

Review

Mitochondria-Targeted Nutraceuticals as Metabolic Adjuncts to Physical Rehabilitation in Older Adults with Sarcopenia or Frailty: A Narrative Review

Alessio Turco ¹, Lorenzo Lippi ^{1,2,*}, Francesca Uberti ³, Alessandro de Sire ^{4,5} and Marco Invernizzi ^{1,2}

¹ Physical and Rehabilitative Medicine, Department of Health Sciences, University of Eastern Piedmont “A. Avogadro”, 28100 Novara, Italy; alessio.turco.phys@gmail.com (A.T.); marco.invernizzi@med.uniupo.it (M.I.)

² Dipartimento Attività Integrate Ricerca e Innovazione (DAIRI), Translational Medicine, Azienda Ospedaliero-Universitaria (AOU) SS. Antonio e Biagio e Cesare Arrigo, 15121 Alessandria, Italy

³ Department for Sustainable Development and Ecological Transition, University of Eastern Piedmont “A. Avogadro”, 13100 Vercelli, Italy; francesca.uberti@uniupo.it

⁴ Physical and Rehabilitative Medicine, Department of Medical and Surgical Sciences, University of Catanzaro “Magna Graecia”, 88100 Catanzaro, Italy; alessandro.desire@unicz.it

⁵ Research Center on Musculoskeletal Health, MusculoSkeletalHealth@UMG, University of Catanzaro “Magna Graecia”, 88100 Catanzaro, Italy

* Correspondence: lorenzo.lippi@uniupo.it

Abstract

Age-related skeletal muscle wasting, clinically expressed as sarcopenia and frailty, significantly limits the efficacy of physical rehabilitation due to an underlying cellular bioenergetic decline, mitochondrial dysfunction, and chronic inflammaging. This narrative review synthesizes current physiological and clinical evidence evaluating mitochondria-targeted nutraceuticals as targeted metabolic adjuvants to physical exercise in older adults. Comprehensive literature searches were executed across PubMed, Web of Science, and Scopus following SANRA guidelines and the SPIDER framework to evaluate functional and bioenergetic outcomes in geriatric cohorts. The findings demonstrate that target-specific biofactors directly impact mitochondrial restrictions: ubiquinol and NAD⁺ precursors restore electron transport chain efficiency and biogenesis; urolithin A upregulates mitophagy to prevent the cytosolic extrusion of pro-inflammatory mitochondrial DNA, while creatine monohydrate and omega-3 polyunsaturated fatty acids selectively restore downstream myofibrillar anabolic pathways. When translated to specialized clinical settings, including post-fracture orthopedic immobilization, chronic pain syndromes managed, and post-ICU-acquired weakness, these bioenergetic substrates safely mitigate tissue proteolysis and enhance recovery kinetics. In conclusion, structurally integrating biomarker-driven nutritional rehabilitation pathways with tailored exercise protocols provides the precise pro-anabolic microenvironment necessary to overcome anabolic resistance, ultimately shortening recovery timelines and maximizing functional independence in the aging population.



Academic Editor: Iain A. Brownlee

Received: 9 July 2026

Revised: 18 August 2026

Accepted: 31 August 2026

Published: 2 September 2026

Copyright: © 2026 by the authors.

Licensee MDPI, Basel, Switzerland.

This article is an open access article distributed under the terms and conditions of the [Creative Commons Attribution \(CC BY\)](https://creativecommons.org/licenses/by/4.0/) license.

Keywords: mitochondrial dysfunction; geriatric rehabilitation; sarcopenia; nutraceuticals; urolithin A; Coenzyme Q10; muscle recovery; healthy aging

1. Introduction

The global demographic landscape is undergoing a profound structural transition characterized by an exponential expansion of the geriatric cohort, posing profound challenges

to healthcare systems worldwide [1]. Although advancements in medical science have successfully extended absolute chronological lifespan, a critical disparity persists between lifespan and healthspan [2]. In older adults, acute pathophysiological stressors, surgical interventions, or brief periods of enforced muscle disuse frequently trigger an accelerated depletion of appendicular lean mass and skeletal muscle strength [3]. This phenomenon is significantly modulated by senescent phenotype alterations clinically expressed as frailty and sarcopenia [3]. Physical rehabilitation constitutes the primary non-pharmacological intervention designed to restore functional autonomy, attenuate permanent disability, and mitigate healthcare institutionalization [4,5]. However, conventional rehabilitative outcomes in geriatric cohorts are limited by an age-related impairment in physiological adaptation to exercise. This attenuated plasticity is characterized by early-onset myofibrillar fatigue, prolonged metabolic recovery periods, and impaired hypertrophy, underscoring the need for targeted adjuvant therapeutic strategies [6,7].

At the molecular level, this compromised physiological resilience is primarily driven by the progressive decline in cellular bioenergetics, a fundamental mechanism driving the mitochondrial theory of aging [8]. As an energetically demanding post-mitotic tissue, skeletal muscle relies on a coordinated mitochondrial network to sustain the ATP flux required for contraction and cellular remodeling [9]. Advancing age induces critical disruptions in mitochondrial quality control (MQC) and structural integrity. Key molecular features of this decline include the transcriptional downregulation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α), which fundamentally compromises mitochondrial biogenesis, concurrently with progressive somatic mtDNA damage [10].

Consequently, the enzymatic activity of the electron transport chain (ETC) macromolecular complexes, particularly Complexes I and IV, is significantly compromised [11]. Furthermore, the systematic failure of mitophagy leads to the intracellular retention of dysfunctional, uncoupled mitochondria [12]. These damaged organelles exhibit a degraded inner mitochondrial membrane potential, compromising ATP synthesis while elevating intra-myocellular ROS production [8]. This oxidative stress impairs mTORC1 translation, the systemic pro-inflammatory profile, and excitation–contraction coupling [13].

To counteract this bioenergetic restriction, traditional clinical nutrition in rehabilitation settings has focused almost exclusively on macronutrients, specifically the administration of high-density proteins and essential amino acids to stimulate muscle protein synthesis [14,15]. Importantly, mitochondrial-targeted supplementation should be viewed as a complementary strategy rather than a replacement for adequate protein and energy intake, which remain the cornerstone of nutritional management in older adults undergoing rehabilitation. While structurally necessary, standard nutritional supplementation regimens in elderly populations often fail to achieve satisfactory outcomes in functional improvements if the recipient's intracellular apparatus remains bioenergetically compromised; providing structural substrates to a myofiber with failing respiratory networks cannot sustain optimal functional hypertrophy [16]. Therefore, nutritional science must pivot toward target-specific biofactors capable of permeating the mitochondrial double-membrane system to directly optimize organelle metabolism [17]. By stabilizing the inner mitochondrial membrane microenvironment, reinforcing endogenous antioxidant defenses, and inducing the clearance and renewal of dysfunctional organelles, mitochondrial-targeted nutraceuticals offer a precise biochemical mechanism to prime senescent skeletal muscle for physical exertion [8,18].

While previous syntheses in the field have predominantly examined the impact of broad dietary supplements on general mitochondrial biomarkers in healthy older adults [17], significant knowledge gaps remain regarding their targeted application in

clinical rehabilitation. Specifically, there is a need to synthesize evidence focusing on frail geriatric cohorts presenting with acute disuse atrophy, chronic pain, or post-ICU muscle weakness. Furthermore, rapidly emerging evidence in recent years on novel bioenergetic modulators, such as Urolithin A and NAD⁺ precursors, demands an updated translational framework. Therefore, this narrative review addresses these gaps by evaluating the synergistic cross-talk between organelle-targeted nutraceuticals and active physical therapy protocols, establishing how metabolic support can be synchronized with exercise loading to enhance functional recovery in vulnerable older populations.

Consequently, this narrative review aims to synthesize the current biological foundations and translational clinical evidence regarding mitochondrial-targeted supplementation as an essential metabolic adjuvant to geriatric physical rehabilitation. Specifically, we evaluate the therapeutic parameters of key bioenergetic compounds and delineate the complementary mechanisms established when these nutraceutical agents are coupled as adjunctive support with tailored exercise protocols to overcome age-related muscle resistance and accelerate functional recovery in the elderly.

2. Materials and Methods

The Scale for the Assessment of Narrative Review Articles (SANRA) informed the preparation and self-appraisal of this narrative review [19]. Comprehensive systematic literature searches were conducted across the PubMed/MEDLINE, Web of Science (WoS), and Scopus electronic databases utilizing a combination of Medical Subject Heading (MeSH) terms and specific text keywords, including “Mitochondria”, “Mitochondrial Dysfunction”, “Nutraceuticals”, “Dietary Supplements”, “Sarcopenia”, “Frailty”, “Aged”, “Geriatrics”, “Exercise”, “Rehabilitation”, “Physical Activity”, “Function”, “Performance”, “Disability”, and “Quality of Life”. Table 1 reported a detailed search strategy for each database.

The literature search strategy and study selection criteria were structured according to the PICOS (Population, Intervention, Comparison, Outcomes, Study Design) framework, as systematically summarized in Table 2.

The comprehensive literature retrieval phase was conducted between March 2026 and June 2026 by two independent investigators (A.T. and L.L.). The initial search across electronic databases identified a total of 715 records (PubMed: $n = 437$; Scopus: $n = 19$; Web of Science: $n = 259$). Following the removal of duplicates ($n = 77$), 638 records underwent title and abstract screening. A total of 215 full-text articles were evaluated for eligibility, and 128 studies ultimately met all inclusion criteria and were included in this narrative review. Following the primary database search, the identified records were systematically screened for eligibility. In instances where a dual-reviewer consensus could not be established, a senior third investigator (M.I.) was consulted to adjudicate.

The inclusion criteria were calibrated to address the core investigative question: “*What is the mechanistic and clinical impact of mitochondrial-targeted supplementation on enhancing physical rehabilitation outcomes in the sarcopenic geriatric population?*” In detail, eligible articles comprised human clinical investigations involving older adults (aged > 65 years) presenting with sarcopenia, physical frailty, or post-use muscle deconditioning, and evaluated the therapeutic efficacy of target-specific bioenergetic nutraceutical interventions to improve functional outcomes, muscle performance metrics, and physiological well-being during structured physical rehabilitation.

Table 1. Search strategy.**PubMed/MEDLINE**

(“aging”[MeSH Terms] OR “aging”[All Fields] OR “ageing”[All Fields] OR (“geriatric”[All Fields] OR “geriatrics”[MeSH Terms] OR “geriatrics”[All Fields]) OR (“sarcopenia”[MeSH Terms] OR “sarcopenia”[All Fields] OR “sarcopenia s”[All Fields]) OR (“frailty”[MeSH Terms] OR “frailty”[All Fields] OR “frailties”[All Fields])) AND (“mitochondria”[MeSH Terms] OR “mitochondria”[All Fields] OR “mitochondria s”[All Fields] OR “mitochondriae”[All Fields] OR “mitochondrias”[All Fields] OR (“mitochondrial diseases”[MeSH Terms] OR (“mitochondrial”[All Fields] AND “diseases”[All Fields]) OR “mitochondrial diseases”[All Fields] OR (“mitochondrial”[All Fields] AND “dysfunction”[All Fields]) OR “mitochondrial dysfunction”[All Fields])) AND (“dietary supplements”[MeSH Terms] OR (“dietary”[All Fields] AND “supplements”[All Fields]) OR “dietary supplements”[All Fields] OR “nutraceutical”[All Fields] OR “nutraceuticals”[All Fields] OR “nutraceutic”[All Fields] OR “nutraceutically”[All Fields] OR “nutraceutics”[All Fields] OR (“dietary supplements”[MeSH Terms] OR (“dietary”[All Fields] AND “supplements”[All Fields]) OR “dietary supplements”[All Fields])) AND (“quality of life”[MeSH Terms] OR (“quality”[All Fields] AND “life”[All Fields]) OR “quality of life”[All Fields] OR (“exercise”[MeSH Terms] OR “exercise”[All Fields] OR “exercises”[All Fields] OR “exercise therapy”[MeSH Terms] OR (“exercise”[All Fields] AND “therapy”[All Fields]) OR “exercise therapy”[All Fields] OR “exercising”[All Fields] OR “exercise s”[All Fields] OR “exercised”[All Fields] OR “exerciser”[All Fields] OR “exercisers”[All Fields]) OR (“physical therapy modalities”[MeSH Terms] OR (“physical”[All Fields] AND “therapy”[All Fields] AND “modalities”[All Fields]) OR “physical therapy modalities”[All Fields] OR (“physical”[All Fields] AND “therapy”[All Fields]) OR “physical therapy”[All Fields]) OR (“rehabilitant”[All Fields] OR “rehabilitants”[All Fields] OR “rehabilitate”[All Fields] OR “rehabilitated”[All Fields] OR “rehabilitates”[All Fields] OR “rehabilitating”[All Fields] OR “rehabilitation”[MeSH Terms] OR “rehabilitation”[All Fields] OR “rehabilitations”[All Fields] OR “rehabilitative”[All Fields] OR “rehabilitation”[MeSH Subheading] OR “rehabilitation s”[All Fields] OR “rehabilitational”[All Fields] OR “rehabilitator”[All Fields] OR “rehabilitators”[All Fields]) OR (“exercise”[MeSH Terms] OR “exercise”[All Fields] OR (“physical”[All Fields] AND “activity”[All Fields]) OR “physical activity”[All Fields]) OR (“functional”[All Fields] OR “functional s”[All Fields] OR “functionalities”[All Fields] OR “functionality”[All Fields] OR “functionalization”[All Fields] OR “functionalizations”[All Fields] OR “functionalize”[All Fields] OR “functionalized”[All Fields] OR “functionalizes”[All Fields] OR “functionalizing”[All Fields] OR “functionally”[All Fields] OR “functionals”[All Fields] OR “functioned”[All Fields] OR “functioning”[All Fields] OR “functionings”[All Fields] OR “functions”[All Fields] OR “physiology”[MeSH Subheading] OR “physiology”[All Fields] OR “function”[All Fields] OR “physiology”[MeSH Terms]))

