Supplementary Material

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

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SUPPLEMENTARY TABLE 1. Summary of Reports Included in The Article

No	Title	Method	Objective	Results	References
1.	Ten weeks of high-intensity interval walk training is associated with reduced disease activity and improved innate immune function in older adults with rheumatoid arthritis: a pilot study.	Clinical trial	(1) To determine the efficacy of 10 weeks of HIIT walking for improving disease activity and aerobic capacity in older (> 55 years) adults with low to moderate rheumatoid arthritis (RA) (2) To assess the effects of HIIT walking on peripheral blood neutrophil and monocyte antibacterial function and systemic inflammatory cytokine concentrations	Disease activity changes reduce ESR and joint swelling (38%). Changes in innate immunity increase neutrophil migration, phagocytosis capacity, and neutrophil ROS production	[86]

2.	Rejuvenation of Neutrophil Functions in Association with Reduced Diabetes Risk Following Ten Weeks of Low-Volume High-Intensity Interval Walking in Older Adults with Prediabetes - A Pilot Study	Clinical trial	To determine if neutrophil functions could be improved in association with changes in fitness and metabolic parameter in older adults at risk for type 2 diabetes mellitus (T2DM) using ten weeks of low-volume high-intensity interval exercise training (HIIT)	(1) 10 weeks of HIIT improved glucose homeostasis and insulin sensitivity; fasting glucose and insulin concentrations were reduced by 6% and 14%, respectively, resulting in lower insulin resistance and increased insulin sensitivity. (2) HIIT improved neutrophil function, including increased chemotactic index, phagocytic capacity, mitogen-stimulated ROS production, reduced basal unstimulated ROS production, increased basal respiration, ATP production, maximal mitochondrial respiration, bioenergetic health index, and mitochondrial membrane potential, and also a reduction in proton leak.	[6]
3.	Resistance exercise training and in vitro skeletal muscle oxidative capacity in older adults	Randomized controlled trial	(1) To test the hypothesis that RET would increase skeletal muscle oxidative capacity (2) To address whether RET reduces the mitochondrial production of ROS	Low volume resistance exercise intervention does not increase skeletal muscle oxidative capacity or reduce mitochondrial ROS production in older adults.	[8]

4.	Lifelong physical activity prevents an age-related reduction in arterial and skeletal muscle nitric oxide bioavailability in humans.	Controlled clinical trial	To examine the effect of IV infusion of the antioxidant N-acetylcysteine (NAC) on central and peripheral hemodynamics during resting conditions and exercise at the same absolute and relative exercise intensity in young sedentary, older lifelong sedentary, and older lifelong endurance-trained subjects.	Due to increased oxidative stress, NO bioavailability is compromised in the systemic circulation and the musculature of sedentary aging humans. Lifelong physical activity opposes this effect within the trained musculature and arterial circulation. The reduced blood flow to contracting muscle with aging does not appear to be related to changes in NO bioavailability.	[54]
5.	Effect of ubiquinol supplementation on biochemical and oxidative stress indexes after intense exercise in young athletes	Randomized controlled trial	To evaluate the effect of ubiquinol supplementation on biochemical and oxidative stress indexes after an intense bout of exercise.	Ubiquinol supplementation prevented exercise-induced CoQ deprivation and decreased paraoxonase activity and was associated with a significant decrease in cytosolic ROS. At the same time, mitochondrial membrane potential and oxidative DNA damage remained unchanged.	[87]

6.	Acute mitochondrial antioxidant intake improves endothelial function, antioxidant enzyme activity, and exercise tolerance in patients with peripheral artery disease.	Randomized controlled trial	To understand the roles of the vascular mitochondria in PAD in vivo by examining the impacts of acute MitoQ intake on endothelial function, BP, arterial stiffness, walking capacity, and oxygen utility capacity in patients with PAD.	(1) MitoQ intake significantly improved brachial artery endothelial function and popliteal artery endothelial function (2) There were improvements in the physical functional capacity in PAD patients: significantly increased maximal walking time, maximal walking distance, and delayed claudication. (3) SOD concentration significantly increased. (4) No significant changes in the oxygen utility capacity measurements of SpO_2, [HbO_2], or [HHb] during walking	[88]
7.	Effect of C242T Polymorphism in the Gene Encoding the NAD(P)H Oxidase p22phox Subunit and Aerobic Fitness Levels on Redox State Biomarkers and DNA Damage Responses to Exhaustive Exercise: A Randomized Trial	Randomized controlled trial	To investigate the effect of single-bout exhaustive exercise on redox state biomarkers and oxidative DNA damage based on the C242T polymorphism in the gene encoding NOXs subunit p22phox (CYBA) and aerobic fitness levels.	(1) Single-bout exhaustive exercise induces the accumulation of a peripheral fatigue marker, temporary redox imbalance, and oxidative DNA damage (2) High aerobic fitness and the presence of the T allele potentially alleviate exercise-induced redox imbalance and DNA damage while simultaneously facilitating rapid OS	[26]

