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Antioxidant supplements and endurance exercise: Current evidence and mechanistic insights

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A B S T R A C T

Antioxidant supplements are commonly consumed by endurance athletes to minimize exercise-induced oxidative stress, with the intention of enhancing recovery and improving performance. There are numerous commercially available nutritional supplements that are targeted to athletes and health enthusiasts that allegedly possess antioxidant properties. However, most of these compounds are poorly investigated with respect to their *in vivo* redox activity and efficacy in humans. Therefore, this review will firstly provide a background to endurance exercise-related redox signalling and the subsequent adaptations in skeletal muscle and vascular function. The review will then discuss commonly available compounds with purported antioxidant effects for use by athletes. N-acetyl cysteine may be of benefit over the days prior to an endurance event; while chronic intake of combined 1000 mg vitamin C + vitamin E is not recommended during periods of heavy training associated with adaptations in skeletal muscle. Melatonin, vitamin E and α-lipoic acid appear effective at decreasing markers of exercise-induced oxidative stress. However, evidence on their effects on endurance performance are either lacking or not supportive. Catechins, anthocyanins, coenzyme Q10 and vitamin C may improve vascular function, however, evidence is either limited to specific sub-populations and/or does not translate to improved performance. Finally, additional research should clarify the potential benefits of curcumin in improving muscle recovery post intensive exercise; and the potential hampering effects of astaxanthin, selenium and vitamin A on skeletal muscle adaptations to endurance training. Overall, we highlight the lack of supportive evidence for most antioxidant compounds to recommend to athletes.

1. Introduction

Intense exercise and muscle contraction increase production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and promote oxidative stress in skeletal muscle [1–8]. Excessive ROS levels are deleterious to cells [9,10] through increased damage and modifications to cellular proteins, lipids and DNA [11]. Moreover, elevated ROS levels have been implicated in the pathogenesis of numerous chronic diseases, including cardiovascular disease [12–14] and type 2 diabetes [15]. On the other hand, emerging evidence shows that several ROS and RNS produced in physiological amounts are important signalling molecules, acting through mechanisms such as post-translational redox modifications of cysteine thiols on proteins [16,17]. Recent research has highlighted the importance of redox signalling in physiological processes, including normal molecular and cellular responses to exercise [10]. In particular, redox-signalling pathways have been implicated in the acute and chronic responses of skeletal muscle to endurance exercise, including skeletal muscle glucose uptake and insulin sensitivity [18,19]; induction of endogenous antioxidant enzymes [6,20,21]; mitochondrial biogenesis [22–24]; and muscle contraction force [25–27]. There is also growing evidence of redox regulation of vascular function, with relevance to exercise and its adaptations that require further examination [28–31]. Factors such as the magnitude and/or duration of altered rates of ROS generation/exposure, the (sub) cellular origin of ROS production [32] and the proximity of reactive protein thiols to sites of ROS/RNS production [33] may impact on redox signalling events that either promote healthful effects or promote disease.

Antioxidants play important roles in regulating ROS levels through direct free radical scavenging mechanisms, through regulation of ROS/RNS-producing enzymes, and/or via adaptive electrophilic-like mechanisms. Acute and chronic endurance exercise tends to increase expression and activity of endogenous antioxidant enzymes in skeletal muscle [6,20,21], in turn enabling an improved capacity to moderate adverse effects of ROS. To enhance the capacity of skeletal muscle to neutralize ROS produced during exercise, athletes regularly consume exogenous antioxidant supplements [34,35]. Benefits of antioxidant supplements might relate to an improvement in cellular redox state and decreased oxidative modifications to DNA, lipids and proteins. Some evidence shows an ameliorating effect of antioxidants on muscle recovery following intense muscle-damaging exercise [36–39]. ROS have also been implicated in premature muscular fatigue during sustained muscle contraction and exercise [40–42]. Therefore, the use of exogenous antioxidants might help to delay muscular fatigue and improve endurance exercise performance.

Despite the potential benefits of antioxidant supplementation in

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exercising humans, growing research has implicated hampering effects of exogenous antioxidant supplementation on some acute and chronic responses of skeletal muscle to exercise [22,24,26,43,44]. These impairments in adaptive changes within skeletal muscle are presumably a result of an attenuation of normal redox-signalling pathways in muscle by antioxidants [10]. In particular, antioxidant supplementation has been found in some studies to impair adaptive responses to endurance exercise training [24,43,44]. There are numerous compounds with purported antioxidant properties that are available commercially over the counter or via online vendors for athletes and other health consumers. However, for many of these compounds, there is a lack a critical evaluation of their efficacy and benefits. Thus, there is a need to further evaluate the current evidence on potential benefits and risks of these compounds for athletes.

The present review aims to firstly discuss endurance exercise-related skeletal muscle redox signalling, with key focus areas of (a) sites of ROS production and their temporal changes with respect to exercise; and (b) mechanisms of ROS as a signal in skeletal muscle adaptations to exercise, including adaptations such as mitochondrial biogenesis, antioxidant enzyme induction and vascular functional changes. The second half of the review will focus on current evidence on effects of commercially available compounds with purported antioxidant effects on oxidative stress, endurance exercise-related outcomes and muscle recovery post exercise. Where possible, we have focussed on evidence arising from studies using healthy human participants given the potential applicability of such findings to human athletic endeavours. Moreover, we have focussed, where possible, on effects that are specific to skeletal muscle.

2. Endurance exercise and skeletal muscle redox signalling

2.1. Redox signalling mechanisms in skeletal muscle

ROS (such as superoxide [$O_2^{\bullet-}$] and hydrogen peroxide [H_2O_2]) and RNS (such as nitric oxide [NO] and peroxynitrite [$ONOO^-$]) can participate in redox signalling in cells either directly or indirectly [45]. Transient and reversible post translational chemical modifications of reactive cysteine thiol residues on proteins through processes such as S-nitrosylation, S-glutathionylation, sulfenylation and disulphide formation are important redox modifications through which cells respond to altered levels of ROS and RNS [17,27,46]. For instance, protein S-nitrosylation can promote cellular effects such as altered regulation of enzyme activities, altered receptor and transporter activities, altered gene transcription and translation, and protein-protein interactions [47]. S-glutathionylation of a protein can result in its activation or deactivation, which may be important in the regulation of cell signalling mediators [17,48]. Post-translational redox modifications such as S-nitrosylation and S-glutathionylation may play important molecular signalling roles in skeletal muscle given their intricate associations with key proteins linked to muscle contraction and exercise adaptations [49–65].

In addition to ROS and RNS, antioxidants are involved in redox signalling in cells. Antioxidants can regulate thiol redox state and therefore regulate redox signalling pathways [66]. Endogenous antioxidants, which include enzymes and small molecules such as thioredoxins (Trx), sulfiredoxins (Srx), glutathione reductases (GR), peroxiredoxins (Prdx) and glutathione (GSH) are fundamental to the control of redox signalling networks [67]. Additionally, exogenous compounds with antioxidant properties such as polyphenols, vitamin C and vitamin E that are consumed either in the diet or as dietary supplements may also participate in and interact with these redox signalling networks. Exercise-related redox signalling in skeletal muscle induced by ROS/RNS and regulated by antioxidants, might include acute and/or chronic alterations in gene expression, modified kinase and phosphatase activities, and altered levels of molecular chaperones, transporters, proteasomes, and transcription factors [27,68].

2.2. Sites of ROS production before, during and post endurance exercise

Total intracellular ROS levels reflect the net rates of formation and removal across numerous individual subcellular sites. In the context of physiological stressors such as exercise, these have most often been studied under defined steady state bioenergetic conditions, i.e. either at rest or during exercise/contraction [69,70]. The following section not only summarises the known sites of ROS formation and removal under these conditions, but also focusses on the dynamic temporal shifts in site-specific ROS generation and removal that occur during the transition periods between steady state bioenergetic situations. Specifically, these are the transitions from i) rest to work, ii) work to rest, and iii) the early post-exercise recovery period.

In resting skeletal muscle, intracellular ADP concentrations are low relative to ATP since energy supply exceeds demand. This low ADP/ATP ratio serves to supress mitochondrial oxidative phosphorylation (OXPHOS) activity [72], while also promoting a highly reduced redox environment (i.e. high $NADH/NAD^+$). This 'reducing pressure' caused by surplus electron flow into the ubiquinone (Q) complex in the electron transport chain (ETC) can promote the leakage of unpaired electrons from the ETC [73–75]. Reduction of molecular oxygen by a single electron results in the formation of the superoxide anion ($O_2^{\bullet-}$). While $O_2^{\bullet-}$ is the primary form of ROS, it is rapidly dismutated either spontaneously or enzymatically to the more stable hydrogen peroxide (H_2O_2). The formation of $O_2^{\bullet-}$ occurs from at least 11 distinct sites within mitochondria at complexes I, II and III, four dehydrogenases in the matrix compartment and others in the intermembrane space including glycerol-3-phosphate and dihydroorotate dehydrogenases [76]. In addition, NADPH-oxidase (NOX)-4, an H_2O_2 generating enzyme, has been shown to be localised within skeletal muscle mitochondria [70,77]. Under *in vitro* conditions mimicking 'rest', the main contributing sites of mitochondrial $O_2^{\bullet-}$ production are the complex-I ubiquinone reducing site (I_Q, ~23% of total $O_2^{\bullet-}$) and the flavin site (I_F, ~20%), the complex III ubiquinol oxidising site (III_{QO}, ~15%), the flavin in complex-II (II_F, ~24%), and a site involved in the fatty acid β-oxidation pathway (E_F, ~13%) [69].

In addition to these mitochondrial sites of ROS formation, non-mitochondrial NOX enzymes localised to the cytosol and sarcolemma also contribute to the overall cellular $O_2^{\bullet-}$ formation at rest. Recent advances in pharmacological tools to study redox biology have revealed that in mouse myoblast cells, $O_2^{\bullet-}$ from mitochondria contributes to ~45% and non-mitochondrial NOX enzymes contribute to ~40% of the total cellular $O_2^{\bullet-}$ generation under basal conditions, respectively [78,79].

