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REVIEW ARTICLE

Impact of nutraceuticals and dietary supplements on mitochondria modifications in healthy aging: a systematic review of randomized controlled trials

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Abstract

Background To date, the mitochondrial function has been related to several pathways involved in the cellular aging process. Dietary supplements might have reciprocal and multilevel interactions with mitochondria network; however, no systematic review assessed the role of different nutraceuticals in mitochondria modification of healthy older adults.

Aim To assess the effects of different dietary supplements on mitochondria modifications in older adults.

Methods On February 22, 2022, PubMed, Scopus, Web of Science, and Cochrane were systematically searched from inception for randomized controlled trials (RCTs). According to PICO model, we considered healthy older adults as participants, nutraceutical treatment as intervention, any treatment as comparator, mitochondrial modifications as outcome. Jadad scale was used for the quality assessment.

Results Altogether, 8489 records were identified and screened until 6 studies were included. A total of 201 healthy older adults were included in the systematic review (mean age ranged from 67.0 ± 1.0 years to 76.0 ± 5.6 years). The dietary supplements assessed were sodium nitrite, N-3 polyunsaturated fatty acids, hydrogen-rich water, nicotinamide riboside, urolithin A, and whey protein powder. Positive effects were reported in terms of mitochondrial oxidative and antioxidant capacity, volume, bioenergetic capacity, and mitochondrial transcriptome based on the nutritional supplements. The quality assessment underlined that all the studies included were of good quality.

Discussion Although dietary supplements might provide positive effects on mitochondria modifications, few studies are currently available in this field.

Conclusion Further studies are needed to better elucidate the reciprocal and multilevel interactions between nutraceuticals, mitochondria, and environmental stressors in healthy older adults.

Keywords Aging · Mitochondria · Dietary supplements · Precision medicine · Muscle · Rehabilitation

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Introduction

Healthy aging is a critical issue in the current literature due to the increase in overall survival and age-related pathological conditions affecting older people [1–3]. Moreover, age-related changes in cardiorespiratory, nervous and musculoskeletal systems might significantly affect the risk of developing physical function impairment and limitations in independence in the activities of daily living, with crucial implications on global health care burden and social costs [4, 5].

In this scenario, understanding the biological mechanisms underpinning the aging process might be a cornerstone of a comprehensive and tailored management of age-related

pathological conditions. Interestingly, mitochondrial modifications have been proposed as biological targets in cellular aging due to their key role in molecular processes involved in energy production, oxidative stress regulation, mitophagy, and regulation of programmed cell death [6]. In addition, muscle mitochondrial modifications in older people are characterized by alterations in terms of bioenergetic capacity, mitochondrial oxidative and antioxidant capacity, and transcriptome, leading to inflammatory response dysregulation and increased oxidative stress [7–10]. In this context, recent research underlined that mitochondrial modifications might be associated with the impairment of cardiorespiratory, nervous and musculoskeletal systems with detrimental consequences on body function and physical performance [11–14].

Although the mechanisms underpinning age-related mitochondrial impairment are far from being fully understood, in the recent years, a growing amount of literature underlined the potential role of different interventions targeting age-related mitochondrial modifications to slow down the complex framework of the aging process [11, 15–19]. Recently, our research group focused on the role of physical activity in improving mitochondrial function to pave the way to a future concept integrating a translational approach in lifestyle medicine [12]. Concurrently, growing evidence suggests a positive role of nutraceuticals and nutritional interventions to promote healthy aging with several reports underlining positive effects of specific integration in age-related diseases [13, 14]. In particular, lifestyle interventions, physical exercise and supplementation are widely used interventions to treat osteoporosis (i.e., dietary supplements, vitamin D, calcium, probiotics) in older subjects [20–22]. Accordingly, protein and amino acid supplementations might counteract sarcopenia boosting the positive effect of physical exercise in frail patients [23–25].

Recent research is now focusing on nutraceuticals with antioxidant activity to reduce autoxidation by reacting with reactive oxygen species (ROS) and consequently reduce oxidative stress, one of the major contributors to the aging process [26, 27]. ROS increase is a major hallmark of aging and is strictly related to the progressive impairment of mitochondrial oxidative phosphorylation due to constitutive age-related changes in mitochondrial structure [28, 29].

On the other hand, to the best of our knowledge, no previous systematic reviews have investigated the effects of nutraceuticals on mitochondria modifications of healthy older adults. Moreover, strong evidence supporting the role of integrating biological advances in the tailored nutritional management of older people is still lacking.

Therefore, this systematic review of randomized controlled trials (RCTs) aimed at summarizing the role of nutraceuticals and dietary supplements in modifying age-related mitochondria modifications, to guide clinicians to integrate these interventions in the complex treatment framework of mitochondria modifications in older subjects.

Methods

Registration and search strategy

This systematic review of randomized clinical trials (RCTs) has been performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [30]. The study protocol has been realized before study initiation and has been submitted to the International prospective register of systematic reviews (PROSPERO, https://www.crd.york.ac.uk/prospero; registration number: CRD42022313118).

Four databases (PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) were systematically searched for studies published until February 22nd, 2022, adopting the strategy depicted by Supplementary Table 1. The keywords considered were: "aged", "elderly", "aging", "diet", "supplement", "nutrition", "macronutrient", "micronutrients", and "mitochondria". Additionally, the reference lists of all the primary studies have been screened for all the potentially relevant papers and these articles were reviewed for additional references. The analysis was performed independently and synchronously by two of the authors.

Selection criteria

After duplicates removal, two authors independently screened the title and abstract of all papers identified for eligibility. If agreement was not achieved by the two reviewers, a third reviewer was consulted. The selected articles were subsequently screened in full text by the two authors. Likewise, if a consensus was not achieved, the discrepancy was resolved by consulting one of the other authors.

The inclusion criteria for the screened articles were set in accordance with the PICO model:

1. (P) Participants: healthy older people (aged more than 60 years), according to the definition by World Health Organization [31];
2. (I) Intervention: any nutraceutical treatment administered as exclusive intervention;
3. (C) Comparator: any comparator, including placebo, other pharmacological treatment, non-pharmacological treatment, or no treatment;
4. (O) Outcomes: mitochondrial modifications assessed by plasmatic changes or tissue biopsies. Mitochondrial modifications assessed included: (a) mitochondrial oxidative capacity; (b) mitochondrial antioxidant capacity;

(c) mitochondrial volume; (d) mitochondrial bioenergetic capacity; (e) mitochondrial transcriptome.

We included only RCTs, published in peer-reviewed international journals. Exclusion criteria were: (a) language other than English; (b) study design different from RCTs; (c) papers involving animal models; (d) participants with metabolic, cardiovascular, pulmonary, or other pathological conditions related to potential mitochondrial alterations; (e) other treatments as main intervention.

Data extraction and synthesis

Full-text assessments and data extraction were performed by two authors, independently. Any divergences between the two reviewers were solved by collegial discussion among the authors. In case of further disagreement, a third author was asked.

The following data were extracted: (1) title; (2) authors; (3) publication year; (4) nationality; (5) participants (number, mean age and age range, gender, body mass index — BMI); (6) interventions' characteristics; (7) comparator; (8) study results. For all studies, both study characteristics and data extracted were summarized.

Quality assessment and risk of bias

The quality of the RCTs included was assessed by two of the authors independently, according to the Jadad scale [32]. Discordance between the two authors was resolved collegially among the research team. Jadad scale is composed by five items, with a total score ranging from zero to five based on adherence and the items evaluated were the following: (a) random sequence generation; (b) appropriate randomization; (c) blinding of participants or personnel; (d) blinding of outcome assessors; (e) withdrawals and dropouts. A Jadad score between three to five points was considered high quality.