Records: 437

Scopus

(Aging OR geriatrics OR sarcopenia OR frailty) AND (Mitochondria OR Mitochondrial Dysfunction) AND (Nutraceuticals OR Dietary Supplements) AND (Quality of Life OR Exercise OR Physical Therapy OR Rehabilitation OR Physical Activity OR Function)

Records: 19

Table 1. *Cont.***Web of Science**

(((((TS = Aging) OR (TS = geriatrics)) OR (TS = sarcopenia)) OR (TS = frailty)) AND ((TS = Mitochondria) OR (TS = Mitochondrial Dysfunction))) AND ((TS = Nutraceuticals) OR (TS = Dietary Supplements))) AND (((((TS = Quality of Life) OR (TS = Exercise)) OR (TS = Physical Therapy)) OR (TS = Rehabilitation)) OR (TS = Physical Activity)) OR (TS = Function)))

Records: 259

Table 2. Literature eligibility criteria based on the PICOS framework.

	Inclusion Criteria	Exclusion Criteria
<i>Population (P)</i>	Older adults (aged ≥ 65 years) with sarcopenia, physical frailty, or acute muscle deconditioning (post-orthopedic, chronic pain, post-ICU weakness)	Healthy young/middle-aged adults, pediatric populations, non-geriatric animal models, or in vitro cell cultures
<i>Intervention (I)</i>	Targeted mitochondrial nutraceuticals (CoQ10, Creatine, Urolithin A, NAD ⁺ precursors, ALCAR, Omega-3, Nitrates) with or without exercise	Non-mitochondrial supplements, undefined multi-ingredient commercial blends, or pharmacological therapies
<i>Comparison (C)</i>	Placebo, physical rehabilitation alone, baseline pre-intervention values, or non-supplemented control groups	Studies lacking appropriate control groups or baseline measurements
<i>Outcomes (O)</i>	Mitochondrial and bioenergetic biomarkers, and functional outcomes	Studies lacking functional or cellular bioenergetic outcome measurements
<i>Study Design (S)</i>	Randomized controlled trials (RCTs), non-randomized prospective clinical trials, cohort studies, and controlled intervention studies published in peer-reviewed journals	Gray literature, conference abstracts, editorials, theses, and preprints

To ensure complete transparency and avoid over-interpretation of translational data, eligibility criteria were refined to stratify all included literature into three evidence tiers:

- Direct Clinical Evidence: Randomized controlled trials (RCTs) and clinical studies conducted in older adults (>65 years) with diagnosed sarcopenia, physical frailty, or undergoing active physical rehabilitation.
- Indirect Human Evidence: Clinical studies in healthy older adults or middle-aged cohorts evaluating muscular bioenergetics, exercise capacity, or physical performance.
- Preclinical Evidence: In vivo animal models and in vitro cellular studies, included strictly to elucidate organelle-level pathways and biochemical mechanisms.

Conversely, manuscripts published in languages other than English, studies lacking full-text availability, preclinical investigations utilizing animal models or in vitro architectures, and gray literature, including conference abstracts, master's theses, or doctoral dissertations, were excluded.

Qualitative methods were deployed for systematic data extraction and synthesis. The investigators (A.T. and L.L.) independently extracted and synthesized primary datasets regarding the distinct mitochondrial supplementation protocols and their respective integration with rehabilitation modalities. In cases of analytical disagreement, the third reviewer (M.I.) provided definitive input. To synthesize the findings, included studies

were first categorized according to the specific nutraceutical agent, its primary organelle target (e.g., ETC electron transport, mitochondrial quality control/mitophagy, or membrane phospholipid stabilization), and the specific rehabilitation setting (e.g., post-operative orthopedic recovery, chronic pain, or post-ICU muscle weakness). Outcomes were qualitatively cross-compared across two main levels: (1) surrogate bioenergetic and cellular biomarkers (such as ATP resynthesis rates, ROS emission, cardiolipin protection, and mitochondrial biogenesis markers), and (2) clinical and functional endpoints (including peak VO₂, 5-repetition chair stand time, gait speed, and appendicular lean mass). This multi-layered comparative analysis enabled the integration of mechanistic pathways with clinical efficacy, forming the foundation for the synergistic models and conclusions presented in this review.

3. Narrative Synthesis and Clinical Evidence

The literature on mitochondria-targeted nutraceuticals spans a broad continuum, from basic organelle physiology to applied clinical rehabilitation in geriatric populations. To provide a rigorous and clinically actionable synthesis, the available evidence is evaluated by distinguishing the cellular mechanisms from direct therapeutic efficacy. Particular emphasis is placed on clinical trials and rehabilitation studies that assess hard functional endpoints in vulnerable older cohorts, including changes in muscle strength, walking performance, appendicular lean mass, daily functional independence, and the time required to achieve rehabilitation milestones. The clinical characteristics, posologies, functional outcomes, and safety profiles of the reviewed interventions are summarized in Table 3.

Table 3. Summary of clinical evidence, intervention parameters, and functional outcomes for targeted nutraceuticals.

Compound	Target Setting and Population	Key Functional Outcomes (Strength, Gait, Mass, ADLs)	Safety and Adverse Events
Creatine Monohydrate	Sarcopenia, disuse atrophy, resistance training	↑ Knee extensor strength, ↑ Appendicular lean mass, ↑ 30-s chair stand test	High safety profile; no significant adverse renal or GI events reported.
Urolithin A	Frail and pre-frail older adults	↑ Muscle endurance (6MWT distance), ↑ Hamstring peak torque, ↑ ATP kinetics	Well tolerated; mild GI symptoms reported in rare cases.
CoQ10/Ubiquinol	Geriatric rehabilitation, post-deconditioning	↑ Peak VO ₂ , ↓ Fatigue scale scores, ↑ Gait speed	Excellent safety profile; well tolerated across older cohorts.
Omega-3 PUFAs	Post-operative orthopedic rehab, sarcopenia	↑ Muscle protein synthesis rate, ↑ Grip strength, preservation of muscle volume	Minor gastrointestinal discomfort (e.g., eructation) in isolated cases.
NAD ⁺ Precursors (NR/NMN)	Sarcopenic older adults, age-related frailty	↑ Whole-blood NAD ⁺ pool, modest improvements in isometric muscle force and physical capacity	Safe and well tolerated at tested doses; no serious adverse events.

4. Mechanistic and Clinical Evidence of Mitochondrial-Targeted Nutraceuticals in Geriatric Muscle Health

Age-related sarcopenia and physical deconditioning are driven by a progressive decline in mitochondrial function. In senescent myofibers, the accumulation of mitochondrial DNA mutations, impaired biogenesis, and impaired mitophagy induce an energetic deficit that mediates anabolic resistance. To overcome this therapeutic barrier, clinical strategies utilize mitochondrial-targeted nutraceuticals as precise metabolic modulators. These specialized biofactors optimize intracellular energy flux through three distinct vectors: direct bioenergetic restoration of the electron transport chain, site-specific redox regulation, and

activation of mitochondrial quality control pathways. By restoring ATP availability, these compounds overcome the energetic deficit of the aging muscle, priming it to effectively translate rehabilitative exercise into measurable functional recovery.

4.1. Coenzyme Q10 (CoQ10) and Ubiquinol

Coenzyme Q10 (CoQ10) is an essential lipophilic electron carrier located within the inner mitochondrial membrane (IMM) that transports reduced equivalents from Complexes I and II to Complex III [20]. Because aging systemically downregulates endogenous CoQ10 biosynthesis, oral supplementation with ubiquinol, the fully reduced and highly bioavailable form of CoQ10, is preferred in geriatric cohorts [21,22]. Once integrated into the IMM, ubiquinol exerts a dual-action therapeutic effect by reintroducing the intramitochondrial lipid pool to restore the proton motive force (Δp) driving Complex V ATP synthesis while simultaneously acting as a localized antioxidant that suppresses electron leakage at Complexes I and III [23]. This site-specific redox regulation prevents lipid peroxidation of cardiolipin and carbonylation of myofibrillar proteins without disrupting the physiological hydrogen peroxide (H_2O_2) signaling essential for training adaptations [24]. When evaluated in deconditioned older adults, ubiquinol supplementation paired with physical rehabilitation shows potential to support physiological recovery, including peak oxygen consumption VO_2 peak, ventilatory parameters, and post-exercise phosphocreatine resynthesis kinetics, although primary study findings remain heterogeneous across trial protocols [25]. As highlighted in recent evidence syntheses, the available clinical trial base evaluating CoQ10 as an adjunct to structured exercise in older cohorts remains modest, necessitating cautious interpretation regarding definitive clinical guidelines [26]. Within combined exercise and supplementation frameworks, observed functional gains are most consistently reflected in lower-body muscular power and resistance to fatigue, such as performance improvements in the 5-repetition (5XSST) and 30-s chair stand tests (30CST), rather than uniform changes across all balance or upper-limb metrics [26]. Consequently, rather than directly driving systemic aerobic capacity gains, co-administration of ubiquinol serves primarily as a supportive metabolic adjunct that enhances training volume tolerance and lower-limb force output during rehabilitative protocols in aged muscle [27].

4.2. Creatine Monohydrate

Creatine monohydrate is a nitrogenous organic compound that modulates rapid cellular energy homeostasis via the phosphagen system [28]. Upon myocellular uptake through the sodium-dependent transporter SLC6A8, it is phosphorylated into phosphocreatine (PCr) to serve as a high-energy phosphate reserve that rephosphorylates ADP into ATP during high-intensity muscular contractions [29]. To mitigate the age-related reduction in endogenous creatine pools and creatine kinase activity, supplementation maximizes intracellular PCr reserves to accelerate post-exertional ATP resynthesis facilitated by supramolecular VDAC/ANT-CK phosphotransfer complexes, thereby prolonging the time to muscle fatigue [30,31]. As an intracellular osmolyte and metabolic sensor, creatine induces cellular hydration that triggers mechanotransduction, upregulating MyoD and activating the PI3K/Akt/mTORC1 signaling axis to mitigate anabolic resistance [28,32]. Clinical evidence indicates that combining creatine supplementation with structured resistance exercise significantly enhances therapeutic outcomes in older adults, resulting in a greater increase in appendicular lean mass, superior gains in maximal strength, and marked improvements in physical function compared with exercise alone [33–35].

4.3. Urolithin A

Urolithin A (UA) is a gut microbiome-derived metabolite derived from the bacterial catabolism of polyphenolic ellagitannins and ellagic acid, rich in pomegranates, walnuts,

and berries [36]. Within rehabilitation nutrition, UA has emerged as a first-in-class modulator of mitochondrial quality control (MQC) that selectively restores mitophagy [37,38]. In geriatric skeletal muscle, where the downregulation of mitophagy leads to an accumulation of dysfunctional organelles, UA acts as a potent molecular agent that upregulates mitophagy via both PINK1/Parkin-dependent and independent pathways [39,40]. This targeted mechanism eliminates damaged mitochondria that leak reactive oxygen species (ROS), facilitating the biogenesis of highly coupled mitochondrial networks [41]. Concurrently, preventing mitochondrial DNA (mtDNA) leakage into the cytosol inhibits the NLRP3 inflammasome, blunting the chronic low-grade inflammation that impairs muscle recovery [41,42]. In older adults, daily supplementation of UA has been shown to significantly enhance skeletal muscle endurance while markedly reducing plasma levels of acylcarnitines, ceramides, and C-reactive protein (CRP) [43]. Collectively, these findings establish UA as a precise and effective tool to optimize mitochondrial health, muscle quality, and functional performance across the lifespan.