In addition to the various sites of ROS formation, specific subcellular distributions of various antioxidant enzymes enable precise spatial regulation of ROS scavenging for the maintenance of intracellular redox homeostasis [80]. These include superoxide dismutase which uses a copper/zinc or manganese ion as the active site, of which isoform 1 (SOD1) is cytosolic and intermembrane space localised, while isoform 2 (SOD2) is located in mitochondrial matrix. Glutathione (GSH), a cysteine-containing tripeptide functions both as a direct scavenger of H_2O_2 and also as a substrate for the NADPH-dependent glutathione peroxidases localised in the cytosol (GPx 1 and 2) and the mitochondria (GPx 1 and 4). Thioredoxins and peroxiredoxins comprise another key NADPH-dependent scavenging pathway both in the cytosol (Trx 1 and Prdx 1 and 2) and mitochondrial compartment (Trx 2 and Prdx 3 and 5). The lower K_m for H_2O_2 of Prdx compared with GPx is critical for fine-tuning physiological H_2O_2 fluxes [81,82].

2.3. ROS during rest-to-work transition

At the onset of myofibril contraction, ATP hydrolysis increases up to 100-fold from rest [83]. In order to maintain energy homeostasis, mitochondrial oxidative phosphorylation is upregulated within seconds, primarily in response to the increasing ADP:ATP ratio [84]. Consequently, a rapid decrease in reducing-pressure occurs at the electron

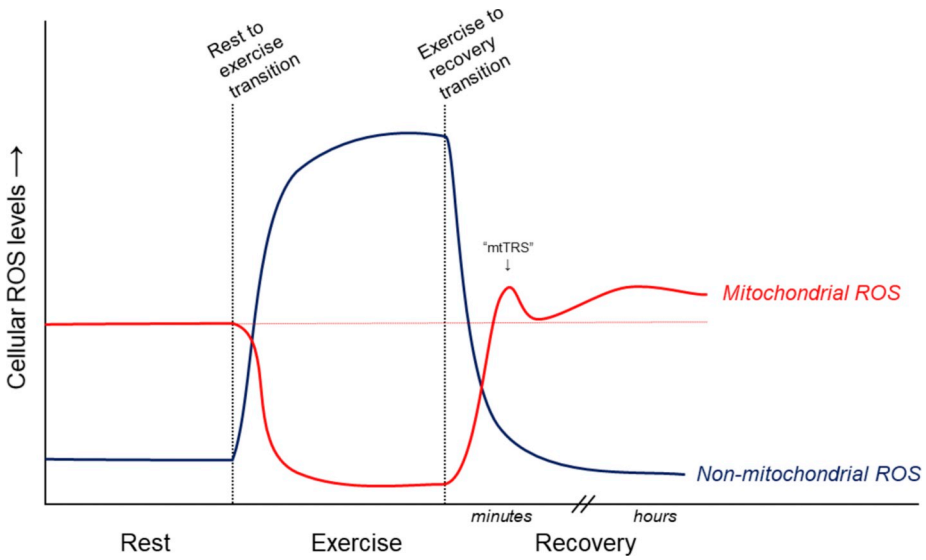

Fig. 1. Proposed relative contributions of mitochondrial and non-mitochondrial sources of ROS to overall cellular ROS levels in skeletal muscle during and in the minutes and hours following a single session of endurance exercise. mtTRS, mitochondrial transition spike (refer to text and reference [71]).

entry points of the mitochondrial ETC, thereby attenuating the majority of $O_2^{\cdot-}$ generation from these mitochondrial ETC sites [69] (Fig. 1). Thus, although mitochondria have the *capacity* to generate large quantities of $O_2^{\cdot-}$ under specific bioenergetic conditions, native $O_2^{\cdot-}$ generation rates *in vivo* are dynamic and approximately inversely proportional to the oxidative phosphorylation rate. Indeed, in isolated mitochondrial preparations *in vitro*, it is well established that when ADP is added to stimulate oxidative phosphorylation to induce the classical experimental respiratory 'state-3', rates of mitochondrial $O_2^{\cdot-}/H_2O_2$ emission decrease dramatically [69,85] (Fig. 1). Notably, under *in vitro* conditions mimicking those of intense exercise, it was shown that total mitochondrial $O_2^{\cdot-}/H_2O_2$ production is only about 15% of rest values, which is mostly attributable to site I_F [69]. Thus, on the basis of fundamental bioenergetic principles as well as experimental evidence, mitochondria are negligible contributors to total muscle ROS generation *during* exercise. Mitochondria can also consume $O_2^{\cdot-}/H_2O_2$ produced within the matrix compartment or H_2O_2 that diffuses into mitochondria from cytosolic origins [86]. It is therefore possible that mitochondria could consume more ROS than is generated during energetic conditions similar to exercise [87]. Despite this, total levels of skeletal muscle ROS are well known to increase in muscle fibres during *in vitro* contractions [3], and *in vivo* during exercise in rodents and humans [2,5,88,89]. Primary sources of ROS formation during skeletal muscle contraction include the NOXs, which are 'professional' $O_2^{\cdot-}$ generating enzymes (i.e. no other known function), along with a minor contribution from xanthine oxidase [89–93]. In addition, exercise-induced calcium fluxes may contribute to increased activity of calcium-dependent phospholipase A2 (PLA_2) which forms arachidonic acid and subsequently activates the $O_2^{\cdot-}$- generating enzyme, lipoxygenase [94]. Other potential sources of $O_2^{\cdot-}$ that have not yet been studied in the context of exercise include the protein p66shc which is known to translocate to the mitochondrial intermembrane space where it can oxidize cytochrome-*c* to form H_2O_2 [95], and pyruvate dehydrogenase which has been shown to generate ROS under *in vitro* conditions similar to exercise [96].

2.4. ROS during transition from work-to-rest

After the cessation of myofibril contraction that occurs during exercise, energy demand and ATP synthesis declines at an exponential rate returning to near-resting values within the first minute [97]. During these changing energetic conditions, a short-lived surge in ROS has been described, termed the 'mitochondrial ROS transition spike'(mTRS) (Fig. 1), as demonstrated *in vitro* during the transition from state 3 (ADP stimulated oxidative phosphorylation) to state 4 (non-phosphorylating) [71]. The underlying mechanism for this phenomenon was reported to involve the nicotinamide nucleotide transhydrogenase (NNT). This work by Sharaf et al. [71] showed that when the rate of oxidative respiration slows during transition from state 3 to 4, the increased *proton motive force* promotes $O_2^{\cdot-}$ formation from complex I. This presents as the upward phase of the ROS spike. Simultaneously, the slowing energy demand during state 3 to 4 transition also allows NADH levels to increase (due to slowing complex-I activity), which drives NNT activity to restore NADPH levels, thereby fueling the NADPH-dependent glutathione (GSH) and thioredoxin (Trx) antioxidant systems. This enhances the rate of ROS removal to begin restoring redox homeostasis, which presents as the downward phase of the ROS transition spike (Fig. 1). Whether this occurs in skeletal muscle at the cessation of exercise/contraction remains to be investigated.

2.5. ROS in the early post-exercise recovery period

In the hours following exercise, when muscle bioenergetic demands have returned to near resting/basal levels, ROS formation returns to being primarily of mitochondrial origin and has been shown to be elevated for at least 3 h post exercise [85]. Various mechanisms could contribute to this, because exercise causes homeostatic challenges within the cellular milieu and various exercise-induced factors may modify macromolecules. For instance, elevation in the circulation and oxidation of free fatty acids (FFA) in the post exercise period [98] could modulate the production of ROS [99] by increasing H_2O_2 emission at complex-II and the electron-transferring flavoprotein (ETF) in skeletal muscle mitochondria [100]. Inflammation resulting from microtrauma to sarcomeres due to unaccustomed and/or eccentric exercise [101] leads to infiltration of neutrophils that generate bursts of superoxide via NOX activation [102]. Further, a number of proinflammatory cytokines released from skeletal muscle (i.e.: 'myokines') during contraction [103] such as interleukin-6 (IL-6) can persist in the circulation after exercise and continue to stimulate ROS generating enzymes including xanthine oxidase, lipoxygenase and NOXs [104].

Other mechanisms causing post-exercise increases in ROS generation might involve post translational modifications (PTMs) such as phosphorylation, O-GlcNAcylation or acetylation to mitochondrial proteins [105]. Notably, oxidative PTMs such as S-glutathionylation

and S-nitrosylation, are known to affect activity of protein complexes within the ETS and can occur as a result of exercise [85,106–108]. Localised accumulation of H_2O_2 occurs via reversible inactivation of Prdx antioxidant enzyme activity as a result of oxidation by H_2O_2 itself [81], which may occur in response to exercise [109]. Moreover, the abundance of the Prdx1 protein was also shown to be lower 3 h post exercise [85], thereby allowing localised increases in H_2O_2 at the subcellular level. Another factor that may impact post-exercise ROS homeostasis is changes in mitochondrial morphology. Exercise induces changes in mitochondrial membrane morphology and this is known to impact respiratory function [110], and thereby ROS formation rates [111]. Moreover, some of the molecular machinery responsible for mitochondrial dynamics/morphological changes are redox sensitive [110–113]. Mitochondrial quality is regulated by mitochondrial autophagy processes (termed 'mitophagy'), via ubiquitin kinase PINK1-Parkin pathway [114] or via redox sensitive Nix and Bnip3 [115,116] which may play a role in mitochondrial respiratory function and ROS generation in the post-exercise period. Similarly, antioxidant proteins in the mitochondria may be tagged for autophagy in the face of oxidative stress via stress-activated pathways and proteolysis decreasing their abundance and enzymatic function, thus impacting rates of ROS removal [117]. Taken together, these factors may explain the acute changes in skeletal muscle mitochondrial ROS that have been observed in the hours following acute bouts of exercise [85]. The major implications of elevated post-exercise mitochondrial ROS are that they could modulate redox sensitive cysteine residues throughout the entire proteome [118] and alter the expression of exercise-responsive genes and adaptive responses [119,120].

