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SYSTEMATIC REVIEW

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Mitotherapy in Alzheimer's and Parkinson's diseases: A systematic review of preclinical studies

Aynur Modiri[1], Leila Hosseini[1*], Nasrin Abolhasanpour[2], Hosein Azizi[3,4] and Reza Naghdi Sadeh[1*]

Abstract

Background Alzheimer's disease (AD) and Parkinson's disease (PD) are prevalent neurodegenerative disorders and strongly affect both the patients' lives and their caregivers. Strategy to improve and restore mitochondrial function, as well as to treat mitochondria-associated diseases, as observed in the pathophysiology of AD and PD. The current study aimed to investigate the potential of mitotherapy in AD and PD in preclinical studies.

Methods We conducted a systematic search of articles in English related to mitotherapy in AD and PD animal models published until October 2024 in the selected bibliographic databases, including PubMed, Scopus, EMBASE, and Google Scholar, and the reference lists of relevant review articles published. The quality of the final selected studies was assessed using the Collaborative Approach to Meta-Analysis and Review of Animal Studies (CAMARADES) checklists and the SYRCLE risk of bias tool. The initial search resulted in 231 studies, and after screening the titles and abstracts, 30 studies were recognized. Finally, 7 studies met the inclusion criteria.

Results Despite restricted knowledge of the mitotherapy mechanisms, evidence shows that exogenous mitochondria exert neuroprotective effects via improving mitochondrial function, reducing oxidative stress and inflammation in preclinical models of AD and PD.

Conclusion This systematic review summarizes the preclinical studies on mitotherapy and provides evidence favoring mitochondria transplantation's protective effects in animal PD and AD models.

Keywords Mitochondrial transfer, Alzheimer's disease, Parkinson's disease, Mitochondrial dysfunction

Introduction

Neurodegenerative disorders impact a substantial population globally. The predominant neurodegenerative diseases include Alzheimer's disease (AD) and Parkinson's disease (PD) [1]. AD and PD currently affect about 50 million and 10 million people, respectively, and these numbers are predicted to surge to 150 million and 12 million people by 2050 [2]. These diseases are distinguished by the gradual deterioration of neuronal structure or function and loss of neuronal function, which ultimately diminishes cognitive, memory, and motor capabilities [3]. Although there has been remarkable progress in the

*Correspondence:
Leila Hosseini
leilahosseini337@gmail.com
Reza Naghdi Sadeh
naghdir@tbzmed.ac.ir
[1]Research Center of Psychiatry and Behavioral Sciences, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Research Center for Evidence-Based Medicine, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Clinical Research Development Unit of Alzahra Hospital, Women's Reproductive Health Research Center, Tabriz University of Medical Sciences, Tabriz, Iran
[4]Sarab Faculty of Medical Sciences, Sarab, Iran

development of therapeutics designed to manage the symptoms of AD and PD, a cure or successful treatment for neurodegeneration remains elusive within the scientific community.

Mitochondria play a crucial role in the normal functioning of the nervous system, as neurons require significant energy to sustain their continuous communication and signaling processes [4]. Mitochondrial dysfunction is recognized as a key contributor to the pathogenesis and progression of diverse neurodegenerative diseases [5]. Disruptions in the function and metabolism of mitochondria may lead to synaptic damage and neuronal loss, especially in AD and PD. Mitochondria are significantly involved in numerous mechanisms associated with neurodegeneration: oxidative stress through reactive oxygen species (ROS) generation, apoptosis, iron metabolism, and energy dysregulation [4, 5]. A close connection between the accumulation of α-synuclein and mitochondrial disturbance has been noted in PD. Increasing evidence shows that mitochondrial complex I activity decreases in patients' PD platelets [6, 7]. Elevated levels of α-synuclein lead to disturbances in neurotransmitter release, energy production, and mitochondrial function, and also trigger neuroinflammation and neuron death [8].

Findings supporting the involvement of mitochondria in AD are characterized by decreased oxygen and glucose metabolism in the patient's brain and reduced cytochrome oxidase activity in the platelets of patients with AD [9]. A diminished cytochrome oxidase activity in AD patients' frontal and temporal cortices has been reported [10]. Mitochondria are a direct site for the accumulation of Aβ in neurons affected by AD, indicating a role in free radical production and oxidative damage that contributes to the progression of the disease. These results imply that therapeutic strategies aimed at the mitochondria could be beneficial in slowing down the progression of AD in older adults and treating patients with the condition [11].

A novel therapeutic method known as mitochondrial transplantation focuses on restoring or replacing impaired native mitochondria with healthy mitochondria (mitotherapy) [12]. Several studies have examined the neuroprotective properties of mitochondrial transplantation in the central nervous system [13–15]. Mitotherapy has demonstrated potential therapeutic effects in neurological diseases by enhancing cell proliferation, restoring adenosine triphosphate (ATP), reducing excessive inflammation, and preventing oxidative damage [14, 16]. This systematic review aims to comprehensively assess the existing preclinical evidence on the neuroprotective effects of mitotherapy in AD and PD. Specifically, we will investigate the efficacy of mitotherapy and explore the underlying molecular mechanisms of its neuroprotective effects.

Methods

The present systematic review was done according to the Cochrane Collaboration Handbook and PRISMA Statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Moreover, the review methodology is consistent with the guidelines established by the Joanna Briggs Institute (JBI) for systematic reviews [17].

