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Antioxidant System Interventions for Enhancing Spinal Health in Astronauts and Terrestrial Workers

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Abstract *Nutraceutical (NIs) and Environmental (EIs)* antioxidant systems are reviewed toward reducing *Excessive Reactive Oxidative Species* (E-ROS) and *associated Spinal Maladies.* Spinal *discs, muscles, and nerve*s are adversely impacted by E-ROS. Such impacts arise – esp. with prolonged static disc loadings – from E-ROS reduced erythrocyte (RBC) flexibilities and required "foldings" for RBC passage through capillary bores smaller than their breadths. With apoptotic potential, this can block: *1) Delivery of required O_2, nutrients, hormones etc., 2) Removal of CO_2 and other waste products (esp,, inflammatory substances promoting local, if not general E-ROS*). Given this cascade, NIs (e.g., Vitamin C and ORP-reducing *Probiotic*s) have been recommended to address E-ROS. Of these, "nutritionals" have dose limitations (e.g., diarrhea for Vit. C). EIs include *Negative-ion air, H^+Water (neg. ORP), H_2-*gas and *H_2-*saline. EIs and NIs altogether offer a wide-spectrum of interventions toward addressing E-ROS. Recommended is research to optimize EI&NI mixes toward optimal spinal health.

Keywords: Spinal Health, Reactive Oxidative Species (ROS), RBC Inflexibility, Impaired Capillary Flow, Environmental & Nutraceutical Interventions (NIs &EIs)

1. INTRODUCTION

1.1 Overview

This report reviews two systems of antioxidant interventions – *Nutraceutical (NIs) and Environmental (EIs)* – and outlines their potential for reducing spinal maladies in at-risk populations: *astronauts and earth-bound workers*. In the body of this section, we will focus on the scope of spinal issues in these two populations. This will set the stage for later sections where: (2.0) Reactive Oxidative Species (ROS) is defined and its positive and negative roles overviewed, (3..0) Antioxidant System Interventions (ASIs) delineated; and (4.0) Research Opportunities and Recommendations Considered.

1.2 Spinal Maladies in Astronautic and Terrestrial Workers

Terrestrial and astronautic worker communities both suffer from substantial levels of disc and other back-related maladies that arise under gravitationally opposite environments (Yurube et al, 2023; Dasgupta et al., 2022). Regarding terrestrial workers, Yurube et al. (2023) note that Low back pain (LBP) is associated with 4-5% annual days-lost-work. The most common reason for worker's disability in the USA, LBP altogether represents a socioeconomic burden up to $102.0 billion/year. The proximate report of LBP – Yurube et al. note – is largely nonspecific; however, *intervertebral disc degeneration* (IDD) has been identified as the main risk-factor for disabling LBP. Terrestrial IDD, as shown by Williams and Sambrook (2011), is especially associated with occupational exposures (i.e., heavy lifting, prolonged heavy physical work, etc. which occasion).

Regarding astronauts, Dasgupta et al. (2022) note that they tend to experience increasing disc and paraspinal muscle degeneration under microgravitational reduced spinal loading patterns (as experienced in space). In this regard, Bailey et al.

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(2022) found half of 12 astronauts – studied pre- and post-space-flight for 6 months – experienced lumbar disc profusion, decreased muscle quality of the multifidus, and decreased lean muscle mass. Additionally, Bailey et al. (2022) found a decreased range of motion in flexion and extension of the lumbar spine, as well as fixed end-plate pathology in the upper lumbar spine. Not surprisingly, LBP was experienced on earth-return as the muscles – supporting the lumbar spine – were not properly maintained in space. Further, herniated discs – due to torn nucleus pulposus – have long been reported in astronauts, especially while returning from their mission (Johnston et al., 2010; Saysom et al., 2013). Dasgupta et al. (2022) recently suggested that the precise pathology of LBP in microgravity is unknown; albeit, others might suggest it arises from relatively static disc loadings (Chan et al., 2011) and consequent interstitial fluid changes and bone cell responses in microgravity (Wei et al., 2022). These, it is noteworthy, would have overlap with the demonstration of disc degeneration under E-ROS (Suzuki et al., 2015).

We consequently later posit (Sec 2.1) that profound disc and other spinal derogations are the result of a cascade of E-ROS impaired spinal tissue microcirculations that especially occurs under static disc-loading, heavy work conditions normo-gravity and unloaded microgravity space conditions (Chan et al., 2011; Williams & Sambrook, 2011; Gómez et al., 2021).

