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Mitochondrial Dysfunction as a Convergent Mechanism in Spaceflight-Associated Pathology: Implications for Countermeasure Development

Leah F. Quinto, PhD[1], Ramon George Atento, PhD[2], William Dela Cruz, PhD[3], Charmaine O. Castañeda, MS Bio[4], Joel Morcilla, MSMLS[5]

[1]De La Salle Medical and Health Sciences Institute
[2]First Asia Institute of Technology and the Humanities
[3]Austin Independent School District, United States
[4]Adamson University, Manila
[5]Mayo Clinic, United States

Abstract

Long-duration human spaceflight exposes crews to chronic microgravity and elevated space radiation, producing interacting cellular stresses that affect multiple organ systems. This thematic analytical review examines mitochondrial dysfunction as a convergent mechanism linking these environmental stressors to spaceflight-associated pathology and evaluates the potential of mitochondrial-targeted countermeasures. Evidence from human and animal spaceflight missions, ground-based analogs, and mechanistic studies was synthesized across five areas: microgravity and radiation exposure, mitochondrial homeostasis, pathways of mitochondrial impairment, organ-specific manifestations, and emerging countermeasures. The reviewed evidence indicates that spaceflight conditions can suppress mitochondrial biogenesis, impair electron transport chain activity, increase reactive oxygen species production, damage mitochondrial DNA, and disrupt mitochondrial dynamics and quality-control processes. The causal evidence is strongest for skeletal muscle atrophy, where mitochondrial impairment appears to interact bidirectionally with unloading and proteolytic pathways. In neurological, ocular, and cardiovascular outcomes, mitochondrial dysfunction is consistently observed but remains one of several interacting mechanisms. Mitochondrial-targeted antioxidants, NAD+ precursors, and mitophagy-modulating agents demonstrate potential in terrestrial and ground-based models, although direct validation under actual spaceflight conditions remains limited. The findings support treating mitochondrial protection as a complementary strategic component of space biomedical countermeasure development. Priorities include in-space intervention studies, validated mitochondrial biomarkers, long-duration safety evaluation, combination-countermeasure testing, and assessment of individual susceptibility.

Keywords: *spaceflight; microgravity; space radiation; mitochondrial dysfunction; oxidative stress; biomedical countermeasures*

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1. INTRODUCTION

Human space exploration is entering a period in which missions beyond low Earth orbit are expected to become longer, more complex, and more operationally demanding. Proposed lunar surface operations, extended habitation in cislunar space, and eventual crewed missions to Mars will expose astronauts to physiological conditions that differ substantially from those encountered during shorter missions in low Earth orbit. Two of the most consequential environmental stressors are prolonged microgravity and space radiation. Microgravity produces mechanical

unloading, cephalad fluid redistribution, altered mechanotransduction, and changes in cellular architecture, whereas galactic cosmic radiation and solar particle events expose biological tissues to ionizing particles capable of producing complex molecular and cellular damage (Cialdai et al., 2023; Juhl et al., 2021; Wadhwa et al., 2024).

The biomedical consequences of spaceflight are distributed across multiple organ systems. Documented and anticipated effects include skeletal muscle atrophy, bone loss, cardiovascular deconditioning, neurovestibular disturbances, immune dysregulation, cognitive and behavioral changes, and ocular abnormalities associated with spaceflight-associated neuro-ocular syndrome. These conditions have commonly been investigated within organ-specific research programs, resulting in countermeasures directed toward particular physiological outcomes. Exercise is used to reduce musculoskeletal deconditioning, fluid-management protocols address orthostatic intolerance, and shielding strategies seek to limit radiation exposure. Although these approaches remain essential, an exclusively organ-centered framework may overlook molecular pathways that are shared across multiple spaceflight-associated pathologies.

Mitochondrial dysfunction has increasingly been proposed as one such convergent pathway. Mitochondria are responsible not only for adenosine triphosphate production through oxidative phosphorylation but also for the regulation of cellular redox balance, calcium signaling, apoptosis, metabolic adaptation, and innate immune responses. Their functional integrity is particularly important in tissues with high energy requirements, including skeletal muscle, cardiac muscle, neural tissue, and the retina. Because mitochondria respond to mechanical, metabolic, and radiation-induced stress, they are plausible cellular integrators of the combined environmental pressures experienced during spaceflight (Guaragnella et al., 2024; Nguyen et al., 2021; Rudolf & Hood, 2024).

Microgravity can disturb mitochondrial function through several interrelated mechanisms. Mechanical unloading alters cytoskeletal tension and mechanotransduction pathways, potentially affecting calcium handling, mitochondrial distribution, and signaling involved in mitochondrial biogenesis. Reduced activity of peroxisome proliferator-activated receptor gamma coactivator 1-alpha, a principal regulator of mitochondrial biogenesis and oxidative metabolism, has been associated with disuse and unloading conditions. These changes may reduce mitochondrial content, respiratory capacity, and the ability of cells to adapt to metabolic stress. In skeletal muscle, they can interact with proteolytic pathways and contribute to progressive losses in mass and function (Chen et al., 2023; Memme & Hood, 2021; Takahashi et al., 2024).

Space radiation can affect mitochondria through partially distinct but complementary pathways. Ionizing radiation damages cellular macromolecules, including mitochondrial DNA, proteins associated with the electron transport chain, and membrane lipids. Because mitochondrial DNA is located near major sites of reactive oxygen species generation and has fewer protective structures than nuclear DNA, it may be particularly vulnerable to oxidative injury. Damage to electron transport chain components can increase electron leakage and reactive oxygen species production, thereby producing a feedback cycle in which mitochondrial damage generates additional oxidative stress (Nguyen et al., 2021; Shimura, 2023).

The interaction between microgravity and radiation is especially important for long-duration missions. These stressors do not necessarily produce independent or merely additive effects. Microgravity-induced reductions in mitochondrial biogenesis, antioxidant defenses, or cellular repair capacity may increase susceptibility to radiation injury. Conversely, radiation-mediated damage may limit the capacity of cells to adapt to mechanical unloading. Combined exposure may therefore create heightened mitochondrial vulnerability in which oxidative stress, impaired energy production, disturbed mitochondrial dynamics, and defective quality-control mechanisms reinforce one another (Wadhwa et al., 2024; Xu et al., 2022).

Evidence of mitochondrial alteration has been reported across several spaceflight-relevant organ systems. In skeletal muscle, reductions in oxidative capacity and mitochondrial content have been associated with unloading, fiber-type transitions, fatigue, and atrophy. In neural tissues, mitochondrial oxidative stress and altered morphology have been linked in animal models to impaired synaptic function and neurocognitive outcomes. Ocular tissues may also be vulnerable because retinal ganglion cells have high metabolic demands and limited regenerative capacity. Cardiovascular tissues similarly demonstrate altered mitochondrial respiration and oxidative stress following spaceflight or simulated microgravity (Mair et al., 2024; Masarapu et al., 2024; Murgia et al., 2024; Waisberg et al., 2024).

These findings suggest that mitochondrial dysfunction may function as a convergent and amplifying mechanism rather than as an exclusive explanation for spaceflight pathology. The strength of causal evidence differs among organ systems. It is most developed in skeletal muscle, where mitochondrial impairment appears to interact directly with unloading and proteolytic signaling. In neurological, ocular, and cardiovascular conditions, mitochondrial dysfunction remains embedded within broader networks involving inflammation, altered circulation, fluid redistribution, neuroendocrine changes, and tissue-specific responses.