4.4. Nicotinamide Adenine Dinucleotide (NAD⁺) Precursors (NR and NMN)

Nicotinamide Adenine Dinucleotide (NAD⁺) is a pivotal coenzyme modulating cellular redox reactions and serving as a substrate for energy-sensing enzymes, including sirtuins (SIRT1–7) and PARPs [44,45]. Aging is characterized by a systemic depletion of the intracellular NAD⁺ pool, driven by the upregulation of the NAD⁺-consuming enzyme CD38 and a decline in the NAMPT-mediated resynthesis pathway, which compromises mitochondrial biogenesis and oxidative phosphorylation (OXPHOS) [46,47]. To overcome these metabolic limitations, oral supplementation with highly soluble intermediates such as Nicotinamide Riboside (NR) and Nicotinamide Mononucleotide (NMN) is implemented [48–50]. Upon myocellular uptake, these precursors rapidly restore intracellular and intramitochondrial NAD⁺ pools, activating nuclear SIRT1 to deacetylate and stimulate PGC-1 α [48]. Concurrently, elevated intramitochondrial NAD⁺ drives SIRT3 activity, optimizing the deacetylation of critical electron transport chain complexes and antioxidant proteins like MnSOD, thereby maximizing ATP generation efficiency while mitigating mitochondrial ROS production [51–53]. Clinical evaluation of NAD⁺ precursors, such as NR and NMN, in older cohorts indicates that oral supplementation significantly increases systemic NAD⁺ levels and its metabolites [54]. While specific trials demonstrate that daily NMN intake can effectively maintain walking speed and improve functional markers like handgrip strength [54], a recent systematic review and meta-analysis suggests that these benefits are not yet consistent across all sarcopenia-related measures, such as skeletal muscle index (SMI) [55]. However, preserving functional parameters like handgrip strength remains clinically paramount, as upper-limb strength deficits are strongly associated with adverse geriatric outcomes, including fracture risk and frailty [56]. Lastly, these findings establish NAD⁺ precursor supplementation as a safe and effective strategy for boosting systemic NAD⁺ levels, which in turn supports the maintenance of walking speed, improves functional markers like handgrip strength, and enhances overall sleep quality in older adults [54,55].

4.5. L-Carnitine and Acetyl-L-Carnitine

L-Carnitine and its acetylated ester, Acetyl-L-Carnitine (ALCAR), are quaternary ammonium compounds required for the translocation of long-chain fatty acids (LCFAs) across the inner mitochondrial membrane via the carnitine palmitoyltransferase (CPT) enzyme complex [57]. Within the mitochondrial matrix, these substrates undergo β -oxidation to yield acetyl-CoA, directly feeding the tricarboxylic acid (TCA) cycle to generate reducing equivalents for ATP production [58]. In geriatric populations, a tissue-specific depletion of

the intramyocellular carnitine pool induces metabolic inflexibility, where skeletal muscle cannot effectively shift from carbohydrate utilization to lipid utilization [57,59,60].

Supplementation with L-carnitine or ALCAR delivers a dual-action metabolic intervention by reactivating the CPT complex to mitigate cytosolic lipotoxicity and restore lipid-driven oxidative phosphorylation [61]. Clinical trials in frail older adults demonstrate that combining carnitine supplementation with structured physical therapy significantly reduces fat mass, increases appendicular lean mass, attenuates post-exertional fatigue, and improves walking capacity and handgrip strength [59,62,63].

4.6. Omega-3 Polyunsaturated Fatty Acids (n-3 PUFAs)

Fish oil-derived n-3 polyunsaturated fatty acids serve as structural modifiers of the myocellular lipidome. Beyond their classic anti-inflammatory systemic properties, n-3 PUFAs physically integrate into mitochondrial membranes, altering membrane fluidity and modulating the activity of embedded transport proteins [17,64]. In healthy older adults, clinical evidence demonstrates that a 6-month supplementation protocol induces significant structural and bioenergetic adaptations within skeletal muscle [65]. Specifically, this intervention downregulates mitochondrial degradation and mitophagy pathways and significantly upregulates the gene expression of crucial structural and uncoupling factors, such as ubiquinol-cytochrome c reductase core protein 1 of Complex III (UQCRC1) and the inner membrane uncoupling protein 3 (UCP3) [65]. Furthermore, microarray and pathway analyses confirm a significant enhancement in chemiosmotic ATP synthesis, oxidative phosphorylation kinetics, and tricarboxylic acid (TCA) cycle efficiency compared to baseline, effectively driving phenotypic adaptations in muscle quality [66]. When combined with physical exercise and rehabilitation protocols, these bioenergetic improvements translate into a potent anabolic-sensitizing effect in geriatric patients [67,68]. Integrating n-3 PUFA supplementation into structured exercise regimens yields superior clinical outcomes in frail cohorts, demonstrating enhanced gains in isometric and dynamic muscle strength, marked improvements in walking capacity, and an accelerated recovery of functional autonomy during post-acute rehabilitation [68–70].

4.7. Inorganic Nitrates, Sodium Nitrites, and Hydrogen-Rich Water

Other targeted dietary interventions evaluated in geriatric clinical trials focus on localized oxidative stress mitigation and alternative coenzyme support pathways [17]. Functioning as a key intermediary of the nitrate-nitrite-nitric oxide pathway, oral administration of sodium nitrite attenuates mitochondrial ROS production and decreases cellular nitrotyrosine markers by 35% [71]. This targeted modulation preserves inner membrane integrity without altering total mitochondrial volume [71]. Concurrently, hydrogen-rich water functions as a selective antioxidant agent of highly cytotoxic hydroxyl radicals [72]. Its long-term intake has been shown to protect organelle networks from senescent oxidative collapse, though data regarding short-term shifts in the cellular NAD^+/NADH ratio remain conservative [73].

When evaluated in physical rehabilitation and exercise contexts, these interventions support specific physiological targets. The sodium nitrite-mediated optimization of the nitric oxide pathway primarily enhances microvascular perfusion and local oxygen delivery, lowering the oxygen cost of submaximal exertion [74,75]. However, clinical trial data evaluating dietary nitrate in middle-aged and older cohorts demonstrate no statistically significant between-group advantage for direct muscular performance or strength gains [76]. Simultaneously, the selective antioxidant action of hydrogen-rich water mitigates acute, contraction-induced oxidative stress and exertion biomarkers without disrupting essential mitohormetic signaling pathways [77]. Given the small sample sizes and preliminary

nature of available clinical trials, findings for hydrogen-rich water should be interpreted strictly as pilot evidence for accelerating post-exercise recovery, without extrapolating these micronutrient interventions to clinical frailty reversal or functional independence [76,78].

5. Molecular Cross-Talk and Adjunctive Benefits of Bioenergetic Supplementation and Physical Exercise

5.1. Mitochondrial Adaptations to Exercise and Nutrition

The core of rehabilitation nutrition lies in the complementary interplay between mechanical loading and metabolic support. Muscle contraction exerts mechanical tension across the sarcolemma, activating costamere proteins and the FAK/mTORC1 axis to drive myofibrillar protein synthesis [79,80]. In geriatric cohorts, however, this mechanical signal is frequently decoupled from downstream anabolic outputs due to age-related mitochondrial dysfunction and chronic ATP restriction [13,81].

Physical exercise serves as a potent non-pharmacological stimulus to rescue this pathway by directly remodeling mitochondrial architecture and reversing respiratory chain decline [82,83]. This cellular adaptation is driven by transient contraction-induced energetic stress, which alters intracellular AMP/ATP and NAD⁺/NADH ratios to trigger the metabolic sensors AMP-activated protein kinase (AMPK) and Sirtuin 1 (SIRT1) [84,85]. This dual enzymatic activation induces the simultaneous phosphorylation and deacetylation of PGC-1 α , thereby upregulating mitochondrial enzyme transcription, accelerating lipid β -oxidation, and optimizing oxidative phosphorylation (OXPHOS) kinetics [82,86].

Introducing mitochondrial-targeted nutrition rehabilitation therapy into this exercise microenvironment establishes a highly effective metabolic coupling [87,88]. While the physical stimulus upregulates the transcriptional and structural machinery of the organelle, the targeted nutraceuticals supply the precise bioenergetic substrates and redox stability required to sustain it [54,89]. This integrated biological cooperation circumvents age-related anabolic resistance, maximizing the translation of rehabilitative exercise into measurable myofiber hypertrophy, structural plasticity, and functional kinetic recovery [89,90].

5.2. Mitochondrial Dysfunction and Inflammaging

A primary barrier to muscle recovery in older adults is inflammaging, a chronic, low-grade systemic inflammation driven by senescent cells and their pro-inflammatory secretome. In aged skeletal muscle, this persistent inflammatory state degrades the extracellular matrix, disrupts stem cell niches, and directly suppresses the mTORC1 hypertrophic pathway, thereby accelerating muscle wasting [91,92].

At the cellular level, this process is due to mitochondrial decline and dysfunction [91,92]. When the structural integrity of the inner mitochondrial membrane collapses, uncoupled respiratory chains leak excessive mtROS. This localized oxidative stress triggers the NLRP3 inflammasome, while the leakage of mtDNA into the cytosol activates the cGAS-STING pathway, heavily reinforcing inflammatory signaling [93,94].

Targeted bioenergetic supplementation directly disrupts this degenerative process [95]. At the cellular level, in vitro and immune cell models and preclinical and translational models demonstrate that ubiquinol and NAD⁺ precursors stabilize the mitochondrial membrane environment to neutralize electron leaks and reduce mtROS production, while urolithin A accelerates the autophagic clearance of damaged mitochondria to prevent cytosolic mtDNA accumulation [96]. Although these immunometabolic mechanisms have been characterized in human neuro-immune and cellular models [96], similar mitochondrial-targeted pathways operate systemically and within skeletal muscle [96]. When paired with physical exercise, which naturally downregulates systemic inflammatory receptors, this combined

approach mitigates senescent signaling, suppressing chronic inflammation to establish the pro-anabolic environment necessary for successful rehabilitative remodeling.

5.3. Chrono-Nutritional Strategies in Rehabilitation

To maximize the physiological cross-talk between mechanical loading and metabolic support, bioenergetic nutraceuticals must be precisely synchronized with physical exercise. Chrono-nutrition exploits the transient biochemical and hemodynamic windows opened by muscular contraction, ensuring that peak circulating nutrient levels coincide with heightened cellular responsiveness and microvascular perfusion [97]. In geriatric patients with compromised blood flow, this strategic timing is crucial to overcome transport limitations and optimize myocellular uptake [98,99].

The optimal administration schedule depends on each compound's distinct pharmacokinetic profile and primary metabolic vector. Transitioning from non-specific daily dosing to targeted chrono-nutritional programming guarantees that peak nutrient bioavailability aligns with post-exercise cellular signaling [97,98]. By ensuring that metabolic substrates are efficiently directed toward tissue repair, this approach circumvents transport barriers and maximizes functional outcomes in vulnerable older adults.

6. Targeted Nutraceutical Strategies in Clinical Rehabilitation and Pathological Settings

6.1. Orthopedic Rehabilitation: Post-Fracture and Arthroplasty Atrophy

Following acute hip fractures or elective total joint arthroplasty, prolonged physical immobilization induces rapid disuse muscle atrophy, heavily mediated by an acute burst of mitochondrial oxidative stress and subsequent activation of proteolytic pathways. In this phase, geriatric patients present with profound anabolic resistance, making conventional protein feeding insufficient to prevent appendicular muscle mass loss [100].

Integrating creatine monohydrate directly offsets immobilization-induced downregulation of muscle glycogen and GLUT4 expression [101], facilitating muscle force and cross-sectional area recovery during post-immobilization physical rehabilitation [102]. Concurrently, post-operative administration of targeted nutritional support, including omega-3 fatty acids and ubiquinol, helps attenuate localized mitochondrial ROS spikes and modulate biomarkers of sarcopenia and myocellular degradation such as myostatin during forced rest [103], with omega-3 supplementation showing clinical efficacy in preserving muscle volume and strength in older cohorts [104,105]. While these targeted interventions provide a strong metabolic rationale, direct evidence confirming a shortened time to independent walking in post-arthroplasty cohorts requires further dedicated investigation.