2 REACTIVE OXIDATIVE SPECIES (ROS)

ROS arises during oxidative-metabolism but can be exacerbated by *infective and toxic agents, use and injury related inflammation, and age-related physiological changes, as well as reportedly Low-G effects directly at the cellular level* (Mohanty et al., 2014; Patel et al, 2018; Gómez et al., 2021). As Patel et have recently overviewed, ROS plays a two-sided role in the body. On the one hand, ROS is imperative for redox homeostasis, as well as proper function in the cardiovascular and immune systems. Hence, the body requires a balance in its ROS levels for homeostasis. If, on the other hand, the level of ROS exceeds that which the body can handle (i.e., "E-ROS"), then oxidative stress occurs with progressively adverse impacts (Bittner & Sakuragi, 2006; Liemburg-Apers et al., 2015; Patel et al., 2018; Raposo et al., 2021). E-ROS's adverse impacts – as addressed in the next section – will be seen to be both: (1) Near-term on: performance (cognitive and physical), stressor resistance, and perceived wellbeing (Bittner & Sakuragi, 2006) , and (2) Longer-term regarding a remarkable spectrum of cardiac, vascular, renal, metabolic, neuropsychiatric, and other diseases (Patel et al., 2018; Raposo et al., 2021).

2.1 E-ROS Impacts on Blood Flow and Microcirculation

Bittner and Colleagues – toward identifying antioxidant systems – summarized research showing that E-ROS both serves to: (1) Reduce RBC flexibility and consequently (2) Impair, if not block, blood flow through capillary bores smaller than RBC breadths (Bittner & Sakuragi, 2006; Bittner, Croffut et al., 2007). These, as they pointed out, would impact serviced-tissue with disruptions to: *1) Deliveries of required O_2, nutrients, hormones etc., 2) removal of CO_2 and other waste products (including inflammatory substances that promote high-levels of local, if not general ROS*). Not addressed by Bittner and colleagues – as beyond their scope – were the long-term implications of such servicing disruptions. These longer-term disruptions could ultimately lead to a spectrum of spine and other pathological conditions in both astronauts and terrestrial workers (e.g., Patel et al., 2018; Gómez et al., 2018; Raposo et al., 2021).

2.2 Adverse Spinal Tissue Impacts

E-ROS – considering the above – might be anticipated to present specific risks to spinal tissues: *Disc; Nerve; and Muscles(Paraspinal and Other).* Regarding the avascular discs, Suzuki et al. (2015) were remarkably early in both 1) demonstrating that E-ROS induced intervertebral disc degeneration (IDD) and 2) in suggesting use of "therapeutic targets" for addressing IDD (e.g., nutritional antioxidants as delineated in Sec. 3.0). Feng et al. (2017) and Cao et al. (2022) – building on Suzuki et al. – progressively amplified on the interactions that accelerate the rate of IDD (i.e., in keeping with earlier noted E-ROS and inflammation feedbacks noted above). Among IDD progressive effects is an associated peripheral neuropathy, leading to pain, weakness, and nerve-damage associated numbness. In turn, paraspinal muscle atrophy – not surprisingly – may occur in the afflicted via reduced physical activity; though. atrophy may more directly be induced by E-ROS (Steinbacher & Ecki, 2015; Lian et al., 2022). In sum, E-ROS clearly plays significant roles in a cascade toward spinal tissue pathologies, especially IDD.

3. ANTIOXIDANT SYSTEM INTERVENTIONS (ASIs)

Antioxidant systems (ASIs) are a primary means for addressing E-ROS. In this regard, Vitamin C is a very familiar "nutritional" component of the Nutraceutical Interventions (NIs), which also include the oft overlooked transformative probiotics. Most generally missed among ASIs (e.g., Gómez et al., 2021; Cao et al., 2022) are the various Environmental Intervention (EIs). The breadth of the ASIs (NI and EI) are delineated in the following, building on the earlier review by Bittner and Sakuragi (2006).

3.1 Nutraceutical Antioxidant Interventions (NIs)

Nutraceutical antioxidants (NIs) – as delineated below -- may be classified into two categories: Nutritional Supplements (3.1.1) and Probiotics (3.3.2).

3.1.1 Nutritional Supplements

These include Vitamin C and other nutritional supplements already identified for addressing E-ROS respectively in both astronauts (Gómez et al. 2021), and terrestrial workers (Suzuki et al., 2015; Cao et al., 2022). 'Nutritionals" unfortunately often have limited applications, given side- and adverse-effects at high-doses (as noted earlier). Among nutritionals – beyond vitamins – are previously-studied cellular glutathione (GSH) promoters, e.g., N-Acetyl-Cysteine (NAC). Regarding exercise induced E-ROS, Kerksick and Willoughby (2005) early proposed a therapeutic role of NAC. More directly, Cao et al. (2022) report specific evidence that NAC – promoting cellular GSH – addressed the adverse aspects of IDD. Not considered by Cao et al – though separately established – is the possible in-place refurbishment of oxidized cellular GSH – thereby extending its efficacy (e.g., via earlier noted Vit. C or the later addressed EIs). Regarding this possibility, Bittner and Sakuragi (2006) earlier reported sustained increases >10% in aerobic capacity for 1.5 hours periods with a combination of efficient cysteine sources and Vit. C (TAS-α^{TM}). This was not surprising as the augmenting combination of NAC and Vitamin C had been previously demonstrated in different regards (e.g., Neri et al., 2005). These results anticipate broader – and prospectively more impactful – NI+EI augmentations as discussed later (Sec. 3.3)