In summary, under basal/resting conditions the sites of ROS formation in skeletal muscle are primarily mitochondrial, yet these become negligible during exercise (Fig. 1). Total muscle ROS formation rates increase sharply during exercise primarily due to the contributions of cytosolic and sarcolemmal ROS-forming enzymatic systems. The concept of the mitochondrial ROS 'transition spike' represents an interesting avenue for further investigation during the transition from exercise to recovery/rest. Finally, further studies are warranted to identify and functionally characterise post-translational protein modifications that cause or are a consequence of changes in rates of ROS formation and removal in response to exercise.

3. Mechanisms of ROS as a signal in skeletal muscle adaptations to endurance exercise

3.1. Role of redox signalling in mitochondrial biogenesis

Increased mitochondrial volume and functional capacity is a hallmark adaptation to exercise training in skeletal muscle. Peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC1-α) is considered the master regulator in programming the transcriptional response to an aerobic exercise stimulus [121]. PGC-1α activation is achieved by signals from upstream kinases including such as AMPK and p38 MAPK [122,123]. This initiates transcription of downstream targets that lead to upregulation of mitochondrial genes and proteins [124]. Importantly, mitochondrial biogenesis appears to be a redox sensitive process [125,126]. This may be associated with the redox sensitive AMPK regulation of PGC-1α [127], although, it was recently shown by mutation of a putative redox sensitive Cys residue in the AMPKα subunit, that the response to H_2O_2 is indirect [128]. On the other hand, it was demonstrated in the absence of confounding bioenergetic variables, that $O_2^{\cdot-}/H_2O_2$ specifically formed within the mitochondrial matrix activates p38 MAPK [129]. Also, recent studies using knockout mice have demonstrated that $O_2^{\cdot-}/H_2O_2$ formed during exercise by NOX2 is required for the normal post exercise increases in p38 MAPK phosphorylation [89]. Allopurinol, a xanthine oxidase inhibitor, was shown to decrease muscle ROS production in rats which blunted exercise induced PGC1-α gene expression and downstream mitochondrial biogenesis related transcriptional activity [130]. In contrast, we did not identify changes in PGC-1α gene expression in allopurinol supplemented rats following 60 min of acute exercise, although components of upstream stress signalling (ERK and p38 MAPK phosphorylation) as well as downstream gene expression (Tfam) were blunted [90]. It is possible that allopurinol influences only some aspects of these redox sensitive responses. On the other hand, it was shown that PGC-1α mRNA expression was augmented after exercise in rats treated with diethyl maleate which depletes glutathione - a primary endogenous antioxidant pool in skeletal muscle [131]. This is also consistent with a previous finding that glutathione depletion induces a redox-dependant activation of PGC-1α via p53 binding to the promotor region of the *PPARGC1A* gene [132].

3.2. Role of redox signalling in antioxidant enzyme induction

The increased ROS during contraction is also partly responsible for the induction of antioxidant enzymes. This occurs via the induction of several distinct but interrelated pathways to mediate many of the redox adaptations to exercise, including activation of mitochondrial biogenesis, the Keap1-Nrf2-ARE pathway and nuclear factor κB (NFκB) signaling. These pathways are regulated, in part, by the activation of several redox-sensitive kinases including AMPK, the MAP kinases p38 MAPK, JNK and ERK1/2, which are all increased to some extent during skeletal muscle contraction [93,133–135]. Both AMPK and p38 MAPK activate the mitochondrial biogenesis pathway via PGC-1α, with PGC-1α required for the induction of superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase [136]. The redox sensitive transcription factor NFκB is also increased during muscle contraction and is known to regulate SOD2 transcription [137].

One of the major pathways for exercise-induced antioxidant induction is the Keap1-Nrf2-ARE pathway, which is dependent on the induction of the redox sensitive transcription factor Nuclear factor erythroid-derived 2-like 2 (Nrf2, also referred to as NFE2L2 (but not to be confused with nuclear respiratory factor 2)). Merry and Ristow [138] have shown using Nrf2 knockout mice that Nrf2 is required for the increases in antioxidant gene expression of SOD1, SOD2 and catalase normally observed following a single bout of exercise and also SOD activity following endurance training. Briefly, during unstressed conditions, Nrf2 remains bound to Keap1 in the cytosol. In response to oxidative stress, cysteine residues are modified on Keap1, resulting in the dissociation of the complex and the translocation of Nrf2 to the nucleus. Upon entering the nucleus, Nrf2 activates the transcription of antioxidant enzymes through its binding to the antioxidant response element (ARE). For more detailed information on the activation and regulation of Nrf2 mediated redox adaptations to exercise, see review by Done and Traustadottir [139]. However, ROS induced cysteine modifications on Keap1 are not the only avenue of Nrf2 activation, since the redox sensitive kinases such as AMPK, ERK and JNK are also known to activate Nrf2 [140,141]. Interestingly, AMPK activation by AICAR *in vitro*, also directly phosphorylates Nrf2 in the cytosol, leading to its nuclear accumulation and ARE binding *in vitro* [140]. This activation of Nrf2 independent of oxidative stress, suggests that during exercise the energetic stress (AMP/ATP ratio) and/or oxidative stress could be acting alone or together to regulate redox adaptions to exercise training.

3.3. Redox regulation of blood flow: implications for exercise, health and disease

The vascular system is essential for nutrient and gas exchange between blood and peripheral tissues such as skeletal muscle. Contracting skeletal muscle can lead to a 100-fold increase in metabolic demand, which is offset by balancing vascular tone with haemodynamics within the central (cardiac), macro- (large arteries) and micro-vascular (resistance arteries, peripheral arterioles and capillaries) systems to meet

metabolic demand of the working muscles [142,143]. However, even minor alterations in blood flow can lead to profound effects in various tissue including the heart, brain, skin, liver, and skeletal muscle, affecting components of exercise capacity and performance including cognitive function and fatigue, substrate metabolism, thermoregulation, and muscular contraction and force production [142,144,145]. Although blood flow is considered to be one of the primary rate-limiting steps for exercise performance and capacity, the precise mechanisms controlling vascular function, both at rest and during exercise, in both health and disease, have yet to be completely elucidated [143]. Considering the well-established and previously discussed relationship between skeletal muscle contraction and ROS production [41], redox regulation of vascular function has emerged as a potentially important mechanism contributing to exercise capacity, performance and adaptation, and overall health and disease [143,144,146–148].

3.4. ROS-mediated vascular pathophysiology

Several studies have reported ROS production and subsequent oxidative stress in the vasculature tissue itself during conditions of increased blood flow or vascular shear stress [144,149–152]. Predominant sources of vascular derived oxidative stress include mitochondria, NOX, xanthine oxidase (XO), and uncoupled endothelial nitric oxide synthase (eNOS), which can be found in endothelial cells, vascular smooth muscle cells and fibroblasts [153]. ROS-mediated regulation of blood flow is predominantly known for its pathophysiological role in promoting vasoconstriction, aberrant vascular remodeling, inflammation, and fibrosis, which can both acutely and chronically lead to impaired cardiac, macro and microvascular function [149,153–165].

3.5. ROS-mediated vascular dysfunction in healthy individuals

Antioxidant treatment (e.g., vitamin C, E, α-lipoic acid, and MitoQ10) has been reported to acutely restore or improve measures of endothelial function, vascular and myogenic tone, cardiac hypertrophy, and myocardial function in a variety of vascular derived conditions that are characterised by chronic low-grade oxidative stress including type 2 diabetes, chronic hypertension, atherosclerosis, cardiovascular disease, and ageing [165–181]. However, excess ROS can also lead to transient vascular dysfunction in healthy populations. For example, increased systemic oxidative stress and/or decreased antioxidant capacity following acute hyperlipidemia and hyperglycemia in healthy humans and rodents coincides with macro- and micro-vascular endothelial dysfunction [154,156,182], effects which can be largely prevented via acute co-infusion of vitamin C, N-acetylcysteine, and apocynin [154,156]. In the absence of an oxidative stress insult (e.g., nutrient overload) or chronically elevated levels of oxidative stress (e.g., oxidative stress associated disease), antioxidant treatment in healthy individuals rarely leads to improved vascular function [183], with the vast majority of evidence supporting little to no benefit [165,166,168–171,173,174]. As such, acute antioxidant treatment for improving vascular function appears to be only effective under conditions of acute and/or chronic oxidative stress associated vascular pathophysiology.

3.6. ROS-mediated vascular physiology

Despite a clear role for ROS in vascular dysfunction, ROS is paradoxically required for flow mediated dilatation (FMD), a measure of arterial endothelial function and its ability to dilate in response to increased blood flow or shear stress. For example, H_2O_2 is required for normal FMD in isolated coronary resistance arteries [184,185] and becomes the predominant mechanism for FMD, rather than NO, in isolated visceral adipose tissue arterioles from patients with coronary disease [186,187]. In both young and old rodents, treatment of soleus muscle arterioles with the $O_2^{\bullet-}$ and H_2O_2 scavengers tempol and catalase, respectively, prevents FMD [164]. Likewise, Liu, Zhao [187] reported that shear stress induced $O_2^{\bullet-}$ production from vascular-derived mitochondria respiration contributes to FMD of isolated human coronary resistance arteries. ROS-mediated vascular function may explain why acute antioxidant treatment (vitamin C, 1000 mg; vitamin E, 600 IU; alpha-lipoic acid, 600 mg) in healthy young humans leads to impaired brachial artery FMD [175]. ROS also play a role in healthy vascular adaptations including endothelial cell and vascular smooth muscle cell proliferation, differentiation and migration [188–190] and the upregulation of eNOS expression in endothelial cells [30]. Angiogenesis and vascular adaptations occur predominantly through ROS-stimulated vascular endothelial growth factor expression, but also indirectly through activating redox-sensitive signaling pathways including p38 MAPK, PGC-1α, eNOS, and hypoxia inducible factor (HIF)-1α [191,192].

Current findings support a clear role for redox regulation of macro and microvascular function in various tissues including skeletal muscle, heart, and the pulmonary system. During conditions of excessive oxidative stress (such as during nutrient overload or oxidative stress associated disease) ROS appear to contribute to vascular dysfunction, whereas in the absence of excessive oxidative stress, such as observed in healthy young humans, ROS are likely beneficial and even necessary for normal vascular function.

