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REVIEW

Natural Products from Chinese Medicine Targeting NF-κB Signaling: Emerging Therapeutic Avenues for Neurodegenerative Diseases

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Abstract: This review summarizes recent advances in leveraging natural products from Chinese medicine to modulate the nuclear factor kappa B (NF-κB) signaling pathway for the prevention and treatment of neurodegenerative diseases (NDDs), focusing specifically on Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic lateral sclerosis (ALS). NF-κB proteins regulate cellular biological activity by binding to promoter regions in the nucleus and transcribing various protein-coding genes. Emerging evidence indicates that NF-κB plays a pivotal role in driving key hallmarks of NDD progression, including neuroinflammation, oxidative stress, mitochondrial dysfunction, and dysregulation of the cell cycle. Natural products from Chinese medicine exert modulatory effects on NF-κB signaling through diverse pharmacological mechanisms, ultimately improving cognitive and motor impairments in preclinical NDDs models. The pleiotropic nature of natural products derived from traditional Chinese medicine (TCM)—which operate through subunit-specific modulation of NF-κB—underscores their potential as next-generation therapeutics. Investigating the intricate regulation of NF-κB by natural products from Chinese medicine will not only enrich our understanding of the pathogenesis of NDDs but also establish a theoretical foundation for the development of new therapeutic drugs for NDDs, providing innovative strategies for prevention and treatment.

Keywords: Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, neuroinflammation, oxidative stress

Introduction

Neurodegenerative diseases (NDDs) encompass a diverse array of neurological disorders characterized by the progressive loss of neurons in the central nervous system (CNS) and peripheral nervous system. These neurons, due to their terminal differentiation, are unable to efficiently self-renew. This degeneration disrupts essential communication circuits, leading to symptoms such as impaired memory, cognitive deficits, behavioral changes, and sensory or motor dysfunction.[1,2] As the global population ages, the incidence of NDDs related to aging, such as Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic lateral sclerosis (ALS), is increasing.[3] According to the Global Burden of Disease 2023 report, over 55 million individuals are currently living with AD worldwide, a number projected to rise to 139 million by 2050. The annual cost of care for individuals with AD is estimated to reach $2 trillion.[4] PD, the second most prevalent neurodegenerative illness following AD, currently affects over 10 million individuals worldwide. Notably, the incidence of PD has been rising among younger populations in recent years.[5] In addition to motor symptoms, non-motor symptoms in individuals with PD significantly reduce quality of life, leading to care dependency rates of up to 70%.[6] ALS is a rare and progressive motor neuron disease, with an incidence rate of 2.16 per 100,000 individuals. Despite the relatively low absolute number of cases, the disease progresses rapidly, with a median survival time of approximately 2 to 4 years.[7] However, current therapeutic

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medications provide only symptomatic relief and do not halt or reverse the progression of the disease, raising concerns regarding their safety and efficacy.[8] To meet the demands of patients, drug innovation and therapeutic techniques must be continually refined. AD, PD, and ALS are profoundly disabling and fatal NDDs. Not only do these conditions lead to aberrant protein aggregation and dysfunction of synaptic and neural networks,[9] but they also share genetic risk loci.[10] Therefore, researching the similar pathomechanisms and therapeutic targets of these three diseases can provide insights into the complexity of NDDs and facilitate the development of novel therapeutic strategies. Amyloid-β (Aβ) oligomers and Tau, which are key pathological features of AD, activate nuclear factor kappa B (NF-κB) through the TLR4/RAGE receptor. This activation initiates BACE1 expression, which in turn promotes Aβ production and exacerbates the neuropathological responses associated with AD. Similarly, abnormal α-Synuclein (α-Syn) aggregates during the progression of PD activate NF-κB via TLR2/4, leading to the maturation of the NLRP3 inflammasome and further causing dopaminergic neuronal damage.[11] The activation of NF-κB in ALS is significantly associated with mutant proteins, such as superoxide dismutase 1 (SOD-1) and transactive response DNA-binding protein 43 (TDP-43). Additionally, NF-κB down-regulates the glutamate transporter-1 (GLT-1), which ultimately contributes to the accumulation of excitotoxicity.[12] NF-κB can be found to be an indispensable hub linking the three disease-specific pathological processes in tandem, which amplifies pathological markers such as Aβ, α-Syn, and mutant proteins through positive feedback, mediating an imbalance in neuroglial cell function and ultimately driving neurodegenerative injury. NF-κB is a family of five transcription factors, namely NF-κB2 (p52/p100), NF-κB1 (p50/p105), c-Rel, RelA/p65, and RelB. These factors can form transcriptionally active homo- or heterodimers that regulate gene expression and influence various biological processes,[13] such as innate immune responses, inflammatory responses, cell proliferation, apoptosis, and stress responses to various injurious stimuli.[14] Clinical investigations indicate that traditional Chinese medicine (TCM) has the potential to prevent and ameliorate AD, PD, and ALS. Further research suggests that NF-κB is a critical target in this context. However, a detailed study examining how the active components of TCM specifically target NF-κB for the treatment of these disorders is lacking. This study aims to investigate the role of natural products from Chinese medicine in the prevention and treatment of NDDs such as AD, PD, and ALS through the NF-κB signaling pathway. The findings will provide valuable insights for future drug development and therapeutic strategies.

Mechanisms of NF-κB Signaling Pathway in Neurodegenerative Diseases

NF-κB Signaling Pathway

NF-κB transcription factors play a crucial role in CNS processes such as neurogenesis and synaptic plasticity, which are closely linked to memory and learning.[15] NF-κB remains inactive at the synapse. When activated, NF-κB translocates to the nucleus of the neuron.[16] NF-κB target genes are activated through two fundamental signaling pathways: the classical and non-classical pathways. In its inactive state, IκBα inhibits the p65/p50 dimer within the classical NF-κB pathway. Three "classic" IκB proteins exist: IκBα, IκBβ, and IκBε, which bind to NF-κB and obstruct its DNA-binding domains. Upon exposure to stimuli such as pro-inflammatory cytokines, lipopolysaccharides, growth factors, and antigen receptors, the IKK complex is activated. This complex comprises two kinases, IKKα and IKKβ, along with the essential NF-κB regulator, NEMO.[17] This results in a cascade reaction involving the phosphorylation of IκBα, alongside the degradation of its own ubiquitylation and proteasome. Consequently, the p65/p50 dimer is released from IκBα. The p65/p50 dimer then enters the nucleus, where it binds to κB motifs, leading to the activation and expression of NF-κB target genes.[18] Activated NF-κB induces the production of IκBα, which translocates into the nucleus, binds to the released NF-κB, and facilitates its export back to the cytoplasm, thereby halting transcription and maintaining regulatory control. Conversely, a non-classical mechanism activates NF-κB-inducible kinase (NIK) via a subset of tumor necrosis factor receptor (TNFR) superfamily members, independently of NEMO.[19] NIK phosphorylates IκB kinaseα (IKKα), which subsequently phosphorylates the C-terminus of p100, converting it into p52. Following this phosphorylation cascade, p52/RelB translocates to the nucleus, where it activates the transcription of NF-κB target genes that are crucial for immune cell development.[20] The two pathways are typically distinguished by their use of either the p50 product of p105 (classical pathway) or the p52 product of p100 (nonclassical pathway). Most research has primarily concentrated on the regulation of these two NF-κB heterodimers (Figure 1), as p50 is commonly associated with RelA, while p52 is linked to RelB.[21]

