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Review

Keap1-Nrf2 Signaling Pathway-Mediated Antioxidant Defense in Neurodegenerative Diseases: Mechanisms and Traditional Chinese Medicine Therapeutic Strategies

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Abstract

Neurodegenerative diseases (NDs) are incurable, progressively disabling disorders marked by sustained neuronal degeneration and loss. Their molecular basis involves intricate regulatory networks, while current therapeutic strategies remain inadequate. Oxidative stress (OS) constitutes a major driver in the initiation and progression of age-related pathologies. Kelch-like enoyl-CoA hydratase-associated protein-1 (Keap1)-Nuclear factor Erythroid 2-related factor 2 (Nrf2) signaling pathway, an essential antioxidant system, exerts protective effects by limiting OS-mediated cellular injury. Extensive evidence demonstrates a close association between Nrf2 signaling and the pathological processes of NDs, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). Traditional Chinese medicine, characterized by multi-target and multi-pathway regulatory actions of its bioactive constituents, offers distinctive therapeutic potential for NDs. This review provides an integrated analysis of current advances of Nrf2 involvement in NDs and evaluates therapeutic strategies based on traditional Chinese medicine and its active components, with the aim of guiding future clinical translation.

Keywords: NF-E2-related factor 2; oxidative stress; neurodegenerative diseases; molecular mechanisms of pharmacological actions; traditional Chinese medicine

1. Introduction

With the rapid demographic transition toward an aging population, neurodegenerative diseases (NDs) have become a major healthcare challenge worldwide [1]. Disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS) are characterized by progressive functional impairments, including cognitive, memory, and motor function [2]. The global burden of NDs is considerable; the prevalence of AD alone has already exceeded 50 million and is projected to reach 152 million by 2050 [3,4]. Likewise, the number of PD cases surpassed 6 million in 2015 and is expected to exceed 17 million by 2040 [5].

The development of NDs arises from a complex interplay of mechanisms, including inflammatory signaling, oxidative stress (OS), pyroptosis, mitochondrial dysfunction, amyloid accumulation, and infection-related factors [6–10]. Exposure to harmful stimuli provokes excessive generation of reactive species such as reactive oxygen species (ROS), disrupting redox equilibrium and initiating OS [11]. Elevated ROS levels induce structural and functional injury to lipids, proteins, and DNA, thereby destabilizing cellular homeostasis. This oxidative imbalance is closely associated with both neurodegenerative progression and biological aging [12–15]. In brain tissues of patients with NDs, high levels of oxidative products are consistently observed, accompanied by extensive neuronal oxidative damage [12,16].

Nuclear factor E2-related factor 2 (Nrf2), an endogenous antioxidant transcription factor, serves as a principal regulator of cellular defense against OS-induced injury [17]. By controlling the transcription of antioxidant genes, cytoprotective enzymes, and efflux transporters, Nrf2 establishes an integrated protective network that preserves intracellular redox equilibrium. Increasing evidence demonstrates that pharmacological modulation of Nrf2 attenuates NDs [9]. In AD models, enhanced Nrf2 activity alleviates ROS-driven damage and mitochondrial impairment [18]. In MPTP-induced PD mice, Nrf2 upregulation improves motor coordination, diminishes dopaminergic neuronal loss, suppresses neuroinflammation, and prevents ferroptotic degeneration, collectively yielding neuroprotective outcomes [19,20]. In 3-NPA-induced HD rats, protopanaxtriol enhances Nrf2 nuclear translocation and elevates HO-1 and NQO1 expression, thereby reducing OS and restor-

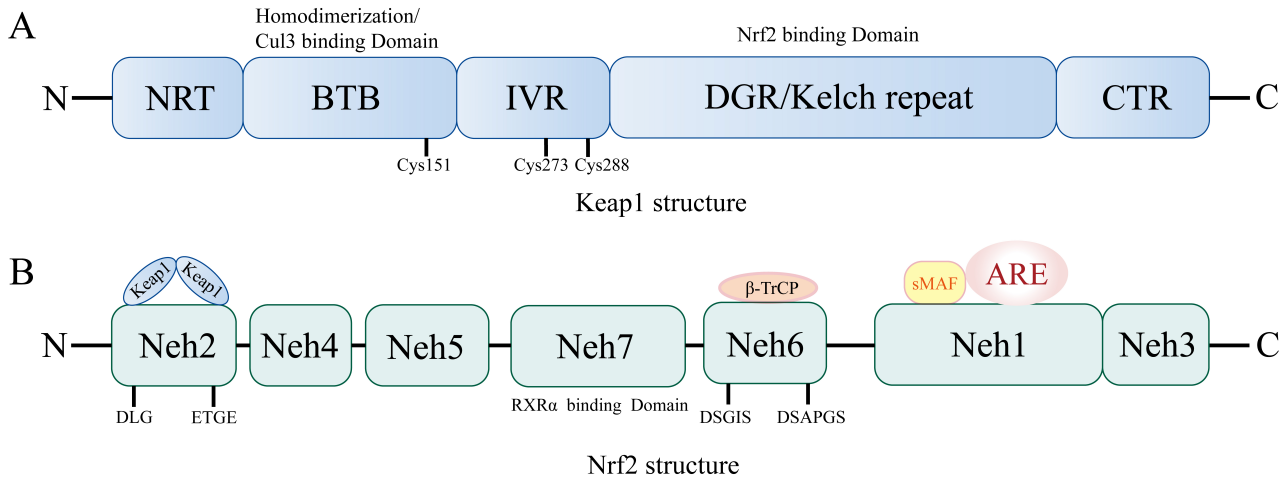

Fig. 1. Structures of Kelch-like enoyl-CoA hydratase-associated protein-1 (Keap1) and Nuclear factor Erythroid 2-related factor 2 (Nrf2). (A) Keap1 comprises five distinct regions: the N-terminal region (NTR); the BTB (Broad-Complex, Tramtrack, and Bric-à-brac) domain, which mediates homodimerization and interaction with Cul3; the intervening region (IVR) containing Cys273 and Cys288; the double glycine repeat (DGR)/Kelch repeat domain responsible for Nrf2 binding; and the C-terminal region (CTR). (B) Nrf2 consists of seven functional domains (Neh1–Neh7). Neh1 facilitates heterodimerization with sMaf proteins and binds to antioxidant response elements (ARE). Neh2 includes the DLG and ETGE motifs essential for Keap1 interaction and subsequent Nrf2 degradation. Neh3–Neh5 serve as transcriptional activation regions. Neh6 contains DSGIS and DSAPG degron motifs, regulating Nrf2 stability. Neh7 interacts with retinoic acid receptor alpha (RXRα).

ing neuronal structure [21]. Targeting Nrf2 thus represents a promising therapeutic strategy for NDs by modulating oxidative stress, neuroinflammation, and mitochondrial homeostasis. Given the multifactorial pathogenesis of NDs, interventions designed to influence multiple molecular targets and signaling pathways present substantial potential. Notably, bioactive compounds derived from traditional Chinese medicine provide a compelling direction for ND treatment [22,23].

This review summarizes recent progress in elucidating the structural and functional roles of Nrf2 in NDs, highlights the contribution of Nrf2 dysregulation to disease progression, and examines emerging therapeutic strategies with potential clinical relevance.

2. Materials and Methods

Relevant literature was collected using PubMed database search using ("NF-E2-Related Factor 2" OR "Nrf2") AND (neurodeg* OR "Alzheimer Disease" OR "Parkinson Disease" OR "Huntington Disease" OR "amyotrophic lateral sclerosis" OR "Medicine, Chinese Traditional") retrieved 2493 articles published between Jan. 2015 and May. 2025. Inclusion criteria were: ① Articles addressing neurodegenerative disease regulation via the Nrf2 signaling pathway; ② Article titles or abstracts containing either 'NF-E2-Related Factor 2' or 'Nrf2' alongside any other search term. Exclusion criteria: ① Articles lacking full text were excluded; ② Articles unrelated to neurodegenerative diseases were excluded. This yielded 936 articles. Following final screening based on manuscript subject and full-text content, 70 articles met the criteria: 33 review articles and 37 experimental or other types of articles.

3. Molecular Regulatory Network of Nrf2

3.1 Biological Structure of Keap1 and Nrf2

The Keap1–Nrf2 signaling axis plays a central role in maintaining oxidative equilibrium. Keap1 consists of five distinct domains: NTR, BTB, IVR, DGR (Kelch repeat), and CTR (Fig. 1A) [24]. Nrf2, a basic leucine zipper (bZip) transcription factor, is organized into seven conserved domains (Neh1–Neh7) (Fig. 1B) [25,26]. Neh1 associates with sMaf proteins to recognize and bind the ARE, thereby driving the transcription of antioxidant and anti-inflammatory genes [27]. Neh2 functions as the principal regulatory module, containing the conserved DLG and ETGE motifs that engage the Keap1 Kelch domain to govern Nrf2 degradation [28]. The ETGE motif binds with high affinity, while the DLG motif exhibits weaker interaction [29,30]. Neh3–Neh5 act as transcriptional activation regions through co-activator recruitment, although their precise roles remain unclear [31,32]. Neh6 carries DSGIS and DSAPG degrons; phosphorylation of DSGIS by GSK-3β increases its affinity for β-TrCP, directing proteasomal degradation of Nrf2 [33,34]. Neh7 interacts with RXRα, which can disrupt the association of Neh4/Neh5 with CBP and suppress transcriptional initiation [35]. Overall, Nrf2 regulation occurs through both Keap1-dependent and alternative Keap1-independent pathways.