The risk of bias was assessed by the Cochrane risk-of-bias tool for randomized trials (RoBv.2) [33]. Bias was classified as low, high, or with some concerns based on the item of the RoBv.2. In particular, the following domains were assessed by RoBv.2: (a) randomization process; (b) deviation from the intended interventions; (c) missing outcome data; (d) measurement of the outcome; (e) selection of the reported result.

Results

Study characteristics

Altogether, 8489 records were identified from the 4 databases. After duplication removal, 4534 studies were assessed for eligibility and screened for title and abstract. Therefore, 4495 records were excluded, and 39 full-text studies were screened. Subsequently, 33 articles were excluded for inconsistency with the eligibility criteria. Supplementary Table 2 reported the list of excluded studies along with the reasons for exclusion. Finally, 6 studies [34–39] were included in the qualitative synthesis. The search process is shown in detail in the PRISMA flow diagram depicted in Fig. 1.

The studies included in this systematic review were published between 2016 [36] and 2022 [38]. Three studies (50%) were conducted in the USA [35, 36, 38], while the remaining 3 studies were carried out in Serbia ($n=1$, 16.7% [37]), the UK ($n=1$, 16.7% [34]), and the Netherlands ($n=1$, 16.7% [39]). The sample size of the RCTs included ranged from 12 [34] to 66 [38], for a total of 201 healthy older adults included in the systematic review.

The mean age of the subjects included ranged from 67.0 ± 1.0 years [35] to 76.0 ± 5.6 years [37]. It should be noticed that Yoshino et al. [36] did not characterize the study sample for gender differences. As a result, based on the remaining 181 participants, the sample of the present study was composed of 83 males and 98 females, with a body composition assessed by BMI ranging from 25.3 ± 1.3 kg/m^2 [36] to 28.6 ± 3.9 kg/m^2 [37]. Interestingly, 4 studies did not report any standardization in terms of diet and physical activity during the study protocol, while both Zanini et al. [37] and Yoshino et al. [36] instructed study participants to maintain usual diet and physical activity.

Control groups were characterized by placebo administration in all the studies included in the present review ($n=6$, 100% [34–39]), indistinguishable from the nutraceutical treatment administered in the intervention group. The characteristics of the studies included are presented in detail in Table 1.

Nutraceutical intervention

The intervention was characterized by the administration of several nutraceuticals based on the study included. More in detail, the experimental treatment included: sodium nitrite [35], fish oil-derived n-3 polyunsaturated fatty acids (PUFA) [36], hydrogen-rich water [37], nicotinamide riboside (NR) [34], urolithin A [38], and whey protein powder (L-Tryptophan [L-Trp], nicotinic acid [NA], and nicotinamide [NAM]) [39].

– *Sodium Nitrite*. Sodium nitrite was considered as a key intermediary of nitrate–nitrite–NO pathway, increasing NO bioavailability and affecting nitrite-mediated oxidative stress [40]. It was administrated in the study of Rossman et al. [35] for a total of 80 mg per day (40 mg, 2 times per day). The duration of sodium nitrite supplementation was 12 weeks [35].

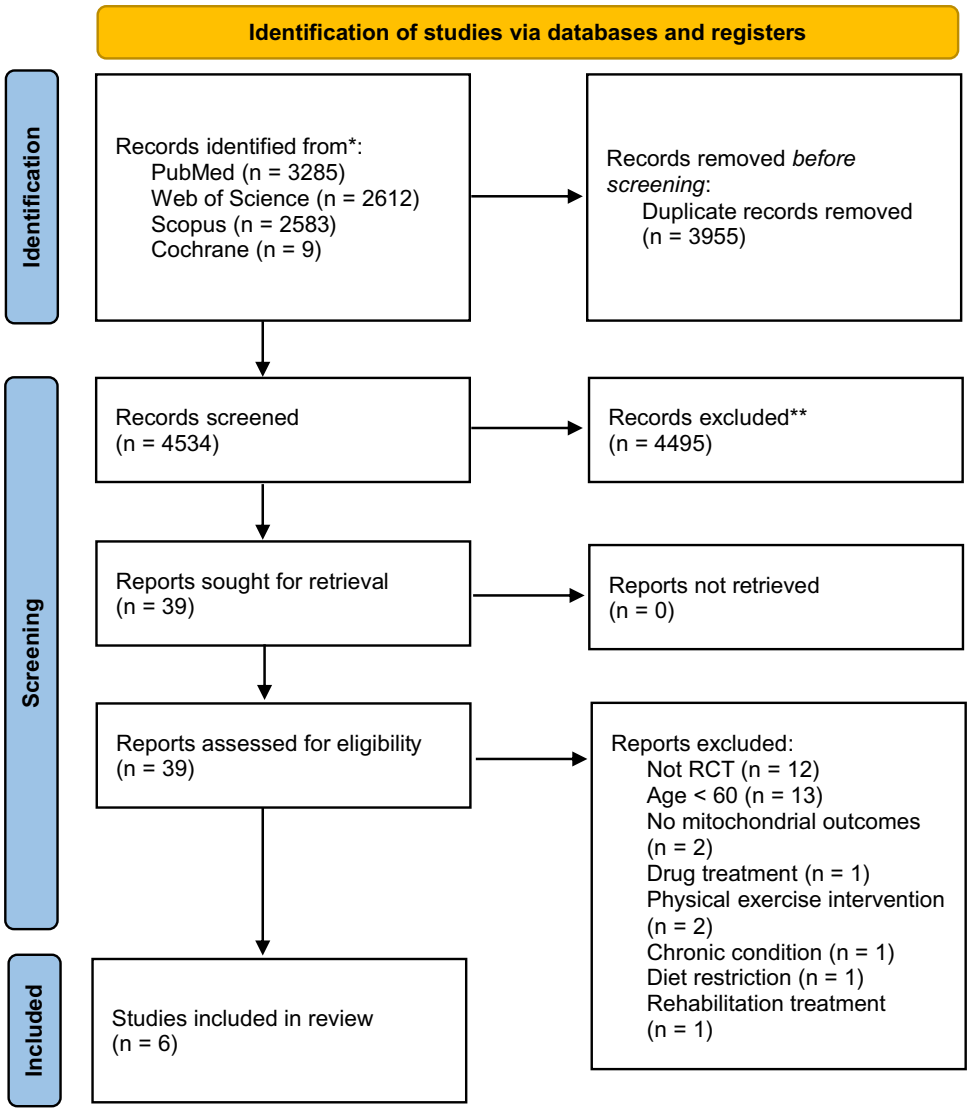

Fig. 1 PRISMA 2020 Flow Diagram

– *Fish oil-derived n-3 PUFA*. N-3 PUFAs supplementation was performed in older subjects according to the preclinical evidence about the increased gene expression of master regulators of mitochondrial function (PPARGC1A and UCP3) and the effects on metabolic and regenerative pathways potentially related to the inhibition of autophagy and atrophy pathways [41, 42]. Fish oil-derived n-3 PUFA was administrated in the study by Yoshino et al. [36]. The study participants in the n-3 PUFA group received four 1-g (LOVAZA®) pills per day, composed of 1.86 g eicosapentaenoic acid (20:5 n-3 PUFA) and 1.50 g docosahexaenoic acid (22:6 n-3 PUFA. The protocol duration was 6 months [36].
– *Hydrogen-rich water*. Hydrogen-rich water supplementation has been proposed due to the evidence supporting hydrogen selective interaction with hydroxyl radical and peroxynitrite, promoting the reduction of oxidative stress and positive effects in inflammatory and apoptotic pathways [43]. Hydrogen-rich water was administrated in the study by Zanini et al. [37]. Hydrogen-rich water was administered 2 times per day. The protocol duration of hydrogen-rich water supplementation was 6 months [37].
– *Nicotinamide Riboside*. Nicotinamide riboside is a NAD precursor, increasing NAD^+ availability with potential implications in preventing age-related mitochondria functional decline and mitochondria bioenergetic capacity in animal models [44]. NR was administrated in the study by Elhassan et al. [34]. The study participants in the intervention group were orally supplemented with 2 capsules of 250 mg of NR (Niagen, ChromaDex, Irvine, CA), administered twice a day for a total of 1000 mg per day. The protocol duration was 21 days [34].
– *Urolithin A*. Urolithin A has been proposed to induce mitochondrial gene expression, stimulating mitophagy and improving muscle function in preclinical studies

