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Targeting mitochondria with natural polyphenols for treating Neurodegenerative Diseases: a comprehensive scoping review from oxidative stress perspective

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Abstract

Neurodegenerative diseases are a class of conditions with widespread detrimental impacts, currently lacking effective therapeutic drugs. Recent studies have identified mitochondrial dysfunction and the resultant oxidative stress as crucial contributors to the pathogenesis of neurodegenerative diseases. Polyphenols, naturally occurring compounds with inherent antioxidant properties, have demonstrated the potential to target mitochondria and mitigate oxidative stress. This therapeutic potential has garnered significant attention in recent years. Investigating the mitochondrial targeting capacity of polyphenols, their role in functional regulation, and their ability to modulate oxidative stress, along with exploring novel technologies and strategies for modifying polyphenol compounds and their formulations, holds promise for providing new avenues for the treatment of neurodegenerative diseases.

Keywords Neurodegenerative disease, Polyphenols, Mitochondria, Oxidative stress

Introduction

Neurodegenerative diseases, also known as neurodegenerative disorders, are conditions characterized by the progressive degeneration of neuronal cells in the brain and spinal cord [1, 2]. Comprising neurons with diverse functionalities such as motor control, sensory processing, and decision-making, the cells within the brain and spinal cord do not regenerate [3]. Consequently, excessive damage can be devastating and irreversible [4]. These diseases result from losing neurons or their myelin sheaths, worsening and leading to functional impairments [5, 6]. Neurodegenerative diseases encompass conditions such as amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), Parkinson's disease, Alzheimer's disease, Huntington's disease, multiple system atrophy, tauopathies, and prion diseases [7]. Globally, an estimated 55 million people were living with dementia in 2019, a number projected to increase to 139 million by 2050. Currently, only a handful of drugs are available for some neurodegenerative diseases. Thus, there is an urgent need to elucidate the mechanisms underlying neurodegenerative diseases and develop corresponding small-molecule therapeutics [8, 9].

Research indicates that oxidative stress and inflammation are two primary factors contributing to

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neurodegeneration [10, 11]. The most common form of cell death in neurodegeneration occurs through the intrinsic mitochondrial apoptotic pathway [12, 13]. This pathway regulates the activation of caspase-9 by modulating the release of cytochrome c into the mitochondrial intermembrane space [14, 15]. Reactive oxygen species (ROS) are one of the byproducts of oxidative metabolism in cells, possessing active oxidative capabilities [16]. They mainly originate from pathways such as the mitochondrial respiratory chain, endoplasmic reticulum, and oxidases [17]. Excessive ROS can be reduced by cellular antioxidant systems, such as the Nrf2-mediated antioxidant system, GSH, and NADPH [18, 19]. Under physiological conditions, the production and reduction of ROS form a balance known as redox homeostasis [20, 21]. However, under pathophysiological conditions, the production of ROS far exceeds reduction, leading to damage to biomolecules and mitochondria, thus causing cellular dysfunction and even death [22, 23]. This imbalance between oxidation and reduction is known as oxidative stress [24, 25]. Excessive generation of ROS is a hallmark feature of all neurodegenerative diseases [26, 27].

Mitochondria, often described as the powerhouses of the cell, play a vital role in ensuring cellular vitality through their involvement in energy production and metabolic regulation [28, 29]. Mitochondrial dysfunction caused by oxidative stress is closely associated with the occurrence and development of neurodegenerative diseases [30, 31]. ROS are normal byproducts of mitochondrial respiratory chain activity [32, 33]. The concentration of ROS is mitigated by mitochondrial antioxidants such as manganese superoxide dismutase (SOD2) and glutathione peroxidase [34, 35]. Overproduction of ROS is a central feature in all neurodegenerative diseases [36, 37]. In addition to ROS generation, mitochondria also participate in vital functions such as calcium homeostasis, programmed cell death (PCD), mitochondrial fission and fusion, lipid composition of the mitochondrial membrane, and permeability transition of mitochondria [38, 39]. For example, axonal swelling and spheroids have been observed across neurodegenerative diseases [40, 41], suggesting that defective axons are not only present in affected neurons and may also result from the accumulation of organelles, causing specific pathological damage. Axonal transport can be disrupted through various mechanisms, including damage to motor proteins and cytoplasmic dynein, microtubules, cargo, and mitochondria [42, 43]. When severely disrupted axonal transport, it often triggers a degenerative pathway known as Wallerian-like degeneration. Mitochondrial disorders contributing to neurodegeneration may involve all these functions to some extent [44]. Evidence suggests that mitochondrial dysfunction and oxidative stress play a causal role in the pathogenesis of neurodegenerative diseases (Fig. 1).

Polyphenols, also known as polyhydroxyphenols, constitute a class of naturally occurring phenolic compounds widely distributed in plant tissues, characterized by their abundant content and diverse structures [45, 46]. Additionally, polyphenols can be obtained through synthesis or semi-synthesis, distinguished by numerous phenolic structural units within their molecules [47]. The quantity and characteristics of these phenolic structures define polyphenols'unique physicochemical and biological properties, including but not limited to their metabolic, toxicological, and therapeutic attributes [48, 49]. Polyphenols can be broadly categorized into four major classes: phenolic acids, flavonoids, stilbenes, and lignans [50, 51]. Since the late twentieth century, polyphenols have garnered increasing attention. Numerous epidemiological studies suggest that diets rich in polyphenols contribute to reducing the incidence of chronic inflammatory diseases, including but not limited to cardiovascular diseases [52, 53], type 2 diabetes [54, 55], neurodegenerative diseases [56, 57], osteoporosis [58, 59], and cancer [60, 61]. Research also indicates that polyphenols aid in enhancing brain function and preventing the onset of neurodegenerative diseases such as Alzheimer's disease [62]. For instance, elderly individuals who regularly consume curcumin-containing curry show improved cognitive function compared to their peers with lower consumption [63]. Additionally, it has been found that elderly individuals who frequently drink green tea exhibit superior brain function compared to those consuming coffee or black tea [64]. These benefits may be attributed to the antioxidant effects of polyphenols and their improvement of cerebral blood flow [65, 66]. The antioxidant mechanisms of polyphenols primarily involve neutralizing free radicals by electron and/or hydrogen atom transfer, reducing metal-dependent hydroxyl radicals via chelation mechanisms, mitigating mitochondrial dysfunction to reduce cell apoptosis, and enhancing the endogenous antioxidant enzyme defense system by activating nuclear factor E2-related factor 2 (NRF2), among other pathways [67, 68]. These actions can inhibit reactive oxygen species and their associated inflammatory responses, exerting neuroprotective effects [69, 70]. Therefore, research on polyphenols and the development of small-molecule compounds and formulations holds promise for providing new therapeutic strategies for the treatment of neurodegenerative diseases.

