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Review Article

Effects of Acupuncture on Oxidative Stress Amelioration via Nrf2/ARE-Related Pathways in Alzheimer and Parkinson Diseases

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Oxidative stress is responsible for the pathogeneses of various diseases. Mitochondrial dysfunction, impaired DNA repair, and cellular damage followed by oxidative stress contribute to neurodegenerative diseases, such as Alzheimer disease (AD) and Parkinson disease (PD). Acupuncture is a traditional therapy that has been practiced for >3000 years in Asia. Many studies have demonstrated that acupuncture has notable antioxidative, anti-inflammatory, and antiapoptotic effects. However, the exact mechanism remains unclear. Nuclear factor erythroid 2-related factor (Nrf2) is crucial in regulating the redox equilibrium. Activated Nfr2 translocates into the nucleus, binds to the antioxidant response element (ARE), and initiates antioxidative enzyme transcription. In this review, we demonstrated the effects of acupuncture on oxidative stress amelioration in AD and PD animal models through Nrf2/ARE pathway activation and Nrf2/ARE-related pathway regulation. Thus, acupuncture could be a therapeutic option for AD and PD.

1. Introduction

Oxidative stress is defined as the imbalance between reactive oxygen species (ROS)/reactive nitrogen species (RNS) and antioxidant defense system [1]. ROS, such as hydrogen peroxide (H_2O_2), superoxide radical ($O_2^{\bullet-}$), and hydroxyl radical ($^{\bullet}OH$) [2], have a single unpaired electron in their outermost shell [3]. $O_2^{\bullet-}$ can react with nitric oxide to generate peroxynitrite, a highly active RNS, and cause significant damage to intracellular components [4]. The highly reactive ROS/RNS readily interact with biomolecules to initiate a cascade of events, leading to mitochondrial dysfunction, impaired DNA repair, and cellular damage [5]—eventually contributing to the pathogeneses of neurodegenerative diseases [6].

Antioxidant enzymes, such as heme oxygenase (HO) 1), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT), glutathione-*S*-transferase, and nicotinamide adenine dinucleotide phosphate (NAD(P)H) dehydrogenase [quinone] 1 (NQO1), can quench excess free radicals or facilitate a combination of free radicals with other molecules [7]. The endogenous antioxidant defense system is mainly regulated by nuclear factor erythroid 2-related factor 2 (Nrf2), one of the most important transcription factors in regulating redox equilibrium. Nrf2 can enhance the expression of downstream antioxidant genes by binding to the antioxidant response element (ARE) [8]. In addition to having an antioxidative effect, Nrf2 can modulate mitochondrial metabolic functions and protect cells from apoptosis caused by oxidative stress [9].

The brain, a complex organ containing >100 billion neurons, is susceptible to oxidative stress owing to its high oxygen consumption and lipid-rich content [10]. Neurodegenerative diseases, including Alzheimer disease (AD), Parkinson disease (PD), and Huntington disease, are caused by progressive neuron degeneration. The pathophysiologies of these diseases are complicated and warrant further clarification. Nevertheless, genetic and environmental

factors are considered to be strongly associated with neurodegenerative disease initiation [11].

Acupuncture, based on the meridian theory of traditional Chinese medicine, has been practiced for >3000 years in Asia. Over time, acupuncture has evolved into several types, including manual acupuncture, electroacupuncture (EA), and laser acupuncture (LA). In manual acupuncture, medical professionals use thin and sterile metal needles to penetrate stimulation points (i.e., acupoints) on the body and manipulate the needle to achieve a state of "de-qi." EA combines electric stimulation and acupuncture to improve the effectiveness of acupuncture. LA, a novel form of acupuncture, uses low-intensity laser to stimulate acupoints. Many studies have demonstrated the antioxidative, anti-inflammatory, and anti-apoptotic effects of acupuncture in treating diseases [12]. However, few reviews have focused on the relationship between the effects of acupuncture and redox biology. Herein, we provide an overview of several pathways in oxidative stress regulation related to acupuncture in AD and PD.

2. Materials and Methods

We searched the PubMed, ClinicalKey, and Cochrane Library databases for eligible studies published from database inception to June 2020 by using Medical Subject Headings keywords alone or in combination: "acupuncture," "Alzheimer's disease," "Parkinson's disease," "oxidative damage," "oxidative stress," and "Nrf2." The search was limited to only English-language articles. First, the search yielded 1914 articles. After manual screening, we excluded 1771 articles including those without abstracts or with abstracts lacking the terms "oxidative stress" or "acupuncture" and obtained 143 articles for further screening. Next, we excluded 64 articles, including those with unavailable full text, those identical to articles from other databases, or those lacking the terms "oxidative stress" or "acupuncture" in the main text; we also added one article identified from the references cited in a selected article. Finally, 80 articles were included in the review. The flow of the search process is shown in Figure 1.

3. Results and Discussion

3.1. Nrf2/ARE-Related Signaling Pathways in Oxidative Stress. Nrf2, belonging to the leucine zipper transcription factor family, is a crucial transcription factor in regulating redox equilibrium. Nrf2 consists of seven functional domains, spanning from Nrf2-ECH homology (Neh) 1 to Neh7 : Neh1 allows Nrf2 binding to DNA in the nucleus; Neh2 promotes Nrf2 binding to kelch-like ECH-associated protein 1 (Keap1, which is responsible for Nrf2 ubiquitination and degradation in cytosol) [13, 14]; Neh3–Neh5 are associated with the activation of ARE genes and transcriptional coactivators; Neh6 is a serine-rich region regulated by glycogen synthase kinase (GSK) 3β, which can phosphorylate specific residues in Neh6 and thus induce nuclear export and proteasome degradation functions of Nrf2 [15]; and finally, Neh7 binds to the retinoid acid receptor alpha and represses Nrf2 activity. Under homeostatic conditions, Nrf2 is predominantly present in the cytosol and binds to Keap1. Keap1 acts as an adaptor protein for cullin-3/RING box protein 1-dependent E3 ubiquitin ligase complex and further promotes ubiquitination and degradation of Nrf2 [16]. On exposure to oxidative stress, the Keap1 structure changes, allowing Nrf2 to detach from Keap1 and translocate into the nucleus. After translocation into the nucleus, Nrf2 binds to ARE and enhances downstream antioxidant gene expression to maintain the redox balance in cells [17]. The Nrf2 nuclear translocation and ARE transactivation processes are regulated by multiple pathways including protein kinase C (PKC), phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt)/GSK-3β, p38 mitogen-activated protein kinase (MAPK), and nuclear factor kappa B (NF-κB).

3.1.1. PKC. PKC isozymes belong to the serine/threonine kinase family and are highly associated with cell apoptosis and autophagy. The alternation of PKC activities contributes to the progression of several neurodegenerative diseases [18, 19]. PKCs can phosphorylate Nrf2 at Ser40, which lies in Neh2, and further promote the dissociation of Nrf2 from Keap1 and nuclear translocation [20]. However, Nrf2 stabilization and accumulation in the nucleus are dependent on cellular Src activation, which is induced by H_2O_2 and regulated by PKCδ phosphorylation at Tyr311 [21].

3.2. PI3K/Akt/GSK-3β. The PI3K/Akt pathway, essential in cell growth, survival, differentiation, and metabolism, is necessary for neuroprotection against oxidative damage [1]. This pathway is typically activated by trophic factors such as nerve growth factor or brain-derived neurotrophic factor (BDNF) [22]. BDNF, a neurotrophin, is essential for inducing the nuclear translocation of Nrf2. In a recent study [23], incubating hippocampal neurons of rats with BDNF (50 ng/mL) for 6 h was noted to significantly enhance Nrf2 nuclear translocation. However, this effect disappeared when PI3K was blocked. These results suggest that BDNF can promote Nrf2 nuclear translocation via the PI3K pathway. Another study [24] reported that cortical and hippocampal BDNF levels decreased in $Nrf2^{-/-}$ mice, indicating that Nrf2 is also crucial in BDNF expression regulation. Moreover, when BDNF binds to tropomyosin-related kinase receptor type B (TrkB.T1), p75 neurotrophin receptor ($p75^{NTR}$) is not inhibited, and ceramide can be generated with $p75^{NTR}$. At low levels, ceramide can activate PKCζ, further activating casein kinase 2 [25]—which is crucial for nuclear translocation and transcription activation of Nrf2 [26].