3.1.2 Probiotic Supplements

Probiotic products – microbiome supplements – can serve as "transformational antioxidants" (Bittner & Sakuragi, 2006). Such antioxidants have been recently confirmed to: 1) Reduce E-ROS and 2) Protect muscle and other tissues (e.g., Daliri et al., 2016; Vasquez et al., 2019; Vignuad et al, 2023). Of heightened recent interest, this transformative aspect was suggested in a body of much earlier research (e.g., Philip, 1997; Kawakami et al., 1998). Philip (1997), in particular, noted the antioxidant aspect, whereas Kawakami et al. (1998) – building on this – reported a remarkable (23%, $p<0.05$) increase in 0_2-uptake after two weeks probiotic use. Toward understanding the mechanism-of-action (MOA) underlying these early results, Bittner and Sakuragi (2006) – exploring a probiotic product (Prescript-Assist^{TM}) – reported: (1) In-vitro ORP reductions in a water: molasses (10:1) solution from +230mv (0 Hrs.) to +30mv (16Hrs) in non-optimized conditions, and (2) More optimized reductions to -150mv by other researchers. This transformative antioxidant activity – given later experience with high neg. ORP water (Bittner, Lile et al., 2007) – currently is believed to be responsible for a linear $r= -.99$ ($p<.007$) decrease in "General Ill Feelings" ["i.e. , increased " Well-Being"] seen weeks after disease sub-syndromes ceased in IBS patients (Bittner et al. , 2006). One of us (AB) was – limited only as the assessment scale floored out – able to track this continuing trend for a few months beyond previous reports (Bittner, Croffut et al., 2007).

NIs – nutritional and probiotic – altogether have potential for reducing E-ROS, enhancing microcirculation, and supporting the health of skeletal and other tissues.

3.2 Environmental Interventions (EIs)

EIs – surprisingly ignored as noted earlier – offer a qualitatively different means for addressing E-ROS than the nutraceuticals. Previously noted, Bittner and Sakuragi (2006) identified EIs that – in addition to increasing the RBC flexibility and microcirculation – evidenced common positive patterns re: Performance, Stressor Resistances, and Wellbeing. These included: (1) *Negative-ion air; and* (2) H^+*Water* (with effects paralleling H_2*-Gas*).

3.2.1 Negative Ion Air (NIA).

NIA research – indicating antioxidant capabilities – was very early shown to increase performance, stressor resistance, and wellbeing (e.g., Halcomb & Kirk, 1965; Ryushi et al., 1998, Tom et al., 1981). Later studies – as reviewed by

Bittner and Sakuragi (2006) – supported NIA's antioxidant effects, with Iwama (2004) classically demonstrating increased flexibility of stressed erythrocytes (RBCs). Xiao et al. (2023) – in their contemporary review and research – have shown that negative-ion air is broadly *antioxidative, anti-inflammatory, and antiapoptotic* (i.e., supportive of Iwama, 2004 and Bittner & Sakuragi, 2006).

3.2.2 Molecular Hydrogen (MH^2)

H+Water (H^2-enriched water) – with antioxidant capabilities paralleling NIA – was also early shown to increase *performance, stressor resistance, and wellbeing* (Bittner & Sakuragi, 2006; Bittner, Lile et al., 2007). This again was not surprising given an earlier 4-week study that revealed substantial (25%, p = 0.02) reductions in blood *Lipid Peroxide*, an indicator of ROS (Yonei, 2006). Recently, the antioxidant properties of H^+Water have been extended to other MH^2 therapeutics. Specifically, Alwazeer et al. (2021) have – given broad therapeutic commonalities – collectively included among "molecular hydrogen" therapeutics: H^2 gas, H^2-enriched water (H+Water) and H^2-infused-saline (respectively delivered via inspiration, drinking, and IV). Paralleling Xiao et al. (re. NIA), Alwazeer et al. summarized the therapeutic effects of MH^2 to also include: *antioxidative, anti-inflammatory, and antiapoptotic* (i.e., in keeping with Abisso et al., 2020; Bittner & Sakuragi, 2006; Bittner, Lile et al., 2007).