Search strategy

Potentially eligible studies were identified by searching PubMed, Scopus, and EMBASE. The following search terms were used: "Exogenous mitochondria" OR "Mitochondrial transfer" OR "Mitochondrial transfusion" OR "Mitotherapy" OR "Mitochondrial transplantation" AND "Alzheimer's disease" OR "Neurodegenerative diseases" OR "Neurodegenerative disorders" OR "Parkinson's disease". Moreover, we manually scanned reference lists, Google Scholar, and grey literature, including annual reports, research reports, technical reports, project reports, government documents, and evaluation studies. Two authors (L.H. and A.M.) independently screened the titles and abstracts of the studies. Duplicate and non-relevant publications were excluded. A third independent author solved any disagreement over the exclusion and inclusion of an article (R.N.S). A total of 7 articles were included. The search strategy is presented in Appendix 1. The Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.VCR. REC.1402.586) approved the research.

Inclusion/exclusion criteria and screening

Inclusion criteria

(1) Mitochondrial transplantation was administered alone, (2) Experimental AD and/or PD was induced in rodents (i.e., rats or mice), (3) The Article was published in English.

Exclusion criteria

(1) The article was a review and an in-vitro study, (2) Mitochondria were not administered alone, (3) Absence of a correct control group, (4) The study did not evaluate PD or AD, (4) Only the abstract was available, (5) Duplicate publications.

Data collection

Data were extracted for study and sample characteristics (first author and year of publication, Species, age, sex, and animal's disorder), mitotherapy intervention (administration route, dose, duration, and source mitochondria), behavioral tests, and main findings (improved motor function and locomotor activity, cognition, mitochondrial function).

Assessment of study quality and risk of bias

The quality of the studies included in this systematic review was assessed using the Collaborative Approach to Meta-Analysis and Review of Animal Studies (CAMARADES) checklist [18]. This evaluation comprised 10 questions: (1) publication in a peer-reviewed journal, (2) statement regarding temperature control, (3) randomization of treatment or control, (4) allocation concealment, (5) blinded assessment of outcomes, (6) avoidance of anesthetics with significant intrinsic properties, (7) animal model description, (8) calculation of sample size, (9) compliance with animal welfare regulations, and (10) disclosure of potential conflicts of interest. We utilized the Risk of Bias tool from the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE) to evaluate potential selection, performance, detection, attrition, and reporting biases. Each domain is rated as having a low, high, or unclear risk of bias. The risk of bias was visualized using Review Manager software (RevMan). Two authors performed the Quality assessment independently, and a third author resolved discrepancies.

Results

Study selection and study characteristics

Figure 1 illustrates the PRISMA diagram of the comprehensive search and the reasons for the exclusions of studies. Of the 231 potential articles identified in our electronic search for AD and PD animal studies, 90 duplicates were removed. After screening abstracts and titles, 111 papers were excluded due to the inaccessibility of abstracts, articles written in non-English, and review articles. The full texts of 30 articles were evaluated for