The possibility that mitochondrial dysfunction contributes to several spaceflight-associated conditions has important implications for countermeasure development. Existing countermeasures largely address organ-level consequences. A strategy that protects mitochondrial integrity could complement these approaches by targeting a shared upstream or intermediate mechanism. Candidate interventions include mitochondrial-targeted antioxidants, compounds that support NAD+ metabolism, agents that improve mitophagy, nutritional interventions, and combinations of pharmacological and exercise-based countermeasures (Faitg et al., 2024; Pedriali et al., 2022; Russo et al., 2022; Yusri et al., 2025).

Several scientific and translational gaps remain. Human spaceflight data are constrained by small samples, limited access to tissue specimens, differences in mission duration, and the difficulty of linking molecular biomarkers with organ-level outcomes. Ground-based analogs cannot fully reproduce the integrated spaceflight environment. Studies also vary substantially in species, exposure protocols, radiation type, dose, duration, tissue, and mitochondrial endpoints. Candidate interventions have generally been assessed individually, leaving the value and safety of combination countermeasures insufficiently examined.

A cross-system synthesis is therefore needed to determine whether mitochondrial dysfunction is sufficiently consistent, mechanistically plausible, and therapeutically actionable to merit greater prominence in space biomedical research. Such an analysis must distinguish evidence obtained from actual spaceflight from findings derived from analog and terrestrial models, evaluate differences in causal strength across organ systems, and assess the translational maturity of proposed interventions. This is particularly important because the duration and distance of future missions will restrict resupply, medical evacuation, and access to advanced clinical care.

Objectives of the Study

This thematic analytical review aimed to examine mitochondrial dysfunction as a convergent mechanism in spaceflight-associated pathology and to evaluate its implications for biomedical countermeasure development. Specifically, it sought to:

1. synthesize evidence from human and animal spaceflight missions, ground-based analogs, and mechanistic studies concerning the effects of microgravity and space radiation on mitochondrial function;
2. identify the principal pathways through which spaceflight stressors affect mitochondrial biogenesis, electron transport, reactive oxygen species production, mitochondrial DNA integrity, and mitochondrial quality control;
3. evaluate the strength of the evidence linking mitochondrial dysfunction to skeletal muscle, neurological, ocular, and cardiovascular manifestations of spaceflight;
4. assess the mechanistic rationale, current evidence, and translational maturity of mitochondrial-targeted countermeasures; and
5. identify research priorities necessary to determine whether mitochondrial protection should become a complementary strategic component of biomedical risk mitigation for long-duration human spaceflight.

2. REVIEW OF RELATED LITERATURE

2.1 Microgravity and Space Radiation as Interacting Biological Stressors

The spaceflight environment exposes the human body to a combination of physical and biological stressors that do not occur together under normal terrestrial conditions. Among these, prolonged microgravity and space radiation are major contributors to physiological deterioration during extended missions. Microgravity produces mechanical unloading, cephalad fluid redistribution, altered cellular architecture, and changes in mechanotransduction, whereas space radiation exposes tissues to high-energy charged particles capable of producing complex molecular damage (Cialdai et al., 2023; Juhl et al., 2021; Xu et al., 2022).

Microgravity affects cells partly through the loss of normal mechanical loading. Changes in cytoskeletal tension, integrin signaling, intracellular calcium regulation, and extracellular fluid movement can alter gene expression and cellular metabolism. Space radiation, by contrast, produces ionization events that can damage DNA, proteins, and membrane lipids. Galactic cosmic radiation is particularly concerning because it contains high-charge and high-energy particles that penetrate deeply into biological tissues.

The two stressors may interact. Microgravity-induced reductions in antioxidant capacity, cellular repair processes, or mitochondrial biogenesis may increase tissue susceptibility to radiation injury. Radiation-mediated damage may in turn limit the capacity of cells to adapt to mechanical unloading. Evidence from combined-exposure models suggests that their interaction can be additive or synergistic depending on the organ system, exposure sequence, dose, and biological endpoint (Wadhwa et al., 2024; Xu et al., 2022).

Actual mission data remain limited. Studies conducted aboard the International Space Station provide valuable evidence concerning the biological effects of microgravity and low-Earth-orbit radiation, but the radiation environment in low Earth orbit is less severe than that expected during lunar or Mars missions. Current evidence therefore supports the existence of interacting biological stressors, but the cumulative effects of long-duration deep-space exposure remain uncertain.

2.2 Mitochondrial Homeostasis and Cellular Stress Regulation

Mitochondria are central to cellular energy production and stress regulation. Their best-known function is the generation of adenosine triphosphate through oxidative phosphorylation, but they also regulate calcium homeostasis, redox signaling, apoptosis, metabolic adaptation, and innate immune responses (Guaragnella et al., 2024). These functions make mitochondria particularly important in tissues with high energy demands, including skeletal muscle, cardiac muscle, neural tissue, and the retina.

Oxidative phosphorylation occurs through the electron transport chain located in the inner mitochondrial membrane. During normal respiration, a small proportion of electrons escape from the transport chain and contribute to reactive oxygen species production. Under physiological conditions, these molecules function in cellular signaling and are controlled by antioxidant systems. Excessive production or inadequate removal, however, can damage mitochondrial proteins, membrane lipids, and mitochondrial DNA, thereby impairing respiration and increasing further oxidative stress (Kıran et al., 2023; Shimura, 2023).

Mitochondrial quality is maintained through coordinated processes of fusion, fission, biogenesis, and mitophagy. Fusion enables mitochondria to share functional components, while fission helps isolate damaged segments for removal. Mitophagy eliminates dysfunctional mitochondria, and mitochondrial biogenesis replaces damaged or insufficient organelles. Disruption of these processes can lead to the accumulation of poorly functioning mitochondria, reduced energy production, elevated oxidative stress, and activation of apoptotic or inflammatory pathways (Lei et al., 2024; Liu et al., 2024; Lü et al., 2023).

Peroxisome proliferator-activated receptor gamma coactivator 1-alpha is a major regulator of mitochondrial biogenesis and oxidative metabolism. Reduced activation of this pathway has been associated with disuse, muscle deconditioning, and impaired cellular adaptation. Conversely, exercise and electrical stimulation that support mitochondrial biogenesis may preserve mitochondrial content and metabolic flexibility (Memme & Hood, 2021; Takahashi et al., 2024).

The vulnerability of mitochondria varies across tissues. Post-mitotic cells such as neurons and cardiomyocytes cannot readily dilute damaged mitochondria through cell division, making efficient quality control essential. This tissue-specific variability is important because a mitochondrial disturbance that is partially reversible in skeletal muscle may produce more persistent effects in neural or ocular tissues.

2.3 Mechanisms of Spaceflight-Associated Mitochondrial Dysfunction

Evidence from actual missions, simulated microgravity, hindlimb unloading, and radiation models indicates that spaceflight-related stressors can impair mitochondrial structure and function through several converging pathways. These include reduced mitochondrial biogenesis, altered electron transport, increased oxidative stress, mitochondrial DNA damage, and disruption of fusion, fission, and mitophagy (Nguyen et al., 2021; Rudolf & Hood, 2024).