This review aims to explore the role of polyphenols in regulating mitochondria and to introduce innovative approaches for harnessing the therapeutic potential of polyphenols in mitochondrial regulation. A systematic methodology was employed to assess the role of

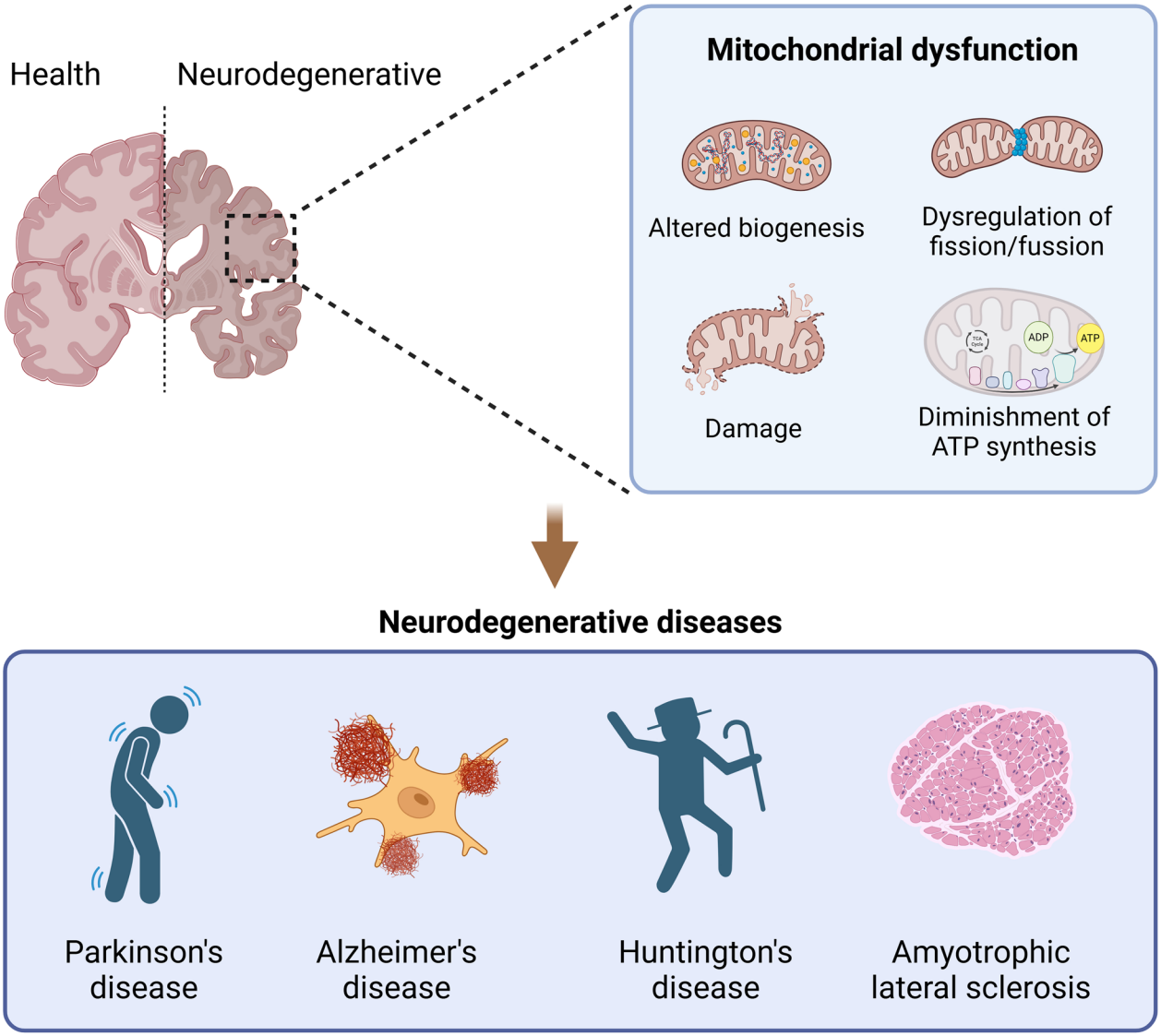

Fig. 1 Mitochondrial dysfunction in the formation of neurodegenerative diseases. Mitochondrial dysfunction is closely associated with the onset and progression of neurodegenerative diseases. Abnormalities in mitochondrial biogenesis, fission/fusion, damage, and ATP synthesis are frequently implicated in the progression of neurodegenerative disorders, contributing to the pathogenesis of diseases such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis

polyphenols in mitochondrial regulation. A comprehensive search strategy was utilized to identify relevant studies published in peer-reviewed journals from 2019 to 2024. Studies were selected based on their focus on polyphenols and mitochondrial regulation, with priority given to clinical trials and in vitro experiments. A structured search was conducted across multiple databases, including PubMed, Scopus, and Web of Science, using keywords such as"polyphenols,""mitochondrial regulation,"and"oxidative stress."Studies published between 2019 and 2024 were reviewed, and only those with relevant methodologies and outcomes were retained. All study inclusion and exclusion decisions were independently reviewed by two researchers, with disagreements resolved by a third reviewer. The search strategy was pre-registered to minimize the risk of selection bias.

The antioxidant effects of natural polyphenols in neurodegenerative diseases

Classification and chemical structures of natural polyphenols and their antioxidant properties

Polyphenols are a class of secondary metabolites widely present in plants, primarily including four major groups:

phenolic acids, flavonoids, lignans, and stilbenes [71, 72]. These compounds exhibit diverse structures but commonly feature multiple phenolic groups, which form the chemical basis for their antioxidant properties [72, 73]. Among polyphenols, flavonoids represent the largest and most renowned group, encompassing a wide variety of compounds such as flavones, flavonols, flavanols, flavanones, isoflavones, anthocyanins, and proanthocyanidins [74, 75]. These compounds are rich in dietary sources; for example, catechins are predominantly found in tea and fruits, hesperetin is abundant in citrus fruits, and anthocyanins are widespread in red fruits and berries [76, 77]. These flavonoid compounds possess potent antioxidant capabilities, effectively scavenging free radicals and reducing oxidative stress to protect cellular integrity.

Phenolic acids, encompassing benzoic acid and cinnamic acid derivatives, also exhibit outstanding antioxidant characteristics [78, 79]. They are primarily sourced from tea, red fruits, black radishes, and onions [80, 81]. These compounds can interrupt oxidative chain reactions by stabilizing free radicals through their phenolic hydroxyl groups [82, 83]. Lignans, a class of polyphenols derived from the amino acid phenylalanine found in flaxseeds and other grains, demonstrate robust antioxidant and anti-inflammatory properties, counteracting inflammation and oxidative stress within the body [84, 85]. Representative substances within the stilbene group, such as resveratrol, have been extensively studied for their anticancer and cardiovascular protective effects [86, 87].