6.2. Rehabilitation in Chronic Pain

Rehabilitation protocols for elderly patients suffering from chronic pain conditions, such as chronic low back pain, osteoarthritic degenerative diseases, and persistent musculoskeletal syndromes, require multimodal interventions that break the pathological loop between nociceptive signaling, kinesiophobia, and muscle wasting [106,107]. Chronic pain induces a nociceptive sarcopenia or disuse atrophy, in which persistent nociceptive inputs and central sensitization restrict active movement, alter muscle fiber recruitment kinetics, and accelerate myofibrillar proteolysis [108,109]. At the sub-cellular level, this chronic immobility compromises mitochondrial complex activities, leading to an intracellular depletion of ATP pools and an upregulation of oxidative stress within deconditioned muscle tissues [110].

In this clinical scenario, bioactive lipid mediators such as Palmitoylethanolamide (PEA), amino acid derivatives like Acetyl-L-Carnitine (ALCAR), and phytotherapeutic ex-

tracts (e.g., *Astragalus membranaceus*) have been evaluated for mitigating neuroinflammation, peripheral nociceptor sensitization, and osteoarthritic joint pain [111,112]. Mechanistically, optimizing cellular energy charge, maintaining membrane lipid homeostasis, and harnessing natural anti-inflammatory pathways may help stabilize mitochondrial function and limit local reactive oxygen species (ROS) spikes involved in nociceptive signaling [47].

However, direct clinical evidence confirming mitochondrial synergy between these compounds and physical therapy remains insufficient, and their routine integration into formal rehabilitation protocols warrants further investigation.

6.3. Post-ICU Syndrome and Intensive Care Unit Acquired Weakness

Intensive Care Unit Acquired Weakness (ICUAW) and Post-Intensive Care Syndrome (PICS) in older adults represent critical manifestations of bioenergetic failure [113–115]. The combination of systemic inflammation, heavy sedation, mechanical ventilation, and corticosteroid use triggers widespread mitochondrial disintegration, characterized by cardiolipin peroxidation, mtDNA leakage, and a collapse of oxidative phosphorylation capacity. From a bioenergetic perspective, targeting organelle dysfunction represents a potential research framework to address this metabolic gridlock, given that severely damaged mitochondria may poorly metabolize standard macronutrient loads [113,114].

Under this theoretical model, compounds such as Urolithin A are being investigated for their capacity to stimulate mitophagy and clear dysfunctional mitochondria [40], while creatine monohydrate, high-quality proteins, and NAD⁺ precursors are hypothesized to support phosphagen recharging and cellular bioenergetics [116,117]. However, this multi-ingredient approach currently lacks verification from dedicated clinical trials in critically ill cohorts and should be regarded purely as a mechanistic research proposal rather than a clinical recommendation. Translating such targeted metabolic strategies into ICU and post-ICU care faces substantial challenges due to the extreme clinical heterogeneity of critically ill patients. Furthermore, rigorous safety evaluations are mandatory, particularly regarding renal and hepatic functional tolerance, metabolic clearance, and the physiological feasibility of enteral nutrition delivery in patients with altered gastrointestinal motility or organ dysfunction.

7. Methodological Considerations, Safety Profiles, and Translational Limitations

The clinical translation of mitochondrial-targeted nutraceuticals into geriatric rehabilitation is significantly challenged by methodological heterogeneity, variable safety margins, and distinct biochemical limitations [118]. To ensure internal consistency and avoid overstating clinical efficacy, the evaluation of these interventions must follow a strict hierarchy of evidence: (1) direct evidence from rehabilitation trials; (2) indirect clinical evidence from non-rehabilitation human cohorts; (3) human biomarker evidence; and (4) preclinical mechanistic data. Currently, most compounds rely heavily on preclinical or surrogate biomarker findings, while direct rehabilitation trials demonstrating hard functional improvements remain scarce.

A primary confounding factor across current clinical trials is the substantial variation in dosing strategies and baseline consumer profiles. For instance, while creatine monohydrate exhibits an exceptionally robust safety profile in older adults, optimal loading protocols remain debated, often varying between high-dose acute loading phases and low-dose long-term maintenance regimens, both of which face compliance issues due to mild gastrointestinal discomfort in frail cohorts [119]. Similarly, NAD⁺ precursors like nicotinamide riboside and nicotinamide mononucleotide demonstrate excellent tolerability at standard clinical doses up to one gram daily; however, their long-term effects on systemic

metabolic homeostasis, potential interaction with cellular methylation pathways, and safety in patients with undiagnosed pre-malignant conditions require deeper investigation [47]. These dosing discrepancies are further exacerbated by variable bioavailability, as seen with standard Coenzyme Q10 and ubiquinol, where absorption rates fluctuate widely based on the concurrent intake of dietary lipids, necessitating advanced lipid-nanoparticle delivery systems to achieve reproducible therapeutic plasma concentrations [21,120].

Furthermore, a significant translational gap arises from the reliance on surrogate metabolic biomarkers rather than hard functional endpoints [121]. Many randomized controlled trials report statistically significant improvements in intracellular ATP synthesis, mitochondrial DNA copy number, or circulating oxidative stress markers yet fail to translate these biochemical shifts into clinically meaningful improvements in gait speed, appendicular lean mass, or independence in activities of daily living [122]. This mismatch is heavily driven by small sample sizes, brief follow-up durations that rarely capture long-term tissue remodeling, and the omission of baseline nutritional screening, which frequently bundles nutrient-deficient responders with well-nourished non-responders. Additionally, safety evaluations in these trials often fail to adequately account for polypharmacy, a defining characteristic of geriatric rehabilitation populations. For example, the potential for mitochondrial nutraceuticals to alter cytochrome P450 enzyme kinetics or interfere with the pharmacokinetics of standard cardiovascular and antidiabetic drugs represents a critical unmapped risk [123]. Consequently, until large-scale, multi-center trials establish standardized, biomarker-validated dosing frameworks that demonstrate unequivocal functional efficacy over extended observation periods, and until findings move up the hierarchy from preclinical and biomarker data to direct rehabilitation evidence, the widespread clinical prescription of these compounds within standardized rehabilitation protocols remains constrained by systemic methodological uncertainty.

8. Structural Integration of Targeted Supplementation and Exercise

To overcome the complex anabolic resistance observed in geriatric rehabilitation, mitochondrial-targeted nutraceuticals must be strategically synchronized with specific training modalities to function as precise metabolic primers rather than parallel, isolated interventions [124]. In endurance and aerobic reconditioning paradigms aimed at vascular remodeling and mitochondrial network expansion, the clinical objective centers on maximizing the AMPK/SIRT1/PGC1- α axis. In this context, combining NAD⁺ precursors and ubiquinol with aerobic physical therapy is hypothesized to optimize the intracellular coenzyme pool and support inner mitochondrial membrane stability [125]. However, optimal nutrient-exercise timing protocols, such as pre-workout administration, and their capacity to enhance adaptive responses to lower-intensity training remain experimental strategies that require rigorous clinical validation in older rehabilitation cohorts.

Conversely, when physical therapy shifts toward progressive resistance training to counteract disuse atrophy and drive myofibrillar hypertrophy, the target becomes the mechanosensitive FAK/mTORC1 cascade. In this framework, continuous substrate loading with creatine monohydrate elevates intramuscular phosphocreatine reserves to sustain mechanical power output during resistance bouts, while the long-term incorporation of omega-3 fatty acids physically alters the sarcolemmal lipidome to enhance membrane fluidity [126,127]. By combining these structural adaptations with post-exercise whey protein matrices, this integrated approach simultaneously maximizes the muscle protein synthetic response and suppresses the chronic, low-grade systemic inflammation that drives muscle proteolysis [128]. Ultimately, this coordinated strategy ensures that the bioenergetic infrastructure is repaired and expanded in lockstep with hypertrophic growth, translating biochemical synergy into a rapid, sustained recovery of functional independence.

9. Summary of Key Evidence

The following table (Table 4) provides a structured, comprehensive overview of the mitochondrial-targeted nutraceuticals analyzed throughout this review, detailing their specific molecular mechanisms, targeted organelle pathways, and primary indications within geriatric rehabilitation contexts. To provide an intuitive overview of these molecular pathways, the targeted organelle sites and their corresponding nutraceutical modulators are visually synthesized in Figure 1.

Table 4. Molecular targets, primary mechanisms, and therapeutic indications of mitochondrial-targeted nutraceuticals in geriatric rehabilitation.

Nutraceutical Compound	Primary Target/Molecular Mechanism	Primary Geriatric Rehabilitation Indication
<i>Coenzyme Q10/Ubiquinol</i>	Electron transport chain (ETC) lipid-soluble antioxidant; transfers electrons from Complexes I/II to Complex III; mitigates inner mitochondrial membrane lipid peroxidation.	Sarcopenia mitigation, cardiovascular reconditioning, and management of chronic fatigue syndromes.
<i>Creatine Monohydrate</i>	Rapid phosphagen resynthesis via the creatine kinase system; upregulates GLUT4 expression and glycogen storage; stimulates downstream mTOR muscle anabolic signaling pathways.	Orthopedic rehabilitation, disuse muscle atrophy counteraction (post-fracture/arthroplasty), and ICUAW.
<i>Urolithin A</i>	Activates mitophagy pathways via both PINK1/Parkin-dependent and -independent mechanisms; clears dysfunctional, uncoupled mitochondria; reduces systemic mitochondrial DNA leakage and inflammation.	Post-ICU Syndrome (PICS), advanced physical frailty, and chronic systemic low-grade inflammation (inflammaging).
<i>NAD⁺ Precursors (NR/NMN)</i>	Replenishes cellular and mitochondrial NAD ⁺ pools; activates sirtuins (SIRT1/SIRT3); enhances OXPHOS kinetics and stimulates mitochondrial biogenesis via PGC-1 α .	Neurological rehabilitation, metabolic syndrome, and myofibrillar kinetic rescue.
<i>Acetyl-L-Carnitine (ALCAR)</i>	Facilitates long-chain fatty acid transport across the inner mitochondrial membrane via CPTI/CPTII; enhances central cholinergic neurotransmission and neural drive.	Neurogenic sarcopenia, central motor fatigue mitigation, and peripheral neuropathy recovery.
<i>Omega-3 PUFAs (EPA/DHA)</i>	Modulates myocellular lipidome and mitochondrial membrane fluidity; upregulates structural and uncoupling genes (UQCRC1, UCP3); dampens pro-inflammatory signaling.	Anabolic resistance reversal, muscle quality restoration, and post-operative orthopedic recovery.
<i>Inorganic Nitrate (NO₃[−])</i>	Substrate for NO ₃ [−] —NO ₂ [−] —NO pathway; modulates cellular energetics and mononuclear oxidative markers.	Microvascular reconditioning and exercise tolerance support (efficacy on muscle strength unproven in trials).
<i>Sodium Nitrite (NO₂[−])</i>	Direct precursor in nitric oxide pathway; suppresses mitochondrial-specific ROS bioactivity and preserves IMM integrity.	Localized oxidative stress mitigation, vascular endothelial deconditioning, and peripheral arterial performance.
<i>Hydrogen-Rich Water (HRW)</i>	Selective scavenger of hydroxyl radicals; mitigates acute contraction-induced muscle injury biomarkers.	Adjunctive post-exercise recovery and exertional oxidative stress reduction (pilot clinical evidence).

Abbreviations: ALCAR: Acetyl-L-Carnitine; DHA: Docosahexaenoic Acid; EPA: Eicosapentaenoic Acid; ETC: Electron Transport Chain; GLUT4: Glucose Transporter Type 4; ICUAW: Intensive Care Unit-Acquired Weakness; mTOR: Mechanistic Target of Rapamycin; NAD⁺: Nicotinamide Adenine Dinucleotide; NMN: Nicotinamide Mononucleotide; NR: Nicotinamide Riboside; OXPHOS: Oxidative Phosphorylation; PGC-1 α : Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha; PICS: Post-Intensive Care Syndrome; PINK1: PTEN-Induced Kinase 1; PUFAs: Polyunsaturated Fatty Acids; ROS: Reactive Oxygen Species; UCP3: Uncoupling Protein 3; UQCRC1: Ubiquinol-Cytochrome C Reductase Core Protein 1.