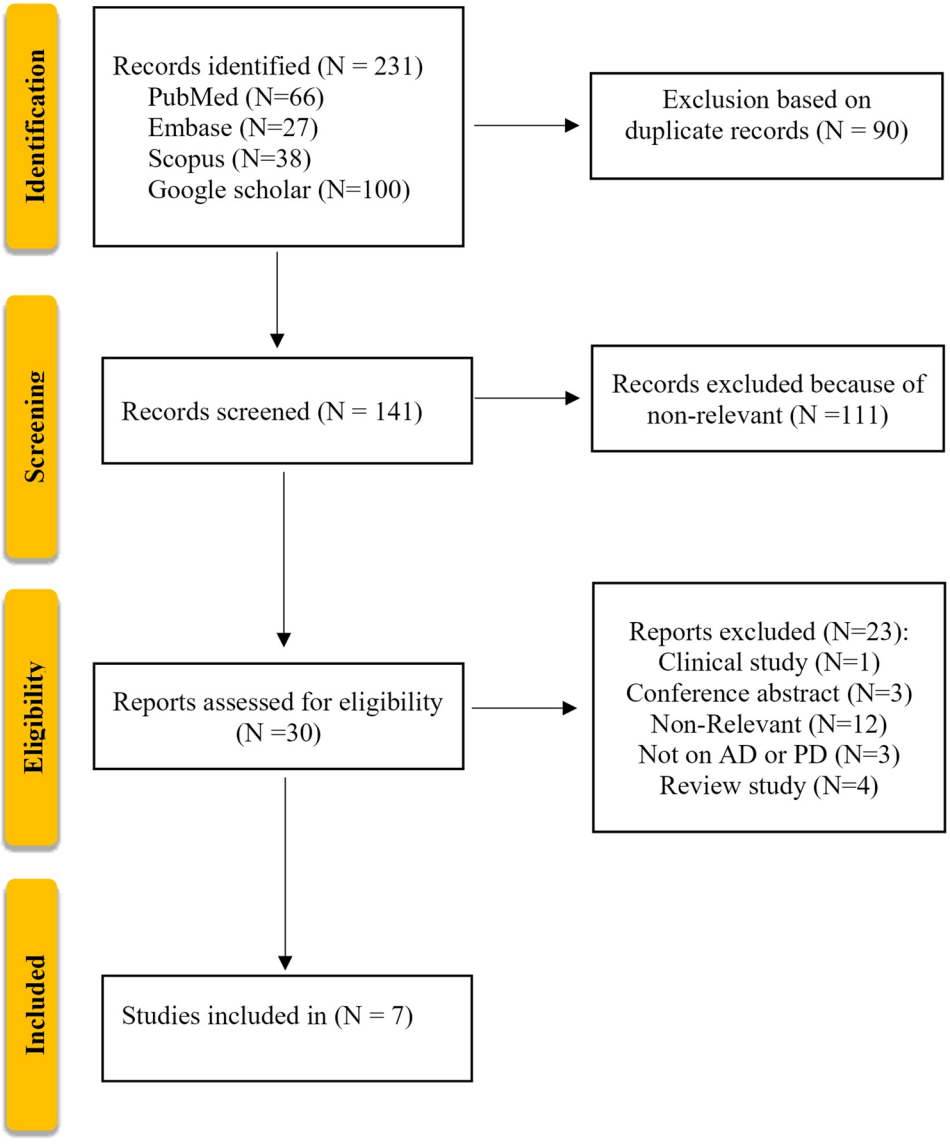

Fig. 1 Flow chart of study selection for inclusion in the systematic review

eligibility, resulting in the exclusion of 23 articles owing to not being relevant to the systematic review topic. Finally, 7 articles met the inclusion criteria and were included in our systematic review.

The characteristics of each study are summarized in Table 1. Six studies were performed on mice [13, 15, 16, 19–21] and 1 on rats [22]. Regarding the sex of the animals, the majority of studies used males, and only one study used females. Of the PD models used in these studies, 2 used the methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) -induced PD model [15, 16], 1 used the 6-hydroxydopamine (6-OHDA)-induced PD model [22], and 1 study used the rotenone-induced PD model [21]. Of the AD models used in these studies, 2 used the Aβ-induced AD model [13, 19], and 1 used the genetic AD model [20]. In the majority of studies, the mitochondria delivery route was intravenous [13, 15, 16, 19–21]. The source mitochondria were from cells in most of the studies [15, 16, 19, 20, 22].

Quality of included studies

All investigated articles are published in peer-reviewed journals and reported statements describing temperature control. A disclosure statement for conflict of interest and random allocation was mentioned in 85.71% of the studies. No study used aged animals. Compliance with animal welfare regulations was stated in all of the articles. Random allocation to treatment or control was reported in 71.43% of publications. The sample size calculation was not reported in any of the articles. The blind outcome assessment and blinded building of the model were reported in 28.57% and 14.28% of the papers, respectively. No research has mentioned inducing significant intrinsic neuroprotective activity because of anesthetics (Fig. 2).

Details of the quality assessment of the included studies using SYRCLE's Risk of Bias tools are shown in Fig. 3A and B. The Cochrane Collaboration tool showed that most studies were at an uncertain risk of sequence generation and incomplete outcome data. Moreover, random housing had a low risk of bias in 71.42% of studies. The allocation concealment and random outcome assessment were unclear risks of bias in 57.14% and 71.42% of the articles, respectively. The baseline characteristics and investigator blinding were low risk in 57.14% of the studies. Blinding of outcome assessment in 28.57% was a high risk of bias. The reporting of selective outcomes and other biases had a low risk of bias in 42.85% of the studies.

Alzheimer's disease

Of all included studies, three articles have evaluated the efficacy of mitochondrial transplantation in AD models. Nitzan et al. [19] showed that a single intravenous (IV) injection of the active isolated mitochondria from HeLa cells to AD mice improved cognitive deficits and mitochondrial function, increasing citrate-synthase and citrate-cytochrome c oxidase activities, in the hippocampus and cortex. They also found a decrease in gliosis and neuronal loss in the hippocampus of AD mice following miotherapy.

Furthermore, research has shown that transplantation therapy of healthy mitochondria derived from mouse brain tissue significantly reduced deficits of short-term memory, fear memory, long-term non-associative memory, working, spatial learning, and cognitive ability, decreased Aβ deposition, oxidative stress, enhanced energy production, enzyme activities in the tricarboxylic acid cycle (TCA), and Forkhead Box O3 (FOXO3) level, and regulated autophagy in the hippocampus of AD mice [13]. Mitochondrial therapy could increase the levels of brain-derived neurotrophic factor (BDNF) production and extracellular signal-regulated Kinase (ERK) phosphorylation through nicotinamide adenine dinucleotide (NAD^+)/ sirtuin 1 (SIRT1) [13].

A study investigated mitotherapy in a chronic long-term AD model. They found that exogenous mitochondria (IV tail vein injections of mitochondria derived from HeLa cells) could ameliorate cognitive deficits and reduce neuronal injury, Aβ plaques, and mitochondrial dysfunction in the cortex of 5XFAD mice. This beneficial effect of mitotherapy is mediated by metabolic signaling from the liver through the serum to the brain. The liver exhibits altered metabolites that play a role in neurodegenerative processes, notably carnosine, C24:1-OH sphingomyelin, putrescine, and amino acids that act as neurotransmitters or their precursors [20].

Parkinson's disease

Among the included studies, four examined the effects of mitochondrial transfer on PD. Shi et al. [16] reported that systemic administration of mitochondria (IV injection, isolated from human hepatoma cells) inhibited the progression of experimental MPTP-induced PD by enhancing the functionality of the electron transport chain, reducing ROS levels, and averting cellular apoptosis and necrosis in the striatum. This study also found that mitochondrial transplantation reduced behavioral disorders in PD mice, as assessed using the pole and rotarod tests.