Mechanical unloading can reduce the metabolic demand placed on skeletal muscle and alter signaling pathways involved in mitochondrial maintenance. Experimental studies have reported reductions in mitochondrial content, oxidative enzyme activity, and respiratory capacity under unloading or spaceflight conditions. Changes in the skeletal muscle proteome following actual spaceflight also support altered oxidative metabolism and muscle-fiber remodeling (Murgia et al., 2024).

Space radiation can directly damage mitochondrial DNA and respiratory-chain components. Damage can interfere with the expression of mitochondrial respiratory proteins, reduce electron transport efficiency, and increase electron leakage. The resulting oxidative stress can further damage mitochondrial DNA and proteins, producing a self-reinforcing cycle of dysfunction (Nguyen et al., 2021; Shimura, 2023).

Mitochondrial responses have also been observed in neural and cardiac models. Spaceflight-related changes in the hippocampus include altered mitochondrial morphology and region-specific molecular changes associated with neuronal function (Masarapu et al., 2024). Heart-on-a-chip experiments conducted during spaceflight have demonstrated contractile and mitochondrial dysfunction, indicating that reduced gravity can affect both cellular metabolism and tissue-level performance (Mair et al., 2024).

Experimental models differ in species, exposure duration, radiation composition, simulated-gravity technique, and mitochondrial endpoints. Some studies measure gene expression, while others assess respiration, morphology, oxidative damage, or functional outcomes. Such heterogeneity complicates direct comparison. Nevertheless, the recurrence of mitochondrial abnormalities across models supports the conclusion that mitochondrial stress is a reproducible feature of spaceflight exposure.

2.4 Organ-Specific Manifestations of Mitochondrial Stress

Skeletal muscle provides the strongest evidence linking mitochondrial dysfunction with spaceflight-associated pathology. Mechanical unloading reduces muscle use, alters fiber composition, and contributes to losses in strength, endurance, and mass. Mitochondrial changes can intensify this process by reducing oxidative capacity and increasing reactive oxygen species, which can activate proteolytic and autophagic pathways associated with muscle degradation (Chen et al., 2023; Lei et al., 2024; Moosavi et al., 2021). The relationship is likely bidirectional: unloading reduces mitochondrial maintenance, while mitochondrial impairment accelerates muscle deterioration.

Neurological effects are more difficult to interpret. Animal studies indicate that radiation and spaceflight-related stress can produce oxidative damage, altered hippocampal function, and neurocognitive impairment (Alaghband et al., 2023; Simmons et al., 2022). Spaceflight studies in rodents also demonstrate molecular and structural changes in neural tissues (Masarapu et al., 2024). However, cognitive and behavioral outcomes are influenced by numerous factors, including sleep disruption, isolation, stress, inflammation, circadian changes, and altered sensory input.

A similar qualification applies to spaceflight-associated neuro-ocular syndrome. SANS includes optic disc edema, globe flattening, choroidal folds, and visual changes. Its pathophysiology is generally understood as multifactorial, with cephalad fluid shifts, vascular changes, altered intracranial pressure, and possible glymphatic dysfunction among the proposed mechanisms (Bateman & Bateman, 2024; Munster et al., 2024). Mitochondrial dysfunction has been proposed as an additional mechanism because retinal and optic-nerve tissues have high energy requirements and are vulnerable to oxidative stress. Animal studies reporting retinal mitochondrial alterations support this possibility, but direct human evidence remains limited (Mu et al., 2023; Waisberg et al., 2024).

Cardiovascular deconditioning is likewise associated with altered mitochondrial function. Spaceflight and simulated microgravity can reduce cardiac mitochondrial respiration, affect cardiomyocyte contractility, and contribute to oxidative stress (Baran et al., 2022; Han et al., 2024; Mair et al., 2024). However, orthostatic intolerance and reduced cardiovascular performance are also shaped by plasma-volume loss, vascular remodeling, autonomic adaptation, and fluid redistribution. Mitochondrial stress is therefore best interpreted as an amplifying mechanism that interacts with hemodynamic changes.

2.5 Mitochondrial-Targeted Countermeasures

The identification of mitochondrial dysfunction as a recurring feature of spaceflight-related pathology has encouraged interest in interventions that preserve mitochondrial structure, redox balance, and quality control. Candidate approaches include mitochondrial-targeted antioxidants, compounds that support NAD+ metabolism, mitophagy-modulating agents, exercise, and selected nutritional interventions.

Mitochondrial-targeted antioxidants are designed to accumulate within mitochondria and reduce oxidative damage at or near its principal source. MitoQ is a ubiquinone derivative linked to a lipophilic cation that promotes mitochondrial uptake. SS-31, also known as elamipretide, binds to cardiolipin in the inner mitochondrial membrane and may stabilize membrane structure and electron transport. These compounds have shown protective effects in several terrestrial models of mitochondrial and cardiovascular dysfunction (Pedriali et al., 2022; Russo et al., 2022; J. Yang et al., 2022; Q. Yang et al., 2022). Their relevance to spaceflight is mechanistically plausible, but direct evidence under actual spaceflight conditions is lacking.

NAD+ is required for cellular energy metabolism and for sirtuin-mediated regulation of mitochondrial biogenesis, stress responses, and antioxidant defenses. NAD+ precursors such as nicotinamide riboside and nicotinamide mononucleotide have therefore been proposed as interventions for preserving mitochondrial function (Yusri et al., 2025). However, evidence specific to spaceflight remains preliminary, and efficacy in terrestrial aging or disease models should not be treated as proof of in-flight benefit.

Mitophagy-enhancing compounds such as urolithin A and spermidine have also been proposed because they may improve the removal of damaged mitochondria and preserve mitochondrial quality (Faitg et al., 2024; Srivastava & Gross, 2023). These agents remain at an early translational stage in relation to spaceflight.

Exercise continues to be the most operationally established countermeasure for musculoskeletal and cardiovascular deconditioning. Its benefits include stimulation of mitochondrial biogenesis, maintenance of oxidative capacity, and support of muscle and cardiovascular function (Memme & Hood, 2021; Moosavi et al., 2021). A mitochondrial-centered approach should therefore complement rather than replace exercise-based protocols.

The principal limitations of the countermeasure literature are the lack of in-space pharmacological validation, uncertainty regarding long-duration safety, inadequate study of combined interventions, and limited knowledge of how microgravity affects drug absorption, distribution, metabolism, and efficacy. The current evidence supports further testing but not routine operational deployment.

2.6 Synthesis and Gaps in the Literature

The reviewed literature supports a coherent but qualified model in which mitochondrial dysfunction acts as a convergent mechanism linking microgravity, radiation exposure, and multi-system physiological deterioration. Across skeletal muscle, neural, ocular, and cardiovascular tissues, recurring findings include impaired mitochondrial respiration, elevated oxidative stress, reduced mitochondrial biogenesis, mitochondrial DNA damage, and altered quality-control processes (Mair et al., 2024; Masarapu et al., 2024; Murgia et al., 2024; Nguyen et al., 2021; Rudolf & Hood, 2024).