3.7. ROS-mediated vascular function, exercise capacity and training adaptations

Redox regulation of exercise-induced blood flow, and the subsequent effects on exercise capacity, performance and muscle function, has received limited empirical investigation. Nevertheless, current research supports a role for ROS in regulating exercise/contraction induced blood flow, and exercise capacity, performance and vascular adaptation [28,157,193].

The majority of evidence supporting redox regulation of vascular function during exercise comes from antioxidant treatment studies, and much like basal redox regulation of vascular function, the effects depend on the context and redox environment. For example, antioxidant ingestion prior to hand-grip exercise (300 mg of α-lipoic acid, 500 mg of vitamin C, and 200–400 IU of vitamin E) decreases ROS production as measured by electron paramagnetic resonance spectroscopy, and restores exercise-induced brachial vasodilation in sedentary older adults [29]. In contrast, the same antioxidant treatment in younger individuals leads to impaired exercise-induced brachial artery dilation [28]. Vitamin C infusion has been robustly shown to improve forearm blood flow in older individuals during hand grip exercise [194–197], which is largely abolished with NOS inhibition; however, the direct role of free radical quenching by vitamin C during these conditions remains contentious [195,197]. Furthermore, exercise-induced total leg blood flow in chronic obstructive pulmonary disease patients is improved with prior ingestion of an antioxidant cocktail (300 mg of α-lipoic acid, 500 mg of vitamin C, and 200–400 IU of vitamin E) [198]. In contrast, others have reported no benefit of antioxidant treatment on contraction-induced blood flow in young healthy individuals [196,198]. Similar findings have been reported using mitochondrial specific antioxidant treatment (MitoQ) which prevents cardiac dysfunction and exercise intolerance in cardiomyocyte-specific NOX4 knockout rodents, but has no additive benefits on cardiac function and exercise capacity in healthy control animals [157]. In humans, daily (10 mg) oral ingestion of MitoQ in young healthy men failed to augment, or alter, adaptations to 3 weeks of endurance training including exercise capacity, muscle mitochondrial capacity, and training-induced increases in numerous types of circulating angiogenic cells [31]. Taken together, these findings support that some vascular responses to exercise may be improved with acute antioxidant treatment in populations where chronic oxidative stress and perturbed redox homeostasis is likely to be present. In

contrast, in healthy individuals where redox homeostasis is likely to be retained, vascular responses to exercise are unlikely to be improved by antioxidant treatment, and in some cases may even lead to perturbed redox homeostasis and impaired vascular function.

Exercise also alters redox status in other tissues such as the heart which can directly affect cardiac and vascular function and exercise capacity. For example, wild type mice that undergo acute exercise stress over two consecutive days exhibit increased myocardial ROS, as measured by EPR, and upregulation of the Keap1-Nrf2-ARE antioxidant signaling pathway in the heart [199]. It is likely that this exercise-induced redox response is directly involved in cardiac function, as cardiomyocyte-specific NOX4 and Nrf2 knockout mice exhibit impaired cardiac performance and exercise capacity which is largely restored by Nrf2 activators or mitochondrial targeted antioxidant treatment [157]. Furthermore, six weeks of moderate-intensity exercise training in rodents upregulates myocardial Nrf2 and Nrf2-antioxidant genes and protects against cardiac dysfunction and injury incurred through isoproterenol induced oxidative stress [200]. These findings support exercise-induced myocardial ROS, and subsequent upregulation of antioxidant activity, to directly affect cardiac function and exercise capacity. Other examples of how exercise can lead to improved vascular function via promoting a shift in the redox balance has been reported in humans. For example, a prior bout of acute moderate or high-intensity interval exercise in healthy humans improves brachial artery FMD responses to a high-fat meal ingested 16–18 h later, with improved FMD strongly correlating with increased plasma total anti-oxidant capacity [155]. Likewise, acute hyperglycemia-induced oxidative stress and impaired macro and microvascular endothelial dysfunction, which can be prevented by either N-acetylcysteine or apocynin treatment in rodents [154], can also be prevented by a prior bout of aerobic exercise in humans [201]. These findings support the growing ideology of exercise as a natural antioxidant which can improve vascular dysfunction during conditions of elevated oxidative stress.

Exercise training is also known to promote long-term antioxidant effects that can be beneficial for vascular function and adaptation. For example, 6-weeks of knee extensor exercise training decreases systemic oxidative stress, improves blood pressure and flow-mediated and contraction-mediated arterial dilation in older individuals [29,202]. On the other hand, these training-induced improvements in vascular function were prevented with acute antioxidant treatment prior to testing [29,202]. Similarly, intravenous vitamin C infusion (bolus infusion of 0.06 g/kg over 20 min followed by 0.02 g/kg over 60 min) improves brachial artery FMD in sedentary older individuals, whereas no benefits were reported in endurance-exercise trained older adults [203]. Exercise training in both young and aged rodents improves FMD in isolated soleus arterioles, which is blunted by acute antioxidant co-treatment with tempol, catalase, and tempol plus catalase [164]. The same group reported increased aortic and myocardial eNOS expression following 3 weeks of training in wild-type mice whereas this training effect is absent in transgenic littermates overexpressing human catalase [204]. These findings support *in vitro* experiments showing that H_2O_2 treatment can directly increase eNOS expression in endothelial cells [205].

3.8. Summary

Research investigating ROS-mediated regulation of vascular function support the notion that ROS play both a physiological and pathophysiological role. In certain situations in which ROS are elevated and redox homeostasis is perturbed, vascular dysfunction can ensue. Importantly, much like the effects of antioxidant supplementation on training adaptations in healthy and/or trained individuals, current findings support the general consensus that antioxidant treatment is unlikely to provide meaningful benefits, and may even impair vascular function and adaptations in healthy and trained individuals both at rest, and after acute and chronic exercise training. This may not be surprising, as ROS are now known to be necessary for normal vascular function, both in the acute setting and for long-term vascular health. Likewise, exercise leads to the upregulation of antioxidant defenses which maintain vascular function, at rest and during exercise. As such, continual disruption of the redox environment via antioxidant treatment during exercise may impair beneficial training vascular adaptations in both healthy and clinical populations.

4. Antioxidant supplementation and endurance exercise

This section of the review will provide an overview of various redox-modulating compounds that are available commercially with potential application to athletes. This section will focus on their antioxidant effects and their effects on exercise-related outcomes. As already discussed, there is the potential for antioxidants to have negative effects on exercise-related outcomes. Where such evidence exists, this will be discussed, with a focus on their effects in skeletal muscle. It is beyond the scope of this paper to provide a comprehensive review of each antioxidant compound with respect to their bioavailability, antioxidant mechanisms and clinical safety profile. Therefore, for a more detailed discussion of these factors, it is recommended that readers seek out review articles on the specific antioxidants.

Table 1 summarises the redox-related effects of antioxidant compounds in skeletal muscle (and systemically, where skeletal muscle data is unavailable) in humans, particularly with respect to exercise. Effects of these antioxidant compounds on skeletal muscle mitochondrial biogenesis, exercise performance, vascular function and post-exercise muscle recovery (focussing on recovery of muscle strength, delayed onset of muscle soreness (DOMs) and systemic markers of muscle damage such as creatine kinase [CK] and lactate dehydrogenase [LDH]) are also summarized in Table 1.

4.1. Polyphenols

Polyphenols, such as those discussed below, have potent free radical scavenging and/or metal chelation effects *in vitro* [338–344]. However, the *in vivo* relevance of these mechanisms is debatable due to their (1) generally poor oral bioavailability with transient low accumulation only [345–349]; (2) relatively poor uptake into peripheral tissues like skeletal muscle [350–353]; and (3) competition for ROS/RNS with endogenous antioxidants. Indirect antioxidant mechanisms of polyphenols might include induction of endogenous antioxidant gene expression [354–357] and regulation of ROS/RNS producing enzymes [358–361] and redox-related transcription factors [362–365]. Ingested polyphenols undergo extensive metabolism and modification in the liver and intestines. Metabolites of polyphenols may exert important redox-related effects given their typically much higher concentrations reached in the body compared to parent compounds [366–368]. However, redox-related effects of polyphenol metabolites have generally been poorly studied to date. A recent meta-analysis of RCTs involving predominantly trained males concluded that polyphenol supplementation (average dose 688 mg/day) for at least 7 days can improve exercise performance by ~1.9% [246]. Potential ergogenic mechanisms proposed by the authors include enhanced mitochondrial biogenesis, improved vascular function and blood flow, and enhanced fat oxidation [246]. With few exceptions, polyphenols are believed to be largely safe when consumed at high doses, including within the ranges used in the studies described below [246,369–374].

4.1.1. Anthocyanins

Evidence is limited and mixed in terms of systemic antioxidant effects of anthocyanins (ACNs) in relation to exercise in humans (Table 1). Moreover, antioxidant effects of ACNs have not been clearly explored in skeletal muscle of either humans or animals. Findings are equivocal with respect to benefits of ACN supplementation on endurance performance, VO_2max and post-exercise muscle recovery

Table 1
Reported effects of antioxidant compounds on exercise-related redox markers, mitochondrial biogenesis, vascular function and performance outcomes 18.

