Am J Transl Res 2025;17(5):3703-3717
www.ajtr.org /ISSN:1943-8141/AJTR0164347

*Review Article*

# Acupuncture for neurodegenerative diseases: mechanisms, efficacy, and future research directions

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Received March 5, 2025; Accepted May 7, 2025; Epub May 15, 2025; Published May 30, 2025

**Abstract:** In recent years, acupuncture has shown good therapeutic efficacy in treating neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis. Studies have demonstrated that acupuncture alleviates symptoms primarily by suppressing neuroinflammation, enhancing autophagy, improving synaptic plasticity, and optimizing mitochondrial function. As molecular research advances, the underlying mechanisms of acupuncture in these conditions have become increasingly clear. This review summarizes recent progress in understanding the efficacy and molecular mechanisms of acupuncture in neurodegenerative diseases, providing a theoretical support for its clinical application.

**Keywords:** Acupuncture, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis

## Introduction

Neurodegenerative diseases are a heterogeneous group of neurological disorders characterized by the pathologic accumulation of insoluble filamentous aggregates derived from normally soluble proteins, leading to the progressive loss of neurons in the central nervous system (CNS). These diseases include Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), and Multiple sclerosis (MS), adversely affecting the lives of millions of people worldwide [1, 2]. Although current pharmacological treatments can alleviate some symptoms, their therapeutic effects are limited and often accompanied by severe side effects [3-5]. Therefore, exploring safe and effective nonpharmacological therapeutic approaches is of utmost importance.

Acupuncture, a traditional Chinese medical technique with a history of over 2000 years, has been widely used for treating various diseases [6]. It stimulates reflexes and activates peripheral nerves, which transmit sensory signals to the CNS, thereby modulating physiological processes [7]. Previous studies have demonstrated that acupuncture can regulate neurotransmitter levels, reduce inflammation, modulate oxidative stress, and maintain blood-brain barrier (BBB) integrity [8, 9]. Numerous clinical studies have reported its therapeutic efficacy in treating AD, PD, ALS, and MS, although the underlying mechanisms remain unclear [10, 11]. This review summarizes recent advances in mechanistic research on acupuncture for neurodegenerative diseases, providing new insight for their prevention and treatment.

## Alzheimer's disease

AD is characterized by the accumulation of amyloid-β (Aβ) plaques and neurofibrillary tangles, as well as neuroinflammation, oxidative stress, and cholinergic neuron dysfunction [12]. Its primary clinical features include progressive cognitive decline and behavioral anomalies [13, 14], which impose a substantial socioeconomic burden on healthcare systems worldwide [15]. While antibody drugs have shown potential to slow disease progression, their long-term efficacy and safety remain uncertain [16, 17].

https://doi.org/10.62347/QFJO6227

Acupuncture offers a safe and promising alternative, with demonstrated benefits in improving cognitive function of AD patients [18], particularly when used in combination with donepezil [19, 20]. Clinical evidence indicates that acupuncture exhibits a remarkable therapeutic effect on patients with mild to moderate AD [18, 21]. Nevertheless, its precise mechanisms of action require further exploration.

*Regulation of neuroinflammation*

Neuroinflammation plays a pivotal role in the pathologic progression of AD. Excessive activation of microglia and astrocytes leads to the release of pro-inflammatory cytokines (e.g., interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF-α)), inducing neuronal damage and resulting in cognitive dysfunction [22, 23]. Previous evidence has demonstrated that acupuncture at acupoints such as Baihui in AD model rats can inhibit the activation of microglia and astrocytes, promote M2 polarization of microglia, and exert anti-inflammatory effects by upregulating IL-4 and IL-10 while downregulating TNF-α, IL-1β, and IL-6 levels [24], as summarized in **Table 1**. Sphingosine-1-phosphate receptor 1 (S1PR1), expressed in astrocytes, microglia, and oligodendrocytes, serves as a key biomarker of neuroinflammation [25, 26]. Electroacupuncture at Baihui and Sishencong significantly improved cognitive and memory performance in transgenic (APP/PS1) mouse model of AD with reduced S1PR1 expression [27]. Moreover, NLRP3 inflammasome, predominantly expressed in microglia, is a crucial mediator of neuroinflammation [28, 29]. Electroacupuncture at Zusanli was found to suppress hippocampal microglial activation by inhibiting NLRP3 inflammasome signaling, thereby alleviating motor and cognitive impairments in 5 × FAD mice [30]. Electroacupuncture has also been shown to mitigate neuroinflammation and improve AD-related cognitive deficits by modulating key inflammatory signaling pathways, including TLR4/NF-κB/NLRP3 [31], JAK2/STAT3 [32], and TLR4/MyD88 [33] (**Figure 1**).

