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Review paper

Mitochondrial quality control disorder in neurodegenerative disorders: Potential and advantages of traditional Chinese medicines

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ABSTRACT

Neurodegenerative disorders (NDDs) are prevalent chronic conditions characterized by progressive synaptic loss and pathological protein alterations. Increasing evidence suggested that mitochondrial quality control (MQC) serves as the key cellular process responsible for clearing misfolded proteins and impaired mitochondria. Herein, we provided a comprehensive analysis of the mechanisms through which MQC mediates the onset and progression of NDDs, emphasizing mitochondrial dynamic stability, the clearance of damaged mitochondria, and the generation of new mitochondria. In addition, traditional Chinese medicines (TCMs) and their active monomers targeting MQC in NDD treatment have been demonstrated. Consequently, we compiled the TCMs that show great potential in the treatment of NDDs by targeting MQC, aiming to offer novel insights and a scientific foundation for the use of MQC stabilizers in NDD prevention and treatment.

1. Introduction

Neurodegenerative disorders (NDDs) are characterized by disruptions in neuronal function, synaptic impairments, and the gradual degeneration of susceptible neuronal populations. Major NDDs, including Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD), rank among the leading global causes of disability and mortality, particularly affecting aging populations [1]. By 2022, over 70 million individuals were diagnosed with NDDs, with PD alone affecting approximately 10 million people worldwide [2]. These disorders present significant health challenge, with projected economic burdens expected to surpass one trillion dollars by 2050 [3]. Patients with NDD typically experience chronic neuronal cell death, diminished motor function, impaired coordination, mobility issues, respiratory complications, and cognitive decline [4]. Therefore, NDDs have been currently regarded as a major health threat to humanity and attracted wide attention from medical researchers worldwide [5].

Mitochondrial dysfunction has been increasingly recognized as a critical factor in NDDs, disrupting cellular metabolism and signaling pathways [6]. Recent studies underscore mitochondrial impairment as a primary driver of neurodegeneration, closely linked to calcium (Ca^{2+}) dysregulation, disrupted mitochondrial dynamics, and mitochondrial membrane permeability (MMP) defects [7]. Therefore, maintaining mitochondrial homeostasis and proteostasis is essential for neuronal health [8]. Mitochondrial quality control (MQC) constitutes a complex network responsible for preserving mitochondrial function through processes such as biogenesis, dynamics, and mitophagy [9,10]. Mitochondria adapt their morphology via fission or fusion in response to cellular demands and stress. Under severe stress conditions, mitophagy is activated to eliminate damaged mitochondria and generate new ones [11]. Emerging evidence suggests that specific protein aggregates may interfere with mitophagy, potentially exacerbating disease progression, an area warranting further investigation. Given the pivotal role of MQC in

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NDDs, ongoing research is exploring therapeutic interventions aimed at modulating MQC mechanisms.

Unfortunately, current treatments primarily address symptoms, rather than the underlying causes [12,13]. Pharmacological interventions often lead to adverse effects. For example, long-term dopamine (DA) replacement therapy in PD can result in drug resistance and withdrawal symptoms, which may worsen the condition and pose significant risks [14,15]. This creates substantial challenges for neurologists, necessitating careful and frequent dosage adjustments [16]. As a result, the development of new therapeutic strategies is critically needed. Traditional Chinese medicine (TCM) has emerged as a promising alternative for managing age-related neurodegenerative conditions [17]. Its multi-pathway, multi-target nature offers potential to mitigate drug resistance in NDDs while minimizing adverse reactions [18]. Although NDD mechanisms remain only partially understood [19], growing evidence highlights the pivotal role of MQC and TCM's potential in regulating these processes. Consequently, understanding how TCM targets MQC for NDD treatment has become increasingly important.

Despite this, the literature summarizing the effects of TCM on NDD progression through MQC modulation is sparse. To address this, a systematic search of studies published up to June 29, 2024 was conducted, across Web of Science, PubMed, Google Scholar, Chinese National Knowledge Infrastructure (CNKI), Wanfang Database, and ScienceDirect using key terms such as “neurodegenerative disease”, “mitochondrial quality control”, “traditional Chinese medicine”, “herbal formulas”, and “plant extracts”. This review primarily focused on the pathophysiological mechanisms through which TCMs modulate MQC in NDDs, detailing the role of MQC in these disorders. Additionally, it critically examined the ongoing challenges in MQC research related to NDDs and proposed specific solutions to guide future investigations.

2. Overview of MQC

Mitochondria are central to cellular energy production and oxidative stress regulation, making MQC, which preserves mitochondrial homeostasis, vital for cellular health [20]. This section outlines the processes involved in MQC and the various mechanisms governing mitochondrial homeostasis (Fig. 1).

2.1. Mitochondrial dynamics

Mitochondrial dynamics refers to the ongoing changes in mitochondrial distribution, morphology, and function through the processes of fission and fusion [21]. These processes ensure the equitable distribution of mitochondrial content, with MQC and intracellular transport occurring in conjunction with fission and fusion, to support neuronal integrity [22,23].

Mitochondrial fission is primarily regulated by the cytosolic guanosine-triphosphate (GTP) hydrolase (GTPase) dynamin-related protein 1 (Drp1) [24]. Identified in 1999, Drp1 functions as a GTPase that drives mitochondrial fission [25]. Although Drp1 lacks a

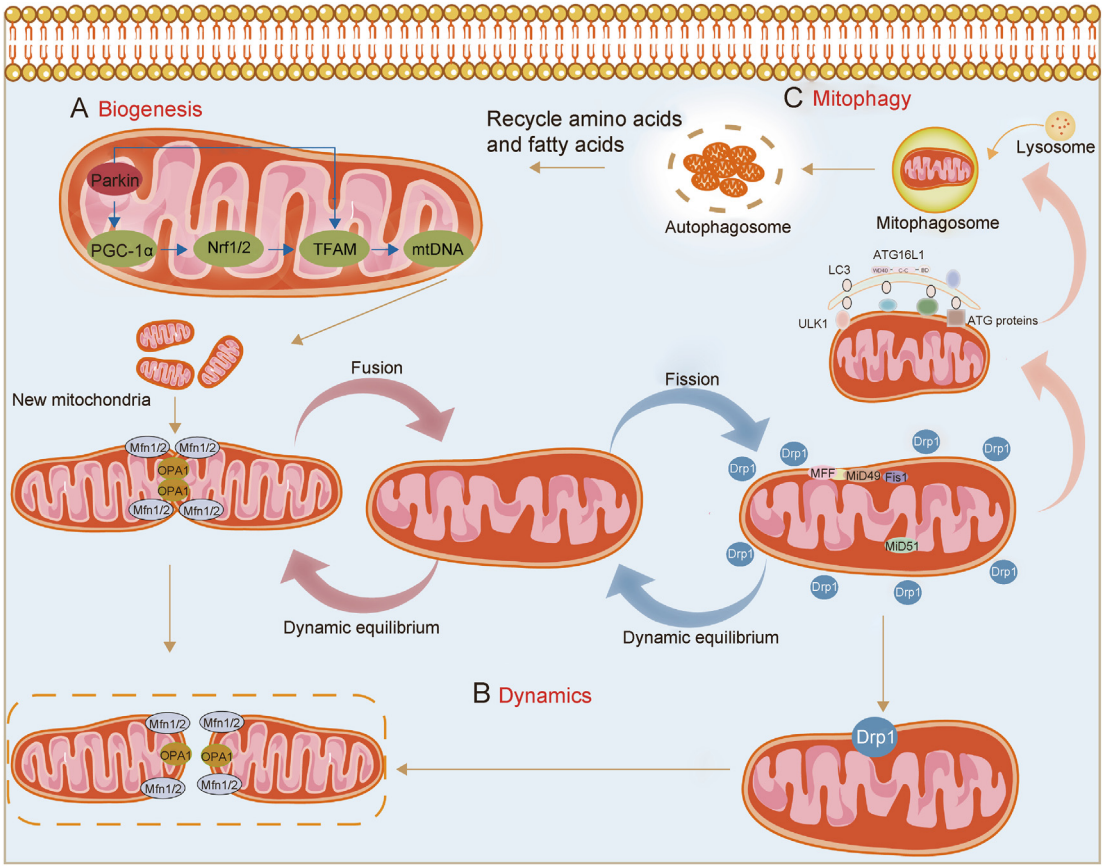

Fig. 1. Overview of mitochondrial quality control (MQC). MQC is a cellular mechanism that maintains the healthy state of mitochondria within the cell by regulating their quantity and function. This cycle encompasses (A) biogenesis, (B) dynamics, and (C) mitophagy. PGC-1α: peroxisome proliferator-activated receptor-γ (PPARγ) coactivator-1α; Nrf1/2: nuclear factor erythroid 2-related factor 1/2; TFAM: mitochondrial transcription factor A; mtDNA: mitochondrial DNA; Mfn1/2: mitofusin 1/2; OPA1: optic atrophy 1; ATG16L1: autophagy related 16-like 1; WD40: WD40 repeat-containing proteins; CC: coiled-coil domain; BD: Atg5-binding domain; LC3: microtubule-associated protein 1 light chain 3; ULK1: uncoordinated 51-like kinase 1; ATG: autophagy-related proteins; Drp1: dynamin-related protein 1; MFF: mitochondrial fission factor; MiD49/51: mitochondrial dynamics proteins of 49/51; Fis1: fission protein 1.

transmembrane domain, it shuttles between the cytoplasm and the outer mitochondrial membrane (OMM) by interacting with proteins such as fission protein 1 (Fis1), mitochondrial fission factor, and mitochondrial dynamics protein 49 (MiD49) [26]. Specific adaptor proteins in the OMM facilitate Drp1 recruitment, where it translocates to contact sites with the endoplasmic reticulum. Drp1 oligomerizes into a helical structure, encircling and cleaving mitochondria into daughter organelles in a GTP-dependent manner [27]. Drp1 dysfunction hinders cytochrome C release during apoptosis, underscoring its role in mitochondrial fission [28]. MiD49 and MiD51 also independently recruit Drp1 and are essential for mitochondrial fission [29]. Various stressors, both intracellular and extracellular, trigger Drp1 translocation to the OMM, activating GTPase activity and initiating mitochondrial fission, a key early event associated with impaired apoptosis or autophagy. Research links mitochondrial dysfunction with reduced brain metabolism, an early hallmark of NDDs [30].