PI3K/Akt pathway activation can cause inhibitory phosphorylation of GSK-3β. As a negative regulator of Nrf2, GSK-3β enhances nuclear export and Nrf2 degradation via both direct and indirect pathways. In the direct pathway, GSK-3β phosphorylates the specific residues in the Neh6 domain of Nrf2, targeting it for degradation through SCFβ/TrCP, whereas in the indirect pathway, GSK-3β promotes Src kinase accumulation in the nucleus and further results in

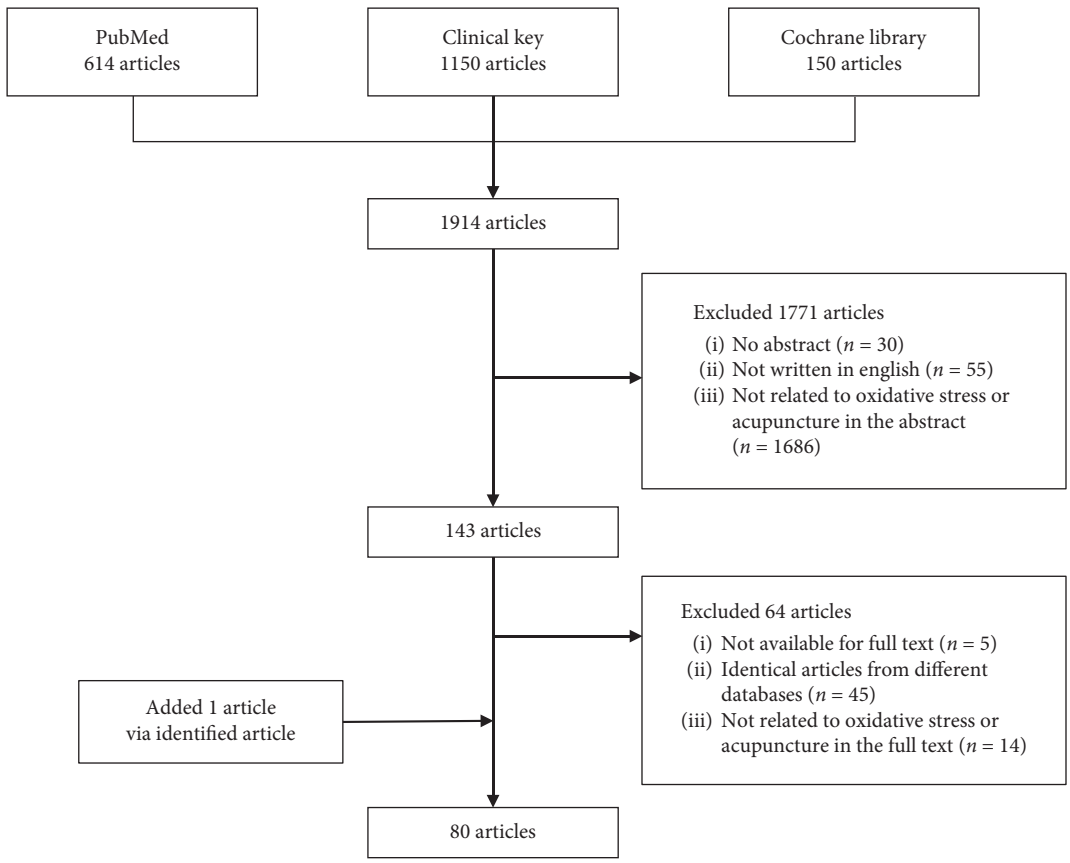

Figure 1: Flow of the search process.

Nrf2 phosphorylation at Tyr568, leading to Nrf2 nuclear export and degradation [27, 28].

3.2.1. p38 MAPK. MAPK belongs to the silk proteins/threonine kinase family. One of the most studied subpathways of MAPK is p38 MAPK, which plays a crucial role in cell growth, apoptosis, and inflammation. p38 MAPK promotes an association between Nrf2 and Keap1 and limits the nuclear accumulation of Nrf2 in the human hepatoma cell line HepG2 [29]. However, Jung et al. [30] demonstrated that p38 MAPK inhibition significantly decreases the binding of the nuclear proteins to ARE and ARE-mediated transcriptional activity in C2 ceramide-treated astrocytes cells, indicating that p38 MAPK activation is crucial for activating the ARE-related antioxidative effects. Thus, p38 MAPK has a dual characteristic in regulating neurological diseases: neurotoxicity induction in the acute phase and neuroprotective antiapoptotic effect promotion in the subacute phase [31].

3.2.2. NF-κB. In addition to Nrf2, NF-κB is another key transcription factor regulating cellular responses to oxidative stress [32]. However, the effects of Nrf2 and NF-κB are completely contradictory. Oxidative stress promotes NF-κB inhibitor (IκB) phosphorylation and degradation and further enhances NF-κB release and nuclear translocation. After translocation into the nucleus, NF-κB binds to DNA and initiates the transcription of proinflammatory cytokines, such as interleukins 1 and 6, tumor necrosis factor (TNF) α, and inducible nitric oxide synthase [8]. The proinflammatory molecules further enhance oxidative stress in the cell, forming a vicious cycle.

Nrf2, which exhibits a notable ability of maintaining redox equilibrium, can inhibit NF-κB pathway activation in two modes: (1) reducing ROS levels by increasing the levels of transcription and releasing antioxidative enzymes and (2) reducing NF-κB nuclear translocation by preventing IκB degradation [33]. By contrast, NF-κB can also inhibit the antioxidative effect of Nrf2 by blocking the ARE region and thus preventing ARE gene transcription [8]. In other words, NF-κB and Nrf2 are redox-regulated transcription factors that can interfere with one another.

The Nrf2/ARE-related signal transduction pathways are illustrated in Figure 2.

3.3. Effect of Acupuncture on Oxidative Stress Amelioration via Nrf2/ARE-Related Pathways in AD

3.3.1. Oxidative Stress and AD. AD, the most common cause of dementia, is expected to affect >131 million people by 2050 [34]. The clinical manifestations of AD include progressive cognitive decline (including memory loss), behavioral change, and language impairment. The pathological