Isolated mitochondria of human umbilical cord mesenchymal stem cells exert anti-inflammatory effects via the reduction of pro-inflammatory cytokines expression in microglial cells and inhibition of microglial activation in the striatum. Besides, mitochondrial transfer was related to an improvement in motor deficits, an increase in the number of tyrosine hydroxylase (TH) + cells, and higher expression of Nissl + neurons in the substantia nigra (SN) in MPTP-induced PD mice [15]. Recently, it has been

Table 1 Characteristics of included studies

First Author & year	Species & Sex	Modeling	Dose, route & duration	Source mitochondria	Behavioral tests	Main findings in vivo	Main findings in vitro
Keren Nitzan et al.2019	C57BL/6 mice, male	AD, Aβ-ICV	A single IV injection two days after AD induction	Hela cells	Fear conditioning, Radial arm water maze, Open field test, Y-maze	Reduced neuronal loss and gliosis in the hippocampus, decreased mitochondrial dysfunction, increased citrate-synthase and citrate-cytochrome c oxidase activities in the hippocampus and cortex, improved working memory and spatial learning &memory	
Sahar Sweetat et al.2023	C57Bl/6J mice, male	AD, Hemizygous 5XFAD transgenic	IV tail vein injection 200 µg mitochondria/mouse, four or two injections	Hela cells	Y-maze, Open field test, Novel Object Recognition, and T-maze	Improved cognitive performance, reduced neuronal damage and amyloid burden, increased mitochondrial enzymatic activity in the cortex, modified proteomic and metabolomic alterations in the serum and liver	
Xiaoxi Yang et al.2023	C57BL/6 mice, male	AD,200 mol/L Aβ 1–42	Mitochondria at a dose of 3×10^6/0.2 mL, through the caudal vein, for 4 days	Mouse brain tissue	Morris water maze	Improved the cognitive ability, increased BDNF, reduced Aβ deposition and ROS content, increased complexes I and IV activities, NAD^+/NADH ratio, and SIRT1 activity, elevated levels of FOXO3, and LC3II/LC3I, increased activity of α-KGDH and SDH	Increased the MMP and SH-SY5Y cell viability, reduced Aβ aggregation and oxidative stress, increased ATP/ADP ratio, promoted *ERK* Phosphorylation, induced autophagy
Jui-Chih Chang et al.2016	Sprague-Dawley rats, female	PD, 30 mg of 6-OHDA in a total of 5 mL in 0.02% ascorbic acid	1.05 mg of Pep–1–conjugated mitochondria isolated from rat or human cells in a total of 5 mL PBS by a local injection in the MFB	PC12 cells (allogeneic source) and human osteosarcoma cybrids (xenogeneic source)	Open field test	Improved locomotive behavior, dopaminergic function, and mitochondrial function, reduced oxidative DNA damage in SN neurons, increased neuronal survival and TH in SN and ST, regulated mitochondrial dynamics	Improved cell viability from apoptotic death caused by the neurotoxin, enhanced neurite outgrowth
Xianxun Shi et al.2017	C57BL/6J mice, male	PD, MPTP, 10 mg/kg, IP, once a day for 5 days	0.5 mg/kg, IV, at the last time of MPTP administration	Human hepatoma cells	Pole and Rotarod tests and Forced swimming test	Increased latent period in rotarod test, increased mouse endurance, decreased turn time and locomotion activity time in pole test, ATP level, GSH, and complex I activity, reduced ROS	Improved SH-SY5Y cells viability, increased ATP content, GSH levels, reduced ROS, improved cell survival, and function by increasing mitochondrial respiratory chain complex I activity, reduced apoptosis, and necrosis

Table 1 (continued)

First Author & year	Species & Sex	Modeling	Dose, route & duration	Source mitochondria	Behavioral tests	Main findings in vivo	Main findings in vitro
Hyeyoon Eo et al.2024	C57BL/6J mice, male	PD,30 mg/kg of MPTP, for 5 days, IP	0.5 µg, 2.5 µg, and 10 µg, IV, one dose	Human umbilical cord mesenchymal stem cell	Pole and Rotarod tests	Reduced dopaminergic neuronal loss, improved motor function, T-turn and T-LA, and decreased number of falls, increased latency to fall, increased TH-positive cells in ST and SN, and Nissl-positive cells in SN, reduced Iba-1 in ST	Attenuated TNF-α and IL-6, iNOS, and IL-1β, increased TH expression, improved the abnormalities of neurites
Rachit Jain et al.2024	C57BL/6 mice, male	PD, Rotenone (1.5 mg/kg in 0.1% (w/v), IP for 21 days	0.5 mg/kg/day, IV for three alternative days after PD induction	Allogeneic mitochondria from the liver of healthy mice	Actimeter and Rotarod tests	Increased expression of TFAM and PGC 1α, improved motor function and locomotor activity, increased TH, and reduced the damage of TH neurons in SN, increased activity of complex (I-V), decreased α-synuclein	