*Regulation of autophagy function*

Autophagy serves as a fundamental cellular process responsible for the degradation of damaged organelles, misfolded proteins, and metabolic waste [34]. The pathologic progression of AD is closely linked to autophagy dysfunction, which can result in the abnormal accumulation of Aβ and Tau proteins [35, 36]. Evidence suggests that activating autophagy can alleviate cognitive deficits and reduce amyloid burden in AD models [37]. The adenosine monophosphate-activated protein kinase/mammalian target of rapamycin (AMPK/mTOR) pathway plays a crucial role in regulating autophagy [38]. Guo et al. reported that electroacupuncture at Baihui and Shenshu improved cognitive function in AD mice by modulating the AMPK/mTOR signaling pathway [39]. This modulation led to increased autophagic activity and Aβ clearance, as evidenced by elevated levels of LC3-II, a key marker of autophagosomes.

Additionally, transcription factor EB (TFEB), a central regulator of autophagy, coordinates autophagosome formation and lysosomal biogenesis [40, 41]. Electroacupuncture stimulation at the Baihui and Yongquan acupoints was shown to upregulate nuclear TFEB expression, thereby enhancing lysosomal function and reducing Aβ deposition [42]. Similarly, electroacupuncture at Shenting and Benshen promoted TFEB nuclear translocation via suppression of the AKT-ERK-mTORC1 axis, thereby enhancing autophagic flux [43].

*Modulation of synaptic plasticity*

Synaptic plasticity refers to the activity-dependent modulation of synaptic strength, which is fundamental to learning and memory processes [44]. Impairments in synaptic plasticity are recognized as a vital pathogenic factor and hallmark feature of AD [44, 45]. Previous reports have shown that electroacupuncture stimulation at Baihui and Shenshu can enhance synaptic transmission and mitigate AD-induced memory deficits [46]. Synaptophysin (SYN), postsynaptic density protein 95 (PSD-95), and growth-associated protein 43 (GAP-43) are key proteins involved in synaptic plasticity, playing critical roles in learning and memory [47]. Electroacupuncture has been shown to upregulate SYN expression in the hippocampus of AD mice, thereby increasing synaptic vesicle numbers [48]. It also enhances synaptic transmission efficiency by elevating PSD-95 expression [49, 50]. Additionally, acupuncture can promote synaptic structural remodeling by upregulating GAP-43 expression [51], thereby mitigating AD-associated cognitive impairment.