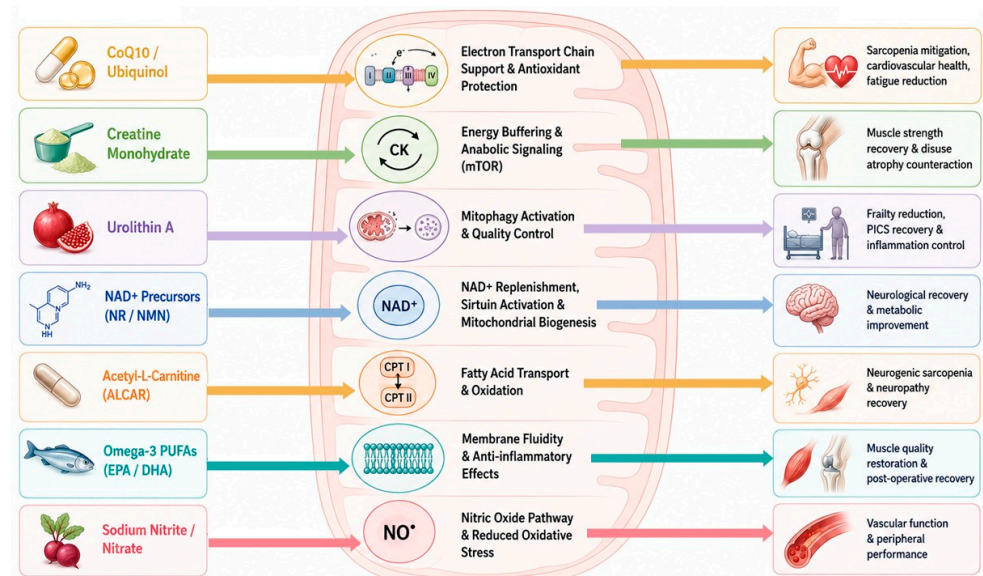


Figure 1. Targeted nutraceuticals and mitochondrial mechanisms in geriatric rehabilitation. Schematic overview illustrating the primary cellular targets, organelle-level mechanisms, and functional clinical benefits of bioenergetic supplementation in older adults undergoing physical therapy.

10. Future Perspectives and Conclusions

The translation of mitochondrial-targeted nutraceuticals into geriatric rehabilitation warrants a transition from empirical supplementation toward a rigorous, evidence-informed research framework. To date, the most robust clinical evidence supports the adjunctive use of creatine monohydrate during resistance exercise to counteract muscle atrophy and enhance functional strength in older populations. Conversely, for the majority of other bioenergetic substrates, including NAD⁺ precursors, Urolithin A, Coenzyme Q10, and specialized phytotherapeutics, current support relies primarily on surrogate bioenergetic markers, non-rehabilitation clinical cohorts, or preclinical models, with direct trial evidence in physical therapy settings remaining limited. Moreover, the clinical rationale for complex, synchronized multi-ingredient formulations and specific timing protocols awaits empirical validation.

Moving forward, the research agenda must prioritize adequately powered, randomized controlled trials centered on hard functional endpoints, such as gait velocity, physical autonomy, and performance in activities of daily living, rather than isolated biochemical metrics. While emerging multi-omics profiling and digital metabolic monitoring offer intriguing prospective tools for identifying baseline mitochondrial phenotypes, their clinical utility in guiding targeted nutritional interventions requires systematic testing.

In conclusion, targeting organelle bioenergetics offers a compelling mechanistic framework to complement physical rehabilitation in aging cohorts. However, its routine clinical adoption remains limited by methodological heterogeneity, potential polypharmacy interactions, and variable bioavailability. Establishing standardized dosing regimens, verifying long-term safety, and demonstrating tangible functional recovery will be essential to define the true therapeutic value of mitochondrial interventions in geriatric care.

Author Contributions: Conceptualization, A.T. and L.L.; methodology, A.T. and L.L.; validation, A.T., L.L. and M.I.; formal analysis, A.T., L.L. and M.I.; investigation, A.T. and L.L.; data curation, A.T. and L.L.; writing—original draft preparation, A.T. and L.L.; writing—review and editing, M.I., F.U. and A.d.S.; visualization, A.T., L.L. and F.U.; supervision, M.I. and A.d.S.; project administration, A.T. and L.L.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

5XSST	5-Repetition Chair Stand Test
30CST	30-Second Chair Stand Test
ALCAR	Acetyl-L-Carnitine
AMP	Adenosine Monophosphate
AMPK	AMP-Activated Protein Kinase
ANT	Adenine Nucleotide Translocator
ATP	Adenosine Triphosphate
CD38	Cluster of Differentiation 38
cGAS-STING	Cyclic GMP-AMP Synthase-Stimulator of Interferon Genes
CK	Creatine Kinase
CoQ10	Coenzyme Q10
CPT	Carnitine Palmitoyltransferase
CRP	C-Reactive Protein
DHA	Docosahexaenoic Acid
DNA	Deoxyribonucleic Acid
EPA	Eicosapentaenoic Acid
ETC	Electron Transport Chain
FAK	Focal Adhesion Kinase
GLUT4	Glucose Transporter Type 4
HIIT	High-Intensity Interval Training
ICUAW	Intensive Care Unit-Acquired Weakness
IMM	Inner Mitochondrial Membrane
LCFAs	Long-Chain Fatty Acids
MeSH	Medical Subject Heading
MnSOD	Manganese Superoxide Dismutase
MQC	Mitochondrial Quality Control
mtDNA	Mitochondrial DNA
mTOR/mTORC1	(Mechanistic) Target of Rapamycin Complex 1
mtROS	Mitochondrial Reactive Oxygen Species
n-3 PUFAs	Omega-3 Polyunsaturated Fatty Acids
NAD ⁺ /NADH	Nicotinamide Adenine Dinucleotide (oxidized/reduced)
NAMPT	Nicotinamide Phosphoribosyltransferase
NF-κB	Nuclear Factor Kappa B
NLRP3	NLR Family Pyrin Domain Containing 3
NMES	Neuromuscular Electrical Stimulation
NMN	Nicotinamide Mononucleotide
NR	Nicotinamide Riboside
OXPHOS	Oxidative Phosphorylation
PARPs	Poly(ADP-ribose) Polymerases
PCr	Phosphocreatine
PEA	Palmitoylethanolamide
PGC-1α	Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-Alpha
PICS	Post-Intensive Care Syndrome
PI3K/Akt	Phosphoinositide 3-Kinase/Protein Kinase B
PINK1	PTEN-Induced Kinase 1

ROS	Reactive Oxygen Species
SIRT	Sirtuin
SMI	Skeletal Muscle Index
TCA	Tricarboxylic Acid
UA	Urolithin A
UCP3	Uncoupling Protein 3
UQCRC1	Ubiquinol-Cytochrome C Reductase Core Protein 1
VDAC	Voltage-Dependent Anion Channel
VO2 peak	Peak Oxygen Consumption

References

1. The Lancet Healthy Longevity. Care for ageing populations globally. *Lancet Healthy Longev.* **2021**, *2*, e180. [[CrossRef](#)] [[PubMed](#)]
2. Crimmins, E.M. Lifespan and Healthspan: Past, Present, and Promise. *Gerontologist* **2015**, *55*, 901–911. [[CrossRef](#)] [[PubMed](#)]
3. Damanti, S.; Senini, E.; De Lorenzo, R.; Merolla, A.; Santoro, S.; Festorazzi, C.; Messina, M.; Vitali, G.; Sciorati, C.; Rovere-Querini, P. Acute Sarcopenia: Mechanisms and Management. *Nutrients* **2024**, *16*, 3428. [[CrossRef](#)] [[PubMed](#)]
4. Crocker, T.; Forster, A.; Young, J.; Brown, L.; Ozer, S.; Smith, J.; Green, J.; Hardy, J.; Burns, E.; Glidewell, E.; et al. Physical rehabilitation for older people in long-term care. *Cochrane Database Syst. Rev.* **2013**, *2013*, Cd004294. [[CrossRef](#)]
5. Lista, A.J.; de Pinho, L.G.; Correia, T.; Afonso, C.; Cardoso, I.; Fonseca, C. Psychosocial and rehabilitation interventions and health gains in older persons in long-term care: A systematic review. *Int. J. Nurs. Stud.* **2025**, *172*, 105219. [[CrossRef](#)] [[PubMed](#)]
6. Phillips, B.E.; Williams, J.P.; Greenhaff, P.L.; Smith, K.; Atherton, P.J. Physiological adaptations to resistance exercise as a function of age. *JCI Insight* **2017**, *2*, e95581. [[CrossRef](#)] [[PubMed](#)]
7. Verstraeten, L.M.G.; Reijnierse, E.M.; Spoelstra, T.; Meskers, C.G.M.; Maier, A.B. The impact of mobility limitations on geriatric rehabilitation outcomes: Positive effects of resistance exercise training (RESORT). *J. Cachexia Sarcopenia Muscle* **2024**, *15*, 2094–2103. [[CrossRef](#)] [[PubMed](#)]
8. Zhang, X.; Gao, Y.; Zhang, S.; Wang, Y.; Pei, X.; Chen, Y.; Zhang, J.; Zhang, Y.; Du, Y.; Hao, S.; et al. Mitochondrial dysfunction in the regulation of aging and aging-related diseases. *Cell Commun. Signal. CCS* **2025**, *23*, 290. [[CrossRef](#)] [[PubMed](#)]
9. Crescenzo, R.; Bianco, F.; Mazzoli, A.; Giacco, A.; Liverini, G.; Iossa, S. Skeletal muscle mitochondrial energetic efficiency and aging. *Int. J. Mol. Sci.* **2015**, *16*, 10674–10685. [[CrossRef](#)] [[PubMed](#)]
10. Wenz, T. Mitochondria and PGC-1 α in Aging and Age-Associated Diseases. *J. Aging Res.* **2011**, *2011*, 810619. [[CrossRef](#)] [[PubMed](#)]
11. Patyal, P.; Azhar, G.; Verma, A.; Sharma, S.; Shrivastava, J.; Abdi, S.A.H.; Zhang, X.; Wei, J.Y. Mitochondrial Dynamics in Aging Heart. *Biomedicines* **2025**, *13*, 2603. [[CrossRef](#)]
12. Chen, G.; Kroemer, G.; Kepp, O. Mitophagy: An Emerging Role in Aging and Age-Associated Diseases. *Front. Cell Dev. Biol.* **2020**, *8*, 200. [[CrossRef](#)]
13. Fry, C.S.; Drummond, M.J.; Glynn, E.L.; Dickinson, J.M.; Gundermann, D.M.; Timmerman, K.L.; Walker, D.K.; Dhanani, S.; Volpi, E.; Rasmussen, B.B. Aging impairs contraction-induced human skeletal muscle mTORC1 signaling and protein synthesis. *Skelet. Muscle* **2011**, *1*, 11. [[CrossRef](#)]
14. Wall, B.T.; Cermak, N.M.; van Loon, L.J. Dietary protein considerations to support active aging. *Sports Med.* **2014**, *44*, S185–S194. [[CrossRef](#)] [[PubMed](#)]
15. Liu, S.; Zhang, L.; Li, S. Advances in nutritional supplementation for sarcopenia management. *Front. Nutr.* **2023**, *10*, 1189522. [[CrossRef](#)] [[PubMed](#)]
16. Kaufman, M.W.; DeParis, S.; Oppezzo, M.; Mah, C.; Roche, M.; Frehlich, L.; Fredericson, M. Nutritional Supplements for Healthy Aging: A Critical Analysis Review. *Am. J. Lifestyle Med.* **2025**, *19*, 346–360. [[CrossRef](#)] [[PubMed](#)]
17. Lippi, L.; Uberti, F.; Folli, A.; Turco, A.; Curci, C.; d’Abrosca, F.; de Sire, A.; Invernizzi, M. Impact of nutraceuticals and dietary supplements on mitochondria modifications in healthy aging: A systematic review of randomized controlled trials. *Aging Clin. Exp. Res.* **2022**, *34*, 2659–2674. [[CrossRef](#)]
18. Johnson, M.L.; Robinson, M.M.; Nair, K.S. Skeletal muscle aging and the mitochondrion. *Trends Endocrinol. Metab. TEM* **2013**, *24*, 247–256. [[CrossRef](#)] [[PubMed](#)]
19. Baethge, C.; Goldbeck-Wood, S.; Mertens, S. SANRA—a scale for the quality assessment of narrative review articles. *Res. Integr. Peer Rev.* **2019**, *4*, 5. [[CrossRef](#)] [[PubMed](#)]
20. Hernández-Camacho, J.D.; Bernier, M.; López-Lluch, G.; Navas, P. Coenzyme Q₁₀ Supplementation in Aging and Disease. *Front. Physiol.* **2018**, *9*, 44. [[CrossRef](#)]
21. Mantle, D.; Dybring, A. Bioavailability of Coenzyme Q₁₀: An Overview of the Absorption Process and Subsequent Metabolism. *Antioxidants* **2020**, *9*, 386. [[CrossRef](#)]