Overall, the antioxidant activity of polyphenols primarily operates through the following mechanisms: firstly, they directly scavenge detrimental free radicals, reducing cellular damage and aging processes; secondly, polyphenols can upregulate the body's antioxidant enzyme systems, such as superoxide dismutase and glutathione peroxidase, further enhancing the antioxidant defense system; finally, polyphenols also participate in regulating various signaling pathways to counteract inflammatory responses induced by oxidative stress. Therefore, polyphenols hold a significant position in food science and demonstrate tremendous potential in medicine and pharmacology.

Impact of natural polyphenols on mitochondrial Function in neurodegenerative diseases

The targeted action of natural polyphenols on mitochondria

Polyphenols, naturally occurring compounds found in plants, have been identified as potent modulators of mitochondrial function, offering protective effects against oxidative stress and enhancing cellular energy metabolism. Polyphenols interact with various molecular targets within the mitochondria, leading to improved functionality [88, 89]. These interactions enhance ATP production efficiency and reduced ROS generation, thereby shielding cells from oxidative stress damage [90, 91]. For instance, polyphenolic substances such as resveratrol have demonstrated targeted effects on mitochondrial biogenesis [92]. This improvement in mitochondrial function is facilitated by activating key pathways such as SIRT1/PGC-1α, critical for enhancing mitochondrial DNA replication and transcription, both essential processes for efficient cellular energy production [93, 94]. Additionally, curcumin, a polyphenolic compound found in turmeric, enhances mitochondrial function through its potent antioxidant effects [95]. It participates in the regulation of mitochondrial dynamics, including fusion and division processes, which are vital for maintaining mitochondrial integrity and function [96]. The regulation of these dynamics helps prevent mitochondrial dysfunction that often leads to cell death and has been implicated in various age-related diseases [97, 98]. Another powerful polyphenol, epigallocatechin gallate (EGCG), found in green tea, has been shown to elevate mitochondrial oxidative phosphorylation capacity [99]. This increase in capacity directly correlates with enhanced cellular energy production, which is crucial for maintaining the energy demands of the cell [100, 101]. EGCG also protects against mitochondrial damage by scavenging free radicals and reducing oxidative stress within the cell [102]. Furthermore, polyphenols like quercetin and catechins have been observed to influence mitochondrial potential and help maintain the optimal electron transport chain function, which is crucial for ATP production [103, 104]. These compounds enhance the bioenergetic efficiency of mitochondria, reducing the leakage of electrons, which can form harmful ROS.

In summary, the interaction of polyphenols with mitochondrial components helps boost ATP production and also plays a protective role by mitigating oxidative stress (Fig. 2). This dual function is critical in maintaining cellular health and preventing the onset of mitochondrial-related diseases. Research into how polyphenols enhance mitochondrial function continues to be a promising area for therapeutic development, especially in aging and associated diseases where mitochondrial dysfunction is a common factor.

Regulation of mitochondrial function by natural polyphenols

Natural polyphenolic substances enhance mitochondrial capacity and efficiency [105, 106]. They benefit by modulating crucial signaling pathways and activating transcription factors involved in mitochondrial biogenesis [107]. Among these transcription factors are NRF1/2 and Estrogen-Related Receptors (ERRs), which play central roles in mitochondrial function and energy production [108, 109]. By engaging these pathways, polyphenols help