**Table 1.** Mechanisms of acupuncture in treating neurodegenerative diseases in animal experimentss

| Animal model | Time (year) | Acupoints | Result | Signal pathway | References |
|---|---|---|---|---|---|
| AD model | 2024 | Baihui, Shenshu | Cognitive function↑, The neuron count↑, Aβ↓, LC3-II/LC3-I↑, ATG5↑, ATG7↑, p-AMPKα↑, p-AMPKβ1↑, p-mTOR↓, p-p70S6K↓ | AMPK/mTOR↑ | [39] |
| | 2024 | Baihui, Yongquan | Cognitive function↑, Aβ42↑, p-CTSD↑, TFEB↑, LAMP1 | - | [42] |
| | 2024 | Baihui, Shenshu | Cognitive function↑, GSK-3β↑, GAP-43↓ | - | [51] |
| | 2023 | Baihui, Shenting | Cognitive function↑, TGF-β1↓, Iba1↓, JAK2, STAT3↓, IFN-γ↓ | JAK2/STAT3 | [32] |
| | 2023 | Zusanli | Cognitive function↑, Iba1↓, NLRP3↓, IL-1β↓, IL-18↓, Aβ↓ | | [30] |
| | 2022 | Baihui, Dachangshu, Zusanli | Cognitive function↑, The number of Nissl bodies↑, TLR4↓, NF-kB p65↓, NLRP3↓, IL-1β↓, TNF-α↓ | TLR4/NF-kB/NLRP3↓ | [31] |
| | 2021 | Baihui | Cognitive function↑, Stat6↑, IL-4↑, 10↑, IL-6I↓, L-1β↓, TNF-α↓, Iba1↓, GFAP↓, p65 | NF-κB↓ | [24] |
| | 2021 | Baihui, Yintang, Shuigou | Cognitive function↑, TLR4↓, MyD88↓, NF-kB↓, iNOS↓, Iba1↓ | TLR4/MyD88↓ | [33] |
| | 2021 | Baihui, Dazhui, Shenshu | SYN↑, PSD-95↑ | - | [49] |
| | 2019 | Baihui, Dazhui, Shenshu | Cognitive function↑, SOCS3↑, JAK2↓, STAT3↓ | JAK2/STAT3↓ | [32] |
| | 2019 | Baihui, Dazhui, Shenshu | Cognitive function↑, SYN↑, PSD-95↑, p-AMPK↓, p-eEF2↓, p-eEF2K↓ | AMPK/eEF2K/eEF2↓ | [48] |
| PD model | 2024 | Fengfu, Taichong, Zusanli | Exercise function↑, TH↑, SIRT3↑, α-syn↓, NLRP3↓, GSDMD↓ | SIRT3/NLRP3/GSDMD | [74] |
| | 2024 | Taichong, Hegu, Baihui, Fengchi, Fengfu, Zusanli | Exercise function↑, TH↑, DA↑, α-syn↓ | IRE1/XBP1↑ | [75] |
| | 2024 | Fengfu, Taichong, Zusanli | Exercise function↑, TH↑, SIRT3↑, PINK1↑, Parkin↑, α-syn↓ | SIRT3/PINK1/Parkin↑ | [80] |
| | 2024 | Baihui, Quchi, Zusanli | Exercise function↑, GSH-Px↑, SOD↑, MDA↓, ROS↓, Nrf2↓ | - | [84] |
| | 2024 | Fengfu, Taichong, Zusanli | Exercise function↑, TH↑, BDNF↑, DAT↑, GDNF↑, NLRP3↓, IL-1β↓ | - | [93] |
| | 2023 | Tian Shu | Exercise function↑, TH↑ | - | [94] |
| | 2023 | Yanglingquan, Kunlun | Exercise function↑, TH↑, BDNF↑, pERK/ERK↑ | BDNF/ERK↑ | [76] |
| | 2022 | Fengfu, Taichong, Zusanli | Exercise function↑, TH↑, GLP-1R↑, p-PI3K↑, p-Akt↑ | GLP-1R/p-PI3K/p-Akt↑ | [73] |
| | 2022 | Yanglingquan | Exercise function↑, TH↑ | - | [86] |
| ALS model | 2024 | The Jiaji points at L1-L2 and L5-L6 of the lumbar region | Exercise function↑, Survival time↑, The number of Nissl bodies↑, Iba-1↓, TLR4↓, NF-κB↓, TNF-α↓ | TLR4/NF-κB↓ | [112] |
| | 2023 | Zusanli, Yanglingquan | Exercise function↑, The neuronal count↑, TDP-43↓, PPIA↓, NF-κB↓ | PPIA/NF-κB↓ | [111] |
| | 2021 | Zusanli, Quchi | Exercise function↑, SOD1↑, GSH-Px↑, Bcl-2↑, IBax↓ | - | [113] |
| MS model | 2020 | Baihui, Zhiyang | MBP↑, Axl↑, Iba-1↑, Olig2↑, Myelin debris↓ | - | [125] |
| | 2020 | Dazhui, Shenshu, Zusanli | body weight↑, Neurological functional scoring↓, Extent of demyelination↓, p-p38MAPK↓ | - | [124] |
| | 2019 | Dazhui, Shenshu, Zusanli | Neurological functional scoring↓, TNF-α↓, COX-2↓, Iba-1↓ | - | [123] |

Note: ↑ represents promotion and enhancement, while ↓ represents inhibition and reduction.