3.2 Keap1-Dependent Nrf2 Regulation

Under redox equilibrium, Nrf2 and Keap1 form homodimers in the cytoplasm. Keap1 dimers interact with the Cul3-Rbx1 E3 ubiquitin ligase complex, directing Nrf2 toward ubiquitination and subsequent proteasomal degradation via the 26S system [24]. When intracellular oxidative or electrophilic stress increases, Nrf2 activation follows the "hinge-lock" paradigm. Covalent modifications of key cysteine residues on Keap1, particularly Cys151 within the BTB domain and Cys273 and Cys288 in the IVR domain, trigger zinc release and structural rearrangements. In this altered state, the DLG motif of Nrf2, functioning as a lock, disengages, whereas the ETGE motif remains bound as a hinge. This partial dissociation prevents ubiquitination and degradation of Nrf2 [29,36]. Newly synthesized Nrf2 then evades Keap1-mediated repression, translocates into the nucleus, and binds ARE sequences to initiate transcription of antioxidant genes (Fig. 2) [37].

3.3 Keap1-Independent Nrf2 Regulation

Nrf2 is also subject to regulation beyond Keap1 control through several mechanisms, including modulation by p62/SQSTM1, the cyclin-dependent kinase inhibitor p21, and epigenetic processes [38].

3.3.1 p62/SQSTM1-Mediated Nrf2 Regulation

p62/SQSTM1 acts as a selective autophagy receptor containing distinct structural elements such as the N-terminal Phox-BEM1 (PB1) domain, ZZ-type zinc finger domain, TRAF6-binding sequence (TBS), LC3-interacting region (LIR), Keap1-interacting region (KIR), and the C-terminal ubiquitin-associated (UBA) domain (Fig. 3A). It additionally functions as an activator of the non-canonical Keap1–Nrf2 pathway [39,40]. Within the KIR domain, the 349-DPSTGE-354 motif mimics the ETGE motif located in the Neh2 domain of Nrf2, thereby enabling strong Keap1 binding [41]. Phosphorylation of S351 in the KIR domain markedly strengthens the interaction of p62 with Keap1, displacing Nrf2 from Keap1. The resulting p62–Keap1 complex is targeted to autophagosomes, which leads to Nrf2 stabilization, its nuclear import, and transcriptional induction of cytoprotective genes (Fig. 3B) [42]. In addition, p62/SQSTM1 enhances the association of AMPK with ULK1, promoting ULK1 phosphorylation and initiating bulk autophagy. This process accelerates Keap1 degradation, further reinforcing Nrf2 activation [43].

3.3.2 p21-Mediated Nrf2 Regulation

p21 engages Keap1 while simultaneously binding to Nrf2 via its DLG motif, whereas Keap1 remains attached to the ETGE motif of Nrf2 [44]. This ternary complex disrupts Nrf2 ubiquitination and subsequent proteasomal degradation (Fig. 3C), thereby stabilizing Nrf2 and enhancing cellular antioxidant defense capacity [45].

3.3.3 Epigenetic Regulation

Epigenetic regulation, defined as heritable alterations in gene expression without modification of the DNA sequence, represents a central mechanism in controlling cellular adaptation to OS. Principal processes include DNA methylation, histone modification, and non-coding RNA-mediated regulation [31]. Among them, epigenetic modifications modulate Nrf2 activity through Keap1-independent mechanisms. For example, miR-139 directly suppresses cJUN and the nuclear transport regulator KPNA2, leading to reduced Nrf2 activation and heightened sensitivity of NSCLC cells to radiation-induced oxidative stress, thereby restraining tumor progression [46]. Likewise, miR-144-3p targets the 3′-UTR of Nrf2 mRNA in renal tubular epithelial cells, diminishing Nrf2 signaling and accelerating chronic kidney disease (CKD) progression [47]. Under hypoxic conditions, upregulation of miR-140-5p directly suppresses Nrf2 activity, limiting the proliferative capacity of breast cancer (BC) cells [48]. In addition, sulforaphane (SFN) promotes histone H3 acetylation within the Nrf2 promoter region, activating the cardiac Nrf2 pathway and conferring cardioprotective effects [31]. Conversely, CpG methylation within the Nrf2 promoter region reduces Nrf2 and NQO1 protein expression, strongly correlating with prostate cancer development [49] (Fig. 4).

4. Mechanisms of Nrf2 in NDs

4.1 Alzheimer's Disease (AD)

AD is a progressive neurodegenerative disorder characterized by cognitive decline, with its pathological hallmarks being senile plaques derived from β-amyloid (Aβ) aggregation and neurofibrillary tangles (NFTs) resulting from aberrant tau phosphorylation (Fig. 5A) [50]. Pathological accumulation of Aβ increases intracellular ROS levels [51], which in turn drives a cascade of deleterious events including tau modifications, impaired heme metabolism, and mitochondrial dysfunction, thereby sustaining a self-reinforcing cycle of neurotoxicity [52,53]. Among genetic determinants, APOE polymorphisms—particularly carriage of the ε4 allele—constitute the strongest risk factor for sporadic AD. The resulting apolipoprotein E (apoE) protein influences not only Aβ aggregation and clearance but also modulates neuroinflammation and synaptic activity, thereby shaping the trajectory of disease progression [54]. Oxidative injury induced by ROS against proteins and nucleic acids disrupts synaptic integrity and promotes neuronal loss, while ROS also enhances activation of the senescence-associated secretory phenotype (SASP), aggravating neuroinflammation and tissue damage [55]. The reciprocal relationship between ROS accumulation and cellular senescence is increasingly regarded as a central mechanism driving AD pathogenesis [56].

Aβ, the primary component of senile plaques, is a 4.0–4.2 kDa peptide generated by sequential cleavage of

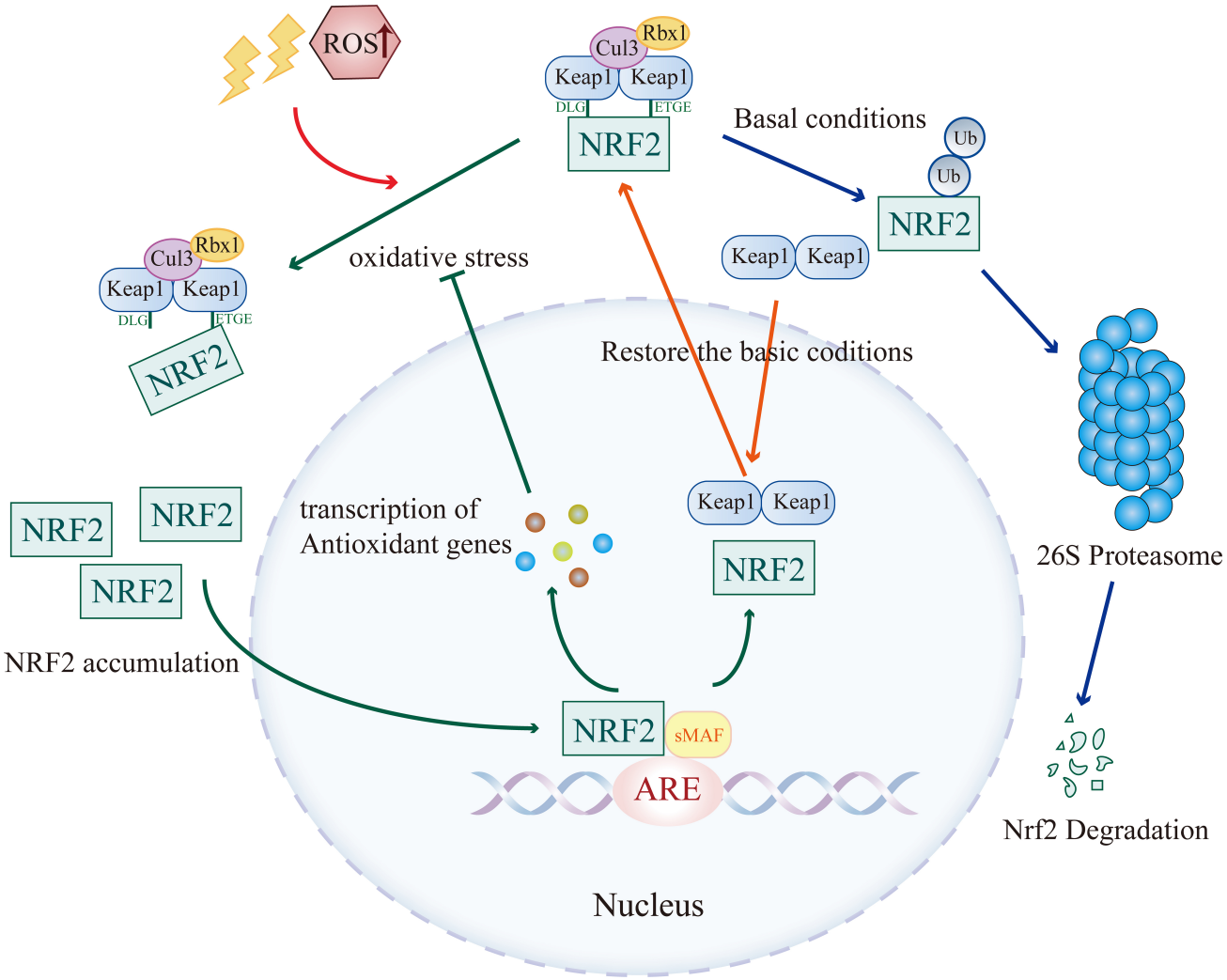

Fig. 2. Keap1-dependent regulation of Nrf2. Under homeostatic conditions, Keap1 interacts with the ETGE and DLG motifs of Nrf2, promoting its ubiquitination via the Keap1/Cul3/Rbx1 complex and subsequent proteasomal degradation by the 26S proteasome (blue arrow). In response to electrophilic agents or elevated ROS levels, the Keap1–Nrf2 association is attenuated, permitting Nrf2 to evade ubiquitination and degradation. Stabilized Nrf2 accumulates in the cytoplasm, translocates to the nucleus, forms heterodimers with sMaf proteins, and binds to AREs to initiate transcription of antioxidant genes, thereby mitigating oxidative stress (green arrow). Upon reestablishment of redox balance, Keap1 shuttles into the nucleus, promotes the nuclear export of Nrf2, and re-engages the cytoplasmic ubiquitination machinery, restoring its degradation (orange arrow).

amyloid precursor protein (APP) through β-secretase and γ-secretase. Among its isoforms, $A\beta_{1-42}$ demonstrates markedly higher neurotoxicity owing to its strong tendency for oligomerization and plaque deposition [57,58]. Oligomeric $A\beta$ disrupts the entorhinal cortex–hippocampal circuitry essential for memory integration and triggers glial activation, which in turn contributes to indirect neuronal damage [59]. Once activated, microglia and astrocytes release proinflammatory mediators and ROS, creating a "secondary assault" that further increases neuronal susceptibility [60]. During this cascade, apoE isoforms—particularly apoE4—exert a decisive influence on the magnitude of neurotoxic release by modulating microglial inflammatory responses, thereby accelerating or attenuating AD progression [61]. Importantly, $A\beta$-driven pathology is mediated largely through amplification of neuroinflammation and OS rather than direct neuronal assault, providing a mechanistic rationale for therapeutic interventions targeting inflammatory and oxidative pathways in AD [62].