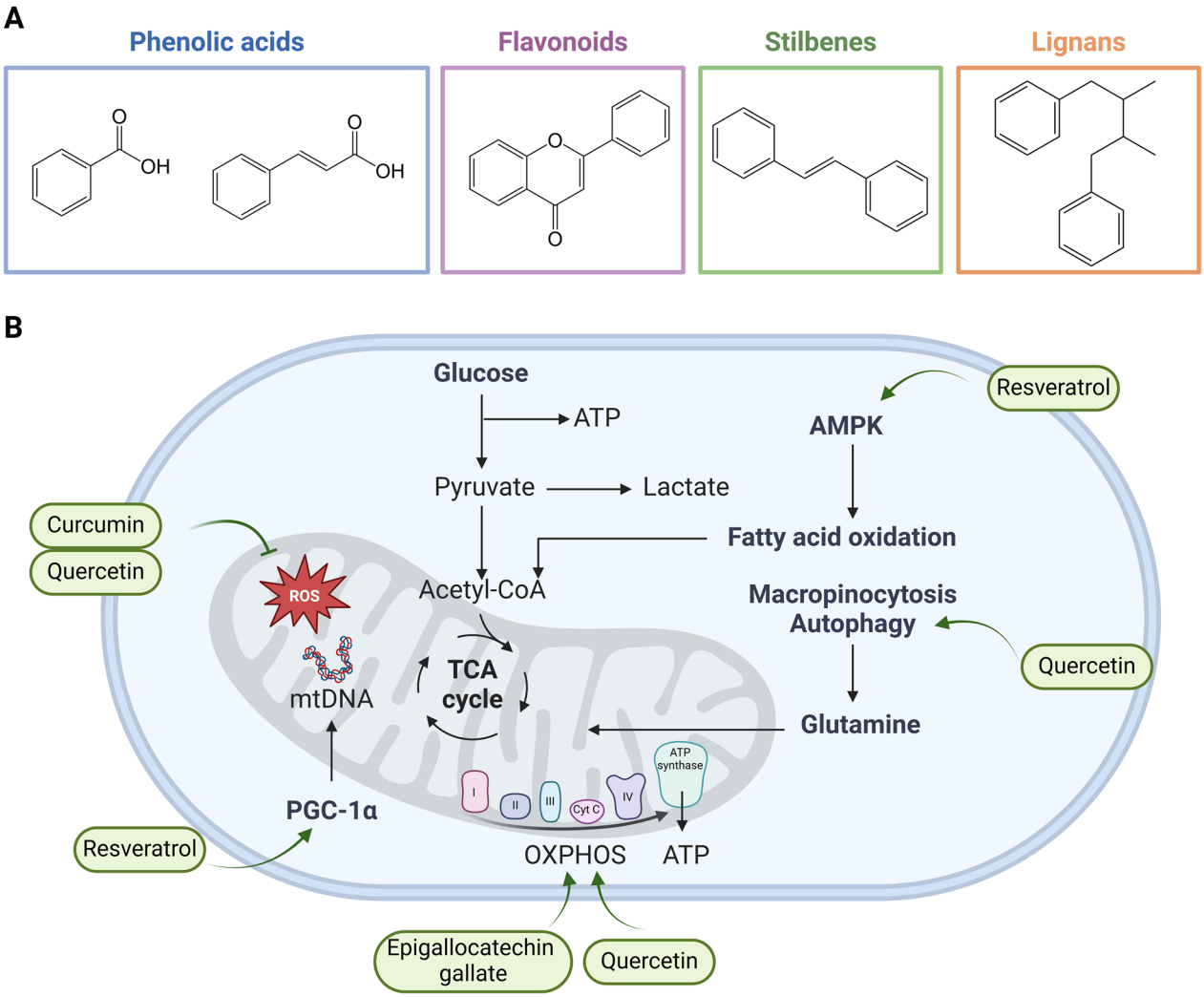

Fig. 2 The category of polyphenols and the effect on mitochondria. **A** Polyphenols can categorized into phenolic acids, flavonoids, stilbenes, and lignans. **B** Polyphenols can influence mitochondrial function through various mechanisms. For example, curcumin and quercetin activate antioxidant systems to inhibit ROS accumulation, while resveratrol promotes the expression of mitochondrial DNA by enhancing PGC-1α, thereby stimulating mitochondrial biogenesis. Additionally, EGCG and quercetin protect the electron transport chain (ETC), facilitating ATP synthesis in mitochondria. Moreover, resveratrol activates the AMPK pathway, and quercetin promotes autophagy, both of which contribute to the enhancement of mitochondrial biological function

maintain optimal energy utilization and reduce the cellular impact of aging and related diseases.

Resveratrol is one of the most studied polyphenolic compounds, renowned for its role as a SIRT1 activator and optimizing energy utilization by influencing the AMP-activated protein kinase (AMPK) pathway [110, 111]. AMPK acts as an energy sensor within cells, promoting energy production in response to cellular stress and nutrient deprivation [112]. Through activation of SIRT1 and AMPK, resveratrol enhances mitochondrial function, increases ATP production, and improves metabolic efficiency, making it an effective agent against age-related decline in mitochondrial function [113]. Curcumin, another powerful polyphenolic compound found in turmeric, extends its benefits beyond mitochondrial regulation. It enhances the cellular antioxidant response by activating the NRF2 pathway [114]. NRF2 is a critical element in the cellular defensive strategy against oxidative stress, regulating the expression of antioxidant proteins that protect against oxidative damage triggered by injury and inflammation [115, 116]. Through these mechanisms, curcumin supports mitochondrial integrity and prevents the functional decline that accompanies neurogenic disease [117]. Quercetin, a flavonoid abundant in fruits and vegetables, contributes to mitochondrial health by activating NRF1 and Peroxisome

Proliferator-Activated Receptor Gamma (PPARγ) [118]. These factors are crucial for mitochondrial biogenesis and function, facilitating the increase in both the number and efficiency of mitochondria. By enhancing mitochondrial biogenesis, quercetin improves cellular energy status, vital for reducing fatigue, boosting physical performance, and mitigating the effects of aging.

The interaction between natural polyphenols and mitochondrial oxidative stress

In addition to individual effects, polyphenols collectively support cellular health through synergistic actions. They stabilize mitochondrial membranes, enhance electron transport chain efficiency, and reduce electron leakage, which can lead to excessive production of ROS. This reduction in ROS is essential for preventing oxidative damage, which is a major cause of cellular aging and dysfunction.

Epicatechin gallate is particularly effective at reducing oxidative stress [119, 120]. It does so not only by directly scavenging free radicals but also by modulating the activity of various antioxidant enzymes such as SOD and glutathione peroxidase [120, 121]. These enzymes are critical in converting harmful ROS into less reactive molecules, thereby protecting cells from oxidative damage.

The protective effects of polyphenols on mitochondrial DNA are significant, given that mitochondrial DNA (mtDNA) is more susceptible to oxidative damage than nuclear DNA [122]. This susceptibility stems from the proximity of mtDNA to the inner mitochondrial membrane, where most ROS are generated, and from its limited protective histone proteins and less efficient DNA repair mechanisms [123]. By preserving mtDNA integrity, polyphenols help ensure the proper functioning of mitochondria and the longevity of cells [124]. Moreover, the cumulative effects of polyphenols in modulating oxidative stress go beyond individual antioxidant activities. They stimulate signaling pathways that enhance the cell's intrinsic antioxidative defenses, leading to a more robust response against oxidative stress [125]. This includes the upregulation of NRF2, a key transcription factor that orchestrates the expression of multiple antioxidative proteins and detoxifying enzymes [126].

Polyphenols regulate downstream events of mitochondrial oxidative stress in neurodegenerative diseases

Oxidative stress can modulate various intracellular pathways [127]. On one hand, oxidative stress can directly induce redox damage to DNA and proteins, leading to gene mutations or protein degradation, thereby disrupting key signaling molecules and altering cellular functions [128, 129]. On the other hand, oxidative stress can result in redox modifications of biomolecules within the cell; for instance, free cysteine residues in proteins may undergo oxidation to form disulfide bonds and other redox modifications, which can change protein activity and impact the activation of signaling pathways [130, 131]. The interaction between polyphenols and mitochondria can also regulate the activation of various downstream pathways in cells through ROS generated by mitochondrial oxidative stress, thereby influencing the onset and progression of neurodegenerative diseases (Fig. 3).

Polyphenol modulation of oxidative stress-induced genetic mutations

Oxidative stress can damage biomolecules within cells, including genomic DNA, which can result in genetic mutations [128, 132, 133]. The brain consumes as much as one-fifth of the oxygen, and reactive oxygen species generated by oxidative metabolism are the main source of DNA damage in the brain [134, 135]. Many neurodegenerative diseases are caused by genetic mutations, most of which are located in entirely unrelated genes [136, 137]. Across many different diseases, mutated genes share a common feature: the repetition of CAG nucleotide triplets [138, 139]. CAG encodes the amino acid glutamine. Repeated CAG sequences result in the formation of polyglutamine (polyQ) tracts. Diseases associated with such mutations are termed trinucleotide repeat disorders. PolyQ repeats typically lead to dominant disease mechanisms [140]. Additional glutamine residues can confer toxicity through various mechanisms, including irregular protein folding and degradation pathways, altered subcellular localization, and aberrant interactions with other cellular proteins [141]. PolyQ research often employs various animal models due to a well-defined trigger factor—repeat expansion [142]. Numerous studies have shown polyphenolic compounds to alleviate gene mutations and the onset of degenerative diseases by combating oxidative stress, thereby mitigating the inflammatory microenvironment [143, 144]. Extensive studies have been conducted using models such as the C. elegans [145], Drosophila [146], mice [147], and non-human primate models [148].