Alzheimer's disease (AD), Intravenously (IV), Amyloid-β (Aβ), Parkinson's disease (PD), Intracere- broventricular (ICV), Reactive oxygen species (ROS), Phosphate-buffered saline (PBS), Medial forebrain bundle (MFB), 6-hydroxydopamine (6-OHDA), Tyrosine hydroxylase (TH), Substantia nigra pars compacta (SN), Striatum (ST), Methyl-4-phenyl- 1,2,3,6-tetrahydropyridine (MPTP), Intraperitoneally (IP), Peroxisome proliferator-activated receptor-gamma coactivator (PGC-1α), Transcription factor mitochondria (TFAM), Mitochondrial Membrane Potential (MMP), Brain-derived neurotrophic factor (BDNF), Forkhead Box O3 (FOXO3), Extracellular signal-regulated Kinase (ERK), and Glutathione (GSH)

demonstrated that the effects of the administration of exercised mitochondria on the reduction of damage to TH neurons in SN and α-synuclein and improvement of mitochondrial function, and behavioral deficits were more effective than those of non-exercised mitochondria [21]. Similarly, allogeneic and xenogeneic transplantation of peptide-labeled mitochondria resulted in enhanced locomotor activity in PD rats, accompanied by a reduction in the loss of dopaminergic neurons and enhancement of TH-positive immunoreaction of dopaminergic neurons in the SN [22].

Discussion

The prevalence of neurodegenerative diseases is becoming a significant health concern within the aging population. AD and PD are the most common among these disorders, with their incidence rates rising annually [23]. The lack of effective prevention and treatment strategies for the two diseases will exacerbate the socio-economic burden. Although the clinical symptoms of AD and PD differ, they share similar underlying mechanisms and are both linked to the process of normal aging [23]. Mitochondrial impairment is a hallmark of the pathogenesis of AD and PD, contributing to oxidative stress and neuronal degeneration [24].

Mitochondria are dynamic intracellular organelles that contribute significantly to energy generation, calcium level regulation, and cell survival and apoptosis processes [25]. Neurodegenerative diseases may lead to mitochondrial dynamic imbalance, heightened generation of free radicals, calcium overload, and the intrinsic cell death pathway [26]. So, the maintenance or enhancement of mitochondrial functionality may serve as a viable therapeutic strategy for managing neurodegenerative disorders. Mitochondria are essential for sustaining the equilibrium between producing and removing ROS. Enzymatic and non-enzymatic antioxidant systems rigorously regulate this equilibrium within the mitochondria, encompassing manganese-superoxide dismutase (Mn-SOD) and the ascorbate-glutathione cycles [27]. Generally, following mitochondrial dysfunction, the levels of ROS production increase, which leads to the induction of inflammatory responses via activation of the NFκB pathway and the NLR family. In neurological disorders, glial activation intensifies the production of ROS and pro-inflammatory cytokine secretion, which leads to more mitochondrial dysfunction [28].

Mitotherapy is emerging as a new therapeutic strategy for treating mitochondrial diseases. The mitochondrial transplantation process comprises isolating healthy, active mitochondria from various donor cells, which are then introduced into cells exhibiting mitochondrial dysfunction [29]. Mitochondria, as dynamic organelles with the potential for fusion and fission, have interconnecting