The evidence is not equally strong across organ systems. Skeletal muscle research provides the most direct support for a causal and bidirectional relationship between unloading, mitochondrial impairment, and tissue atrophy. In neural, ocular, and cardiovascular conditions, mitochondrial dysfunction appears contributory but coexists with inflammation, vascular changes, autonomic adaptation, fluid redistribution, and other tissue-specific mechanisms.

Several gaps remain. Human spaceflight studies are limited by small samples, restricted biospecimen access, and short mission durations relative to anticipated Mars missions. Ground-based analogs do not fully reproduce simultaneous exposure to microgravity and deep-space radiation. Evidence is also unevenly distributed across organ systems, with considerably more research devoted to skeletal muscle than to ocular and neural outcomes. Mitochondrial-targeted interventions have rarely been evaluated in actual spaceflight, and the safety and efficacy of long-duration or combination regimens remain uncertain.

The present review responds to these gaps by integrating evidence across biological systems and distinguishing direct mission evidence from analog and terrestrial findings. It further evaluates the extent to which mitochondrial dysfunction can serve not only as a mechanistic explanation but also as a strategic target for countermeasure development.

3. METHODOLOGY

3.1 Research Design

This study employed a thematic analytical review design to examine mitochondrial dysfunction as a convergent mechanism in spaceflight-associated pathology and as a potential target for biomedical countermeasure development. The design was appropriate because the available evidence was derived from heterogeneous sources, including human and animal spaceflight studies, ground-based microgravity analogs, radiation experiments, cellular models, mechanistic investigations, and terrestrial studies of mitochondrial-targeted interventions.

The review was designed to identify recurring biological patterns, compare the strength of evidence across organ systems, distinguish direct spaceflight evidence from analog and terrestrial findings, and integrate the literature into a coherent conceptual framework. It was not intended as a formal meta-analysis because the included studies differed substantially in research design, exposure protocol, species, tissue examined, radiation dose, mission duration, and mitochondrial outcome measures.

The study was not classified as a systematic review because complete systematic-review documentation, including record counts, duplicate-removal procedures, formal screening statistics, and risk-of-bias assessment, was not available. Instead, it used a structured literature-search and thematic synthesis process oriented toward conceptual and translational analysis.

3.2 Sources of Literature

The literature base included peer-reviewed journal articles, reviews, and mechanistic studies relevant to the effects of spaceflight conditions on mitochondrial structure and function. Priority was given to studies involving:

- human spaceflight participants;
- animals exposed to actual spaceflight;
- ground-based microgravity analogs, including hindlimb unloading, bed rest, clinostats, and random positioning systems;
- simulated or experimental space-radiation exposure;
- combined microgravity-radiation models;
- mitochondrial mechanisms in skeletal muscle, neural, ocular, and cardiovascular tissues; and
- mitochondrial-targeted interventions with potential relevance to long-duration spaceflight.

The primary databases identified in the original review were PubMed, Scopus, and Web of Science. Reference lists from relevant review articles and spaceflight-oriented publications were also examined. Greater evidentiary weight was assigned to peer-reviewed studies involving actual spaceflight conditions. Ground-based analog and terrestrial studies were used to clarify mechanisms or assess intervention feasibility but were not treated as equivalent to direct human or animal spaceflight evidence.

3.3 Search Orientation

The literature search used combinations of terms related to spaceflight exposure, mitochondrial biology, organ-specific pathology, and countermeasure development. Principal concepts included spaceflight, microgravity, simulated microgravity, galactic cosmic radiation, space radiation, mitochondria, mitochondrial dysfunction, oxidative stress, reactive oxygen species, mitochondrial DNA, mitochondrial biogenesis, PGC-1alpha, electron transport chain, mitophagy, skeletal muscle atrophy, cardiovascular deconditioning, neurocognitive impairment, spaceflight-associated neuro-ocular syndrome, MitoQ, SS-31, elamipretide, NAD+, nicotinamide riboside, and mitochondrial countermeasures.

The original search covered English-language publications issued from 2000 to 2025, with greater emphasis on studies from the most recent decade because of advances in space omics, commercial spaceflight biospecimen collection, organ-on-a-chip technologies, and mitochondrial-targeted therapeutics. The search strategy was intended to obtain a broad but relevant evidence base rather than exhaustive systematic-review coverage.

3.4 Eligibility and Source Selection

Studies were considered eligible when they provided evidence relevant to at least one of the following areas:

- biological effects of microgravity or space radiation;
- mitochondrial structure, respiration, biogenesis, dynamics, or quality control;
- mitochondrial oxidative stress or mitochondrial DNA damage;
- organ-level manifestations associated with mitochondrial impairment;
- interventions intended to preserve mitochondrial function; or
- translational considerations for long-duration human spaceflight.

Priority was given to original research articles that reported molecular, cellular, histological, physiological, or functional outcomes. Peer-reviewed reviews were retained when they provided useful synthesis, conceptual framing, or identification of major gaps.

Sources focused entirely on unrelated physiological mechanisms were not considered central unless they clarified an alternative explanation for a spaceflight-associated condition. Conference abstracts without sufficient methodological and results information, opinion pieces without supporting evidence, and sources with no clear relationship to mitochondrial or spaceflight-related outcomes were not considered adequate as principal evidence. Preprints and repository-based materials were excluded when stronger peer-reviewed publications were available.

3.5 Evidence Classification

To prevent evidence derived from different research settings from being treated as equivalent, the reviewed literature was interpreted according to a qualitative hierarchy. The highest level consisted of human spaceflight studies reporting mitochondrial, molecular, physiological, or clinical outcomes. These studies offered the greatest direct relevance but were frequently limited by small samples and restricted tissue access.

The second level consisted of animal studies conducted during actual spaceflight. These permitted tissue-level and molecular analyses that are difficult to perform in human astronauts, although interspecies differences limited direct clinical generalization. The third level included ground-based models that simulated microgravity, radiation, or both. These studies provided greater experimental control but did not fully reproduce integrated spaceflight conditions. The fourth level consisted of terrestrial mechanistic and intervention studies used to clarify pathways and assess candidate countermeasures.

This classification guided the interpretation of findings and the strength of the conclusions. Direct mission evidence was prioritized when available, while mechanistic and terrestrial evidence was used to explain biological plausibility and identify potential interventions.

3.6 Thematic Organization and Data Synthesis

The literature was organized into five themes derived from the principal components of the research problem:

1. microgravity and space radiation as interacting biological stressors;

2. mitochondrial homeostasis and cellular stress regulation;
3. mechanisms of spaceflight-associated mitochondrial dysfunction;
4. organ-specific manifestations of mitochondrial stress; and
5. mitochondrial-targeted countermeasures.

The themes represented a logical progression from environmental exposure to cellular mechanism, organ-level outcome, and intervention. Studies could contribute to more than one theme when their findings addressed multiple levels of analysis.

The synthesis was qualitative and comparative. Findings were examined for consistency across models, tissues, and exposure conditions. Particular attention was given to reduced mitochondrial biogenesis, altered electron transport and oxidative phosphorylation, increased reactive oxygen species, mitochondrial DNA damage, impaired fusion, fission, or mitophagy, reduced tissue function, and attenuation of pathology following mitochondrial-targeted intervention.