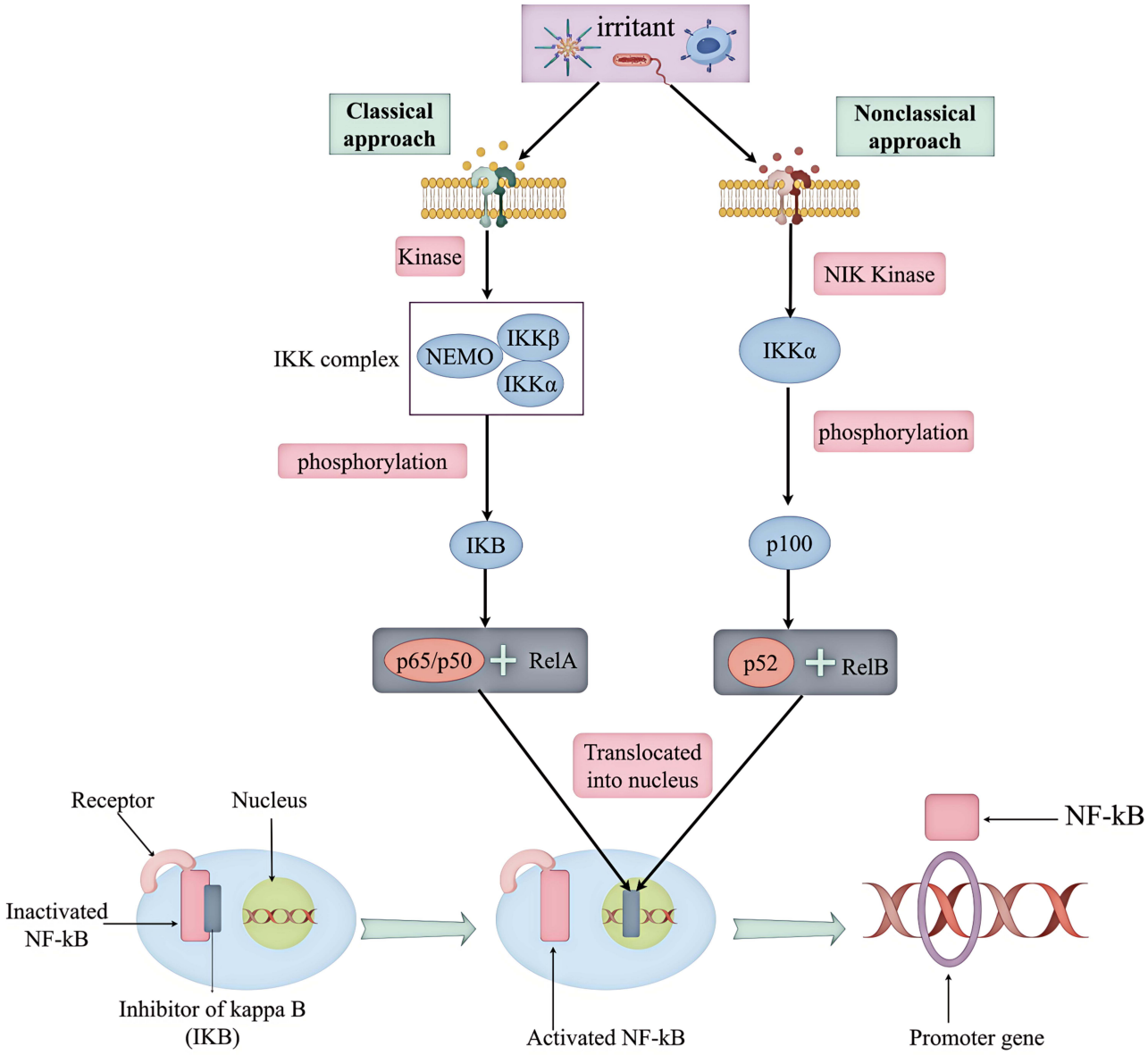

Figure 1 NF-κB activation occurs through both classical and non-classical pathways. In the classical pathway, the IKK complex is activated, triggering an IκB phosphorylation cascade that results in the release of p65/p50, which translocates to the nucleus to initiate the transcription of NF-κB target genes. Conversely, the non-classical pathway activates NF-κB-inducible kinase (NIK), and subsequent phosphorylation leads to the translocation of p52/RelB to the nucleus, where it participates in transcription.

NF-κB plays a crucial role in activating gene transcription and is involved in various physiological processes, including inflammation, oxidative stress, cell proliferation, and apoptosis.[22,23]

Mechanisms of NF-κB Signaling Pathway in Regulating Neuroinflammation in Neurodegenerative Diseases

Neuroinflammation is a crucial characteristic of NDDs, referring to the complex immune response of the CNS to various endogenous and exogenous stimuli, such as misfolded proteins, toxins, and pathogens. This response results in the inflammatory infiltration of brain tissues, gliotic proliferation, and neuronal loss. The role of neuroinflammation is influenced by the specific microenvironment of the brain. Initially, inflammation acts as a defense mechanism, protecting the integrity of brain tissue by eliminating pathogens, cellular debris, misfolded proteins, and other harmful stimuli.[24] However, chronic inflammation can result in neuronal damage and compromise the integrity of the blood-brain barrier

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(BBB). This phenomenon is attributed to the excessive production of pro-inflammatory cytokines, chemokines, and small-molecule messengers, including interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), interleukin-8 (IL-8), and transforming growth factor-β (TGF-β), predominantly released by activated microglia.[25]

NF-κB Signaling Pathway Affects Glial Cell Activation

Neuroglia, which includes microglia and astrocytes, primarily mediates the inflammatory response, often accompanied by the activation of the immune system. Microglia, as large phagocytes, typically eliminate danger signals in the CNS and perform active immune surveillance of the brain. However, the neuroinflammatory response driven by over-activated microglia significantly contributes to the exacerbation of NDDs.[26] Activated microglia exhibit two conflicting phenotypes: the conventional M1 and the selective M2. The M1 phenotype is characterized by the release of pro-inflammatory cytokines and chemokines, including IL-6, IL-1β, TNF-α, and MCP-1, which contribute to uncontrolled and persistent neuroinflammation.[27] NF-κB regulates microglia polarization towards M1.[28] M2 microglia, characterized by the expression of Ym-1, FIZZ-1, and Arg-1 markers, release anti-inflammatory cytokines such as IL-4, IL-10, and IL-13, along with neurotrophic factors. These substances contribute to the reduction of inflammatory damage and provide neuroprotective benefits.[29] Microglia in the brain parenchyma of patients with AD exhibit an M1 phenotype, which contributes to neuroinflammation and the accumulation of Aβ. Numerous genetic loci associated with an increased risk of AD, PD, and ALS have been linked to microglial function, indicating that neuroinflammation plays a crucial role in the pathogenesis of these disorders.[30] Many glial cell response factors, including p38 mitogen-activated protein kinase,[31] fractalkine signaling,[32] and Notch signaling pathway,[33] regulate and activate NF-κB.

Astrocytes contribute to neurodegeneration by promoting the production of pro-inflammatory cytokines and inducible Nitric Oxide Synthase (iNOS) through the NF-κB signaling pathway. Brigid et al[34] identified TNF-α as a significant driver of mtFUS-induced astrocytotoxicity, with its transcription regulated by NF-κB. Both astrocytes and microglia possess a variety of pattern recognition receptors, particularly cell membrane-bound Toll-like receptors (TLRs), which play a crucial role in the pathology of NDDs. Among these, TLR2 and TLR4 are the most extensively studied.[35] Oligomeric Aβ and α-Syn activate NF-κB signaling pathways and increase the production and release of pro-inflammatory proteins by binding to TLR4 through the mouse microglia cell line or the rat primary astrocyte cell line MyD88, a junction protein associated with TLR.[36] The oligomeric form of α-Syn binds to the TLR1/2 heterodimer, resulting in the nuclear translocation of the p65 NF-κB subunit and the activation of microglia.[37] The interaction between microglia, astrocytes, and neurons generates feedback loops that lead to the dysregulation and self-amplification of neuroinflammatory responses. Under physiological conditions, astrocytes provide nutritional support to microglia, promoting their structural and functional stabilization. However, during disease progression, cytokines secreted by microglia induce neurotoxic phenotypes in astrocytes. Additionally, the release of inflammatory mediators by A1 astrocytes and the increased permeability of the BBB enhance migration capacity while activating M1 microglia,[38] which further amplifies neuroinflammation. Pro-inflammatory mediators generated by A1/M1 directly induce neuronal death.[39] Surprisingly, E. Leandrou et al[40] discovered that persistent NF-κB activation upregulates astrocyte T-type Cav3.2 Ca^{2+} channels, thereby altering the astrocyte secretome and promoting the secretion of IGFBPL1. IGFBPL1, a binding protein with neuroprotective properties, facilitates the transformation of inflammatory microglia into a state of homeostasis, thereby reducing neuroinflammation. Glial cells, regulated by NF-κB, play crucial roles in maintaining CNS homeostasis and in the remodeling of neuronal circuits.

This shows that controlling the overproduction of pro-inflammatory and pro-oxidative factors in glial cells, while maintaining the levels of anti-inflammatory factors, appears to be a more promising therapeutic strategy for treating NDDs than completely inhibiting neuroglial overreactivity.

NF-κB Signaling Pathway Affects Inflammasome Activation

Inflammasomes are innate immune signaling platforms that facilitate acute responses to pathogenic infections or local tissue injury, with the NLRP3 inflammasome being the most extensively investigated.[41] In the CNS, inflammasomes are primarily located in microglial cells, and misfolded proteins associated with NDDs contribute to dysregulated inflammasome assembly.[29] Tau aggregates, for example, have been demonstrated to activate the NLRP3 inflammasome, leading to NLRP3-dependent amplification of tau pathology in mice.[42] Recent research indicates that NF-κB regulates the NLRP3

inflammasome, thereby balancing the immunological response.[43] Inflammasome initiation commences with the NF-κB-dependent transcription of cytokine precursors, such as pro-IL-1β, alongside the up-regulation of NLRP3. Ligands from Pattern Recognition Receptors or cytokine receptors act as signals to activate NF-κB signaling.[44] The NF-κB pathway stimulates the expression of NLRP3, which facilitates the assembly of NLRP3, apoptosis-associated speck-like proteins containing CARD, and pro-caspase-1 into the NLRP3 inflammasome complex. This assembly results in the activation and self-cleavage of caspase-1. Activated caspase-1 subsequently converts gasdermin D (GSDMD) and pro-IL-1β/18 into their mature forms, IL-1β and IL-18, thereby promoting inflammation and cell death.[45,46] Numerous investigations, however, have demonstrated that mitochondrial damage is a common signaling event downstream of all NLRP3 activators. This damage results in the release of oxidized mitochondrial DNA, which subsequently binds to and activates NLRP3.[47] Zhong et al[48] discovered that the activation of NF-κB results in the overexpression of the autophagy junction molecule p62, which subsequently leads to impaired autophagic degradation of mitochondria.[49] The "NF-κB-p62-mitochondrial autophagy" axis functions as a negative regulatory network in macrophages, inhibiting NLRP3 inflammasome activity to prevent immunopathology. Activated NF-κB is associated with neuroinflammation that arises at the onset of NDDs. NF-κB modulates the activation of glial cells and the inflammasome, influencing the levels of inflammatory factors, which may exacerbate or prolong disease progression (Figure 2). Targeting NF-κB to limit the release of downstream pro-inflammatory factors may offer new therapeutic avenues for NDDs.