22. Nankivell, M.C.; Rosenfeldt, F.; Reddan, J.M.; de Haan, J.B.; Zhang Ping, C.; Campbell-Brown, B.; Pipingas, A.; Pase, M.P.; Ou, R.; Cooke, M.B.; et al. Effect of Ubiquinol on Cognitive Function, Blood Pressure, Arterial Stiffness, and Biomarkers of Oxidative Stress and Inflammation in the Elderly: A Randomized Trial. *Antioxidants* **2026**, *15*, 806. [\[CrossRef\]](#)
23. Apostolova, N.; Victor, V.M. Molecular strategies for targeting antioxidants to mitochondria: Therapeutic implications. *Antioxid. Redox Signal.* **2015**, *22*, 686–729. [\[CrossRef\]](#)
24. Wang, Y.; Lilienfeldt, N.; Hekimi, S. Understanding coenzyme Q. *Physiol. Rev.* **2024**, *104*, 1533–1610. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Bolt, J.; Sandhu, S.; Mohammadi, A. Effect of Coenzyme Q10 Supplementation on Sarcopenia, Frailty, and Falls: A Scoping Review. *J. Nutr. Health Aging* **2023**, *27*, 586–592. [\[CrossRef\]](#)
26. Bagheri, N.; Kargarfard, M.; Bagheri, R.; Dutheil, F. Effects of Coenzyme Q₁₀ Supplementation on Physical Function Adaptations to High-Intensity Interval Training in Older Adults. *Nutrients* **2025**, *17*, 3959. [\[CrossRef\]](#) [\[PubMed\]](#)
27. de la Bella-Garzón, R.; Fernández-Portero, C.; Alarcón, D.; Amián, J.G.; López-Lluch, G. Levels of Plasma Coenzyme Q₁₀ Are Associated with Physical Capacity and Cardiovascular Risk in the Elderly. *Antioxidants* **2022**, *11*, 279. [\[CrossRef\]](#) [\[PubMed\]](#)
28. Su, Y. Three-dimensional network of creatine metabolism: From intracellular energy shuttle to systemic metabolic regulatory switch. *Mol. Metab.* **2025**, *100*, 102228. [\[CrossRef\]](#) [\[PubMed\]](#)
29. Bonilla, D.A.; Kreider, R.B.; Stout, J.R.; Forero, D.A.; Kerksick, C.M.; Roberts, M.D.; Rawson, E.S. Metabolic Basis of Creatine in Health and Disease: A Bioinformatics-Assisted Review. *Nutrients* **2021**, *13*, 1238. [\[CrossRef\]](#) [\[PubMed\]](#)
30. Stout, J.R.; Sue Graves, B.; Cramer, J.T.; Goldstein, E.R.; Costa, P.B.; Smith, A.E.; Walter, A.A. Effects of creatine supplementation on the onset of neuromuscular fatigue threshold and muscle strength in elderly men and women (64–86 years). *J. Nutr. Health Aging* **2007**, *11*, 459–464. [\[PubMed\]](#)
31. Candow, D.G.; Forbes, S.C.; Chilibeck, P.D.; Cornish, S.M.; Antonio, J.; Kreider, R.B. Effectiveness of Creatine Supplementation on Aging Muscle and Bone: Focus on Falls Prevention and Inflammation. *J. Clin. Med.* **2019**, *8*, 488. [\[CrossRef\]](#) [\[PubMed\]](#)
32. Ribeiro, F.; Forbes, S.C.; Candow, D.G.; Perim, P.; Kerksick, C.; Johnson, K.; Lancha, A.H.; Rosa Neto, J.C. Creatine supplementation for preventing muscle atrophy in patients taking incretin-based pharmacotherapies: A perspective. *J. Nutr. Physiol.* **2026**, 100028. [\[CrossRef\]](#)
33. Candow, D.G.; Ostojic, S.M.; Chilibeck, P.D.; Longobardi, I.; Gualano, B.; Tarnopolsky, M.A.; Wallimann, T.; Moriarty, T.; Kreider, R.B.; Forbes, S.C.; et al. Creatine monohydrate supplementation for older adults and clinical populations. *J. Int. Soc. Sports Nutr.* **2025**, *22*, 2534130. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Chami, J.; Candow, D.G. Effect of Creatine Supplementation Dosing Strategies on Aging Muscle Performance. *J. Nutr. Health Aging* **2019**, *23*, 281–285. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Sharifian, G.; Aseminia, P.; Heidary, D.; Esformes, J.I. Impact of creatine supplementation and exercise training in older adults: A systematic review and meta-analysis. *Eur. Rev. Aging Phys. Act. Off. J. Eur. Group Res. Elder. Phys. Act.* **2025**, *22*, 17. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Ribeiro, M.; Alvarenga, L.; Cardozo, L.; Baptista, B.G.; Nascimento, D.; Esgalhado, M.; Mafra, D. Urolithin as a Metabolite of Ellagitannins and Ellagic Acid from Fruits and Nuts Produced by the Gut Microbiota: Its Role on Non-Communicable Diseases. *Curr. Nutr. Rep.* **2025**, *14*, 55. [\[CrossRef\]](#) [\[PubMed\]](#)
37. Singh, A.; D'Amico, D.; Andreux, P.A.; Fouassier, A.M.; Blanco-Bose, W.; Evans, M.; Aebischer, P.; Auwerx, J.; Rinsch, C. Urolithin A improves muscle strength, exercise performance, and biomarkers of mitochondrial health in a randomized trial in middle-aged adults. *Cell Rep. Med.* **2022**, *3*, 100633. [\[CrossRef\]](#) [\[PubMed\]](#)
38. Tsui, K.-H.; Cheng, S.-H.; Wang, B.; Lin, P.-H.; Raj, E.N.; Lin, L.-T.; Chang, R.; Wen, Z.-H.; Tsai, A.P.; Li, C.-J. Mitochondrial quality control as a central pharmacological target in aging. *Pharmacol. Res.* **2026**, *227*, 108188. [\[CrossRef\]](#) [\[PubMed\]](#)
39. Faitg, J.; D'Amico, D.; Rinsch, C.; Singh, A. Mitophagy Activation by Urolithin A to Target Muscle Aging. *Calcif. Tissue Int.* **2024**, *114*, 53–59. [\[CrossRef\]](#) [\[PubMed\]](#)
40. Denk, D.; Singh, A.; Kasler, H.G.; D'Amico, D.; Rey, J.; Alcobér-Boquet, L.; Gorol, J.M.; Steup, C.; Tiwari, R.; Kwok, R.; et al. Effect of the mitophagy inducer urolithin A on age-related immune decline: A randomized, placebo-controlled trial. *Nat. Aging* **2025**, *5*, 2309–2322. [\[CrossRef\]](#) [\[PubMed\]](#)
41. Wang, Q.; Sun, Y.; Li, T.Y.; Auwerx, J. Mitophagy in the pathogenesis and management of disease. *Cell Res.* **2026**, *36*, 11–37. [\[CrossRef\]](#) [\[PubMed\]](#)
42. Chen, X.; Wu, Z.; Yu, K.; Zhang, J.; Di, H. Mitochondrial Regulation of the NLRP3 Inflammasome in Diabetic Kidney Disease: From Mechanisms to Therapeutic Strategies. *Int. J. Mol. Sci.* **2026**, *27*, 4819. [\[CrossRef\]](#) [\[PubMed\]](#)
43. Liu, S.; D'Amico, D.; Shankland, E.; Bhayana, S.; Garcia, J.M.; Aebischer, P.; Rinsch, C.; Singh, A.; Marcinek, D.J. Effect of Urolithin A Supplementation on Muscle Endurance and Mitochondrial Health in Older Adults: A Randomized Clinical Trial. *JAMA Netw. Open* **2022**, *5*, e2144279. [\[CrossRef\]](#) [\[PubMed\]](#)
44. Xie, N.; Zhang, L.; Gao, W.; Huang, C.; Huber, P.E.; Zhou, X.; Li, C.; Shen, G.; Zou, B. NAD⁺ metabolism: Pathophysiologic mechanisms and therapeutic potential. *Signal Transduct. Target. Ther.* **2020**, *5*, 227. [\[CrossRef\]](#) [\[PubMed\]](#)

45. Poltronieri, P.; Ćerekovic, N. Roles of Nicotinamide Adenine Dinucleotide (NAD⁺) in Biological Systems. *Challenges* **2018**, *9*, 3. [[CrossRef](#)]
46. Imai, S.; Guarente, L. NAD⁺ and sirtuins in aging and disease. *Trends Cell Biol.* **2014**, *24*, 464–471. [[CrossRef](#)] [[PubMed](#)]
47. Yusri, K.; Jose, S.; Vermeulen, K.S.; Tan, T.C.M.; Sorrentino, V. The role of NAD⁺ metabolism and its modulation of mitochondria in aging and disease. *npj Metab. Health Dis.* **2025**, *3*, 26. [[CrossRef](#)] [[PubMed](#)]
48. Alegre, G.F.S.; Pastore, G.M. NAD⁺ Precursors Nicotinamide Mononucleotide (NMN) and Nicotinamide Riboside (NR): Potential Dietary Contribution to Health. *Curr. Nutr. Rep.* **2023**, *12*, 445–464. [[CrossRef](#)] [[PubMed](#)]
49. Freeberg, K.A.; Udovich, C.C.; Martens, C.R.; Seals, D.R.; Craighead, D.H. Dietary Supplementation With NAD⁺-Boosting Compounds in Humans: Current Knowledge and Future Directions. *J. Gerontol. Ser. A Biol. Sci. Med. Sci.* **2023**, *78*, 2435–2448. [[CrossRef](#)] [[PubMed](#)]
50. Sun, Y.; Han, J.-C.; Tran, K.; Pham, T.; Zhou, Q.; Lu, J. An integrated anti-aging framework targeting NAD⁺ homeostasis, mitochondrial quality control, and redox stability: Roles of NMN/NR, PQQ, and EGT. *Redox Biol.* **2026**, *93*, 104191. [[CrossRef](#)] [[PubMed](#)]
51. Šešelja, K.; Šimunić, E.; Sobočanec, S.; Podgorski, I.I.; Pinterić, M.; Hadžija, M.P.; Balog, T.; Belužić, R. SIRT3-Mediated Mitochondrial Regulation and Driver Tissues in Systemic Aging. *Genes* **2025**, *16*, 1497. [[CrossRef](#)] [[PubMed](#)]
52. You, Y.; Wang, Z. Roles of SIRT3 in aging and aging-related diseases. *Int. J. Biol. Sci.* **2025**, *21*, 5135–5163. [[CrossRef](#)] [[PubMed](#)]
53. Elhassan, Y.S.; Kluckova, K.; Fletcher, R.S.; Schmidt, M.S.; Garten, A.; Doig, C.L.; Cartwright, D.M.; Oakey, L.; Burley, C.V.; Jenkinson, N.; et al. Nicotinamide Riboside Augments the Aged Human Skeletal Muscle NAD⁺ Metabolome and Induces Transcriptomic and Anti-inflammatory Signatures. *Cell Rep.* **2019**, *28*, 1717–1728.e1716. [[CrossRef](#)] [[PubMed](#)]
54. Morifuji, M.; Higashi, S.; Ebihara, S.; Nagata, M. Ingestion of β -nicotinamide mononucleotide increased blood NAD levels, maintained walking speed, and improved sleep quality in older adults in a double-blind randomized, placebo-controlled study. *GeroScience* **2024**, *46*, 4671–4688. [[CrossRef](#)] [[PubMed](#)]
55. Prokopidis, K.; Moriarty, F.; Bahat, G.; McLean, J.; Church, D.D.; Patel, H.P. The Effect of Nicotinamide Mononucleotide and Riboside on Skeletal Muscle Mass and Function: A Systematic Review and Meta-Analysis. *J. Cachexia Sarcopenia Muscle* **2025**, *16*, e13799. [[CrossRef](#)] [[PubMed](#)]
56. De Sire, A.; Marotta, N.; Prestifilippo, E.; Calafiore, D.; Lippi, L.; Sconza, C.; Muraca, L.; Invernizzi, M.; Mezzan, K.; Ammendolia, A. Influence of hand grip strength test and short physical performance battery on FRAX in post-menopausal women: A machine learning cross-sectional study. *J. Sports Med. Phys. Fit.* **2023**, *64*, 293–300. [[CrossRef](#)] [[PubMed](#)]
57. Virmani, M.A.; Cirulli, M. The Role of L-Carnitine in Mitochondria, Prevention of Metabolic Inflexibility and Disease Initiation. *Int. J. Mol. Sci.* **2022**, *23*, 2717. [[CrossRef](#)] [[PubMed](#)]
58. Panov, A.V.; Mayorov, V.I.; Dikalov, S.I. Role of Fatty Acids β -Oxidation in the Metabolic Interactions Between Organs. *Int. J. Mol. Sci.* **2024**, *25*, 12740. [[CrossRef](#)] [[PubMed](#)]
59. Chee, C.; Shannon, C.E.; Burns, A.; Selby, A.L.; Wilkinson, D.; Smith, K.; Greenhaff, P.L.; Stephens, F.B. Increasing skeletal muscle carnitine content in older individuals increases whole-body fat oxidation during moderate-intensity exercise. *Aging Cell* **2021**, *20*, e13303. [[CrossRef](#)] [[PubMed](#)]
60. Malaguarnera, G.; Catania, V.E.; Bonfiglio, C.; Bertino, G.; Vicari, E.; Malaguarnera, M. Carnitine Serum Levels in Frail Older Subjects. *Nutrients* **2020**, *12*, 3887. [[CrossRef](#)] [[PubMed](#)]
61. Nemkov, T.; Key, A.; Stephenson, D.; Earley, E.J.; Keele, G.R.; Hay, A.; Amireault, P.; Casimir, M.; Dussiot, M.; Dzieciatkowska, M.J.B. Genetic regulation of carnitine metabolism controls lipid damage repair and aging RBC hemolysis in vivo and in vitro. *Blood* **2024**, *143*, 2517–2533. [[CrossRef](#)] [[PubMed](#)]
62. Badrasawi, M.; Shahar, S.; Zahara, A.M.; Nor Fadilah, R.; Singh, D.K. Efficacy of L-carnitine supplementation on frailty status and its biomarkers, nutritional status, and physical and cognitive function among prefrail older adults: A double-blind, randomized, placebo-controlled clinical trial. *Clin. Interv. Aging* **2016**, *11*, 1675–1686. [[CrossRef](#)] [[PubMed](#)]
63. Malaguarnera, M.; Cammalleri, L.; Gargante, M.P.; Vacante, M.; Colonna, V.; Motta, M. L-Carnitine treatment reduces severity of physical and mental fatigue and increases cognitive functions in centenarians: A randomized and controlled clinical trial. *Am. J. Clin. Nutr.* **2007**, *86*, 1738–1744. [[CrossRef](#)] [[PubMed](#)]
64. Ticinesi, A.; Meschi, T.; Lauretani, F.; Felis, G.; Franchi, F.; Pedrollo, C.; Barichella, M.; Benati, G.; Di Nuzzo, S.; Ceda, G.P.; et al. Nutrition and Inflammation in Older Individuals: Focus on Vitamin D, n-3 Polyunsaturated Fatty Acids and Whey Proteins. *Nutrients* **2016**, *8*, 186. [[CrossRef](#)] [[PubMed](#)]
65. Yoshino, J.; Smith, G.I.; Kelly, S.C.; Jullian, S.; Reeds, D.N.; Mittendorfer, B. Effect of dietary n-3 PUFA supplementation on the muscle transcriptome in older adults. *Physiol. Rep.* **2016**, *4*, e12785. [[CrossRef](#)] [[PubMed](#)]
66. Gray, S.R.; Mittendorfer, B. Fish oil-derived n-3 polyunsaturated fatty acids for the prevention and treatment of sarcopenia. *Curr. Opin. Clin. Nutr. Metab. Care* **2018**, *21*, 104–109. [[CrossRef](#)] [[PubMed](#)]
67. Huang, Y.H.; Chiu, W.C.; Hsu, Y.P.; Lo, Y.L.; Wang, Y.H. Effects of Omega-3 Fatty Acids on Muscle Mass, Muscle Strength and Muscle Performance among the Elderly: A Meta-Analysis. *Nutrients* **2020**, *12*, 3739. [[CrossRef](#)] [[PubMed](#)]