Antioxidant compound (Oral doses used)	Oxidative stress	Antioxidant enzyme levels	Mitochondrial biogenesis	Vascular function	Endurance performance/VO_2 max	Post-exercise muscle recovery (Muscle strength, DOMs, CK, LDH)
Anthocyanins (80–547 mg/day)	Chronic studies (6-21d) *Systemic measures:* ↓ [206–208] ↔ [209–211]	Chronic studies (8-21d) *Systemic measures:* ↑ [207] ↔ [210]	N/A	Chronic studies (7d) ↑ [212] (resting only) ↑ [213] (during exercise)	Chronic studies (3—21d) ↑ [212,214,215] ↔ [210,216,217]	Chronic studies (7-8d) Beneficial [211] No impact [206,207]
Astaxanthin (4–20 mg/day)	Chronic studies (21-90d) *Systemic measures:* ↓ [218] ↔ [219–223]	Chronic studies (21-90d) *Systemic measures:* ↑ [223] ↔ [222]	N/A	N/A	Chronic studies (28d) ↔ [222]	Chronic studies (21-90d) Beneficial [219,223] No impact [221,224]
Catechins (30–1800 mg/day)	Acute studies *Systemic measures:* ↔ [225] (resting only) Chronic studies (14-90d) *Systemic measures:* ↓ [226] ↔ [227–229] *In Skeletal Muscle* ↓ [230]	Acute studies *Systemic measures:* ↑ [225] (resting only) Chronic studies (14-28d) *Systemic measures:* ↔ [227–229]	Chronic studies (28-90d) ↑ [229] (SDH protein expression) [230] ↔ [229] (CS, Cytochrome C protein expression)	Acute studies ↑ [231] Chronic studies (56-84d) ↑ [232] ↑ [233] (resting only)	Chronic studies (2-90d) ↑ [230] ↔ [232,234–236]	Acute studies No impact [237] Chronic studies (2-90d) Beneficial [227,228]
Curcumin (50–2120 mg/day)	Chronic studies (4d) *Systemic measures* ↔ [238]	N/A	N/A	Chronic studies (56d) ↑ [239](resting only)	N/A	Acute studies Beneficial [38] Chronic studies (4-56d) Beneficial [36–38]
Quercetin (250–1000 mg per day – most studies used 1000 mg/day)	Chronic studies (21-24d) *Systemic measures* ↔ [240,241]	Chronic studies (21-24d) *Systemic measures* ↔ [240,241]	Chronic studies (14-24d) ↔ [242,243]	N/A	Chronic studies (7-42d) ↑ [243–247] ↔ [240,242,248,249]	Chronic studies (9-24d) Beneficial [242,250] No impact [249]
Resveratrol (150–600 mg/day)	Chronic studies (56d) *In Skeletal Muscle* Attenuated ↓ [251]	Chronic studies (84d) *In Skeletal Muscle* ↔ [252]	Chronic studies (24-84d) ↑ [252] ↔ [251] Attenuated [253]	Chronic studies (56 d) Attenuated [254]	Chronic studies (28-180d) ↑ [252] ↔ [251,253,255] Attenuated [254]	Chronic studies (7d) No impact [256]
Vitamin C (400–3000 mg/day)	Acute studies *Systemic measures* ↓ [257] ↔ [39] Chronic studies (8-17d) *Systemic measures* ↓ [258–260] ↔ [261,262]	Chronic studies (42d) *In Skeletal Muscle* ↔ [263,264] (resting only)	Chronic studies (42d) *In Skeletal Muscle* ↔ [264] (resting only)	Acute studies (Intravenous or Oral) ↑ [194–197,265] *(ref* [196] *in older adults only)* ↔ [196] *(ref* [196] *in younger adults)* ↔ [203,266] Chronic studies (30d) ↔ [203]	Chronic studies (7-56d) ↔ [22,261,267] ↓ [210]	Acute studies No impact [39] Chronic studies (3-17d) Beneficial [258,259,268] No impact [262,269,270] Detrimental [271]
Alpha-lipoic acid (600–1200 mg/day)	Chronic studies (3-10d) *Systemic measures* ↓ [272–275]	Chronic studies (3-10d) *Systemic measures* ↑ [273–275]	N/A	Acute studies ↔ [276]	N/A	Chronic studies (3-10d) Beneficial [272] No impact [273,274]
Coenzyme Q10 (90–300 mg/day)	Chronic studies (20-56d) *Systemic measures* ↓ [277] ↔ [278–281]	Chronic studies (28d) *Systemic measures* ↔ [278]	N/A	Chronic studies (30d) ↑ [282,283]	Chronic studies (8-180d) ↑ [280,282–286] ↔ [31,279,281,287–290] ↓ [291,292]	Chronic studies (20-56d) Beneficial [277] No impact [278,279,293,294]
Vitamin A/β-carotene (Vitamin A: 300 mg/day; β-carotene 30 mg/day)	Chronic studies (28-30d) *Systemic measures* ↔ [295,296]	Chronic studies (28d) *Systemic measures* ↔ [295]	N/A	N/A	Chronic studies (30d) ↔ [296]	N/A
Vitamin E (450-1200 IU)	Chronic studies (14-48d) *Systemic measures* ↓ [297–301] ↑ [302] *In Skeletal Muscle* ↓ [300]	Chronic studies (42d) *Systemic measures* ↑ [302] ↔ [300]	N/A	N/A	Chronic studies (42-180d) ↑ [303,304] ↔ [300,301,305,306]	Chronic studies(30-150d) Beneficial [301] No impact [268,307,308]

(*continued on next page*)

Table 1 (*continued*)

Antioxidant compound (Oral doses used)	Oxidative stress	Antioxidant enzyme levels	Mitochondrial biogenesis	Vascular function	Endurance performance/VO_2 max	Post-exercise muscle recovery (Muscle strength, DOMs, CK, LDH)
Melatonin (acute doses 2.5–6 mg; chronic doses 9–100 mg/day)	Acute studies *Systemic measures* ↓ [309] Chronic studies (3-28d) *Systemic measures* ↓ [310–312]	Acute studies *Systemic measures* ↑ [309] Chronic studies (3-28d) *Systemic measures* ↑ [310–312]	N/A	Acute studies ↑ [313] (Systolic BP decrease post-exercise only)	Acute studies ↔ [314,315]	Chronic studies (28d) Beneficial [311]
N-acetyl cysteine (acute: oral 1800 mg - 150 mg/kg (chronic: 1200 mg/day – 250 mg/kg/day	Acute studies *In Skeletal Muscle* (Intravenous) ↓ [19]	Acute studies *In Skeletal Muscle* (Intravenous) ↑ [316] Attenuated ↑ [317]	Acute studies (Intravenous) ↔ [317]	Acute studies (Intravenous) ↑ [318] (MAP in older adults) ↔ [318] (Blood flow, vascular conductance; and MAP in young adults) Acute studies (Oral) ↔ [319]	Acute studies (Intravenous) ↑ [40,316,320,321] *(ref* [321]*-at low frequency only)* ↔ [40,321,322] *(ref* [321]*-at higher frequencies)* (Oral) ↑ [323–325] *(ref* [325] *at 80% VO_2 max only)* ↔ [319,325] *(ref* [325] *at > 80% VO_2 max)* Chronic studies (4-9d) ↑ [326–328] ↓ [329]	Chronic studies (14d) Beneficial [228]
Selenium (180–240 μg/day	Chronic studies (21 d) *Systemic measures* ↓ [330] (in overweight only)	Chronic studies (21–70 d) *Systemic measures* ↑ [331] ↔ [330] *In Skeletal Muscle* ↑ [332] ↔ [331]	Chronic studies (70d) ↔ [331] Attenuated [333]	N/A	Chronic (70d) ↔ [331]	N/A
Zinc (20–30 mg/day)	Chronic studies (6-84d) *Systemic measures* ↓ [334,335]	Chronic studies (84d) *Systemic measures* ↔ [335]	N/A	N/A	Chronic studies (7-42d) ↔ [336,337]	N/A

(↑ = Increased; ↔ = No effect; ↓ = Decreased; DOMs – delayed onset muscle soreness; CK – creatine kinase; LDH – lactate dehydrogenase; SDH – succinate dehydrogenase; CS – citrate synthase; MAP – mean arterial pressure).

(Table 1). It is possible that underlying mechanisms relating to improved performance following ACN supplementation might include improved endothelial function and alterations in blood flow. Morgan et al. [212] found improved muscle tissue oxygenation at rest after 7 days of supplementation with Montmorency cherry supplementation in trained cyclists; although this did not occur during exercise, despite an improved time trial performance. In another study, 7 days of New Zealand blackcurrant supplementation was found to decrease blood pressure and total peripheral resistance; but increase femoral artery diameter, during submaximal isometric contraction of the knee extensors [213]. Further research is required to better elucidate mechanisms of performance enhancement with ACNs. Studies investigating ACNs with exercise in humans have been limited by small sample sizes, use of predominantly male-only trained participants, and supplementation periods of less than 6 weeks. Furthermore, some studies have used supplements that contain additional polyphenols or other antioxidant compounds, which makes it difficult to clearly isolate the effects of ACNs. Mechanistic insights into skeletal muscle adaptations to training in response to ACNs have not currently been undertaken in humans or animals, requiring future investigation to elucidate any potential effects.

4.1.2. Astaxanthin

Evidence is limited and unclear with respect to benefits of astaxanthin (ASX) supplementation on systemic oxidative stress markers in humans (Table 1). In rodents, ASX has been found to increase skeletal muscle ASX concentration [375,376] and decrease skeletal muscle markers of oxidative stress [376–378]. In one study, ASX hampered exercise-induced expression of Nrf2 and induction of endogenous antioxidant enzymes at higher doses [378]. While evidence in rodent studies shows improved endurance performance after chronic ASX supplementation [375,377,379], a study in athletes [222] found no ergogenic effect after chronic supplementation. A study in rodents [380] reported enhanced fat oxidation rate and sparing of muscle glycogen during exercise, which is suggestive of a possible ergogenic mechanism of action of ASX. Beneficial effects on post-exercise muscle recovery are equivocal in the limited human studies published (Table 1). Overall, studies in rodents implicate endurance performance enhancement with ASX, although with possible hampering of some skeletal muscle training adaptations. Given these findings and a lack of studies in human participants, future research should focus on effects of ASX on endurance performance and training-related adaptations in skeletal muscle of humans.