Table 1 Main characteristics of the articles included in the present systematic review

Authors	Journal	Publication year	Nationality	Participants				Intervention	Comparator	Results	
				Sample size	Gender	Age (years)	BMI (kg/m2)			Intragroup analysis	Intergroups analysis
Rossman et al.	*Hypertension*	2021	USA	N=49 *IG=26* *CG=23*	M=25 F=24	IG: 67±1.0 CG: 68±1.0	IG: 25.5±0.7 CG: 26.0±0.7	Sodium Nitrite Dosage: 40 mg Frequency: 2x/day Protocol duration: 12 weeks	Placebo Dosage: 40 mg Frequency: 2x/day Protocol duration: 12 weeks	Nitrotyrosine: IG: –45%; $p<0.05$; CG: NS, p = NS Mitochondrial-specific ROS-bioactivity: IG: -35%; $p<0.05$; CG: NS; p= NS Mitochondrial abundance: IG: p = NS; CG: NP	–

Table 1 (continued)

Authors	Journal	Publication year	Nationality	Participants				Intervention	Comparator	Results	
				Sample size	Gender	Age (years)	BMI (kg/m2)			Intragroup analysis	Intergroups analysis
Yoshino et al.	*Physiol Rep.*	2016	USA	N=20 *IG=10* *CG=10*	NP	IG: 68±2.0 CG: 70±2.0	IG: 26.5±1.4 CG: 25.3±1.2	LOVAZA® pill providing a total of 1.86 g eicosapentaenoic acid (20:5 n-3 PUFA) and 1.50 g docosahexaenoic acid (22:6 n-3 PUFA) Dosage: 1g Frequency: 4x/day Protocol duration: 6 months	Corn oil pills Dosage: 1g Frequency: 4x/day Protocol duration: 6 months	Mitochondrial function: Reactome respiratory electron transport ATP synthesis by chemiosmotic IG = $p<0.05$; CG: p= NP Coupling and heat production by uncoupling proteins IG = $p<0.05$; p= NP Reactome respiratory electron transport IG = $p<0.05$; p= NP Kegg oxidative phosphorylation IG = p<0.05; p= NP Reactome tricarboxylic acid cycle and respiratory electron transport IG = $p<0.05$; p= NP Mitochondrial transcriptome UCP3 IG = +30%; $p<0.05$; CG = NP UQCRC1 IG = +20%; $p<0.05$; CG = NP PPARGC1A, PPARA, PDHA1, CPT1B, CS, UQCRC2, COX4I1, and COX5B expression IG: p = NS; CG: p = NS	-

Table 1 (continued)

Authors	Journal	Publication year	Nationality	Participants				Intervention	Comparator	Results	
				Sample size	Gender	Age (years)	BMI (kg/m2)			Intragroup analysis	Intergroups analysis
Zanini et al.	*Exp Gerontol*	2021	Serbia	N=40	M=20 F=20	76.0±5.6	IG: 28.6±3.9 CG: 28.4±4.6	HRW produced by dissolving a tablet of Rejuvenation into a cup of tap water (250 mL) Dosage: 250 mL Frequency: 2x/day Protocol duration: 6 months	Control water Dosage: 250 mL Frequency: 2x/day Protocol duration: 6 months	NAD+/NADH ratio: IG: 9.7 ± 10.4 vs 8.2 ± 5.6; p =NS CG: 1.7 ± 1.1 vs 4.8 ± 6.6; p =NS	NAD+/NADH ratio: IG: 8.2 ± 5.6 vs CG 4.8 ± 6.6; p= NS
Elhassan et al.	*Cell Reports*	2019	UK	N=12	M=12 F=0	75.0 (72, 78)	26.6 (25.0, 30.0)	Nicotinamide Riboside Dosage: 250 mg Frequency: 2x2/day Protocol duration: 21 days	Placebo capsules Dosage: 250 mg Frequency: 2x2/day Protocol duration: 21 days	Skeletal muscle mitochondrial resident proteins: IG: p = NS; CG: p = NS NR-mediated changes to muscle protein acetylation: IG: p = NS; CG: p = NS	NAD+ metabolome: MeNAM IG 1.45 pmol/mg vs CG 0.35 pmol/mg; p< 0.01 N1-methyl-2-pyridone-5-carboxamide IG 6.6 pmol/mg vs CG 1.1 pmol/mg; p< 0.001 N1-methyl-4-pyridone-5-carboxamide IG 1.6 pmol/mg vs CG 0.3 pmol/mg; p< 0.001 High-resolution respirometry IG vs CG p = NS

Table 1 (continued)

Authors	Journal	Publication year	Nationality	Participants				Intervention	Comparator	Results	
				Sample size	Gender	Age (years)	BMI (kg/m2)			Intragroup analysis	Intergroups analysis
Liu et al.	*JAMA Netw Open*	2022	USA	N = 66 *IG=33* *CG=33*	M = 16 F = 50	IG: 72.5±5.24 CG: 71±4.58	IG: 25.7±3.45 CG: 26.7±3.77	Urolithin A Dosage: 250 mg Frequency: 4x/day Protocol duration: 4 months	Placebo softgel Dosage: 250 mg Frequency: 4x/day Protocol duration: 4 months	Biomarkers of mitochondrial health and inflammation: Plasma Acylcarnitine levels IG: $p<0.05$; CG: p= NS Ceramide levels IG: $p<0.05$, CG: p= NS Mitochondria transcriptome: CV-ATP5A, CI-NDUFB8, CII-SDHB, CIII-UQCRC2, CIV-MTCO1 expression IG: p= NS; CG: p= NS	Mean change in mitochondrial oxidative phosphorylation capacity (maximal ATP production) in the hand FDI: IG: 0.07 ± 0.23 mM/s vs CG: 0.06 ± 0.20 mM/s; p = NS Mean change in mitochondrial oxidative phosphorylation capacity (maximal ATP production) in the leg TA: IG: −0.03 ± 10 mM/s vs CG: 0.03 ± 0.10 mM/s; p = NS

Table 1 (continued)

Authors	Journal	Publication year	Nationality	Participants				Intervention	Comparator	Results	
				Sample size	Gender	Age (years)	BMI (kg/m2)			Intragroup analysis	Intergroups analysis
Connell et al.	*J Nutr*	2021	The Netherlands	N=14	M=10 F=4	72.9±4.0	25.2±2.3	Whey protein powder (L-Trp + NA + NAM) Dosage: 207.5 mg/day niacin equivalents of NAD+ precursors were supplemented through L-Trp (210 mg/day), NA (4 mg/day), and NAM (200 mg/day) Frequency: 1x/day Protocol duration: 32 days	Amino acid powder mixture resembling whey protein, but lacking L-Trp, NA, and NAM Dosage: NP Frequency: 1x/day Protocol duration: 32 days	-	NAD+ levels: IG vs CG p = NS Metabolome analysis of NAD+ IG vs CG: p = NS MeNAM concentrations: IG: 0.098± 0.063 vs CG: 0.025 ± 0.014; p = 0.001 Skeletal muscle acylcarnitine levels: IG vs CG p = NS Ex vivo high-resolution respirometry IG vs CG p = NS ADP-stimulated IG: 82.1±19.0 vs CG: 84.0±19.2; p = NS Maximally uncoupled mitochondrial respiration IG: 103.4±30.7 vs CG: 108.7±33.4; p = NS

ATP adenosine triphosphate, *CG* control group, FDI first dorsal interosseus, *IG* intervention group, L-*Trp* L-Tryptophan, *NA* nicotinic acid, *NAM* nicotinamide, *NAD* nicotinamide adenine dinucleotide, *NP* not provided, *PUFA* polyunsaturated fatty acids, *ROS* reactive oxygen species, *RT-PCR* real-time polymerase chain reaction, *TA* tibialis anterior

[45, 46]. Urolithin A supplementation was assessed in the study by Liu et al. [38]. The study participants in the intervention group were orally supplemented with 250 mg of softgel containing urolithin A, 4 times per day, for a total of 1000 mg daily. The protocol duration was 4 months [38].