Marked disruption of redox balance in the brains of AD patients initiates lipid peroxidation, which reduces membrane fluidity and impairs ion channel activity, thereby diminishing neuronal excitability and weakening synaptic transmission, ultimately progressing to neuronal dysfunction and apoptosis [63,64]. The apoE4 isoform has been implicated in lowering neuronal tolerance to oxidative stress and in aggravating mitochondrial impairment, thereby heightening vulnerability to cell death [65]. Pro-

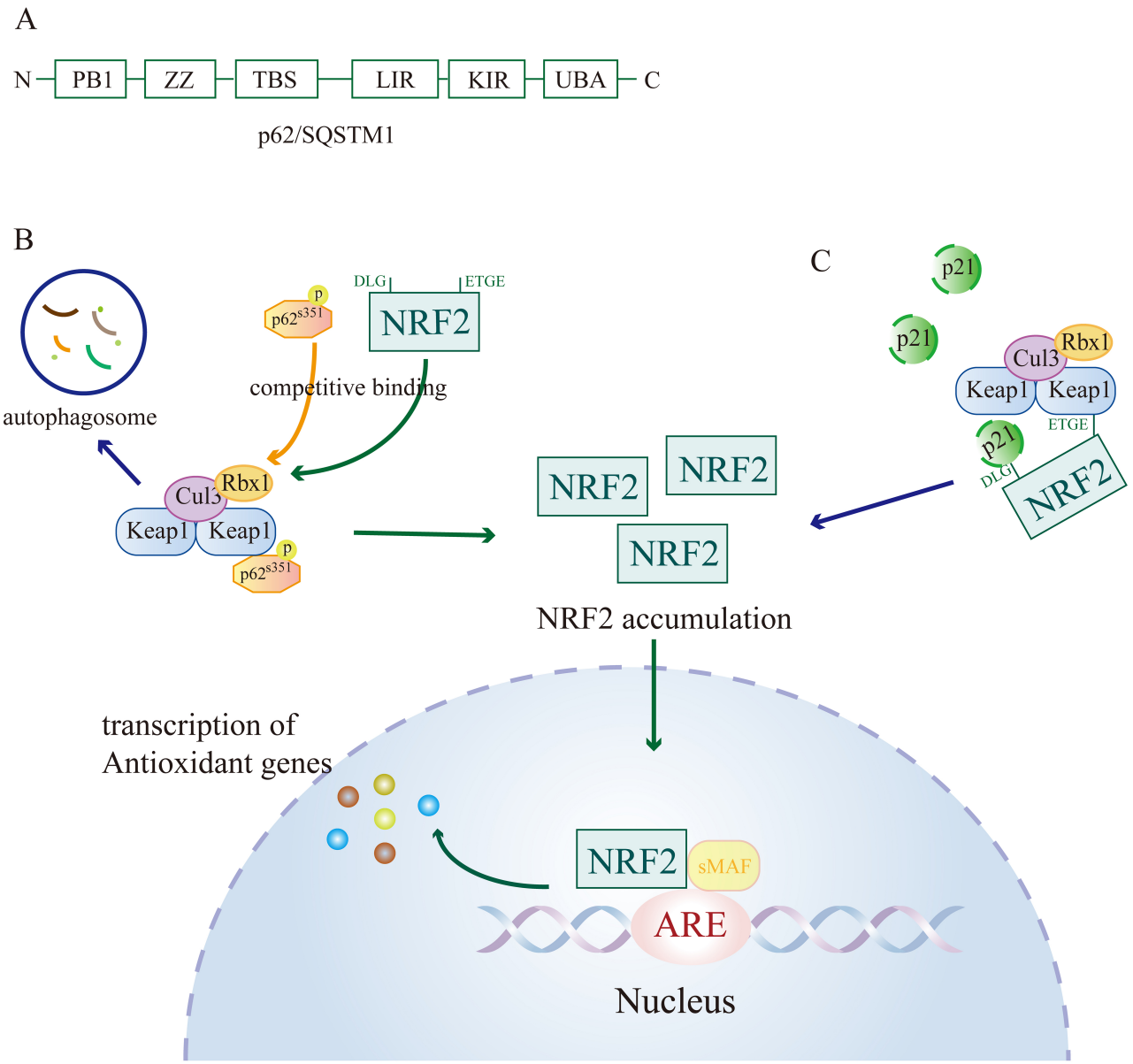

Fig. 3. Non-dependent regulation of Nrf2 by p62 and p21. (A) Domain structure of p62/SQSTM1, comprising the N-terminal PhoxBEM1 (PB1) domain, ZZ-type zinc finger domain, TRAF6-binding sequence (TBS), LC3-interacting region (LIR), Keap1-interacting region (KIR), and the C-terminal ubiquitin-associated (UBA) domain. (B) Phosphorylation of p62 at S351 enables competitive binding with Keap1, displacing Nrf2. The p62–Keap1 complex is sequestered into autophagosomes, resulting in Nrf2 stabilization, nuclear translocation, and activation of antioxidant gene expression. (C) p21 binds to the Nrf2 motif, while Keap1 interacts with ETGE, and the combined effect blocks Nrf2 ubiquitination and degradation, leading to Nrf2 accumulation in the cytoplasm and subsequent nuclear translocation, thereby promoting antioxidant gene transcription.

gressive neuronal loss disrupts local microcircuitry and diminishes integrative network function, driving further cognitive decline and reinforcing a pathological cycle that accelerates AD progression. Within this setting, Nrf2 acts as a central regulator of oxidative defense by inducing endogenous antioxidant systems. Upon oxidative challenge, Nrf2 migrates to the nucleus, dimerizes with sMAF, and binds to ARE sequences in promoter regions of target genes, initiating the transcription of antioxidant enzymes such as HO-1, GSH-Px, and CAT (Fig. 5E) [66,67]. The concerted activity of these enzymes neutralizes excess ROS and supports the repair of oxidative damage, thereby restoring redox balance and attenuating neurodegenerative processes in AD [68]. Emerging evidence further indicates that ApoE expression may intersect with Nrf2 activity, providing new insight into the relationship between genetic susceptibility and antioxidant regulation in AD [65].