4.1.3. Catechins

Catechins are naturally found in high concentrations in green tea, red wine, berries, cocoa and chocolate. Evidence is equivocal overall in terms of effects of supplemental catechins on systemic antioxidant effects in relation to exercise in humans (Table 1). However, cocoa flavanols have been shown to produce small positive effects on markers of oxidative stress across untrained and trained participants [226]. Limited human [230] and rodent [381,382] data is equivocal with respect to beneficial effects of catechin supplementation on oxidative stress in skeletal muscle with or without concomitant exercise training. Evidence of improvements in endurance performance is also equivocal in rodent studies after catechin supplementation [383–387], while evidence is not supportive of its ergogenic effects across untrained and trained human participants (Table 1). Catechin supplementation may improve vascular function, although these changes don't appear to translate to improvements in exercise performance. Studies in overweight/obese individuals have found an attenuated blood pressure response to submaximal exercise after acute cocoa flavanol supplementation [231] and a reduced blood pressure after chronic cocoa flavanol supplementation (without additive effects of exercise training) [233]. Studies have also shown increased FMD after acute [231,233] and chronic [233] cocoa flavanol supplementation in overweight/obese humans. A recent meta-analysis concluded that cocoa flavanol supplementation improves FMD, although not exercise performance, across untrained and trained participants [226]. In healthy rats, catechin supplementation (4 mg epicatechin/kg/day for 3 wks) modestly improved mean arterial blood pressure at rest and during exercise, but had no effects on exercise capacity, VO_2 peak, exercising skeletal muscle blood flow and vascular conductance, or contraction induced muscle microvascular function [196].

Increased skeletal muscle β-oxidation activity and whole-body fat oxidation (and decreased carbohydrate oxidation) were shown in rodents after catechin supplementation [383]. Human studies appear mixed with regards to substrate oxidation [225,234–236,388], although a recent meta-analysis reported significantly decreased RER and increased energy expenditure after catechin supplementation of between 300 and 600 mg/day for 2–12 weeks [389]. Rodent studies appear to indicate improved mitochondrial biogenesis after catechin supplementation [384,385], while studies in humans are limited and mixed [229,230]. Studies on muscle recovery post muscle damaging exercise have also produced mixed findings in humans, and evidence is equivocal (Table 1). Given a potential risk of elevated liver injury with high catechin doses (i.e. > 800 mg EGCG/day [390]), a lack of an unclear threshold dose of safety [390], and a lack of convincing exercise-related benefits, green tea-based catechin supplements are potentially undesirable choices of antioxidant supplements for athletes. Modest cocoa flavanol supplementation may, however, be potentially beneficial for overweight/obese athletes or exercisers who want to improve their vascular health.

4.1.4. Curcumin

Investigations into either skeletal muscle-related or systemic antioxidant effects of curcumin are lacking in exercise studies in humans. In rodents, acute and chronic curcumin supplementation has been shown to decrease skeletal muscle markers of oxidative stress [361,362,364,365,391]. Studies investigating effects of curcumin supplementation on endurance performance in humans are lacking. Limited studies in rodents show an improvement in exercise capacity after chronic curcumin supplementation [364,391,392]. Moreover, limited rodent data suggests enhanced mitochondrial biogenesis with curcumin supplementation when combined with exercise training [393]. There is a paucity of studies investigating effects of curcumin on exercise-related vascular function in humans. Curcumin supplementation (150 mg/day for 8 weeks) was found to increase FMD in post-menopausal women to a similar extent as did moderate aerobic exercise training [239]. However, the combined effects of curcumin plus exercise training were not explored in this study [239]. Studies in humans show an attenuated decline in muscle recovery post-muscle damaging eccentric exercise after curcumin supplementation (Table 1), although further investigation is required to confirm these findings. There is a need for further investigation of curcumin supplementation in exercising humans given some potentially promising findings in animals with respect to performance outcomes and mitochondrial biogenesis.

4.1.5. Quercetin

There is currently limited evidence of any systemic changes in oxidative stress markers or antioxidant capacity when quercetin is supplemented along with exercise training in athletes (Table 1). Moreover, limited findings in rodents have not been supportive of improvements in oxidative stress or antioxidant enzyme activation in skeletal muscle when undertaking exercise training [394]. Some evidence shows enhanced markers of mitochondrial biogenesis in muscle after quercetin and exercise training in rodents [394,395]; although effects of quercetin on exercise performance are equivocal in animal studies [394,395]. There appears to be no effect of quercetin supplementation on mitochondrial biogenesis in humans undertaking exercise training [242,243] and effects on exercise performance appear small and inconsistent (Table 1). Published meta-analyses [245–247] have

Table 2
Summary and recommendations regarding antioxidant supplementation for people undertaking endurance training.

Antioxidant compound	Evidence summary – exercise-related effects
Anthocyanins	- Effects on oxidative stress and antioxidant enzymes are mixed and limited to systemic data only - Equivocal effects on endurance performance, VO_2 max and post-exercise muscle recovery - May improve blood flow and vascular function, although this does not appear to translate to performance benefits - **Insufficient supportive evidence to recommend to athletes**
Astaxanthin	- Rodent studies show decreased muscle oxidative stress and improved endurance performance; although with possible hampering of training-induced Nrf2 signalling and antioxidant enzyme induction in muscle - Studies in humans are lacking and unclear with respect to effects on oxidative stress, antioxidant enzyme levels, skeletal muscle adaptations, endurance performance and post-exercise muscle recovery - **Insufficient supportive evidence to recommend to athletes**
Catechins	- Overall, effects on oxidative stress and antioxidant enzymes are equivocal; although cocoa flavanols can produce small beneficial effects on systemic markers of oxidative stress - Evidence not supportive of beneficial effects on endurance performance - Evidence equivocal on effects on skeletal muscle mitochondrial biogenesis and post exercise muscle recovery - Can improve vascular function, particularly in overweight/obese individuals – however, this does not appear to translate to improvements in exercise performance - Chronic supplementation may lower RER, increase fat oxidation, decrease carbohydrate oxidation and increase energy expenditure - Potential adverse effects on liver enzymes at high doses (EGCG > 800 mg/day) and lack of clear safety threshold dose - **Insufficient supportive evidence to recommend to athletes**
Curcumin	- Rodent studies show improvements in skeletal muscle oxidative stress, mitochondrial biogenesis and endurance performance - Studies in humans are lacking and unclear with respect to effects on oxidative stress, antioxidant enzyme levels, skeletal muscle adaptations and endurance performance - Limited studies in humans are supportive of benefits on post-exercise muscle recovery, although further research is required to confirm this - **Insufficient supportive evidence to recommend to athletes**
Quercetin	- Minimal evidence of any beneficial effects on systemic markers of oxidative stress - No evidence currently in humans to suggest it will impact on mitochondrial biogenesis in muscle - May result in small beneficial effects on endurance performance, although this is mostly limited to untrained individuals - Effects on muscle recovery post muscle-damaging exercise are equivocal - **Insufficient supportive evidence to recommend to athletes**
Resveratrol	- Findings of rodent studies support improvements in skeletal muscle oxidative stress, antioxidant enzymes and exercise performance. However, evidence on these outcomes is limited and unclear in humans. - Limited evidence in humans suggests some hampering of skeletal muscle mitochondrial biogenesis and vascular function, but evidence is mixed - Future studies should use higher doses (i.e. > 2g/day) for which systemic concentrations of resveratrol and its metabolites are much higher (However, there is an increased risk of adverse effects at high doses) - **Insufficient supportive evidence to recommend to athletes**
Vitamin C	- Has been shown to have mixed effects on systemic markers of exercise-induced oxidative stress and on post-exercise muscle recovery - No convincing evidence of endurance performance benefits - May improve vascular function with exercise, although this appears to be mostly limited to older individuals after acute infusion - While some rodent data suggests impairments in skeletal muscle mitochondrial biogenesis, this has not been explored in humans in the absence of other additional antioxidants - **Insufficient supportive evidence to recommend to athletes**
Alpha-lipoic acid	- Limited evidence is suggestive of benefits on systemic markers of oxidative stress and antioxidant enzymes - Evidence from animal studies shows mixed effects on skeletal muscle oxidative stress, antioxidant enzymes, mitochondrial biogenesis and endurance performance. However, there is a lack of studies in humans investigating these outcomes - **Insufficient supportive evidence to recommend to athletes**
Coenzyme Q10	- No convincing evidence of improvements in markers of oxidative stress, antioxidant enzymes or post-exercise muscle recovery - Unlikely to affect skeletal muscle mitochondrial biogenesis - May improve vascular function, particularly in individuals with heart disease; for whom improvements in VO_2max may occur - Evidence largely mixed for effects on endurance performance - **Insufficient supportive evidence to recommend to athletes**
Vitamin A/β-carotene	- The limited available evidence does not support either vitamin A or β-carotene in improving markers of oxidative stress or improving endurance performance - Limited evidence from rodents shows a hampering of exercise-induced skeletal muscle antioxidant enzyme adaptations after supplementation with retinyl palmitate; however this has not been explored in humans - **Insufficient supportive evidence to recommend to athletes**
Vitamin E	- Studies mostly show improvements in oxidative stress markers - Studies mixed in terms of effects on endurance performance; with most beneficial effects shown in trained athletes at high altitude - Some rodent data indicates hampering of skeletal muscle adaptations to exercise; although effects of vitamin E alone on these outcomes (in the absence of other antioxidants) has not been explored in humans - **Insufficient supportive evidence to recommend to athletes**
Melatonin	- Studies show improvements in systemic markers of oxidative stress and antioxidant enzymes - Rodent studies are supportive of beneficial effects on skeletal muscle oxidative stress and antioxidant enzymes; however, these outcomes have not been explored in humans - Limited studies show acute supplementation is unable to improve time trial performance; but effects of chronic supplementation on performance in humans are lacking - **Insufficient supportive evidence to recommend to athletes**
N-acetylcysteine	- Evidence tends to favour an improvement in sustained exercise performance after acute and chronic NAC supplementation - Evidence from limited acute infusion studies is mixed with respect to effects on skeletal muscle antioxidant levels - Limited evidence suggests NAC might improve aspects of vascular function in older, but not younger participants - Adverse effects limit use of high doses of NAC (> 70 mg/kg), although newer effervescent forms may overcome issues of taste and tolerance - WADA restrictions limit the use of infusions [442], which might limit the applicability of NAC infusion - **Insufficient evidence to recommend to athletes. However, it may be beneficial and well tolerated with doses (< 70 mg/kg) taken chronically over several days prior to an endurance event**

