



Review Article

Antioxidant Countermeasures for Oxidative Stress in Spaceflight and Terrestrial Environments

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Abstract

Oxidative stress (OS) occurs when the body produces more reactive oxygen species (ROS), commonly known as free radicals, than its natural antioxidant defenses can effectively neutralize. When this imbalance persists, it can damage cells and tissues, contributing to the development of various chronic diseases. These highly reactive molecules can affect important cellular components such as lipids, proteins, and DNA, disrupting normal biological functions. On Earth, oxidative stress is often linked to factors such as environmental pollution, exposure to ultraviolet (UV) radiation, unhealthy diets, smoking, and other lifestyle habits that increase free radical production. The challenge becomes even greater in space. Astronauts are exposed to conditions far more extreme than experienced on Earth, including microgravity, prolonged isolation, disrupted sleep cycles, and intense exposure to ionizing cosmic radiation. Together, these factors place additional stress on the body, increasing the likelihood of mitochondrial dysfunction, reduced cellular repair capacity, and genetic damage. As a result, astronauts may face accelerated physiological changes that can affect multiple body systems during and after space missions. This study investigates how oxidative stress develops and influences human health in both terrestrial and spaceflight environments. It also investigates the efficacy of various preventative methods for reducing oxidative damage. Both enzymatic and non-enzymatic antioxidants receive specific attention, including naturally occurring antioxidant enzymes, vitamins, dietary flavonoids, polyphenols, and specialized nutritional supplements. Current research suggests that these measures can help reduce cellular damage, increase the body's defenses, and boost resilience under difficult situations. Understanding oxidative stress in normal and extreme environments allows researchers to design more effective techniques to safeguard human health. Advances in nutrition, biomedical sciences, and technology may give useful tools for reducing oxidative damage, improving long-term well-being, and enhancing human performance on Earth and in space.

Keywords

Oxidative Stress, Prooxidants, Spaceflight, Terrestrial Environments, Antioxidants

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1. Introduction

Oxidative stress (OS) is an imbalance between reactive oxygen species (ROS) and antioxidant defenses that disrupts redox signaling and regulation and causes molecular damage to lipids, proteins, and DNA, resulting in cellular injury. These changes cause the production of reactive oxygen species (ROS) [1]. These ROS are generated in great numbers, either as inevitable by-products of several metabolic processes or, in some cases, intentionally. In terrestrial habitats, exogenous stressors such as environmental contaminants, ultraviolet (UV) radiation, and lifestyle habits including smoking and unhealthy eating contribute to increased ROS production and chronic illnesses [2]. In Space, microgravity is one of the causes contributing to oxidative stress in astronauts. Other factors include disruption of cellular processes, inflammation, decreased mitochondrial function, changed fluid distribution, and increased radiation exposure. Cell damage, genetic alterations, and a higher risk of disease may result [3].

In healthy persons, antioxidants scavenge tiny levels of ROS, including hydroxyl radical (OH), superoxide (O_2^-), hydrogen peroxide (H_2O_2), and peroxynitrite (ONOO⁻). However, in pathological and extreme situations (e.g., space environment), the generation of ROS surpasses the capacity of antioxidants to neutralize them, resulting in OS [1]. Oxidative stress has been reported to be involved in many chronic and degenerative diseases in the terrestrial environment, such as atherosclerosis, coronary heart disease, diabetes mellitus, neurodegenerative disease (such as Alzheimer's and Parkinson's diseases), ageing, and cancer [4]. Fortunately, oxidative stress from free radicals can be mitigated by antioxidants [5]. Antioxidants operate by preventing or retarding chemical oxidation through the elimination of reactive species and by metal-ion chelation. Antioxidants are categorized into enzymatic and non-enzymatic groups working in extracellular and intracellular contexts to detoxify reactive oxygen species [6].

1.1. Space-specific Stressors

The combination of environmental variables to which the human body is exposed during spaceflight greatly increases the oxidative burden. A major contributor is exposure to ionizing radiation, like galactic cosmic rays (GCR) and solar particle events. These high-energy particles can penetrate spacecraft shielding and interact with biological tissues, producing reactive oxygen species (ROS) and inducing molecular and DNA damage [7, 8]. Unlike Earth's protection by its atmosphere and geomagnetic field, astronauts on long-duration missions are exposed to prolonged radiation, causing cumulative oxidative damage. Besides radiation, microgravity also changes cellular physiology in ways that favor redox imbalance. Decreased mechanical loading and changed fluid distribution decrease mitochondrial efficiency, resulting in increased electron leakage and ROS production [9]. These changes are linked to muscle atrophy, decreased bone density,

immune system abnormalities, and possibly neurocognitive consequences seen during long-duration missions [10]. These interconnected stresses together generate a distinctive oxidative environment associated with spaceflight.