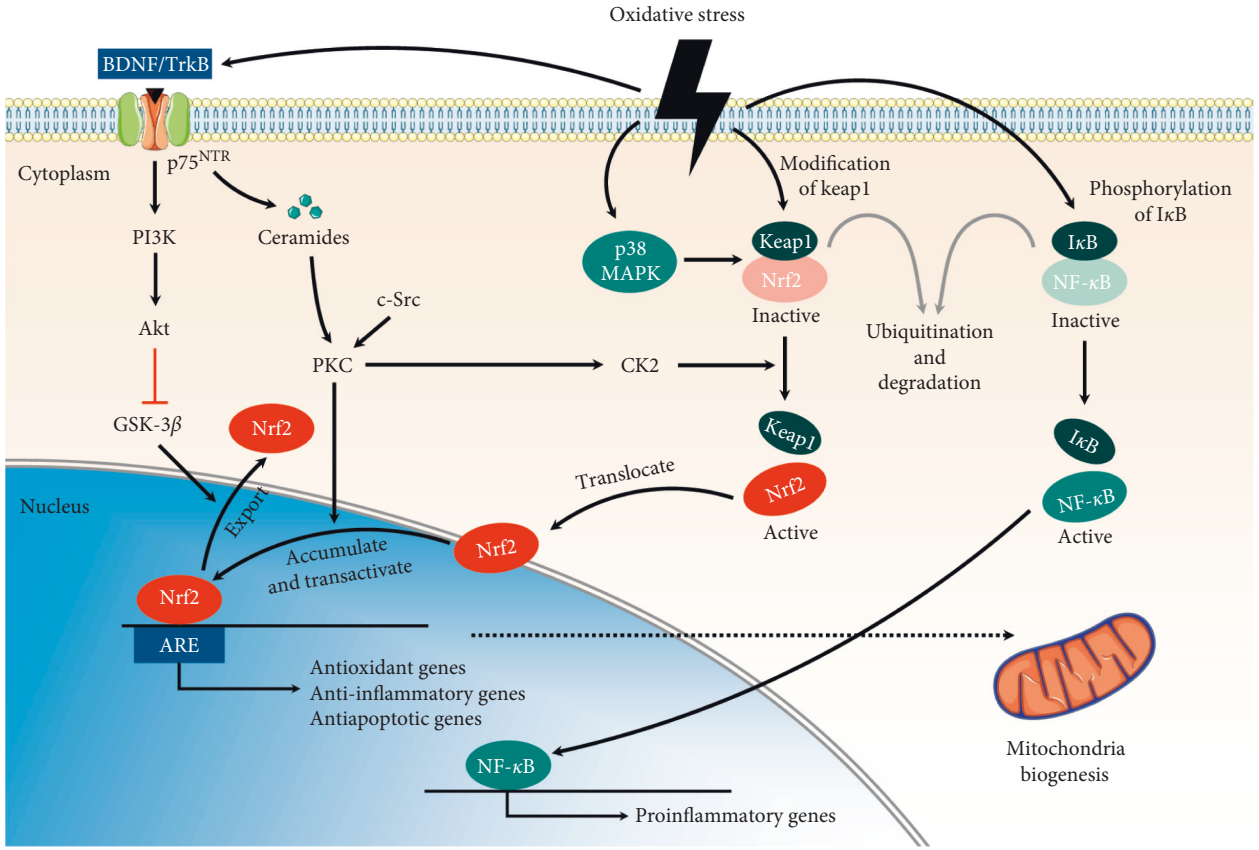

FIGURE 2: Summary of Nrf2/ARE-related pathways. Under homeostasis condition, Nrf2 and NF-κB would bind to the inhibitors and further be degraded. Oxidative stress induces modification of Keap1 and phosphorylation of IκB, resulting in the dissociation of Nrf2 from Keap1 and NF-κB from IκB. The active Nrf2 translocates into the nucleus, binds to ARE, and initiates antioxidants transcription. p38 MAPK would enhance the combination of Nrf2 and Keap1, thus reducing the active Nrf2. BDNF can enhance the accumulation and transactivation of Nrf2 via PKC pathway. GSK-3β would enhance Nrf2 nuclear export and degradation, which would be inhibited by PI3K/Akt pathway. Furthermore, Nrf2 can promote mitochondria biogenesis. BDNF: brain-derived neurotrophic factor; TrkB: tropomyosin-related kinase receptor type B; p75 ^{NTR}: p75 neurotrophin receptor; PI3K: phosphatidylinositol-3-kinase; Akt: protein kinase B; GSK-3β: glycogen synthase kinase-3 beta; Nrf2: nuclear factor erythroid 2-related factor 2; ARE: antioxidant response element; PKC: protein kinase C; c-Src: cellular src; CK2: casein kinase 2; MAPK: mitogen-activated protein kinase; Keap1: kelch-like ECH-associated protein 1; IκB: NF-κB inhibitor; NF-κB: nuclear factor kappa B.

characteristics of AD include extracellular aggregation of amyloid beta (Aβ) plaques, intracellular neurofibrillary tangles, and loss of cholinergic neurons and synapses [34, 35].

A$\beta_{1-40/42}$ peptides are the product of amyloid precursor protein (APP) metabolism that are cleaved consecutively by β- and γ-secretases. In healthy brains, A$\beta_{1-40/42}$ peptides are degraded by Aβ-degrading proteases. Nevertheless, in patients with AD, due to metal homeostasis disruption, Aβ peptides further interact with metal ions, such as zinc, copper, and iron, and form Aβ oligomers and then fibrils [36]. Aβ accumulation and metal ion misregulation both induce oxidative stress [36].

In addition to destroying protein, lipid, and DNA structures, oxidative stress increases mitochondrial dysfunction and activate downstream caspases, leading to apoptosis [37]. Under severe oxidative stress, mitochondrial permeability transition pores, which are regulated by the B-cell lymphoma 2 (Bcl-2) family [38–40], open to allow protons, Ca^{2+}, and large molecules (molecular mass up to 1500 Da, such as GSH) to pass through the inner membrane of mitochondria. Proton gradient loss leads to mitochondrial depolarization, resulting in respiratory chain uncoupling, ROS hypergeneration, substantial release of matrix Ca^{2+}, and depletion of GSH and other reductants [37, 41]. The increase in intracellular Ca^{2+} activates cyclin-dependent kinase 5, resulting in the hyperphosphorylation of the tau protein and self-assembly of neurofibrillary tangles [42]. Moreover, the opening of the mitochondrial permeability transition pore induces the release of cytochrome c, caspase-9, proapoptotic factors, and apoptotic protease-activating factor-1, thereby leading to apoptotic cell death [37].

3.3.2. Effect of Acupuncture in AD. Acupuncture improves cognitive function by increasing the connectivity between cognition-related regions, including the insula, dorsolateral prefrontal cortex, hippocampus, thalamus, inferior parietal

lobule, and anterior cingulate cortex [43, 44]. This effect is caused by regional brain blood flow increase, neurotransmitter modulation, synaptic plasticity improvement, endogenous antioxidant defense system enhancement, and neuronal apoptosis attenuation [1, 45–49]. Moreover, several studies revealed that acupuncture may induce neurogenesis [50]. In the studies we reviewed, *Zusanli* (ST36) and *Baihui* (GV20) are the most commonly used acupoints to enhance brain cell proliferation. Kim et al. [51] demonstrated that acupuncture at *Zusanli* (ST36) increased cell proliferation in the dentate gyrus of ischemic gerbils. Huang et al. [52] revealed that both acupuncture and EA at *Zusanli* (ST36) and *Baihui* (GV20) enhanced cell proliferation in the subgranular zone of the dentate gyrus. Though acupuncture appeared to enhance neurogenesis, further research exploring the mechanisms and pathways is needed.

(1) Nrf2/ARE Pathway. Zhou et al. [53] reported that EA at *Baihui* (GV20) enhances neurogenesis and the expression of Nrf2, HO-1, and BDNF in the hippocampus of enhanced single prolonged stress-treated rats. The neuroprotective effect of EA pretreatment would be blocked in Nrf2-knockdown models. Another study [13] revealed that acupuncture at *Baihui* (GV20) and *Zusanli* (ST36) ameliorates cognitive impairment and hippocampus neuronal loss in models of vascular dementia, accompanied by significant enhancement of HO-1 and NQO1 protein levels in the hippocampus. Interestingly, the neuroprotective effect of acupuncture is also abolished in $Nrf2^{(-/-)}$ mice, which indicates that EA protects neuronal loss and promotes neurogenesis via the Nrf2/HO-1 pathway. A study [14] demonstrated that EA at *Zusanli* (ST36) reduced plasma TNF-α and interleukin-6 levels, increased SOD, GSH-Px, and CAT levels, and increased HO-1 and Nrf2 expression considerably, suggesting that EA attenuates oxidative stress-induced-tissue injury by activating the Nrf2/ARE pathway.

Several studies have reported that Nrf2 can upregulate antiapoptotic proteins Bcl-2 and Bcl-xL and thus enhance cell survival and prevent cellular apoptosis [54, 55]. A study [56] demonstrated that acupuncture at the acupoints of *Shenting* (GV24) and *Benshen* (GB13) could suppress oxidative stress by upregulating Bcl-2 expression and downregulating Bax, cytochrome c, and caspase 3 and 9 expression, thereby reducing the concentrations of ROS and malondialdehyde (MDA; a lipid peroxidation product) and increasing SOD generation. The antiapoptotic effect of acupuncture may be mediated by Nrf2. However, further research is needed to elucidate possible mechanisms.

(2) Nrf2/ARE-Related Pathways. In addition to activating Nrf2/ARE directly, acupuncture has shown neuroprotective and antioxidative effects via other Nrf2/ARE-related pathways, including PKC, PI3K/Akt/GSK-3β, p38 MAPK, and NF-κB. EA increased PKC expression in the hippocampus of a rat depression model [57]. However, studies that have explored the effect of acupuncture on the PKC pathway in an AD model are limited. EA at *Baihui* (GV20) with disperse waves of 1 and 20 Hz for 30 min daily for 4 weeks can significantly improve learning and memory functions and upregulate BDNF expression levels in APP/PS1 transgenic mice [58, 59]. BDNF can promote Nrf2 nuclear translocation via the PI3K pathway, further bind to ARE, and initiate transcription of antioxidants. Yu et al. found that high-frequency (50-Hz) EA could downregulate GSK-3β activity and ameliorate cognitive impairment in rats [60]. Mammalian target of rapamycin (mTOR), the downstream factor of PI3K/Akt pathway, is a leading autophagy regulator [61]. A reduction of mTOR activity triggers autophagy to decrease the deposition of Aβ plaques and improve memory impairment [62]. Liu et al. found that EA at *Baihui* (GV20) could decrease mTOR levels in APP/PS1 transgenic mice [63]. In a rat AD model, EA at *Baihui* (GV20), *Taixi* (KI3), and *Zusanli* (ST36) with 1 mA, 2 Hz for 15 min daily for 12 sessions could restrain the inflammatory reaction in the CNS by reducing p38 MAPK levels [64]. A study [65] revealed that oxidative stress induces the activation of NF-κB and its target gene TP53 and that acupuncture at the *Zusanli* (ST36) acupoint for 30 seconds, once daily (with a rest every seventh day) for 2 weeks, can inhibit the nuclear translocation of NF-κB and TP53 expression in the hippocampus in a multi-infarct model. EA at *Baihui* (GV20), *Yintang* (EX-HN3), and *Shuigou* (GV26) could reduce β-secretase1 deposition, which is regulated by NF-κB, in APP/PS1 transgenic mice [66].