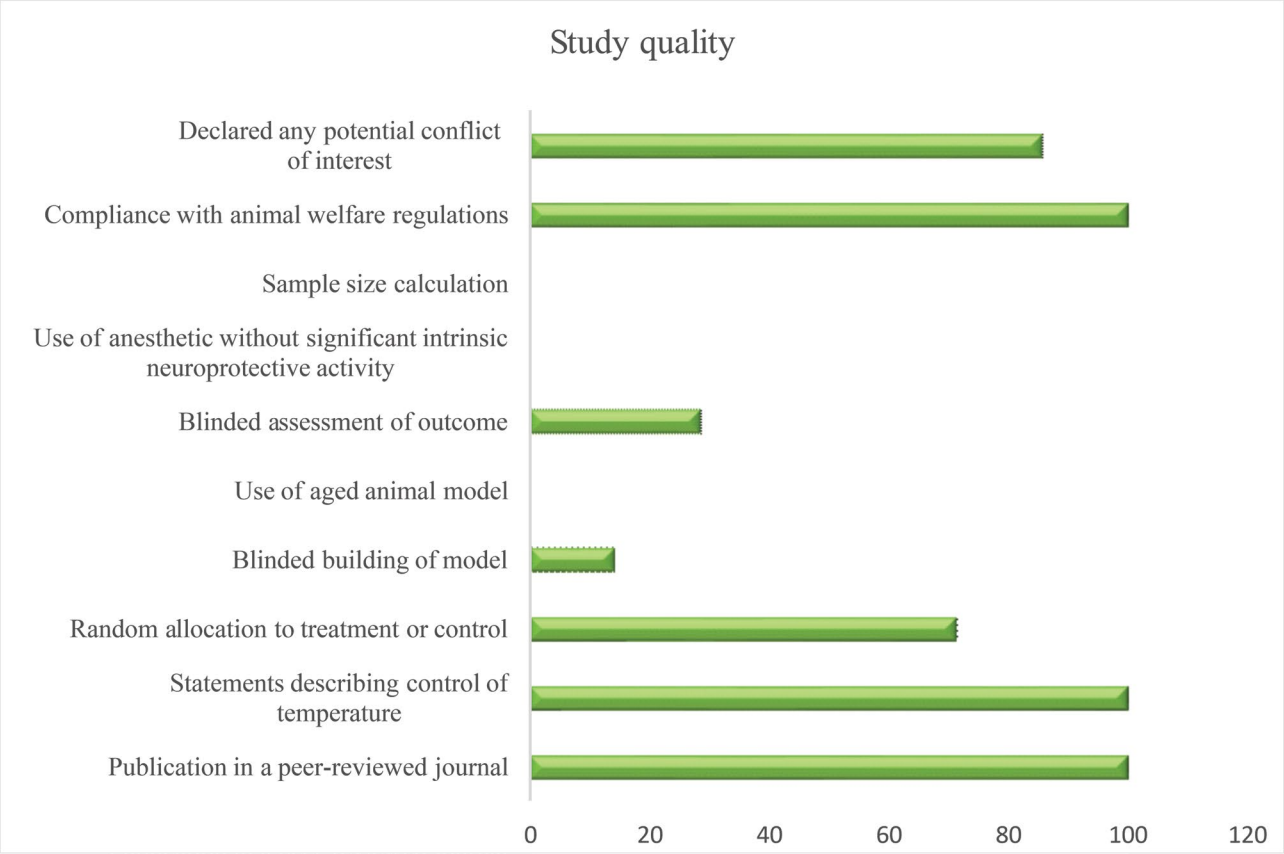

Fig. 2 Evaluation of the included studies based on the modified CAMARADES quality checklist

networks with each other. Cells can eliminate damaged mitochondria via fission, thereby reducing cellular stress. Concurrently, fusion enables the exchange of functional components to assist and supplement impaired mitochondria. Following mitotherapy, the fusion of exogenous mitochondria with the recipient cells' endogenous mitochondria increases oxygen consumption rates, enhances ATP generation, and restores depleted mitochondrial DNA [30].

Mitotherapy and Alzheimer's disease

Neurological studies have shown that impairment in mitochondrial function results in the induction of AD/tauopathy brain pathology [5, 31, 32]. In animals and AD patients, abundant injured mitochondria are observed via electron microscopy [33]. A reduction in the enzyme activities of the TCA and the electron transport chain was reported in the neuronal mitochondria [34, 35]. Following the reduction of oxidative phosphorylation ability in the neuronal mitochondria, a decrease in the production of ATP and destruction in the redox balance occur, subsequently influencing the cell's normal function. Additionally, the main pathological cause of AD is a dysfunction in mitochondrial autophagy, which is detected in human and animal AD samples [36].

Mitochondria are the primary site of ATP production through oxidative phosphorylation (OXPHOS) in neurons. Due to a high demand for energy and a limited capacity for glycolysis, neuronal cells show a significant dependence on OXPHOS. Subsequently, mitochondrial dysfunction can significantly impact neuronal function [37]. Additionally, ATP levels are closely linked to autophagy. Mitochondrial damage leads to impaired autophagy, which is weakened by energy deficiency, despite autophagy's capacity to boost energy levels by degrading proteins and organelles. However, ATP is vital for the initiation of autophagy, as the fusion of the autophagosome with the lysosome requires adequate energy [38]. Reduced autophagy facilitates the production and aggregation of Aβ, thereby exacerbating mitochondrial damage through the generation of high ROS levels [39]. This cycle will ultimately result in neuronal dysfunction and cognitive deficits in patients suffering from AD [13]. Therefore, the recovery of mitochondrial function to increase energy generation is mainly considered a critical approach to avoid AD progression. Some studies have demonstrated that mitochondrial transfer in AD animals improves cognitive function, reduces Aβ deposition, and ameliorates mitochondrial function [13, 19, 20].