Mitochondrial fusion complements fission by enabling the exchange of mitochondrial DNA (mtDNA) and supporting mitochondrial function [31]. Impaired fusion can lead to the accumulation of dysfunctional mitochondria [32]. Fusion involves both the OMM and inner mitochondrial membrane (IMM), and is regulated by 3 large GTPases: mitofusin 1 (Mfn1), Mfn2, and optic atrophy 1 (OPA1) [33]. Mfn1 and Mfn2 interact through their coiled-coil domains, promoting OMM fusion and membrane tethering [34]. The absence or inhibition of Mfn1/2 disrupts fusion, resulting in fragmented mitochondria, impaired protein transport, and neurodegenerative changes [35]. Mice deficient in Mfn1/2 exhibit fragmented mitochondria and die mid-pregnancy, with their embryonic fibroblasts displaying disrupted mitochondrial structures [36]. Conversely, overexpression of Mfn1 and Mfn2 inhibits fission and reduces B-cell lymphoma-2 (Bcl-2)-associated X (Bax)-induced apoptosis [37].

OPA1 mediates IMM fusion and exists in into two forms: long (L-OPA1) and short (S-OPA1), both anchored to the IMM under normal conditions [38]. Under stress, L-OPA1 is cleaved into S-OPA1, inhibiting mitochondrial fusion [39]. OPA1 dysfunction can lead to the accumulation of tricarboxylic acid (TCA) cycle intermediates [40]. Impaired fusion also reduces mitochondrial mobility, disrupts cellular fusion processes, and impairs directional cell movement [41].

In summary, mitochondrial dynamics play a critical role in maintaining mtDNA integrity, Ca^{2+} signaling, and neuronal remodeling. Disrupted mitochondrial dynamics often result in mitochondrial dysfunction and fragmentation. Thus, achieving a balance between mitochondrial fusion and fission is essential for understanding diseases related to mitochondrial dynamics.

2.2. Mitophagy

Neurons, as highly specialized post-mitotic cells with expansive dendritic and axonal cytoplasm, rely heavily on the proper distribution and function of mitochondria to maintain cellular integrity [42,43]. Mitophagy, a form of selective mitochondrial degradation through autophagy, is an evolutionarily conserved process essential for cellular health [44]. Acting as a key component of MQC, mitophagy safeguards neuronal cells by eliminating dysfunctional or surplus mitochondria [45].

Autophagy, a lysosome-mediated degradation pathway, includes macroautophagy, microautophagy, and chaperone-mediated autophagy [46]. Macroautophagy is a broad cellular mechanism capable of degrading diverse structures such as organelles and protein aggregates [47]. Mitophagy, a specialized form of macroautophagy, selectively targets damaged mitochondria, categorizing it under selective autophagy [48]. Across all types of autophagy, the process involves initiation, prolongation, autophagosome-lysosome fusion, degradation, and clearance [49]. Triggers for mitophagy include mitochondrial aging, decreased MMP, and mtDNA damage [50]. These triggers result in adenosine triphosphate (ATP) depletion, excessive reactive oxygen species (ROS) production, and defects in the electron transport chain (ETC), ultimately leading to mitochondrial dysfunction [51]. Thus, maintaining appropriate levels of mitophagy is critical for mitochondrial turnover, function, and overall neuronal health.

Mitophagy is regulated via both ubiquitin (Ub)-dependent and Ub-independent pathways (e.g., Bcl-2/adenovirus E1B 19 kDa interacting protein 3 (BNIP3), BNIP3-like (BNIP3L/NIX), FUN 14 domain-containing 1 (FUNDC1), and Bcl-2-like 13 (BCL2L13)-mediated mitophagy) [52] (Fig. 2). Mutations in proteins of the Ub-proteasome system (UPS), such as F-box protein 7 (FBXO7) and Parkin, are linked to dopaminergic (DA) neuron degeneration in PD [53]. Among these, the phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1)/Parkin-mediated Ub-dependent mitophagy is the most extensively studied pathway [54]. Parkin, a homologous to E6-associated protein C terminus (HECT/RING) finger E3 ligase, functions as a catalytic hub, transferring Ub to substrates [55]. The process initiates with PINK1 accumulation on damaged mitochondria, which recruits Parkin from the cytosol to the mitochondria Parkin subsequently ubiquitinates OMM proteins, activating the UPS [56]. The combined actions of UPS and adenosine triphosphatase (ATPase)-associated with diverse cellular activities (AAA) + ATPase p97 then degrade OMM proteins, prompting autophagosome formation and isolating the damaged mitochondria for degradation [57].

Beyond the classical PINK1-Parkin pathway, additional receptors such as Beclin1-regulated autophagy protein 1 (AMBRA1), NIX, and FUNDC1 also play pivotal roles in mitophagy regulation [58]. FUNDC1 modulates mitochondrial dynamics and promotes mitophagy under hypoxic conditions [59], while AMBRA1 interacts with LC3 to induce mitophagy in a manner similar to Parkin [60]. NIX has been shown to mediate mitophagy across various cell types, including neurons [61]. In summary, these autophagy-related proteins maintain the delicate balance of mitophagy necessary for cellular health. Emerging evidence highlights the critical role of moderate mitophagy in preserving metabolic homeostasis and cellular survival *in vivo* and *in vitro*. For instance, inhibiting BNIP3 expression restored normal MMP in muscle cells of patients with HD [62]. Additionally, overexpression of $AMBRA1^{ActA}$ enhanced mitochondrial clearance in SH-SY5Y cells, and AMBRA1-induced mitophagy reduced apoptosis triggered by 6-hydroxydopamine (6-OHDA) and rotenone (Rot) [63]. In a *Drosophila* model of HD, PINK1 overexpression mitigated mitochondrial aggregation and alleviated neurotoxicity associated with mutant huntingtin (mHTT) [64]. Furthermore, in a *Drosophila* PD model, grape skin extract activated mitophagy, preserved mitochondrial function, and delayed PD onset [65].

Mitophagy represents a vital mechanism within MQC, with significant implications for neuronal integrity. However, the impact of heightened mitophagy on neuronal health requires investigation. As a key cellular process in NDDs, mitophagy will be discussed in subsequent sections. Further research into enhancing mitophagy holds promise for protecting neurons from functional decline and degeneration.

2.3. Mitochondrial biogenesis

Mitochondrial biogenesis is a complex, coordinated process encompassing the replication, transcription, and translation necessary for generating new mitochondria, a critical function for numerous ATP-dependent processes essential for neuronal activity

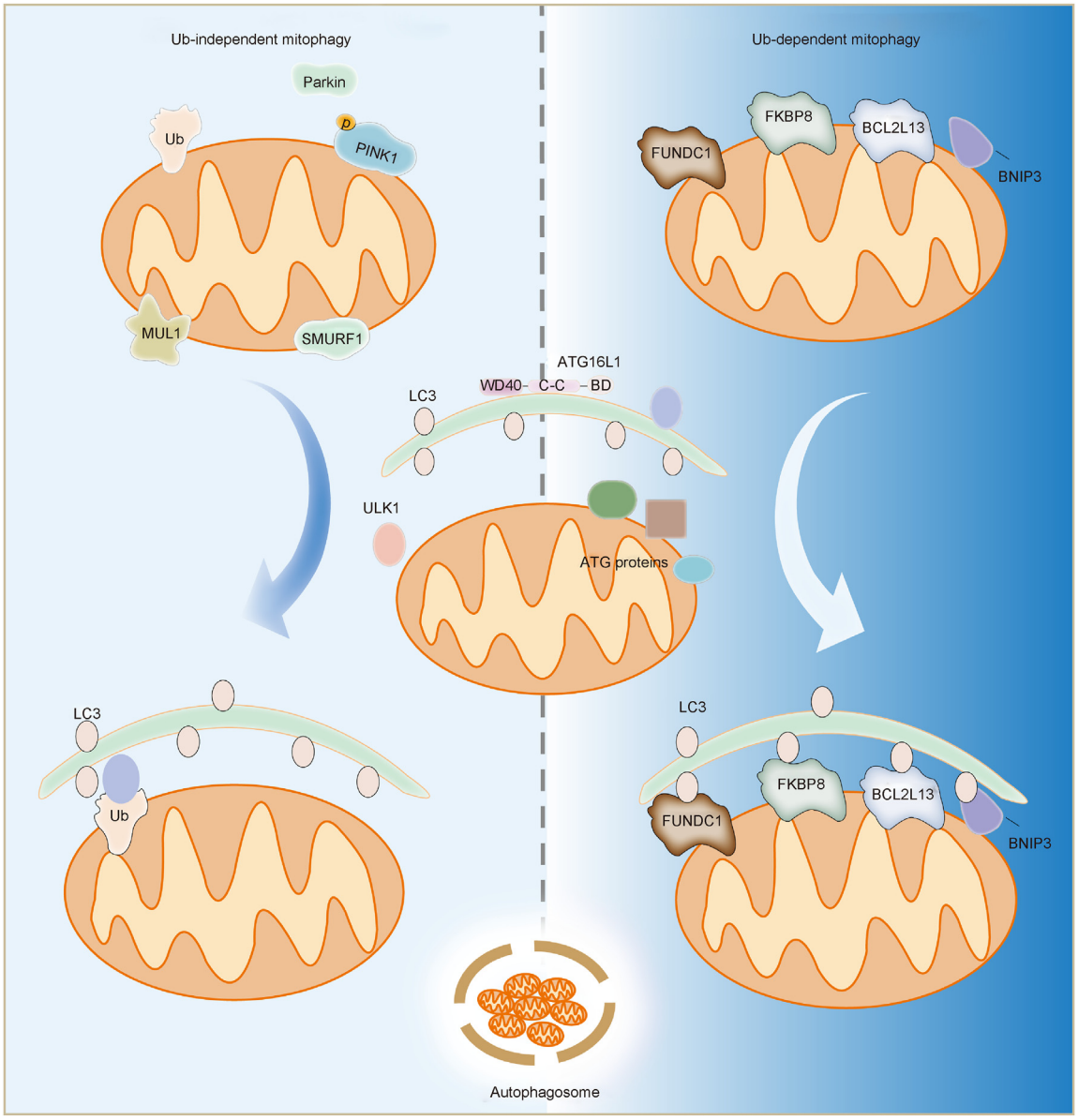

Fig. 2. Ubiquitin (Ub) dependent and independent mitophagy pathways. Ub-dependent mitophagy leads to ubiquitination of mitochondrial surface proteins and their binding to Ub chains. In contrast, Ub-independent mitophagy occurs through direct interaction between mitochondrial receptors, such as FUN 14 domain-containing 1 (FUNDC1) and B-cell lymphoma-2 (Bcl-2)/adenovirus E1B 19 kDa interacting protein 3 (BNIP3), with microtubule-associated protein 1 light chain 3 (LC3) on the autophagosomal membrane. This interaction enhances the formation of autophagosomes around the mitochondria, facilitating their sequestration and subsequent degradation. PINK1: phosphatase and tensin homolog (PTEN)-induced putative kinase 1; MUL1: mitochondrial E3 Ub protein ligase 1; SMURF1: smad ubiquitination regulatory factor 1; FKBP8: FK506 binding protein 8; BCL2L13: B-cell lymphoma-2 (Bcl-2)-like 13; ATG16L1: Atg16-like proteins; WD40: WD40 repeat-containing proteins; CC: coiled-coil domain; BD: Atg5-binding domain; ULK1: uncoordinated 51-like kinase 1; ATG: autophagy-related proteins.