1.2. Oxidative Stress in Spaceflight

Experiments in true microgravity are usually conducted during spaceflight, e.g., on rockets, on the ISS, or in parabolic flight. But space experiments are pricey, and work schedules limit the time frames for testing. Hence, experiments in simulated microgravity on the ground have become an important approach. The experimental techniques are performed in vivo and in vitro models mimicking microgravity. In vivo models include hindlimb unloading (HLU), bed rest, and long-duration dry immersion. There are other in vitro models, like the rotating wall vessels, random positioning machine, and 3D clinostat. Each has its own pros and disadvantages, and each approach has its own value [9].

1.3. Terrestrial Oxidative Stress Models

Oxidative stress is well known as playing a significant role in ageing and many chronic illnesses, such as cardiovascular disease, metabolic disorders, dementia, and osteoporosis on Earth [11]. Ageing is characterized by rapid mitochondrial dysfunction and reduced antioxidant capacity, making it a valuable biological model for the physiological decline found in astronauts. Environmental contaminants, UV light, and chronic inflammatory conditions significantly increase ROS generation in terrestrial populations [11]. Some of the harsh conditions on Earth also resemble aspects of oxidative stress in space. High-altitude exposure causes hypoxia-induced mitochondrial ROS production [7]. Exposure to radiation in medical or occupational settings provides insight into the effects of ionizing radiation encountered outside Earth's atmosphere. These terrestrial analogs enable controlled studies of oxidative processes and testing of antioxidant techniques before they are used in space missions. The intersection between Earth-based oxidative diseases and alterations generated by spaceflight adds translational value to this study.

1.4. Rationale for Antioxidant Countermeasures

The human body possesses endogenous antioxidant mechanisms controlled by enzymes (superoxide dismutase (SOD), catalase, and glutathione peroxidase) and regulatory networks like the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway that govern the redox status. However, breakdown of these protective systems may occur under prolonged or intense oxidative stresses [9]. Radiation exposure and metabolic

alterations during long-term space flight may surpass the capacity of endogenous defenses, leading to chronic cellular harm. Therefore, antioxidant preventive and therapeutic approaches are being examined to boost resistance to oxidative damage. Nutritional substances, such as vitamins C and E, polyphenols, and omega-3 fatty acids, and pharmaceutical

treatments, such as N-acetylcysteine and mitochondria-targeted antioxidants, have been shown to support redox stability [5]. The current study emphasizes the importance of optimizing endogenous defense systems rather than eliminating ROS, as they play critical signaling functions in cellular adaptation.