				alleviation and restoration of damaged DNA during recovery after exercise.	
8.	Effects of ascorbic acid supplementation on oxidative stress markers in healthy women following a single bout of exercise	Randomized controlled trial	To evaluate ascorbic acid supplementation before exercise support antioxidant defenses and its ability to prevent inflammation and muscle damage following a single bout of moderate-intensity cycling exercise in untrained healthy adults.	Ingesting ascorbic acid before 30 min, cycling exercise increased antioxidant ability 30 min post-exercise in plasma as shown in FRAP assay. The study also showed that cycling for 30 minutes significantly increased SOD activity at 30 minutes post-exercise in the placebo group. In contrast, no significant differences were found in the AA group. Thus, supplementing with AA attenuated this effect.	[19]

8.	Vitamin C and E supplementation prevent some cellular adaptations to human endurance training.	Randomized controlled trial	To determine whether daily supplementation of 1 g vitamin C and 400 IU vitamin E (1) reduces skeletal muscle oxidative stress and (2) attenuates the increase in gene expression of mitochondrial biogenesis markers following acute endurance exercise, and (3) $VO2_{peak}$ and the mitochondrial and antioxidant enzymes following endurance training.	(1) Vitamin C and E supplementation did attenuate some of the cellular adaptations in skeletal muscle (TFAM and SOD) following four weeks of endurance training (2) vitamin C and E supplementation did not attenuate skeletal muscle oxidative stress or the increase in gene expression of mitochondrial biogenesis markers following acute exercise in healthy young males. (3) most of the skeletal muscle adaptations related to oxidative capacity and the whole-body adaptations to endurance training such as $VO2_{peak}$ and W_{max} were not hampered by vitamin C and E supplementation	[89]

9.	Oxidative stress assessment in response to ultra-endurance exercise: thiols redox status and ROS production according to the duration of a competitive race	Clinical trial	(1) To determine the redox thiols status in plasma and erythrocytes, plasmatic ROS production, total antioxidant capacity, and oxidative damage markers concentration in ultra-endurance elite athletes according to the duration of a running race to test the presence of relationships and integration of the different components of the blood redox system. (2) To investigate whether prerace antioxidant and/or thiol redox status and ROS production may predict performance.	(1) Ultra-endurance, very prolonged (>4 hours) exercise caused an increase in plasmatic ROS production and oxidative stress and perturbation of aminothiols redox status. Redox status of erythrocytes was substantially unchanged, suggesting preservation of cellular and tissue equilibrium. (2) Thiols antioxidants appear to improve performance during endurance exercise.	[90]
10.	Avenanthramide supplementation attenuates eccentric exercise-inflicted blood inflammatory markers in women.	Randomized controlled trial	Investigate whether dietary supplementation of avenanthramides (AVA) in oats would increase antioxidant protection and reduce inflammatory blood markers in humans after an acute bout of eccentric exercise (downhill running)	Long-term AVA supplementation can (1) attenuate blood inflammation markers, (2) decrease ROS generation and NFkB activation, and (3) increase antioxidant capacity during an eccentric exercise bout.	[91]

11.	Effect of N-acetylcysteine infusion on exercise-induced modulation of insulin sensitivity and signaling pathways in human skeletal muscle	Randomized controlled trial	To assess the effects of exercise-induced ROS on insulin action and protein signaling in humans.	(1) Novel human in vivo data showed that attenuation of ROS with antioxidant infusion impaired IS 3 h after exercise, which occurs independently of the Akt-signaling pathway in skeletal muscle. (2) Phosphorylation of p70S6K, which is involved in protein translation regulation, was shown to be impaired by NAC following insulin stimulation.	[92]
12.	Exercise during hemodialysis does not affect the phenotype or prothrombotic nature of microparticles but 1alters their pro-inflammatory function.	Randomized controlled trial	To assess the acute effect of intradialytic exercise (IDE) on microparticle number and phenotype and their ability to induce endothelial cell reactive oxygen species (ROS) in vitro.	(1) Acute session of moderate-intensity IDE does not further increase prothrombotic microparticle numbers that occur during hemodialysis. (2) Acute proinflammatory responses to exercise stimulate an adaptation toward a circulating anti-inflammatory environment, microparticle-induced transient increases of endothelial cell ROS in vitro with IDE may indicate the potential for a longer-term anti-inflammatory adaptive effect	[93]