[66]. This process typically initiates from pre-existing mitochondria, with peroxisome proliferator-activated receptor γ (PPARγ) coactivator 1-α (PGC-1α) as its central regulator [67]. PGC-1α forms transcriptional complexes with DNA, activating factors that regulate nuclear genes encoding mitochondrial proteins [68]. Mitochondrial transcription factor A (TFAM), synthesized from nuclear DNA, is essential for transcribing 13 key enzymes encoded by the mitochondrial genome, vital for ETC assembly [69]. Given their substantial energy demands, neurons express high levels of PGC-1α [70]. Cytosolic proteins are imported into the mitochondria via the translocase of the OMM (TOM), which recognizes positively charged N-terminal presequences. These proteins are subsequently transferred to the IMM through the translocase of the IMM 23 (TIM23)-dependent pathway [71].

PGC-1α knockout mice exhibited behavioral abnormalities consistent with NDDs, along with sponge-like lesions in the striatum and dysfunctions in both the motor cortex and hippocampus, underscoring the critical role of mitochondrial biogenesis in synaptic and brain development [72].

In conclusion, MQC is fundamental to preserving neuronal functionality and integrity, facilitating the removal of damaged mitochondria and protein aggregates while promoting the generation of new mitochondria. Although MQC's pivotal role in NDDs is widely recognized, a significant gap remains between the efficacy of pharmacological interventions targeting MQC and the anticipated therapeutic outcomes. Therefore, further research is needed into the specific roles of alternative MQC pathways in NDD pathogenesis.

3. Potential roles of MQC in NDDs

Neurons are highly energy-demanding, with mitochondria playing a critical role in ATP production. Mitochondrial dysfunction and impaired quality control are key features of NDDs [73]. Therefore, identifying pathways that regulate mitochondrial content and quality is essential for developing therapeutic strategies for NDDs. This section explores the pivotal role of MQC in several major NDDs.

3.1. AD

AD is among the most prevalent forms of dementia, affecting approximately 50 million people worldwide, a figure expected to rise to 150 million by 2050, imposing significant economic burdens [74]. Pathologically, AD is marked by the deposition of amyloid β (Aβ) peptide, the formation of neurofibrillary tangles, and the progressive loss of neurons in the brain [75]. Although the precise etiology of AD remains elusive, growing evidence suggests that disruptions in MQC contribute to synaptic and neuronal degeneration in the disease's onset and progression [76].

Mitochondria are dynamic organelles that undergo continuous fission (regulated by Drp1 and Fis1) and fusion (regulated by OPA1, Mfn1, and Mfn2) to maintain mitochondrial homeostasis [77]. In Aβ-overloaded mice, dysregulation of mitochondrial dynamics, particularly in the cerebral cortex and hippocampus, has been attributed to Aβ accumulation, with mitochondrial dysfunction potentially representing an early hallmark of AD [78]. Increasing evidence suggests that Drp1 interacts with both Aβ and Tau in human brain tissues and mouse models [79]. In patients with AD, mitochondrial dynamics are skewed toward excessive fission [80], with elevated levels of the key mitochondrial fission protein Drp1 observed in postmortem AD tissues [81]. Research involving primary neurons has shown that exposure to Aβ peptides reduced mitochondrial fusion proteins (Mfn1, Mfn2, and OPA1) while simultaneously increasing the expression of Drp1 [82,83]. *Drp1* knockout studies in mice revealed that a deficiency in *Drp1* led to mitochondrial fragmentation and loss, exacerbating the neurotoxicity associated with mutant amyloid precursor protein (APP) [81]. Additionally, in animal models pretreated with Aβ, inhibition of Drp1 alleviated mitochondrial fragmentation, restored MMP, reduced ROS production, improved ATP levels, and mitigated synaptic depression [84]. In $A\beta_{25-35}$-induced rat models, *PINK1* knockout led to enhanced mitochondrial fission and fusion, resulting in more pronounced cellular damage, whereas *PINK1* overexpression mitigated the abnormal increase in mitochondrial fusion proteins induced by $A\beta_{25-35}$ [85]. Mdivi1, a selective Drp1 inhibitor, has shown promise as a therapeutic strategy for AD by promoting mitochondrial fusion and biogenesis while reducing mitochondrial fission and dysfunction [86]. In summary, targeted suppression of Drp1 represents a promising approach for mitigating AD-related mitochondrial dysfunction and neurodegeneration.

Recent research suggests that C-terminal fragments (CTFs) derived from APP-CTFs may play a critical role in the pathology of AD [87]. Vaillant-Beuchot et al. [88] reported a correlation between impaired mitophagy and the accumulation of mitochondrial APP-CTFs in sporadic AD brain samples. Beyond the "amyloid hypothesis", increasing evidence emphasizes the significant involvement of phosphorylated tau (p-tau) in AD pathogenesis [89]. Tau hyperphosphorylation is a hallmark of AD, and both autophagy and mitophagy are integral to the processes involved in tauopathies [90]. Impaired mitophagy has been observed in both AD animal models and patients [91,92], where AD hippocampal neurons exhibit reduced mitochondrial size, increased damage, and accumulated dysfunctional mitochondria compared to healthy controls [93]. Emerging evidence highlights several potent mitophagy inducers, such as nicotinamide riboside, urolithin A, and actinonin, which have demonstrated efficacy in promoting cell survival, enhancing mitophagy-related gene expression, and exerting neuroprotective effects in preclinical models [94–96]. For instance, in the 5× familial AD (FAD) mouse model, melatonin treatment restored mitophagy by promoting the fusion of mitophagosomes with lysosomes, thereby alleviating mitochondrial dysfunction. Chloroquine, an autophagy inhibitor, was found to block this melatonin-induced mitophagy and aggravate Aβ deposition pathology [97]. Disruption of autophagosome-lysosome fusion has also been identified as a contributing factor to impaired mitophagy in AD [98]. For example, Zhang et al. [99] reported that inhibiting autophagosome-lysosome fusion in HT22 cells exacerbated axonal dystrophy. Additionally, transient receptor potential mucolipin 1 (TRPML1), a channel involved in Ca^{2+} release from endosomes and lysosomes, was found to interact with sequestosome 1 (p62) to promote autophagosome-lysosome fusion in APP/presenilin 1 (PS1) mouse neurons [100]. These cross-species findings underscored the consistent association between disrupted mitophagy and AD.

AD is also characterized by the downregulation of mitochondrial oxidative phosphorylation (OXPHOS) and disruptions in the mitochondrial import pathways [101]. A primary factor in impaired mitochondrial biogenesis in AD is the increased interaction of pathogenic proteins, such as Aβ and p-tau, with mitochondria [102]. While the exact mechanisms through which Aβ disrupts mitochondrial biogenesis remain unclear, decreased messenger RNA (mRNA) and protein levels of key mitochondrial biogenesis genes, including *PGC-1α*, nuclear factor erythroid 2-related factor 1 (*Nrf1*), *Nrf2*, and *TFAM*, have been observed in postmortem brain tissue from patients with AD, as well as in cellular and mouse models [103–105]. Building on earlier findings that neural stem cell-derived exosomes (NSC-ex) enhanced mitochondrial function in the mouse cerebral cortex, Li et al. [106] demonstrated that NSC-ex upregulated sirtuin 1 (SIRT1) expression and restored the distribution of key mitochondrial biogenesis proteins, such as PGC-1α, Nrf1, and cytochrome C oxidase subunit IV in AD mice. Additionally, pharmacological activation or overexpression of *PGC-1α* has been shown to prevent neuronal apoptosis, oxidative stress, and inflammation, while alleviating neuronal loss and cognitive deficits in AD models [107,108]. PGC-1α overexpression also improved spatial and recognition memory in APP23 mice and significantly reduced Aβ deposition [109]. Furthermore, recent studies indicated that Nrf2 activation offered protection against pro-inflammatory microglial activation and tau pathology in AD minibrains [110]. These findings indicate that dysregulated signaling of mitochondrial biogenesis genes plays a key role in AD pathophysiology. Given the pleiotropic regulatory functions of MQC in AD, closely monitoring and targeting MQC pathways may offer promising therapeutic strategies.

3.2. PD

PD is the most common neurodegenerative movement disorder, currently affecting approximately 10 million individuals worldwide, with this number projected to rise to 12 million by 2050 [74]. Key symptoms of PD include bradykinesia, resting tremors, and abnormal gait [111]. Pathologically, PD is marked by the progressive degeneration of DA neurons in the substantia nigra (SN) pars compacta (SNpc) and the presence of Lewy bodies in surviving neurons [112]. Increasing evidence suggests that impaired MQC, particularly defective mitophagy and mitochondrial dysfunction, plays a pivotal role in PD pathogenesis. During disease onset, neuronal cells experience chronic stress due to failures in MQC mechanisms [113].

Disruption of mitochondrial dynamics has been linked to nigrostriatal defects, posing a risk for retrograde degeneration of DA neurons [114]. In PD, mitochondrial dynamics tend to shift toward excessive fission, with cells from patients with idiopathic PD showing greater variability in mitochondrial morphology [115]. Neurotoxins such as 6-OHDA, Rot, and 1-methy-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) have been implicated in DA neuron loss, primarily by disturbing Drp1/Mfn2-mediated mitochondrial dynamics [116,117]. Recent studies suggest that aberrant mitochondrial fission and apoptosis induced by MPTP *in vitro* can be partially reversed through *Drp1* knockdown [118]. Disruption in the balance of mitochondrial fission and fusion, caused by the downregulation of key proteins such as Mfn1/2 and Drp1, impairs Ca^{2+} homeostasis and increases mitochondrial Bax levels, leading to excitotoxic neuronal death [119]. On the other hand, *Mfn2* overexpression has been shown to protect DA neurons from paraquat (PQ)-induced mitochondrial dysfunction, reducing fragmentation and selective DA neuron loss in both the SNpc and striatal axonal terminals [120].