Table 1. *Classes of agents with Prooxidant properties. Reproduced from: [12].*

External stressors that induce OS	Mechanism of OS generation	Antioxidant Countermeasures
Air pollutants: ozone (O ₃), sulphur dioxide (SO ₂), cigarette smoke, nitrogen oxides (NO _x), particulate matter (PM)	Generate large amounts of superoxide, hydrogen peroxide, and hydroxyl radical, resulting in increased oxidative DNA lesions, Increased 8-isoprostane, 8-Hydroxy-2'-deoxyguanosine Inhibitory effects on oxidative stress-related enzymes, Inflammation	Catalases, glutathione peroxidases, peroxiredoxins, Vitamins C, E, GSH, beta-carotene, N-acetylcysteine, deferoxamine, and green tea extracts
Ionizing and non-ionizing radiation	Increased superoxide (O ₂) H ₂ O ₂ , singlet oxygen, peroxy radical, and hydroxyl radical (OH [•]) formation, Increased DNA damage and lipid membrane damage, Altered antioxidant defense systems, depletion of endogenous antioxidants	Melatonin, vitamin A, C, E, lycopene, L-selenomethionine, alpha-lipoic acid, N-acetyl cysteine, curcumin, green tea polyphenols, ginkgo biloba, L-carnitine, selenium, lutein, and pycnogenol
Pesticides: paraquat, organophosphorus insecticides, aldrin and dieldrin, DDT, polychlorinated dibenzo-para-dioxins (dioxins) and polychlorinated dibenzo furans (furans), polychlorinated biphenyls (PCBs)	Stimulation of free radical production, Alterations in antioxidant enzymes and the glutathione redox system, Decreased antioxidant defense, Increased level of malondialdehyde, lipid peroxidation, and DNA damage	Dietary flavonoids (epigallocatechin-3-gallate (EGCG) and quercetin, Vitamins A, C, E, Selenium, Lycopene, Melatonin, Zinc
Redox-active metals: iron, copper, chromium, vanadium, and cobalt	Reduced forms of redox-active metal ions participate in the Fenton reaction, where hydroxyl radical (HO [•]) is generated from hydrogen peroxide. The Haber-Weiss reaction, which involves the oxidized forms of redox-active metal ions and superoxide anion, generates the reduced form of the metal ion, which can be coupled to Fenton chemistry to generate hydroxyl radical.	Metal-chelating antioxidants such as transferrin, albumin, and ceruloplasmin avoid radical production by inhibiting the Fenton reaction catalysed by copper and iron.
Sport activity, excessive exercise	Increased ROS formation: Excessive amounts of superoxide, hydrogen peroxide, and hydroxyl radical	Increases in endogenous free radical defense systems by increasing muscle levels of SOD, glutathione peroxidase, and reduced glutathione (GSH)
Drugs: Analgesic (paracetamol) or anticancerous drug (methotrexate)	ROS generation	Increases in endogenous antioxidative and damage repair systems
Excessive psychophysical stressful situations	Increased catecholamine metabolism, which increases oxidative stress by increasing the production of free radicals. Emotional stress can diminish the effectiveness of the immune system, antioxidant system, and repair processes; it also increases biomarkers for oxidative stress.	Glutathione, relaxing techniques such as yoga
Water disinfection byproducts	ROS production (OH [•] , H ₂ O ₂ , and singlet O ₂)	Ascorbate, desferal, N-acetyl-cysteine Deferoxamine, green tea, catechins Melatonin, thioallyl compounds from garlic, Trolox, glutathione
Antioxidants: ascorbic acid, vitamin E, polyphenols	Act as a prooxidant under certain circumstances, for example, in the presence of transitional metals or in excessive amounts.	Increased activity of endogenous antioxidative and repair systems

2. Antioxidant Countermeasures

2.1. Endogenous Antioxidant Pathway Modulators

The glutathione system is a primary intracellular antioxidant defense, directly scavenging ROS and maintaining redox homeostasis [13]. Increased synthesis or recycling of glutathione may boost resistance to oxidative damage. Activation of the Nrf2 (nuclear factor erythroid 2-related factor 2) pathway has been shown to influence antioxidant enzyme production and can mitigate oxidative injury in preclinical models [14]. Pharmacologic activators and genetic therapies are among the options to change these pathways.

2.2. Nutritional and Dietary Antioxidants

Vitamins C, E, and A are key dietary antioxidants that neutralize free radicals and enhance immune protection [15]. Polyphenols and flavonoids are abundant in fruits and vegetables, and have antioxidant and anti-inflammatory properties via several mechanisms, including metal chelation and modulation of signaling pathways [16]. Omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to reduce oxidative stress by modifying membrane fluidity and inflammatory responses [17].

2.3. Pharmacological Antioxidants

Synthetic antioxidants, such as N-acetylcysteine (NAC), are precursors for glutathione production and directly scavenge ROS [18]. Mitochondria-targeted antioxidants, such as MitoQ, are designed to accumulate in mitochondria, the principal site of ROS formation, and thereby prevent mitochondrial oxidative damage [19]. These chemicals are being investigated for potential use in treating diseases related to oxidative stress.

2.4. Combined and Systems-Level Countermeasures

Exercise, when paired with antioxidant supplementation, has shown synergistic advantages, bolstered endogenous antioxidant defenses, and yielded improved physiological results [20]. Furthermore, the integration of nutritional and pharmaceutical antioxidants may yield additive or synergistic effects, necessitating additional investigation [21].

3. Evidence from Spaceflight and Analog Studies

3.1. Human Spaceflight Studies

Comparative assessments of short- and long-duration mis-

sions indicate elevated oxidative stress biomarkers over prolonged spaceflight, implying cumulative damage [22]. Biomarkers such as 8-oxo-2'-deoxyguanosine and malondialdehyde offer significant insights into oxidative damage to DNA and lipids, respectively [23].