13.	Prior endurance exercise prevents postprandial lipaemia-induced increases in reactive oxygen species in circulating CD31+ cells.	Controlled clinical trial	To examine the effects of a high-fat meal with and without prior endurance exercise on several molecular aspects of CAC function, including levels of reactive oxygen species (ROS), nitric oxide (NO), intracellular lipids, and gene expression.	(1) High-fat meal induced significant oxidative stress (i.e., ROS production) in the CACs that expressed the cell surface protein CD31. (2) Prior endurance exercise could prevent the PPL-induced increases in intracellular ROS production in CD31+ cells	[94]
14.	Infusion with the antioxidant N-acetylcysteine attenuates early adaptive responses to exercise in human skeletal muscle.	Randomized controlled trial	To investigate the effects of infusion of the potent ROS scavenger NAC during exercise on activation of NF-jB and MAPK pathways and expression of genes involved in stress–response (HSP70), inflammation (IL-6, monocyte chemotactic protein 1, MCP-1), antioxidant defense (MnSOD) and mitochondrial biogenesis (PGC-1a) in human skeletal muscle.	(1) Exercise increased phosphorylation of JNK by 49 and 40% at 45 min and fatigue, respectively, and this was entirely blocked by infusion of NAC before and during exercise. JNK activation is associated with regulating genes in cell proliferation, apoptosis, inflammation, and DNA repair and thus plays a vital role in exercise adaptation. A JNK signaling pathway is ROS-dependent in human skeletal muscle (2) NAC infusion had no effect on the phosphorylation status of ERK1/2 or p38 MAPK (3) The NAC impact was particular within mitogen protein kinase (MPAK)	[95]

15.	Assessment of a Standardized ROS Production Profile in Humans by Electron Paramagnetic Resonance	Clinical trial	Evaluate the efficacy of ROS generation assessment by Electron Paramagnetic Resonance (EPR) coupled to a specific spin probe (CMH: 1-hydroxy-3-methoxycarbonyl-2,2,5,5-tetramethylpyrrolidine)	(1) Exercise-induced EPR detectable ex vivo formation in capillary blood with the EPR signal intensity can estimate the kinetics of ROS production (2) Antioxidant supplementation induced EPR detectable changes in the formation of ex vivo in capillary blood with the EPR signal intensity can estimate the kinetics of ROS production	[96]
16.	Erdosteine reduces the exercise-induced oxidative stress in patients with severe COPD: Results of a placebo-controlled trial.	Randomized controlled trial	To assess the effect of erdosteine on exercise-induced oxidative stress by measuring and comparing the release of pro-inflammatory mediators before and after exercise in patients with severe COPD receiving erdosteine or placebo.	After the second 6MWT, the percentage change in ROS plasma levels and 8-isoprostane plasma levels were significantly increased compared to baseline.	[58]
17.	Ryanodine receptor fragmentation and sarcoplasmic reticulum Ca2+ leak after a session of high-intensity interval exercise	Clinical trial	To assess whether a single session of HIIT induces ROS-dependent RyR1 modifications.	A fragmentation of RyR1 linking high-intensity exercise and increased ROS levels, via a prolonged increase in resting cytosolic Ca2+, to altered gene transcription and muscle adaptations	[97]