Polyphenol-mediated epigenetics regulated by oxidative stress

Oxidative stress is a pivotal factor influencing epigenetic mechanisms, which play significant roles in the pathogenesis of neurodegenerative diseases [127, 149, 150]. Oxidative stress arises when excess ROS disrupts cellular balance, overwhelming the antioxidant defenses [151]. ROS can modify the structure and function of cellular macromolecules, including DNA, proteins, and lipids [152, 153]. At the epigenetic level, oxidative stress

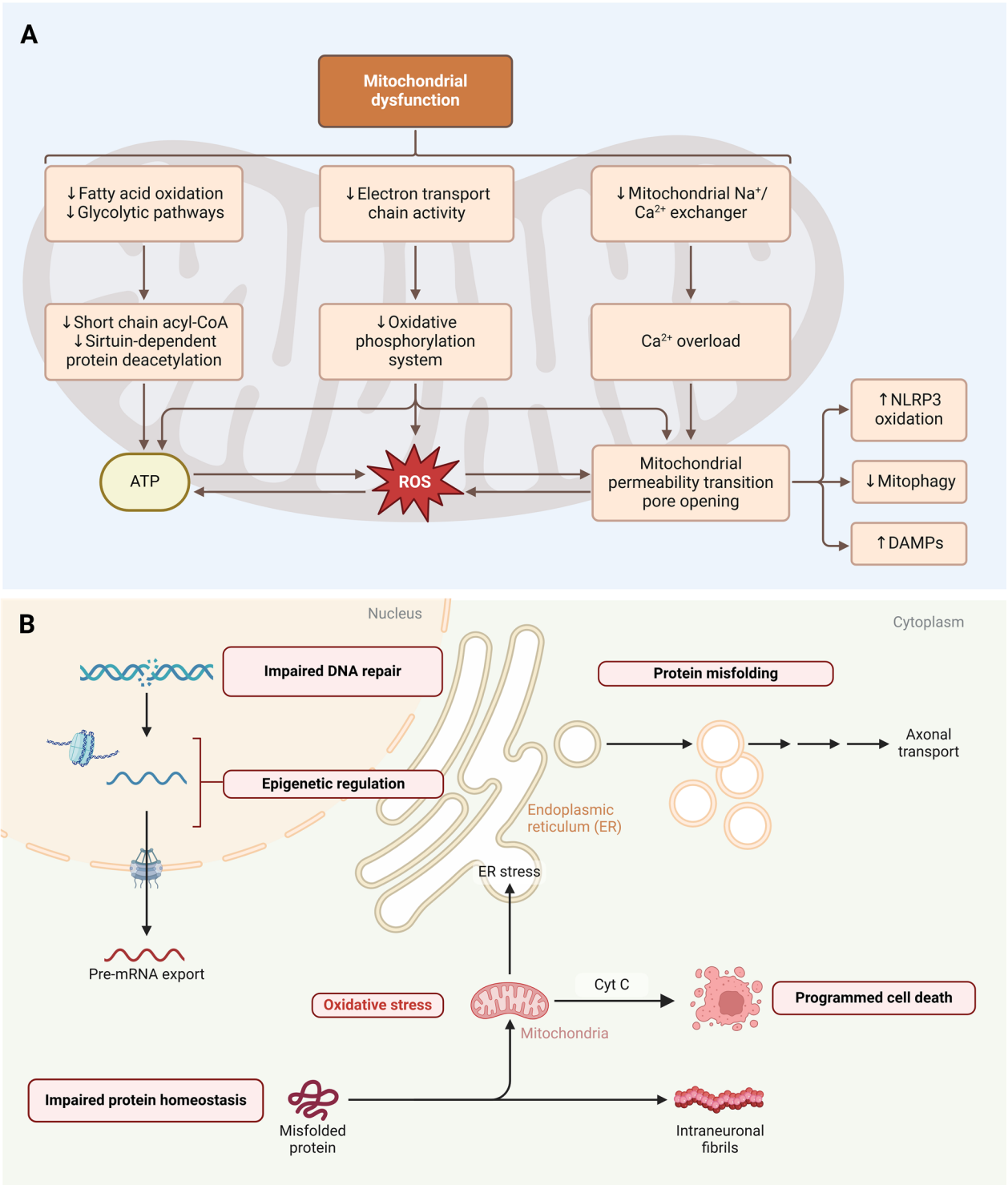

Fig. 3 Mitochondria-induced oxidative stress promotes progression of neurodegenerative diseases. **A** Mitochondrial dysregulation often involves disturbances in lipid and glucose metabolism, abnormalities in the electron transport chain, and dysregulation of calcium signaling, all of which contribute to mitochondrial homeostasis imbalance. **B** This imbalance leads to the accumulation of ROS and can promote cell death. Specifically, oxidative stress resulting from mitochondrial dysfunction can affect processes such as DNA repair, epigenetics, protein folding, and protein degradation, ultimately triggering the onset of programmed cell death

affects DNA methylation patterns, histone modifications, and non-coding RNA expression [131, 154, 155]. Therefore, polyphenols can also influence the epigenetic status within cells by regulating ROS levels, thereby affecting the progression of neurodegenerative diseases [156, 157].

DNA methylation, a critical epigenetic modification involving adding a methyl group to the 5'position of cytosine, is particularly susceptible to oxidative stress [158, 159]. ROS can induce hypomethylation by directly damaging DNA or affecting DNA methyltransferases (DNMTs) activity [160]. This alteration in DNA methylation status can lead to aberrant gene expression, including the dysregulation of genes involved in apoptosis, cell cycle control, and neuronal function [161]. Natural products like curcumin, quercetin, and resveratrol exhibit specific effects by modulating epigenetic processes, particularly DNA methylation, which can modulate downstream gene expression and disease progression [162, 163].

Histone modifications are also affected by oxidative stress [164]. ROS can alter histone acetylation and methylation statuses, influencing chromatin structure and gene expression [165]. For instance, oxidative stress increases histone acetylation, leading to a more relaxed chromatin structure and increased transcriptional activity [166–168]. Conversely, changes in histone methylation can either activate or repress transcription depending on the specific residues and types of modifications affected. Polyphenols, through their oxidized forms, can bind to histones and regulate histone modifications. This interaction, involving a variety of polyphenol-derived compounds, contributes to the chemoprotective functions of dietary polyphenols [169, 170].