3.2. Ground-Based Space Analogs

Bed rest investigations replicate microgravity effects, demonstrating heightened oxidative stress and reduced antioxidant levels [24]. Radiation simulation experiments employing gamma rays or heavy ions elucidate dose-dependent oxidative damage and evaluate countermeasure performance [25]. Individuals exposed to ionizing radiation, including radiology staff and nuclear industry employees, face heightened oxidative stress and related health hazards. To understand and mitigate these impacts, ground-based space radiation analogues, such as those developed at the NASA Space Radiation Laboratory, are used to replicate cosmic radiation exposure in controlled environments. These analogue systems facilitate the examination of radiation-induced oxidative damage and the assessment of preventative treatments, including antioxidant supplementation [26].

3.3. Animal and Cellular Models

Animal and cellular models offer mechanistic insights into oxidative stress pathways and dose-response relationships. Rodent models subjected to simulated microgravity and radiation exhibit mitochondrial dysfunction and oxidative damage, which can be alleviated by antioxidant interventions including vitamin C and E, polyphenols, and glutathione [27].

4. Translational Insights from Terrestrial Clinical and Environmental Studies

4.1. Antioxidants in Aging and Chronic Disease

Oxidative stress has been attributed to the pathogenesis of aging and chronic diseases like cardiovascular disease, neurodegeneration, and diabetes [11]. Antioxidant therapies have shown varying degrees of efficacy in clinical trials [28], highlighting the need for targeted approaches.

4.2. Occupational and Environmental Radiation Exposure

Occupational exposure to ionizing radiation is a recognized source of oxidative stress among workers in healthcare, nuclear power generation, industrial radiography, aviation, and research laboratories. Although strict radiation protection measures have significantly reduced exposure levels, chronic

low-dose ionizing radiation can continuously generate reactive oxygen species, resulting in cumulative cellular damage over time. These ROS oxidize lipids, proteins, and nucleic acids, thereby disrupting normal cellular function and contributing to inflammation, genomic instability, accelerated aging, and an increased risk of cancer and cardiovascular diseases [29].

Healthcare professionals, particularly radiologists, radiographers, nuclear medicine technologists, and interventional cardiologists, are among the occupational groups most frequently exposed to ionizing radiation. Similarly, employees in nuclear power plants, uranium mining, and industrial radiography facilities may experience prolonged radiation exposure despite compliance with established safety regulations. Environmental radiation exposure may also occur through naturally occurring radioactive materials, radon gas, medical procedures, or following nuclear accidents. Although environmental exposure levels are generally much lower than occupational doses, long-term exposure can still contribute to oxidative stress and adverse health outcomes [29].

The biological effects of ionizing radiation are primarily mediated through the radiolysis of water molecules, which produce highly reactive free radicals such as hydroxyl radicals ($\bullet\text{OH}$), superoxide anions ($\text{O}_2\bullet^-$), and hydrogen peroxide (H_2O_2). These reactive species can overwhelm endogenous antioxidant defense systems, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), leading to oxidative stress when antioxidant capacity is exceeded. Persistent oxidative stress has been linked to DNA strand breaks, chromosomal abnormalities, mitochondrial dysfunction, inflammation, and impaired immune function [29].

Because oxidative stress plays a central role in radiation-induced tissue injury, antioxidant supplementation has been investigated as a complementary strategy to reduce oxidative damage. Several experimental and clinical studies have evaluated antioxidants such as vitamins C and E, selenium, N-acetylcysteine, coenzyme Q10, and plant-derived polyphenols for their ability to scavenge free radicals, reduce lipid peroxidation, and protect cellular structures from radiation-induced injury [30, 31]. Although these studies have demonstrated promising radioprotective effects, evidence from large human occupational studies remains limited. Consequently, antioxidant supplementation should be regarded as an adjunct rather than a substitute for established radiation protection measures, including adherence to the ALARA (As Low as Reasonably Achievable) principle, appropriate shielding, personal protective equipment, exposure monitoring, and routine medical surveillance [30].

Overall, minimizing occupational and environmental radiation exposure remains the cornerstone of preventing radiation-induced oxidative stress. Nevertheless, nutritional strategies and antioxidant supplementation may provide additional protection by enhancing endogenous antioxidant defenses in individuals chronically exposed to low-dose ionizing radiation.

Future well-designed clinical trials are needed to establish the efficacy, optimal dosage, and long-term safety of antioxidant supplementation in radiation-exposed workers.