68. Dam, D.L.; Christensen, J.A.; Olsen, P.Ø.; Wilson, J.J.; Tully, M.A.; Buhl, S.F.; Caserotti, P. Impact of Omega-3 Fatty Acids Supplementation Combined with Resistance Training on Muscle Mass, Neuromuscular and Physical Function in Older Adults: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *J. Ageing Longev.* **2025**, *5*, 4. [\[CrossRef\]](#)
69. Okut, S.; Ozan, M.; Buzdağlı, Y.; Uçar, H.; İnaç, M.R.; Han, M.T.; Bayram, E.; Kiliç Baygutalp, N. The Effects of Omega-3 Supplementation Combined with Strength Training on Neuro-Biomarkers, Inflammatory and Antioxidant Responses, and the Lipid Profile in Physically Healthy Adults. *Nutrients* **2025**, *17*, 2088. [\[CrossRef\]](#) [\[PubMed\]](#)
70. Cornish, S.M.; Cordingley, D.M.; Shaw, K.A.; Forbes, S.C.; Leonhardt, T.; Bristol, A.; Candow, D.G.; Chilibeck, P.D. Effects of Omega-3 Supplementation Alone and Combined with Resistance Exercise on Skeletal Muscle in Older Adults: A Systematic Review and Meta-Analysis. *Nutrients* **2022**, *14*, 2221. [\[CrossRef\]](#) [\[PubMed\]](#)
71. Rossman, M.J.; Gioscia-Ryan, R.A.; Santos-Parker, J.R.; Ziemba, B.P.; Lubieniecki, K.L.; Johnson, L.C.; Poliektov, N.E.; Bispham, N.Z.; Woodward, K.A.; Nagy, E.E.; et al. Inorganic Nitrite Supplementation Improves Endothelial Function With Aging. *Hypertension* **2021**, *77*, 1212–1222. [\[CrossRef\]](#) [\[PubMed\]](#)
72. Hu, D.; Kabayama, S.; Watanabe, Y.; Cui, Y. Health Benefits of Electrolyzed Hydrogen Water: Antioxidant and Anti-Inflammatory Effects in Living Organisms. *Antioxidants* **2024**, *13*, 313. [\[CrossRef\]](#) [\[PubMed\]](#)
73. Mizuno, E.; Sato, T.; Okada, K.; Miura, I.; Shoda, J.; Saito, M.; Mori, Y.; Oh, S.; Isobe, T. Hydrogen-rich water improves endurance by reducing skeletal muscle oxidative stress and inflammatory responses. *Front. Nutr.* **2026**, *13*, 1722091. [\[CrossRef\]](#) [\[PubMed\]](#)
74. Ferrer, M.D.; Capó, X.; Reynés, C.; Quetglas, M.; Salaberry, E.; Tonolo, F.; Suau, R.; Marí, B.; Tur, J.A.; Sureda, A.; et al. Dietary Sodium Nitrate Activates Antioxidant and Mitochondrial Dynamics Genes after Moderate Intensity Acute Exercise in Metabolic Syndrome Patients. *J. Clin. Med.* **2021**, *10*, 2618. [\[CrossRef\]](#) [\[PubMed\]](#)
75. Justice, J.N.; Johnson, L.C.; DeVan, A.E.; Cruickshank-Quinn, C.; Reisdorph, N.; Bassett, C.J.; Evans, T.D.; Brooks, F.A.; Bryan, N.S.; Chonchol, M.B.; et al. Improved motor and cognitive performance with sodium nitrite supplementation is related to small metabolite signatures: A pilot trial in middle-aged and older adults. *Aging* **2015**, *7*, 1004–1021. [\[CrossRef\]](#) [\[PubMed\]](#)
76. Zhang, Y.; Ying, Y.; Zu, X.; Ding, L.; Shi, X.; Wang, J.; Li, X.; Li, C.; Zhou, Q.; Shen, H.; et al. Mechanism by which hydrogen-rich water mitigates exercise-induced fatigue: Activation of the immunoresponsive gene 1-itaconate/nuclear factor erythroid 2-related factor 2/heme oxygenase-1 pathway. *Med. Gas Res.* **2026**, *16*, 26–32. [\[CrossRef\]](#) [\[PubMed\]](#)
77. Kuzmanovic, J.; Todorovic, N.; Ranisavljev, M.; Javorac, D.; Korovljev, D.; Tarnava, A.; Stajer, V.; Ostojic, S.M. The effects of drinking hydrogen-rich water for six weeks on exercise-related biomarkers in exercise-naïve men and women over 50 years following resistance training program: A randomized controlled pilot trial. *Res. Sports Med.* **2025**, *33*, 711–721. [\[CrossRef\]](#) [\[PubMed\]](#)
78. Zhou, Q.; Li, H.; Zhang, Y.; Zhao, Y.; Wang, C.; Liu, C. Hydrogen-Rich Water to Enhance Exercise Performance: A Review of Effects and Mechanisms. *Metabolites* **2024**, *14*, 537. [\[CrossRef\]](#) [\[PubMed\]](#)
79. Bond, P. Regulation of mTORC1 by growth factors, energy status, amino acids and mechanical stimuli at a glance. *J. Int. Soc. Sports Nutr.* **2016**, *13*, 8. [\[CrossRef\]](#) [\[PubMed\]](#)
80. Klossner, S.; Durieux, A.C.; Freyssen, D.; Flueck, M. Mechano-transduction to muscle protein synthesis is modulated by FAK. *Eur. J. Appl. Physiol.* **2009**, *106*, 389–398. [\[CrossRef\]](#) [\[PubMed\]](#)
81. Tang, H.; Inoki, K.; Brooks, S.V.; Okazawa, H.; Lee, M.; Wang, J.; Kim, M.; Kennedy, C.L.; Macpherson, P.C.D.; Ji, X.; et al. mTORC1 underlies age-related muscle fiber damage and loss by inducing oxidative stress and catabolism. *Aging Cell* **2019**, *18*, e12943. [\[CrossRef\]](#) [\[PubMed\]](#)
82. Lippi, L.; de Sire, A.; Mezian, K.; Curci, C.; Perrero, L.; Turco, A.; Andarolo, S.; Ammendolia, A.; Fusco, N.; Invernizzi, M. Impact of exercise training on muscle mitochondria modifications in older adults: A systematic review of randomized controlled trials. *Aging Clin. Exp. Res.* **2022**, *34*, 1495–1510. [\[CrossRef\]](#) [\[PubMed\]](#)
83. Nilsson, M.I.; Tarnopolsky, M.A. Mitochondria and Aging-The Role of Exercise as a Countermeasure. *Biology* **2019**, *8*, 40. [\[CrossRef\]](#) [\[PubMed\]](#)
84. Cantó, C.; Jiang, L.Q.; Deshmukh, A.S.; Matak, C.; Coste, A.; Lagouge, M.; Zierath, J.R.; Auwerx, J. Interdependence of AMPK and SIRT1 for metabolic adaptation to fasting and exercise in skeletal muscle. *Cell Metab.* **2010**, *11*, 213–219. [\[CrossRef\]](#) [\[PubMed\]](#)
85. Fang, Y.; Wang, X.; Yang, D.; Lu, Y.; Wei, G.; Yu, W.; Liu, X.; Zheng, Q.; Ying, J.; Hua, F. Relieving Cellular Energy Stress in Aging, Neurodegenerative, and Metabolic Diseases, SIRT1 as a Therapeutic and Promising Node. *Front. Aging Neurosci.* **2021**, *13*, 738686. [\[CrossRef\]](#) [\[PubMed\]](#)
86. Barcena, M.L.; Aslam, M.; Norman, K.; Ott, C.; Ladilov, Y. Role of AMPK and Sirtuins in Aging Heart: Basic and Translational Aspects. *Aging Dis.* **2024**, *16*, 3335–3360. [\[CrossRef\]](#) [\[PubMed\]](#)
87. Liu, Z.; Yang, P.; Cheng, G.; Kang, X.; Li, L.; Xiang, Y. Mitochondria-targeted delivery strategies for age-related diseases. *Int. J. Pharm. X* **2026**, *11*, 100494. [\[CrossRef\]](#) [\[PubMed\]](#)
88. Igarashi, M.; Nakagawa-Nagahama, Y.; Miura, M.; Kashiwabara, K.; Yaku, K.; Sawada, M.; Sekine, R.; Fukamizu, Y.; Sato, T.; Sakurai, T.; et al. Chronic nicotinamide mononucleotide supplementation elevates blood nicotinamide adenine dinucleotide levels and alters muscle function in healthy older men. *npj Aging* **2022**, *8*, 5. [\[CrossRef\]](#) [\[PubMed\]](#)