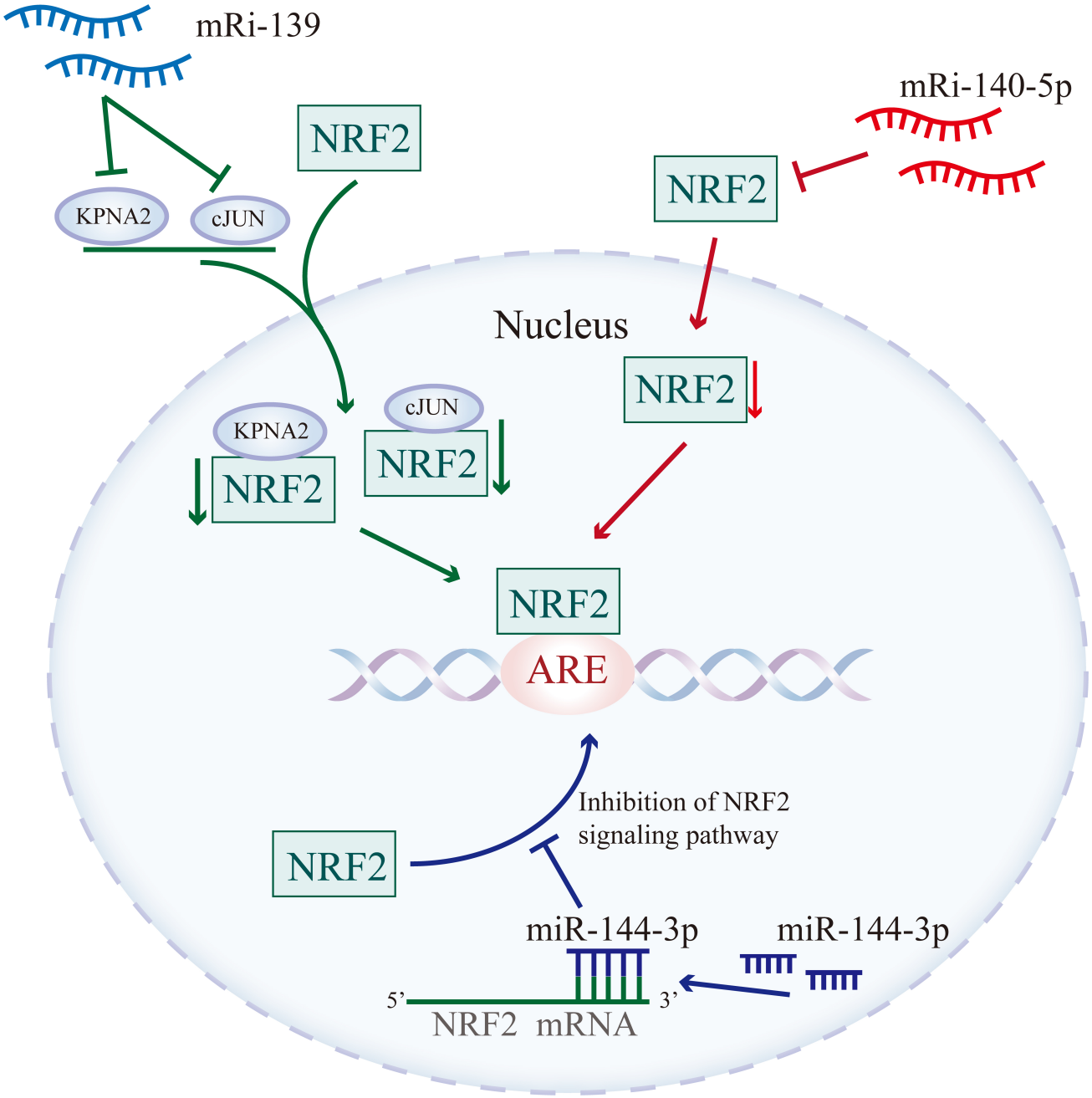

Fig. 4. Epigenetic mechanisms of Nrf2 regulation. miR-139 represses Nrf2 activation by targeting cJUN and KPNA2, thereby limiting nuclear translocation of Nrf2; miR-144-3p binds to the 3′-UTR of Nrf2, suppressing downstream signaling and attenuating activation; miR-140-5p diminishes Nrf2 activity through direct interaction.

4.2 Parkinson's Disease (PD)

PD, the second most common NDs, is defined by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and by abnormal α-Syn accumulation, including Lewy body deposition (Fig. 5B) [69]. Oxidative stress (OS) is widely recognized as a major contributor to PD pathogenesis [70]. Neuronal susceptibility stems from high oxygen demand and limited antioxidant defenses, while the substantia nigra, enriched with dopamine metabolites such as neuromelanin and abundant iron ions, constitutes a particularly vulnerable region to oxidative injury [71]. Genetic alterations linked to PD, notably mutations in *PARK* genes such as leucine-rich repeat kinase 2 (LRRK2), further intensify OS by promoting mitochondrial dysfunction, disrupting autophagy, and driving pathological protein aggregation [72]. Once ROS production exceeds the endogenous scavenging capacity, oxidative damage extends to lipids, proteins, and nucleic acids, leading to mitochondrial failure, metabolic imbalance, and neuroinflammatory activation, with subsequent neuronal degeneration

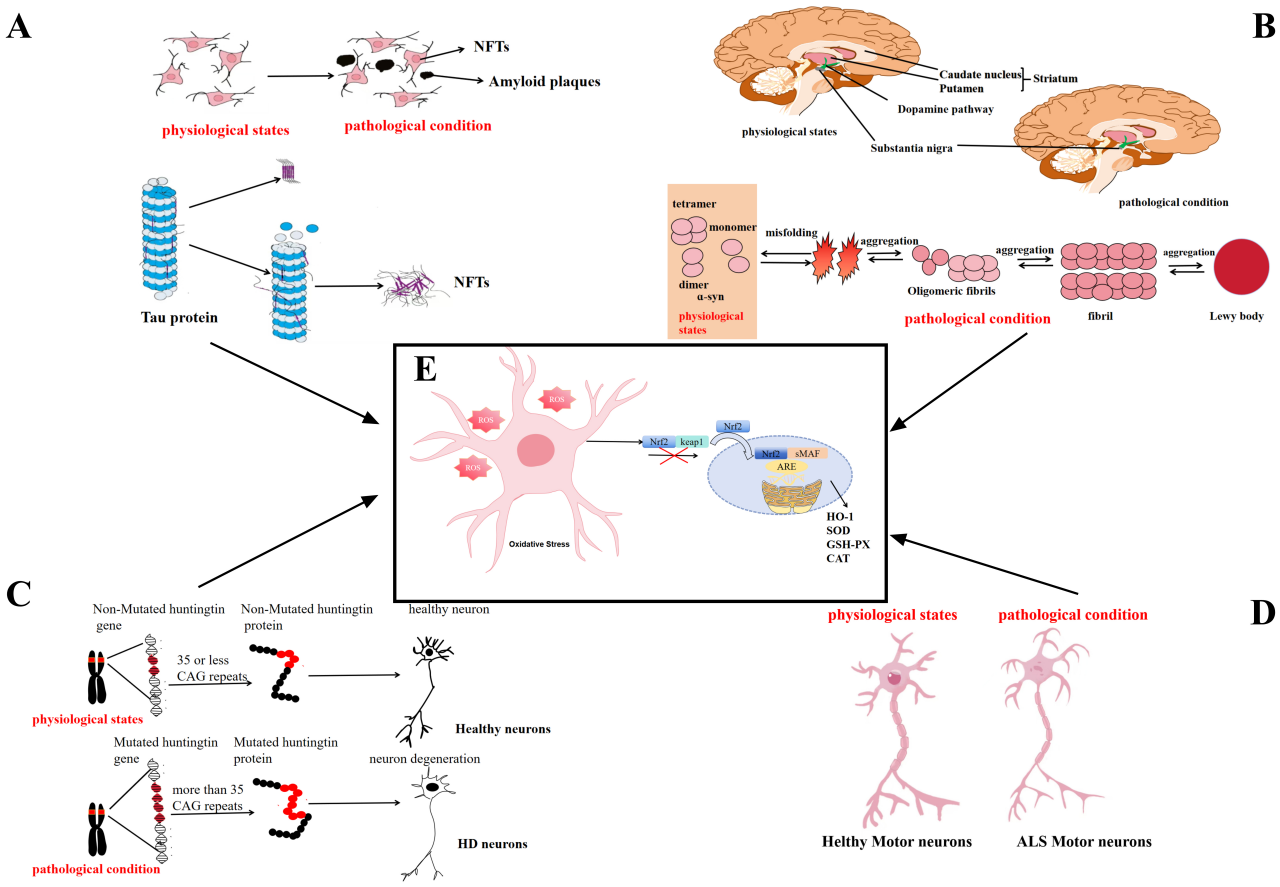

Fig. 5. Core pathological features of NDs in normal and pathological states. (A) Core pathological features of AD. Abnormal Aβ accumulation provokes excessive generation of reactive oxygen species (ROS), which directly damage neuronal lipids, proteins, and DNA while simultaneously accelerating Aβ aggregation and tau hyperphosphorylation, thus reinforcing a self-perpetuating cycle. (B) Core pathological features of PD. Selective degeneration of dopaminergic neurons in the substantia nigra pars compacta coincides with abnormal α-synuclein (α-Syn) aggregation. Dopamine undergoes oxidative degradation, yielding quinones and ROS, while misfolded or aggregated α-Syn induces mitochondrial dysfunction and interacts with mitochondrial membranes, further intensifying ROS production. (C) Core pathological features of HD. Expansion of CAG repeats in the *HTT* gene produces mutant huntingtin protein (mHTt), leading to abnormal aggregation and selective striatal neuronal loss. Elevated ROS levels drive lipid peroxidation, oxidative protein modifications, and mitochondrial DNA (mtDNA) injury, ultimately activating apoptotic pathways and precipitating neuronal death. (D) Core pathological features of ALS. Progressive degeneration of motor neurons in the cerebral cortex, brainstem, and spinal cord, observed in both sporadic and familial ALS, exhibits a distinct oxidative stress phenotype. Mitochondrial dysfunction, glutamate excitotoxicity, glial cell activation, and aberrant biochemical reactions associated with mutations in genes such as SOD1 contribute to excessive ROS accumulation, resulting in protein oxidation, lipid peroxidation, and DNA damage that destabilize motor neuron homeostasis and accelerate degeneration. (E) Mechanism of action of the Nrf2 signaling pathway. Under oxidative stress, Nrf2 translocates into the nucleus and dimerizes with the chaperone protein MAF. This complex binds specifically to antioxidant response elements (ARE) in the promoter regions of target genes, thereby activating transcription of antioxidant enzymes including heme oxygenase-1 (HO-1), glutathione peroxidase (GSH-Px), and catalase (CAT).

[73,74]. This self-reinforcing oxidative process not only accelerates dopaminergic neuronal loss within the substantia nigra but also promotes α-Syn propagation across interconnected brain regions, thereby sustaining PD progression through a feedforward degenerative cascade [75].

α-Syn impairs dopaminergic function through modulation of tyrosine hydroxylase phosphorylation and alteration of dopamine transporter distribution on the neuronal membrane [76]. Accumulating evidence demonstrates that OS profoundly affects α-Syn proteostasis, whereas Nrf2 activation suppresses its pathological accumulation [77]. In neuroblastoma cells, inhibition of the Nrf2–ARE pathway accelerates α-Syn aggregation, aggravating Fe^{2+}-induced mitochondrial dysfunction and activating apoptotic signaling cascades [78]. Conversely, Nrf2 overexpression limits α-Syn aggregation in the CNS [79]. Genetic determinants

such as LRRK2 mutations impair cellular defense against oxidative stress; however, Nrf2 pathway activation partially mitigates the dopaminergic neurotoxicity driven by LRRK2 variants, indicating therapeutic potential in familial PD [80]. Experimental models further demonstrate that Nrf2 enhancement provides measurable neuroprotection: pharmacological inducers attenuate α-Syn-driven neuropathology, and elevated Nrf2 expression in mutant α-Syn transgenic mice reduces neuronal injury [81,82]. Both *in vitro* and *in vivo* observations consistently support the protective function of Nrf2 upregulation in maintaining redox balance and modulating inflammatory responses, thereby sustaining neuronal survival [83]. Increased HO-1 expression, regulated by Nrf2 (Fig. 5E), substantially reduces oxidative damage within substantia nigra neurons, delays α-Syn aggregation, and suppresses early neuroinflammatory processes [84,85]. During initial OS stages, HO-1 acts as a key downstream effector by degrading free heme into biliverdin, CO, and Fe^{3+}. Biliverdin and bilirubin exhibit strong antioxidant activity against lipid peroxides, whereas CO promotes mitochondrial biogenesis and reduces ROS production [86]. Targeting Nrf2 signaling therefore represents a promising approach to counteracting dopaminergic neurodegeneration and motor dysfunction in PD.