4.3. Knowledge Gap and Implications for Future Space Missions

Although antioxidant supplementation has shown promise in reducing oxidative stress biomarkers, the available clinical evidence remains inconclusive. Most human intervention studies are relatively short and are therefore unable to adequately assess their effects on chronic diseases such as cardiovascular disease and cancer, which typically develop over many years. Furthermore, many clinical trials rely on surrogate biomarkers of oxidative stress rather than comprehensive assessments of multiple physiological systems or long-term clinical outcomes, limiting conclusions regarding the overall health benefits of antioxidant supplementation [4, 6]. Variations in antioxidants and their doses, study duration and participant characteristics, as well as variances in study design, sample sizes, and measurement methods, further contribute to contradictory outcomes and make comparisons between studies challenging. Results from laboratory and animal research don't often apply to humans due to biological variances. This translational gap, along with the lack of long-term and multi-system evidence, makes it difficult to make inferences regarding the true influence of antioxidants on human health.

The variations in how astronauts respond to oxidative stress and in their antioxidant defenses suggest that a standard antioxidant treatment may be insufficient or even hazardous. Tailored approaches that target individual genetic makeup, baseline antioxidant capacity, and metabolic features may optimize protection while minimizing needless supplementation [32]. Such techniques may enhance resistance to radiation-induced DNA damage and oxidative stress resulting from microgravity [33]. The combination of space agriculture and personalized nutrition is essential to counteract oxidative stress during long-duration missions, as space-grown plants can provide antioxidant-rich phytonutrients like flavonoids and polyphenols. However, it is noteworthy that the profile of these plants can vary under space conditions, which may affect their protective capacity. Taking into account the effect of oxidative stress on multiple systems including immune, nervous, bone, muscle, vascular, and gastrointestinal systems, individualized antioxidant interventions should be combined with other countermeasures such as exercise, micronutrient supplementation, and microbiome regulation, especially as spaceflight may negatively influence the gut microbiome, which is crucial for antioxidant metabolism, nutrient absorption, and immune regulation [9, 32].

5. Conclusion

Antioxidant countermeasures for stress in spaceflight and terrestrial environments need to be considered in a broader

systems-based framework, especially for future long-duration missions to the Moon, Mars, or deep space, where astronauts are exposed to multiple simultaneous stressors, including microgravity, radiation, isolation, altered nutrition, sleep disruption, and sensory deprivation. These cumulative stressors impact virtually every physiological system, including cardiovascular, neurovestibular, musculoskeletal, immunological, metabolic, and psychological systems, leading to increased oxidative stress and cell damage. Therefore, antioxidant measures should not be used as a single intervention but should be part of personalized, multidisciplinary countermeasures, including nutrition, exercise, and other physiological support to effectively maintain health and performance under extreme conditions in space and comparable high-stress environments on Earth.

Abbreviations

OS	Oxidative Stress
ROS	Reactive Oxygen Species
UV	Ultraviolet
DNA	Deoxyribonucleic Acid
OH	Hydroxyl Radical
GCR	Galactic Cosmic Rays
HLU	Hindlimb Unloading
SOD	Superoxide Dismutase
NrF2	Nuclear Factor Erythroid 2
EPA	Eicosapentaenoic Acid
DHA	Docosahexaenoic Acid
NAC	N-Acetylcysteine
NASA	National Aeronautics and Space Administration
GPx	Glutathione Peroxidase
ALARA	As-Low-As-Reasonably-Achievable

Author Contributions

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Conflicts of Interest

The authors declare no conflicts of interest.

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Research Field

Zainab Ibrahim Suleiman: Space Biochemistry and Human health, Space Nutrition and Functional foods, Space Radiation Biology and Radioprotection, and Space Life Sciences

Otun Augustine Oko: Sustainable Agriculture, Space Physiology and Health, Aquaculture, Space Life Sciences, and Dairy and Feed Production

Aliya Ademu: Space Physiology and Health, Sustainable Agriculture, Agronomy, Controlled Environment Agriculture, and Crop production

Mariya Akilu: Space Human Physiology and Health, Space Medicine, Public Health and Epidemiology, Space Nutrition, and Space Life Science

Nebchukwu William Eneh: Clinical Biochemistry, Public Health, Environmental Health, Preventive Nutrition, and Environmental Management and pollution control

Munirat Usman: Space Life Sciences, Nutrition and Metabolism, Space Human Physiology and Health, Space Medicine, and Respiratory health

Ejura Nana Abu: Space Biomedical Sciences, Biomedical toxicology, Environmental sustainability, Ecotoxicology, and Environmental Health

Muhammed Babaminna Shuaibu: Medical Physics, Radiation Biophysics, Lower Atmosphere Studies, Space Physics, and Space Radiation Biology

Ifeanyichukwu Emmanuel Ezeh: Space Microbiology, Public Health, Epidemiology, Space Life Sciences, and Community Health