89. Murray, K.O.; Gioscia-Ryan, R.A.; Justice, J.N.; Santos-Parker, J.R.; Bispham, N.Z.; Hutton, D.A.; Darvish, S.; Miyamoto-Ditmon, J.; Clayton, Z.S.; Chonchol, M.; et al. Translational studies of chronic supplementation with a mitochondria-targeted antioxidant to improve physical function with ageing. *J. Physiol.* **2026**, *604*, 2898–2922. [[CrossRef](#)] [[PubMed](#)]
90. Zhao, Y.C.; Wu, Y.Y. Resistance Training Improves Hypertrophic and Mitochondrial Adaptation in Skeletal Muscle. *Int. J. Sports Med.* **2023**, *44*, 625–633. [[CrossRef](#)] [[PubMed](#)]
91. Antuña, E.; Cachán-Vega, C.; Bermejo-Millo, J.C.; Potes, Y.; Caballero, B.; Vega-Naredo, I.; Coto-Montes, A.; Garcia-Gonzalez, C. Inflammaging: Implications in Sarcopenia. *Int. J. Mol. Sci.* **2022**, *23*, 15039. [[CrossRef](#)] [[PubMed](#)]
92. Li, X.; Li, C.; Zhang, W.; Wang, Y.; Qian, P.; Huang, H. Inflammation and aging: Signaling pathways and intervention therapies. *Signal Transduct. Target. Ther.* **2023**, *8*, 239. [[CrossRef](#)] [[PubMed](#)]
93. Meyers, A.K.; Zhu, X. The NLRP3 Inflammasome: Metabolic Regulation and Contribution to Inflammaging. *Cells* **2020**, *9*, 1808. [[CrossRef](#)] [[PubMed](#)]
94. Xu, X.; Pang, Y.; Fan, X. Mitochondria in oxidative stress, inflammation and aging: From mechanisms to therapeutic advances. *Signal Transduct. Target. Ther.* **2025**, *10*, 190. [[CrossRef](#)] [[PubMed](#)]
95. Nyáry, D.; Fekete, M.; Lehoczi, A.; Fazekas-Pongor, V.; Lipécz, Á.; Csípő, T.; Major, D.; Péterfi, A.; Csík, B.; Zábó, V.; et al. Inflammaging and Sarcopenia as Interconnected Hallmarks of Aging: Integrative Roles of Bioactive Compounds and Lifestyle Interventions. *Nutrients* **2026**, *18*, 1920. [[CrossRef](#)] [[PubMed](#)]
96. Madsen, H.B.; Navarro, C.; Gasparini, E.; Park, J.H.; Li, Z.; Croteau, D.L.; Bohr, V.A. Urolithin A and nicotinamide riboside differentially regulate innate immune defenses and metabolism in human microglial cells. *Front. Aging Neurosci.* **2024**, *16*, 1503336. [[CrossRef](#)] [[PubMed](#)]
97. Negri, M.; Pivonello, C.; Amatrudo, F.; Cimmino, F.; Trinchese, G.; Vetrani, C.; Iaccarino, G.; Pivonello, R.; Mollica, M.P.; Colao, A. Effects of Chrono-Exercise and Chrono-Nutrition on Muscle Health: Understanding the Molecular Mechanisms Activated by Timed Exercise and Consumption of Proteins and Carbohydrates. *Nutr. Rev.* **2025**, *83*, 1571–1593. [[CrossRef](#)] [[PubMed](#)]
98. Aoyama, S.; Nakahata, Y.; Shinohara, K. Chrono-Nutrition Has Potential in Preventing Age-Related Muscle Loss and Dysfunction. *Front. Neurosci.* **2021**, *15*, 659883. [[CrossRef](#)] [[PubMed](#)]
99. Garrido, M.; Terrón, M.P.; Rodríguez, A.B. Chrononutrition against oxidative stress in aging. *Oxidative Med. Cell. Longev.* **2013**, *2013*, 729804. [[CrossRef](#)] [[PubMed](#)]
100. Min, K.; Smuder, A.J.; Kwon, O.S.; Kavazis, A.N.; Szeto, H.H.; Powers, S.K. Mitochondrial-targeted antioxidants protect skeletal muscle against immobilization-induced muscle atrophy. *J. Appl. Physiol.* **2011**, *111*, 1459–1466. [[CrossRef](#)] [[PubMed](#)]
101. Op 't Eijnde, B.; Ursø, B.; Richter, E.A.; Greenhaff, P.L.; Hespel, P. Effect of oral creatine supplementation on human muscle GLUT4 protein content after immobilization. *Diabetes* **2001**, *50*, 18–23. [[CrossRef](#)] [[PubMed](#)]
102. Hespel, P.; Op't Eijnde, B.; Van Leemputte, M.; Ursø, B.; Greenhaff, P.L.; Labarque, V.; Dymarkowski, S.; Van Hecke, P.; Richter, E.A. Oral creatine supplementation facilitates the rehabilitation of disuse atrophy and alters the expression of muscle myogenic factors in humans. *J. Physiol.* **2001**, *536*, 625–633. [[CrossRef](#)] [[PubMed](#)]
103. de Sire, A.; Baricich, A.; Renò, F.; Cisari, C.; Fusco, N.; Invernizzi, M. Myostatin as a potential biomarker to monitor sarcopenia in hip fracture patients undergoing a multidisciplinary rehabilitation and nutritional treatment: A preliminary study. *Aging Clin. Exp. Res.* **2020**, *32*, 959–962. [[CrossRef](#)] [[PubMed](#)]
104. Smith, G.I.; Julliand, S.; Reeds, D.N.; Sinacore, D.R.; Klein, S.; Mittendorfer, B. Fish oil-derived n-3 PUFA therapy increases muscle mass and function in healthy older adults. *Am. J. Clin. Nutr.* **2015**, *102*, 115–122. [[CrossRef](#)] [[PubMed](#)]
105. Rodacki, C.L.; Rodacki, A.L.; Pereira, G.; Naliwaiko, K.; Coelho, I.; Pequito, D.; Fernandes, L.C. Fish-oil supplementation enhances the effects of strength training in elderly women. *Am. J. Clin. Nutr.* **2012**, *95*, 428–436. [[CrossRef](#)] [[PubMed](#)]
106. Kechichian, A.; Lafrance, S.; Matifat, E.; Dubé, F.; Lussier, D.; Benhaim, P.; Perreault, K.; Filiatrault, J.; Rainville, P.; Higgins, J.; et al. Multimodal Interventions Including Rehabilitation Exercise for Older Adults With Chronic Musculoskeletal Pain: A Systematic Review and Meta-analyses of Randomized Controlled Trials. *J. Geriatr. Phys. Ther.* **2022**, *45*, 34–49. [[CrossRef](#)] [[PubMed](#)]
107. de Sire, A.; Lippi, L.; Aprile, V.; Calafiore, D.; Folli, A.; D'Abrosca, F.; Moalli, S.; Lucchi, M.; Ammendolia, A.; Invernizzi, M. Pharmacological, nutritional, and rehabilitative interventions to improve the complex management of osteoporosis in patients with chronic obstructive pulmonary disease: A narrative review. *J. Pers. Med.* **2022**, *12*, 1626. [[CrossRef](#)] [[PubMed](#)]
108. Chen, J.; Wang, X.; Xu, Z. Sarcopenia and Chronic Pain in the Elderly: A Systematic Review and Meta-Analysis. *J. Pain Res.* **2023**, *16*, 3569–3581. [[CrossRef](#)] [[PubMed](#)]
109. Tinnirello, A.; Mazzoleni, S.; Santi, C. Chronic Pain in the Elderly: Mechanisms and Distinctive Features. *Biomolecules* **2021**, *11*, 1256. [[CrossRef](#)] [[PubMed](#)]
110. Huang, Y.; Wang, C.; Cui, H.; Sun, G.; Qi, X.; Yao, X. Mitochondrial dysfunction in age-related sarcopenia: Mechanistic insights, diagnostic advances, and therapeutic prospects. *Front. Cell Dev. Biol.* **2025**, *13*, 1590524. [[CrossRef](#)] [[PubMed](#)]
111. Lippi, L.; Turco, A.; Rudrappa, G.H.; Moalli, S.; de Sire, A.; Invernizzi, M. Astragalus membranaceus extract reduces functional knee joint pain: A randomized, double-blinded, placebo-controlled trial. *Front. Pain Res.* **2025**, *6*, 1595957. [[CrossRef](#)] [[PubMed](#)]

112. Parisi, S.; Ditto, M.C.; Borrelli, R.; Fusaro, E. Efficacy of a fixed combination of palmitoylethanolamide and acetyl-L-carnitine (PEA+ALC FC) in the treatment of neuropathies secondary to rheumatic diseases. *Minerva Med.* **2021**, *112*, 492–499. [[CrossRef](#)] [[PubMed](#)]
113. Chen, J.; Huang, M. Intensive care unit-acquired weakness: Recent insights. *J. Intensive Med.* **2024**, *4*, 73–80. [[CrossRef](#)] [[PubMed](#)]
114. Petrucci, M.; Gemma, S.; Carbone, L.; Piccioni, A.; Della Polla, D.A.; Simeoni, B.; Franceschi, F.; Covino, M. ICU-Acquired Weakness: From Pathophysiology to Management in Critical Care. *Emerg. Care Med.* **2025**, *2*, 4. [[CrossRef](#)]
115. Kanova, M.; Kohout, P. Molecular Mechanisms Underlying Intensive Care Unit-Acquired Weakness and Sarcopenia. *Int. J. Mol. Sci.* **2022**, *23*, 8396. [[CrossRef](#)] [[PubMed](#)]
116. Watanabe, S.; Hirasawa, J.; Naito, Y.; Mizutani, M.; Uemura, A.; Nishimura, S.; Suzuki, K.; Morita, Y.; Iida, Y. Association Between Intensive Care Unit-Acquired Weakness and Early Nutrition and Rehabilitation Intensity in Mechanically Ventilated Patients: A Multicenter Retrospective Observational Study. *Cureus* **2023**, *15*, e37417. [[CrossRef](#)] [[PubMed](#)]
117. Tarnawski, J.; Czub, M.; Dymecki, M.; Sunil, M.; Folwarski, M. Anabolic Strategies for ICU-Acquired Weakness. What Can We Learn from Bodybuilders? *Nutrients* **2024**, *16*, 2011. [[CrossRef](#)] [[PubMed](#)]
118. Davì, F.; Iaconis, A.; Cordaro, M.; Di Paola, R.; Fusco, R. Nutraceutical Strategies for Targeting Mitochondrial Dysfunction in Neurodegenerative Diseases. *Foods* **2025**, *14*, 2193. [[CrossRef](#)] [[PubMed](#)]
119. Li, N. Creatine supplementation and exercise in aging: A narrative review of the muscle–brain axis and its impact on cognitive and physical health. *Front. Nutr.* **2026**, *12*, 1687719. [[CrossRef](#)] [[PubMed](#)]
120. Barcelos, I.P.; Haas, R.H. CoQ10 and Aging. *Biology* **2019**, *8*, 28. [[CrossRef](#)] [[PubMed](#)]
121. Fleming, T.R.; Powers, J.H. Biomarkers and surrogate endpoints in clinical trials. *Stat. Med.* **2012**, *31*, 2973–2984. [[CrossRef](#)] [[PubMed](#)]
122. Gorgori-Gonzalez, A.; Soto-Rodriguez, S.; Tamayo-Torres, E.; Garcia-Dominguez, E.; Sebastia, V.; Gambini, J.; Olasso-Gonzalez, G.; Gomez-Cabrera, M.C. Leveraging mitochondrial stress to improve healthy aging. *Sports Med. Health Sci.* **2026**, *8*, 23–33. [[CrossRef](#)] [[PubMed](#)]
123. Sprouse, A.A.; van Breemen, R.B. Pharmacokinetic Interactions between Drugs and Botanical Dietary Supplements. *Drug Metab. Dispos. Biol. Fate Chem.* **2016**, *44*, 162–171. [[CrossRef](#)] [[PubMed](#)]
124. Pérez-Castillo, Í.M.; Rueda, R.; Pereira, S.L.; Bouzamondo, H.; López-Chicharro, J.; Segura-Ortiz, F.; Atherton, P.J. Age-Related Anabolic Resistance: Nutritional and Exercise Strategies, and Potential Relevance to Life-Long Exercisers. *Nutrients* **2025**, *17*, 3503. [[CrossRef](#)] [[PubMed](#)]
125. Cai, T.; Li, Y.; Zhang, Y.; Li, C.; Li, S.; Zhang, Q. The role of exercise-mediated mitochondrial quality control remodeling in aging. *Front. Cell Dev. Biol.* **2026**, *14*, 1792645. [[CrossRef](#)] [[PubMed](#)]
126. Lavin, K.M.; Roberts, B.M.; Fry, C.S.; Moro, T.; Rasmussen, B.B.; Bamman, M.M. The Importance of Resistance Exercise Training to Combat Neuromuscular Aging. *Physiology* **2019**, *34*, 112–122. [[CrossRef](#)] [[PubMed](#)]
127. Li, J.; Wang, Y.; Liu, F.; Miao, Y. Effect of Protein Supplementation Combined With Resistance Training in Gait Speed in Older Adults: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *J. Aging Phys. Act.* **2024**, *32*, 668–678. [[CrossRef](#)] [[PubMed](#)]
128. Cruz-Pierard, S.; Iñiguez-Jiménez, S. Synergistic Effects of Protein Intake and Exercise on Biomarkers of Sarcopenia: A Systematic Review. *Biomolecules* **2026**, *16*, 195. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.