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Advances in the Application of Berberine for Neurological Disorders

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Abstract: Berberine (BBR), a natural isoquinoline alkaloid, has demonstrated broad potential in treating neurological disorders in recent years. Its mechanisms encompass antioxidant stress, anti-neuroinflammation, inhibition of neuronal apoptosis, and regulation of neurotransmitter levels. However, challenges remain, including low oral bioavailability and safety concerns such as gastrointestinal discomfort and allergic reactions. Therefore, this systematic review examines the mechanism studies and therapeutic advances of BBR in neurological disorders such as Alzheimer's disease (AD) and Parkinson's disease (PD), aiming to provide references for neuroprotective drug development.

Keywords: Application Progress; Berberine; Mechanism of Action; Neurological Disorders.

1. Introduction

As the global population ages at an accelerated pace, neurological disorders have emerged as a core challenge threatening human health. Neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis, alongside acute or chronic injuries like cerebral ischemia and peripheral nerve damage, are characterized by irreversible neuronal damage, cognitive decline, and motor dysfunction. These conditions not only inflict immense suffering on patients but also impose a heavy burden on society and families [1-2]. Traditional therapeutic drugs have inherent limitations, and long-term use may induce a range of adverse reactions. Therefore, identifying novel therapeutic agents with multi-target mechanisms and high safety profiles is crucial [3]. Berberine (BBR), also known as coptisine, is an isoquinoline alkaloid extracted from plants such as Coptis chinensis, Phellodendron amurense, and Trichosanthes kirilowii [4]. Modern pharmacological research has revealed [5] that BBR not only exhibits antibacterial and antiviral properties but also holds therapeutic potential for cardiovascular diseases, diabetes, neuropathies, and other conditions. In recent years, with deepening insights into the pathogenesis of neurological disorders, BBR's potential in treating such diseases has gained increasing recognition and exploration. Studies indicate[6] that in Parkinson's patients, BBR can influence brain dopamine levels by regulating gut microbiota, thereby improving symptoms. However, current research on BBR for neurological disorders remains in its infancy. Its precise mechanisms of action remain incompletely elucidated, and clinical applications require further validation. Therefore, in-depth investigation of BBR's mechanisms in neurological diseases and the conduct of large-scale clinical studies hold significant importance for developing BBR as a novel therapeutic agent for neurological disorders. This paper reviews the application progress of BBR in neurological diseases, aiming to provide reference for related research.

2. Mechanism of Berberine in Treating Neurological Diseases

2.1. Antioxidant Stress Effects

In the pathological progression of neurological diseases, oxidative stress serves as a core driver. Excessive accumulation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) disrupts redox homeostasis, triggering lipid peroxidation, protein misfolding, and DNA damage, ultimately leading to neuronal dysfunction. BBR specifically modifies the cysteine residue of Keap1 to release nuclear factor E2-related factor 2 (Nrf2), promoting its nuclear translocation and activation of antioxidant response elements. This induces the expression of phase II detoxification enzymes such as superoxide dismutase, glutathione peroxidase, catalase, and quinone oxidoreductase 1. Concurrently, it stabilizes Nrf2 by inhibiting GSK-3β through activation of the PI3K/Akt pathway and upregulates the mitochondrial biogenesis regulator PGC-1α [7]. Mu et al. [8] indicated that 9-OHBBR may enhance mitochondrial function via the Pink1/Parkin pathway, where Parkin (encoding an E3 ubiquitin ligase) regulates mitochondrial autophagy alongside the outer mitochondrial membrane protein Pink1. TSENG H C et al. [9] demonstrated that BBR treatment reduces nitric oxide levels and lipid peroxidation, enhances antioxidant capacity, increases mitochondrial enzyme activity, and alleviates neuroinflammation and oxidative stress in the striatum.

2.2. Anti-Neuroinflammation

Neuroinflammation represents a complex immune response of the nervous system to harmful stimuli such as injury, infection, or toxic substances. It is characterized by immune cell activation, pro-inflammatory cytokine release, and disruption of the blood-brain barrier. Excessive or persistent neuroinflammation plays a pivotal role in the onset and progression of various neurological disorders. Research indicates [10] that BBR inhibits the binding of Toll-like receptor 4 to lipopolysaccharide/damage-associated molecular patterns, thereby blocking the recruitment of

myelin-associated protein 88. This action prevents the activation of the nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways. damage-associated molecular pattern (DAMP) binding, thereby inhibiting the recruitment of myeloid differentiation factor 88 (MDM0). This action suppresses the activation of the nuclear factor κB (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways. This effect manifests as inhibition of IκBα degradation, prevention of NF-κB p65 nuclear translocation, and downregulation of p38/JNK phosphorylation, ultimately leading to a significant reduction in proinflammatory factor expression. Research indicates [11] that BBR specifically targets NIMA-related kinase 7 (NEK7), blocking its interaction with NOD-like receptor pyrocin domain-related protein 3 (NLRP3) to sustainably inhibit IL-1β release, thereby exerting anti-inflammatory effects. At the cellular level, BBR regulates the transformation of microglia from pro-inflammatory M1 to anti-inflammatory M2 types, enhancing their phagocytic function while inhibiting the conversion of astrocytes to neurotoxic A1 types. Additionally, it reduces the expression of chemokine CCL2/MCP-1 and cell adhesion molecule ICAM-1, suppressing the infiltration of neutrophils and monocytes into the central nervous system.