(3) *Other Effects of Acupuncture on Oxidative Stress Amelioration*. In addition to enhancing the endogenous antioxidant defense system by activating Nfr2/ARE, acupuncture can decrease ROS generation directly by regulating NADPH oxidases (NOXs) and adenosine monophosphate-activated protein kinase (AMPK) pathway. EA at *Baihui* (GV20) and *Yongquan* (KI1) can inhibit NOX2 expression and further reduce the hippocampal accumulation of MDA and 8-hydroxy-2′-deoxyguanosine (a DNA damage biomarker) [67]. Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), regulated by AMPK, can decrease ROS generation by regulating mitochondrial biogenesis and degrading damaged mitochondria through the autophagy–lysosome machinery [68]. EA upregulated PGC-1α expression and also improved energy metabolism in the brains of senescence accelerated mouse-prone 8 mice [69].

The heat shock protein (Hsp) family can protect cells against apoptosis under stress by degrading misfolded proteins and preventing denatured protein aggregation [70]. Chang et al. noted that acupuncture at *Danzhong* (CV17), *Zhongwan* (CV12), *Qihai* (CV6), bilateral *Xuehai* (SP10), and *Zusanli* (ST36) could reduce oxidative protein damage and promote Hsp84 and Hsp86 expression, which may delay brain aging and prevent neurodegeneration [70].

In summary, acupuncture ameliorates oxidative stress in AD in five ways: (1) reduction of oxidative stress (increasing antioxidant generation and decreasing ROS generation), (2) suppression of apoptosis (regulating signaling pathways downstream of ROS to suppress cell apoptosis), (3) reduction of Aβ production and deposition, (4) repair of ROS-damaged proteins, lipids, and DNA, and (5)

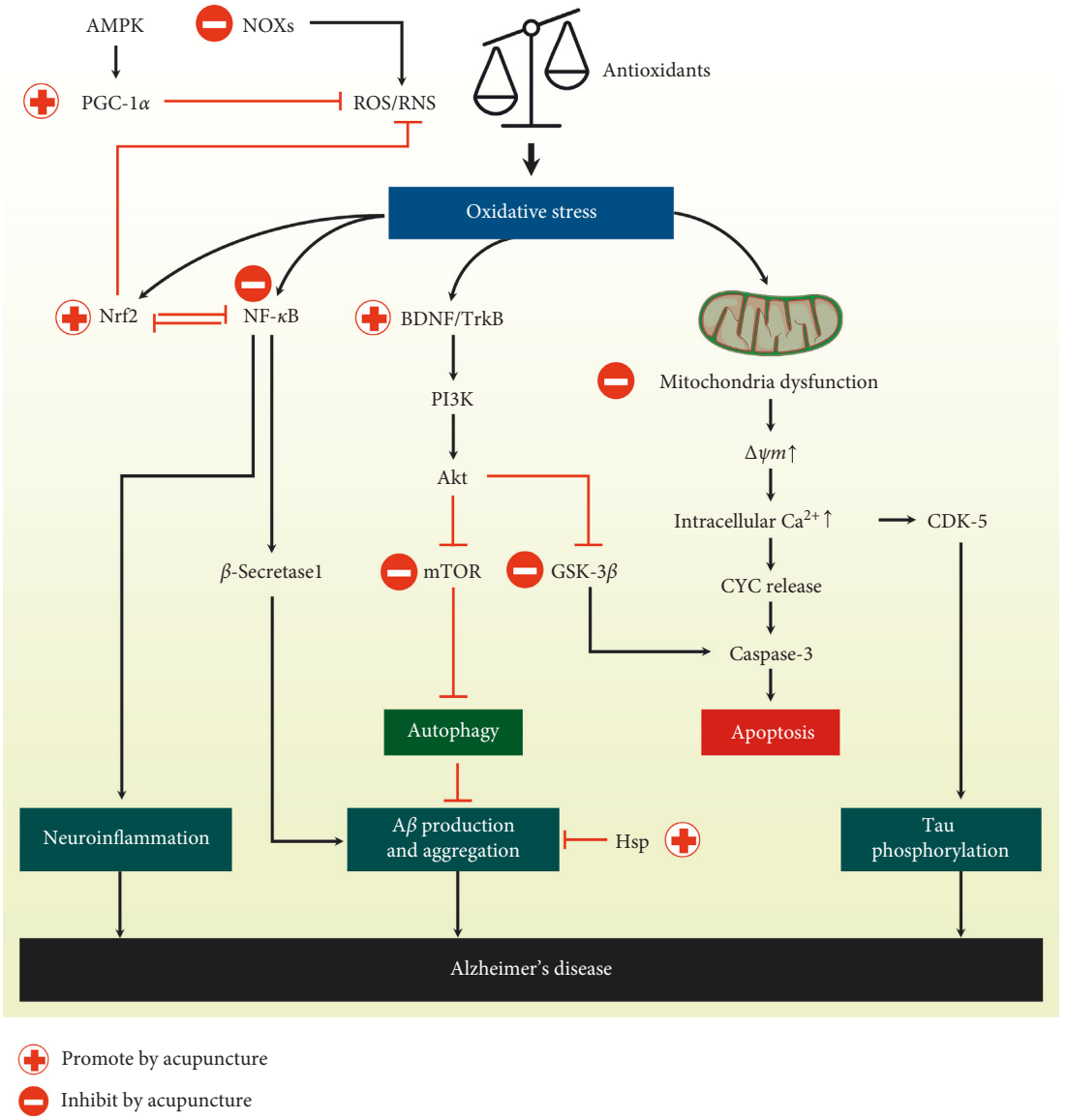

Figure 3: Summary of effect of acupuncture on oxidative stress amelioration in AD. Except for Nrf2/ARE-related pathways, acupuncture can ameliorate oxidative stress and decrease neuroinflammation, Aβ production, and aggregation, and tau phosphorylation via multiple signal transduction pathways. Acupuncture can reduce the generation of ROS by activating Nrf2 and PGC-1α, and inhibiting NOXs. Moreover, acupuncture can reverse mitochondria dysfunction, further reducing tau phosphorylation. ROS: reactive oxygen species; RNS: reactive nitrogen species; AMPK: adenosine monophosphate-activated protein kinase; PGC-1α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; NOX: nicotinamide adenine dinucleotide phosphate oxidases; Nrf2: nuclear factor erythroid 2-related factor 2; NF-κB: nuclear factor kappa B; BDNF: brain-derived neurotrophic factor; TrkB: tropomyosin-related kinase receptor type B; PI3K: phosphatidylinositol-3-kinase; Akt: protein kinase B; mTOR: mammalian target of rapamycin; Aβ: amyloid beta; GSK-3β: glycogen synthase kinase-3 beta; Hsp: heat shock protein; Δψm: the mitochondrial membrane potential; CYC: cytochrome C; CDK-5: cyclin-dependent kinase 5.

neuroinflammation relief. Effects of acupuncture on oxidative stress amelioration in AD are demonstrated in Figure 3.

3.4. Effect of Acupuncture on Oxidative Stress Amelioration via Nrf2/ARE-Related Pathways in PD

3.4.1. Oxidative Stress and PD. PD, a progressive neurodegenerative disease, is characterized by motor (bradykinesia, resting tremor, rigidity, and postural instability) and nonmotor (cognitive impairment, psychiatric symptoms, and dysautonomia) symptoms [71, 72]. PD pathology includes Lewy body formation and dopaminergic neuron degeneration in the substantia nigra [1]. The PD etiology remains unclear; however, PD is strongly associated with oxidative stress. Several studies have suggested that oxidative stress contributes to the formation of Lewy bodies and the degeneration of dopamine cells in PD [73]. Iron (Fe)