4.3 Huntington's Disease (HD)

HD is an autosomal dominant neurodegenerative disorder caused by expansion of CAG repeats in the *HTT* gene, producing mutant Huntington protein (mHTT). Pathological characteristics include striatal neuronal loss and abnormal aggregation of mHTT (Fig. 5C) [87]. Transcriptional dysregulation, mitochondrial dysfunction, and excessive ROS have been identified as major drivers of disease progression [88], with disrupted mitochondrial Ca^{2+} regulation occupying a central position. Impaired buffering by mHTT leads to matrix Ca^{2+} overload, which in turn activates NADPH oxidase and promotes ROS generation [89,90]. The resulting oxidative stress induces lipid peroxidation, protein oxidation, and mitochondrial DNA (mtDNA) damage, ultimately triggering neuronal apoptosis through caspase-dependent mechanisms [91]. This self-amplifying cycle is especially pronounced in the striatum, providing a plausible explanation for its heightened vulnerability in HD [92].

Activation of the Nrf2/ARE signaling cascade in the presence of antioxidant compounds produces a synergistic enhancement of antioxidant enzyme expression, thereby reducing oxidative stress and restricting glutamate release, which in turn delays the manifestation of HD symptoms [93,94]. Experimental studies have further shown that stimulation of the Keap1/Nrf2 axis sustains intracellular ATP levels and preserves mitochondrial membrane potential, thus protecting astrocytes from oxidative injury [95]. During oxidative stress, astrocytes activate Nrf2–ARE signaling, inducing upregulation of antioxidant enzymes such as HO-1 and SOD, thereby strengthening redox homeostasis within neural tissues (Fig. 5E) [96,97]. In HD mouse models, astrocyte-specific Nrf2 overexpression substantially decreases striatal oxidative damage and alleviates motor deficits [98], indicating that glial regulatory pathways contribute significantly to neuroprotection. Impairment of Nrf2 signaling has been associated with disease progression in HD and may drive the gradual neurodegeneration characteristic of the disorder. Future research should assess Nrf2-responsive genes as potential therapeutic targets for HD.

4.4 Amyotrophic Lateral Sclerosis (ALS)

ALS is an aggressive and ultimately fatal form of motor neuron disease (MND) characterized by the progressive degeneration of motor neurons in the cerebral cortex, brainstem, and spinal cord (Fig. 5D) [99]. While most cases occur sporadically, approximately 5–10% are inherited, commonly associated with mutations in C9orf72, SOD1, TARDBP, and FUS [100,101]. Among these, SOD1 mutations hold particular significance, as the Cu^{2+}/Zn^{2+}-binding SOD protein directly influences OS and inflammatory signaling cascades [102,103]. Both sporadic and familial ALS consistently display a pronounced OS profile, widely regarded as a central factor in neuronal degeneration and disease progression. Clinical studies have identified characteristic changes in oxidative stress biomarkers in ALS patients, including diminished total antioxidant capacity (TAC) and reduced enzymatic activities of glutathione peroxidase (GPX), SOD, and glutathione reductase (GR), along with elevated levels of malondialdehyde (MDA), a marker of lipid peroxidation, and 8-OHdG, indicative of oxidative DNA damage [104–106]. Reports of increased total serum antioxidant levels in certain cohorts may instead represent an endogenous adaptive response to persistent free radical burden [107]. Regulation of intracellular ROS and reinforcement of antioxidant defense systems are therefore considered essential therapeutic avenues, with antioxidant capacity itself serving as a promising target for intervention.

The Nrf2/Keap1-ARE signaling cascade constitutes a major protective system against ROS generated under oxidative stress, and its disruption contributes to the pathogenesis of diverse disorders, including NDs (Fig. 5E) [108]. In ALS models carrying the hSOD1 G93A mutation, ferroptotic activation is accompanied by impaired nuclear retention of Nrf2 and reduced expression of the ferroptosis regulators SLC7A11 and GPX4 [19]. Consistently, diminished Nrf2 expression has been documented in the motor cortex and spinal motor neurons of ALS patients [109]. Astrocyte-targeted Nrf2 overexpression alleviates the neurotoxic influence of mutant astrocytes on motor neurons, delaying disease onset and extending lifespan in ALS mice, thereby highlighting the therapeutic potential of reinforcing Nrf2 signaling to counteract progressive neurodegeneration [110].

5. Applications of Nrf2 Activators in NDs

Nrf2 activation enhances its expression in the brain, triggers transcription of cytoprotective genes, reduces OS, and alleviates neurodegenerative pathology, thereby positioning Nrf2-directed agents as therapeutic candidates for NDs. Evidence from both *in vitro* and *in vivo* studies demonstrates that multiple traditional Chinese medicines and their active constituents modulate Nrf2 signaling and confer neuroprotection through antioxidant mechanisms (Table 1, Ref. [111–126]) [127]. Such agents are increasingly regarded as potential interventions in the therapeutic landscape of NDs.

5.1 Flavonoids

Flavonoids, characterized by a 2-phenylchromenone (C6-C3-C6) backbone, display extensive structural variability that determines their bioactivity. Specific subclasses contain α, β-unsaturated carbonyl groups and ortho-dihydroxy substitutions, structural features that enable redox-sensitive interactions with cellular targets. The electrophilic β-carbon of the α, β-unsaturated carbonyl moiety readily participates in Michael addition with cysteine residues such as Cys151, Cys273, and Cys288 on Keap1. This covalent modification induces conformational alterations in Keap1, disrupts its repressive control over Nrf2, promotes Nrf2 nuclear accumulation, and triggers the transcription of ARE-regulated antioxidant genes including HO-1 and NQO1 [128]. The antioxidant capacity of flavonoids is further shaped by hydroxyl group number and positional arrangement, with 3,4-dihydroxy substitutions on the B ring conferring superior radical-scavenging activity [129]. Representative molecules such as baicalin, puerarin, apigenin, quercetin, and luteolin possess α, β-unsaturated carbonyl functionalities; notably, quercetin and luteolin also incorporate ortho-diphenolic hydroxyls, a structural trait linked to enhanced free radical neutralization.

Baicalein, a principal constituent of *Scutellaria baicalensis* Georgi, exhibits anti-inflammatory, antioxidative, antineoplastic, and neuroprotective properties relevant to NDs [105]. Experimental studies further indicate that baicalin protects PC12 cells from 6-OHDA-induced oxidative stress through activation of the Keap1/Nrf2/HO-1 pathway and marked suppression of Keap1 protein expression [111].

Puerarin, a bioactive isoflavone primarily derived from *Pueraria lobata* (Willd.) Ohwi, demonstrates cardioprotective, neuroprotective, antioxidant, anticancer, and anti-inflammatory properties [130]. Experimental studies indicate that puerarin mitigates MPP^+-induced oxidative stress through activation of the Nrf2 signaling cascade. In PC12 cells, puerarin enhances GSH synthesis, promotes nuclear accumulation of Nrf2, and elevates GCLC expression via ARE-dependent transcriptional and translational regulation. These molecular adaptations improve motor performance in wild-type mice exposed to MPP^+ and reduce oxidative injury within the ventral midbrain [112]. In addition, puerarin regulates the Akt/GSK-3β/Nrf2 axis by stimulating Akt activity while inhibiting GSK-3β, thereby facilitating Nrf2 nuclear translocation in amyloid precursor protein/presenilin-1 (APP/PS1) mice. This regulatory effect is linked to reduced lipid peroxidation (LPO) and increased HO-1 expression, ultimately contributing to the attenuation of cognitive impairments in APP/PS1 mice [113].

Apigenin, widely distributed in dietary sources such as *Apium graveolens* L., spinach, chamomile, grapes, and apples, exerts diverse pharmacological actions including antioxidant, antibacterial, and antidiabetic effects [131]. Experimental studies demonstrate that apigenin suppresses neuronal apoptosis by accelerating α-Syn degradation through Nrf2-dependent CMA activation and by modulating an Nrf2/ERK feedback mechanism independent of CMA [127]. In BV2 microglial cells, apigenin enhances phagocytic capacity and attenuates α-Syn-driven neuroinflammation in both *in vitro* and *in vivo* systems [114]. In addition, the Tg(SOD1*G93A)1Gur/J mouse model provided the first evidence that apigenin activated the Nrf2/ARE pathway via upregulation of ALDH1A2, resulting in attenuation of oxidative stress and apoptosis-related markers while correcting dysregulated TAR DNA/RNA-binding protein 43 (TDP-43) expression and its associated neuronal damage, ultimately delaying ALS progression [115].

Quercetin, mainly derived from traditional Chinese medicinal plants such as *Flos Sophorae Immaturus* and *Platycladus orientalis* (L.) Franco, exhibits broad pharmacological activities including anti-cancer, anti-inflammatory, antiviral, and antioxidant effects [132]. Experimental results reveal that quercetin enhances PC12 cell survival under $A\beta_{25-35}$ exposure by promoting proliferation, counteracting cytotoxicity, elevating SOD, GSH-Px, and HO-1 activity, and reducing MDA and LDH accumulation through activation of the sirtuin1/Nrf2/HO-1 signaling pathway [116]. In an Aβ1-42-induced HMC3 cell model, quercetin reduced MDA levels and significantly increased SOD activity and the GSH/GSSG ratio by activating the Nrf2/HO-1 cascade, and simultaneously lowered the levels of IL-1, IL-6, and TNF-α [117].