– *Whey protein powder (L-Trp, NA, and NAM)*. L-Trp, NA, and NAM are involved in the NAD^+ metabolisms pathway, functioning as precursors in the biosynthesis process and enhancing NAD^+ formation [47]. Therefore, their effects on mitochondria might be related to coenzyme NAD^+ and its reduced form NAD(H) that play a role in cellular redox reactions as electron donors in the electron transport chain [48, 49]. In the study by Connell et al. [39], the intervention product was composed of a whey protein powder as a source of tryptophan, to which nicotinic acid (NA) and nicotinamide (NAM) were added. In total, the equivalent of 207.5 mg/day niacin equivalents of NAD^+ precursors were supplemented, through L-Trp (210 mg/day at a 60:1 conversion rate), NA (4 mg/day), and NAM (200 mg/day). Subjects in the intervention group were orally supplemented dissolving the powder in 200 mL of orange juice, once a day. The protocol duration was 32 days [39].

All the interventions assessed in the studies included are summarized in Table 1.

Main findings in terms of muscle mitochondrial modifications

The effects of nutraceuticals on muscle mitochondrial modifications were assessed in 6 terms of: (a) mitochondrial oxidative capacity; (b) mitochondrial antioxidant capacity; (c) mitochondrial volume; (d) mitochondrial bioenergetic capacity; (e) mitochondrial transcriptome.

(a) *Mitochondrial oxidative capacity*: Yoshino et al. [36] assessed mitochondrial function by microarray analyses. In particular, the study showed significant improvements ($p < 0.05$) in respiratory electron transport ATP synthesis, coupling proteins and heat production, respiratory electron transport, oxidative phosphorylation, and tricarboxylic acid cycle and respiratory electron transport after n-3 PUFA therapy compared with baseline [36]. On the other hand, Liu et al. [38] investigated the effect of urolithin A supplementation on the mean change in mitochondrial oxidative phosphorylation capacity assessed by maximal ATP production in the first dorsal interosseous muscle and in the tibialis anterior muscle, without reporting significant differences ($p =$ NS) [38].

The study by Elhassan et al. [34] assessed the high-resolution respirometry on muscle without reporting significant improvement in skeletal muscle oxidative phosphorylation and maximal respiratory capacity after NR supplementation ($p =$ NS). Moreover, to assess sirtuin-mediated deacetylation activity, the western blot analysis was performed on skeletal muscle lysates without reporting a significant increase in muscle protein acetylation ($p =$ NS) [34].

Accordingly, the RCT by Connell et al. [39] assessed mitochondrial oxidative capacity by ex vivo high-resolution respirometry on permeabilized muscle fibers obtained from skeletal muscle biopsies. However, no significant differences between groups were underlined in terms of ADP-stimulated (State 3) respiration fueled by complex I linked (malate and octanoyl-carnitine) substrates ($p = 0.882$) and maximally uncoupled mitochondrial respiration ($p = 0.495$) [39]. Table 1 reported the results of the studies included in detail.

(b) *Mitochondrial antioxidant capacity*: Rossman et al. [35] assessed mitochondrial-specific ROS-bioactivity showing a significant decrease (−35%; $P < 0.05$) after sodium nitrite supplementation. In contrast, there was no significant improvement after placebo intervention [35].

(c) *Mitochondrial volume*: Rossmann et al. [35] assessed mitochondrial volume by MitoTracker fluorescence without reporting significant differences after sodium nitrite supplementation ($p =$ NS) [35].

(d) *Mitochondrial bioenergetic capacity*: Liu et al. [38] assessed the effect of urolithin A on biomarkers of mitochondrial health and inflammation, reporting a significant reduction in plasma acylcarnitine levels ($p < 0.05$) and a significant reduction in ceramide levels ($p < 0.05$) in the experimental group [38]. Elhassan et al. [34] found significant improvement in in the NAM methylation clearance pathways representing the NAD^+ metabolome. More in datail, significant differences were underlined in methyl-nicotinamide (MeNAM) (Intervention Group-IG 1.45 pmol/mg vs Control Group-CG 0.35 pmol/mg; $p = 0.006$), N1-methyl-2-pyridone-5-carboxamide (IG 6.6 pmol/mg vs CG 1.1 pmol/mg; $p < 0.001$), and N1-methyl-4-pyridone-5-carboxamide (IG 1.6 pmol/mg vs CG 0.3 pmol/mg; $p < 0.001$) [34].

Similarly, Connell et al. [39] reported skeletal MeNAM levels were significantly higher in subjects receiving NAD^+ precursor supplementation (IG: 0.098 ± 0.063 compared with CG: 0.025 ± 0.014; $p = 0.001$), suggesting an increased NAD^+ metabolism [39].

Lastly, Zanini et al. [37] reported no significant differences in terms of NAD + /NADH ratio after HRW

supplementation [37]. Table 1 shows the mitochondrial bioenergetic capacity outcomes in detail.

(e) *Mitochondrial transcriptome*: Yoshino et al. [36] showed significant improvements in gene expression of UCP3 (~30%, $p<0.05$) and UQCRC1 (~20%, $p<0.05$) after n-3 PUFA therapy compared with baseline, suggesting potentials effects in mitochondrial biogenesis and function. In contrast, no significant improvements were reported in PPARGC1A, PPARA, PDHA1, CPT1B, CS, UQCRC2, COX4I1, and COX5B gene expression [36].

On the other hand, in the study of Elhassan et al. [34], the western blot analysis did not highlight significant improvements ($p=$NS) in the expression of selected mitochondrial proteins in skeletal muscle lysates (CV-ATP5A, CI-NDUFB8, CII-SDHB, CIII-UQCRC2, CIV-MTCO1) [34]. Further details are shown in Table 1.

Figure 2 summarized the statistically significant effects of dietary supplements on mitochondrial modifications.

Quality assessment and risk of bias

According to the Jadad scale [32], all ($n=6$, 100%) of the RCTs included [34–39] resulted in high-quality studies. Some concerns were present in two studies [36, 37] for the assessors' blindness. Table 2 showed in detail the score of each subitem of the Jadad scale for the RCTs included.