3.3 Mixed Intervention Systems (NIs+EIs)

Mixed antioxidant system interventions offer a remarkably wide-spectrum of prospective combinations to address E-ROS – as portrayed in Fig. 1 (Bittner & Sakuragi, 2006). Perhaps not surprisingly, a few researchers have already begun to touch upon some of the mixed possibilities across NIs and Eis (Vorobjeva, 2005; Million, & Raoult, 2018; Ostojic, 2021). Among these, Vorobjeva (2005) argues that H^+Water (its Neg. ORP) selectively stimulates the growth of commensal anaerobes in the GI tract (with reduced E-ROS associated impacts). Supporting this, Million and Raoult (2018) also report that 1) Vitamins and other "nutritionals" can stimulate the "commensals" and 2) these in-turn may favorably alter the gut's redox and thereby further increase their dominance (and antioxidant capabilities). This latter favorable redox alteration, we note, is in keeping with our earlier discussion of the transformable-nature of probiotics (Sec. 3.1.2). Ostojic's (2021) review – in addition to a unifying focus on H^2 – broadens the span of supporting research (albeit, surprisingly misses the role of H^+Water's Neg. ORP in increasing the commensals and thereby their production of molecular H^2).

These initial studies – limited to only one NI-EI combination (probiotic and H^+Water) – already demonstrate the prospective synergic effects of mixed antioxidant interventions to address E-ROS and associated spinal maladies.

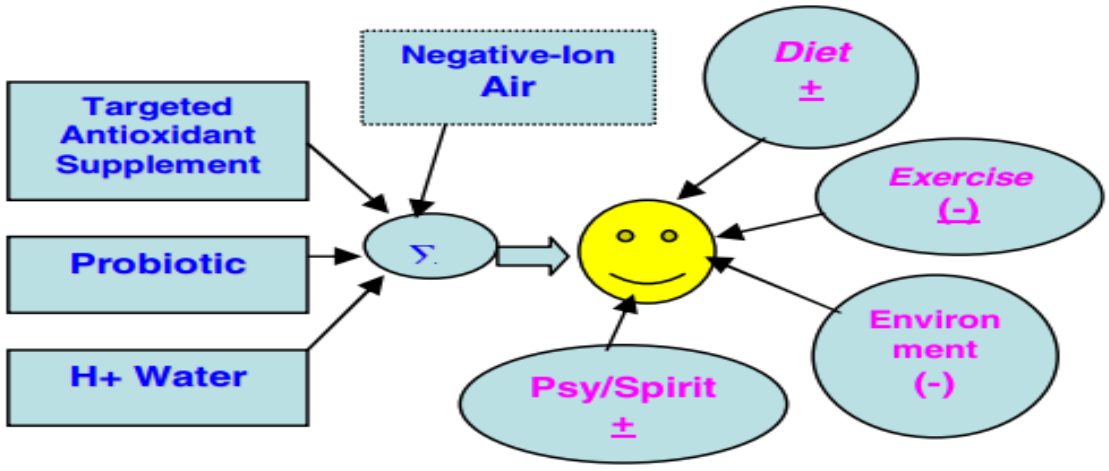

Figure 1. Antioxidant Systems (NIs+EIs) Combinations to Achieve Ideal ROS Balance

4. RESEARCH OPPORTUNITIES AND RECOMMENDATIONS

Nutraceutical (NIs) and Environmental (EIs) antioxidant systems – as reviewed herein – clearly point toward research to address spinal maladies in astronautic and terrestrial populations. Arguably – on a basic level toward subpopulation optimizations – evaluations of the individual and combined pharmacodynamics would appear of early interest (esp. speed and extent of E-ROS reductions). H^+Water, for example, has demonstrated effects within minutes (Bittner et al., 2007), but there are obvious limitations on daily consumption. Alternatively, probiotics may take several days to show effects (cf., Vorobjeva, 2005; Ostojic, 2021), but then they represent a long-continuing antioxidant; as well as offering ancillary gastric disease protections (Bittner et al., 2005; 2006). Impacts on spinal maladies also would appear an especially early target (though some researchers might be diverted toward the spectrum of E-ROS associated cardiac, vascular, renal, metabolic, and other diseases.) In any case, spinal maladies arguably could be explored in selected worker groups where both emergent LBP and associated ROS could be efficiently tracked across under different antioxidant system mixes. Terrestrial populations with medically identified early LBP issues – e.g., manual-handling and/or seat-bound workers – would appear very promising initial populations. In such initial studies, we would recommend co-evaluative inclusion of "stretch maneuvers" (e.g., 6 identified by Harvard Health, 2023) that jointly serve to encourage participant movement, beneficial dynamic disc loading patterns and altogether facilitate NI & EI antioxidant spinal microcirculations. Astronautic evaluations – informed by terrestrial NI&EI results – could shortly follow but with anticipatable stretch-maneuver changes to affect movement and disc loading patterns in light of the microgravitational vas terrestrial issues (Dasgupta et al., 2022)

It is recommended that future research – aided by recently advanced ROS assessment technologies – explore the optimal roles for combined EI-NI interventions on spinal health in at risk terrestrial and astronautic populations.

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