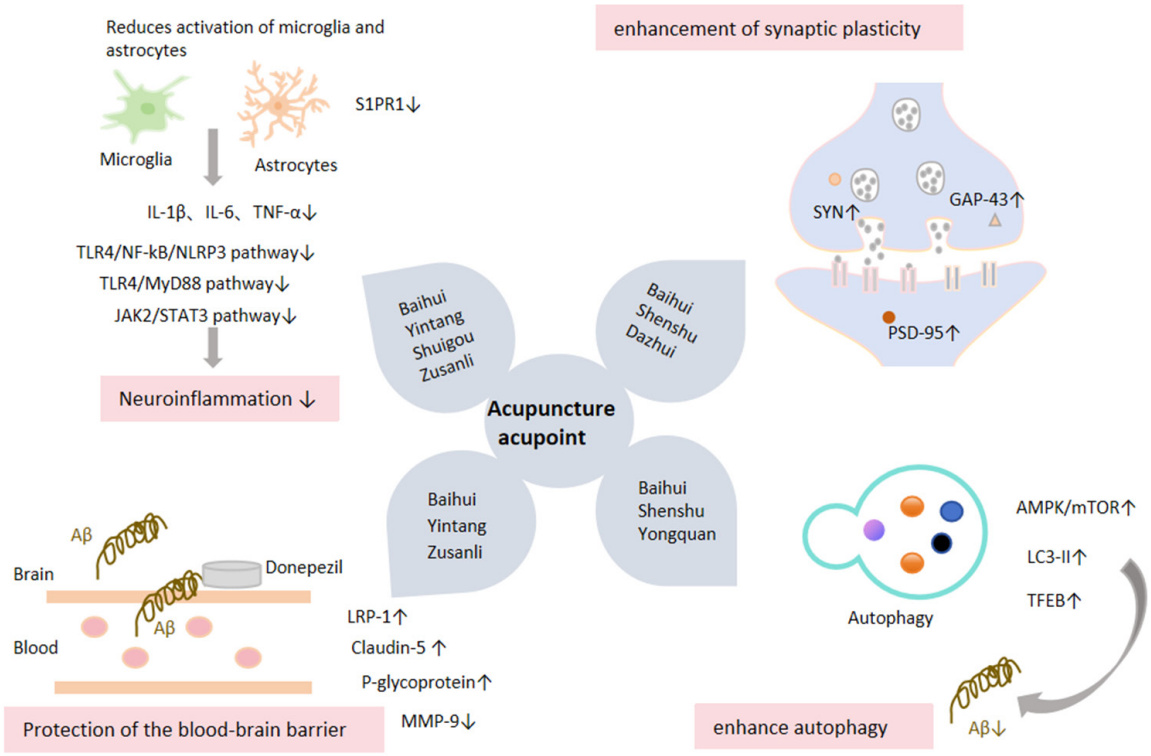


**Figure 1.** Mechanism of acupuncture in the treatment of Alzheimer's disease.

Neurotransmitters are essential mediators of synaptic transmission [52]. In AD, the levels of monoamine neurotransmitters, such as 5-hydroxytryptamine (5-HT), noradrenaline (NA), and dopamine (DA), are significantly reduced [53, 54]. Acupuncture has been shown to significantly improve memory function in dementia models by modulating these neurotransmitter levels [55]. Moreover, the loss of cholinergic neurons and reduced acetylcholine (ACh) levels are major contributor to cognitive decline in AD [56, 57]. Acupuncture may enhance ACh levels by promoting its synthesis and inhibiting acetylcholinesterase (AChE) activity, thereby improving memory in AD rats [58].

*Protection of the blood-brain barrier*

BBB dysfunction is an early event in the pathogenesis of AD, occurring even before the appearance of hallmark pathologic changes and clinical symptoms [59, 60]. BBBB disruption impairs bidirectional molecular transport, compromising cerebral nutrient supply while obstructing Aβ efflux. Simultaneously, increased permeability allows infiltration of plasma-derived proteins, microbial pathogens, and peripheral immune cell diapedisis, all of which contribute to the exacerbation of neuroinflammatory pathogenesis [61-63]. Studies have shown that acupuncture at Baihui, Yintang, and Zusanli can regulate gut microbiota to reduce levels of TNF-α and IL-1β, thereby preventing harmful substances from crossing the BBB, preserving BBB integrity and preventing further aggravation of neuroinflammation [64, 65]. Additionally, electroacupuncture at Baihui and Yintang has been reported to enhance the effectiveness of Donepezil in improving learning and memory abilities in AD mice, potentially by modulating the expression of MMP-9, LRP-1, P-glycoprotein, and Claudin-5 mRNAs, and by reinforcing Donepezil's role in transporting Aβ across the BBB [66].

In short, acupuncture significantly alleviates neuroinflammation by suppressing excessive activation of microglia and astrocytes by regulating inflammation-related signaling pathways like TLR4/NF-κB/NLRP3. It enhances autophagic function and facilitates the clearance of Aβ by regulating autophagy-related signaling pathways, and improves cognitive function by enhancing synaptic plasticity and preserving