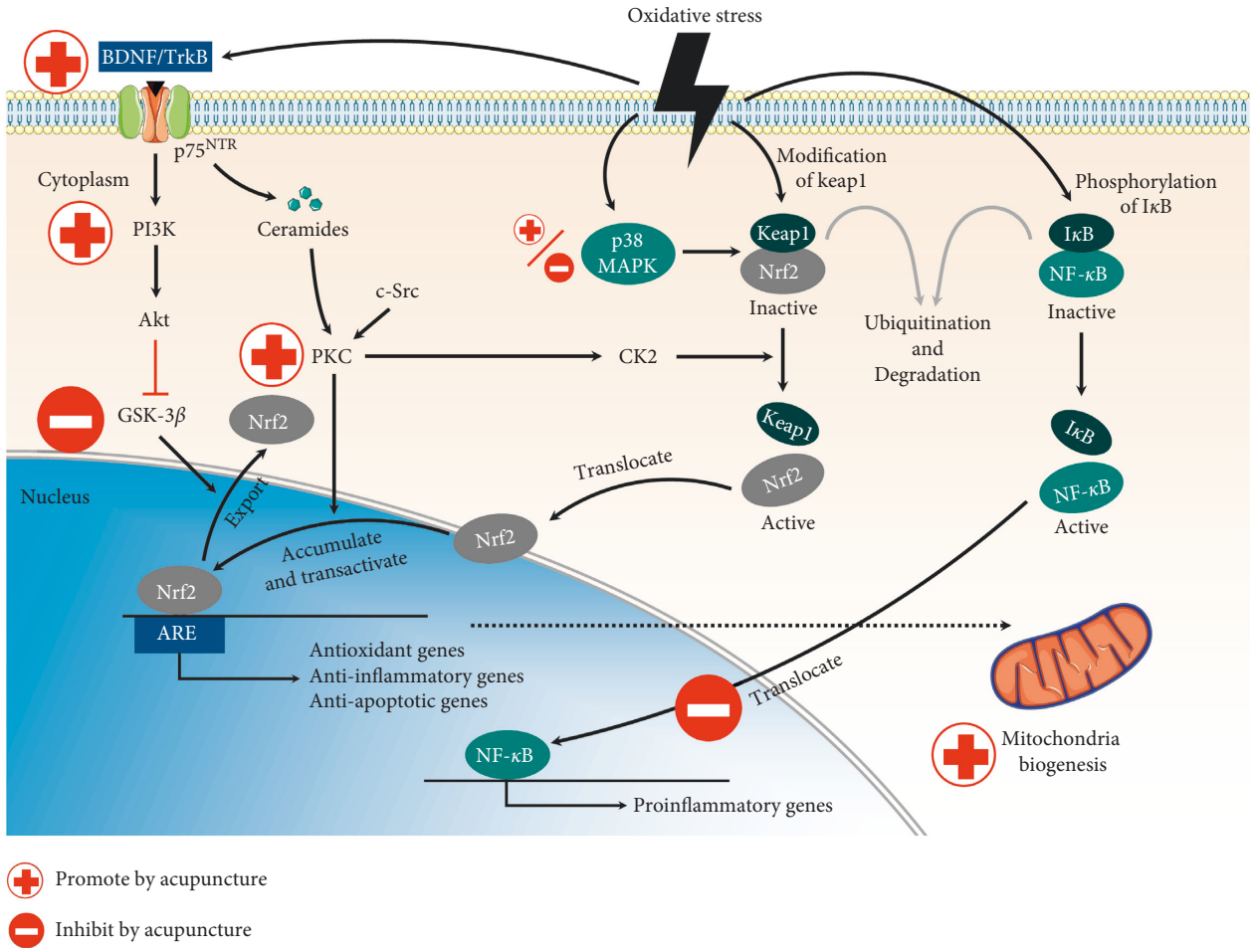

Figure 4: Summary of effect of acupuncture on oxidative stress amelioration via Nrf2/ARE-related pathways. Acupuncture can upregulate the expression of BDNF, PI3K/Akt, and PKC and inhibit GSK-3β pathway, further increasing the nuclear translocation, accumulation, and transactivation of Nrf2. In addition, acupuncture can inhibit NF-κB translocate into the nucleus, hence downregulating the expression of proinflammatory genes. Moreover, acupuncture can promote mitochondria biogenesis. Interestingly, effect of acupuncture on p38 MAPK pathway has a dual characteristic. BDNF: brain-derived neurotrophic factor; TrkB: tropomyosin-related kinase receptor type B; p75 ^{NTR}: p75 neurotrophin receptor; PI3K: phosphatidylinositol-3-kinase; Akt: protein kinase B; GSK-3β: glycogen synthase kinase-3 beta; Nrf2: nuclear factor erythroid 2-related factor 2; ARE: antioxidant response element; PKC: protein kinase C; c-Src: cellular src; CK2: casein kinase 2; MAPK: mitogen-activated protein kinase; Keap1: kelch-like ECH-associated protein 1; IκB: NF-κB inhibitor; NF-κB: nuclear factor kappa B.

metabolism disruption, GSH depletion, and MDA (a lipid oxidation biomarker) elevation have been observed in patients with PD [1]. The equilibrium between apoptosis and autophagy is crucial in the degradation of α-synuclein, the major Lewy body component [74].

3.4.2. Effect of Acupuncture on PD. Acupuncture can improve motor and nonmotor symptoms in patients with PD and animal models [75] by reducing oxidative stress, modulating neurotransmitters, and attenuating neuronal loss [76–78].

(1) *Nrf2/ARE Pathway.* In 6-hydroxydopamine (6-OHDA) rats, acupuncture at *Yanglingquan* (GB34), *Taichong* (LV3), *Zusanli* (ST36), and *Xuehai* (SP10) acupoints increased SOD and GSH-Px levels, reduced MDA level, and inhibited oxidative stress [79]. Moreover, in the striatum of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine- (MPTP-) treated mice, acupuncture at *Yanglingquan* (GB34) could enhance SOD and CAT activities [80]. High-frequency (100-Hz) EA at *Zusanli* (ST36) and *Sanyinjiao* (SP6) acupoints can reduce H_2O_2 and MDA levels and increase SOD, GSH, and GSH-Px levels [81]. Wattanathorn et al. found that LA at *Shenmen* (HT7) reduced MDA and monoamine oxidase type B levels and increased GSH-Px levels in the hippocampus of 6-OHDA rats [82].

Nrf2-deficient mice are hypersensitive to PD-generating neurotoxins [83]. A study [84] revealed that high-frequency (100-Hz) EA at *Zusanli* (ST36) and *Sanyinjiao* (SP6) could reverse the suppression of the Nrf2/ARE system induced by MPTP in a mouse model of PD, indicating that EA exhibits notable antioxidative effects by increasing Nrf2/ARE

expression. A similar upregulating effect of EA on Nrf2/ARE expression was reported in another animal study [85].

(2) *Nrf2/ARE-Related Pathways*. Acupuncture at *Yanglingquan* (GB34) can protect dopaminergic neurons from apoptosis and improve motor symptoms by triggering the PI3K/Akt cascade [86]. In an animal model of PD, acupuncture at *Yanglingquan* (GB34) promoted the autophagic clearance of α-synuclein by activating an mTOR-independent pathway [87], which is positively regulated with PI3K/Akt cascade.

In the MPTP mouse model, EA at *Baihui* (GV20) and *Yintang* (GV29) could increase BDNF expression [88]. Notably, Liang et al. compared the effect of different frequencies of EA (0, 2, and 100 Hz) on BDNF regulation in the substantia nigra and ventral tegmental area of PD mice and found that only high-frequency (100-Hz) EA significantly increased the BDNF level [89].

Several studies have reported that EA can protect cells from oxidative-stress-induced injury by inhibiting p38 MAPK pathway [90–93]. In acute-phase oxidative stress-induced injury, p38 MAPK enhances the link between Nrf2 and Keap1 and decreases Nrf2 nuclear accumulation. Thus, p38 MAPK inhibition could aid translocation and accumulation of Nrf2 in the nucleus. Nevertheless, few studies have explored the effect of acupuncture on regulating PD and p38 MAPK.

Acupuncture attenuates cognitive impairment and oxidative stress by reducing NF-κB expression in the rat cerebral multi-infarct model [65]. NF-κB inhibits TP53, which is highly associated with apoptosis [94]. Park et al. revealed that acupuncture showed predominant neuroprotective effects in the rat PD model. However, these protective effects were abrogated in the p53-knockout mice, indicating that p53 mediates acupuncture-induced neuroprotection in PD [95].

In summary, acupuncture lowers oxidative stress in PD in three ways: (1) reduction of oxidative stress (increasing antioxidant generation and decreasing ROS generation), (2) suppression of apoptosis (regulating signaling downstream of the ROS pathway to suppress cell apoptosis), and (3) reduction of α-synuclein production and deposition.

Effects of acupuncture on ameliorating oxidative stress via Nrf2/ARE-related pathways in AD and PD are illustrated in Figure 4.

4. Conclusions

Acupuncture exhibits notable neuroprotective and antioxidative effects by activating the Nrf2/ARE pathway. The nuclear translocation and accumulation of Nrf2 are regulated via several pathways including PKC, PI3K/Akt/GSK-3β, p38 MAPK, and NF-κB. In addition to increasing the activity of endogenous antioxidants, acupuncture reduces ROS generation and inhibits neuronal apoptosis. Moreover, acupuncture can promote the repair of ROS-damaged lipids, proteins, and DNA and improve autophagy, thus reducing the production or deposition of pathological products, such as Aβ and Lewy bodies. This review article demonstrated that acupuncture effectively ameliorates oxidative stress in AD and PD animal models by activating the Nrf2/ARE pathway and regulating the Nrf2/ARE-related pathways. Thus, acupuncture could be a therapeutic option for AD and PD. However, acupuncture has demonstrated dual-regulatory characteristics in several pathways, such as p38 MAPK and p53. Therefore, further research focusing on the molecular mechanisms of acupuncture is needed.