NF-κB Signaling Pathway Bi-Directionally Regulates Oxidative Stress in Neurodegenerative Diseases

Numerous investigations have demonstrated that oxidative stress (OS) is a prevalent hallmark of NDDs caused by the unregulated production of reactive oxygen species (ROS).[50] Under normal circumstances, ROS play critical roles in physiological functions, redox balance, and the regulation of essential transcription factors. However, an imbalance in the production and elimination of free radicals leads to an excess of ROS,[51] which subsequently causes oxidative alterations of cellular macromolecules. ROS can induce cytotoxicity and play a significant role in the aging process and the development of various diseases. This occurs through their interaction with proteins, particularly cysteine residues, lipids, leading to lipid peroxidation, and nucleic acids, resulting in DNA damage and strand breaks.[52] Therefore, OS is not inherently harmful; rather, it is the accumulation of ROS due to cellular redox imbalance that leads to neuronal injury. Excessive ROS production in

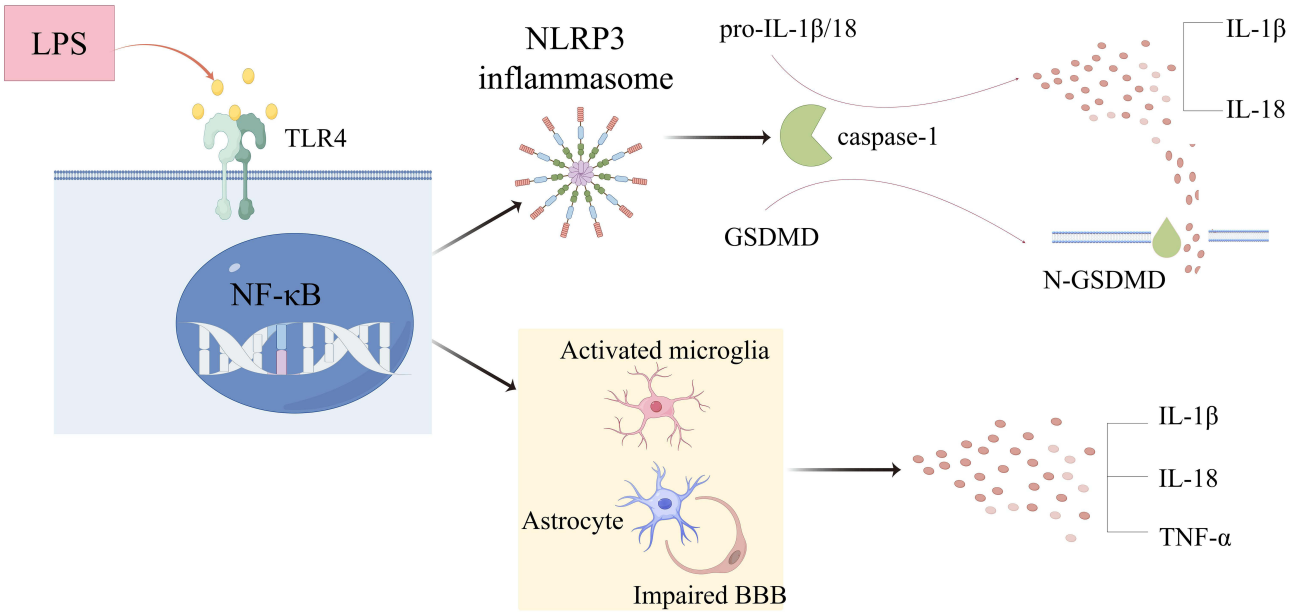

Figure 2 The mechanisms of action of the NF-κB signaling pathway in regulating neuroinflammation involve the activation of microglia and astrocytes upon exogenous stimulation. This activation results in the release of pro-inflammatory factors, including IL-1β, IL-8, and TNF-α. Additionally, the NF-κB pathway enhances the expression of NLRP3, leading to the assembly of NLRP3 inflammatory vesicles, which subsequently activate caspase-1, thereby further triggering inflammation and apoptosis.

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NDDs is triggered by several pathways, including neuroinflammation, mitochondrial dysfunction, cellular senescence, elevated iron and calcium levels, and the breakdown of dopamine.[53] The brain, being an organ that demands a significant amount of oxygen and is rich in lipids, is particularly susceptible to OS damage. ROS-induced oxidative stress contributes to the formation and deposition of β-amyloid,[54] which leads to mitochondrial dysfunction and further exacerbates OS, creating a vicious cycle. It has been established that OS is a critical factor in the degeneration of dopaminergic neurons across all forms of PD, and the deletion of mitochondrial complex I is directly associated with PD.[55] Approximately 20% of familial ALS cases are attributed to mutations in superoxide dismutase 1 (SOD1), an antioxidant enzyme[26] that converts superoxide anions into less harmful ROS. Dysregulation of iron homeostasis results in excessive ROS production via the Fenton reaction, which ultimately leads to iron-dependent cell death. The final product of iron death, 4-hydroxy-2-nonenal, exacerbates inflammatory responses by promoting the production of Aβ and α-syn.[56]

The transcription of NF-κB-dependent genes increases the production of ROS within cells, which in turn regulates NF-κB activity. ROS can activate IKK-β, resulting in the direct release of NF-κB.[57] Additionally, ROS phosphorylate the PI3K-Akt pathway, thereby indirectly activating NF-κB.[58] Moreover, the production of NEMO dimers induced by ROS may play a crucial role in this mechanism. The formation of these dimers could be significantly involved in the underlying processes.[59] Research indicates that ROS activate NF-κB, leading to neuroinflammation and contributing to carcinogenesis. Furthermore, inflammatory cytokines phosphorylate IκBα at Ser32 and Ser36, resulting in its proteasomal degradation. Sirtuin (SIRT), a member of the NAD^+-dependent deacetylase family, regulates ROS production and accumulation, thereby reducing oxidative stress associated with neurodegeneration.[60] Activation of NF-κB inhibits SIRT1 and increases pro-inflammatory cytokine production.[61] Molecular redox switches, such as Nrf2/Keap1 and NF-κB, regulate cycles of activation and inactivation. Upon exposure to OS, Nrf2 dissociates from Keap1 and translocates to the nucleus, where it forms a heterodimer with Maf. The Nrf2-Maf complex then binds to the antioxidant response element, leading to the expression of antioxidant and metabolic genes.[62] Endogenous cues, including endoplasmic reticulum stress and autophagy impairment, can provide initial cellular protection for the Nrf2 system. NF-κB inhibits Nrf2 activation by competing for the transcriptional co-activator CBP-p300 complex, and a reduction in Nrf2 levels in cells enhances IKK-β function.[63,64] OS induces pro-inflammatory mediators in NDDs through various methods, while antioxidants inhibit NF-κB activation by stimulation. N-acetylcysteine suppresses the activation of NF-κB in human T lymphocytes when exposed to micromolar doses of hydrogen peroxide, as previously demonstrated.[65] Recent studies indicate that ROS can activate NF-κB during the early stages; however, prolonged exposure to ROS subsequently inhibits the basal activity of NF-κB in a time-dependent manner.[19] This inhibition may be attributed to the continuous dephosphorylation of Akt. The ROS-mediated oxidation of upstream kinases can significantly impact the NF-κB pathway. Korn et al[66] discovered that H2O2 markedly inhibited the ability of TNF to promote IKK activity, thereby inhibiting I-κB degradation and subsequent NF-κB activation. Two compounds targeting the cysteine residue of IKK-β, arsenite[67] and NO,[68] exhibited similar inhibitory effects. The ROS-UPR pathway may contribute to the bidirectional regulation of NF-κB under oxidative stress. Notably, NF-κB may mitigate ROS accumulation and confer neuroprotection during OS. In the context of H2O2-induced OS, NF-κB p65 is phosphorylated at Ser-536, leading to the upregulation of p62 and the promotion of autophagy.[69] Ferritin Heavy Chain 1 (FTH1), a subunit of ferritin, plays a crucial role in storing ferric ions and preventing the formation of damaging free radicals within the cell. The NF-κB signaling pathway has been shown to upregulate FTH1 expression,[56] thereby reducing OS levels and preventing TNF-α-induced apoptosis. Furthermore, NF-κB has been demonstrated to inhibit the aggregation of reactive oxygen species by enhancing the expression of antioxidant proteins, such as MnSOD and SOD2,[70] which are well-established antioxidant targets of NF-κB.

The rapid activation of NF-κB during early ROS exposure may aid cells in combating pathogenic microorganisms by enhancing survival signaling and recruiting immune cells. However, persistent activation of NF-κB can lead to chronic inflammation and tissue damage (Figure 3). Therefore, further research is necessary to elucidate the detrimental effects of OS-induced NF-κB activation on cells and organisms.

NF-κB Signaling Pathway Influences Mitochondrial Dysfunction

Mitochondria are the organelles responsible for essential functions, including energy metabolism, calcium homeostasis, and signal transduction.[71] They meet the brain's high energy demands through oxidative phosphorylation and ATP generation.