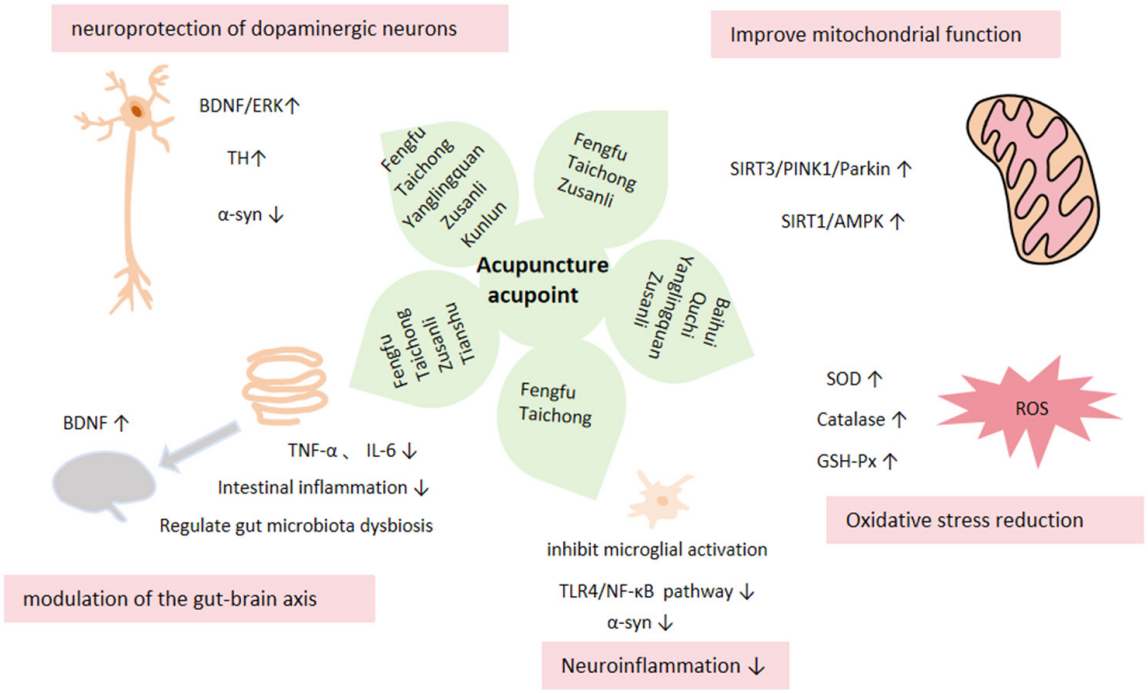


**Figure 2.** Mechanism of acupuncture in the treatment of Parkinson's disease.

BBB integrity. Targeting molecules that regulate these pathology-related pathways of AD may offer promising therapeutic strategies for the prevention and treatment of AD.

## Parkinson's disease

PD is clinically characterized by bradykinesia, muscular rigidity, resting tremor, and postural instability [67]. Although its exact pathogenic mechanism remains incompletely understood, factors such as mitochondrial dysfunction, oxidative stress, protein misfolding, and neuroinflammation are widely regarded as major contributors to disease onset and progression. The hallmark pathologic feature of PD is the progressive degeneration and loss of dopaminergic neurons in the substantia nigra [68]. In recent years, numerous clinical studies have indicated that acupuncture significantly alleviates both motor and non-motor symptoms in PD patients. A prospective randomized controlled trial revealed that after three weeks of electroacupuncture treatment, the gait function of PD patients improved significantly [69]. In addition, acupuncture has been shown to mitigate the neuropsychiatric symptoms (e.g., depression and anxiety), enhance cognitive function and improve the quality of life [10]. Notably, acupuncture has demonstrated sustained efficacy in improving sleep quality in PD patients [70]. Acupuncture therapy has also yielded remarkable effects in improving gastrointestinal symptoms commonly associated with PD, such as constipation [71]. Accumulating preclinical studies have begun to elucidate the potential mechanisms of acupuncture in the treatment of PD, indicating its ability to modulate multiple pathways involved in disease progression.

### *Protection of dopaminergic neurons*

The hallmark pathological feature of PD is the progressive loss of dopaminergic neurons in the substantia nigra and the reduction of dopamine (DA) levels [67]. Tyrosine hydroxylase (TH) serves as a marker for dopaminergic neurons [72]. Research has revealed that acupuncture at Fengfu, Taichong, and Zusanli in PD model rats can mitigate neuronal injury by upregulating TH expression [73] and reducing alpha-synuclein (α-syn) aggregation [74, 75]. Furthermore, acupuncture can activate the BDNF/ERK signaling pathway, promote neurogenesis, and enhance neuronal survival [76] (**Figure 2**). Additionally, acupuncture at Yanglingquan has been shown to improve motor function in PD

model mice by modulating hypothalamic neural circuit [77].

*Improvement of mitochondrial function*

Mitochondrial dysfunction is a key contributor to pathogenesis of PD [78]. Acupuncture has demonstrated notable efficacy in improving mitochondrial function by enhancing oxidative phosphorylation and regulating mitochondrial protein expression, thereby reducing oxidative stress-induced neuronal damage [79]. Mitophagy, the selective degradation of damaged mitochondria, is essential for mitochondrial quality control. Studies have shown that acupuncture at Fengfu, Taichong, and Zusanli acupoints activates the SIRT3/PINK1/Parkin signaling pathway, thereby promoting mitophagy, reducing α-synuclein (α-syn) aggregation, and protecting neuronal integrity [80]. Additionally, acupuncture improves mitochondrial quality by activating he SIRT1/AMPK signaling pathway, which facilitates the clearance of dysfunctional mitochondria and mitigates mitochondrial dysfunction [81].