Mitophagy, a key protective mechanism that eliminates damaged mitochondria, is essential for maintaining neuronal health [121]. Abnormal mitochondrial morphology and accumulation of damaged mitochondria are common pathological features of PD, particularly in cellular and animal models with *PINK1* or *Parkin* deletion or mutation [122]. Approximately 50 % of recessively inherited early-onset PD cases result from loss-of-function mutations in the Parkin ring-between-ring E3 Ub protein ligase (*PARK2*) gene, which encodes the E3 Ub ligase Parkin [123]. Knockout studies in mice revealed that PINK1 downregulation led to impaired dendritic spine maturation, reduced axonal synaptic vesicles, abnormal synaptic connections, and diminished long-term synaptic potentiation, underscoring the essential role of PINK1-mediated mitophagy in polarized neurons [124]. In MPTP-pretreated PD mouse models, activation of the PINK1-Parkin pathway via *Clostridium butyricum* has been shown to reduce oxidative stress and alleviate mitochondrial damage, suggesting a potential neuroprotective role of PINK1-Parkin-regulated mitophagy *in vivo* [125]. Moreover, studies on lipopolysaccharide (LPS)-1-methyl-4-phenylpyridinium $(MPP)^+$-treated mouse microglia indicated that Parkin-mediated mitophagy acted upstream in neuroprotection, with Parkin activation alleviating downstream effects, including DA neuron loss [121]. In addition to *PINK1* and *Parkin*, mutations in other PD-related genes, such as leucine-rich repeat kinase 2 (*LRRK2*), glucocerebrosidase-1 (*GBA1*), and PD protein 7 (*PARK7*/*DJ-1*), also contribute to mitochondrial dysfunction and altered autophagy [111]. For example, $LRRK2^{R1441G}$ mutant mice exhibited abnormal mitochondrial morphology and impaired autophagy in the striatum, while *DJ-1β* deletion mutant flies showed similar autophagic defects. *GBA1* knockout mice displayed mitochondrial defects and reduced MMP [126–128].

A reduction in *PGC-1α* levels and the suppression of its target genes in DA neurons are essential for supporting mitochondrial biogenesis [129]. Laser capture microdissection of SN neurons from patients with PD has revealed a significantly higher mtDNA deletion burden compared to age-matched controls [130]. In MPP^+-induced PD mouse models, a bionic nanoparticle designed to target mitochondrial biogenesis effectively enhanced mitochondrial function and MMP by activating the nicotinamide adenine dinucleotide (NAD^+)/SIRT1/PGC-1α/Nrf1/TFAM signaling pathway, thereby mitigating neuronal toxicity [131]. Similarly, in 6-OHDA-treated SH-SY5Y cells, chiisanoside (a saponin from *Acanthopanax sessiliflorus*) was shown to restore the expression of *PGC-1α* and its downstream genes, which had been suppressed by 6-OHDA exposure [132]. Notably, animal studies demonstrated that inhibiting PGC-1α can result in DA neuron loss and mitochondrial dysfunction, with *PGC-1α* knockout mice exhibiting progressive DA degeneration in the SNpc and striatal DA deficits with age [133]. These findings strongly suggest that alterations disruptions in MQC may underlie in a common pathogenic mechanism associated with multiple genetic risk factors for PD, highlighting the therapeutic potential of targeting these pathways for novel treatment strategies.

3.3. HD

HD is characterized by progressive motor, psychiatric, and cognitive decline. It is caused by the expansion of a CAG repeat sequence (>36) in exon 1 of the huntingtin protein gene (*HTT*), leading to the aggregation of polyglutamine [134]. The age of onset and disease severity are closely correlated with the length of these CAG repeats [135].

Pathologically, the accumulation of mHTT oligomers has been linked to mitochondrial fragmentation, disrupted mitochondrial dynamics, and oxidative DNA damage in affected neurons [136]. Regulators of mitochondrial fusion and fission, such as Drp1 and Fis1, are notably altered in the brains of patients with HD [137]. The presence of mHTT on mitochondria facilitates Drp1 recruitment, while activated calcineurin and mitogen-activated protein kinase 1 dephosphorylate Drp1, further promoting its recruitment [138]. Evidence suggests that mitochondrial dynamics in HD are skewed towards fission [139], with mHTT interacting with Drp1 to enhance its GTPase activity, accelerating fragmentation [140]. Mitochondrial dysfunction and mitochondrial fragmentation are also observed in neurons treated with 3-nitropropionic acid (3-NP), mirroring the abnormal mitochondrial morphology seen in HD models [141]. In mHTT bacterial artificial chromosome (BAC) mice, mRNA levels of *Drp1* and *Fis1* were elevated, while *Mfn1/2* levels decreased [136]. Notably, antioxidant treatments in the 3-NP model restored normal mitochondrial dynamics, indicating that mitochondrial damage in HD likely drove these changes [142]. Furthermore, the direct interaction between the N-terminal fragment of mHTT and Mfn2 severely disrupts mitochondrial morphology, inhibiting mitochondrial elongation [143].

Mitophagy plays a critical role in HD pathogenesis. Increased Parkin levels and enhanced degradation of Mfn1 via the proteasome have been observed in fibroblasts from juvenile patients with HD, suggesting a protective mechanism. Overexpression of PINK1 ($PINK1^{OE}$) in HD fly models has been shown to reduce mitochondrial aggregates, enhance ATP levels, and improve neuronal integrity and survival [64]. PINK1 also mitigates mHTT neurotoxicity, indicating that enhancing the PINK1/Parkin/MQC pathway may preserve mitochondrial integrity and provide neuroprotection in HD. Imbalanced mitophagy, particularly through the PINK1/Parkin pathway, influences HD progression.

Impaired PGC-1α signaling has been associated with defective mitochondrial biogenesis and increased vulnerability of striatal neurons, as observed in a *PGC-1α* knockout mouse model [144]. In a *CAG140* knock-in mouse model, *PGC-1α* mRNA levels were reduced in medium spiny neurons but elevated in cholinergic interneurons, though overall *PGC-1α* levels in HD remain largely unchanged [145]. mHTT interferes with the transcriptional activation of *PGC-1α*, reducing its capacity to stimulate downstream target genes. Remarkably, ectopic expression of *PGC-1α* in transgenic HD and 3-NP mouse models has demonstrated neuroprotective effects [146].

In conclusion, as illustrated in Fig. 3 [147], the dysregulation of MQC leads to mitochondrial damage and fragmentation, disrupting the balance between fusion and fission. Impaired mitophagy further exacerbates the problem by failing to clear damaged mitochondria, which hampers biogenesis processes. This ultimately results in compromised mitochondrial energy metabolism

and elevated oxidative stress, contributing to neurodegeneration. Therefore, maintaining MQC is critical for mitigating the progression of NDDs.

4. Chinese herbal medicine combats NDDs through the MQC pathway

Extensive research has explored the impact of herbal medicine on NDDs, particularly focusing on the vital regulatory role of MQC in these conditions. In the following section, the specific mechanisms and regulatory effects of herbal prescriptions and active monomers will be discussed. The TCM formulas for treating NDDs by targeting MQC are listed in Table 1 [148–160] and pharmacological effects of TCM formulas on non-target organs are listed in Table 2 [148–160]. The active monomers of TCM for treating NDDs by targeting MQC are listed in Table S1 [161–197]. The active monomers of TCM for treating NDDs by targeting MQC are illustrated in Fig. 4.