Non-coding RNAs, including microRNAs (miRNAs), are another target of oxidative stress [171]. ROS can modulate the expression of miRNAs, which in turn regulate gene expression post-transcriptionally [172, 173]. Changes in miRNA levels affect protein synthesis and cellular pathways critical in neurodegenerative diseases, influencing neuronal survival and function [174]. For instance, curcumin can modulate miRNA activity to regulate key processes like autophagy and inflammation, offering a promising approach to slowing Alzheimer's disease progression by regulating miRNA expression [175, 176].

Polyphenol interventions in oxidative stress and protein misfolding

The spatial conformation of proteins is crucial for their biological functions, and protein folding plays a key role in the protein synthesis process [177, 178]. Protein folding typically occurs in the endoplasmic reticulum, where the endoplasmic reticulum also conducts protein quality control [179, 180]. Oxidative stress plays a crucial role in regulating protein folding and misfolding, processes intimately linked to the pathogenesis of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis [129, 181]. ROS can directly modify proteins'chemical structure by oxidizing amino acids, leading to aberrant covalent modifications such as carbonylation, nitration, and oxidation of specific residues [182, 183]. These oxidative modifications can result in misfolded protein conformations and the exposure of hydrophobic patches, which are prone to aggregation [184]. Furthermore, oxidative stress can overwhelm the protein quality control systems, including the ubiquitin–proteasome system and autophagy, impairing their ability to effectively degrade misfolded or damaged proteins [185, 186].

In neurodegenerative diseases, the accumulation of misfolded proteins is a hallmark feature [187, 188]. For example, in Alzheimer's disease, oxidative stress is implicated in the abnormal folding and aggregation of amyloid-beta peptides and tau proteins, forming plaques and neurofibrillary tangles, respectively [189, 190]. Similarly, in Parkinson's disease, oxidative modifications contribute to the misfolding of alpha-synuclein, leading to the formation of Lewy bodies [191, 192]. These protein aggregates exert toxic effects on neurons, leading to cellular dysfunction and death [193]. Polyphenols, such as resveratrol and green tea polyphenols, can modulate oxidative stress and Ca^{2+} signaling pathways, reducing ER stress caused by misfolding protein aggregation, which may help alleviate the progression of neurodegenerative diseases [194, 195].

The role of polyphenols in redox control of protein degradation

Parkinson's disease and Huntington's disease are both late-onset disorders associated with the accumulation of toxic proteins within cells [196, 197]. Diseases caused by protein aggregation are termed proteinopathies, primarily driven by the aggregation of cytoplasmic, nuclear, endoplasmic reticulum, and extracellular secreted proteins [198–200]. Recent research indicates that oxidative stress can influence the development and progression of neurodegenerative diseases by modulating protein degradation [201–203]. Eukaryotic cells have two main pathways for removing troublesome proteins or organelles: ubiquitin–proteasome and autophagy-lysosome [204, 205]. Protein ubiquitination with enzymes is crucial for the degradation of many proteins implicated in proteinopathies, including PolyQ expansions and α-synuclein [206, 207].

Polyphenols can regulate the progression of neurodegenerative diseases by modulating key protein

degradation pathways, including ubiquitin–proteasome system (UPS) and autophagy–lysosome pathway (ALP). For instance, polyphenols can modulate the UPS to enhance protein degradation, potentially slowing the progression of neurodegenerative diseases by addressing protein aggregation and improving UPS efficiency [208, 209]. In addition, polyphenols from extra-virgin olive oil, such as oleuropein aglycone and hydroxytyrosol, can activate autophagy to enhance protein degradation and protect against neurodegeneration by reducing oxidative stress, mitochondrial damage, and protein aggregation [210]. By enhancing the efficiency of these pathways, polyphenols promote the clearance of toxic protein aggregates, such as PolyQ expansions and α-synuclein, which are central to diseases like Parkinson's and Huntington's [211, 212]. Through their ability to influence protein degradation, polyphenols help alleviate cellular stress, oxidative damage, and mitochondrial dysfunction, thereby slowing the progression of neurodegenerative disorders [213, 214]. This underscores the therapeutic potential of polyphenols in addressing proteinopathies by enhancing cellular proteostasis.

Programmed cell death regulated by oxidative stress

Programmed cell death (PCD) is any form of cell death mediated by intracellular programs [215]. This process can be activated in neurodegenerative diseases, including Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, and Huntington's disease [216]. PCD observed in neurodegenerative diseases may have direct pathogenic implications; alternatively, PCD may also occur as a result of other injuries or disease processes. The mitochondrial pathway is one of the primary mechanisms by which oxidative stress regulates apoptosis [217–219]. ROS can lead to the permeabilization of the mitochondrial outer membrane, an event largely governed by the Bcl-2 family of proteins [220]. The pro-apoptotic members of this family, such as Bax and Bak, promote this permeabilization, releasing cytochrome c into the cytosol [221–223]. Cytochrome c then binds to apoptotic protease activating factor-1 (Apaf-1) and ATP, which then triggers the formation of the apoptosome, subsequently activating caspase-9 and then caspase-3, culminating in cellular apoptosis [224, 225]. Additionally, oxidative stress influences the endoplasmic reticulum (ER) stress pathway [226, 227]. Accumulating misfolded proteins in the ER under oxidative stress triggers the unfolded protein response (UPR), which can initiate apoptosis if homeostasis is not restored [228, 229]. This involves the activation of CHOP and the ER-resident caspase-12, further propagating the apoptotic signal.

In neurodegenerative diseases, the chronic oxidative stress environment exacerbates the vulnerability of neurons to apoptosis [230, 231]. The high metabolic demand of neurons and their rich lipid content make them particularly susceptible to oxidative damage [232–234]. For example, in Alzheimer's disease, oxidative stress facilitates the hyperphosphorylation of tau protein and enhances beta-amyloid aggregation, promoting neuronal death [235, 236]. In Parkinson's disease, oxidative stress contributes to the dysfunction and death of dopaminergic neurons in the substantia nigra, a hallmark of the disease pathology [237, 238]. Polyphenols have shown potential in neuroprotection, particularly by reducing naturally occurring neuronal death (NOND) during cerebellar maturation, which is relevant for neurodegenerative diseases. Ex vivo testing demonstrated that PPs such as taxifolin, quercetin-3-O-glucoside, and (+)-catechin effectively reduced neuronal death by up to 72% [239]. These polyphenols likely exert their neuroprotective effects by modulating oxidative stress-induced apoptosis, possibly by inhibiting executioner caspase-3, highlighting their potential for therapeutic applications in neurodegeneration [240].