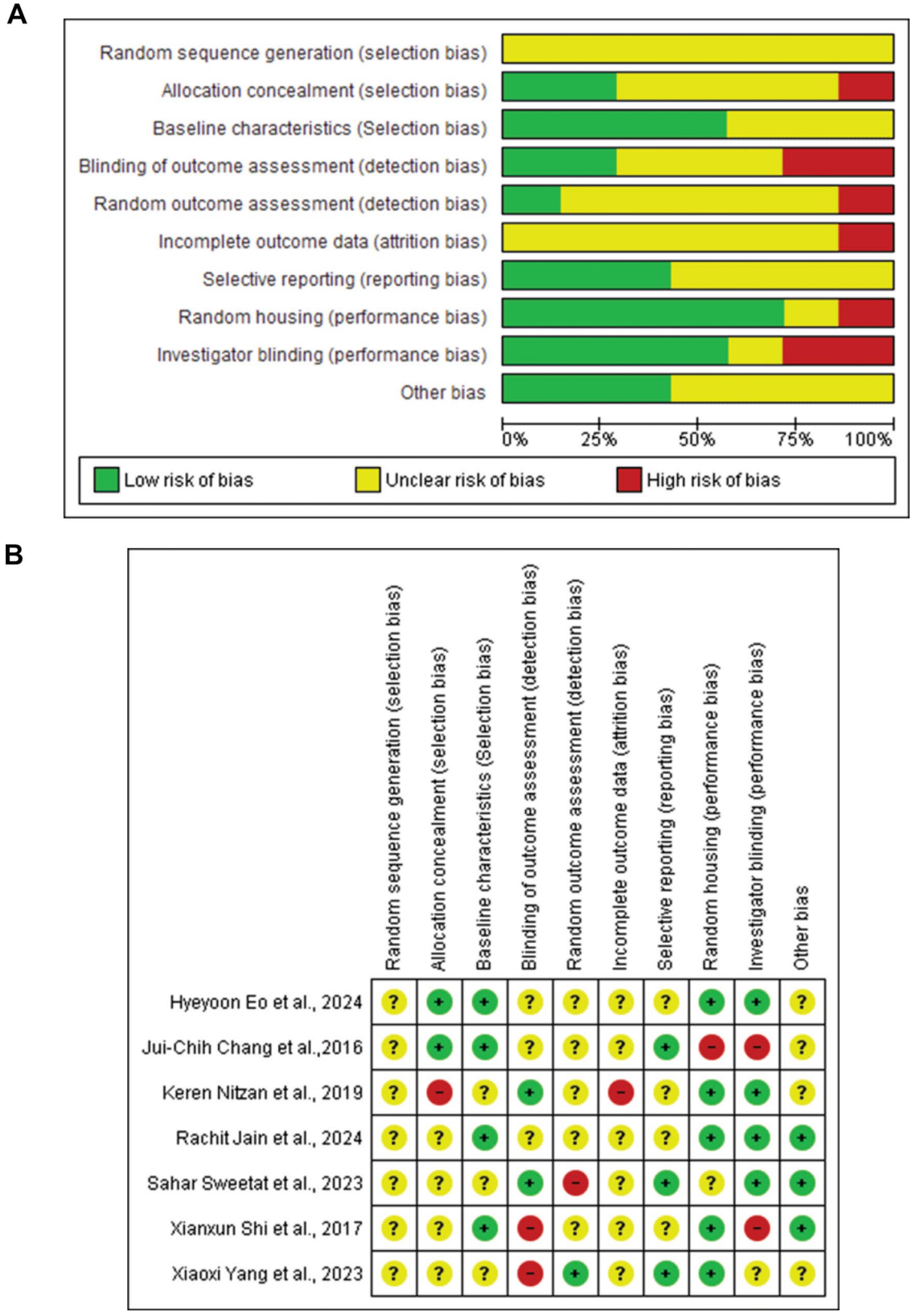

Fig. 3 Risk of bias (RoB) assessment using the Cochrane RoB tool. (**A**) The upper panel shows the RoB graph of each RoB item, which is presented as percentages across all included studies. (**B**) The down panel shows the RoB summary of each RoB item included in each study. In this color-coded ranking, green represents a low RoB, yellow means an unclear, and red represents a high RoB.

Emerging research highlights the NAD^+/SIRT1 pathway as a critical regulator of neuronal health, with disruptions in this axis contributing to AD pathogenesis. Mitochondrial complex I, which is responsible for converting NADH to NAD^+, is commonly impaired in AD, resulting in NADH /NAD^+ redox imbalance. Energy metabolism is disrupted following the depletion of NAD^+, leading to a cycle that speeds up neuronal degeneration [40]. SIRT1, an NAD^+-dependent deacetylase, modulates pathways that are vital for AD. It boosts the activity of α-secretase ADAM10, promoting the non-amyloidogenic cleavage of APP and decreasing Aβ production [41]. Reduced SIRT1 activity is associated with tau hyperphosphorylation and cognitive decline in AD patients. In addition, SIRT1 inhibits NF-κB signaling, attenuating the neuroinflammation induced by microglial activation. It also promotes neuronal survival by deacetylating stress-response proteins such as p53 and FOXO [42]. In the brains of individuals with AD, decreased NAD^+ levels were associated with diminished SIRT1 activity compared with the healthy elderly population. Decreased SIRT1 activity results in cognitive impairment [43]. NAD^+/SIRT1, a positive regulator of autophagy, activates the deacetylation of FOXO3 [13].

In a recent study, Bobkova and collaborators showed that intranasal administration of isolated mitochondria to olfactory bulbectomized mice with AD-like degeneration resulted in spatial memory recovery [44]. Their results showed that following intranasal injection of isolated mitochondria, they could be detected in a dose-dependent manner in different parts of the brain, like the neocortex, hippocampus, and olfactory bulbs [44]. In another similar study on an animal model of cisplatin-induced cognitive impairments, they observed that intranasal administration of isolated mitochondria from human mesenchymal stem cells reached the brain meninges within 30 min after injection. They were able to reverse cisplatin-induced synaptic loss and, most importantly, hippocampal synaptosomal mitochondrial anomalies, so that function approved the effectiveness of mitochondria in restoring the brain cell's homeostasis via crossing the blood-brain barrier [45]. These findings suggest that mitotherapy may offer potential therapeutic avenues for treating AD. Nevertheless, further research is needed to confirm these findings in larger studies and translate them to clinical settings.

Emerging research proposes that factors related to lifestyle, such as regular physical exercise and a nutritious diet, could significantly contribute to postponing the onset and advancement of AD [24]. It has been reported that a diet high in antioxidants, polyphenols, and small molecules that specifically target mitochondria can improve mitochondrial function and provide defense against oxidative stress, particularly in neurons of older adults and individuals with mild cognitive impairment or AD [24].

Mitotherapy and Parkinson's disease (PD)

The classic pathogenic feature of PD is the decline of dopaminergic neurons in the SN, resulting in decreased dopamine levels in the striatum. TH, the rate-limiting enzyme in DA synthesis, plays a central role in this process, and its dysregulation is tightly linked to PD pathogenesis [46]. Four studies evaluated the effects of mitotherapy on PD. These studies found that transplantation of mitochondria exerts a neuroprotective effect in PD animals. Mitotherapy could reduce motor deficits, improve mitochondrial function, and increase the number of TH + cells in animal models of PD [15, 16, 21, 22]. A study reported that exogenous mitochondria can be directly transferred into dopaminergic cells, resulting in decreased dopaminergic neuronal damage and neuroinflammation [15].