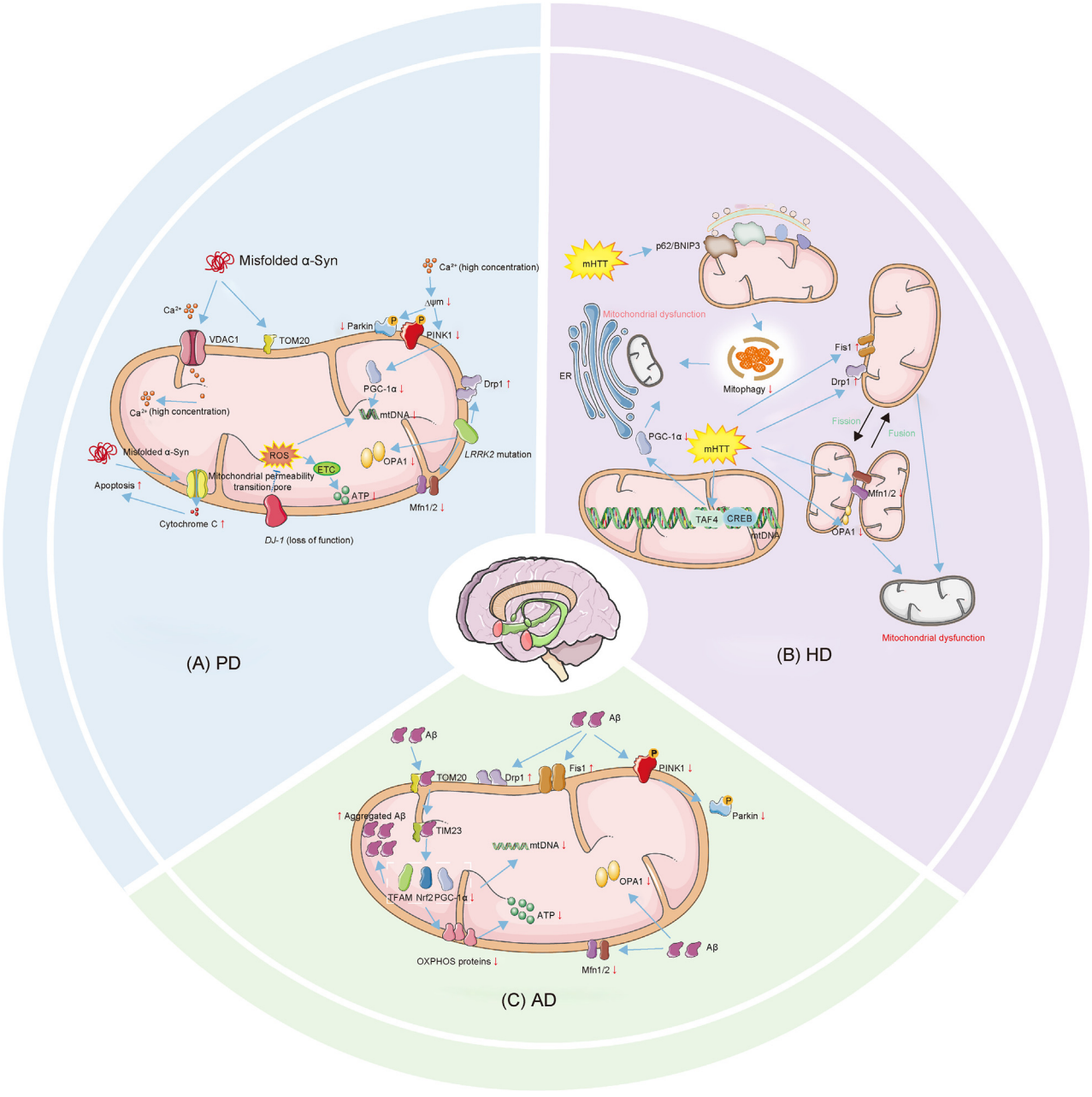

Fig. 3. Mitochondrial quality control (MQC) failure in neurodegenerative diseases (NDDs): (A) Parkinson's disease (PD), (B) Huntington's disease (HD), and (C) Alzheimer's disease (AD) [147]. The arrows ↑ indicates stimulation/promoting and ↓ indicates reduction/inhibition. α-Syn: α synuclein; VDAC1: voltage dependent anion channel 1; TOM20: translocase of the outer membrane 20; Ca^{2+}: calcium; Δψm: mitochondrial membrane potential; PINK1: phosphatase and tensin homolog (PTEN)-induced putative kinase 1; PGC-1α: peroxisome proliferator-activated receptor-γ (PPARγ) coactivator-1α; Drp1: dynamin-related protein 1; mtDNA: mitochondrial DNA; ROS: reactive oxygen species; ETC: electron transport chain; OPA1: optic atrophy 1; *LRRK2*: leucine-rich repeat kinase 2; Mfn1/2: mitofusin 1/2; ATP: adenosine triphosphate; *DJ-1*: Parkinson disease protein 7; mHTT: mutant huntingtin; p62: sequestosome 1; BNIP3: B-cell lymphoma-2 (Bcl-2)/adenovirus E1B 19 kDa interacting protein 3; ER: endoplasmic reticulum; Fis1: fission protein 1; TAF4: TATA-box binding protein (TBP) associated factor 4; CREB: cyclic adenosine monophosphate (cAMP) response element-binding protein; Aβ: amyloid β; TIM23: translocase of the inner mitochondrial membrane 23; TFAM: mitochondrial transcription factor A; Nrf2: nuclear factor erythroid 2-related factor 2; OXPHOS: oxidative phosphorylation. Reprinted with permission from Ref. [147].

4.1. TCM formulas

Over recent decades, clinical trials and animal studies have investigated the efficacy of various Chinese herbal formulations for NDD treatment. Reserpine, an indole alkaloid employed for hypertension and psychosis, was shown by Dong et al. [148] to enable Bu Zhong Yi Qi decoction to mitigate reserpine-induced mild cognitive impairment by alleviating mtDNA damage through the SIRT3/manganese superoxide dismutase (MnSOD)/8-oxoguanine DNA glycosylase-1 (OGG1) pathway, and reducing H_2O_2-induced mitochondrial damage in PC12 cells. Notably, Bu Zhong Yi Qi decoction has been found to inhibit Aβ accumulation in the hippocampus of AD mice while upregulating brain-derived neurotrophic factor (BDNF) expression, significantly improving cognitive deficits in these models [149].

Bu Shen Yi Zhi formula, composed of 12 Chinese herbs, has long been recognized for its efficacy in treating AD. In a bilateral common carotid artery occlusion rat model, Bu Shen Yi Zhi formula improved cognition and memory by reducing abnormal Aβ deposition and exerting neuroprotective effects. It also reduced neuronal oxidative stress by promoting spontaneous lysosome formation and inhibiting excessive mitophagy [150]. In scopolamine-induced AD mice, two weeks of Bu Shen Yi Zhi formula administration alleviated neuronal apoptosis [151].

Da Bu Yin Wan, a traditional formula with over 600 years of use, has been applied clinically for PD. Zhang et al. [152] confirmed that Da Bu Yin Wan could regulate mitochondrial gene expression and improve mitochondrial morphology in PD models. Further research showed that Da Bu Yin Wan significantly decreased the expression in mitochondrial fission proteins (Drp1 and Fis1) while modulating the expression of fusion regulators (Parkin, Mfn1, Mfn2, and OPA1) induced by MPP^+ [153].

Both *in vivo* and *in vitro* studies have shown that Kai Xin San significantly enhanced mitochondrial fusion (Mfn1 and Mfn2), SIRT3 expression, and increased neurotrophic factors (BDNF and nerve growth factor (NGF)) in APP/PS1mice, mitigating $A\beta_{1-42}$-induced cytotoxicity [154]. Dang Gui Shao Yao San, a renowned herbal formula, has been demonstrated to improve cognitive deficits and activate PINK1-Parkin-dependent mitophagy [155].

Dang Gui Bu Xue decoction is an ancient herbal combination. Recent findings indicated that a two-month oral administration of Dang Gui Bu Xue decoction in APP/PS1 mice effectively alleviated memory impairments and reduced Aβ plaque deposits, with these neuroprotective effects linked to the upregulation of mitochondrial biogenesis via PGC-1α signaling [156]. Di Huang Yi Zhi, another traditional formula, has shown significant clinical efficacy, reducing ROS production induced by $A\beta_{25-35}$ and cytochrome C release while enhancing MMP in PC12 cells [157].

Huang Lian Jie Du decoction demonstrates neuroprotective effects in SH-SY5Y cells exposed to PQ-induced cytotoxicity, by restoring MMP and preventing excessive mitophagy through the PINK1-Parkin pathway [158]. Cerebral ischemia, a leading cause of mortality globally, has been associated with the aggregation of NDD-related proteins and increased AD risk. Treatment with Tao Hong Si Wu decoction upregulated LC3-II/LC3-I, Beclin1, Parkin, and PINK1 expression, which improved neurological outcomes and reduced cerebral infarction [159].

Suan Zao Ren decoction, an herbal formula traditionally used to treat insomnia, has also been recognized for its beneficial effects in AD. In 2024, Long et al. [160] reported that Suan Zao Ren decoction significantly ameliorated synaptic damage and neuronal loss in the hippocampus of APP/PS1 mice by activating the DJ-1/Nrf2 signaling pathway.

4.2. Active monomers from TCM

4.2.1. Flavonoids

Puerarin (Pue), a flavonoid extracted from *Pueraria lobata*, is a potent antioxidant isoflavone. In 2022, Wen et al. [161] demonstrated that Pue protected rat cortical neurons from cadmium-induced neurotoxicity by ameliorating mitochondrial dysfunction and restoring MMP. Mechanistically, Pue activated the PINK1-Parkin and NIX pathways, preventing the decline in neuronal mitochondrial mass.

Oxyphylla A (OA), a novel compound derived from *Alpinia oxyphylla*, which has a long history in the treatment of neurological disorders like AD and PD, has shown increasing promise. Growing evidence supports the neuroprotective effects of *Alpinia oxyphylla* extracts in AD and PD models. Subsequent studies revealed that OA reduced APP and Aβ expression levels, mitigated cognitive decline in SAMP8 mice, and exerted antioxidant effects through GSK-3β and Keap1-heme oxygenase-1 (HO-1) pathways [162].

Quercetin (QUE) has been shown to inhibit acetylcholinesterase (AChE) in PC12 cell models, reducing AChE degradation and Aβ production [163]. In the MitoPark transgenic mouse model of PD, Ay et al. [164] found that QUE activated the protein kinase D1 (PKD1)-protein kinase B (Akt) signaling cascade, providing neuroprotection by reversing behavioral deficits, DA depletion in the striatum, and the loss of tyrosine hydroxylase (TH)-positive neurons related to mitochondrial dysfunction.

Naringenin (NAR), a flavonoid primarily found in *Citrus aurantium*, exhibits strong neuroprotective effects. In AD mice model, NAR enhanced hippocampal neurogenesis through the adenosine monophosphate (cAMP)-activated protein kinase (AMPK)/BDNF/tropomyosin receptor kinase B/cAMP response element-binding protein (CREB) signaling pathway, reducing Aβ accumulation and improving memory function [165]. In zebrafish models of 6-OHDA-induced neurotoxicity, NAR alleviated motor deficits and downregulated the expression of PD-related genes *(pink1, LRRK2*, ploymerase γ gene (*polg*), and cysteine-aspartic acid protease 9 (*casp9*)) [166].

Icariin (ICA), an active compound derived from *Epimedii folium*. In APP/PS1 mice, the combination of β-asarone (a styrene compound) and ICA significantly improved memory function and reduced levels of AD-related metabolites and toxic proteins, such as APP, Aβ, synuclein, and β-site APP cleaving enzyme 1 (BACE1), showing superior therapeutic efficacy compared to either compound alone. This combination also preserved MMP and increased the expression of autophagy and mitochondrial proteins, including Beclin 1, LC3I/II, p62, and PINK1 in the hippocampus [167].

Wogonin (WO), derived from *Scutellaria baicalensis* Georgi, has been found to activate the cholinergic system and the BDNF-CREB pathway in AD rat models, enhancing learning and memory processes [168]. Furthermore, WO has been shown to reduce Aβ secretion and BACE1 levels in SH-SY5Y cells by modulating the mechanistic target of rapamycin (mTOR)/autophagy pathway and inhibiting GSK-3β, which decreased p-tau, highlighting its potential as a therapeutic agent for AD [169].

Luteolin (LUT), found in medicinal plants such as *Lonicera japonica* Thunb., *Chrysanthemum morifolium* Ramat, and *Perilla frutescens* (L.) Britt.. Wang et al. [170] demonstrated that LUT activated AMPK pathway, improved mitochondrial dysfunction, and restored MMP and ATP levels in APP_{swe}/PS1dE9 mice. However, He et al. [171] reported that LUT's anti-AD effects diminished when peroxisome proliferator-activated receptor γ (*PPARγ*) was knocked down using small interfering RNA (siRNA), highlighting its reliance on this pathway.

Table 1
Traditional Chinese medicine (TCM) formulas for treating neurodegenerative disorders (NDDs) through targeting mitochondrial quality control (MQC).