2.3. Inhibition of Neuronal Apoptosis

BBR blocks neuronal apoptosis through multi-cascade regulation. It activates the PI3K/Akt/GSK-3β signaling axis, promoting Bad protein Ser136 phosphorylation, thereby preventing Bad-Bcl-xL complex formation. Concurrently, it upregulates anti-apoptotic proteins Bcl-2/Bcl-xL while downregulating pro-apoptotic proteins Bax/Bak's mitochondrial translocation, stabilizing mitochondrial outer membrane permeability (MOMP) and inhibiting cytochrome c release. Research indicates [12] that BBR inhibits Aβ42 production by phosphorylating the extracellular signal-regulated kinase/eukaryotic translation initiation factor 2α/pre-synapin 1 pathway, while enhancing autophagic clearance of Aβ to slow its accumulation, thereby improving neurofibrillary tangles. Regarding endoplasmic reticulum stress-induced apoptosis, it downregulates the activity of the endoplasmic reticulum stress sensors IRE1α/XBP1 and PERK/eIF2α pathways, inhibits the expression of the transcription factor CHOP, and blocks CHOP-mediated Bim upregulation and activation of the TRAF2-JNK pathway [13]. Concurrently, its metabolite dihydro-BBR crosses the blood-brain barrier to inhibit GSK-3β-mediated tau hyperphosphorylation, thereby blocking NFT-associated apoptosis, while modulating the Parkin/PINK1 pathway to enhance mitochondrial quality control.

2.4. Regulation of Neurotransmitter Levels

In the cholinergic system, BBR reversibly inhibits acetylcholinesterase activity, reducing acetylcholine (ACh) hydrolysis rates. It also upregulates choline acetyltransferase expression to promote ACh synthesis, elevating ACh levels in cortical and hippocampal regions [14]. For the dopaminergic system, BBR selectively inhibits monoamine oxidase B to reduce dopamine (DA) metabolism while activating tyrosine hydroxylase (TH) and aromatic L-amino acid decarboxylase to enhance DA synthesis. It also downregulates dopamine transporter expression to delay synaptic DA reuptake; In the serotonergic system, it promotes 5-HT production by activating tyrosine hydroxylase 2 (TH2), downregulates serotonin transporter membrane localization to prolong synaptic 5-HT retention time, and modulates 5-HT1A/2C receptor sensitivity to improve depressive-like behaviors.

3. Berberine in Common Neurological Disorders

3.1. Alzheimer's Disease (AD)

AD is a progressive neurodegenerative disorder primarily characterized by cognitive impairment, memory loss, and the accumulation of β-amyloid (Aβ) plaques and neurofibrillary tangles in the brain. Related data indicate [15] that combined administration of BBR and curcumin significantly reduces inflammatory factor expression levels in hippocampal tissue of AD model mice, upregulates autophagy-related genes, decreases oxidative stress responses, and lowers phosphorylation levels in the AMPK pathway. This effectively improves neuroinflammatory symptoms and cognitive decline in mice. In the water maze test, mice in the combined treatment group exhibited shorter escape latency and increased crossings of the target platform, outperforming the untreated group. These studies collectively confirm BBR's potential therapeutic efficacy for AD. Research indicates [16] that following BBR administration to cognitively impaired mice, the expression levels of autophagy-related genes in their brains increased, suggesting BBR can reverse cognitive dysfunction in mice through autophagy.

3.2. PD

The primary pathological feature of PD is the progressive degeneration and death of dopaminergic neurons in the substantia nigra of the midbrain, leading to a significant reduction in striatal dopamine levels. BBR demonstrates significant therapeutic effects in PD through multi-target mechanisms. Research indicates [17] that in a 6-hydroxydopamine-induced PD zebrafish model, BBR significantly reduces abnormal PINK1 protein accumulation and LC3 protein overexpression, effectively protecting dopaminergic neurons. Additionally, BBR exerts effects through the gut microbiota-brain axis by enhancing TH activity in the intestine. TH, which uses BH4 as a coenzyme, is the key rate-limiting enzyme catalyzing the hydroxylation of tyrosine to produce levodopa. Research by Wang Y et al. [18] indicates that BBR can provide nitroreductase via bacterial-generated dihydro-BBR, promoting dihydro-BBR conversion to BH4. This enhances TH activity and accelerates intestinal bacterial synthesis of levodopa. Concurrently, fecal microbiota transplantation with Enterococcus faecalis or Enterococcus faecium combined with BBR more effectively elevates dopamine levels in PD mouse brains and alleviates PD symptoms.