Luteolin, a flavonoid abundant in traditional Chinese medicinal plants such as *Lonicera japonica* Thunb. and *Dendranthema morifolium* Ramat., exhibits antioxidant, anti-inflammatory, antitumor, and neuroprotective properties [133]. Experimental studies demonstrate that luteolin improves cell survival and suppresses apoptosis, thereby reducing the cytotoxicity associated with mutant huntingtin protein. In neuroblastoma cells expressing 160Qhtt, luteolin diminishes both soluble and insoluble mHTt aggregates, indicating its potential to modulate protein misfolding and aggregation pathways [118].

Table 1. Active ingredients in traditional Chinese medicine.

Category	Active ingredient	Source	Models	Treatment	Major Finding	Ref.
Flavonoids	Baicalein	*Scutellaria baicalensis* Georgi	1 mM 6-OHDA treated PC12 cells 8 h	50∼200 μM baicalein treated PC12 cells 12 h	↑Nrf2, ↑HO-1, ↓Keap1	[111]
	Puerarin	*Pueraria lobata* (Willd.) Ohwi	250 μM MPP^+ treated PC12 cells for 24 h	10 μM Pueraria Mirifica treated PC cells for 1 h	↑Nrf2, ↑GSH, ↑GCLC	[112]
			APP/PS1 transgenic mice	Puerarin (30 mg/kg) dissolved in 1,2-propanediol and administered by gavage for 28 consecutive days	↑HO-1, ↓MDA	[113]
	Apigenin	*Apium graveolens* L.	1 mg/L doxycycline (Dox) treatment of $SNCA^{WT}$SH-SY5Y cells for 24 hours	$SNCA^{WT}$SH-SY5Y cells were treated with 50 μM and 100 μM apigenin for 24 h, respectively	↑CMA, ↓Bax, ↓α-Syn, ↑Bcl-2 ↑Caspase-3, ↓TNF-α, ↓IL-1β, ↓IL-6	[114]
			Male C57BL/6J mice were taken and rotenone (3 mg/kg) was injected subcutaneously continuously for 5 weeks	Male C57BL/6J mice were administered orally, low dose (25 mg/kg) and high dose (50 mg/kg) apigenin for 5 weeks prior to modeling	↓TNF-α, ↓IL-1β, ↓Iba1	
			Tg(SOD1*G93A)1Gur/J transgenic mice	Oral apigenin (80 mg/kg) once daily, sh-ALDH1A2 treatment initiated at symptom onset (day 90)	↓MDA, ↓4-HNE, ↓ROS, ↑SOD, ↑ALDH, ↑Bcl-2, ↓Caspase-3, ↓Bax, ↓TDP-43	[115]
	Quercetin	*Flos Sophorae Immaturus*; *Platycladus orientalis* (L.) Franco	PC12 cells were treated with 20 μmol/L β_{25-35} for 24 h	PC12 cells were pretreated with 10 μmol/L, 20 μmol/L, 40 μmol/L and 80 μmol/L quercetin for 24 h, 48 h and 72 h, respectively	↑SOD, ↑GSH-Px, ↑HO-1, ↓MDA, ↓LDH, ↑CAT, ↓AChE, ↑T-AOC, ↑Sirtuin1, ↑Nrf2	[116]
			APP/PS1 transgenic mice	Quercetin (100 mg/kg) administered by gavage for 6 consecutive months	↓MDA, ↑SOD, ↑GSH-Px, ↑CAT, ↑GSH, ↑AChE, ↑Nrf2, ↑HO-1, ↑NQO1, ↓Keap1, ↓Aβ, ↓ROS	[117]
	Luteolin	*Lonicera japonica* Thunb; *Dendranthema morifolium* Ramat.	Mouse neuroblastoma Neuro2A (ATCC) cells were transfected with a plasmid encoding an htt N-terminal fragment containing 20Q (htt20Q) and 160Q (htt160Q) to obtain cell models expressing normal (20Q htt) and mutant (160Q htt) cells	Mutant (160Q htt) cells were treated with lignocaine (5 ng/mL) for 48 h	↑Nrf2, ↑HO-1, ↓Caspase-3	[118]
	Icariin	*Epimedium brevicornu* Maxim.	40 μM 6-OHDA treatment of PC12 cells for 24 h	0.005 μM and 0.05 μM Icariin pretreated PC12 cells for 24 h	↑Nrf2, ↑HO-1, ↑NQO1, ↑GCLC, ↑SOD, ↓ROS, ↓Caspase-3	[119]

Table 1. Continued.

Category	Active ingredient	Source	Models	Treatment	Major Finding	Ref.
Terpenoids	Andrographolide	*Andrographis paniculata* (Burm. f.) Wall. ex Nees	1.5 mM MPP^+ treated SH-SY5Y cells 24 h	1.5 μM Andrographolide Pretreatment of SH-SY5Y cells 24 h	↑SOD, ↑HO-1, ↑GPX, ↑CAT, ↑GSTP1, ↑Bcl-2, ↓Bax, ↓Caspase-3	[120]
	Tanshinone IIA	*Salviae Miltiorrhizae* Radix et Rhizoma	100 μM 6-OHDA treated SH-SY5Y cells for 24 h	20 μg/mL tanshinone IIA treated SH-SY5Y cells 24 h	↑Nrf2, ↑HO-1, ↑GCLC, ↑GCLM, ↑NQO1, ↓LDH, ↓ROS	[121]
	Celastrol	*Tripterygium wilfordii* Hook. F.	Continuous 5 days intraperitoneal injection of 20 mg/kg MPTP induced PD in mice	10 μg/kg tretinoin intraperitoneally for 7 days	↑TH, ↑Nrf2, ↑HO1, ↑NQO1, ↑GCLC, ↑GCLM, ↓NLRP3, ↓Caspase-1, ↓TNF-α, ↓IL1, ↓IL6	[122]
			AAV-mediated human wild-type α-Syn (h-α-Syn) overexpression PD model by stereotactic injection in the SNC	10 μg/kg tretinoin intraperitoneal injection for 42 days	↓GFAP, ↓Iba1, ↑TH, ↑DAT	
Phenols	Curcumin	*Curcuma longa* L.	Subcutaneous injection of 2.5 mg/kg of rotenone induced PD in mice for 35 days	Pregavage administration of 80 mg/kg Curcumin for 7 days, then co-treatment with rotenone for 35 days for a total of 42 days	↑Nrf2, ↑LC3-II, ↓MDA, ↓α-Syn, ↓Keap1	[123]
	Resveratrol	grapes; *Reynoutria japonica* Houtt	50 μM MPP^+ treated SH-SY5Y cells for 24 h	Cells were replaced from medium containing MPP^+ to human neural stem cell-derived exosomes (hNSCs-Exos) medium treated with 10 μg/mL resveratrol for another 48 h	↑PGC1α, ↑Nrf1, ↑Tfam, ↑AMPK, ↑Nrf2, ↑ATP, ↓ROS, ↓NLRP3, ↓IL-1β, ↓IL-18	[124]
Others	Dimethyl fumarate	Synthetic	App-KI Mouse	300 mg/kg dimethyl fumarate administered by gavage 3 times weekly for 1 month (short-term dosing) and 5 months (long-term dosing)	↑Osgin1, ↑HO-1, ↑GCLM, ↑NQO1, ↓GFAP, ↓C3, ↓Iba1, ↓p-STAT3	[125]
			Primary astrocytes	Primary astrocytes treated with 35 μM dimethyl fumarate for 1 h	↓C3, ↓H2d, ↓H2t23, ↓Gbp2, ↓Socs3	
	Sulforaphane	*Brassica oleracea* L. var. *Italica* Plenck; *Brassica oleracea* var. *capitata* Linnaeus	GFP, GFP - T4, and GFP-T4C3 were injected into the right hippocampal CA1 region of pure C57BL/6J tau knockout (tau (-/-)) male mice (1.5 μL of each AAV at a titer of 10^{13}), respectively. Two months later, the expression of AAVs in the hippocampus was observed and quantified	50 mg/kg radicicol intraperitoneally three times per week for two weeks	↑OPA-1, ↓ROS, ↑HO-1, ↑ATP, ↑HAT	[126]

↑ increase; ↓ decrease.

Abbreviations: 4-HNE, 4-hydroxynonenal; 6-OHDA, 6-hydroxydopamine; α-Syn, alpha synuclein; Aβ, amyloid β-protein; AAV, adeno-associated virus; AChE, acetylcholinesterase; ALDH, Aldehyde dehydrogenase; AMPK, AMP-activated protein kinase; Bax, Bcl-2 associated x; Bcl-2, B-cell lymphoma-2; C3, Complement component 3; CMA, chaperone-mediated autophagy; CAT, catalase; DAT, Dopamine transporter; GSH, glutathione; GCLM, Glutamate-Cysteine Ligase Modifier Subunit; GCLC, glutamate cysteine ligase catalytic subunit; GFAP, glial fibrillary acidic protein; GSH-Px/GPX, Glutathione peroxidase; Gbp2, Guanylate binding protein 2; HO-1, heme oxygenase 1; H2d, Histocompatibility 2, D region; H2t23, Histocompatibility 2, T region locus 23; Iba-1, Ionized calciumbinding adapter molecule 1modifier subunit; Keap1, Kelch-like enoyl-CoA hydratase-associated protein-1; LC3, light chain 3; LDH, Lactate dehydrogenase; MDA, Malondialdehyde; Nrf1, nuclear respiratory factor 1; Nrf2, nuclear factor erythroid 2-related factor 2; NLRP3, NOD- LRR- and pyrin domaincontaining 3; OPA-1, Optic atrophy protein 1; Osgin1, Oxidative stress induced growth inhibitor 1; PGC1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; ROS, reactive oxygen species; SOD, superoxide dismutase; Socs3, Suppressor of cytokine signaling 3; TDP-43, TAR DNA-binding protein 43; T-AOC, total antioxidant capacity; TH, Tyrosine Hydroxylase; Tfam, transcription factor A, mitochondrial.