3.7 Evaluation of Causal and Translational Claims

Mechanistic claims were assessed by considering temporal sequence, biological plausibility, consistency, intervention response, and functional association. Evidence was considered stronger when mitochondrial impairment occurred before an organ-level pathological outcome, was reproduced across independent studies or models, was linked to a defined molecular pathway, correlated with functional deterioration, or was reduced by an intervention directed at mitochondrial function.

Claims based only on co-occurrence were interpreted as associative rather than causal. This distinction was especially important for neurological, ocular, and cardiovascular outcomes, where mitochondrial abnormalities coexist with inflammation, fluid redistribution, vascular changes, autonomic adaptation, and other mechanisms.

Countermeasures were evaluated according to their proposed mechanism, evidence of efficacy, relevance to spaceflight conditions, safety profile, and translational maturity. Interventions supported only by terrestrial disease models were regarded as promising but preliminary.

3.8 Ethical Considerations

The study involved no direct recruitment of human participants, intervention with animals, or collection of primary biological data. It relied exclusively on published literature. Institutional ethics approval and informed consent were therefore not required. Ethical responsibility centered on accurate representation of evidence, avoidance of fabricated or unsupported claims, clear differentiation between direct and indirect evidence, and acknowledgment of uncertainty where findings were limited or conflicting.

3.9 Methodological Limitations

The review was limited by the heterogeneity of the available literature. Studies differed in mission duration, simulated-gravity technique, radiation type and dose, species, tissue, age, sex, and outcome measurement. These differences prevented quantitative pooling and limited direct cross-study comparison.

Human spaceflight studies were relatively scarce and frequently involved small samples. Much of the mechanistic evidence was therefore derived from animal, cellular, or ground-based models. Although these models are valuable for investigating causal pathways, they cannot fully reproduce simultaneous and prolonged exposure to microgravity, radiation, isolation, altered circadian conditions, and operational stress.

The review may also have been affected by publication bias because studies reporting significant mitochondrial alterations are more likely to be published than studies reporting null findings. In addition, the absence of complete search and screening records prevented calculation of the number of studies identified, excluded, and retained.

Some candidate countermeasures were supported primarily by terrestrial aging, metabolic, cardiovascular, or neurological research. Their inclusion established biological plausibility but did not demonstrate efficacy or safety during actual spaceflight.

4. RESULTS AND DISCUSSION

The thematic synthesis produced three principal findings. First, microgravity and space radiation converge on several interdependent mitochondrial pathways, particularly mitochondrial biogenesis, electron transport, redox regulation, mitochondrial DNA integrity, and organelle quality control. Second, the strength of the association between mitochondrial dysfunction and organ-level pathology differs across physiological systems, with the most developed causal evidence observed in skeletal muscle. Third, mitochondrial-targeted interventions constitute a biologically plausible but operationally immature class of countermeasures because most supporting evidence derives from terrestrial or ground-based models rather than actual spaceflight.

4.1 Convergent Mechanisms of Spaceflight-Associated Mitochondrial Dysfunction

The reviewed evidence supports a model in which microgravity and space radiation affect mitochondria through distinct but interacting pathways. Microgravity primarily alters mechanical loading, cellular architecture, intracellular signaling, and metabolic demand. Radiation produces molecular injury through ionization, oxidative damage, and disruption of DNA and protein integrity. Although the initiating processes differ, both stressors converge on mitochondrial function and may reinforce one another under prolonged exposure (Nguyen et al., 2021; Rudolf & Hood, 2024; Wadhwa et al., 2024).

Mechanical unloading reduces normal stimulation of mechanosensitive pathways in skeletal muscle and other load-dependent tissues. Altered cytoskeletal tension and intracellular signaling may reduce pathways responsible for mitochondrial biogenesis and oxidative metabolism. The resulting decline in mitochondrial content and respiratory capacity can reduce energy availability and metabolic flexibility. In skeletal muscle, these effects coexist with reduced contractile activity, fiber-type remodeling, and activation of proteolytic systems associated with disuse atrophy (Chen et al., 2023; Lei et al., 2024; Moosavi et al., 2021).

Proteomic findings from actual spaceflight provide direct support for alterations in skeletal muscle metabolism. Murgia et al. (2024) reported changes in the skeletal muscle proteome of astronauts following International Space Station exposure, including modifications related to energy metabolism and muscle-fiber characteristics. Although the limited number of available astronaut specimens restricts generalization, these findings demonstrate that mitochondrial and metabolic alterations observed in analog studies are also detectable in human spaceflight.

Space radiation contributes through direct and indirect mitochondrial injury. Ionizing particles can damage mitochondrial DNA, electron transport chain proteins, and membrane lipids. Damage to respiratory-chain components reduces electron-transfer efficiency and increases electron leakage, thereby promoting reactive oxygen species formation. Excessive reactive oxygen species can further damage mitochondrial DNA and respiratory proteins, establishing a feedback process in which initial injury produces additional mitochondrial dysfunction (Nguyen et al., 2021; Shimura, 2023).

The convergence of microgravity and radiation is important because a cell with reduced mitochondrial biogenesis or antioxidant capacity may be less able to respond to radiation-induced damage. Conversely, radiation-related injury may impair the ability of the cell to replace damaged mitochondria or adapt metabolically to unloading. Combined-exposure studies therefore suggest that spaceflight stressors may produce effects that exceed those expected from either stressor in isolation, although the direction and magnitude of interaction vary according to the model and endpoint examined (Wadhwa et al., 2024; Xu et al., 2022).

Mitochondrial quality-control processes constitute another point of convergence. Fusion allows partially damaged mitochondria to exchange functional components, while fission separates damaged regions for removal. Mitophagy subsequently eliminates dysfunctional organelles. Disturbance of these processes can lead to the persistence of damaged mitochondria, reduced respiration, increased oxidative stress, and activation of inflammatory or apoptotic pathways (Lei et al., 2024; Liu et al., 2024; Lü et al., 2023).

Spaceflight-associated mitochondrial dysfunction is therefore not represented by a single lesion. It is a network-level condition involving reduced biogenesis, impaired respiration, oxidative injury, mitochondrial DNA damage, and inadequate removal of dysfunctional organelles. These processes interact bidirectionally and can potentially generate a self-reinforcing decline in mitochondrial quality. The current evidence supports a positive-feedback model but does not define a universal threshold at which mitochondrial impairment becomes irreversible.

4.2 Organ-System Evidence and Strength of Causal Inference

Mitochondrial abnormalities were identified across skeletal muscle, neural tissue, ocular structures, and cardiovascular systems. The consistency of these findings supports the concept of mitochondrial dysfunction as a cross-system feature of spaceflight exposure. Nevertheless, the strength of causal inference varies considerably among organ systems.

Skeletal Muscle

Skeletal muscle presents the strongest case for a causal relationship. Mechanical unloading reduces contractile demand and suppresses pathways involved in oxidative metabolism and mitochondrial maintenance. Reduced mitochondrial content and respiratory capacity can subsequently increase fatigability and oxidative stress. Reactive oxygen species and mitochondrial signaling may activate proteolytic pathways, including the ubiquitin-proteasome and autophagy-lysosome systems, thereby contributing to muscle degradation (Chen et al., 2023; Lei et al., 2024).