The risk of bias was assessed by RoBv2 [33], showing that 4 studies [38, 39, 42, 43] had a low risk of bias, while some concerns emerged for 1 RCTs [41], and 1 [40] showed a high risk of bias. The process showed that all studies (100%) [34–39] ensured a correct randomization, while Zanini et al. [37] (25%) showed some concerns in the second domain due to the lack of details on the blinding of study operators and assessors. All studies ($n=6$, 100%) showed a low risk of bias in missing outcome data and outcome

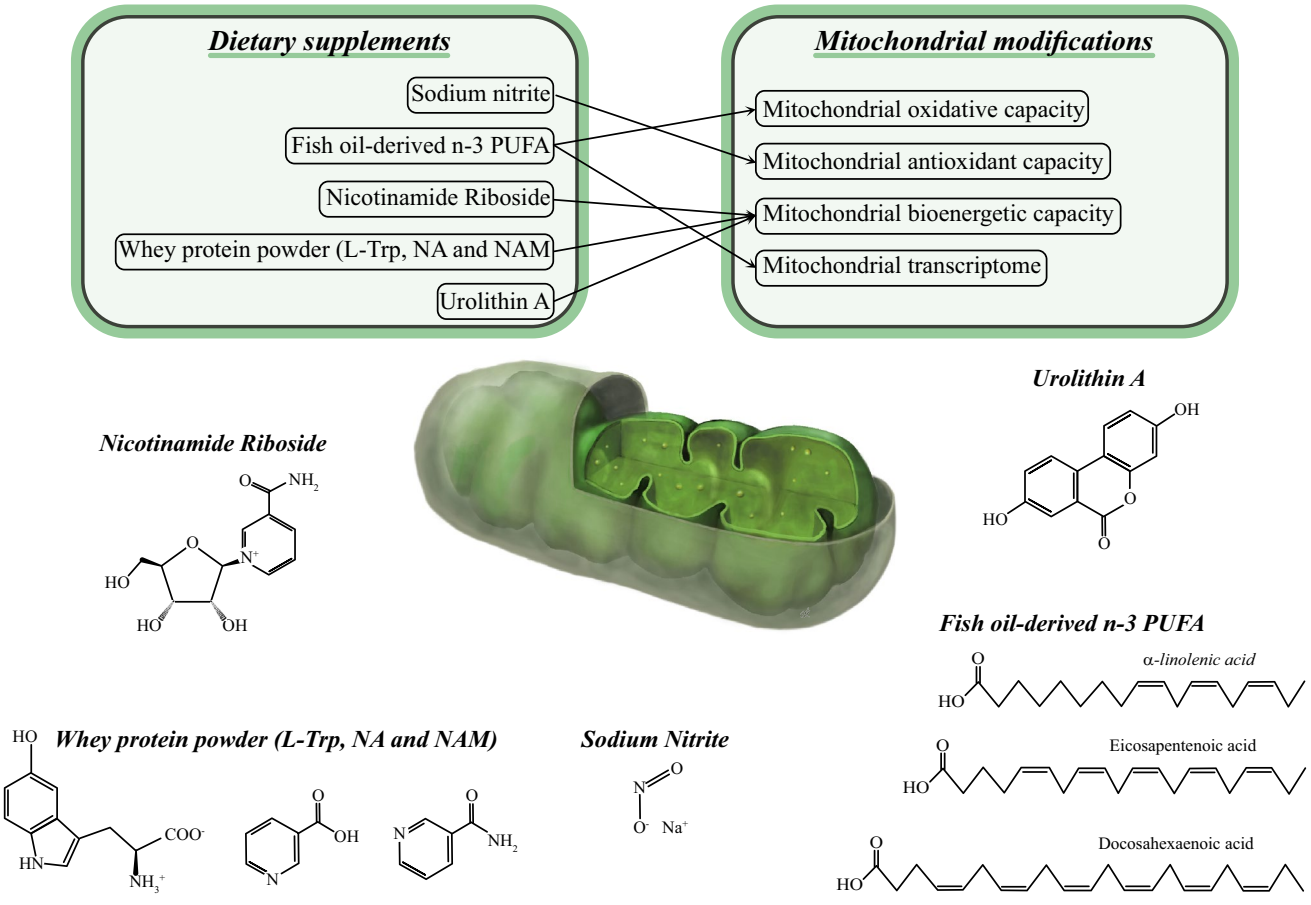

Fig. 2 Dietary supplements effects in mitochondrial modifications

Table 2 Quality assessment of the studies included in the present systematic review

Articles	Domain					Score
	Random sequence generation	Appropriate randomization	Blinding of participants or personnel	Blinding of outcome assessors	Withdrawals and dropouts	
Elhassan et al. 34	1	1	1	1	1	5
Rossman et al. 35	1	1	1	1	1	5
Yoshino et al. 36	1	1	1	0	1	4
Zanini et al. 37	1	1	1	0	1	4
Liu et al. 38	1	1	1	1	1	5
Connell et al. 39	1	1	1	1	1	5

Points were awarded as follows: study described as randomized, 1 point; appropriate randomization, 1 point; subjects blinded to intervention, 1 point; evaluator blinded to intervention, 1 point; description of withdrawals and dropouts, 1 point

assessment [34–39]. One study (25%) [36] resulted in high risk of bias in selection of the reported results because it selected patients and controls from previous randomization [36]. See Fig. 3 for further details.

Discussion

Dietary supplements have been proposed in the last decade as a valid therapeutic option in the multidisciplinary approach to counteract the aging process[13, 14] and, to date, several benefits have been reported after dietary supplements administration on age-related functional and cognitive impairment [23–25, 50–52].

Although specific mechanisms underpinning cellular aging are far from being fully understood, mitochondria might play a key role in the complex framework regulating the senescence process, being a potential target of precise interventions aiming at slowing down the age-related cellular and subcellular modifications [6, 11, 15–19]. Despite these promising considerations, to the best of our knowledge, no previous systematic review assessed the effects of dietary supplements on mitochondria modifications in healthy older subjects.

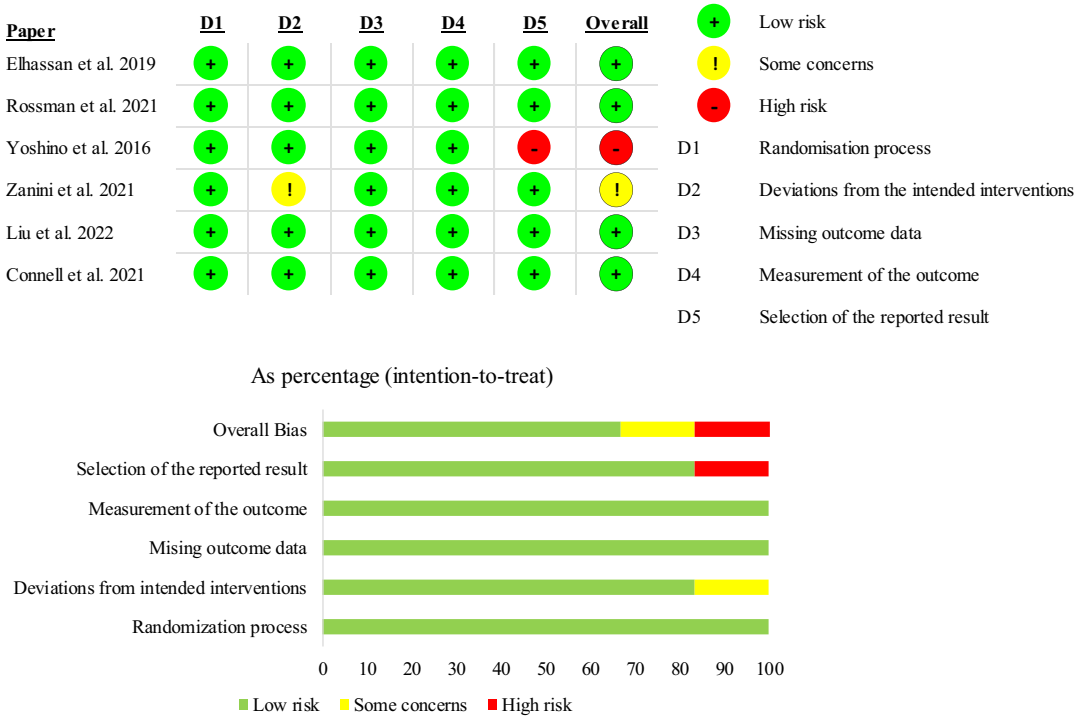

Fig. 3 Risk of bias of the included studies according to the RoB2

In this context, the results of this systematic review of RCTs summarized the different effects of specific dietary supplements and their possible link to specific mitochondrial modifications (see Fig. 2). More in detail, sodium nitrite showed significant results in terms of antioxidant capacity, suggesting intriguing implications for this dietary supplement in targeting oxidative stressors pathways [35]. In this scenario, increased ROS production and concentration are major hallmarks of aging and strictly related to the progressive impairment of mitochondrial oxidative phosphorylation due to constitutive age-related changes in the mitochondrial structure [28, 29]. The supplementation of dietary antioxidants could be useful to counteract the damaging effects of ROS and to protect mitochondrial functions, limiting, for example, the loss of neuronal cells in neurodegenerative disorders [53, 54]. This correlation is due to the fact that mitochondrial functions are directly regulated by mitochondrial DNA. Thus, impairment in mitochondrial DNA due to ROS overproduction could trigger the pathogenesis of age-related pathological conditions, including neurodegenerative and metabolic disorders [55]. However, to date, data about the effects of nutraceuticals supplementation in these conditions are controversial and the reciprocal and multilevel interactions between nutraceuticals, mitochondria, and environmental stressors are far from being fully understood [56].