The dynamic balance between fission and fusion processes is crucial in determining mitochondrial morphology. Mitochondrial fusion is orchestrated by the protein optic atrophy 1 and mitofusin proteins, whereas fission is regulated by dynamin-related protein 1 and fission protein 1. It was revealed that the equilibrium between mitochondrial fission and fusion is disrupted in PD [47]. Chang et al. reported lower expression of mitochondrial fusion proteins in PD models than in healthy rats. Mitochondrial dynamics were ameliorated in PD rats treated with allogeneic or xenogeneic transplantation of peptide-labeled mitochondria [22].

Mammalian sirtuins (SIRT-1-7) have been associated with numerous cellular and physiological processes, including regulating apoptosis, gene silencing, mitochondrial function, energy homeostasis, and lifespan enhancement [48]. The activation of SIRT1 has been demonstrated to enhance both the expression and functionality of peroxisome proliferator-activated receptor gamma coactivator-1alpha (PGC-1α), which serves as a key regulator in the process of mitochondrial biogenesis [48]. PGC-1α is a coactivator for TFAM (mitochondrial transcription factor A), increasing mtDNA and promoting mitochondrial biogenesis [49]. Mitochondrial biogenesis is a key factor influencing the progression of PD. An imbalance in mitochondrial biogenesis, along with the dysfunction of mitochondria, contributes to the advancement of the disease [50]. In the cellular model of PD, the activation of PGC-1α inhibits the degeneration of dopaminergic neurons induced by mutant α-synuclein or the pesticide rotenone [49, 51]. Moreover, PGC-1α activity decreases due to the loss of parkin function and α-synuclein binding to the PGC-1α promoter, indicating that reduced PGC-1α expression may be involved in the progression of PD [52]. So, therapies designed to

promote mitochondrial biogenesis will be vital as potential treatment avenues for PD. Jain et al. [21] studied the functions of exercised allogenic mitochondria on mitochondrial biogenesis in the midbrain of PD mice. They found that intravenous administration of exercised allogenic mitochondria (0.5 mg/kg/day) restores mitochondrial biogenesis (TFAM and PGC-1α) in the midbrain of the rotenone-treated mice.

Physical exercise is recognized as a non-pharmacological strategy to maintain the integrity of mitochondrial function. Physical exercise reduces excessive fragmentation of mitochondria, enhances mitophagy, and improves mitochondrial dynamics [53]. These effects may help mitigate the mitochondrial dysfunction associated with PD. Besides, dietary approaches aimed at enhancing mitochondrial health, including ketogenic, Mediterranean, and low protein-to-carbohydrate ratio diets, serve to complement pharmacological interventions by mitigating energy shortages, oxidative stress, and neuroinflammation. Personalized nutritional strategies, which may involve the use of nutrients that support mitochondrial function, could provide a valuable supplementary strategy for managing PD [54]. However, additional research is needed to confirm these findings in larger studies and translate them to clinical settings.

Limitation

Our study is subject to several limitations. Variations in parameters such as the source of mitochondria, the induction of animal models, the duration of interventions, the dosages used, and the behavioral tests assessed were evident across the included studies. Additionally, the exclusion of non-English publications posed a constraint during the review process, compounded by the limited number of studies and small sample sizes. These factors and the considerable heterogeneity observed among the studies precluded the possibility of conducting a meta-analysis.

Conclusion

Neurodegenerative diseases are one of the challenging issues worldwide, and no effective drugs are available for effective treatment. Mitochondria, as vital cell organelles, are responsible for providing cellular energy demands and are affected mainly by numerous neurological dysfunctions, including AD and PD. Mitotherapy has emerged as a potential therapeutic strategy. Overall, mitotherapy protects neuron cells from death by modulating mitochondrial bioenergetics and, most importantly, decreasing oxidative stress and inflammatory response. Moreover, despite limited knowledge of the mechanisms of mitotherapy, evidence demonstrates neuroprotective effects of exogenous mitochondria in vivo model of AD and PD. However, further studies are needed to understand the underlying mechanisms and address the possibility of clinical treatment, pending every ethical and security issue.

Abbreviations

AD	Alzheimer's disease
Aβ	Amyloid-β
ATP	Adenosine triphosphate
CAMARADES	Collaborative Approach to Meta-Analysis and Review of Animal Studies
MPTP	Methyl-4-phenyl- 1,2,3,6-tetrahydropyridine
6-OHDA	6-hydroxyvitamin
PD	Parkinson's disease
PGC-1α	Peroxisome proliferator-activated receptor gamma coactivator-1alpha
ROS	Reactive oxygen species
SN	Substantia nigra
TCA	Tricarboxylic acid cycle
TFAM	Mitochondrial transcription factor A
FOXO3	Forkhead Box O3
BDNF	Brain-derived neurotrophic factor
ERK	Extracellular signal-regulated Kinase
NAD^+	Nicotinamide adenine dinucleotide
TH	Tyrosine hydroxylase
OXPHOS	Oxidative phosphorylation
IV	Intravenous

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12883-025-04241-1.

Supplementary Material 1

Supplementary Material 2

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Author contributions

L.H. and R.N.S. designed the study. A.M., H.A., and L.H. conducted a systematic search. L.H. and A.M. performed the study screening. L.H. and N.A. performed the data extraction and risk of bias assessment. A.M. and L.H. wrote the original manuscript draft. All authors significantly contributed to the study and approved the final submitted version.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Due to the nature of systematic reviews, no ethical approval is required.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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