The relationship is not unidirectional. Reduced muscle use decreases metabolic demand and can itself produce mitochondrial decline. Mitochondrial dysfunction may then intensify muscle loss, generating a positive-feedback relationship between disuse, reduced oxidative capacity, oxidative stress, and proteolysis. Human proteomic evidence and repeated findings from animal and analog studies make skeletal muscle the most defensible organ system in which mitochondrial dysfunction may be described as a central contributor (Moosavi et al., 2021; Murgia et al., 2024).

Central Nervous System

Neural tissue demonstrates mitochondrial vulnerability, but causal interpretation is more complex. Animal studies of simulated galactic cosmic radiation have reported neurocognitive impairments, including changes in memory and executive function (Alaghband et al., 2023; Simmons et al., 2022). Spaceflight studies in mice have further identified spatially resolved molecular alterations in neural tissue, including changes relevant to cellular metabolism and mitochondrial function (Masarapu et al., 2024).

Neurons have high energy requirements and limited regenerative capacity. Mitochondrial dysfunction can therefore affect synaptic transmission, calcium regulation, neurotransmitter metabolism, and resistance to oxidative injury. Nevertheless, cognitive and behavioral outcomes are influenced by altered sleep, circadian disruption, isolation, confinement, radiation exposure, operational stress, neuroinflammation, and sensory adaptation. Mitochondrial dysfunction is therefore a plausible contributor but not an established exclusive cause.

Ocular System and SANS

Mitochondrial involvement in spaceflight-associated neuro-ocular syndrome remains a developing hypothesis. Retinal ganglion cells and optic nerve tissues have high metabolic demands, making them sensitive to mitochondrial and oxidative injury. Animal studies involving simulated weightlessness or spaceflight-related exposures have reported retinal and choroidal abnormalities consistent with disturbed energy metabolism and oxidative stress (Mu et al., 2023; Waisberg et al., 2024).

These findings provide biological plausibility for a mitochondrial contribution to SANS. However, SANS is strongly associated with cephalad fluid shifts and may involve changes in venous pressure, intracranial pressure, choroidal circulation, cerebrospinal fluid dynamics, and glymphatic clearance (Bateman & Bateman, 2024; Munster et al., 2024). Direct human evidence remains insufficient, and mitochondrial dysfunction should be described as a plausible contributory mechanism rather than an established primary cause.

Cardiovascular System

Cardiovascular studies indicate that microgravity and spaceflight can alter cardiac metabolism, mitochondrial respiration, contractile function, vascular regulation, and oxidative balance. Human pluripotent stem cell-derived cardiomyocytes and heart-on-a-chip platforms have demonstrated metabolic and contractile changes under spaceflight or simulated microgravity conditions (Han et al., 2024; Mair et al., 2024).

Cardiac muscle depends heavily on oxidative phosphorylation. Reduced mitochondrial respiratory capacity may impair contractility, recovery, and physiological adaptation. Nevertheless, cardiovascular deconditioning is strongly affected by plasma-volume reduction, cephalad fluid redistribution, altered baroreceptor responses, autonomic adaptation, and reduced cardiac loading (Baran et al., 2022). Mitochondrial impairment is therefore likely to interact with hemodynamic mechanisms rather than independently explain orthostatic intolerance.

Table 1. *Qualitative Evidence Linking Mitochondrial Dysfunction to Major Spaceflight-Associated Pathologies*

Organ system	Principal mitochondrial findings	Causal inference	Major limitation
Skeletal muscle	Reduced oxidative capacity, altered biogenesis, elevated oxidative stress, and metabolic remodeling.	Relatively strong; likely bidirectional and contributory to atrophy.	Disuse itself can initiate mitochondrial decline, complicating temporal attribution.
Central nervous system	Oxidative stress, altered mitochondrial morphology and metabolism, and association with neurocognitive changes.	Moderate but predominantly indirect.	Human tissue-level confirmation is unavailable, and multiple confounders coexist.
Ocular system and SANS	Retinal oxidative stress, mitochondrial injury, and altered choroidal and retinal physiology.	Preliminary to moderate; contributory role plausible.	No direct human link between mitochondrial biomarkers and SANS severity.
Cardiovascular system	Reduced respiration, altered cardiomyocyte metabolism, oxidative stress, and impaired contractility.	Moderate; likely interacts with hemodynamic adaptation.	Fluid redistribution and autonomic changes remain major alternative mechanisms.

Table 1 indicates that mitochondrial dysfunction is consistently present across multiple spaceflight-affected tissues but does not possess the same explanatory strength in every organ system. The evidence is strongest where molecular, functional, temporal, and interventional findings converge. It is weaker where mitochondrial abnormalities occur alongside several equally plausible mechanisms and where direct human confirmation is limited.

4.3 Mitochondrial-Targeted Countermeasures and Translational Readiness

The review identified several classes of interventions with potential to preserve mitochondrial function. These include mitochondrial-targeted antioxidants, NAD+-supporting compounds, mitophagy-enhancing agents, exercise, and combination approaches. However, the evidence supporting these interventions is derived mainly from terrestrial disease models, aging studies, cell cultures, and ground-based analogs.

Mitochondrial-Targeted Antioxidants

MitoQ and SS-31 are among the most frequently discussed mitochondrial-targeted compounds. MitoQ combines a ubiquinone antioxidant with a lipophilic cation that promotes mitochondrial accumulation. SS-31, or elamipretide, interacts with cardiolipin in the inner mitochondrial membrane and may stabilize membrane structure, preserve electron transport, and reduce oxidative injury.

These agents have demonstrated protective effects in terrestrial models of mitochondrial, cardiac, and oxidative dysfunction (Pedriali et al., 2022; Russo et al., 2022; J. Yang et al., 2022; Q. Yang et al., 2022). SS-31 is of particular translational interest because it has been investigated in human clinical development for mitochondrial and cardiovascular conditions. However, terrestrial efficacy does not demonstrate operational effectiveness during spaceflight. Prolonged antioxidant administration may also interfere with physiological redox signaling and mitohormesis.

NAD+-Supporting Interventions

NAD+ is an essential metabolic cofactor involved in oxidative metabolism, DNA repair, and sirtuin activity. NAD+ precursors such as nicotinamide riboside and nicotinamide mononucleotide have therefore been proposed as interventions for preserving mitochondrial function during prolonged stress (Yusri et al., 2025). Their efficacy under spaceflight conditions remains uncertain, and long-duration supplementation in healthy astronauts would require evidence concerning safety, metabolic effects, interaction with exercise, and influence on other physiological systems.

Mitophagy-Modulating Agents

Urolithin A, spermidine, and related compounds may enhance the removal of damaged mitochondria. Improved mitophagy could theoretically prevent the accumulation of dysfunctional organelles and preserve cellular energy production (Faitg et al., 2024; Srivastava & Gross, 2023). These agents remain at an early stage of spaceflight translation, and much of the evidence concerns aging, muscle health, or neurodegenerative disease rather than actual or simulated spaceflight.

Exercise-Based Mitochondrial Protection

Exercise is the most operationally mature intervention identified in the review. Resistive and aerobic exercise counteract several effects of microgravity by maintaining muscle loading, stimulating mitochondrial biogenesis, supporting cardiovascular function, and preserving oxidative capacity (Memme & Hood, 2021; Moosavi et al., 2021). Exercise does not fully eliminate deconditioning and may be constrained by equipment mass, crew time, compliance, and injury risk. Nevertheless, it should serve as the foundation against which pharmacological and nutritional mitochondrial interventions are evaluated.