In addition, recent research is now focusing on specific pathological conditions and there is still a large gap of knowledge on the role of specific dietary supplements in healthy older adults.

On the other hand, it should be noted that our systematic review identified just one study [35] reporting significant improvement in mitochondrial-specific ROS-bioactivity after sodium nitrite supplementation. Therefore, the antioxidant activity of dietary supplements in healthy aging should be further studied to deeply characterize the role of specific nutraceuticals in mitochondria modifications of patients without pathology-induced organelle alterations.

Also the nutrigenomics might play a key role in counteracting the aging process [57, 58]. In this scenario, nutrition can be a key factor to delay the onset of age-related degenerative pathological mechanisms, also from a molecular point of view [59]. In addition, nutrigenomics has been proposed to play a crucial role in aging process and in particular in neuronal health [59]. It has been proposed that neuronal degeneration can be prevented by various foods rich in polyphenols or other bioactive compounds [60, 61]. These mechanisms are related to epigenetic regulation of anti-inflammatory and antioxidant pathways and regulation of gene expression. For example, as recently demonstrated by Uberti et al. [62], the increased ROS levels in the brain during aging (caused by oxidative stress) can be reduced by dietary supplementation with lipoic acid and vitamin D3. The same concept is also valid for suppressed H_2O_2-induced mitochondrial dissipation [62]. Interestingly, this study reported significant results in terms of mitochondrial transcriptome modifications only after fish oil-derived n-3 PUFA supplementations [36]. In addition, fish oil-derived n-3 PUFA supplementation seems to be effective in increasing mitochondrial oxidative capacity [36]. On the other hand, it should be noted that several studies supported macroscopical effects in terms of anabolic and function enhancement after n-3 PUFA supplementation [63–65]. Therefore, these data might partly explain the mechanisms underpinning macroscopical effects of n-3 PUFA supplementations through changes in key gene set pathways involved in muscle structure, growth and oxidative metabolism regulation [36]. Future research might clarify the optimal n-3 PUFA supplementation modality in the bioregulation of molecular pathways involved in the aging process to maximize the n-3 PUFA interaction with mitochondrial oxidative capacity and transcriptome regulation.

In the past few years, several papers suggested a possible association between aging and progressive decline in mitochondria bioenergetic capacity and energy homeostasis [66, 67]. In particular, mitochondrial electron transport chain dysfunction might reduce ATP production, thereby increasing anaerobic metabolism and free radical production [56]. In this scenario, it has been reported that mitochondrial ATP production might be increased using dietary supplements, as well as the removal of toxic metabolites and the exclusion of cellular defects such as deficiency of complex I, II, or III activity in electron transport chain [68]. Therefore, dietary supplements can be useful in the treatment of primary mitochondrial disease: the most commonly used ingredients are antioxidants, such as vitamin C, vitamin E and alpha-lipoic acid; electron donors and acceptors, such as CoQ10 and riboflavin; compounds that can be used as alternative energy sources, such as creatine [69] and compounds that can conjugate or bind mitochondrial toxins, such as carnitine [68]. On the other hand, previous data suggested that few dietary supplements could have a positive role in increasing mitochondria energy production in healthy older adults and significant results are reported only after supplementation with urolithin A [38], NR [34], and whey protein powder [38].

Similarly, the positive effects on mitochondria quality in older adults might be related to physical activity, suggesting a strict link between mitochondrial modifications and the progressive improvement of energy supply induced by exercise-induced conditioning [12]. Unfortunately, evidence from in vivo studies in healthy older adults is limited and few studies assessed the effects of physical activity in this context [66, 67]. Thus, future research might focus on the synergic proprieties between physical activity and dietary supplements to set up tailored multidisciplinary

interventions aiming at optimizing the preventive and protective role of lifestyle intervention in the aging processes.

Although dietary supplements are designed only to supplement the diet and not to treat, mitigate or cure diseases [60, 61], several nutraceuticals are frequently prescribed in common clinical practice in wide range of pathological conditions. Thus, growing evidence is now focusing on the efficacy of dietary supplements in several pathological conditions but no previous systematic review focused on healthy older adults.

To date, mitochondria modifications are considered a cornerstone of the aging process and a key target for healthy aging. In the last few years, several dietary supplements have been proposed to treat this condition. Unfortunately, the currently available literature mainly focused on animal models, whereas the effects of dietary supplements on mitochondrial modifications in humans are still far from being deeply characterized. In light of these considerations, it should be noted that the low number of studies included reflect a large gap of knowledge about subcellular effects of dietary supplements in human subjects, although they could benefit from this kind of nutritional intervention. However, the improvement of clinical and research approaches to aging is strictly related to a deeper understanding of the pathophysiological mechanisms underpinning this condition. Therefore, the biological effects of these therapeutic interventions should be better investigated to fulfill the need for a translational approach to implement effective and tailored interventions to treat these subjects. In conclusion, despite macroscopical effects of dietary supplements and nutraceuticals have been previously described, controversies are still open in this field.

In this context, our findings might promote a better understanding of the biological effects of specific dietary supplements and could be considered as a catalyst for the development of precise treatment protocols targeting specific subcellular modifications that play a crucial role in the complex framework underpinning the aging process.

Despite these considerations, we are aware that the present work is not free from limitations. First, the few studies included might represent the main limitation of the present work. However, it should be noted that the strict eligibility criteria allow to provide specific data about the effectiveness of specific mitochondria modifications in healthy older adults. Moreover, the present work underlined a large gap of knowledge in this field, emphasizing the need for good-quality studies assessing the role of dietary supplements in healthy aging to pave the way to a precise prescription of dietary supplements targeting cellular and subcellular pathways involved in the aging process. Second, the large heterogeneity of the dietary supplements assessed is another study limitation. Nevertheless, it should be noted that the present study is the first systematic review of RCTs providing a broad overview on the effects of dietary supplements on mitochondria modifications in older adults. Lastly, a meta-analysis has not been performed due to the heterogeneity of dietary supplements considered, in accordance with the Cochrane Handbook for Systematic Review of Intervention [70].

Conclusion

In the recent years, a growing interest has been rising about the correlation among dietary supplements, mitochondria modifications and age-related functional impairment. However, to date, evidence supporting the role of single dietary supplements in targeting specific mitochondrial modification is still lacking. Taken together, the results of the present systematic review underlined potential effects of sodium nitrite, PUFA, NR, urolithin A and whey protein powder in modulating specific mitochondria modification. On the other hand, the few studies included by the present work severely limit the strength of our results. Thus, further good-quality studies are needed to better characterize the clinical implications of dietary supplements prescription to target specific cellular modifications involved in cellular aging processes.

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Declarations

Conflict of interest All the authors declare that they have no conflicts of interest.

Statement of human and animals rights This review reports no participant data or original research findings that require ethics approval.

Consent to participate For this type of study, formal consent is not required.

Consent for publication All the authors declare that they give their consent for publication.