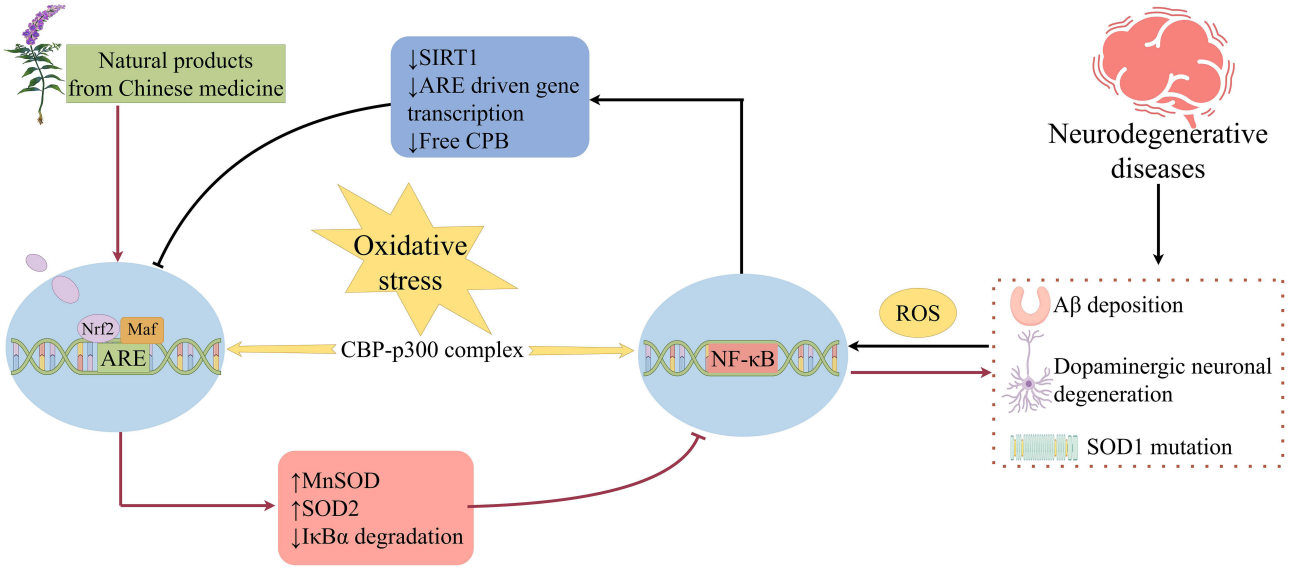

Figure 3 Excessive accumulation of ROS caused by NDDs can activate NF-κB, induce the expression of downstream inflammation-related genes and form a vicious cycle. Nrf2, a key regulator against OS, binds to the antioxidant response element to drive the expression of a series of antioxidant enzyme genes and prevents the entry of NF-κB into the cell nucleus by reducing the degradation of IκBα. Conversely, the NF-κB p65 subunit competes with Nrf2 for binding to the transcriptional co-activator CBP-p300, thereby inhibiting the activity of the Nrf2 pathway.

Consequently, mitochondrial dysfunction and the resulting energy deficit act as triggers for NDDs. It has been well established that mitochondrial dysfunction is linked to the progression of NDDs.[72] Functional deficits and structural abnormalities of mitochondria have been observed in postmortem tissues from patients with ALS as well as in animal models.[73] ALS-associated fusion sarcoma (FUS) mutations cause cognitive and motor impairments in mice. In a neuron-specific FUS transgenic mice model, M.C.Pelaez et al[74] discovered that IMS-088,[75] a classical NF-κB pathway inhibitor, mitigated the detrimental effects of OS and mitochondrial arrest, enhanced the dendritic branching of motor neurons, and restored motility. It has been demonstrated that the deletion of mitochondrial complex I is directly associated with PD.[55] This abnormality, which arises from mutations in specific proteins, disrupts mitochondrial function, heightens vulnerability to OS, and leads to damage in dopaminergic neurons. Another research suggests that mitochondria may initiate the integrated stress response[76] in reaction to environmental stressors, contributing to the prevention of AD and the protection of neurons.

It is hypothesized that the production of ROS is due to the accumulation of various oxidoreductases in mitochondria, along with mitochondrial dysfunction. NADPH is essential for maintaining glutathione and thioredoxin in a reduced state within mitochondria, playing a critical role in combating OS.[77] Under the metabolic demands of pathological environments, NADPH is depleted to support the production of NADH and ATP, thereby weakening antioxidant defenses.[78] O. Harding et al[59] discovered that NEMO, a key regulator of NF-κB, is recruited to damaged mitochondria in a Parkin-dependent manner. Furthermore, NEMO, p62, and OPTN are recruited in conjunction with ubiquitinated mitochondria. This process initiates innate immune signaling and activates the IKK complex, thereby stimulating NF-κB target genes and increasing the production of pro-inflammatory factors. On the other hand, NF-κB plays a crucial role in regulating energy metabolic networks by balancing glycolysis and mitochondrial respiration. Xin et al[79] discovered that the telomere-associated gene TINF2 promotes mitochondrial function and is positively correlated with NF-κB expression. Activation of the NF-κB signaling pathway leads to a reduction in ROS levels, an increase in ATP content, and an enhancement of mitochondrial function following TINF2 enhancement, ultimately slowing the aging process of mesenchymal stem cells. Additionally, C. Mauro et al[80] identified cytochrome C oxidase 2 as a physiological regulator of mitochondrial respiration and found that NF-κB enhances mitochondrial production. P62 selectively recognizes damaged mitochondria and stimulates their autophagic clearance. NF-κB mitigates inflammation by inducing a delayed accumulation of the autophagy receptor p62/SQSTM1.[48] NF-κB regulates the internal environment via the NF-κB-p62-mitophagy loop, functioning both as an inflammatory activator and as an inhibitor of pro-inflammatory activity.

The intricate interplay between NF-κB and mitochondria necessitates precise regulation to develop novel therapies for NDDs.

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NF-κB Signaling Pathway Regulates Apoptosis

Apoptosis is a genetically regulated, cell-autonomous process of programmed cell death that is essential for proper organismal growth and development, maintenance of tissue homeostasis, and the functioning of the immune system.[81] Endogenous apoptosis is initiated by stressors such as oxidative stress, DNA damage, and growth factor deficiency, leading to the release of cytochrome C from the mitochondria. In contrast, exogenous apoptosis is activated by extracellular signaling molecules, including TNF-α and Fas ligand, which bind to specific membrane receptors.[82] NF-κB regulates the transcription and protein production of apoptosis-related genes, playing a dual role in both preventing and promoting apoptosis.[83] The NF-κB signaling pathway modulates synaptic plasticity and enhances neuronal survival by inducing the production of neurotrophic factors such as nerve growth factor and brain-derived neurotrophic factor.[84] Pro-survival signaling cannot be successfully transduced by NF-κB in cells with aSyn or Htt-polyQ aggregates due to the isolation of p65.[85] Some experts suggest that proteins exhibiting anti-apoptotic effects possess κB binding elements within their promoter regions, making them target genes of NF-κB. These proteins also preserve the integrity of the outer mitochondrial membrane, thereby preventing the release of cytochrome C and inhibiting endogenous apoptosis.[86] NF-κB can indirectly inhibit apoptosis by increasing antioxidant transcript levels (MnSOD and FHC).[87] It is well established that p53 functions as a tumor suppressor by inducing cell growth arrest, senescence, and apoptosis.[88] In contrast, NF-κB inhibits p53 activity through the activation of E3 ligase, thereby exhibiting its anti-apoptotic effects. Furthermore, the crosstalk between the NF-κB and JNK pathways represents another mechanism influencing apoptosis. C. G. Pham et al[89] discovered that the FHC plays a crucial role in the antioxidant and protective functions of NF-κB. FHC mitigates TNF-α-induced apoptosis by activating downstream signaling of NF-κB and inhibiting JNK activation. In response to pathogen invasion, NF-κB initiates protective immune responses and facilitates tissue healing. However, chronic or excessive activation of NF-κB can lead to OS, excitotoxicity, and inflammation, ultimately shifting neuronal survival toward apoptosis. Additionally, p53 can synergize with NF-κB and IRF-1 to enhance iNOS production, thereby disrupting cellular metabolism and promoting apoptosis.[90] This finding contrasts with the previously reported suppression of p53 by NF-κB. Notably, p53 has the capacity to activate the expression of pro-apoptotic factors within the Bcl-2 family, including Bax. In their experiments with human osteosarcoma cells, Campbell et al[91] demonstrated that NF-κB, when induced by ultraviolet light, erythromycin, or azithromycin, was capable of reducing the expression of anti-apoptotic molecules such as XIAP, Bcl-xL, and A20. This observation implies that activated NF-κB may exert an inhibitory effect under specific external stimuli. A recent study[92] also demonstrated that GSDMD, an inhibitory target of melatonin, promotes focal death in adipocytes, with NF-κB signaling playing a critical role. NF-κB regulates apoptosis through multiple pathways, including the direct activation of pro-apoptotic proteins, the indirect activation of tumor suppressors, and the suppression of anti-apoptotic factors.

In summary, NF-κB modulates cell survival and apoptosis depending on the specific subunit activated, the site of injury, and the associated healing mechanism.[93] Consequently, the NF-κB signaling pathway emerges as a critical target for the regulation of apoptosis.

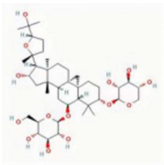
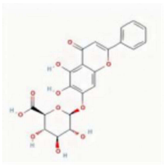
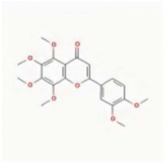
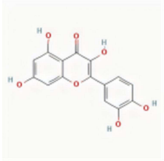
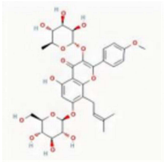
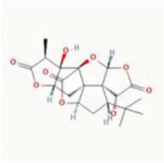
Current status of research on the modulation of NF-κB signaling pathway by Chinese medicine natural products for the treatment of neurodegenerative diseases

Natural products from Chinese medicine are defined as chemical components with biological activity that are derived from TCM. These include a variety of compounds such as alkaloids, flavonoids, terpenoids, steroids, phenols, quinones, and numerous other chemicals.[94] Natural resources, including plants, animals, and minerals, serve as the foundation for the pharmacological effects of TCM. Recent studies on NDDs have concentrated on natural products from Chinese medicine that modulate the NF-κB signaling pathway, as discussed below (Table 1).