*Regulation of oxidative stress and neuroinflammation*

Oxidative stress plays a pivotal role in the pathogenesis of PD, where excessive reactive oxygen species (ROS) and free radicals can induce neuronal damage [82, 83]. Acupuncture modulates the antioxidant system, thereby reducing oxidative stress and protecting dopaminergic neurons [84]. Research has demonstrated that acupuncture at Yanglingquan increased the activity of superoxide dismutase (SOD) and catalase (CAT), which in turn alleviates oxidative stress-induced damage [85, 86]. Electroacupuncture at Baihui, Quchi, and Zusanli acupoints has been shown to reduce lipid peroxidation, increase the activity of SOD and glutathione peroxidase (GSH-Px), and help maintain a balance in oxidative stress within the brain [84]. In addition to mitigating oxidative stress, acupuncture also effectively modulates neuroinflammation. In PD model rats, stimulation of Fengfu and Taichong acupoints regulates the TLR4/NF-κB signaling pathway, inhibits the sustained activation of microglia, decreases pro-inflammatory cytokines (TNF-α and IL-6), and reduces α-syn aggregation, ultimately attenuating neuroinflammation-mediated neuronal damage [87].

*Regulation of the brain-gut axis*

The brain-gut axis has recently emerged as a critical player in the onset of PD [88]. Dysbiosis of the gut microbiota is closely associated with the occurrence and progression of PD, with the brain-gut axis mediating bidirectional communication via neural, immune, and endocrine systems [89]. Notably, gastrointestinal symptoms (e.g., constipation) in PD patients often precede neurodegenerative alterations, suggesting that gut abnormalities may serve as early indicators of PD [90]. Acupuncture exhibits distinctive regulatory functions on the brain-gut axis [91, 92]. For example, electroacupuncture at Fengfu, Taichong, and Zusanli reduces intestinal goblet cell loss and inflammatory infiltration, upregulates the expression of brain-derived neurotrophic factor (BDNF), and enhances the motor function of PD mice [93]. Similarly, electroacupuncture at Tianshu alleviates gut microbiota dysbiosis and intestinal inflammation, not only ameliorating intestinal symptoms but also possibly slowing PD progression [94].

In summary, acupuncture demonstrates multifaceted therapeutic potential in PD treatment. It not only protects dopaminergic neurons, enhances mitochondrial function, and mitigates oxidative stress and neuroinflammation, but also ameliorates motor and non-motor symptoms via brain-gut axis modulation. Nevertheless, further clinical studies are needed to evaluate acupuncture's long-term efficacy and its systemic effects on PD symptoms.

**Amyotrophic lateral sclerosis**

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder primarily characterized by progressive degeneration of both upper and lower motor neurons, resulting in muscle weakness, atrophy, and impaired speech, swallowing, and respiratory functions [95]. ALS patients often present non-motor symptoms including depression, anxiety, and cognitive impairment, yet these symptoms are frequently overlooked in clinical assessments [96]. As the disease progresses, patients experience significant declines in daily functioning, communication abilities, and self-care capacity, severely impacting the quality of life and imposing a substantial psychological and economic burden on the family [97]. The pathogenesis of ALS is com-

plex, involving the interactions among genetic mutations, mitochondrial dysfunction, neuroinflammation, and oxidative stress [98, 99]. Current therapeutic options remain limited, focusing primarily on symptom management and quality-of-life improvement. The two main drugs include riluzole and edaravone [100, 101], demonstrating modest efficacy and are frequently associated with adverse effects such as vomiting, diarrhea and dizziness [101, 102]. Growing evidence suggests acupuncture may serve as an alternative therapy in the treatment of ALS. Clinical studies report potential benefits in symptom relief and quality-of-life enhancement [103-105]. For example, a 55-year-old female ALS patient experienced significant improvement in muscle strength and quality of life after 16 weeks of acupuncture treatment [104]. Another 51-year-old male patient demonstrated obvious improvement in ALS functional scores, particularly in speech and respiratory functions, after 8 months of combined electroacupuncture and TCM treatment [106]. A randomized controlled trial further revealed that two weeks of acupuncture combined with rehabilitation therapy significantly improved clinical symptoms in ALS patients while reducing inflammatory marker levels [107]. These findings suggest acupuncture's therapeutic mechanisms may involve neuromodulation, anti-inflammatory effects, and improved microcirculation.