Combination Strategies

No single mitochondrial intervention is likely to address the complete network of dysfunction. Antioxidants reduce oxidative injury but may not restore biogenesis. NAD+ precursors may support metabolic signaling but may not remove damaged mitochondria. Mitophagy enhancers may improve quality control but may be insufficient if new mitochondrial production remains suppressed.

Combination approaches are conceptually attractive, including exercise combined with an NAD+ precursor, mitochondrial antioxidant therapy combined with mitophagy enhancement, and pharmacological intervention guided by mitochondrial biomarkers. However, combining interventions may also increase the likelihood of adverse effects, metabolic interference, or excessive suppression of adaptive stress signaling. Combination strategies must therefore undergo staged evaluation rather than being assumed superior.

Table 2. *Mitochondrial-Targeted Countermeasures and Translational Maturity*

Intervention	Proposed action	Spaceflight maturity	Principal unresolved issue
MitoQ	Mitochondrial antioxidant activity and reduction of oxidative damage.	Low	Long-duration efficacy, dosing, and possible interference with adaptive redox signaling.
SS-31 / elamipretide	Cardiolipin stabilization, membrane protection, and improved electron transport.	Low to moderate	Direct validation in actual microgravity and healthy astronaut populations.
NAD+ precursors	Support for sirtuin activity, energy metabolism, and mitochondrial biogenesis.	Low	Inconsistent efficacy, optimal dosage, and chronic safety in healthy crews.
Mitophagy modulators	Enhanced removal of damaged mitochondria.	Low	Spaceflight relevance and interaction with mitochondrial biogenesis.
Exercise	Mechanical loading, stimulation of biogenesis, and preservation of oxidative capacity.	High	Incomplete protection, logistical burden, and variable individual response.
Combination strategies	Simultaneous targeting of oxidative stress, biogenesis, and quality control.	Very low	Safety, interaction effects, sequencing, dosage, and operational feasibility.

Table 2 shows that mitochondrial-targeted pharmacological and nutritional interventions remain substantially less mature than exercise. The strongest current rationale is to investigate these agents as adjuncts to established countermeasures rather than as replacements.

4.4 Discussion

The findings support a qualified interpretation of mitochondrial dysfunction as a convergent and amplifying mechanism in spaceflight-associated pathology. This interpretation is stronger than describing mitochondrial changes as incidental markers of stress, but more cautious than treating mitochondrial dysfunction as the sole cause of multi-system deterioration.

Several features support its mechanistic importance. Mitochondrial alterations recur across different tissues, species, missions, and experimental models. The observed abnormalities involve multiple components of mitochondrial biology, including biogenesis, respiration, redox regulation, mitochondrial DNA integrity, morphology, and quality control. Furthermore, tissues with high energy requirements or limited regenerative capacity appear particularly vulnerable (Nguyen et al., 2021; Rudolf & Hood, 2024).

The strongest evidence arises from skeletal muscle. Mechanical unloading, reduced oxidative metabolism, mitochondrial impairment, and atrophy are linked through biologically plausible and experimentally supported pathways. The relationship is reciprocal: unloading reduces mitochondrial demand, while mitochondrial dysfunction increases oxidative stress and may accelerate protein degradation. This reciprocal model explains why exercise remains indispensable and why purely antioxidant approaches may be insufficient.

In the central nervous, ocular, and cardiovascular systems, the mitochondrial-centered interpretation should be more restrained. Spaceflight-associated changes in these systems are influenced by fluid shifts, vascular regulation, radiation, inflammation, autonomic adaptation, circadian disturbance, and operational stress. Mitochondrial dysfunction may integrate or amplify these processes without initiating all of them.

The findings therefore argue against replacing organ-specific countermeasures with a single mitochondrial intervention. Instead, mitochondrial protection should be incorporated into a layered countermeasure architecture. Exercise, radiation shielding, fluid-management strategies, sleep and circadian support, nutritional planning, and organ-specific monitoring remain necessary. Mitochondrial-targeted approaches may enhance these measures by addressing a shared cellular vulnerability.

A mitochondrial-centered framework may nevertheless improve research efficiency. Space biomedical research has historically been organized around organ systems and mission risks. Treating mitochondrial dysfunction as a cross-cutting mechanism would encourage coordinated measurement of mitochondrial endpoints across muscle, cardiovascular, neural, and ocular studies.

Such coordination would also support biomarker development. Potential indicators include circulating cell-free mitochondrial DNA, mitochondrial DNA copy number, metabolites associated with oxidative phosphorylation, and stress-related proteins such as FGF-21 and GDF-15. These biomarkers are not specific to spaceflight and can be influenced by exercise, age, infection, diet, and other stressors. Their operational use would require baseline measurement, longitudinal monitoring, and validation against meaningful physiological outcomes.

Individual variability represents another important consideration. Astronauts may differ in mitochondrial reserve capacity, antioxidant response, metabolic flexibility, exercise adaptation, and susceptibility to radiation injury. Future studies should therefore move beyond average group effects and investigate whether pre-flight mitochondrial characteristics predict in-flight physiological response.

The translational implications are substantial but preliminary. SS-31, MitoQ, NAD+ precursors, and mitophagy modulators are scientifically plausible candidates, yet no reviewed evidence supports routine operational deployment. Long-duration missions involve healthy, highly selected individuals rather than patients with established mitochondrial disease. The tolerance for adverse effects is therefore low.

The absence of direct in-space intervention trials constitutes the principal barrier. Ground-based analogs cannot fully reproduce microgravity, deep-space radiation, confinement, mission workload, and altered circadian exposure simultaneously. Translation will require a staged pathway involving terrestrial mechanistic studies, combined-exposure analogs, low-Earth-orbit validation, and eventually testing under conditions representative of deep-space missions.

Alternative interpretations must also be retained. Mitochondrial dysfunction may partly represent a general cellular response to injury rather than a unique causal mechanism. In some tissues, it may occur downstream of inflammation, vascular disruption, or hormonal change. However, the repeated involvement of mitochondrial pathways, their functional importance, and protective effects of mitochondrial interventions in several non-spaceflight models make a purely epiphenomenal interpretation unlikely.

The principal contribution of the synthesis is not the claim that all spaceflight pathologies originate in mitochondria. Rather, it is the identification of mitochondrial dysfunction as a common biological vulnerability capable of linking environmental exposure with tissue-specific deterioration. Its importance is likely to vary according to organ system, exposure duration, individual susceptibility, and the effectiveness of existing countermeasures.

5. CONCLUSIONS, RECOMMENDATIONS, AND IMPLICATIONS

5.1 Conclusions

This thematic analytical review examined mitochondrial dysfunction as a convergent mechanism in spaceflight-associated pathology and evaluated its potential significance for biomedical countermeasure development. The synthesis supports the conclusion that mitochondrial impairment is a recurring, biologically plausible, and potentially actionable consequence of exposure to microgravity and space radiation. Its importance, however, differs according to tissue, exposure condition, and the strength of the available evidence.