Data Availability

The data used to support the study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

T.-I. Huang collected data and wrote the manuscript; C.-L. Hsieh designed the protocol and revised the paper. The authors have read and agreed to the published version of the manuscript.

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References

[1] X. H. Zeng, Q. Q. Li, Q. Xu, F. Li, and C. Z. Liu, "Acupuncture mechanism and redox equilibrium," *Evidence-Based Complementary and Alternative Medicine*, vol. 2014, Article ID 483294, 7 pages, 2014.

[2] A. V. Snezhkina, A. V. Kudryavtseva, O. L. Kardymon et al., "ROS generation and antioxidant defense systems in normal and malignant cells," *Oxidative Medicine and Cellular Longevity*, vol. 2019, Article ID 6175804, 17 pages, 2019.

[3] G.-Y. Liou and P. Storz, "Reactive oxygen species in cancer," *Free Radical Research*, vol. 44, no. 5, pp. 479–496, 2010.

[4] R. Ahmad, A. Hussain, and H. Ahsan, "Peroxynitrite: cellular pathology and implications in autoimmunity," *Journal of Immunoassay and Immunochemistry*, vol. 40, no. 2, pp. 123–138, 2019.

[5] S. Madireddy and S. Madireddy, "Protection from the pathogenesis of neurodegenerative disorders, including alzheimer's disease, amyotrophic lateral sclerosis, huntington's disease, and Parkinson's diseases, through the mitigation of reactive oxygen species," *Journal of Neuroscience and Neurological Disorders*, vol. 3, no. 2, pp. 148–161, 2019.

[6] H. Ischiropoulos and J. S. Beckman, "Oxidative stress and nitration in neurodegeneration: cause, effect, or association?," *Journal of Clinical Investigation*, vol. 111, no. 2, pp. 163–169, 2003.

[7] E. Birben, U. M. Sahiner, C. Sackesen, S. Erzurum, and O. Kalayci, "Oxidative stress and antioxidant defense," *World Allergy Organization Journal*, vol. 5, no. 1, pp. 9–19, 2012.

[8] F. Sivandzade, S. Prasad, A. Bhalerao, and L. Cucullo, "NRF2 and NF-κB interplay in cerebrovascular and neurodegenerative disorders: molecular mechanisms and possible therapeutic approaches," *Redox Biology*, vol. 21, p. 101059, 2019.

[9] K. M. Holmstrom, L. Baird, Y. Zhang et al., "Nrf2 impacts cellular bioenergetics by controlling substrate availability for mitochondrial respiration," *Biology Open*, vol. 2, no. 8, pp. 761–770, 2013.

[10] S. Salim, "Oxidative stress and the central nervous system," *Journal of Pharmacology and Experimental Therapeutics*, vol. 360, no. 1, pp. 201–205, 2017.

[11] S. Przedborski, M. Vila, and V. Jackson-Lewis, "Series Introduction: neurodegeneration: what is it and where are we?," *Journal of Clinical Investigation*, vol. 111, no. 1, pp. 3–10, 2003.

[12] M. Cai, J. H. Lee, and E. J. Yang, "Electroacupuncture attenuates cognition impairment via anti-neuroinflammation in an Alzheimer's disease animal model," *Neuroinflammation*, vol. 16, no. 1, p. 264, 2019.

[13] X.-R. Wang, G.-X. Shi, J.-W. Yang et al., "Acupuncture ameliorates cognitive impairment and hippocampus neuronal loss in experimental vascular dementia through Nrf2-mediated antioxidant response," *Free Radical Biology and Medicine*, vol. 89, pp. 1077–1084, 2015.

[14] J. B. Yu, J. Shi, L. R. Gong et al., "Role of Nrf2/ARE pathway in protective effect of electroacupuncture against endotoxic shock-induced acute lung injury in rabbits," *PLoS One*, vol. 9, no. 8, Article ID e104924, 2014.

[15] A. Cuadrado, "Structural and functional characterization of Nrf2 degradation by glycogen synthase kinase 3/β-TrCP," *Free Radical Biology and Medicine*, vol. 88, pp. 147–157, 2015.

[16] J. Jiang, L. M. Tam, P. Wang, and Y. Wang, "Arsenite targets the RING finger domain of Rbx1 E3 ubiquitin ligase to inhibit proteasome-mediated degradation of Nrf2," *Chemical Research in Toxicology*, vol. 31, no. 5, pp. 380–387, 2018.

[17] S. Guha, S. Chaurasia, and S. Roy, "Oxidative stress in the pathogenesis of corneal endothelial dystrophies and other corneal diseases," *Reactive Oxygen Species*, vol. 6, no. 17, pp. 299–310, 2018.

[18] H. N. Kaleli, E. Ozer, V. O. Kaya, and O. Kutlu, "Protein kinase C isozymes and autophagy during neurodegenerative disease progression," *Cells*, vol. 9, no. 3, 2020.

[19] J. de Barry, C. M. Liégeois, and A. Janoshazi, "Protein kinase C as a peripheral biomarker for Alzheimer's disease," *Experimental Gerontology*, vol. 45, no. 1, pp. 64–69, 2010.

[20] D. A. Bloom and A. K. Jaiswal, "Phosphorylation of Nrf2 at Ser40 by protein kinase C in response to antioxidants leads to the release of Nrf2 from INrf2, but is not required for Nrf2 stabilization/accumulation in the nucleus and transcriptional activation of antioxidant response element-mediated NAD(P)H:quinone oxidoreductase-1 gene expression," *Journal of Biological Chemistry*, vol. 278, no. 45, pp. 44675–44682, 2003.

[21] L. Fao, S. I. Mota, and A. C. Rego, "c-Src regulates Nrf2 activity through PKCdelta after oxidant stimulus," *Biochim Biophys Acta Mol Cell Res*, vol. 1866, no. 4, pp. 686–698, 2019.

[22] S. N. Rai, H. Dilnashin, H. Birla et al., "The role of PI3K/Akt and ERK in neurodegenerative disorders," *Neurotoxicity Research*, vol. 35, no. 3, pp. 775–795, 2019.

[23] B. Bruna, P. Lobos, R. Herrera-Molina, C. Hidalgo, A. Paula-Lima, and T. Adasme, "The signaling pathways underlying BDNF-induced Nrf2 hippocampal nuclear translocation involve ROS, RyR-Mediated Ca2+ signals, ERK and PI3K," *Biochemical and Biophysical Research Communications*, vol. 505, no. 1, pp. 201–207, 2018.

[24] I. Mendez-David, L. Tritschler, Z. E. Ali et al., "Nrf2-signaling and BDNF: a new target for the antidepressant-like activity of chronic fluoxetine treatment in a mouse model of anxiety/depression," *Neuroscience Letters*, vol. 597, pp. 121–126, 2015.

[25] T. Ishii, E. Warabi, and G. E. Mann, "Circadian control of BDNF-mediated Nrf2 activation in astrocytes protects dopaminergic neurons from ferroptosis," *Free Radical Biology and Medicine*, vol. 133, pp. 169–178, 2019.

[26] P. L. Apopa, X. He, and Q. Ma, "Phosphorylation of Nrf2 in the transcription activation domain by casein kinase 2 (CK2) is critical for the nuclear translocation and transcription activation function of Nrf2 in IMR-32 neuroblastoma cells," *Journal of Biochemical and Molecular Toxicology*, vol. 22, no. 1, pp. 63–76, 2008.

[27] X. Chen, Y. Liu, J. Zhu et al., "GSK-3beta downregulates Nrf2 in cultured cortical neurons and in a rat model of cerebral ischemia-reperfusion," *Sci Rep*, vol. 6, 20196.

[28] P. Shelton and A. K. Jaiswal, "The transcription factor NF-E2-related Factor 2 (Nrf2): a protooncogene?," *The FASEB Journal*, vol. 27, no. 2, pp. 414–423, 2013.

[29] Y.-S. Keum, S. Yu, P. P.-J. Chang et al., "Mechanism of action of sulforaphane: inhibition of p38 mitogen-activated protein kinase isoforms contributing to the induction of antioxidant response element-mediated heme oxygenase-1 in human hepatoma HepG2 cells," *Cancer Research*, vol. 66, no. 17, pp. 8804–8813, 2006.

[30] J.-S. Jung, M.-J. Choi, H.-M. Ko, and H.-S. Kim, "Short-chain C2 ceramide induces heme oxygenase-1 expression by upregulating AMPK and MAPK signaling pathways in rat primary astrocytes," *Neurochemistry International*, vol. 94, pp. 39–47, 2016.

[31] H. C. Lai, Q. Y. Chang, and C. L. Hsieh, "Signal transduction pathways of acupuncture for treating some nervous system diseases," *Evid Based Complement Alternat Med*, vol. 2019, Article ID. 2909632, 37 pages, 2019.