*Alleviation of neuroinflammation*

Animal experiments have indicated that acupuncture improves motor function in ALS model mice by modulating neuroinflammatory responses [108, 109]. For example, acupuncture at Baihui, Tianzhu, and Tianshu enhanced motor performance in ALS mice, accompanied by reduced serum levels of MCP-1 and TNF-α, downregulated cortical expression of Iba-1, HMGB1, and RhoA proteins, and decreased TDP-43 positive cell rate, suggesting that acupuncture may alleviate neuroinflammation by influencing the HMGB1/RhoA signaling pathway [110]. Additionally, stimulation of Yanglingquan and Zusanli acupoints reduced neuroinflammation and improved motor function in ALS mice through the PPIA/NF-κB signaling pathway [111]. Early electroacupuncture intervention at Jiaji acupoints postponed disease onset and extended survival in ALS mice, possibly through TLR4/NF-κB pathway inhibition, microglia activation suppression, inflammatory cytokine reduction, and motor neuron protection [112].

*Antioxidant stress and neuroprotective effects*

Acupuncture exerts neuroprotective effects in ALS models through antioxidant and anti-apoptotic mechanisms. For instance, acupuncture at Zusanli and Quchi enhances antioxidant enzyme activity, reduced Bax protein expression, and upregulated Bcl-2 levels, thereby significantly improving body weight and motor function in ALS model mice [113]. In the ALS mouse model, electroacupuncture improved the sciatic functional index (SFI), muscle atrophy, muscle structure, and acetylcholinesterase (AChE) expression. These effects facilitate the repair and regeneration of neuromuscular junctions (NMJs) [114].

The mechanisms underlying acupuncture in the treatment of ALS include inhibiting neuroinflammation, counteracting oxidative stress, reducing neuronal cell loss, and enhancing motor function, thereby delaying disease progression. Nevertheless, its long-term efficacy still requires further validation in both basic experiments and clinical studies.

**Multiple sclerosis**

Multiple sclerosis (MS) is a chronic immune-mediated neurodegenerative disease characterized by demyelinating lesions in the central nervous system, with both genetic and environmental contributions to its pathogenesis [115]. The disease typically manifests as motor, sensory, and cognitive impairments that seriously affect their quality of life [116]. Current mainstream therapies (immunomodulators and immunosuppressants) demonstrate limited efficacy and carry risks of complications such as an increased risk of infection [117]. Growing evidence supports acupuncture as a valuable adjunct therapy for MS management. A systematic review confirmed acupuncture's efficacy in reducing fatigue and improving quality of life [118]. Acupuncture treatment can also alleviate pain, gait disorders, and bladder dysfunction in MS patients, and even reduce disease relapses [119, 120]. For example, in a study by Karpatkin et al., they reported significantly improved upper limb strength in MS patients

after 4-weeks of acupuncture treatment [121]. Another study revealed that after acupuncture at Liangqiu, Weizhong, and Chengshan acupoints, the T25FW gait test performance was improved significantly, suggesting that acupuncture might be an effective therapy for gait disorders in MS patients [122].

Animal studies have shown that acupuncture at Dazhui, Zusanli, and Shenshu in mice with autoimmune encephalomyelitis significantly reduced the expression of p-p38MAPK in the brain tissues, decreased the levels of COX-2 and IBA-1 in the spinal cord, and attenuated demyelination severity in mice with multiple sclerosis (MS) [123, 124]. Another investigation on demyelination mouse model indicated that electroacupuncture at Baihui and Zhiyang acupoints could upregulate the expression of myelin basic protein (MBP), Iba-1, and tyrosine kinase (Axl) receptor in the first five days, accelerate the clearance of myelin debris, and facilitate myelin regeneration and repair; on day 10, these indicators gradually declined and returned to normal levels by day 21 [125].

These findings reveal acupuncture's bidirectional immunomodulatory capacity. When a considerable amount of myelin debris is generated, acupuncture can regulate the immune system, activate microglia to exert a phagocytic role, expedite the clearance of myelin debris, and facilitate myelin regeneration. When inflammatory infiltration aggravates, acupuncture can also inhibit the excessive activation of microglia and modulate the immune balance. In conclusion, the candidate mechanisms of acupuncture in the treatment of MS include immune regulation, attenuation of inflammatory responses, and promotion of myelin regeneration and repair. Nevertheless, more experimental research is requisite to further validate its specific mechanisms of action.

### Acupuncture for other neurodegenerative diseases

Beyond the previously discussed disorders, evidence suggests potential therapeutic applications of acupuncture for other neurodegenerative conditions including Huntington's disease (HD), frontotemporal dementia (FTD), multiple system atrophy (MSA), and spinal muscular atrophy (SMA). While these diseases exhibit distinct pathophysiologic mechanisms and clinical presentations, acupuncture has been proposed as a therapeutic option for neurodegenerative diseases such as HD, FTD, MSA, SMA. Mechanisms are speculated to involve modulation of neurotransmitter systems, neuroinflammation, and neuroprotection. Acupuncture may influence neurotransmitter release, such as dopamine in HD, which could alleviate motor symptoms, or serotonin and norepinephrine in FTD, possibly addressing behavioral and cognitive disturbances. Additionally, acupuncture may promote neuroplasticity, enhance cerebral circulation, and reduce oxidative stress, which are important factors in slowing disease progression and improving neuronal function [126].