Disease	Formulations	Composition	*In vivo*/*in vitro* models	Dose (*in vivo*; *in vitro*)	Mode of action	Refs.
NDD	Bu Zhong Yi Qi decoction	*Astragalus membranaceus* (Fisch.) Bge. var. mongholicus (Bge.) Hsiao (Huang Qi), *Panax ginseng* C.A. Mey. (Ren Shen), *Glycyrrhiza uralensis* Fisch. (Gan Cao),	*In vivo*: reserpine-induced SD rats; *In vitro*: H_2O_2-induced PC12 cells	*In vivo*: 7.56 g/kg/day; *In vitro*: 16 mg/mL	Cognitive function ↑, MnSOD ↓, SIRT3 ↑, OGG1 ↑, mtDNA oxidative damage ↓, and mitochondrial function ↑	[148]
AD	Bu Zhong Yi Qi decoction	*Angelica sinensis* (Oliv.) Diels (Dang Gui), *Citrus reticulata* Blanco (Chen Pi), *Cimicifuga heracleifolia* Kom. (Sheng Ma), *Bupleurum chinense* DC. (Chai Hu), and *Atractylodes macrocephala* Koidz. (Bai Zhu)	*In vivo*: $A\beta_{(1-42)}$-induced ICR male mice; *In vitro*: H_2O_2-induced HT22 cells	*In vivo*: 200, 400, and 800 mg/kg/day; *In vitro*: 0, 12.5, 25, and 50 μg/mL	Cognitive impairments ↓, Aβ aggregation and expression ↓, BDNF ↑, and cytotoxicity ↓	[149]
NDD	Bu Shen Yi Zhi formula	*Cnidium monnieri* (L.) Cuss. (She Chuang Zi), *Panax ginseng* C.A. Mey. (Ren Shen), *Polygonum multiflorum* Thunb. (He Shou Wu), *Paeonia suffruticosa* Andr. (Mu Dan Pi), *Ligustrum lucidum* Ait. (Nv Zhen Zi), and *Lycium barbarum* (Gou Qi)	*In vivo*: BCCAo induced SD rats; *In vitro*: OGD/R induced PC12 cells	*In vivo*: 3,6 g/kg/day; *In vitro*: 2.5%–10 % serum	Cognition and memory abilities ↑, neuronal apoptosis ↓, formation of autolysosomes ↑, excessive mitophagy ↓, cell viability ↑, intracellular ROS ↓, MMP ↑, and lysosomal proteins ↑	[150]
AD	Bu Shen Yi Zhi formula		*In vivo*: scopolamine-induced male Kunming mice	*In vivo*: 1.46, 2.92, and 5.84 g/kg	Cognitive ability ↑, SOD ↑, MDA ↓, GSH ↑, Bcl-2 ↑, and Bax ↓	[151]
PD	Da Bu Yin Wan	*Rehmannia glutinosa* Libosch. (Di Huang), *Anemarrhena asphodeloides* Bge. (Zhi Mu), *Phellodendron chinense* Schneid. (Huang Bo), *Chinemys reevesii* (Gray) (Gui Jia), and the spinal cord of *Sus scrofa* domestica Brisson (Zhu Ji Sui)	*In vivo*: MPTP-treated male C57BL/6 mice	*In vivo*: 3.87 and 7.74 g/kg	Behavioral impairments ↓, TH expression ↑, neurotransmitters ↑, and mtDNA damage ↓	[152]
PD	Da Bu Yin Wan		*In vitro*: MPP^+-treated SHSY5Y cells	*In vitro*: 0.5 g/mL	Parkin ↑, Mfn1/2 ↑, OPA1 ↑, Drp1 ↓, Fis1 ↓, MMP ↑, and ATP ↑	[153]
AD	Kai Xin San	*Acorus tatarinowii* Schott (Shi Chang Pu), *Panax ginseng* C.A.Mey. (Ren Shen), and *Polygala tenuifolia* Willd. (Yuan Zhi)	*In vivo*: APP/PS1 mice; *In vitro*: $A\beta_{(1-42)}$ treated HT22 cells	*In vivo*: 2.5, 5, and 10 g/kg/day; *In vitro*: 10 %, 5%–30 % serum	Cognitive deficit ↓, ROS ↓, MDA ↓, neuronal apoptosis ↓, mitochondrial dysfunction ↓, Mfn1 ↑, Mfn2 ↑, Drp1 ↓, BDNF ↑, NGF ↑, SIRT3 ↑, cytotoxicity ↓, fusion ↑, and fission ↓	[154]
AD	Dang Gui Shao Yao San	*Angelica sinensis* (Oliv.) Diels (Dang Gui), *Paeonia lactiflora* Pall. (Bai Shao), *Ligusticum chuanxiong* Hort. (Chuan Xiong), *Poria cocos* (Schw.) Wolf (Fu Ling), *Alisma orientale* (Sam.) Juzep. *Alisma plantago-aquatica* Linn. (Ze Xie), and *Atractylodes macrocephala* Koidz. (Bai Zhu)	*In vivo*: $A\beta_{(1-42)}$-induced SD rats	*In vivo*: 12, 24, and 36 g/kg/day	PINK1 ↑, Parkin ↑, LC3I/LC3II↑, p62 ↓, and cognitive deficits ↓	[155]
AD	Dang Gui Bu Xue decoction	*Angelica sinensis* (Oliv.) Diels (Dang Gui), *Astragalus membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.), and Hsiao. (Huang Qi)	*In vivo*: APP/PS1 mice	*In vivo*: 4.5 mg/g/day	ATP ↑, MMP ↑, MDA ↓, SOD ↑, PGC-1α↑, mitochondrial biogenesis ↑, mitochondrial dysfunction ↓, and memory impairments ↓	[156]
AD	Di Huang Yi Zhi	*Rehmannia glutinosa* Libosch. (Di Huang), *Salvia miltiorrhiza* Bge. (Dan Shen), *Alpinia oxyphylla* Miq. (Yi Zhi), *Poria cocos* (Schw.) Wolf (Fu Ling), and *Acorus tatarinowii* Schott (Shi Chang Pu)	*In vitro*: $A\beta_{(25-35)}$-indued PC12 cells	*In vitro*: 10, 20, and 40 μg/mL	MMP ↑, ROS generation ↓, apoptosis ↓, and cytochrome C release ↓	[157]
PD	Huang Lian Jie du decoction	*Coptis chinensis* Franch. (Huang Lian), *Scutellaria baicalensis* Georgi (Huang Qin), *Phellodendron chinense* Schneid. (Huang Bo), and *Gardenia jasminoides* Ellis (Zhi Zi)	*In vitro*: PQ treated SH-SY5Y cells	*In vitro*: 100 μg/mL	MMP ↑, PINK1 ↓, Parkin ↓, mitophagy ↓, mitochondrial dysfunction ↓, and phosphorylation of Ub-S65 and Parkin-S65 ↓	[158]

(*continued on next page*)

Table 1 (*continued*)

Disease	Formulations	Composition	*In vivo*/*in vitro* models	Dose (*in vivo*; *in vitro*)	Mode of action	Refs.
NDD	Tao Hong Si Wu decoction	*Rehmannia glutinosa* Libosch. (Di Huang), *Angelica sinensis* (Oliv.) Diels (Dang Gui), *Ligusticum chuanxiong* Hort. (Chuan Xiong), *Paeonia lactiflora* Pall. (Bai Shao), *Prunus persica* (L.) Batsch (Tao Ren), and *Carthamus tinctorius* L. (Hong Hua)	*In vivo*: MCAO/R rats	–	LC3-II/LC3-1↑, Beclin1 ↑, PINK1 ↑, Parkin ↑, and damage of mitochondrial structures ↓	[159]
AD	Suan Zao Ren decoction	*Zizipgus jujuba Mill. var. spinosa* (Bunge) Hu ex H. F. Chou (Suan Zao Ren), *Ligusticum chuanxiong* Hort. (Chuan Xiong), *Anemarrhena asphodeloides* Bge. (Zhi Mu), *Poria cocos* (Schw.) Wolf (Fu Ling), and *Glycyrrhiza uralensis* Fisch. (Gan Cao)	*In vivo*: APP/PS1 mice	*In vivo*: 12.96 g/kg/day	Aβ deposit ↓, DJ-1 ↑, Nrf2 ↑, hippocampal neuronal loss ↓, hippocampal synaptic damage ↓, and learning and memory impairments ↓	[160]

–: no data. "↑" represents increase and "↓" represents decrease. PQ: paraquat; SD: Sprague Dawley; MnSOD: manganese superoxide dismutase (SOD); SIRT3: sirtuin 3; OGG1: 8-oxoguanine DNA glycosylase-1; mtDNA: mitochondrial DNA; AD: Alzheimer's disease; Aβ: amyloid-β; ICR: institute of cancer research; BDNF: brain-derived neurotrophic factor; BCCAo: bilateral common carotid artery occlusion; OGD/R: oxygen glucose deprivation/reoxygenation; ROS: reactive oxygen species; MMP: mitochondrial membrane potential; MDA: malondialdehyde; GSH: glutathione; Bcl-2: B-cell lymphoma-2; Bax: Bcl-2 associated X; PD: Parkinson's disease; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; TH: tyrosine hydroxylase; MPP: 1-methyl-4-phenylpyridinium; Mfn1/2: mitochondrial fusion protein 1/2; OPA1: optic atrophy 1; Drp1: dynamin-related protein 1; Fis1: fission protein 1; ATP: adenosine triphosphate; APP: amyloid precursor protein; PS1: presenilin 1; NGF: nerve growth factor; PINK1: phosphatase and tensin homolog (PTEN)-induced putative kinase 1; LC3: microtubule-associated protein 1 light chain 3; p62: sequestosome 1; PGC-1α: peroxisome proliferator-activated receptor-γ (PPARγ) coactivator-1α; Ub: ubiquitin; MCAO/R: middle cerebral ischemia/reperfusion; DJ-1: Parkinson's disease protein 7; Nrf2: nuclear factor erythroid 2-related factor 2.

Apigenin (APG), a natural flavonoid, exhibits broad several pharmacological activities, including antiviral, antioxidant, and anti-inflammatory effects. In a mouse model of LPS-induced neurodegeneration, oral administration of APG for seven consecutive days significantly alleviated neuronal degeneration and reduced hippocampal neuron loss. Its protective mechanism involved the regulation of mitochondrial biogenesis (PGC-1α and TFAM), mitochondrial fusion (Mfn2 and OPA1), and mitophagy (PINK1 and Parkin), while preventing NAD^+ depletion and activating SIRT3 to improve cognitive impairments [172].

Myricetin (MYR), primarily found in *Myrica rubra* Siebold et Zuccarini, promoted mitochondrial biogenesis and integrity in N2a-SW cells by increasing PGC-1α, Nrf1, TFAM, and mtDNA levels. MYR also ameliorated mitochondrial dynamics and mitophagy in AD by influencing key proteins, including OPA1, Mfn2, Drp1, Fis1, PINK1, and Parkin. Additionally, it protected against Aβ toxicity by improving MMP and ATP production [173].

Hyperoside (HYP), a flavonoid abundant in *Hyperici Perforati Herba*, has shown neuroprotective effects in both *in vivo* and *in vitro* PD models. In Rot-treated PD rats, 28 days of oral HYP administration improved behavioral deficits by enhancing locomotor activity and reversing the overexpression of autophagy markers Beclin-1, LC3II, and p62. Furthermore, in SH-SY5Y cells exposed to Rot, HYP restored MMP [174].