(*continued on next page*)

Table 2 (*continued*)

Antioxidant compound	Evidence summary – exercise-related effects
Vitamin C + E	- A combined dose of 500 mg vitamin C + 400 IU vitamin E does not appear to have any adverse effects on skeletal muscle adaptations to endurance exercise training - A combined dose of 1000 mg vitamin C + 260–400 IU vitamin E has been found in some studies to hamper some markers of mitochondrial biogenesis and antioxidant enzyme induction - There appears to be no effect (beneficial or detrimental) of combined vitamin C + E on endurance exercise performance - Effects on post exercise muscle recovery are limited and equivocal - **Insufficient supportive evidence to recommend to athletes. It might also be wise for athletes to avoid the combination of 1000 mg vitamin C + vitamin E during periods of heavy training in which skeletal muscle adaptations are occurring**
Selenium	- Limited studies in humans have shown decreased exercise-related lipid peroxidation in overweight participants with low selenium levels - One study in humans showed hampering of markers of skeletal muscle mitochondrial biogenesis markers with exercise training; although evidence is limited and mixed overall - Limited studies show no beneficial effects on endurance performance - **Insufficient supportive evidence to recommend to athletes**
Zinc	- Limited evidence available shows some beneficial effects of zinc on systemic markers of exercise-induced oxidative stress - Evidence not supportive of effects on endurance performance, with only limited studies using zinc as the sole compound in supplements - **Insufficient supportive evidence to recommend to athletes**

concluded small (0.74%–5%) but significant improvements in endurance exercise performance in human studies involving quercetin supplementation; although effects appear to be largely limited to untrained individuals [247]. Moreover, studies are also currently limited by small sample sizes and use of male participants only. Effects on muscle recovery post muscle-damaging exercise are equivocal in humans (Table 1). There is currently limited convincing evidence to recommend quercetin to trained athletes given a lack of reported improvements in oxidative stress markers along with small, possibly trivial, endurance exercise performance benefits that are limited mostly to untrained individuals.

4.1.6. Resveratrol

Evidence in rodent skeletal muscle has shown improvements in oxidative stress [396–401] and induction of endogenous antioxidant enzymes [396,397,399,400] after resveratrol supplementation was combined with exercise. However, no effects on oxidative stress or antioxidant levels were observed in skeletal muscle of older humans undertaking exercise training [252]. Similarly, while studies in rodents are mostly supportive of endurance performance benefits of resveratrol [398,401–406], limited studies in humans are not currently supportive of its ergogenic effects (Table 1). In humans, findings are equivocal with respect to the impact of resveratrol on exercise-related skeletal muscle mitochondrial adaptations in both younger [253] and older [251,252] individuals. Limited studies have explored the impact of resveratrol on exercise-related vascular function. Gliemann et al. [254] reported that chronic resveratrol supplementation (250 mg/day for 8 weeks) hampered the exercise-training induced blood pressure reduction in older adults. Further exercise studies in humans, including those using more athletic populations and real-world athletic performance tests, are required to clarify the impact of resveratrol. Future studies might also attempt to investigate a possible dose-related impact of resveratrol supplementation, given that no studies in humans involving exercise have utilized high doses of ≥2g/day that result in much higher systemic levels of resveratrol and its metabolites [366,407]. A potential limitation of using higher doses (> 2g/day) is an increased risk of adverse effects such as nausea, flatulence, abdominal discomfort, diarrhoea [408].

4.2. Water-soluble antioxidants

4.2.1. Vitamin C

Acute and chronic vitamin C supplementation have been shown to have mixed effects on systemic markers of exercise-related oxidative stress (Table 1). Studies using healthy individuals (without exercise) found no effect of vitamin C supplementation on resting skeletal muscle antioxidant enzyme levels [234,263] or markers of mitochondrial biogenesis [234]. In rodents, vitamin C supplementation was shown to hamper exercise-induced antioxidant enzyme gene expression and mitochondrial biogenesis in skeletal muscle [22]. Interestingly, studies in animal models have tended to favour null [409] or even ergolytic [22,410] endurance-related effects of vitamin C. In humans, there is no convincing evidence of endurance performance enhancement following vitamin C supplementation (Table 1). Findings implicate improvements in vascular function during exercise with acute vitamin C supplementation in older adults; although limited evidence is supportive of benefits in younger adults or with chronic oral supplementation (Table 1). Observed effects of vitamin C on vascular function may be related to an improved NO bioavailability and antioxidant-related mechanisms [411]. Effects of vitamin C supplementation on muscle recovery post muscle-damaging exercise are equivocal in humans (Table 1). Evidence is not currently supportive of any ergogenic effects of vitamin C supplementation in athletes. A lack of clear effects observed could relate to poor direct *in vivo* redox-modulating effects of vitamin C during exercise [45]. Studies examining the effects of vitamin C supplementation alone on skeletal muscle adaptations to exercise training are lacking, and require further investigation given hampering effects found in rodents; and hampering effects found when vitamin C is combined with vitamin E in some human studies [44,412,413].

4.3. Lipid-soluble antioxidants

4.3.1. Alpha lipoic acid

Limited studies in humans show improvements in systemic markers of oxidative stress and antioxidant capacity following muscle-damaging exercise with short-term ALA supplementation (Table 1). Furthermore, rodent studies show improvements in oxidative stress markers in skeletal muscle following chronic ALA supplementation [414–418], although with mixed effects on endogenous antioxidant levels/activities [414,415,419,420]. Animal studies have shown mixed effects of ALA supplementation on endurance exercise performance [414,415,417,420,421] and mitochondrial biogenesis markers in muscle [414,415,419,420], however, there is currently a lack of evidence on these outcomes in humans. There is also a lack of studies in humans that have investigated vascular function following ALA supplementation without concomitant ingestion of other antioxidants (Table 1). Findings with respect to recovery from muscle damaging exercise are equivocal in humans (Table 1). Current evidence is suggestive of improved exercise-related oxidative stress following ALA supplementation in humans and rodents. However, given a lack of evidence available on effects of ALA on endurance performance and skeletal muscle adaptations in humans, ALA supplementation cannot be recommended at present for athletes.

4.3.2. Coenzyme Q10

Most studies in humans have failed to demonstrate improvements in systemic markers of oxidative stress or antioxidant enzymes after chronic coenzyme Q10 (CoQ10) supplementation with exercise in participants ranging from untrained to highly trained (Table 1). Moreover, limited studies in rodents have found CoQ10 does not alter skeletal muscle markers of oxidative stress or concentrations of endogenous antioxidants when combined with exercise training [422,423]. Effects of exogenous CoQ10 in human skeletal muscle remain unclear, particularly considering that supplementation appears ineffective at increasing muscle CoQ10 concentration [287,288,292,424]. CoQ10 supplementation has beneficial effects on endothelial function [425] which might contribute to functional improvements in patients with cardiovascular diseases. CoQ10 supplementation (300 mg/day for 1 month) in patients with coronary heart disease resulted in improvements in VO_2max as well as endothelial-dependent vasodilation and endothelium-bound extracellular SOD activity [282]. CoQ10 (100 mg/day for 1 month) improved VO_2peak and endothelium-dependent dilation of the brachial artery in patients with chronic heart failure, particularly when combined with regular exercise training [283]. Supplementation with mitochondrial-targeted CoQ10, MitoQ (10 mg/day for 3 weeks), was shown to have no effect on exercise-training induced improvements in VO_2 max or oxidative capacity in healthy young adults [31]. A lack of effect in the latter study might relate to specific exercise-training-related variables (e.g. training intensity and study duration) and/or the targeting of mitochondrial rather than non-mitochondrial sources of ROS. Studies investigating effects of CoQ10 supplementation on endurance performance have produced mixed findings in humans using dosage regimens ranging from 100 to 300 mg/day for 8 days to 6 months (Table 1), with findings suggestive of limited benefit in healthy individuals. Furthermore, most studies are not supportive of beneficial effects of CoQ10 on post-exercise muscle recovery (Table 1). Overall there appears to be no convincing evidence to recommend CoQ10 supplements to enhance endurance performance or post-exercise muscle recovery in athletes.

4.3.3. Vitamin A/β-carotene

The current limited evidence available does not appear to support beneficial effects of chronic supplementation with either preformed vitamin A (e.g. retinol) or β-carotene on systemic markers of exercise-induced oxidative stress [295,296]. In rodents, chronic supplementation with retinyl palmitate in combination with exercise training increased skeletal muscle oxidative stress and decreased exercise-induced induction of endogenous antioxidant enzymes [426]. This finding implicates an impairment in exercise-induced antioxidant adaptations in skeletal muscle with exogenous vitamin A. There is a notable lack of studies investigating effects of vitamin A/β-carotene on either exercise performance or skeletal muscle mitochondrial biogenesis in both humans and animals. Given the overall lack of data in humans along with impairments in some exercise-induced muscle adaptations found in rodents, future research should further investigate effects of vitamin A and β-carotene as stand-alone supplements in human studies involving exercise training.

4.3.4. Vitamin E

Vitamin E supplementation has been shown to decrease systemic markers of exercise-related oxidative stress (Table 1); although increased post-exercise hydroperoxides were reported in one study in triathletes [302]. Vitamin E supplementation also decreased intense eccentric-exercise-induced conjugated dienes in skeletal muscle of humans [300]. Rodent studies indicate hampering effects of chronic vitamin E supplementation on the induction of antioxidant enzymes and mitochondrial biogenesis with exercise training in skeletal muscle [23,427]. Current evidence is equivocal with respect to benefits of vitamin E supplementation on endurance outcomes in humans (Table 1). The most supportive evidence for vitamin E appears to be for performance outcomes at altitude in trained participants [303,304]. Acute vitamin E supplementation was also found to improve endurance exercise-induced acetylcholine-mediated vasodilation in aortas of healthy rats; although chronic supplementation with vitamin E had no additional effects over exercise training alone on vascular function [428]. There is a lack of studies investigating effects of vitamin E (in the absence of other additional antioxidants) on exercise-related vascular function in humans. Evidence for beneficial effects of vitamin E supplementation on muscle recovery post muscle damaging exercise are lacking (Table 1). Despite a considerable number of studies investigating effects of combined vitamin C and E on skeletal muscle exercise adaptations (see below), there is an absence of studies investigating vitamin E alone on skeletal muscle adaptations to exercise training in humans. Given the limited evidence of ergogenic effects of vitamin E for athletes, potentialsafety risks associated with commonly consumed doses [429,430], and hampering effects shown in animal studies on exercise adaptations in muscle; there is currently no clear basis for recommending vitamin E supplements for athletes.