In conclusion, polyphenols have demonstrated significant neuroprotective potential by modulating oxidative stress-mediated PCD pathways, a key mechanism underlying neurodegenerative diseases. Through attenuation of mitochondrial dysfunction and inhibition of pro-apoptotic signaling cascades—such as the release of cytochrome c and activation of caspases—polyphenols help maintain neuronal survival. Furthermore, they may alleviate endoplasmic reticulum stress and suppress related apoptotic pathways. By reducing oxidative damage and inhibiting executioner caspases, polyphenols effectively mitigate neuronal apoptosis, thereby slowing the progression of disorders such as Alzheimer's and Parkinson's disease.

The application of novel technologies and strategies in neurodegenerative diseases

Due to their antioxidant and anti-inflammatory properties, natural polyphenols have shown potential value in the treatment of neurodegenerative diseases [241]. However, the bioavailability of polyphenolic compounds is typically low, and they often struggle to penetrate the blood–brain barrier, limiting their clinical application [242]. To enhance the neuroprotective effects of natural polyphenols, researchers have developed new technologies and strategies, particularly focusing on their modification, combination, and the use of nanotechnology to facilitate their passage through the blood–brain barrier (Fig. 4).

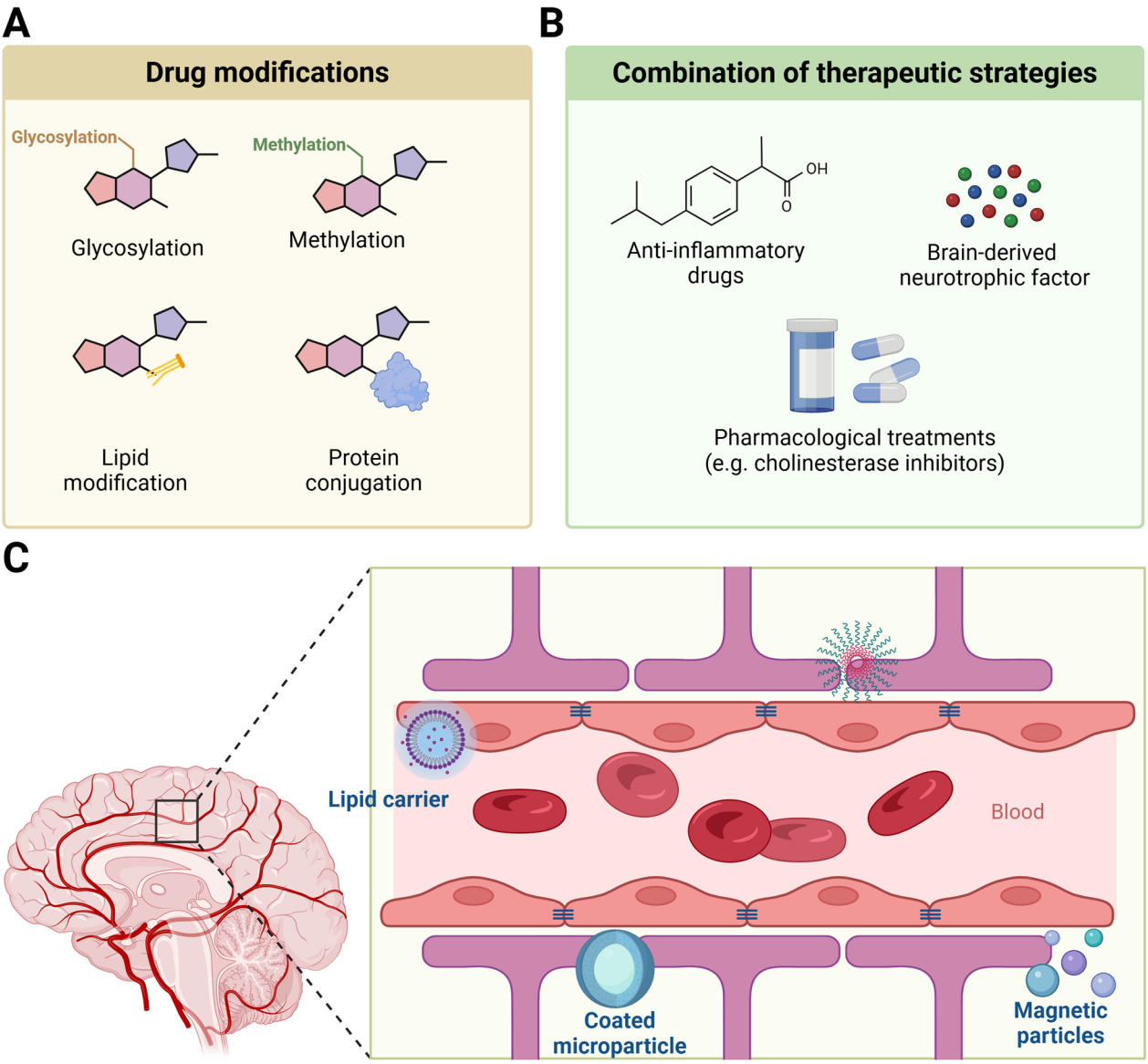

Fig. 4 Novel Technologies and Strategies in Neurodegenerative Diseases. **A** Glycosylation, methylation, lipidation, and protein modifications can enhance the drugability and pharmacokinetic properties of polyphenols; **B** Co-administration of polyphenols with anti-inflammatory drugs, BDNF, and traditional neurodegenerative disease treatments can significantly improve patient outcomes by reducing adverse effects and enhancing therapeutic efficacy; **C** Novel nanotechnology approaches can significantly improve the ability of polyphenols to cross the blood–brain barrier and exert their pharmacological effects

Novel modification of polyphenols

The chemical modification of polyphenols is a critical area of research aimed at enhancing their stability, bioavailability, and therapeutic efficacy [243]. Despite their potent biological activities, polyphenols often face challenges related to poor solubility, rapid metabolism, and limited systemic availability [244]. To address these issues, researchers are exploring various chemical strategies to modify the fundamental structures of polyphenols to improve their functional properties.

Glycosylation, the process of adding sugar moieties to polyphenols, is one such modification that significantly impacts their solubility and absorption [245, 246]. By attaching one or more glucose units, polyphenols become more water-soluble, which enhances their ability to traverse cellular membranes and improves their bioavailability [247]. Additionally, glycosylation can make polyphenols less susceptible to rapid degradation in the gut and liver, allowing more of the active compound to reach the target tissues [248]. Methylation involves the

addition of methyl groups to the hydroxyl groups of polyphenols. This modification reduces the polarity of polyphenols, enhancing their permeability across lipid membranes and potentially increasing their half-life in the bloodstream [249]. In some cases, methylated polyphenols have shown improved bioactivity, as the methylation can prevent premature oxidation and degradation of the active compounds.