Chinese Medicine Natural Products Modulate NF-κB for AD Treatment

AD is the most prevalent form of dementia globally, representing 60–70% of all dementia cases. The prevention and treatment of AD are vital for both individuals and society. AD is characterized by the presence of Aβ plaques and intracellular neurofibrillary tangles (NFTs), which lead to neurotoxicity, apoptosis, inflammatory responses, and a limitation of synaptic plasticity, ultimately resulting in cognitive impairment.[126] Aβ misfolding and aggregation play a crucial role in the progression

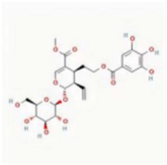
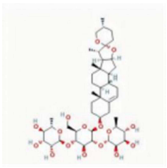
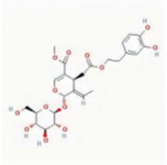
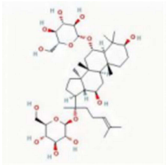
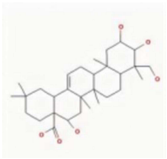
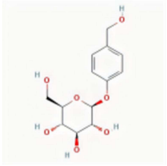
Table 1 Effects of Natural Products from Chinese Medicine on Preventing and Treating NDDs

Active Ingredients	Structure	Herb Source	Experimental Model	Molecular Mechanisms	Disease	Ref.
Astragaloside IV		Huang Qi (*Astragalus membranaceus* (Fisch.) Bunge)	5xFAD mice; BV-2 cells	↓:IκB and p65 phosphorylation, IL-1β, TNF-α, COX - 2, iNOS	AD	[95]
Hedysarum polysaccharides		Huang Qi (*Astragalus membranaceus* (Fisch.) Bunge)		↓:HMGB1, TLR4, NF-κB, IL-1β	AD	[96]
Baicalin		Huang Qin (*Scutellaria baicalensis* Georgi)	3xTg-AD mice	↑:CX3CR1	AD	[97]
			BV-2 cells	↓:TLR4/NF-κB, MAPK; ↓NO, PGE2, IL-1β	AD	[98]
Nobiletin		Chen Pi (*Tangerine Peel*)	Streptozotocin (STZ)-induced mice AD model	↓:PI3K/Akt, NF-κB	AD	[99]
Quercetin		Sang Ji Sheng (*Taxillus sutchuenensis* (Lecomte) Danser)		↓:NF-κB; ↑:SIRT1	AD	[100]
			Human umbilical vein endothelial cells (HUVECs)	↓:NF-κB, AP-1		[101]
Icariin		Yin Yang Huo (*Epimedium brevicornu* Maxim).		↓:TAK1/IKK/NF-κB; ↑:PPARγ	AD	[102]
Ginkgolide		Yin Xing (*Ginkgo biloba* L).	APP/PS1 double gene-transfected HEK293 cell line (APP/PS1-HEK293 cells)	↓:NF-κB p65, Bax; ↑:IκBa, Bcl-2	AD	[103]

(*Continued*)

https://doi.org/10.2147/DDDT.S534706

Table 1 (Continued).

Active Ingredients	Structure	Herb Source	Experimental Model	Molecular Mechanisms	Disease	Ref.
Cornuside		Shan Zhu Yu (*Cornus officinalis* Sieb. and Zucc).	$A\beta_{1\text{-}42}$-induced AD mice model	↓:RAGE/TXNIP/NF-κB; ↑:AKT/Nrf2	AD	[104]
Dioscin		Shu Yu (*Dioscorea polystachya* Turcz).		↓:RAGE/NOX 4/NF-κB; ↑:Nrf2/HO-1	AD	[105]
Oleuropein		Gan Lan (*Canarium album* (Lour). Raeusch).		↓:RAGE/NF-κB	AD	[106]
Ginsenoside Rg1		Ren Shen (*Panax ginseng* C. A. Mey).	Hydrogen peroxide-induced PC12 cells; LPS-induced HT22 cells	↓:NF-κB/NO; ↑:PPARγ	AD	[107]
Polylactic Acid		Yuan Zhi (*Polygala tenuifolia* Willd).	Aβ42 oligomer-induced AD mice model	↓:NF-κB; ↑:PPARγ	AD	[108]
Gastrodin		Tian Ma (*Gastrodia elata* Bl).	APP/PS1 double transgenic AD mice	↓:NF-κB; ↑:PPARγ	AD	[109]

(*Continued*)

Table 1 (Continued).

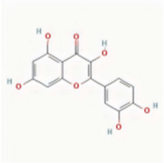
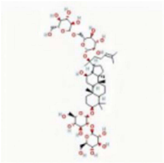
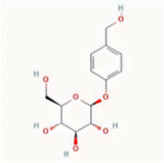
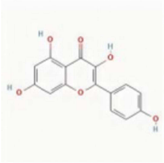
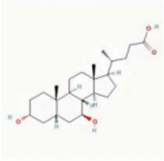
Active Ingredients	Structure	Herb Source	Experimental Model	Molecular Mechanisms	Disease	Ref.
Peony Seed Oil		Mu Dan (*Paeonia* × *suffruticosa* Andrews)	Presenilin1/2 conditional double knockout (PS cDKO) mice model	↓:NF-κB, NOS, COX-2, IL-1β/TNF-α	AD	[110]
Quercetin		Sang Ji Sheng (*Taxillus sutchuenensis* (Lecomte) Danser)		↓:alpha-synuclein; ↑:PINK1, Parkin	PD	[111]
Ginsenoside Rb1		Ren Shen (*Panax ginseng* C. A. Mey).	SH-SY5Y cells; PC12 cells	↑:NF-κB, GLT-1	PD	[112]
Gastrodia elata		Tian Ma (*Gastrodia elata* Bl).	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) -induced mice	↓:TLR4/NF-κB	PD	[113]
Kaempferol		Gao Liang Jiang (*Alpinia officinarum* Hance)	C57Bl/6 mice; LAD2 cells	↓:Lyn kinase, NF-κB	PD	[114]
			6-hydroxydopamine (6-OHDA)-induced PD rats	↓:p38MAPK/NF-κB	PD	[92]
Ursodeoxycholic Acid		Xiong Dan (*Ursi Fellis Pulvis*)	MPTP-induced mice	↓:NF-κB; ↑:TGR5	PD	[115]

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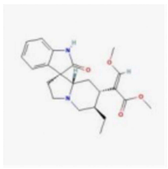
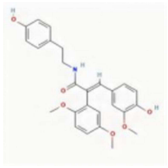
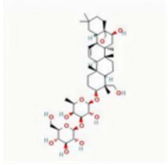
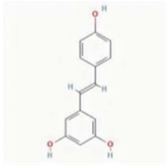
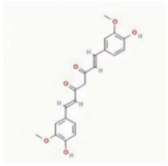
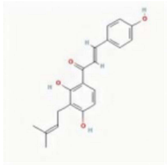
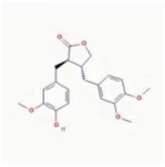
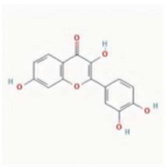
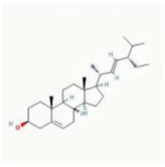
Table 1 (Continued).

Active Ingredients	Structure	Herb Source	Experimental Model	Molecular Mechanisms	Disease	Ref.
Rhyncholphylline		Gou Teng (*Uncaria rhynchophylla* (Miq). Miq. ex Havil).	MPTP-induced mice	↓:TLR4/NF-κB/NLRP3; ↑:Nrf2/HO-1	PD	[116]
Fenlean		Yuan Hua Fan Li Zhi (*Annona glabra* L).	Rotenone -induced mice	↓:TLR4/MyD88/NF-κB	PD	[117]
Saikosaponin A		Chai Hu (*Bupleurum chinense* Franch).	MPTP-induced mice; SH-SY5Y cells;	↓:TLR4/MyD88/NF-κB	PD	[118]
Resveratrol		Hu Zhang (*Reynoutria japonica* Houtt).	MPTP-induced mice	↓:TLR4/MyD88/NF-κB	PD	[119]
Curcumin		Jiang Huang (*Curcuma longa* L).	MPTP-induced mice; 6-OHDA-induced PC12 cells	↓:NF-κB, TNF-α, IL-1β, IL-1α, iNOS, Bax, Bcl-2, Caspase 3 and Caspase 9	PD	[120]
Isobavachalcone		Bu Gu Zhi (*Cullen corylifolium* (L). Medik).	LPS-induced BV-2 cells	↓:NF-κB, Aβ	PD	[121]

(*Continued*)

Table 1 (Continued).

Active Ingredients	Structure	Herb Source	Experimental Model	Molecular Mechanisms	Disease	Ref.
Arctigenin		Niu Bang (*Arctium lappa* L).	SOD1 (G93A) mice model	↓:IL-1β, NF-κB; ↑:AMPK/SIRT1/PGC-1α	ALS	[122,123]
Fisetin		Qi (*Toxicodendron vernicifluum* (Stokes) F. A. Barkley)	SOD1 (G93A) mice model	↓: NF-κB; ↑:Keap-1/Nrf2/ARE	ALS	[124]
Stigmasterol		Da Dou (*Glycine max* (L). Merr).	SOD1 (G93A) mice model	↓:NF-κB; ↑:IGF-1R	ALS	[125]

Notes: The chemical structure is derived from PubChem.

of AD. Studies have indicated that NF-κB levels are elevated in the cerebral cortex of AD patients, which correlates with increased levels of β-amyloid precursor protein cleaving enzyme 1 (BACE 1).[127] The p65 subunit of NF-κB binds to the κB element on the BACE1 promoter, leading to the production of β-secretase. This process stimulates the amyloidogenic pathway, resulting in the aggregation of β-amyloid into plaques. Additionally, Aβ oligomers activate NF-κB in both neurons and glial cells, which further enhances the accumulation of Aβ42 aggregates and contributes to the neuropathological cascade associated with AD.[128,129] The translocation of p-p65 to the cell nucleus induces the transcription and expression of inflammatory mediators, which are closely associated with the development of AD.[130] This is supported by the presence of inflammatory features and an abnormal increase in nuclear factorκlight chain enhancers in astrocytes adjacent to amyloid plaques in autopsy results from AD patients. It is evident that inhibiting NF-κB activation could represent a promising strategy for treating AD, thereby expanding therapeutic possibilities (Figure 4).