Microgravity and space radiation affect mitochondrial function through partially distinct but interacting mechanisms. Mechanical unloading alters cellular mechanotransduction, metabolic demand, calcium regulation, and pathways involved in mitochondrial maintenance. Space radiation can damage mitochondrial DNA, electron transport chain components, and membrane structures. These stressors converge on reduced mitochondrial biogenesis, impaired oxidative phosphorylation, elevated reactive oxygen species production, altered mitochondrial dynamics, and inadequate removal of damaged organelles.

The causal case is most developed in skeletal muscle. Evidence from actual spaceflight, unloading models, and mechanistic studies indicates a bidirectional relationship among reduced mechanical loading, mitochondrial decline, oxidative stress, and muscle atrophy. Mitochondrial dysfunction is neither solely the cause nor merely the consequence of muscle deterioration; rather, it contributes to a reinforcing cycle that accelerates loss of oxidative capacity, endurance, and tissue integrity.

In the central nervous system, ocular tissues, and cardiovascular system, mitochondrial dysfunction appears to be a contributory and amplifying mechanism rather than an exclusive cause. Neurological outcomes are also influenced by radiation injury, neuroinflammation, sleep disruption, circadian disturbance, isolation, and operational stress. SANS remains strongly connected to fluid shifts, vascular changes, intracranial dynamics, and possible glymphatic dysfunction. Cardiovascular deconditioning similarly reflects plasma-volume reduction, altered cardiac loading, vascular remodeling, and autonomic adaptation.

Mitochondrial-targeted interventions are scientifically promising but insufficiently mature for routine operational use. MitoQ, SS-31 or elamipretide, NAD+ precursors, and mitophagy-modulating compounds have plausible mechanisms and varying degrees of terrestrial preclinical or clinical support. Direct evidence of their safety and efficacy during actual spaceflight remains limited. Exercise remains the most established mitochondrial-supportive countermeasure and should continue to serve as the foundation of musculoskeletal and cardiovascular protection.

Mitochondrial protection should consequently be considered a complementary component of space biomedical strategy rather than a replacement for existing organ-specific countermeasures. Its principal value lies in addressing a shared cellular vulnerability that may influence several physiological systems simultaneously.

5.2 Recommendations

In-space validation of candidate interventions

Space biomedical research programs should prioritize controlled in-space studies of the most scientifically developed mitochondrial-targeted interventions. Initial experiments should focus on compounds with established manufacturing standards, existing human safety data, and well-characterized mechanisms. Studies should combine molecular, metabolic, physiological, and functional measurements across multiple organ systems.

Standardized evidence hierarchy

Future reviews and experimental programs should clearly differentiate human spaceflight evidence, animal spaceflight evidence, combined microgravity-radiation analog evidence, single-stressor analog evidence, and terrestrial mechanistic or therapeutic evidence. This distinction is necessary because biological plausibility from terrestrial disease models does not demonstrate operational efficacy under spaceflight conditions.

Development of mitochondrial biomarkers

Research should identify minimally invasive biomarkers capable of detecting cumulative mitochondrial stress during spaceflight. Potential candidates include circulating cell-free mitochondrial DNA, mitochondrial DNA copy number, oxidative phosphorylation-associated metabolites, FGF-21, GDF-15, and markers of oxidative injury. These biomarkers require validation against clinically and operationally meaningful outcomes.

Combined-exposure studies

Ground-based research should improve analog fidelity by examining microgravity and radiation together rather than relying predominantly on sequential or isolated exposures. Longer-duration models are necessary to approximate lunar habitation and Mars transit and to assess reversibility after exposure.

Combination countermeasures

Candidate mitochondrial interventions should be evaluated in combination with established exercise protocols. Studies should examine additive and synergistic effects, treatment sequencing, continuous versus intermittent administration, interaction with nutritional intake, interference with adaptive oxidative signaling, drug stability, and crew-time burdens.

Long-duration safety evaluation

Candidate agents intended for missions lasting several months or years require long-duration safety assessment in healthy populations. Particular attention should be given to chronic metabolic effects, organ function, interactions with other medications, possible suppression of beneficial mitohormetic responses, sex-specific responses, and effects after discontinuation.

Individual susceptibility and personalized countermeasures

Future studies should investigate whether mitochondrial reserve capacity, metabolic flexibility, genetic polymorphisms, mitochondrial haplogroups, age, sex, and prior training status influence vulnerability to spaceflight-associated mitochondrial dysfunction. Pre-flight phenotyping may eventually support individualized countermeasure selection after predictive validity is established.

Integrated space-omics research

Mitochondrial assessment should be incorporated systematically into space-omics and longitudinal astronaut studies. Transcriptomic, proteomic, metabolomic, epigenetic, and functional mitochondrial data should be analyzed together using shared standards and interoperable datasets.

Preservation of organ-specific countermeasures

Exercise, radiation shielding, fluid-management protocols, sleep and circadian support, nutritional planning, and organ-specific monitoring should remain central to mission medicine. Mitochondrial-targeted strategies should complement these measures rather than displace them.

5.3 Implications of the Study

Theoretical Implications

The study supports a systems-level interpretation of spaceflight pathology. Rather than treating skeletal muscle atrophy, neurocognitive effects, ocular abnormalities, and cardiovascular deconditioning as wholly separate phenomena, the findings identify mitochondrial dysfunction as one biological pathway through which multiple environmental stressors may be integrated.

This does not establish mitochondrial dysfunction as a universal or sufficient explanation. Its theoretical significance lies in its ability to connect mechanical unloading, radiation injury, oxidative stress, metabolic disruption, and tissue-specific deterioration within a common convergent and amplifying framework.

Methodological Implications

The review demonstrates the importance of separating direct spaceflight evidence from analog and terrestrial extrapolation. Treating all evidence sources as equivalent risks overstating causal certainty and countermeasure readiness.

Future research would benefit from standardized outcome measures for mitochondrial biogenesis, respiration, oxidative damage, DNA integrity, morphology, and quality control. The study also highlights the need for explicit claim-to-citation verification, particularly when terrestrial studies are used as mechanistic context rather than direct spaceflight evidence.

Biomedical and Operational Implications

A mitochondrial-centered framework may improve countermeasure development by encouraging interventions that support several organ systems simultaneously. Operational utility, however, depends on more than biological efficacy. A viable countermeasure must be safe for long-duration use, stable during storage, compatible with mission schedules, easy to administer, minimally dependent on specialized monitoring, and effective alongside established protocols.

Mitochondrial biomarkers may eventually support adaptive countermeasure deployment by identifying crew members experiencing disproportionate cellular stress. This possibility remains preliminary and requires validation before biomarkers can guide in-flight clinical decisions.

Implications for Long-Duration Exploration

The consequences of mitochondrial dysfunction may become more important as missions extend beyond low Earth orbit. Longer exposure increases the duration of mechanical unloading and cumulative radiation burden while reducing access to medical evacuation, resupply, and advanced diagnostic facilities.

The review supports elevating mitochondrial research within the long-duration spaceflight agenda. Such elevation should be understood as a research priority rather than an endorsement of immediate pharmacological deployment. The necessary progression is from mechanistic confirmation, to analog validation, to low-Earth-orbit testing, and eventually to operational evaluation under conditions representative of deep-space exploration.

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