Icariin, the principal bioactive component of Epimedium brevicornu Maxim., exerts antioxidant, anti-inflammatory, anti-apoptotic, and antitumor effects [134]. Evidence shows that epimedium glycoside attenuates apoptosis by lowering the Bax/Bcl-2 ratio, suppressing cytochrome c release, and inhibiting caspase-3 activation. Moreover, epimedium glycoside activates the Nrf2 pathway, thereby limiting intracellular ROS accumulation, enhancing SOD activity, and upregulating Nrf2, HO-1, and NQO1 expression, ultimately reducing neuronal damage induced by 6-OHDA [119].

Furthermore, the above-mentioned flavonoids possess certain medicinal potential and are commonly used as dietary supplements, such as puerarin, apigenin, and quercetin [135]. Nevertheless, due to challenges such as low bioavailability and toxicity, the development of many flavonoids into clinical drugs has been unsuccessful. The majority of research on flavonoids is based on *in vitro* or animal models, lacking large-scale clinical trials to support their efficacy as medications [136].

5.2 Terpenoid Compounds

Terpenoids constitute a diverse group of natural compounds categorized by structural features into monoterpenes, sesquiterpenes, and diterpenes. Among them, andrographolide, a diterpenoid lactone mainly derived from *Andrographis paniculata* (Burm. f.) Wall. ex Nees., exhibits anti-inflammatory, antioxidant, anticancer, and antihyperglycemic activities [137]. The α, β-unsaturated carbonyl group within its structure enables covalent binding to cysteine residues of Keap1 through a Michael addition reaction. *In vitro* studies indicate that andrographolide exerts neuroprotective effects through activation of the Keap1/Nrf2 pathway, which elevates the activity of antioxidant enzymes including SOD, HO-1, GPX, CAT, and glutathione S-transferase P1 (GSTP1), thereby strengthening cellular redox defenses. Additional neuroprotection has been linked to enhanced mitochondrial autophagy, promoting the clearance of α-Syn aggregates [120].

Tanshinone IIA, a lipophilic diterpene isolated from *Salviae Miltiorrhizae* Radix et Rhizoma, demonstrates anti-inflammatory, antibacterial, and antioxidant properties [138]. Experimental evidence indicates that it preserves dopaminergic neurons in the substantia nigra-striatal pathway by activating Nrf2/ARE signaling. In SH-SY5Y cells, it alleviates 6-OHDA-induced toxicity, reduces LDH release and ROS production, and induces the expression of ARE-regulated genes such as HO-1 and GCLC [121].

Celastrol, a pentacyclic triterpenoid with cork-like characteristics primarily obtained from *Tripterygium wilfordii* Hook. F, exhibits anti-inflammatory, antioxidant, and anti-obesity activities, with emerging relevance for NDs [139]. Leucoanthraquinone has been reported to prevent dopaminergic neuronal loss, preserve nigrostriatal integrity, suppress neuroinflammation, and improve motor outcomes in both MPTP-induced PD mouse models and AAV-mediated α-Syn overexpression models [122].

5.3 Phenolic Compounds

Phenolic compounds act as electrophilic agents that covalently interact with cysteine thiol residues of Keap1, disrupting the Keap1–Nrf2 complex and releasing Nrf2 into the cytoplasm. Following liberation, Nrf2 translocates to the nucleus, associates with ARE sequences in promoter regions, and activates transcription of phase II cytoprotective genes, thereby strengthening cellular defense against OS-induced injury [38]. These electrophilic agents, collectively referred to as Nrf2 activators, frequently contain reactive moieties such as α, β-unsaturated carbonyl groups, which undergo Michael addition or covalent modification with Keap1 cysteines [140].

Curcumin, a natural compound isolated from the rhizome of *Curcuma longa* L., displays antibacterial, antineoplastic, antioxidant, and anti-inflammatory activities [141]. Its α, β-unsaturated carbonyl group selectively reacts with nucleophilic residues, particularly Keap1 cysteine thiols, resulting in Nrf2 release and activation of the Keap1–Nrf2 signaling cascade [142]. Evidence from PD mouse models demonstrates that curcumin improves motor coordination and antioxidant capacity by inducing Nrf2 expression, enhances mitochondrial bioenergetics, and promotes clearance of misfolded α-Syn through LC3-II upregulation while simultaneously suppressing apoptotic signaling [123].

Resveratrol, a polyphenolic compound derived from grapes, *Reynoutria japonica* Houtt, and various other botanicals, exerts diverse pharmacological actions, including antioxidant, anti-inflammatory, cardioprotective, antitumor, antidiabetic, anti-obesity, neuroprotective, and anti-aging effects [143]. In hNSCs-Exos exposed to resveratrol, PGC1α—an essential regulator of mitochondrial biogenesis—together with Nrf1 and Tfam, is markedly upregulated, while activation of AMPK and Nrf2 pathways further strengthens mitochondrial activity and mitigates OS. Simultaneously, neuroinflammatory processes are attenuated through repression of the NLRP3 inflammasome and reduced secretion of IL-1β and IL-18. The combined outcome of these molecular responses includes preservation of mitochondrial integrity, limitation of oxidative injury, and suppression of inflammatory signaling, thereby providing neuroprotection against MPP^+-induced cytotoxicity [124]. Nevertheless, the therapeutic application of resveratrol and other Nrf2 activators continues to be constrained by adverse effects, insufficient target selectivity, and unintended off-target interactions [144].

5.4 Other Types of Compounds

Currently, dimethyl fumarate (DMF) is the only Nrf2 activator approved for clinical use in NDs, with its indication restricted to multiple sclerosis (MS). Developed by

Table 2. The Nrf2 agonists Clinical Trials.

Active ingredient	NDs	Clinical Progress	Clinical Trials.gov Identifier
Sulforaphane	PD	Phase II	NCT05084365
Curcumin	AD	Phase I/II	NCT00164749
		Phase II	NCT00099710
Resveratrol	AD	Phase I	NCT02502253
		Phase II	NCT01504854
		Phase III	NCT00743743
	HD	Phase III	NCT00678431
		Phase III	NCT02336633

Biogen and marketed as Tecfidera, DMF acts as a prodrug that is metabolized *in vivo* to generate the active metabolite monomethyl fumarate (MMF), which mediates its therapeutic efficacy [145,146]. Regulatory authorization was first granted by the US FDA in March 2013 as a first-line therapy for MS, followed by European Medicines Agency approval in January 2014 [147]. Preclinical evidence demonstrates that DMF activates Nrf2 signaling in primary astrocytes, leading to reduced expression of proinflammatory mediators, attenuation of neuroinflammation, and improvement of cognitive deficits. Furthermore, DMF suppresses STAT3/C3 and C3 receptor expression in astrocytes and microglia derived from App gene-knockin (App-KI) mice, indicating its capacity to modulate AD-associated inflammatory pathways [125].

Other Nrf2 agonists under clinical evaluation (Table 2) include sulforaphane (SFN), curcumin, and resveratrol. SFN, a phytochemical abundant in cruciferous vegetables such as *Brassica oleracea* L. var. *Italica* Plenck and *Brassica oleracea* var. *capitata* Linnaeus, exhibits antioxidant, anti-inflammatory, and anti-apoptotic activities [148]. In tau-knockout mice, SFN mitigates caspase-3–cleaved tau–induced ROS accumulation, mitochondrial depolarization, and ATP depletion, while simultaneously upregulating OPA-1, strengthening mitochondrial antioxidant capacity, and improving recognition memory in truncated tau–expressing mice, thereby enhancing spatial cognitive performance [126].

5.5 Single-Ingredient Chinese Herbal Medicines

Recent investigations highlight single-compound Chinese herbal medicines as potential therapeutic agents for NDs, acting through modulation of key signaling networks such as Nrf2 and regulation of pathological mechanisms including oxidative stress, inflammation, and apoptosis via multi-target, multi-pathway interactions (Table 3, Ref. [149–155]).

Extracts of *Uncaria rhynchophylla* (Miq.) Miq. ex Havil. markedly improve MPTP-induced motor deficits and dopaminergic neurodegeneration in mice while normalizing serum oxidative and inflammatory markers. *In vitro* evidence further indicates that the extract attenuates neuroinflammatory injury in SH-SY5Y neurons by suppressing the TLR4/NF-κB/NLRP3 axis, activating the Nrf2/HO-1 pathway, reducing ROS accumulation, and rebalancing the inflammatory secretory profile of LPS-stimulated BV2 microglia [149].

Pilose antler extract demonstrates neuroprotective efficacy by preventing 6-OHDA-induced apoptosis of substantia nigra pars compacta (SNpc) neurons and preserving tyrosine hydroxylase (TH)-positive cell populations [150]. In MPTP-induced PD mouse models, *Pilose antler* peptides have been shown to limit neuronal apoptosis and oxidative stress through activation of the SIRT1-dependent Akt/Nrf2/HO-1 signaling cascade, thereby protecting dopaminergic neurons and improving neurobehavioral performance [151].

Melissa officinalis exhibits anti-inflammatory, antioxidant, sedative, antibacterial, and antiviral activities. According to Choi JW *et al*. [152], ethanol extract of this herb exerts neuroprotective effects by attenuating inflammatory responses and oxidative stress through the upregulation of antioxidant mediators such as Nrf2, HO-1, CAT, and SOD2.

Hericium coralloides has demonstrated therapeutic potential in hyperlipidemia, NDs, and cancer, with evidence indicating modulation of Nrf2 signaling, elevation of antioxidant enzymes including SOD, GSH-Px, and CAT in brain tissue and serum, and suppression of oxidative markers such as 4-HNE and MDA in the brain. In addition, inhibition of Aβ and p-tau aggregation within the hippocampus and cortex contributes to reduced oxidative damage and delayed AD progression [153].