Terpenes are a class of natural products characterized by isoprene as the fundamental structural unit. Astragaloside IV (AS-IV), an active ingredient in the TCM Astragalus, has been demonstrated to be a potent triterpenoid saponin that effectively reduces levels of inflammatory factors and promotes tissue repair.[131] He et al[95] demonstrated that AS-IV significantly reduced Aβ plaque accumulation in LPS-stimulated BV-2 cells derived from 5xFAD mice ($p < 0.01$). Furthermore, AS-IV decreased the mRNA expression levels of IL-1β, TNF-α, COX-2, and iNOS in microglia by inhibiting IκB and p65 phosphorylation, thereby suppressing the NF-κB signaling pathway. This suggests that AS-IV may enhance learning and memory by mitigating NF-κB-mediated neuroinflammatory responses associated with AD. The Receptor for Advanced Glycation End-products (RAGE) is a member of the immunoglobulin superfamily and serves as a pattern recognition receptor that significantly contributes to the pathogenesis of various diseases. RAGE induces inflammation in vascular endothelial and neuronal cells by activating and releasing ROS. This process results in increased deposition of Aβ in the brain during the early stages of AD.[132] The RAGE link of Aβ triggers a cellular

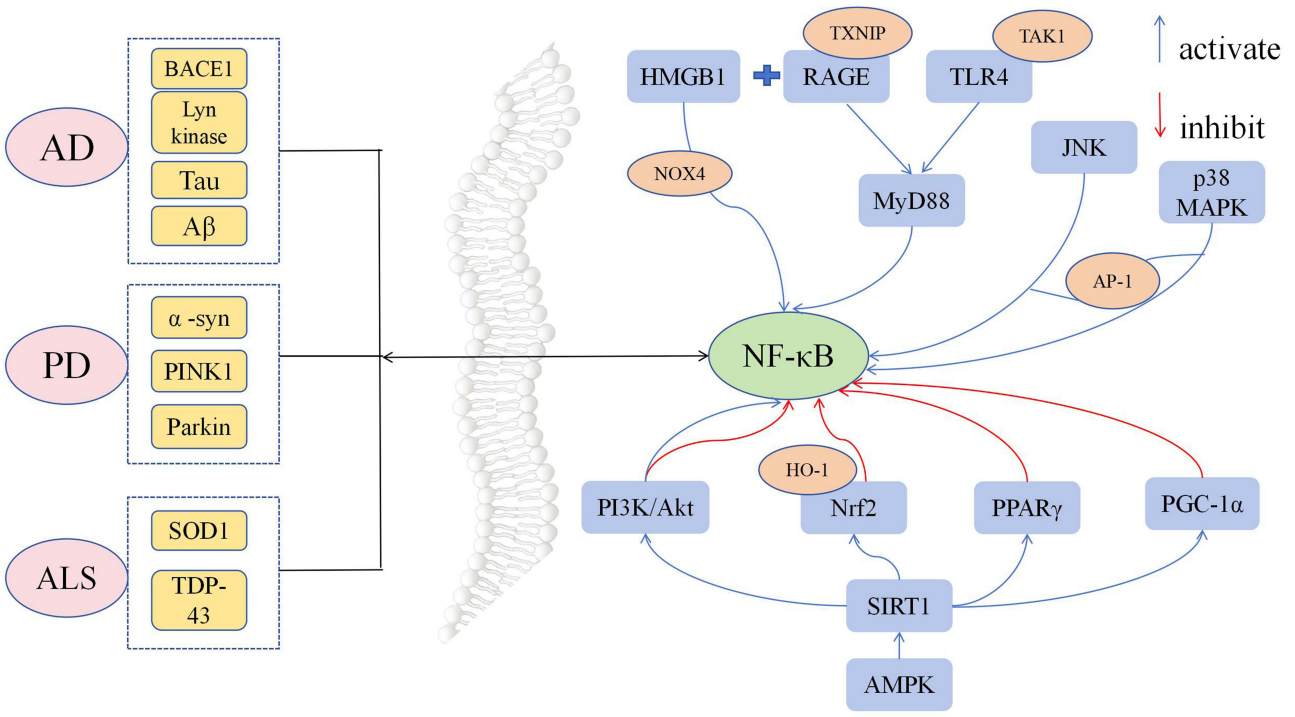


Figure 4 Pathophysiological markers that initiate a neural cascade response involving NF-κB in AD, PD, and ALS, along with the upstream signaling factors that modulate NF-κB activity.

signaling cascade that activates NF-κB, stimulating RAGE synthesis. Shi et al[104] revealed that Cornuside, derived from Cornus officinalis, reduces cognitive impairment. Cornuside demonstrated neuroprotective effects in a model of AD induced by Aβ1-42 by inhibiting NF-κB p65-mediated inflammatory responses and reducing pro-inflammatory cytokine production through the RAGE/TXNIP/NF-κB signaling pathway. Additionally, Cornuside inhibits the activation of astrocytes and microglia and regulates the A1/A2 astrocyte phenotype by upregulating the AKT/Nrf2 pathway while downregulating the NF-κB pathway ($p < 0.01$). Dioscin, a natural steroidal saponin found in Dioscorea spp., inhibits the RAGE/NOX4 pathway, downregulates the expression levels of p-NF-κB (p-p65)/NF-κB (p65), AP-1, and inflammatory factors, and upregulates Nrf2 and HO-1. This results in anti-oxidative stress and decreased neuroinflammatory damage, positioning it as a promising emerging anti-AD drug.[105] The diterpene compound Ginkgolide exhibits potent free radical scavenging and platelet aggregation inhibition capabilities. Additionally, it reduces the protein expression levels of NF-κB p65 and Bax while elevating the expression of IκBa and Bcl-2 in APP/PS1-HEK293 cells. This compound is widely utilized in the treatment of cerebrovascular diseases.[103]

Another significant category is flavonoids, particularly represented by Baicalin (BA). BA, which is extracted from the root of Scutellaria baicalensis, exhibits anti-inflammatory, antioxidant, and neuroprotective properties. BA inhibits the CX3CR1/NF-κB signaling pathway, thereby promoting synaptic plasticity, suppressing neuroinflammatory responses, and enhancing cognitive performance in 3xTg-AD mice.[97] In the in vitro cell experiment of LPS-stimulated BV-2 cells, Li et al[98] demonstrated that BA inhibits the upregulation of NF-κB and the degradation of IκBα, while increasing IκBα phosphorylation ($p < 0.001$). Additionally, BA inhibits TLR4/NF-κB and MAPK activation, leading to a reduction in the expression of neuroimmune mediators such as NO, PGE2, and IL-1β ($p < 0.01$). Furthermore, BA promotes STAT1 expression and inhibits the TLR4/NF-κB pathway in the ischemic semi-dark band of rats subjected to middle cerebral artery occlusion, as evidenced by the inactivation of IκBα, JNK, ERK, and p38, along with the inhibition of p65 nuclear translocation.[133] In addition to BA, several natural flavonoids exhibit potent anti-AD properties, including the reduction of neuroinflammation, combatting oxidative stress, and the regulation of apoptosis. Notably, nobiletin has been shown to inhibit the PI3K/Akt pathway and its downstream target genes, leading to the suppression of NF-κB release and a subsequent decrease in OS.[99] Quercetin boosts SIRT1 activity and inhibits NF-κB

acetylation, lowering ROS levels, decreasing inflammation, and controlling apoptosis.[100] Icariin, a potential acetylcholinesterase inhibitor, has been shown to alleviate AD by effectively crossing the BBB and upregulating peroxisome proliferator-activated receptors α and γ (PPARα and PPARγ). Additionally, it inhibits the TAK1/IKK/NF-κB signaling pathway, leading to the inactivation of microglial cell activity and a reduction in neuroinflammation.[102] Additionally, Hedysarum polysaccharides, an active component of Astragalus, exhibit a range of pharmacological effects, including anti-tumor, anti-aging, and immune-enhancing properties. It also reduces the expression of HMGB1, TLR4, NF-κB, and IL-1β in neural tissues, thereby alleviating neurological impairments induced by inflammatory responses.[96] The anti-inflammatory effect of the phenolic component glycosylated olive bittersweet in olive leaf extract involves reducing RAGE and NF-κB pathways.[106] PPARγ, a ligand-activated transcription factor, plays a significant role in the pathology of AD. It inhibits pro-inflammatory gene expression by either reducing the transcriptional activity of NF-κB or by interacting with the active form of p65,[134] thereby potentially serving as a neuroprotective target. Several herbal products, including Ginsenoside Rg1,[107] Polylactic Acid,[108] Gastrodin,[109] and Chuanxiong ginseng soup,[135] have been shown to improve cognitive behavior in AD by activating PPARγ and inhibiting NF-κB expression. In addition, peony seed oil,[110] mulberry leaf,[136] trehalose,[137] and spinosa 1,6-O,O-diacetylbritannilactone extract[138] all showed promising effects in promoting cognitive ability and treating AD. Their mechanisms were all related to the inhibition of the NF-κB signaling pathway. These results suggest that natural products from Chinese medicine may serve as novel anti-Ad drugs. The results are not always favorable; however, a recent meta-analysis involving 671 AD patients indicated that ginseng did not demonstrate a significant positive effect on overall cognition (SMD = 0.06, 95% CI: −0.64–0.77, p = 0.86), attention (SMD = 0.06, 95% CI: −0.12–0.23, p = 0.54), or executive function (SMD = −0.03, 95% CI: −0.28–0.21, p = 0.79). These findings suggest that further investment is required in the clinical translation of natural products.[139]

