_2O_2.

The redox signaling generates a response from transcription factors p53 and Nrf-2 that regulate antioxidant gene expressions. The activation of tumor suppressor 53 (p53) is modulated by H_2O_2 [79]. The Nrf2-KEAP1 system is the primary sensor of oxidative stress. Oxidation leads to the conformational change of KEAP1 (Nrf2 inhibitor), which prevents Nrf2 ubiquitylation and, therefore, will increase Nrf2 stability [80]. Within the cellular level, the membrane-associated phospholipid hydroperoxide glutathione peroxidase (GPX-4) prevents lipid hydroperoxides accumulation in the plasma membrane [81]. In the nucleus, DNA replication and telomere length maintenance regulation by peroxiredoxin 2 and peroxiredoxin 1, respectively, is sensitive to oxidants. In response to low oxidant levels, peroxiredoxin 2 promotes replication fork progression. Elevated H_2O_2 oxidizes and dissociates peroxiredoxin 2 and thus slowing down the replication fork. Higher oxidants level suppresses the synthesis of deoxynucleotide triphosphate (dNTPs) [82]. Peroxiredoxin 1 counters oxidative damage in telomeric DNA and promotes telomere elongation with 7,8-dihydro-8-oxoguanine triphosphate (MTH1) [83]. In the mitochondria, different levels of oxidant elicit different responses. Low oxidant level triggers mitophagy and selective removal of mitochondria. Higher oxidant level ends up in non-selective autophagy termed macroautophagy [84]. The endoplasmic reticulum has glutathione peroxidase and peroxiredoxins that scavenge H_2O_2 to water [85].

Conclusion

All this evidence showed that giving specific exercise to older people can delay aging by inhibiting the decrease of endogenous antioxidants and ROS formation. This inhibition eventually will lead to physiological function improvement. In addition, the supplementation of antioxidant nutraceutical agents will support the inhibition of cellular aging. As a result, as seen in Fig. 2, exercise and antioxidant supplementation will lead to a healthy aging process and enhance the quality of life of the elderly.

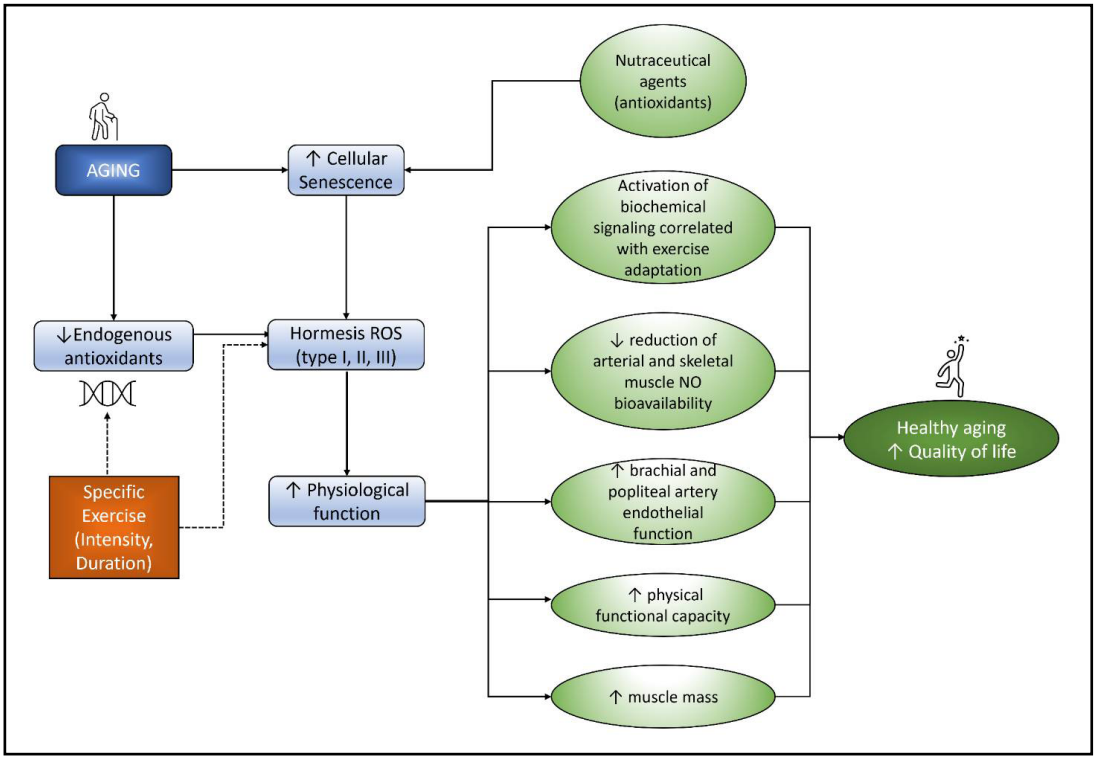
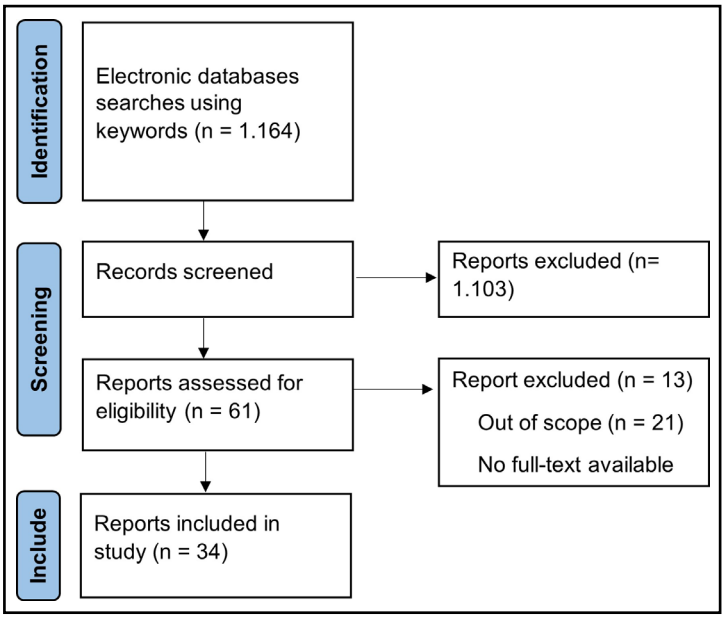


Fig. 2. Exercise and nutraceutical agents modulate hormesis ROS that increased physiological function leads to increased QoL.

Fig. 3. Article collection flow.



Method

Identification of the articles used in this review starts from searching the electronic database using the keywords aging, antioxidant, exercise, oxidative stress, and ROS. After screening and assessing the articles, thirty-four articles were used for discussion in this review. The detailed flow of article selection is represented in Fig. 3.

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Author Contributions

All authors contributed significantly to the conception and design of this review. RL, CP, GFM, JFW, and NJP gathered and analyzed the information. All authors contributed to the original draft, and RL, PTR, and JWG critically revised it. All authors approved the final version submitted for publication and take responsibility for statements made in the published article.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare that no conflict of interests exists.

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