Polydatin (POL), a naturally occurring stilbenoid from *Polygonum cuspidatum*, exhibits potent antioxidant, anti-inflammatory, and neuroprotective effects. Although its specific role in PD is not fully elucidated, POL has been shown to prevent MMP reduction and SIRT1 downregulation in SH-SY5Y cells. Additionally, it inhibited the mTOR/Unc-51-like kinase (ULK) pathway and enhanced PGC-1β/Mfn2-mediated mitochondrial fusion, ameliorating mitochondrial morphology and motor deficits associated with Parkin deficiency [175].

4.2.2. Phenols

Curcumin (CUR), a phenolic compound from *Curcuma longa* L., has been shown to combat AD by inhibiting $A\beta_{42}$ and APP, attributed to its methoxyphenol structure. In SH-SY5Y-APPswe cells, CUR ameliorated OXPHOS dysfunction and restored MMP after H_2O_2-induced damage [176]. Additionally, CUR enhanced mitochondrial fusion, promoted biogenesis, and elevated synaptic protein levels to counteract Aβ toxicity [177].

Ellagic acid, a polyphenolic compound found in fruits and *Granati pericarpium*, offered protection against arsenic trioxide-induced neurotoxicity in SH-SY5Y cells by preserving MMP and cytochrome C levels, thus preventing mitochondrial swelling and fragmentation [178].

Gastrodin (GAS), derived from *Gastrodiae rhizoma*, displays notable anticonvulsant and neuroprotective properties. In in $Pink1^{B9}$ mutant flies, GAS delayed the onset of PD-like symptoms, extending lifespan and increasing DA levels in the brain [179].

Resveratrol, a polyphenol from *Polygonum cuspidatum*, has been shown in recent studies to protect against fluoride-induced neurotoxicity by activating the SIRT1-dependent PGC-1α/Nrf1/TFAM signaling pathway, which enhanced mitochondrial biogenesis and safeguarded cognitive function in rat models [180].

Ferulic acid (FA), derived from *Angelica sinensis* and *Ligusticum chuanxiong*, exhibits neuroprotective effects, evidenced by memory recovery in streptozotocin-induced AD rats and preservation of hippocampal pyramidal cell morphology. Mechanistically, FA suppressed Drp1-mediated mitochondrial fission and upregulated PGC-1α expression [181].

Honokiol (HKL), a biphenolic compound from *Magnolia officinalis*. Recent studies have demonstrated that HKL protected against fluoride-induced mitochondrial damage through the AMPK/PGC-

Table 2
Pharmacological effects of traditional Chinese formulas on non-target organs in the treatment of neurodegenerative disorders (NDDs).

Formulations	Non-target organs/systems	Positive effect (treatment of diseases)	Toxic and side effects	Refs.
Bu Zhong Yi Qi decoction	Cardiovascular system, respiratory system, digestive system, urinary system, and immune system	Increasing myocardial contractility, improving cardiac function and anti-heart failure, alleviating the symptoms of chronic obstructive pulmonary disease and hypoxia, strengthening the protection and repair of gastric mucosa, and reducing blood and protein in urine	Insomnia, ptosis of stomach, and ischemia	[148,149]
Bu Shen Yi Zhi formula	Kidney and skeletal muscle	Anti-mental retardation and anti-aching and limp of the waist and the knees	Rash, itching, dry mouth, dry tongue, and insomnia	[150,151]
Da Bu Yin Wan	Kidney, heart, lung, and immune system	Relieving nephrotic syndrome, intractable insomnia and diabetes, improving spontaneous and night sweating, anti-chronic aplastic anemia, anti-tuberculosis, and anti-systemic lupus erythematosus	Gastrointestinal complaints and pruritus	[152,153]
Kai Xin San	Heart and gastrointestinal tract	Improving insomnia and cardiac blood supply, relieving indigestion, and loss of appetite	Allergic reactions: rash and itching Digestive reactions: nausea and vomiting	[154]
Dang Gui Shao Yao San	Immune system, endocrine system, and digestive system	Anti-inflammatory, regulating the secretion of sex hormones, and promoting blood circulation for remove blood stasis	Gastrointestinal discomfort, liver damage, and anemia	[155]
Dang Gui Bu Xue decoction	Cardiovascular system and lung	Improving myocardial ischemia-reperfusion injury, alleviating diabetic cardiomyopathy and anti-heart failure, inhibiting pulmonary fibrosis, and anti-lung cancer	Tired, lethargy, diarrhea, and maternal abortion	[156]
Di Huang Yi Zhi	Cardiovascular system, kidney, immune system, and digestive system	Lowering lipid and anti-platelet aggregation, anti-diabetes, and boosting immunity	Diarrhea and gastrointestinal bleeding	[157]
Huang Lian Jie du decoction	Digestive system, skin, cerebrovascular system, and immune system	Anti-inflammatory, antibacterial, regulating gut microbiota, lowering blood pressure and blood lipids, and enhancing immunity	Diarrhea, vomiting, and liver and kidney damage	[158]
Tao Hong Si Wu decoction	Skeleton, uterus, and joint	Enhancing osteoblast function and inhibiting osteoclast bone resorption, improving menstrual volume and endometrial thickness, reducing inflammatory factors, and promoting joint function recovery	Weakness and bleeding, excessive increase in menstrual volume, and diarrhea and vomiting	[159]
Suan Zao Ren decoction	Thyroid gland and heart	Improving thyroid levels, lowering blood pressure, improving ventricular premature beats, and coronary atherosclerotic heart disease	Decreasing blood pressure, gastrointestinal discomfort, lethargy, and numbness of the mouth	[160]

1α/SIRT3 pathway, increasing AMPK, CREB, and PGC-1α expression while inhibiting β-secretase activity [182].

Salidroside (SAL), the primary active compound from *Rhodiola crenulata*, has been shown to enhance learning, memory, and brain metabolism in AD models. SAL also mitigated ROS-induced mitochondrial damage and promoted mitochondrial autophagy through the PINK1-Parkin pathway, providing neuroprotection in MPP^+/MPTP-induced PD models [183].

4.2.3. Terpenoids

Senegenin, a triterpenoid from *Polygala tenuifolia*, possesses anti-inflammatory and antioxidant properties. It significantly promoted PINK1/Parkin-mediated mitophagy, reducing damage in $A\beta_{1-42}$-exposed HT22 cells by improving cell viability and MMP [184].

Ginsenoside Rb1 (Rb1), a key component of *Panax ginseng*, shows potential in treating various NDDs and enhancing mitochondrial function. Rb1 has been demonstrated to inhibit α-synuclein aggregation and neurotoxicity and reduce depressive-like behavior in LPS-ATP-lesioned mice. Mechanistically, Rb1 activated mitophagy and inhibited astrocyte activation [185].

Glycyrrhizic acid, derived from *Glycyrrhiza glabra*, has been shown to enhance mitochondrial function and promote biogenesis by upregulating PGC-1α, Nrf1, Nrf2 and TFAM, ultimately restoring MMP and cytochrome C oxidase activity [186].

Astragaloside IV, a triterpenoid from *Astragalus membranaceus*, exhibits a favorable safety profile in clinical trials. Its neuroprotective effects in LPS/MPP^+-induced PD mouse models involved enhancing energy metabolism and activating Nrf2 pathway, thereby protecting DA neurons from loss and behavioral deficits [187].

Catalpol (Cat), an iridoid glycoside from *Rehmannia glutinosa*, exhibits significant neuroprotective effects against AD, characterized by antioxidant, anti-inflammatory, and anti-apoptotic properties. Neuronal structural damage in the hippocampal CA1 region and Aβ deposition play a crucial role in progressive synaptic loss during AD progression. Studies demonstrated that treating AD with Cat inhibited the expression of BACE1 and apoptosis in hippocampal CA1 region of APP/PS1 mice to improve cognitive deficits [188].

Ganoderic acid A (GAA), a tetracyclic triterpenoid from *Ganoderma lucidum*. Several studies have disclosed that GAA ameliorated cognitive deficits in AD mouse models by regulating Axl receptor tyrosine kinase (Axl) and the Park1 pathway in autophagy [189]. In the subsequent studies, ganoderic acid C_2 enhanced NGF expression, activated the downstream effector PGC-1α, restored sensorimotor functions, and reduced neuronal degeneration in 3-NP-induced HD models [190].