Chinese Medicine Natural Products Modulate NF-κB for PD Treatment

PD, also referred to as tremor paralysis, is characterized by clinical features that include motor deficits such as bradykinesia, myotonia, resting tremor, and postural gait abnormalities. Additionally, in the early stages of the disease, a significant number of non-motor symptoms can be observed, including apathy, depression, hyposmia, sleep disturbances, cognitive dysfunction, and autonomic disturbances.[140] Currently, levodopa is the primary clinical treatment for PD; however, it is ineffective in alleviating all PD symptoms. Additionally, adverse side effects such as nausea, vomiting, and delirium may occur, and long-term use can lead to motor deficits and a decrease in treatment efficacy.[141] Therefore, it is essential to identify safe and effective therapies for PD. The typical pathophysiology of PD is characterized by the degeneration and loss of dopaminergic neurons in the substantia nigra (SN) and striatum, along with the formation of Lewy bodies.[142] PD results from a combination of pathological mechanisms, including neuroinflammation, abnormal aggregation of α-Syn, oxidative stress, mitochondrial dysfunction, disruption of calcium homeostasis, and dysregulation of the gut microbiome.[143] These pathways may interact with genetic or environmental factors.[144] Immunohistochemical analysis revealed elevated NF-κB translocation in the nucleus accumbens of midbrain DA neurons.[145] This leads to transcription of pro-inflammatory mediators and overexpression of ROS. ROS lipid peroxidation induces neuronal cell damage, leading to neurodegenerative processes.[146] Research conducted by Kim et al[147] has highlighted the role of p53-mediated apoptosis as a central factor in the loss of dopamine neurons. They also identified the upstream regulator TNF-α-NF-κB, which offers a clinical strategy for transient inhibition of TNF-α. Lewy bodies, a hallmark of PD, are primarily composed of aggregates of α-syn. The dysfunction of both the ubiquitin-proteasome system and the autophagy-lysosomal degradation pathway results in an imbalance between the production and clearance of cytoplasmic α-syn, leading to its abnormal aggregation and ultimately triggering the onset of PD.[148] Evidence suggests that α-syn aggregates provide two "assembly" signals for NLRP3 activation through upregulation of the TLR2/NF-κB pathway and impairment of mitochondrial function.[37] The inflammasome subsequently acts on the translocation of NF-κB, resulting in the release of pro-inflammatory cytokines that exacerbate the neural cascade response and damage dopaminergic neurons. The activation of NF-κB leads to an increase in α-syn expression. Gao et al[149] discovered that elevated levels of Nurr1 inhibit the expression of NF-κB and α-syn, thereby alleviating the inflammatory conditions associated with PD. In summary, targeting the NF-κB pathway presents promising clinical applications for PD.

Flavonoid Kaempferol (KAE), primarily derived from the rhizomes of the traditional Chinese herb galangal, exhibits notable anti-inflammatory, antioxidant, and anticancer properties. The PARK7 gene encodes the DJ-1 protein,

a multifunctional protein whose expression and neuroprotective effects may be diminished in the brains of PD patients.[150] KAE binds to DJ-1 protein,[114] inhibiting its translocation to the plasma membrane. This interaction affects the activity of Lyn kinase and subsequently suppresses distal signaling molecules, including NF-κB. Cai et al[92] observed that in 6-hydroxydopamine (6-OHDA)-induced PD mice, KAE down-regulated the production of pyrolytic proteins and inflammatory mediators within the p38MAPK/NF-κB signaling pathway, thereby mitigating the neuroinflammatory response subsequent to cellular pyroptosis ($p < 0.05$). Additionally, Quercetin therapy alleviated oxidative stress by enhancing mitochondrial quality, elevating the autophagy markers PINK1 and Parkin,[111] and decreasing α-synuclein expression. Quercetin has been demonstrated to inhibit TNF-α-induced apoptosis and inflammation by disrupting the NF-κB and AP-1 signaling pathways in human umbilical vein endothelial cells (HUVECs) in vitro experiments.[101]

Gut flora and their metabolites interact through the gut-brain axis, a mechanism that regulates CNS neuroinflammation, gut inflammation, and barrier function, all of which are implicated in the pathology of PD.[151] Gut microbial dysbiosis can lead to the production of harmful metabolites, such as LPS, which may increase intestinal permeability. TLR4, the primary receptor for LPS immunorecognition, is responsible for the secretion of pro-inflammatory cytokines in both intestinal and systemic circulations.[152] These cytokines subsequently traverse the BBB, activating NF-κB and inducing neuroinflammation. Previous studies have demonstrated that herbal natural products can ameliorate symptoms of PD and safeguard dopaminergic neurons by modulating the TLR4/NF-κB signaling pathway. Zhang et al[116] observed that Rhynchophylline, derived from Uncaria rhynchophylla, blocked the TLR4/NF-κB/NLRP3 pathway while simultaneously activating the Nrf2/HO-1 pathway. This dual action significantly reduced MPTP-induced motor impairments and dopaminergic neurotoxicity in mice ($p < 0.01$). Additionally, Gastrodia elata, a potent component of Aspalathus, inhibited the TLR4/NF-κB pathway and decreased GFAP and inflammatory markers in the brains of PD mice.[113] The traditional Chinese herb Annona glabra was modified with the compound FLZ to mitigate neuroinflammation and motor deficits in a PD mice model induced by rotenone intoxication. This protective effect was mediated through the inhibition of the TLR4/MyD88/NF-κB[117] signaling pathway. Saikosaponin A, derived from Bupleurum, has been shown to prevent dopaminergic neurodegeneration, reduce inflammation and oxidative stress in the SN of PD rats, and inhibit neuronal death by regulating the TLR4/MyD88/NF-κB signaling pathway.[118] Resveratrol (RESV) also exerts neuroprotective benefits through this mechanism.[119] Natural products from Chinese medicine modulate the NF-κB signaling pathway, inhibit α-syn accumulation, reduce the loss of dopaminergic neurons, and significantly enhance motor function in PD.

It has also been established that the regulation of NF-κB transcription contributes to neuroprotection. Triterpenoid saponins Ginsenoside Rb1, the primary active component of ginseng, has been shown to safeguard dopaminergic neurons, SH-SY5Y cells, and PC12 cells in vitro from neurotoxic damage. Zhang et al[112] discovered that Ginsenoside Rb1 enhances the expression of Glutamate Transporter-1 in glial cells ($p = 0.036$). This mechanism may involve the nuclear translocation of NF-κB in astrocytes, which binds to the EAAT2/GLT-1 promoter. Glutamate transporter proteins play a crucial role in the termination of glutamate signaling.[153] Ginsenoside Rb1 enhances motor function in PD by elevating the expression of glutamate transporter proteins, inhibiting excitotoxicity, and modulating synaptic transmission through the activation of NF-κB. Bear bile powder inhibits NF-κB protein phosphorylation and indirectly activates TGR5, reducing inflammation in PD mice.[115] Curcumin,[120] protocatechuic acid[154] and Isobavachalcone,[121] which are active components of TCM, regulate the NF-κB pathway and contribute to the prevention and treatment of PD through their antioxidant, anti-neuroinflammatory, and cytoprotective effects.

Chinese Medicine Natural Products Modulate NF-κB for ALS Treatment

ALS is a severe neurodegenerative disease characterized by the progressive loss of both upper and lower motor neurons, denervation of various skeletal muscles, and the ensuing progressive muscle weakness and paralysis.[155] Ultimately, ALS leads to death due to respiratory failure.[156] ALS develops between the ages of 50 and 65, and males are often more at risk. ALS is classified into two types: sporadic (SALS) and familial (FALS), with SALS representing 90–95% of all cases. Pathogenic mutations in four genes—SOD1, TARDBP, FUS, and C9orf72—account for approximately 60% of FALS cases.[157] Riluzole is the only FDA-approved medication for ALS that operates by reducing glutamatergic neurotransmission.[158] However, it only extends life expectancy by 2 to 4 months,[159] and its efficacy remains a topic of debate. TCM plays a unique role in the treatment of ALS by benefiting lung qi and tonifying the spleen and kidney. Numerous studies[160–162] have suggested that natural products from Chinese medicine, characterized by their multi-target and multi-pathway effects, as well as fewer side effects, demonstrate

significant efficacy in treating ALS. Mutations in the TARDBP gene, which encodes SOD-1 and TDP-43 are among the most common causes of ALS pathogenesis. Transgenic mice that express mutant SOD-1 or mutant TDP-43 are widely utilized as animal models for in vivo research on ALS.[32] Several pathogenic pathways contribute to the development of ALS, including oxidative stress, mitochondrial dysfunction, inflammation, and excitotoxicity. Recent investigations have demonstrated an elevated pro-apoptotic acetylation status of RelA in animal models of ALS.[163] Additionally, microglia-specific NF-κB staining was seen in the white matter of C9-ALS-FTSD cases.[164] Mutations in SOD-1, a crucial enzyme responsible for scavenging superoxide anions, lead to the accumulation of ROS, which subsequently promotes the nuclear translocation of NF-κB. Abnormally aggregated TDP-43 directly binds to NF-κB p65 or induces the release of mitochondrial DNA, thereby indirectly activating NF-κB through the cGAS-STING pathway.[165] Additionally, ALS-associated Optineurin mutants lose their inhibitory effect on TNF-α and linear ubiquitin chain assembly complex-mediated NF-κB activation.[166] Collectively, these findings suggest that impaired regulation of NF-κB is closely linked to the pathogenesis of ALS. Dutta et al[167] selectively expressed the IκBα form of the NF-κB inhibitor in neurons of the TDP-43 mice model, demonstrating that this approach inhibited the nuclear translocation of the p65 subunit of NF-κB. This intervention attenuated neuroglial activation, stimulated autophagy, and reduced TDP-43 protein aggregation. S100A4 is recognized as an activator of the NF-κB axis and is known to impair autophagy. Clonidine exhibits potent anti-inflammatory and antifibrotic properties by indirectly promoting muscle regeneration through the inhibition of S100A4 transcription.[168] Similarly, Ginsenoside Rg1 inhibits the NF-κB/Bcl-2 signaling pathway in SOD1G93A-NSC34 cells, thereby reducing apoptosis and offering neuroprotection against ALS.[169]