Centella asiatica improves cognitive function in experimental models of aging and NDs; in 5xFAD mice, four months of extract administration enhanced spatial memory, episodic recall, and executive performance while markedly decreasing cortical Aβ plaque deposition and increasing the expression of Nrf2, HO-1, and NQO1 [154].

Moschus demonstrates neuroprotective capacity, likely mediated through anti-inflammatory, antioxidant, and anti-apoptotic pathways. By activating the Keap1/Nrf2 axis, *Moschus* lowers MDA, ROS, and lipid peroxide accumulation, restores intracellular GSH content, upregulates GPX4 and SLC7A11, and normalizes iron metabolism, thereby reducing neuronal damage [155].

Table 3. Single-ingredient Chinese herbal medicines.

Traditional Chinese medicine	Models	Treatment	Major Finding	Ref.
Uncaria rhynchophylla (Miq.) Miq. ex Havil.	Male C57BL/6 J mice were injected intraperitoneally with 30 mg/kg MPTP once daily for 3 weeks.	20, 40, 60 mg/kg *Uncaria rhynchophylla* (Miq.) Miq. ex Havil. extract administered by gavage for 3 weeks	↑IL-10, ↑SOD, ↑GSH, ↓IL-1β, ↓TNF-α, ↓IL-6, ↓LDH, ↓MDA, ↓TLR4, ↓NLRP3, ↓COX2	[149]
	100 ng/mL LPS stimulation of BV-2 microglia and SH-SY5Y cells for 24 h	5, 10, 20 μg/mL *Uncaria rhynchophylla* (Miq.) Miq. ex Havil. extract treated BV2 microglia and SH-SY5Y cells for 4 h	↑Nrf2, ↑HO-1, ↓IL-1β, ↓TNF-α, ↓ROS, ↓NO, ↓TLR4, ↓NF-κB, ↓NLRP3, ↓COX2	
Pilose antler	Male Wistar rats stereotactic right brain (A: –4.8 mm, L: +2.0 mm, H: 8.0 mm from substantia nigra (SN), A: –4.8 mm, L: +1.2 mm, H: 8 mm from ventral tegmental area (VTA)) injected with 6-OHDA (8 μg, 2 μL/min)	60, 180 mg/kg *Pilose antler* extract administered by continuous gavage for 14 d	↑Nrf2, ↑HO-1, ↑DA, ↑DOPAC, ↑HVA, ↑5-HT, ↑GAP-43, ↑NF-H, ↓Glu, ↓GABA	[150]
	200, 400 and 800 μg/mL MPP^+, Pre-treatment of PC12 cells for 24 h	200, 400 and 800 μg/mL *Pilose antler* extract treated PC12 cells for 24 h	↑Bcl-2/Bax, ↑SIRT1, ↑p-Akt, ↑Nrf2, ↑HO-1, ↓LDH, ↓Caspase-3, ↓ROS, ↓MDA	[151]
	Male C57BL/6 mice were injected intraperitoneally with 30 mg/kg MPTP daily from d 5 to d 10	30 mg/kg *Pilose antler* extract administered by gavage for 10 d	↑TH, ↑Bcl-2/Bax, ↓Iba-1, ↓p-Akt, ↓Caspase-3, ↓α-Syn	
Melissa officinalis	0.1 μg/mL LPS treated BV2 cells for 18 h	10, 50, and 100 μg/mL ethanol extract of *Melissa officinalis* treated BV2 cells for 18 h	↑Nrf2, ↑HO-1, ↑CAT, ↑SOD2	[152]
Hericium coralloides	APP/PS1 transgenic mice	5 mL/kg *Hericium coralloides* administered by gavage for 49 d	↑Nrf2, ↑GCLC, ↑HO-1, ↑NQO1, ↑SOD1, ↑SOD2, ↑Bcl-2, ↑GSH-Px, ↑CAT, ↓4-HNE, ↓ROS, ↓MDA, ↓Bax, ↓Aβ, ↓p-tau	[153]
Centella asiatica	5xFAD mice	5xFAD were given *Centella asiatica* extract in water (2 g/L) for a total of 4 months of treatment	↑Nrf2, ↑HO-1, ↑NQO1, ↓Aβ	[154]
Moschus	10 μM Erastin treated HT22 cells for 24 h	30 μg/mL and 60 μg/mL *Moschus* extract pre-treated HT22 cells for 24 h	↑GPX4, ↑SLC7A11, ↑GSH, ↑Nrf2, ↑HO-1, ↑FTH1, ↑FPN1, ↓Keap1, ↓TFRC	[155]

Abbreviations: 5-HT, 5-hydroxytryptamine; DA, dopamine; DOPAC, 3,4-Dihydroxyphenylacetic acid; FTH1, ferritin heavy chain 1; FPN1, ferroportin1; GAP-43, growth associated protein-43; Glu, glutamate; HVA, homovanillic acid; GABA, Gamma-aminobutyric acid; NF-H, neurofilament heavy; SLC7A11, cystine/glutamate antiporter subunit; TFRC, transferrin receptor.

5.6 Emerging Technology Interventions

Recent scientific and technological progress has enabled innovative strategies to modulate Nrf2 activity, including gene editing, nanotechnology, and applications from cell therapy and regenerative medicine. These approaches improve the therapeutic profile of Nrf2 activators by enhancing efficacy, safety, and disease-specific applicability.

Gene editing enables targeted correction of genetic defects by directly modifying DNA sequences. In one study, Yang J *et al*. [156] developed AREs-dCAS9-VP64_GFP and Nrf2-sgRNA plasmids to establish oxidative stress–responsive regulatory elements. These constructs were incorporated into nanocarriers, forming a nanozyme-enhanced MOF-CRISPR delivery system. Intravenous administration of this platform markedly improved neuronal integrity and mitigated cognitive deficits in 3xTg-AD mice. The precision of gene editing technology offers critical insights into the regulatory architecture of the Nrf2 signaling axis and supports the advancement of next-generation Nrf2-targeted therapeutics.

Nanotechnology plays a central role in designing delivery systems for Nrf2 agonists, improving bioavailability, targeting specificity, and therapeutic efficiency [157]. Polymer nanoparticles, particularly PLGA-based carriers, represent effective platforms for targeted administration of Nrf2 activators in ALS. Such carriers provide controlled drug release, extending pharmacological activity while increasing stability and systemic availability [158,159]. In ALS transgenic mouse models, PLGA nanoparticle–mediated delivery of Nrf2 activators significantly delayed motor neuron loss and prolonged survival. Adjustment of PLGA molecular weight and copolymer composition further optimizes release kinetics and biocompatibility, thereby expanding the therapeutic potential of Nrf2 activators in NDs [160].

Cell therapy employs autologous or allogeneic cell transplantation to achieve therapeutic outcomes [161]. Transplantation of Human umbilical cord mesenchymal stem cells (HUC-MSCs) has been shown to reduces MDA levels and increases NO, SOD, and nNOS activity in the hippocampus of Tg2576 transgenic mice, thereby significantly reducing oxidative stress in the hippocampus of AD mice. This intervention markedly improved cognitive impairment and reshaped the brain microenvironment in AD mice, while exhibiting antioxidant and neuroreparative properties in *in vitro* AD models [162]. Thus, modulation of the Nrf2 pathway through cell-based therapy constitutes a promising direction for ND treatment.

6. Conclusions and Outlook

Research on the structural and functional characteristics of Nrf2, along with its disease-associated regulatory network, has progressed substantially, particularly regarding the diversification of its regulatory mechanisms. As a transcription factor governing OS, mitochondrial dysfunction, and inflammatory signaling, Nrf2 exerts a decisive influence on ND progression by modulating downstream antioxidant genes such as HO-1 and SOD. Reduced Nrf2 expression has been closely linked to disease advancement in AD, PD, HD, and ALS, reflecting its essential contribution to cellular homeostasis and therapeutic relevance.

In NDs defined by abnormal protein aggregation and neuronal degeneration, Nrf2 activates antioxidant defenses through both Keap1-dependent and Keap1-independent pathways, with ROS-driven OS acting as a central pathogenic driver. Preclinical studies demonstrate that such activation reduces neuronal injury and improves neurological outcomes. Accordingly, therapeutic strategies targeting Nrf2 hold substantial promise. Natural compounds, including flavonoids, terpenoids, and bioactive constituents of Chinese herbal medicine, act as selective Nrf2 activators and confer neuroprotection through this signaling axis. Beyond its role in antioxidant defense, Nrf2 serves as a master regulator capable of integrating multiple protective pathways, including autophagy and anti-inflammatory processes, thereby overcoming the limitations of single-agent antioxidant therapy. Combining Nrf2 agonists with emerging technologies such as nanocarrier-mediated delivery provides a rational approach for multi-target interventions, offering new opportunities to address the escalating burden of NDs.

Abbreviations

3-NPA, 3-nitropropionic acid; β-TrCP, β-transducing repeat-containing protein; BTB, brick-a-brac, tramtrack, broad-complex; CTR, C terminal region; cJUN, Jun proto-oncogene, AP-1 transcription factor subunit; DGR, double glycine repeat; GSK-3β, glycogen synthase kinase-3β; H_2O_2, hydrogen peroxide; IVR, intervening region; LDH, Lactate dehydrogenase; KPNA2, Karyopherin alpha 2; miR, microRNA; NSCLC, non-small cell lung cancer; NTR, N terminal region; Nrf1, nuclear respiratory factor 1; PLGA, Poly lactic-co-glycolic acid; sMaf, small musculoaponeurotic fibrosarcoma.

Author Contributions

WTC, JYW, and QL jointly conceptualized and structured the manuscript, drafted the original version, and contributed substantially to its subsequent revision. LAZ, XW, and SFL were responsible for figure preparation and literature review. YHX and PXG created the tables and analyzed the data; the draft underwent multiple revisions before the final version was completed. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used ChatGpt to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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