However, despite these promising theoretical mechanisms, there is insufficient clinical and basic research to conclusively support acupuncture as an effective treatment for these diseases. Current studies have been limited in sample size, methodological rigor, and clinical application. High-quality, large-scale clinical trials are necessary to provide robust evidence regarding the efficacy and safety of acupuncture in the treatment of HD, FTD, MSA, and SMA. Further research will help determine the precise mechanisms of acupuncture and its potential as an adjunctive therapy in these challenging neurodegenerative conditions.

## Discussion

Acupuncture has emerged as a promising complementary therapy for AD, PD, ALS, and MS. Recent studies reveals that the acupuncture exerts its therapeutic effects through multimodal mechanisms, including regulating neuroinflammation, oxidative stress, autophagy, synaptic plasticity, the brain-gut axis, and protecting the blood-brain barrier. Acupuncture exhibits remarkable multi-target regulatory capabilities, ameliorating patients' cognitive and motor functions as well as non-motor symptoms through diverse signaling pathways. In AD, acupuncture mainly improves cognitive function by regulating neuroinflammation, autophagy, synaptic plasticity, and safeguarding the blood-brain barrier; in PD, acupuncture improves motor and non-motor symptoms by protecting dopaminergic neurons, regulating mitochondrial function, counteracting oxidative stress, and modulating the brain-gut axis; in

the treatment of ALS, acupuncture protects motor neurons by anti-inflammation and anti-oxidative stress, alleviating symptoms; in MS, acupuncture reduces demyelination and improves clinical manifestations through anti-inflammation and immunomodulation.

Across these neurodegenerative conditions, acupuncture demonstrates four fundamental neuroprotective mechanisms. First, acupuncture helps reduce excessive microglial activation, inhibit the release of pro-inflammatory factors like TNF-α and IL-1β, and minimize neuronal damage. Second, acupuncture can alleviate neuronal damage by regulating the oxidative stress response, a mechanism that is particularly significant in PD and ALS. Third, the neuroprotective role of acupuncture in various neurodegenerative diseases is manifested as promoting neuronal survival, increasing neurotrophic factors (such as BDNF), and enhancing neuronal function, all of which are of vital importance for the treatment of AD, PD, ALS, and MS. Additionally, in the treatment of AD and PD, acupuncture improves motor and cognitive functions by regulating the balance of neurotransmitters (such as dopamine and acetylcholine).

Significant progress has been made in research of acupuncture for neurodegenerative diseases; however, there remain several challenges. One such challenge is the multi-target mechanism of acupuncture, which adds to its complexity of. For instance, acupuncture at Baihui can modulate both the IL-4/Stat6 and NF-κB pathways to mitigate neuroinflammation in AD [24], and regulating oxidative stress to protect dopaminergic neurons in PD [84]. Acupuncture at Zusanli plays a role in the treatment of AD, PD, ALS by alleviating neuroinflammation, regulating oxidative stress and enhancing mitochondrial autophagy through TLR4/NF-κB/NLRP3 [31], SIRT3/PINK1/Parkin [80], PPIA/NF-κB [111], and other signaling pathways. The mechanisms to identify the key regulatory pathways within these mechanisms still require further investigation.

Future studies should prioritize molecular mechanisms of acupuncture in regulating inflammation, oxidative stress, autophagy and synaptic plasticity, and clarify the interactions between each signaling pathway and acupuncture therapy. This will be conducive to clarifying its application potential in diverse diseases. By incorporating multi-omics techniques (such as genomics, proteomics and metabolomics, single-cell sequencing, and spatial transcriptomics), electrophysiological methods (such as patch clamp technique) and imaging technologies (such as PET-MRI), the multi-level regulatory mechanisms of acupuncture on the nervous system can be further disclosed, facilitating the individualized and precise development of acupuncture treatment. Conducting large-scale, multi-center, randomized, controlled, and double-blind clinical trials will be helpful in assessing the long-term therapeutic efficacy of acupuncture in AD, PD, ALS and MS. In summary, acupuncture, as a significant adjunctive therapeutic approach for neurodegenerative diseases, holds the potential to modulate multiple pathological mechanisms. Future in-depth investigations are anticipated to offer more compelling evidence-based support for acupuncture treatment, and promote clinical use.

## Disclosure of conflict of interest

None.

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