RESV is a naturally occurring polyphenol known for its neuroprotective properties through various mechanisms. A study conducted by Bankole et al[170] found that the combination of RESV and valproate effectively repaired the pathogenic acetylation of NF-κB/RelA and histone 3 in the SOD1 (G93A) mice model, resulting in a neuroprotective form of NF-κB ($p < 0.0001$). The underlying mechanism involves the enhancement of AMPK phosphorylation in the lumbar spinal cords of mice, which restores the activity of histone acetyltransferases necessary for proper RelA acetylation,[171] thereby reducing motor impairments and motor neuron death. This study demonstrates that the epigenetic modulation of the acetylation state of the NF-κB RelA protein may serve as a viable therapeutic target. The researchers also observed that the drug's ability to prolong mouse survival was more pronounced in female subjects ($p = 0.0025$), which raises concerns regarding gender dimorphism. Arctigenin, an active compound derived from the traditional Chinese medicinal herb burdock, exhibits a wide range of applications, including hypoglycemic, anti-inflammatory, antioxidant, anti-apoptotic, and other therapeutic effects.[172] Xiong et al[122] isolated a derivative of Arctigenin, designated A-1, which demonstrated significant efficacy in a SOD1 (G93A) mice model, resulting in a marked improvement in locomotor capacity ($p < 0.01$). Administration of A-1 activated the AMPK/SIRT1/PGC-1α signaling pathway, which is crucial for the regulation of mitochondrial biogenesis. Concurrently, the AMPK/SIRT1/IL-1β/NF-κB pathway was also activated, leading to a reduction in the levels of IL-1β and pNF-κB/NF-κB. In conclusion, treatment with A-1 enhances mitochondrial function and mitigates neuroinflammation. The synergistic effects of these two mechanisms contribute to a decrease in gastrocnemius muscle fibrosis and the loss of spinal motor neurons, thereby providing a novel therapeutic strategy for the intervention of ALS.[123] In addition, a variety of natural products from Chinese medicine have been found to contribute to the clinical treatment of ALS, such as Fisetin,[124] Stigmasterol,[125] Astragaloside, Astragalus Polysaccharide,[7] and Lycium barbarum polysaccharide.[173] They indirectly modulate the NF-κB pathway by counteracting inflammation, inhibiting oxidative stress, and modulating the immune system, which reduces the accumulation of excitatory amino acids and enhances positive muscle force.

Discussion

Intracellular NF-κB signaling coordinates numerous signals that contribute to immune responses, inflammation, and pathological protein aggregation, and is closely associated with the development of NDDs. From another perspective, NF-κB may be central to the vicious cycle of neurodegeneration. In this study, we summarize the mechanisms of action and potential of natural products from Chinese medicine against NDDs, particularly AD, PD, and ALS, through the lens of the NF-κB signaling pathway. Given the complex nature of the pathomechanism of NDDs, natural products from Chinese medicine with multi-level and multi-targeting capabilities may represent a breakthrough in therapeutic drug development. From the above summary, it is evident that certain natural products directly bind to the NF-κB subunit for regulation, while others exert their effects on NF-κB indirectly by influencing upstream signaling pathways. This leads to anti-inflammatory and antioxidant

stress functions, ultimately achieving therapeutic effects on NDDs. It is clear that the neuroprotective effects of natural products from Chinese medicine are mediated through multiple pathways, with the NF-κB pathway serving as a crucial link among them. However, the current barriers to the transformation of natural components of TCM must be addressed urgently. Researches have shown that the water solubility of most flavonoids and polyphenols is less than 1 μg/mL, which hinders effective absorption in the gastrointestinal tract. Furthermore, the first-pass effect and drug clearance by efflux pumps, such as P-glycoprotein and multidrug resistance-associated protein 2, contribute to the low bioavailability of most TCM monomers. Additionally, the high polarity and molecular weight of many natural products complicate their passive diffusion across the BBB. Balancing the reparative functions of natural products from Chinese medicine on structural damage to the BBB following NDDs while ensuring that an effective concentration reaches the brain to exert neuroprotective effects remains a bottleneck in current research. Moreover, the long-term use of herbs rich in terpenoids or alkaloids necessitates monitoring liver enzymes to prevent hepatotoxicity. Collectively, these physicochemical properties present significant challenges to the clinical translation of natural products from Chinese medicine.

On the other hand, current in vitro and in vivo experimental models suffer from homogenization, with preclinical studies predominantly relying on transgenic rodent models or immortalized cell lines. There are cross-species differences in animal models, making it difficult to accurately capture the spatial and temporal complexity of human NDDs pathology. The lack of interactions between neurophysiological structures and dynamic microenvironmental elements in in vitro single-cell cultures, coupled with the detachment of ex vivo experiments from the systemic regulatory network of the neuroendocrine-immune axis, represents significant deficiencies. These shortcomings can amplify the local effects of a drug while underestimating the potential risk of toxicity, ultimately leading to biased clinical translation. It must be admitted that current research lacks the backing of high-quality human clinical trials. While Curcumin has been shown to inhibit Aβ-induced NF-κB activation and improve cognitive function in animal models of AD, it did not achieve similar efficacy in a Phase II clinical trial (NCT00099710) involving patients with mild AD ($p > 0.05$), primarily due to its low bioavailability (blood concentration < 0.1 μM).[174] The phenomenon of "animal-human translational failure" has also been observed in other natural products. As previously mentioned, RESV protects dopaminergic neurons in PD mice through the modulation of the TLR4/MyD88/NF-κB pathway. However, it encounters a dosage tolerance issue in human trials, as subjects experience gastrointestinal toxicity and are compelled to terminate the test when the dose of RESV exceeds 1 g/day.[119] Furthermore, most current studies focus on the pro-inflammatory properties of NF-κB, while the NF-κB network can exhibit dual roles in the nervous system, depending on the specific combination of cell types and/or NF-κB subunits. The deeper mechanisms of action of natural products from Chinese medicine targeting NF-κB remain unclear, and the multipotency of herbal medicines poses challenges to the traditional "single-target" drug evaluation framework. The potential risk of diminished immune surveillance due to excessive inhibition of NF-κB must also be considered. Consequently, there is an urgent need to explore novel perspectives to establish an innovative research platform for the prevention and treatment of NDDs.

With the advancement of modern science and technology, an increasing number of emerging studies provides insights into brain-targeted delivery strategies for natural products from Chinese medicine. Drawing inspiration from the decoction process inherent in TCM, researchers have utilized the co-assembly of active ingredients to create stable structures for drug delivery, transforming single molecules into multi-component interactions. For instance, BA and panaxoside have been shown to form nanofibers through hydrogen bonding and hydrophobic interactions, resulting in a 2.8-fold increase in bioavailability.[175] Aromatic compound-modified nanocarriers can enhance BBB permeability by down-regulating the expression of tight junction proteins, thereby increasing the concentration of drug distribution in the brain and exerting neuroprosthetic effects.[176] In the future, the integration of spatial proteomics and nanoscale gene modification technology may enable the precise exploration of NF-κB subunit targets regulated by natural products from Chinese medicine, as well as facilitate the real-time visualization of drug distribution in brain microregions. Simultaneously, large-scale multi-center randomized controlled double-blind clinical trials should be conducted to actively facilitate the translation of basic research into clinical practice, thereby accumulating substantial evidence-based medical data to support the efficacy of natural products from Chinese medicine in the treatment of NDDs. The new organoid technology can effectively simulate the three-dimensional structure and function of human organs, accurately reproduce the disease microenvironment, and reflect the complex cellular signaling networks. This technology overcomes

the limitations of traditional models in personalized medicine, drug screening, and ethical considerations, thereby bridging the gap between animal models and human pathology.

Conclusion

Natural products from Chinese medicine can influence NF-κB signaling via multiple mechanisms, including blocking the translocation of NF-κB from the cytoplasm to the nucleus, inhibiting the phosphorylation and degradation of IκB proteins, and modulating their upstream signaling pathways. These products act synergistically on NF-κB activation and expression through multiple targets to mitigate neuroinflammation, inhibit oxidative stress injury, alleviate mitochondrial dysfunction, and regulate the cell cycle. As a result, they emerge as promising candidate drugs for the treatment of NDDs. Due to their physicochemical properties and complex components, the clinical development of natural products from Chinese medicine continues to face numerous challenges. Future research must prioritize the optimization of nanocarrier design to improve bioavailability while simultaneously employing AI-driven models to achieve precise predictions of drug permeability across the BBB. For effective clinical translation, it is essential to conduct adaptive clinical trials and establish standardized animal-to-human dose conversion models based on brain area under the curve.

Abbreviations

AD, Alzheimer's disease; ALSm, Amyotrophic Lateral Sclerosis; AS-IV, Astragaloside IV; α-Syn, α-Synuclein; Aβ, Amyloid-β; BA, Baicalin; CNS, Central nervous system; IL-1β, Interleukin-1β; IL-6, Interleukin-6; iNOS, inducible Nitric Oxide Synthase; KAE, Kaempferol; LPS, Lipopolysaccharide; NDDs, Neurodegenerative disease; NF-κB, nuclear factor kappa B; OS, oxidative stress; PD, Parkinson's disease; RAGE, Receptor for Advanced Glycation End-products; RESV, Resveratrol; ROS, Reactive Oxygen Species; SIRT1, Sirtuin 1; SOD-1, Superoxide Dismutase 1; TCM, Traditional Chinese Medicine; TDP-43, trans-responsive DNA-binding protein 43; TLRs, Toll-like receptors; TNFR, Tumor Necrosis Factor Receptor; TNF-α, Tumor Necrosis Factor-alpha.

Data Sharing Statement

All data used to support the findings of this study are included within the article.

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Pictures by Figdraw.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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