Conjugation with other molecules, such as proteins or lipids, is another strategy used to enhance the therapeutic potential of polyphenols [250]. For example, conjugating polyphenols with lipids can improve lipid solubility, facilitating their incorporation into cell membranes and improving interactions with lipid-rich environments, such as the brain [251]. This is particularly beneficial for targeting neurological disorders where inflammation and oxidative stress are key factors [252]. On the other hand, protein-conjugated polyphenols can be designed to target specific receptors or enzymes within the body, enhancing the specificity and effectiveness of the polyphenol action [253].

Therapeutic combination strategies involving polyphenols

The combined use of polyphenols can produce a synergistic effect, significantly enhancing the treatment of neurodegenerative diseases [254]. Neurodegenerative diseases such as Alzheimer's and Parkinson's are complex and involve multiple pathways, including oxidative stress, mitochondrial dysfunction, and chronic inflammation. Polyphenols, with their multifaceted bioactive properties, are particularly suited for combinatorial strategies to target these pathways effectively [255].

The combination of polyphenols with other therapeutic drugs offers a promising strategy. For example, when polyphenols are used alongside anti-inflammatory agents, such as nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids, they can help reduce the dosage of these drugs required, potentially minimizing side effects while still providing therapeutic benefits [256, 257]. Polyphenols can modulate drug metabolism and increase the bioavailability of these drugs, enhancing their efficacy.

In addition to conventional pharmaceuticals, combining polyphenols with neurotrophic factors (proteins that support the growth, survival, and differentiation of both developing and mature neurons) presents a novel therapeutic avenue [57]. Polyphenols can increase the expression of brain-derived neurotrophic factor (BDNF), a critical molecule involved in neural repair and synaptic plasticity [258]. This increase in BDNF, coupled with the direct application of neurotrophic factors, could synergistically promote neuronal survival and regeneration, offering a powerful approach to combat neurodegeneration [259]. Furthermore, recent studies have explored the potential of combining polyphenols with current pharmacological treatments for Alzheimer's disease, such as cholinesterase inhibitors [260]. These inhibitors, which aim to increase the levels of neurotransmitters in the brain, could be more effective when used in conjunction with polyphenols, which protect neurons from oxidative damage and improve overall brain health.

Development of nanotechnology for polyphenols

The utilization of nanotechnology significantly enhances the ability of polyphenolic compounds to traverse the blood–brain barrier (BBB), a critical challenge in the treatment of neurological disorders [261]. Nanocarriers such as solid lipid nanoparticles, nanostructured lipid carriers, or polymer nanoparticles efficiently encapsulate polyphenols, protecting them from metabolic degradation and augmenting their permeability across the BBB [262–265]. These nanocarriers enhance the brain delivery of polyphenols through specific pathways such as receptor-mediated transport, thereby improving their therapeutic efficacy in treating neurodegenerative conditions like Alzheimer's and Parkinson's diseases.

Advancements in nanotechnology have paved the way for innovative formulations that improve the solubility and stability of polyphenols, which are often limited by their poor bioavailability [266, 267]. For example, solid lipid nanoparticles are composed of biocompatible and biodegradable materials that can deliver polyphenols directly to neuronal cells, thereby reducing systemic side effects and increasing the concentration of these compounds in the brain [268]. Similarly, nanostructured lipid carriers provide a stable matrix that simultaneously accommodates lipophilic and hydrophilic polyphenols, enhancing their sustained release and biological action within the brain [269].

Polymer nanoparticles, such as those made from PLGA (poly(lactic-co-glycolic acid)), offer additional benefits, including the ability to modify the surface properties to target specific receptors on the BBB [270]. By attaching targeting ligands to the surface of these nanoparticles, it is possible to exploit receptor-mediated endocytosis, a process that facilitates the active transport of polyphenols across the BBB [271]. This targeted delivery system increases the efficiency of polyphenol transport and minimizes the potential for off-target effects [272]. Recent research has also explored using magnetic nanoparticles, which can be directed to specific brain regions using external magnetic fields [273]. This precision targeting enhances the concentration of polyphenols in areas most affected by neurodegenerative processes [274, 275]. Furthermore, the combination of polyphenols with other therapeutic agents within a single nanocarrier can lead to

synergistic effects, potentially reducing the progression of diseases like Alzheimer's more effectively than polyphenols alone [276, 277].

Concluding remarks

In this review, we systematically evaluated the antioxidant properties and mitochondrial-targeting potential of polyphenolic compounds. These compounds show promising biological activities, which may play a crucial role in treating neurodegenerative diseases. However, despite the encouraging evidence, further research is needed to fully understand their mechanisms of action and refine their therapeutic application. Emerging clinical studies underscore the potential of polyphenols in mitigating the neurotoxic side effects associated with a variety of drugs, including chemotherapeutic agents. This protective role enhances patient quality of life and could contribute to better adherence to primary treatments. However, clinical trials focusing on the long-term safety and efficacy of polyphenols, particularly in combination therapies, remain a critical gap in the field.

Future research should focus on advancing the bioavailability and targeting capabilities of polyphenolic compounds. While recent chemical modifications and the development of polyphenol-based nanomedicines have shown promise in enhancing drug targeting and safety, additional studies are needed to optimize these technologies. Specifically, investigations into how these modifications influence pharmacokinetics and pharmacodynamics in the context of neurodegenerative diseases would be valuable. Furthermore, exploring the potential of polyphenol nanomedicines in clinical settings could offer new insights into their practical application. The continued evolution of nanotechnology, combined with a deeper understanding of polyphenols'molecular interactions, could unlock their full therapeutic potential. As research progresses, a more tailored approach to polyphenol therapy could lead to highly effective, personalized treatments for neurodegenerative diseases, addressing current therapeutic challenges and improving patient outcomes. In conclusion, while polyphenolic compounds hold considerable promise for neurodegenerative disease therapy, future research should prioritize refining their delivery mechanisms, expanding clinical evidence, and exploring their role in combination therapies to maximize their therapeutic benefits.

While this review provides valuable insights into the role of polyphenols in modulating oxidative stress and mitochondrial dysfunction in neurodegenerative diseases, several limitations should be acknowledged. First, the majority of the studies discussed are preclinical or ex vivo, and their direct applicability to human clinical settings remains uncertain. The variability in experimental models, polyphenol dosages, and administration methods further complicates the translation of these findings into therapeutic strategies. Additionally, while the review highlights the potential of polyphenols to modulate redox signaling pathways, the complex interaction between polyphenols and other molecular mechanisms in neurodegenerative diseases is not fully elucidated. Future research should focus on conducting well-designed clinical trials, exploring the optimal therapeutic dosages, and elucidating the broader molecular mechanisms by which polyphenols exert their neuroprotective effects.

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