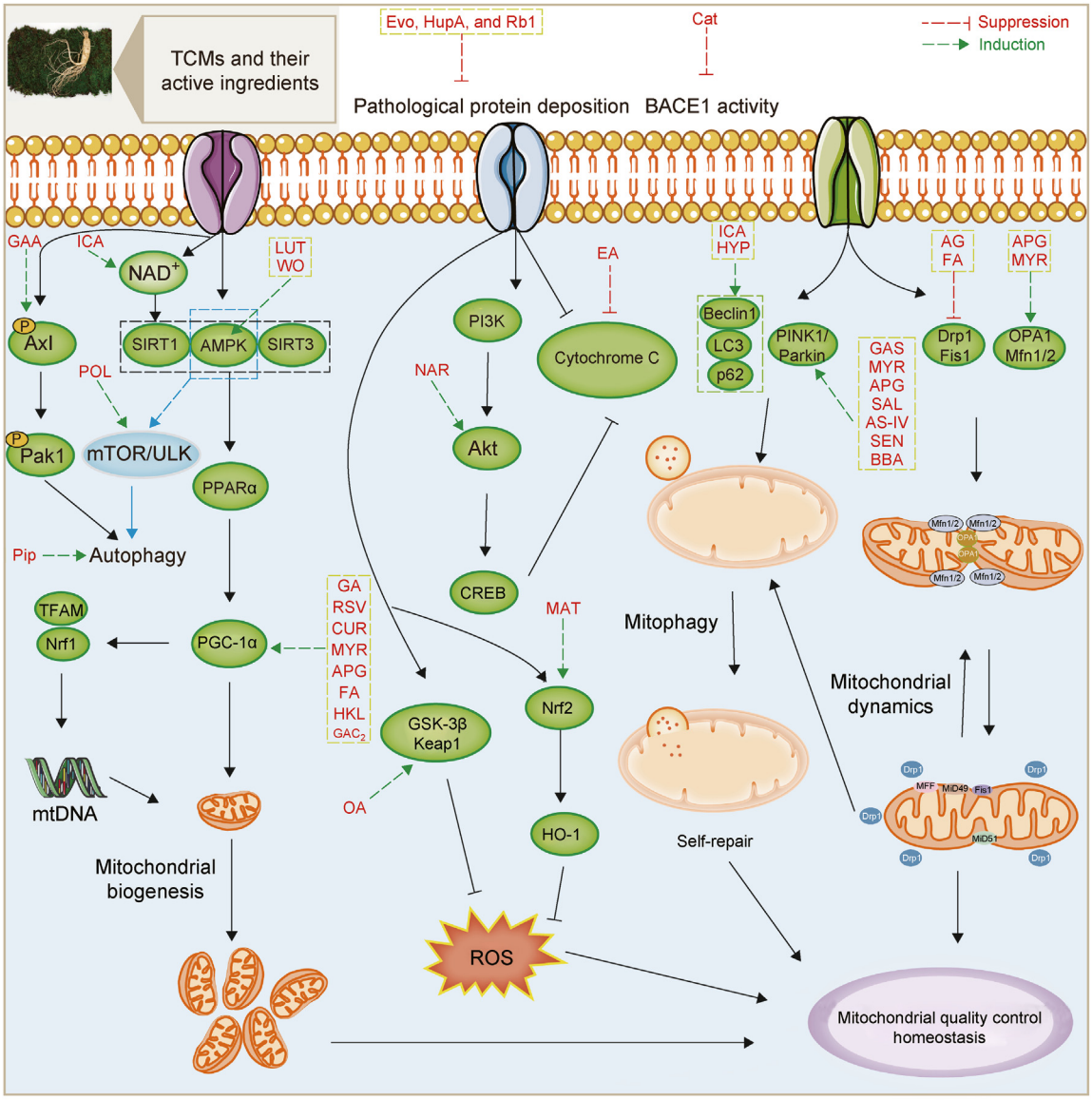

Fig. 4. Traditional Chinese medicine (TCM) active monomers target mitochondrial quality control (MQC) to treat neurodegenerative diseases (NDDs). Evo: evodiamine; HupA: huperzine A; Rb1: ginsenoside Rb1; Cat: catalpol; BACE1: β-site amyloid precursor protein cleaving enzyme 1; GAA: ganoderic acid A; ICA: icariin; NAD^+: nicotinamide adenine dinucleotide; LUT: luteolin; WO: wogonin; Axl: Axl receptor tyrosine kinase; SIRT1/3: sirtuin 1/3; AMPK: adenosine monophosphate (cAMP)-activated protein kinase; POL: polydatin; Pak1: p21-activated kinase 1; mTOR: mechanistic target of rapamycin; ULK: uncoordinated 51-like kinase; Pip: piperine; PPARα: peroxisome proliferator-activated receptor α; TFAM: mitochondrial transcription factor A; Nrf1: nuclear factor erythroid 2-related factor 1; PGC-1α: PPARγ coactivator 1-α; GA: glycyrrhizic acid; RSV: resveratrol; CUR: curcumin; MYR: myricetin; APG: apigenin; FA: ferulic acid; HKL: honokiol; GAC_2: ganoderic acid C_2; mtDNA: mitochondrial DNA; EA: ellagic acid; PI3K: phosphoinositide 3-kinase; NAR: naringenin; Akt: protein kinase B; CREB: cAMP response element-binding protein; MAT: matrine; GSK-3β: glycogen synthase kinase-3β; Keap1: Kelch-like ECH-associated protein 1; OA: oxyphylla A; HO-1: heme oxygenase-1; ROS: reactive oxygen species; HYP: hyperoside; LC3: microtubule-associated protein 1 light chain 3; p62: sequestosome 1; PINK1: phosphatase and tensin homolog (PTEN)-induced putative kinase 1; GAS: gastrodin; SAL: salidroside; AS-IV: astragaloside IV; SEN: senegenin; BBA: berberine; AG: andrographolide; Drp1: dynamin-related protein 1; Fis1: fission protein 1; OPA1: optic atrophy 1; Mfn1/2: mitofusin 1/2; MFF: mitochondrial fission factor; MiD49/51: mitochondrial dynamics proteins of 49/51.

Andrographolide, the principal diterpene lactone from *Andrographis herba*, has been demonstrated to offer neuroprotection across various NDDs models by regulating Drp1 to inhibit excessive mitochondrial fission [191].

4.2.4. Alkaloids

Berberine (BBA) is an isoquinoline alkaloid derived from *Andrographis herba*. Recent studies have demonstrated that BBA alleviated cognitive impairment and reduced AD pathology in APP/PS1 mice by restoring mitophagy mediated by the PINK1-Parkin pathway [192].

Evodiamine (Evo), a quinazolinone alkaloid extracted from *Euodia rutaecarpa*, is a candidate for AD treatment and has been clinically used for headaches, abdominal pain, dysentery, and postpartum hemorrhage. In AD mouse models induced by D-galactose and aluminum trichloride, Evo significantly enhanced mitochondrial function, improved AD-like behavior, and decreased $A\beta_{42}$ deposition in brain [193].

Matrine (MAT), a quinolizidine alkaloid from *Sophora flavescens*, inhibited oxidative damage to DA neurons in MPTP-induced PD models by promoting the Nrf2 signaling pathway [194]. Additionally, MAT has been shown to mitigate memory deficits in AD mice

through the Aβ/receptor for advanced glycation end products pathway [195].

Huperzine A, extracted from *Huperzia serrata*, acts as an AChE inhibitor and mitochondrial protector. Its mechanisms in AD involved in preserving mitochondrial function and reducing intracellular $A\beta_{42}$ levels [196].

Piperine (Pip), derived from *Piperis fructus*, is implicated in the early stages of PD, where α-synuclein/synuclein alpha (SNCA) abnormal deposition occurs in the olfactory bulb. Recent studies have demonstrated that Pip promoted autophagic flux through the macroautophagy/autophagy-lysosome pathway, facilitating α-synuclein degradation and delaying motor deficits in mice [197].

In summary, TCMs and their active compounds target MQC disruptions and cell death mechanisms, offering therapeutic potential against NDDs. Mitochondrial fission, fusion, mitophagy, and biogenesis emerge as promising therapeutic targets for addressing MQC disorders in NDDs through the use of TCMs.

5. Conclusions and future perspectives

NDDs present a significant challenge for both families and the global healthcare community. Current treatment strategies primarily focus on pharmacological and non-pharmacological interventions aimed at symptom relief and improving quality of life, with no curative options available. Mitochondria, as essential energy suppliers, play a pivotal role in regulating both physiological and pathological processes. Mitochondrial dysfunction is a key contributor to cellular injury and functional decline in numerous neurological disorders. The maintenance of mitochondrial function and structure governed by MQC. Disruptions in the balance of mitochondrial fission and fusion, impaired clearance of damaged or aged mitochondria, and suppression of mtDNA expression can contribute to MQC dysregulation, compromising mitochondrial integrity and function. The downregulation of mtDNA expression hampers the renewal and replenishment of mitochondria, leading to the accumulation of dysfunctional mitochondria, further damaging cellular structure and function, and ultimately causing neuronal death. This is characterized by reduced ATP production, decreased MMP, excessive production of mtROS, and increased mitochondrial fission, outcomes linked to impaired MQC. Consequently, targeting MQC mechanisms may represent a promising therapeutic strategy for these disorders.

In recent years, there has been a surge in studies exploring the potential of TCM to modulate MQC in the treatment of NDDs. Notably, many herbal medicines and their active compounds have shown therapeutic potential by promoting the clearance of damaged mitochondria and ameliorating abnormal mitochondrial fission. This review delves into the neuroprotective effects of TCM and its active monomers, which act through various molecular pathways to inhibit excessive mitochondrial fission, induce mitophagy or mitochondrial clearance, and upregulate of transcription factors to enhance mtDNA expression. These compounds target diverse mechanisms, providing valuable insights for the development of novel therapeutics in NDDs. Both *in vivo* and *in vitro* studies have demonstrated the significant impact of TCM on damaged neuronal cells, underscoring the potential of MQC-targeted therapies for NDD treatment.

Current research on targeting MQC in NDDs faces several limitations and challenges. First, while TCM monomers, such as flavonoids, phenolic compounds, terpenoids, and alkaloids, show considerable potential in preventing and treating NDDs, the majority of studies remain at the animal and cellular levels. To establish the efficacy and safety of MQC-targeted therapies for NDDs, real-world evidence and randomized controlled trials are critically needed. Additionally, the potential toxicity of TCM monomers on normal cells and their impact on normal MQC processes should not be overlooked, particularly when targeting MQC to treat or eliminate damaged neuronal cells. This issue requires further investigation in large-scale, multi-center studies. Another concern is the lack of comprehensive pharmacokinetic and toxicity data for many TCM monomers discussed in this review. Further research is necessary to evaluate the pharmacokinetic properties and toxicological profiles of these compounds in both target and non-target organs. Second, the pathogenesis of NDDs is highly complex, involving damage across multiple organs and systems. TCM and its formulations, known for their multi-target and multi-pathway effects, have been applied to NDDs, adding complexity to research efforts. The neuroprotective effects of TCM may result from modulating several MQC pathways, including the PINK1/Parkin/Drp1, Fis1/OPA1, Mfn1/2, and PGC-1α/Nrf2 signaling cascades. However, the mechanisms by which TCM formulations, often administered as decoctions, specifically target cells and organs *in vivo* remain unclear. Recent studies have suggested that the multiple components of TCM formulations may enhance the bioavailability and efficacy of one another through synergistic effects, providing neuroprotection. Nonetheless, a significant challenge is that TCM formulations may affect non-target organs while treating NDDs, potentially leading to side effects such as nausea and palpitations. Therefore, future research should focus on screening TCM components to identify those that can selectively target specific biomarkers. Moreover, the development of advanced drug delivery systems, such as nanocarriers based on MQC-targeting molecular docking, should aim to improve the precision of drug targeting, minimizing adverse effects on non-target organs while enhancing therapeutic efficacy in target tissues.

In brief, MQC plays a pivotal role in the molecular regulation of NDDs progression. This review highlights the potential of TCM and its active monomers in the prevention and treatment of NDDs through the modulation of MQC, providing a foundation for the future screening of novel therapeutic agents for NDDs.

CRediT authorship contribution statement

Lei Xu: Writing – review & editing, Writing – original draft, Investigation, Data curation. **Tao Zhang:** Writing – original draft. **Baojie Zhu:** Investigation, Data curation. **Honglin Tao:** Investigation, Data curation. **Yue Liu:** Supervision. **Xianfeng Liu:** Writing – review & editing. **Yi Zhang:** Writing – review & editing, Supervision, Resources, Funding acquisition. **Xianli Meng:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpha.2024.101146.

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