References

1. Kennedy BK, Berger SL, Brunet A et al (2014) Geroscience: linking aging to chronic disease. Cell 159:709–713. https://doi.org/10.1016/j.cell.2014.10.039

2. Organization WH (2015) World Report on Ageing and Health. https://apps.who.int/iris/bitstream/handle/10665/186463/9789240694811_eng.pdf?sequence=1 Accessed Acces Date 2022
3. Organization WH (2016) The global strategy and ActionPlan on Ageing and Health. https://www.who.int/ageing/global-strategy/en/. Accessed Acces Date 2022
4. TumasianHarish RAA, Kundu G et al (2021) Skeletal muscle transcriptome in healthy aging. Nat Commun 12:2014. https://doi.org/10.1038/s41467-021-22168-2
5. Ukraintseva S, Arbeev K, Duan M et al (2021) Decline in biological resilience as key manifestation of aging: Potential mechanisms and role in health and longevity. Mech Ageing Dev 194:111418. https://doi.org/10.1016/j.mad.2020.111418
6. Petkovic M, O'Brien CE, Jan YN (2021) Interorganelle communication, aging, and neurodegeneration. Genes Dev 35:449–469. https://doi.org/10.1101/gad.346759.120
7. Boengler K, Kosiol M, Mayr M et al (2017) Mitochondria and ageing: role in heart, skeletal muscle and adipose tissue. J Cachexia Sarcopenia Muscle 8:349–369. https://doi.org/10.1002/jcsm.12178
8. Kauppila TES, Kauppila JHK, Larsson NG (2017) Mammalian mitochondria and aging: an update. Cell Metab 25:57–71. https://doi.org/10.1016/j.cmet.2016.09.017
9. Franceschi C, Garagnani P, Vitale G et al (2017) Inflammaging and "Garb-aging." Trends Endocrinol Metab 28:199–212. https://doi.org/10.1016/j.tem.2016.09.005
10. Lopez-Otin C, Galluzzi L, Freije JMP et al (2016) Metabolic control of longevity. Cell 166:802–821. https://doi.org/10.1016/j.cell.2016.07.031
11. Sajjadi E, Venetis K, Scatena C et al (2020) Biomarkers for precision immunotherapy in the metastatic setting: hope or reality? Ecancermedicalscience 14:1150. https://doi.org/10.3332/ecancer.2020.1150
12. Lippi L, de Sire A, Mezian K et al (2022) Impact of exercise training on muscle mitochondria modifications in older adults: a systematic review of randomized controlled trials. Aging Clin Exp Res. https://doi.org/10.1007/s40520-021-02073-w
13. Gurău F, Baldoni S, Prattichizzo F et al (2018) Anti-senescence compounds: A potential nutraceutical approach to healthy aging. Ageing Res Rev 46:14–31. https://doi.org/10.1016/j.arr.2018.05.001
14. Lee J, Koo N, Min DB (2004) Reactive oxygen species, aging, and antioxidative nutraceuticals. Compr Rev Food Sci Food Saf 3:21–33. https://doi.org/10.1111/j.1541-4337.2004.tb00058.x
15. Calcinotto A, Kohli J, Zagato E et al (2019) Cellular senescence: aging, cancer, and injury. Physiol Rev 99:1047–1078. https://doi.org/10.1152/physrev.00020.2018
16. Kubben N, Misteli T (2017) Shared molecular and cellular mechanisms of premature ageing and ageing-associated diseases. Nat Rev Mol Cell Biol 18:595–609. https://doi.org/10.1038/nrm.2017.68
17. Herbst A, Lee CC, Vandiver AR et al (2020) Mitochondrial DNA deletion mutations increase exponentially with age in human skeletal muscle. Aging Clin Exp Res. https://doi.org/10.1007/s40520-020-01698-7
18. Lefkimmiatis K, Grisan F, Iannucci LF et al (2020) Mitochondrial communication in the context of aging. Aging Clin Exp Res. https://doi.org/10.1007/s40520-019-01451-9
19. Corti C, Sajjadi E, Fusco N (2019) Determination of mismatch repair status in human cancer and its clinical significance: does one size fit all? Adv Anat Pathol 26:270–279. https://doi.org/10.1097/PAP.0000000000000234
20. Nuti R, Brandi ML, Checchia G et al (2019) Guidelines for the management of osteoporosis and fragility fractures. Intern Emerg Med 14:85–102. https://doi.org/10.1007/s11739-018-1874-2
21. Iolascon G, de Sire A, Curci C et al (2021) Osteoporosis guidelines from a rehabilitation perspective: systematic analysis and quality appraisal using AGREE II. Eur J Phys Rehabil Med 57:273–279. https://doi.org/10.23736/S1973-9087.21.06581-3
22. Pinheiro MB, Oliveira J, Bauman A et al (2020) Evidence on physical activity and osteoporosis prevention for people aged 65+ years: a systematic review to inform the WHO guidelines on physical activity and sedentary behaviour. Int J Behav Nutr Phys Act 17:150. https://doi.org/10.1186/s12966-020-01040-4
23. de Sire A, Invernizzi M, Lippi L et al (2019) Nutritional supplementation in hip fracture sarcopenic patients a narrative review. Clin Cases Miner Bone Metab 16:27–30
24. Invernizzi M, de Sire A, D'Andrea F et al (2019) Effects of essential amino acid supplementation and rehabilitation on functioning in hip fracture patients: a pilot randomized controlled trial. Aging Clin Exp Res 31:1517–1524. https://doi.org/10.1007/s40520-018-1090-y
25. de Sire A, Baricich A, Renò F et al (2020) 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 32:959–962. https://doi.org/10.1007/s40520-019-01436-8
26. Simioni C, Zauli G, Martelli AM et al (2018) Oxidative stress: role of physical exercise and antioxidant nutraceuticals in adulthood and aging. Oncotarget 9:17181–17198. https://doi.org/10.18632/oncotarget.24729
27. Singh P, Sivanandam TM, Konar A et al (2021) Role of nutraceuticals in cognition during aging and related disorders. Neurochem Int 143:104928. https://doi.org/10.1016/j.neuint.2020.104928
28. Harman D (1956) Aging: a theory based on free radical and radiation chemistry. J Gerontol 11:298–300. https://doi.org/10.1093/geronj/11.3.298
29. Harman D (1972) The biologic clock: the mitochondria? J Am Geriatr Soc 20:145–147. https://doi.org/10.1111/j.1532-5415.1972.tb00787.x
30. Moher D, Liberati A, Tetzlaff J et al (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. https://doi.org/10.1136/bmj.b2535
31. Organization WH (2020) Decade of Healthy Ageing 2020–2030. https://www.who.int/initiatives/decade-of-healthy-ageing. Accessed Acces Date 2022
32. Jadad AR, Moore RA, Carroll D et al (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17:1–12. https://doi.org/10.1016/0197-2456(95)00134-4
33. Sterne JAC, Savovic J, Page MJ et al (2019) RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366:l4898. https://doi.org/10.1136/bmj.l4898
34. Elhassan YS, Kluckova K, Fletcher RS et al (2019) Nicotinamide riboside augments the aged human skeletal muscle NAD(+) metabolome and induces transcriptomic and anti-inflammatory signatures. Cell Rep 28:e6. https://doi.org/10.1016/j.celrep.2019.07.043
35. Rossman MJ, Gioscia-Ryan RA, Santos-Parker JR et al (2021) Inorganic nitrite supplementation improves endothelial function with aging: translational evidence for suppression of mitochondria-derived oxidative stress. Hypertension 77:1212–1222. https://doi.org/10.1161/HYPERTENSIONAHA.120.16175
36. Yoshino J, Smith GI, Kelly SC et al (2016) Effect of dietary n-3 PUFA supplementation on the muscle transcriptome in older adults. Physiol Rep https://doi.org/10.14814/phy2.12785
37. Zanini D, Todorovic N, Korovljev D et al (2021) The effects of 6-month hydrogen-rich water intake on molecular and phenotypic biomarkers of aging in older adults aged 70 years and over: A randomized controlled pilot trial. Exp Gerontol 155:111574. https://doi.org/10.1016/j.exger.2021.111574