18.	The effects of three different exercise modalities on markers of male reproduction in healthy subjects: a randomized controlled trial	Randomized controlled trial	To investigate the effects of moderate-intensity continuous training (MICT), high-intensity continuous training (HICT), and high-intensity interval training (HIIT) on markers of male reproduction, including seminal markers of oxidative stress and inflammation as well as semen quality and sperm DNA integrity in healthy human subjects.	(1) seminal markers of inflammation and oxidative stress improved significantly (decrease) after 24 weeks of MICT, HICT, or HIIT; and these changes corresponded with favorable improvements in semen quality parameters and sperm DNA integrity (2) MICT was more beneficial in improving markers of male reproductive function compared to HICT and HIIT	[98]
19.	Exercise recovery increases skeletal muscle H2O2 emission and mitochondrial respiratory capacity following two weeks of limb immobilization.	Clinical trial	Investigate the effect of immobilization, followed by two subsequent periods of restored physical activity, on mitochondrial H_2O_2 emissions in adult male skeletal muscle	Two weeks of immobilization increases mitochondrial H_2O_2 emissions, but subsequent retraining periods of ambulatory recovery and resistance training also led to robust increases in mitochondrial H_2O_2 emissions in skeletal muscle.	[99]
20.	A pilot study investigating reactive oxygen species production in capillary blood after a marathon and the influence of an antioxidant-rich beetroot juice	Controlled clinical trial	(1) To examine the effects of ROS production and mtDNA damage in capillary blood after a marathon and; (2) to establish whether, post-exercise, these markers can be attenuated with BTJ	ROS increased after a marathon as measured in capillary blood taken from the fingertip. Beetroot juice was unable to mitigate exercise induced-ROS	[100]

21.	Effects of modest hyperoxia and oral vitamin C on exercise hyperemia and reactive hyperemia in healthy young men	Randomized controlled trial	To test the hypothesis that 40 % O2 modulates exercise hyperemia and reactive hyperemia independently of ROS.	(1) Exercise hyperemia following severe muscle contraction and reactive hyperemia are blunted by ROS. (2) Modest hyperoxia-induced by breathing 40 % O2 acts independently of ROS to attenuate not only post-contraction hyperemia but also reactive hyperemia by decreasing the release of O2-dependent vasodilators.	[101]
22.	Tomato juice intake suppressed serum concentration of 8-oxodG after extensive physical activity.	Controlled clinical trial	To investigate the protective effect of tomato juice intake towards ROS induced by 20 min of extensive physical exercise in untrained individuals.	Daily intake of tomato juice, equal to 15 mg lycopene per day, for five weeks significantly reduced the serum levels of 8-oxodG after an extensive physical exercise, suggesting that tomato juice has a potential antioxidant effect and may reduce the elevated level of ROS induced by oxidative stress.	[21]
23.	More than dietary selenium supplementation, submaximal exercise training improves antioxidant status and ameliorates exercise-induced oxidative damage to skeletal muscle	Randomized controlled trial	To evaluate separate and combined effects of training and dietary Se level on blood and muscle antioxidant capacity and the extent of exercise-induced oxidative damage.	Trained young horses resulted in an adaptation that allows them prolonged exercise bout and lessens muscle damage than their untrained counterparts. Elevated dietary Se showed a slight advantage in supporting various antioxidant	[20]

	in young equine athletes.			systems during training and in response to prolonged exercise.	
24.	The Impact of Partial Vascular Occlusion on Oxidative Stress Markers during Resistance Exercise	Randomized controlled trial	To examine the effects of partial vascular occlusion (PVO) on oxidative stress markers at these two different intensities of resistance exercise (low and moderate) and rest in young resistance-trained males.	(1) The addition of PVO in the absence of exercise significantly increase oxidative stress markers protein carbonyls (PC) and glutathione status (2) The combination of PVO and low-intensity resistance exercise resulted in significantly attenuated and no change in glutathione ratio compared to low intensity without PVO (3) the addition of PVO during MIRE increased oxidative stress whereas LIRE resulted in attenuated oxidative stress when compared to LIRE without PVO	[102]

25.	Effect of vitamin C on hyperoxia-induced vasoconstriction in exercising skeletal muscle	Randomized controlled trial	(1) To investigate the role of ROS in hyperoxia-induced reductions in skeletal muscle blood flow during forearm exercise in humans (2) investigate the effect of infusion of vitamin C on the forearm blood flow (FBF) responses to exercise	(1) hyperoxia-induced vasoconstriction is associated with increased production of ROS. ROS could lead to a decreased vascular response by stimulating vasoconstrictor endothelin-1 (ET-1) (2) Vitamin C administration showed a restoration of FBF during hyperoxic exercise only in participants in the group with a reduction in FBF of 20%	[103]
26.	Effects of grape juice consumption on muscle fatigue and oxidative stress in judo athletes: a randomized clinical trial	Randomized controlled trial	To evaluate the effects of grape juice consumption on the oxidative stress and muscle fatigue parameters before and after fighting simulations in judo athletes.	Grape juice consumption can (1) increase antioxidant capacity and decrease lipid damage and DNA at the pre-exercise time and (2) increase upper limb muscle strength in the pre-exercise protocol assessments.	[22]
27.	High-intensity interval training modulates male factor infertility through anti-inflammatory and antioxidative mechanisms in infertile men: A randomized controlled trial.	Randomized controlled trial	To determine if 24 weeks of HIIT is effective in improving markers of male reproductive function and performance.	24-weeks HIIT marked improvements in markers of seminal oxidative stress and inflammation, semen parameters, sperm DNA integrity, body composition measures, and VO_2 max.	[104]