[32] J. D. Wardyn, A. H. Ponsford, and C. M. Sanderson, "Dissecting molecular cross-talk between Nrf2 and NF-κB response pathways," *Biochemical Society Transactions*, vol. 43, no. 4, pp. 621–626, 2015.

[33] M. P. Soares, M. P. Seldon, I. P. Gregoire et al., "Heme oxygenase-1 modulates the expression of adhesion molecules associated with endothelial cell activation," *The Journal of Immunology*, vol. 172, no. 6, pp. 3553–3563, 2004.

[34] S. Tiwari, V. Atluri, A. Kaushik, A. Yndart, and M. Nair, "Alzheimer's disease: pathogenesis, diagnostics, and therapeutics," *International Journal of Nanomedicine*, vol. 14, pp. 5541–5554, 2019.

[35] S. Habtemariam, "Natural products in alzheimer's disease therapy: would old therapeutic approaches fix the broken promise of modern medicines?," *Molecules*, vol. 24, no. 8, 2019.

[36] C. Cheignon, M. Tomas, D. Bonnefont-Rousselot, P. Faller, C. Hureau, and F. Collin, "Oxidative stress and the amyloid beta peptide in Alzheimer's disease," *Redox Biology*, vol. 14, pp. 450–464, 2018.

[37] K. Kannan and S. K. Jain, "Oxidative stress and apoptosis," *Pathophysiology*, vol. 7, no. 3, pp. 153–163, 2000.

[38] J. K. Brunelle and A. Letai, "Control of mitochondrial apoptosis by the Bcl-2 family," *Journal of Cell Science*, vol. 122, no. Pt 4, pp. 437–441, 2009.

[39] S. Kaufmann, W. Meng, and H. Dai, "BCL2 family, mitochondrial apoptosis, and beyond," *Cancer Translational Medicine*, vol. 2, no. 1, 2016.

[40] R. J. Youle and A. Strasser, "The BCL-2 protein family: opposing activities that mediate cell death," *Nature Reviews Molecular Cell Biology*, vol. 9, no. 1, pp. 47–59, 2008.

[41] A. Görlach, K. Bertram, S. Hudecova, and O. Krizanova, "Calcium and ROS: a mutual interplay," *Redox Biology*, vol. 6, pp. 260–271, 2015.

[42] A. S. Bhounsule, L. K. Bhatt, K. S. Prabhavalkar, and M. Oza, "Cyclin dependent kinase 5: a novel avenue for Alzheimer's disease," *Brain Research Bulletin*, vol. 132, pp. 28–38, 2017.

[43] T. T. Tan, D. Wang, J. K. Huang et al., "Modulatory effects of acupuncture on brain networks in mild cognitive impairment patients," *Neural Regeneration Research*, vol. 12, no. 2, pp. 250–258, 2017.

[44] C.-c. Yu, C.-y. Ma, H. Wang et al., "Effects of acupuncture on alzheimer's disease: evidence from neuroimaging studies," *Chinese Journal of Integrative Medicine*, vol. 25, no. 8, pp. 631–640, 2019.

[45] Y. Ye, W. Zhu, X.-R. Wang et al., "Mechanisms of acupuncture on vascular dementia-A review of animal studies," *Neurochemistry International*, vol. 107, pp. 204–210, 2017.

[46] B.-H. Kan, J.-C. Yu, L. Zhao et al., "Acupuncture improves dendritic structure and spatial learning and memory ability of Alzheimer's disease mice," *Neural Regeneration Research*, vol. 13, no. 8, pp. 1390–1395, 2018.

[47] G. Li, X. Zhang, H. Cheng et al., "Acupuncture improves cognitive deficits and increases neuron density of the hippocampus in middle-aged SAMP8 mice," *Acupuncture in Medicine*, vol. 30, no. 4, pp. 339–345, 2012.

[48] C. L. Zhou, L. Zhao, H. Y. Shi et al., "Combined acupuncture and HuangDiSan treatment affects behavior and synaptophysin levels in the hippocampus of senescence-accelerated mouse prone 8 after neural stem cell transplantation," *Neural Regen Res*, vol. 13, no. 3, pp. 541–548, 2018.

[49] P. Liang, Z. Wang, T. Qian, and K. Li, "Acupuncture stimulation of Taichong (Liv3) and Hegu (LI4) modulates the default mode network activity in Alzheimer's disease," *American Journal of Alzheimer's Disease & Other Dementiasr*, vol. 29, no. 8, pp. 739–748, 2014.

[50] M.-H. Nam, K. S. Ahn, and S.-H. Choi, "Acupuncture stimulation induces neurogenesis in adult brain," *International Review of Neurobiology*, vol. 111, pp. 67–90, 2013.

[51] E.-H. Kim, Y.-J. Kim, H. J. Lee et al., "Acupuncture increases cell proliferation in dentate gyrus after transient global ischemia in gerbils," *Neuroscience Letters*, vol. 297, no. 1, pp. 21–24, 2001.

[52] I. K. Hwang, J. Y. Chung, D. Y. Yoo et al., "Comparing the effects of acupuncture and electroacupuncture at Zusanli and Baihui on cell proliferation and neuroblast differentiation in the rat hippocampus," *Journal of Veterinary Medical Science*091125005, vol. 72, no. 3, pp. 279–284, 2010.

[53] C. H. Zhou, F. Xue, S. S. Xue et al., "Electroacupuncture pretreatment ameliorates PTSD-like behaviors in rats by enhancing hippocampal neurogenesis via the keap1/nrf2 antioxidant signaling pathway," *Frontiers Cell Neuroscience*, vol. 13, p. 275, 2019.

[54] S. K. Niture and A. K. Jaiswal, "Nrf2 protein up-regulates antiapoptotic protein bcl-2 and prevents cellular apoptosis," *Journal of Biological Chemistry*, vol. 287, no. 13, pp. 9873–9886, 2012.

[55] S. K. Niture and A. K. Jaiswal, "Nrf2-induced antiapoptotic Bcl-xL protein enhances cell survival and drug resistance," *Free Radical Biology and Medicine*, vol. 57, pp. 119–131, 2013.

[56] J. Zhang, C. Tang, W. Liao, M. Zhu, M. Liu, and N. Sun, "The antiapoptotic and antioxidative stress effects of Zhisanzhen in the Alzheimer's disease model rat," *NeuroReport*, vol. 30, no. 9, pp. 628–636, 2019.

[57] H. Fan Lu, J.-J Xie, H. Zhou, Y. Chen, and J Hu, "Effects of electroacupuncture on behavior, plasma COR and expressions of PKA and PKC in hippocampus of the depression model rat," *Zhongguo Zhen Jiu*, vol. 28, no. 3, pp. 214–218, 2008.

[58] R. Lin, L. Li, Y. Zhang et al., "Electroacupuncture ameliorate learning and memory by improving N-acetylaspartate and glutamate metabolism in APP/PS1 mice," *Biological Research*, vol. 51, no. 1, p. 21, 2018.

[59] R. Lin, J. Chen, X. Li et al., "Electroacupuncture at the Baihui acupoint alleviates cognitive impairment and exerts neuroprotective effects by modulating the expression and processing of brain-derived neurotrophic factor in APP/PS1 transgenic mice," *Molecular Medicine Reports*, vol. 13, no. 2, pp. 1611–1617, 2016.

[60] C. C. Yu, Y. Wang, F. Shen et al., "High-frequency (50 Hz) electroacupuncture ameliorates cognitive impairment in rats with amyloid beta 1-42-induced Alzheimer's disease," *Neural Regeneration Research*, vol. 13, no. 10, pp. 1833–1841, 2018.

[61] O. R. Tamtaji, M. Naderi Taheri, F. Notghi, R. Alipoor, R. Bouzari, and Z. Asemi, "The effects of acupuncture and electroacupuncture on Parkinson's disease: current status and future perspectives for molecular mechanisms," *Journal of Cellular Biochemistry*, vol. 120, no. 8, pp. 12156–12166, 2019.

[62] S. Oddo, "The role of mTOR signaling in Alzheimer disease," *Frontiers in Bioscience*, vol. 4, pp. 941–952, 2014.

[63] W. Liu, P. Zhuo, L. Li et al., "Activation of brain glucose metabolism ameliorating cognitive impairment in APP/PS1 transgenic mice by electroacupuncture," *Free Radical Biology and Medicine*, vol. 112, pp. 174–190, 2017.

[64] S.-X. Z. J.-Q. Fang, Y. Zhang, F. Wang, and Q.-Y. Zhu, "Effect of electroacupuncture on expression of phosphorylated P 38 MAPK and IL-1beta in frontal lobe and hippocampus in rats with Alzheimer's disease," *Zhen Ci Yan Jiu*, vol. 38, no. 1, pp. 35–39, 2013.