4.4. Both water- and lipid-soluble antioxidants

4.4.1. Melatonin

Evidence from acute and chronic supplementation studies in humans shows that melatonin is beneficial in reducing systemic exercise-induced oxidative stress and improving antioxidant capacity in athletes (Table 1). Furthermore, studies in rodents have shown acute and chronic melatonin supplementation to be effective at attenuating acute exercise-associated oxidative stress in muscle [431–433] and improving endogenous antioxidant concentrations [432–434]. However, no evidence currently exists on antioxidant effects of melatonin in skeletal muscle of humans with exercise. There is evidence to support improved endurance performance outcomes in rodent studies [435–438], which might be related to increased fat oxidation and glycogen conservation [437,439]. Findings are mixed in rodents with respect to effects of melatonin on skeletal muscle markers of exercise-induced mitochondrial biogenesis [437,438]. Studies using acute melatonin supplementation have failed to report benefits on time trial performance in human participants [314,315]. However, overall, there is a paucity of studies that have investigated the effects of melatonin on exercise performance, mitochondrial adaptations in muscle and muscle recovery outcomes in humans (Table 1). Studies are also lacking with respect to effects of melatonin on exercise-related vascular function, although one study in humans found a post-exercise systolic hypotensive effect after acute melatonin (2.5 mg) ingestion and intermittent exercise under modest heat stress [313]. Given the demonstrated antioxidant effects of melatonin in human and animal studies with exercise, future investigations should investigate potential ergogenic effects of chronic melatonin supplementation in athletes, along with any effects on skeletal muscle exercise adaptations in humans.

4.4.2. N-acetyl cysteine

N-acetyl cysteine (NAC) infusion was found to increase muscle GSH during fatiguing exercise in endurance-trained humans [316] and decrease GSSG while increasing post-exercise GSH/GSSG in muscle of healthy participants [19]. However, exercise-induced gene expression of SOD2 was attenuated in skeletal muscle with NAC infusion in healthy participants [317]. Despite these findings using infusion of NAC, there is a lack of evidence currently in human skeletal muscle using oral NAC supplementation. Acute NAC infusion was found to decrease mean arterial pressure during low intensity exercise in both active and sedentary older adults; although it had no effect during exercise in sedentary young adults [318]. In the same study, NAC infusion had no effect on exercise leg blood flow or vascular conductance in either young or older adults [318]. Acute oral NAC (70 mg/kg) also had no effect on brachial artery blood flow or tissue oxygenation indices during a sustained intense hand grip exercise in young healthy adults [319]. Study findings

in humans tend to favour an improvement in exercise performance following acute or chronic NAC supplementation (Table 1). Thus, NAC might be a beneficial supplement for endurance athletes. However, at least a few factors may limit the practical efficacy of NAC supplementation in athletes. Firstly, studies using performance tasks characteristic of real-world athletic events have yielded mixed results using NAC supplementation [327–329]. Second, NAC is not well tolerated at high doses, with potential dose-related side effects that mostly include gastrointestinal disturbance and metallic taste sensation; while anaphylactoid reactions have been reported rarely. Findings of Ferreira et al. [440] implicate an acute oral dose of 70 mg/kg as a threshold of intake to avoid adverse effects in individuals undertaking fatiguing exercise. However, it should be noted that there is evidence of improved tolerance with new flavoured effervescent formulations [441]. Thirdly, according to the 2020 World Anti-Doping Agency (WADA) Prohibited List, methods of intravenous infusion > 100 ml per 12 h period are banned [442], therefore potentially restricting intravenous NAC use in athletes.

4.4.3. Combined vitamin C and E

Studies using combined doses of 500 mg/day vitamin C and 400 IU/day E have shown no negative effects on the adaptive responses of skeletal muscle to endurance training in humans, such as increased mitochondrial proteins and antioxidant enzymes [443–445]. However, there are some human studies that have reported blunting of skeletal muscle adaptations to endurance training using 1 g/day vitamin C in combination with vitamin E [44,412,413]. Ristow et al. [44] reported 1 g/day vitamin C in combination with 400 IU/day vitamin E in humans attenuated mRNA responses in several markers of mitochondrial biogenesis and antioxidant enzymes following endurance training. Paulsen et al. [413] observed that following training in humans, the increase in COX IV protein abundance and the cytosolic (but not whole cell) levels of PGC-1α are attenuated with 1 g/day vitamin C combined with 260 IU/day E. Our group found that 1 g/day vitamin C in combination with 400 IU/day vitamin E in humans attenuates the increase in skeletal muscle TFAM protein abundance and SOD enzyme activity [412]. However, there were other skeletal muscle adaptations that were not attenuated, such as increased CS activity [412]. Collectively, there appears to be convincing evidence that 1 g/day vitamin C in combination with vitamin E in humans hampers some skeletal muscle adaptations to endurance training. Despite these effects, there is no evidence from these studies that combined 1 g/day vitamin C and vitamin E supplementation prevents improvements in VO_2 max or endurance performance in humans. A recent systematic review appears to confirm an absence of performance-modulating effects of vitamin C and/or E on these outcomes in adults [446].

A combination of 500 mg/day vitamin C and 1200 IU/day vitamin E was found to enhance the rate of recovery of maximal knee extensor voluntary isometric contraction force after intense repetitive fatiguing eccentric knee extension exercises in humans [447]. In contrast, another study in young healthy adults found that chronic supplementation of combined 1g/day vitamin C and 400 IU/day vitamin E did not alter recovery of muscle function or muscle damage markers following an acute damaging exercise bout in trained or untrained individuals [448]. There is currently a lack of clear evidence to support the use of combined vitamin C and vitamin E for athletic performance. A lack of clear effects observed could relate to poor direct *in vivo* redox-modulating effects of vitamin C and vitamin E during exercise [45]. However, given some potential hampering effects on skeletal muscle adaptations, it might be advisable to avoid this supplementation strategy during extended periods of training that induce adaptations.

4.5. Antioxidant minerals

4.5.1. Selenium

Limited studies in humans have shown decreased exercise-related serum lipid peroxidation markers in overweight participants with low selenium (Se) levels [330]. Effects of Se supplementation on antioxidant concentrations are mixed in humans (Table 1). There have only been limited investigations of Se supplementation on exercise performance in humans and animals, with no beneficial effects shown in humans [331]. Studies investigating effects of Se supplementation in combination with exercise training on mitochondrial biogenesis have shown mixed findings in humans (Table 1). A recent systematic review that investigated 5 studies of Se supplementation on exercise effects concluded that there is some evidence that Se supplementation may blunt some muscle mitochondrial adaptations to exercise; although Se supplementation might also decrease post-exercise (systemic) oxidative stress in overweight individuals with lower Se levels [337]. The systematic review also concluded that there is a current lack of studies that have looked at clear effects of Se supplementation on performance outcomes. Thus, at present evidence is not supportive of Se supplementation in athletes. There is currently limited evidence available on effects of selenium supplementation with exercise in humans. However, given the potential of hampering of some exercise adaptations along with possible safety issues at high oral doses [449,450], Se supplementation is not currently recommended for athletes.

4.5.2. Zinc

Limited evidence available in humans shows some beneficial effects of zinc (Zn) supplementation on systemic markers of exercise-induced oxidative stress (Table 1). Zn supplementation in rodents (injected IP) was found to increase GSH concentration but have no effect on muscle lipid peroxidation in skeletal muscle [451]. There have been limited studies of Zn supplementation on endurance performance in humans (Table 1). A recent systematic review [337] summarized 9 studies involving Zn supplementation and athletic performance. The review concluded inconsistent findings linking Zn supplementation to changes in VO_2 max and athletic performance. It was concluded in the review that it is unlikely that Zn as a standalone supplement will contribute to improved athletic performance. It should be noted however, that few studies have directly assessed the effects of Zn supplements on athletic performance outcomes without the concomitant intake of other nutrients or antioxidant compounds. There is currently limited supportive evidence to recommend Zn supplementation in athletes.

4.6. Personalised antioxidant supplementation

Based on our discussion it is apparent that there is currently limited supportive evidence for the use of antioxidant supplements in athletes and otherwise healthy exercisers to enhance recovery or performance. However, there may be circumstances relevant to an individual that may warrant targeted antioxidant supplementation approaches. If an athlete is deficient in a particular micronutrient (e.g. vitamin E, C, zinc or selenium), then supplementation might be appropriate to restore redox homeostasis and subsequent exercise capacity [452]. A recent study found that NAC supplementation (1200 mg twice daily for 30 days) improved glutathione status, VO_2 max and exercise performance in individuals with low (but not moderate or high) baseline erythrocyte glutathione concentrations [453]. Along with these restorative functional improvements, decreases in markers of oxidative stress and increases in some markers of antioxidant activity were also reported [453]. Further work needs to be done in this area, and a detailed discussion of personalised antioxidant strategies is beyond the scope of this review. However, interested readers are directed to a recent review on this topic [454].

4.7. Summary

The current review paper has provided a discussion on endurance exercise-related redox signalling and the subsequent adaptations in skeletal muscle and vascular function. It has also summarized the

impact of supplementation with diverse antioxidant compounds on these exercise-related outcomes, in addition to endurance performance. Overall, there is a lack of supportive evidence for most compounds reviewed to recommend to athletes (Table 2). A lack of effects for some antioxidants reviewed might relate to their inability to exert direct and potent redox-modulating effects *in vivo*; while for others, evidence on performance-related outcomes and knowledge of their redox-modulating effects *in vivo* is currently scarce.

Declaration of competing interest

The authors have none to declare.

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Appendix A. Supplementary data

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