3.3. Other Neurological Disorders

BBR also demonstrates therapeutic potential in various other neurological disorders. In cerebral ischemia-reperfusion injury models, BBR reduces NEK7 expression levels, inhibits NLRP3 inflammasome activation, thereby decreasing Caspase-1 activation and the release of inflammatory mediators such as IL-1β and IL-18, ultimately exerting neuroprotective effects following cerebral ischemia-reperfusion injury [19]. Ma Shijang et al. [20] demonstrated that BBR modulates key target genes—cyclin D2, estrogen receptor 1, MAPK14, MAPK8, and sarcoplasmic reticulum protein—to intervene in the vascular endothelial growth factor signaling pathway and platelet-activating pathway,

thereby exerting therapeutic effects on ischemic stroke. In a neuropathic pain rat model, BBR suppressed the activation of the NLRP3 inflammasome signaling pathway, reduced the release of inflammatory mediators IL-1β and TNF-α, and simultaneously decreased calcitonin gene-related peptide expression. This resulted in an elevated mechanical pain threshold in the facial sensory area of rats with trigeminal neuralgia induced by infraorbital nerve transection [21].

4. Major Challenges in the Clinical Application of Berberine

4.1. Pharmacokinetic Challenges

BBR is a highly valuable lead compound with broad optimization prospects in drug development. However, its extremely poor water solubility results in inadequate oral absorption and low bioavailability, which has become the primary factor hindering its widespread clinical application. Current research primarily focuses on developing novel drug delivery systems, including nanoparticles and liposomes. These innovative formulations aim to significantly enhance BBR's bioavailability by improving drug solubility, enhancing membrane permeability, and circumventing first-pass metabolism, thereby providing new technical solutions for its clinical application. An animal study [22] demonstrated that BBR hydrochloride delivered via lipid nanoparticles exhibited significantly higher oral bioavailability compared to standard BBR hydrochloride, achieving higher peak plasma concentrations in rats. Additionally, its clearance rate was slower than that of BBR hydrochloride, resulting in prolonged duration of action within the body. Marino et al. [23] developed a novel nanoemulsion delivery system. In vitro cellular model evaluations revealed that BBR formulations prepared under different temperature conditions exhibited absorption rates increased by 4.5 to 6 times.

4.2. Safety Concerns

Despite its broad pharmacological activity, BBR carries certain adverse reactions in clinical use. One study [24] reported that during 12 months of continuous oral BBR hydrochloride treatment, three patients in the BBR group experienced nausea, one developed subcutaneous hemorrhage, and two presented with rash. Wang Jing et al. reported that when treating patients with BBR (single dose of 0.5 g), three cases of nausea, one case of vomiting, and one case of constipation occurred as adverse reactions. After adjusting the dose to 0.3 g administered orally three times daily, all four adverse reactions resolved. These cases indicate that adverse reactions primarily involve gastrointestinal discomfort and allergic reactions. Long-term use may also lead to liver and kidney function impairment, gut microbiota imbalance, and neurological effects. However, in Western countries, BBR extract supplements are sold as over-the-counter products in pharmacies and regulated markets without requiring medical prescriptions or professional medical supervision. Although studies indicate BBR supplements generally exhibit good tolerability and high safety, the potential adverse reaction risks and incomplete clinical guidelines may increase hazards. Consequently, food and drug regulatory authorities should promptly establish stringent regulations to oversee the production and sale of BBR as a dietary supplement. Therefore, clinicians should strictly adhere to indications, avoid overdose or prolonged use, and ensure special populations use these supplements under medical supervision.

5. Conclusion

As a natural alkaloid, BBR demonstrates significant potential in treating neurological disorders. Its core mechanism involves multi-target effects, including antioxidant stress, inhibition of neuroinflammation, blockade of neuronal apoptosis, and regulation of neurotransmitter levels. Research confirms its neuroprotective and symptomatic improvement effects in disease models such as Alzheimer's disease (AD), Parkinson's disease (PD), cerebral ischemia-reperfusion injury, and neuropathic pain. However, clinical application faces two major challenges: pharmacokinetically, its low oral bioavailability may be overcome through novel delivery systems; Regarding safety, risks include gastrointestinal discomfort and allergic reactions, while long-term use necessitates vigilance against hepatic/renal impairment and dysbiosis. Consequently, future efforts should focus on conducting large-scale clinical trials to validate efficacy, optimizing delivery strategies to enhance bioavailability, and rigorously evaluating long-term safety to advance BBR's clinical translation and application in neuroprotection.

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