[65] J.-W. Yang, X.-R. Wang, S.-M. Ma, N.-N. Yang, Q.-Q. Li, and C.-Z. Liu, "Acupuncture attenuates cognitive impairment, oxidative stress and NF-κB activation in cerebral multi-infarct rats," *Acupuncture in Medicine*, vol. 37, no. 5, pp. 283–291, 2019.

[66] Y. Tang, S. Shao, Y. Guo et al., "Electroacupuncture mitigates hippocampal cognitive impairments by reducing BACE1 deposition and activating PKA in APP/PS1 double transgenic mice," *Frontiers in Bioscience*, vol. 2019, Article ID 2823679, 12 pages, 2019.

[67] G. Wu, L. Li, H.-M. Li, Y. Zeng, and W.-C. Wu, "Electroacupuncture ameliorates spatial learning and memory impairment via attenuating NOX2-related oxidative stress in a rat model of Alzheimer's disease induced by Aβ1-42," *Cellular and Molecular Biology*, vol. 63, no. 4, pp. 38–45, 2017.

[68] Y. L. Tain and C. N. Hsu, "Interplay between oxidative stress and nutrient sensing signaling in the developmental origins of cardiovascular disease," *International Journal of Molecular Sciences*, vol. 18, no. 4, 2017.

[69] W. Dong, W. Quo, F. Wang et al., "Electroacupuncture upregulates SIRT1-dependent PGC-1α expression in SAMP8 mice," *Medical Science Monitor*, vol. 21, pp. 3356–3362, 2015.

[70] S. Chang, X. Guo, G. Li et al., "Acupuncture promotes expression of Hsp84/86 and delays brain ageing in SAMP8

mice," *Acupuncture in Medicine*, vol. 37, no. 6, pp. 340–347, 2019.

[71] A. De Virgilio, A. Greco, G. Fabbrini et al., "Parkinson's disease: autoimmunity and neuroinflammation," *Autoimmunity Reviews*, vol. 15, no. 10, pp. 1005–1011, 2016.

[72] L. V. Kalia and A. E. Lang, "Parkinson's disease," *The Lancet*, vol. 386, no. 9996, pp. 896–912, 2015.

[73] C. Zhou, Y. Huang, and S. Przedborski, "Oxidative stress in Parkinson's disease," *Annals of the New York Academy of Sciences*, vol. 1147, no. 1, pp. 93–104, 2008.

[74] R. M. Meade, D. P. Fairlie, and J. M. Mason, "Alpha-synuclein structure and Parkinson's disease - lessons and emerging principles," *Mol Neurodegener*, vol. 14, no. 1, p. 29, 2019.

[75] B.-Y. Zeng and K. Zhao, "Effect of acupuncture on the motor and nonmotor symptoms in Parkinson's disease-A review of clinical studies," *CNS Neuroscience & Therapeutics*, vol. 22, no. 5, pp. 333–341, 2016.

[76] J. Jia, Z. Sun, B. Li et al., "Electro-acupuncture stimulation improves motor disorders in Parkinsonian rats," *Behavioural Brain Research*, vol. 205, no. 1, pp. 214–218, 2009.

[77] L. S. Fang Wang, X.-Z. Zhang, J. Jia et al., "Effect and potential mechanism of electroacupuncture add-on treatment in patients with Parkinson's disease," *Evid Based Complement Alternat Med*, vol. 692795, 2015.

[78] Y. K. Kim, H. H. Lim, Y. K. Song et al., "Effect of acupuncture on 6-hydroxydopamine-induced nigrostratal dopaminergic neuronal cell death in rats," *Neurosci Lett*, vol. 384, no. 1-2, pp. 133–138, 2005.

[79] Y.-P. Yu, W.-P. Ju, Z.-G. Li, D.-Z. Wang, Y.-C. Wang, and A.-M. Xie, "Acupuncture inhibits oxidative stress and rotational behavior in 6-hydroxydopamine lesioned rat," *Brain Research*, vol. 1336, pp. 58–65, 2010.

[80] Y. Lee, G. Choi, H. Jeon et al., "Acupuncture stimulation at GB34 suppresses 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced oxidative stress in the striatum of mice," *The Journal of Physiological Sciences*, vol. 68, no. 4, pp. 455–462, 2017.

[81] H. Wang, Y. Pan, B. Xue et al., "The antioxidative effect of electro-acupuncture in a mouse model of Parkinson's disease," *PLoS One*, vol. 6, no. 5, Article ID e19790, 2011.

[82] J. Wattanathorn and C. Sutalangka, "Laser acupuncture at HT7 acupoint improves cognitive deficit, neuronal loss, oxidative stress, and functions of cholinergic and dopaminergic systems in animal model of Parkinson's disease," *Evidence-Based Complementary and Alternative Medicine*, vol. 2014, Article ID 937601, 8 pages, 2014.

[83] P.-C. Chen, M. R. Vargas, A. K. Pani et al., "Nrf2-mediated neuroprotection in the MPTP mouse model of Parkinson's disease: critical role for the astrocyte," in *Proceedings of the National Academy of Sciences*, vol. 106, no. 8, pp. 2933–2938, 2009.

[84] E. Lv, J. Deng, Y. Yu et al., "Nrf2-ARE signals mediated the anti-oxidative action of electroacupuncture in an MPTP mouse model of Parkinson's disease," *Free Radical Research*, vol. 49, no. 11, pp. 1296–1307, 2015.

[85] J. Deng, E. Lv, J. Yang et al., "Electroacupuncture remediates glial dysfunction and ameliorates neurodegeneration in the astrocytic alpha-synuclein mutant mouse model," *Neuroinflammation*, vol. 12, p. 103, 2015.

[86] S.-N. Kim, S.-T. Kim, A.-R. Doo et al., "Phosphatidylinositol 3-kinase/Akt signaling pathway mediates acupuncture-induced dopaminergic neuron protection and motor function improvement in a mouse model of Parkinson's disease," *International Journal of Neuroscience*, vol. 121, no. 10, pp. 562–569, 2011.

[87] T. Tian, Y. Sun, H. Wu et al., "Acupuncture promotes mTOR-independent autophagic clearance of aggregation-prone proteins in mouse brain," *Science Reports*, vol. 6, Article ID 19714, 2016.

[88] Y. Zhao, D. Luo, Z. Ning, J. Rong, and L. Lao, "Electroacupuncture ameliorated MPTP-induced parkinsonism in mice via TrkB neurotrophic signaling," *Frontiers in Neuroscience*, vol. 13, p. 496, 2019.

[89] X.-Y. L. Xi-Bin Liang, Li Feng-Qiao, Y. Luo et al., "Long-term high-frequency electro-acupuncture stimulation prevents neuronal degeneration and up-regulates BDNF mRNA," *Molecular Brain Research*, vol. 108, no. 1-2, pp. 51–59, 2002.

[90] Z. Wang, T. Yi, M. Long et al., "Electro-acupuncture at Zusanli acupoint (ST36) suppresses inflammation in allergic contact dermatitis via triggering local IL-10 production and inhibiting p38 MAPK activation," *Inflammation*, vol. 40, no. 4, pp. 1351–1364, 2017.

[91] L.-r. Gong, Y.-x. Kan, Y. Lian et al., "Electroacupuncture attenuates limb ischemia-reperfusion-induced lung injury via p38 mitogen-activated protein kinase-nuclear factor erythroid-2-related factor-2/heme oxygenase pathway," *Journal of Surgical Research*, vol. 246, pp. 170–181, 2020.

[92] J. Liu, Q. Wang, S. Yang et al., "Electroacupuncture inhibits apoptosis of peri-ischemic regions via modulating p38, extracellular signal-regulated kinase (ERK1/2), and c-jun N terminal kinases (JNK) in cerebral ischemia-reperfusion-injured rats," *Medical Science Monitor*, vol. 24, pp. 4395–4404, 2018.

[93] S. Li, L. Bao, L. Si, X. Wang, and A. Bo, "Research on roles of Mongolian medical warm acupuncture in inhibiting p38 MAPK activation and apoptosis of nucleus pulposus cells," *Evidence-Based Complementary and Alternative Medicine*, vol. 2018, Article ID 6571320, 8 pages, 2018.

[94] G. A. W. A. N. D. Perkins, "Transcriptional cross talk between NF-κB and p53," *Molecular and Cellular Biology*, vol. 19, no. 5, pp. 3485–3495, 1999.

[95] J.-Y. Park, H. Choi, S. Baek et al., "p53 signalling mediates acupuncture-induced neuroprotection in Parkinson's disease," *Biochemical and Biophysical Research Communications*, vol. 460, no. 3, pp. 772–779, 2015.