28.	N-Acetylcysteine's Attenuation of Fatigue After Repeated Bouts of Intermittent Exercise: Practical Implications for Tournament Situations	Randomized controlled trial	To determine the effects of acute oral N-acetylcysteine (NAC) supplementation on Yo-Yo Intermittent Recovery Test Level 1 (YIRT-L1) performance after repeated bouts of damaging intermittent exercise.	(1) Acute oral NAC supplementation prevents the deterioration in YIRT-L1 performance of repeated bouts of damaging intermittent exercise (2) Plasma creatine kinase values increased significantly over time and were significantly more significant in the NAC group than in the placebo group (3) NAC induced mild gastrointestinal side effects	[105]

29.	Change of walking distance in intermittent claudication: impact on inflammation, oxidative stress and mononuclear cells: a pilot study	Clinical trial	To investigate changes in mononuclear blood cells and ROS production within walking distance of patients with intermittent claudication during home-based exercise training.	(1) A reduced inflammatory state might be achieved by regular walking exercise, possibly in a dimension proportionately to changes in walking distance (2) Patients showed an increased walking distance and reduced ROS production upon stimulation with a phorbol ester derivative -Inflammatory markers like fibrinogen, C-reactive protein or soluble TREM-1 (Triggering receptor expressed on myeloid cells) (sTREM-1) decreased over the observation period (3) A close relation of sTREM-1 with the walking distance, fibrinogen and ROS production	[106]
30.	Dose-Response Effect of tualang honey on postprandial antioxidant activity and oxidative stress in female athletes: a pilot study	Randomized controlled trial	To examine the postprandial response of antioxidant activity and oxidative stress biomarkers after the acute consumption of low and high dosages of TH and determine the time-course effect that could provide optimal protection against	Consumption of TH at doses of 0.75 and 1.5 g/kg BW was protective against lipid peroxidation and oxidative stress.	[107]

			oxidative damage among female athletes.		
31.	Natural antioxidant ice cream acutely reduces oxidative stress and improves vascular function and physical performance in healthy individuals.	Randomized controlled trial	To evaluate the effects of natural antioxidant ice cream on oxidative stress, vascular function, and physical performance.	(1) Natural ice cream rich in polyphenols acutely improved vascular function and physical performance in healthy individuals through a reduction in oxidative stress (2) Serum polyphenols, NOx, the ferric reducing ability of plasma (FRAP), FMD, and reactive-hyperemia index (RHI) increased significantly (3) Oxidative stress decreased and the double product was improved only after antioxidant ice cream ingestion	[108]
32.	Mitochondria-targeted antioxidant supplementation improves 8 km time trial performance in middle-aged	Randomized controlled trial	To investigate whether MitoQ supplementation can improve cycling performance, measured as time to complete an 8 km time trial.	MitoQ can attenuate exercise-induced increases in lipid peroxidation and improve cycling time trial performance in middle-aged, recreationally trained men.	[109]

	trained male cyclists.				
33.	The effect of pilates on metabolic control and oxidative stress of diabetics type 2 – A randomized controlled clinical trial	Randomized controlled trial	To analyze the effect of a Pilates protocol on variables indicative of metabolic control and oxidative stress in patients with Type 2 Diabetes Mellitus.	(1) A significant reduction in glycated hemoglobin and oxidative stress in the intervention group; however, there were no differences in fasting glucose and in the profile lipid, expressed by the total cholesterol, HDL, LDL, and triglycerides (2) A moderate positive correlation between oxidative stress and glycated hemoglobin	[110]
34.		Clinical trial	To explore the impact of Yoga and Meditation based lifestyle intervention on cellular aging in a healthy individual	12 weeks of Yoga and Meditation based lifestyle intervention (YMLI) reduced levels of 8-OH2dG, ROS, cortisol, and IL-6 and significantly increased levels of TAC, telomerase activity, β-endorphin, BDNF, and sirtuin-1	[111]