38. Liu S, D'Amico D, Shankland E et al (2022) Effect of urolithin a supplementation on muscle endurance and mitochondrial health in older adults: a randomized clinical trial. JAMA Netw Open 5:e2144279. https://doi.org/10.1001/jamanetworkopen.2021.44279
39. Connell NJ, Grevendonk L, Fealy CE et al (2021) NAD+-precursor supplementation with L-tryptophan, nicotinic acid, and nicotinamide does not affect mitochondrial function or skeletal muscle function in physically compromised older adults. J Nutr 151:2917–2931. https://doi.org/10.1093/jn/nxab193
40. Butler AR, Feelisch M (2008) Therapeutic uses of inorganic nitrite and nitrate. Circulation 117:2151–2159. https://doi.org/10.1161/circulationaha.107.753814
41. Philp LK, Heilbronn LK, Janovska A et al (2015) Dietary enrichment with fish oil prevents high fat-induced metabolic dysfunction in skeletal muscle in mice. PLoS ONE 10:e0117494. https://doi.org/10.1371/journal.pone.0117494
42. Johnson ML, Lalia AZ, Dasari S et al (2015) Eicosapentaenoic acid but not docosahexaenoic acid restores skeletal muscle mitochondrial oxidative capacity in old mice. Aging Cell 14:734–743. https://doi.org/10.1111/acel.12352
43. Yang Y, Zhu Y, Xi X (2018) Anti-inflammatory and antitumor action of hydrogen via reactive oxygen species (Review). Oncol Lett. https://doi.org/10.3892/ol.2018.9023
44. Dollerup OL, Chubanava S, Agerholm M et al (2020) Nicotinamide riboside does not alter mitochondrial respiration, content or morphology in skeletal muscle from obese and insulin-resistant men. J Physiol 598:731–754. https://doi.org/10.1113/jp278752
45. Ryu D, Mouchiroud L, Andreux PA et al (2016) Urolithin A induces mitophagy and prolongs lifespan in C. elegans and increases muscle function in rodents. Nat Med 22:879–888. https://doi.org/10.1038/nm.4132
46. D'Amico D, Andreux PA, Valdés P et al (2021) Impact of the natural compound urolithin a on health, disease, and aging. Trends Mol Med 27:687–699. https://doi.org/10.1016/j.molmed.2021.04.009
47. Mouchiroud L, Houtkooper RH, Auwerx J (2013) NAD+metabolism: A therapeutic target for age-related metabolic disease. Crit Rev Biochem Mol Biol 48:397–408. https://doi.org/10.3109/10409238.2013.789479
48. Yoshino J, Kathryn M, Imai S-I (2011) Nicotinamide mononucleotide, a Key NAD+ intermediate, treats the pathophysiology of diet- and age-induced diabetes in mice. Cell Metab 14:528–536. https://doi.org/10.1016/j.cmet.2011.08.014
49. Gomes AP, Price NL, Ling AJ et al (2013) Declining NAD(+) induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. Cell 155:1624–1638. https://doi.org/10.1016/j.cell.2013.11.037
50. Maccioni RB, Calfío C, González A et al (2022) Novel nutraceutical compounds in alzheimer prevention. Biomolecules. https://doi.org/10.3390/biom12020249
51. Iolascon G, Gimigliano R, Bianco M et al (2017) Are dietary supplements and nutraceuticals effective for musculoskeletal health and cognitive function? a scoping review. J Nutr Health Aging 21:527–538. https://doi.org/10.1007/s12603-016-0823-x
52. Dominguez LJ, Veronese N, Vernuccio L et al (2021) Nutrition, physical activity, and other lifestyle factors in the prevention of cognitive decline and dementia. Nutrients. https://doi.org/10.3390/nu13114080
53. Liu Z, Ren Z, Zhang J et al (2018) Role of ROS and nutritional antioxidants in human diseases. Front Physiol 9:477. https://doi.org/10.3389/fphys.2018.00477
54. Brambilla D, Mancuso C, Scuderi MR et al (2008) The role of antioxidant supplement in immune system, neoplastic, and neurodegenerative disorders: a point of view for an assessment of the risk/benefit profile. Nutr J 7:29. https://doi.org/10.1186/1475-2891-7-29
55. Bordoni L, Gabbianelli R (2020) Mitochondrial DNA and neurodegeneration: any role for dietary antioxidants? Antioxidants (Basel). https://doi.org/10.3390/antiox9080764
56. Niyazov DM, Kahler SG, Frye RE (2016) Primary mitochondrial disease and secondary mitochondrial dysfunction: importance of distinction for diagnosis and treatment. Mol Syndromol 7:122–137. https://doi.org/10.1159/000446586
57. Luceri C, Bigagli E, Pitozzi V et al (2015) A nutrigenomics approach for the study of anti-aging interventions: olive oil phenols and the modulation of gene and microRNA expression profiles in mouse brain. Eur J Nutr 56:865–877
58. Rescigno T, Micolucci L, Tecce MF et al (2017) Bioactive nutrients and nutrigenomics in age-related diseases. Molecules. https://doi.org/10.3390/molecules22010105
59. Morsanuto V, Galla R, Molinari C et al (2020) A New palmitoylethanolamide form combined with antioxidant molecules to improve its effectivess on neuronal aging. Brain Sci 10:457
60. Di Meo F, Valentino A, Petillo O et al (2020) Bioactive polyphenols and neuromodulation: molecular mechanisms in neurodegeneration. Int J Mol Sci. https://doi.org/10.3390/ijms21072564
61. Chen S-q, Wang Z-s, Ma Y-X et al (2018) Neuroprotective effects and mechanisms of tea bioactive components in neurodegenerative diseases. Molecules 23:512
62. Molinari C, Morsanuto V, Ghirlanda S et al (2019) Role of combined lipoic acid and Vitamin D3 on astrocytes as a way to prevent brain ageing by induced oxidative stress and iron accumulation. Oxid Med Cell Longev. https://doi.org/10.1155/2019/2843121
63. Tachtsis B, Camera DM, Lacham-Kaplan O (2018) Potential roles of n-3 PUFAs during skeletal muscle growth and regeneration. Nutrients 10:309
64. Ticinesi A, Meschi T, Lauretani F et al (2016) Nutrition and inflammation in older individuals: focus on vitamin D, n-3 polyunsaturated fatty acids and whey proteins. Nutrients 8:186. https://doi.org/10.3390/nu8040186
65. Da Boit M, Hunter AM, Gray SR (2017) Fit with good fat? The role of n-3 polyunsaturated fatty acids on exercise performance. Metabolism 66:45–54. https://doi.org/10.1016/j.metabol.2016.10.007
66. Jing E, O'Neill BT, Rardin MJ et al (2013) Sirt3 regulates metabolic flexibility of skeletal muscle through reversible enzymatic deacetylation. Diabetes 62:3404–3417. https://doi.org/10.2337/db12-1650
67. Lantier L, Williams AS, Williams IM et al (2015) SIRT3 is crucial for maintaining skeletal muscle insulin action and protects against severe insulin resistance in high-fat-fed mice. Diabetes 64:3081–3092. https://doi.org/10.2337/db14-1810
68. Pfeffer G, Horvath R, Klopstock T et al (2013) New treatments for mitochondrial disease-no time to drop our standards. Nat Rev Neurol 9:474–481. https://doi.org/10.1038/nrneurol.2013.129
69. Tarnopolsky MA, Raha S (2005) Mitochondrial myopathies: diagnosis, exercise intolerance, and treatment options. Med Sci Sports Exerc 37:2086–2093. https://doi.org/10.1249/01.mss.0000177341.89478.06
70. Higgins JPT TJ, Chandler J, Cumpston M (2021) Cochrane handbook for systematic reviews of interventions version 6.2 (updated February 2021)