Review

A review: Research progress on multi-target neuroprotective effects of *n*-butylphthalide extracted from *Apium graveolens* seeds

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Abstract

***Apium graveolens*, an annual herb belonging to the family of Apiaceae, is widely distributed in North and South America, Southern Europe, Africa and Asia. *Apium graveolens* seeds have a rich history in traditional Chinese medicine for treating hypertension, headaches, vertigo and epilepsy. *N*-butylphthalide, originally extracted from *Apium graveolens* seeds, represents a first-in-class drug developed independently in China. Its broad pharmacological activities on nervous system disorders have garnered significant attention from researchers globally. This review focuses on the pharmacological research of *n*-butylphthalide on central nervous system diseases, including ischemic stroke, Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis. The purpose is to pave the way for future study on the mechanistic targets of *n*-butylphthalide.**

Keywords: *Apium graveolens* seeds; *n*-butylphthalide; central nervous system diseases

1 Introduction

In recent decades, with the steady growth of the elderly population, the prevalence of central nervous system disorders (CNSDs) has increased correspondingly, including ischemic stroke (IS), Alzheimer's disease (AD), Parkinson's disease (PD) and amyotrophic lateral sclerosis (ALS) [1]. These conditions affect the patients' central or peripheral nervous system, damaging brain function, spinal cord function, neuromuscular function and peripheral nerves [2]. By the end of 2021, the population over 60 in China reached 266.84 million, accounting for 18.9% of the total population. At the same time, the incidence of age-related diseases, such as IS, AD and other neurological disorders, also increased significantly [3]. According to the existing research, the pathogenic factors of CNSDs mainly include oxidative stress, mitochondrial dysfunction, neuroinflammation, neuronal apoptosis

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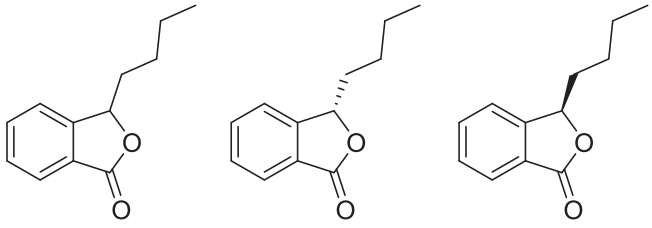
and abnormal protein aggregation [4-10]. Given that the pathological changes accompanying CNSDs are irreversible, current treatment modalities predominantly aim to delay disease progression, rather than fundamentally repair neural network damage. Consequently, achieving the therapeutic goal of preventing or slowing down the progression of CNSDs while restoring neuronal function remains the paramount challenge in both new drug research and clinical practice.

Apium graveolens is an annual herbaceous plant belonging to the family of Apiaceae, which is widely distributed in North and South America, Southern Europe, Africa and Asia. *Apium graveolens* seeds have a long tradition of treating hypertension, headaches, dizziness and epilepsy in China. They contain various bioactive compounds, including volatile oil, luteolin, *d*-limonene, phthalides, apigenin, hesperidin, linalool and quercetin [11,12]. *N*-butylphthalide (NBP) (**1**) (Fig. 1) was originally extracted from *Apium graveolens* seeds. As a First-in-class drug developed independently in China, NBP effectively improves central nervous system damage in patients with IS and expedites neurological function recovery. In 2002, the State Food and Drug Administration approved NBP for clinical treatment of stroke [13,14]. Extensive experimental and clinical studies have revealed that NBP exhibits various beneficial effects, including inhibiting inflammatory action, reducing mitochondrial oxidative stress, regulating apoptosis and decreasing abnormal protein accumulation [15]. These properties endow NBP with immense potential in treating a range of CNSDs, which makes it very important to further investigate its neuroprotective effects.



(**1**) (**2**) (**3**)

Fig. 1 NBP and its enantiomeric forms

2 Neuroprotective activities

2.1 Anti-IS Effect

IS is triggered by vessel blockage and leads to a cascade of pathophysiological reactions including apoptosis, autophagy, inflammation and oxidative stress. These reactions lead to metabolic abnormalities, ultimately resulting in brain damage [16]. Currently, the only intravenous thrombolytic therapy approved by the U.S. Food and Drug Administration for acute ischemic stroke is recombinant tissue plasminogen activator (rt-PA). However, rt-PA treatment has a limited therapeutic window and the surviving patients are at risk of hemorrhagic transformation [17].

As the first drug independently developed in China to treat cerebrovascular diseases, NBP has been clinically used to treat IS for many years. Extensive *in vitro* and *in vivo* studies have demonstrated the anti-ischemic effect of NBP, which involves complex mechanisms, including relaxing micro-blood vessels and inhibiting platelet aggregation and thrombus formation. Research indicates that NBP and its derivatives can block human purinergic G protein-coupled receptor

$P2Y_1$. This may be an important mechanism and a new target for inhibiting platelet aggregation and thrombus formation [18].

Moreover, by elevating Gap43 expression in primary cortical neurons, NBP activates the Sonic Hedgehog (Shh) signaling pathway, thereby promoting neurite outgrowth [19]. NBP also offers neurotrophic effect. It can mitigate neuronal apoptosis in rat post-cerebral ischemia/reperfusion injury (CIRI) by triggering the BDNF/TrkB pathway [20].

Oxidative stress and inflammatory responses are pivotal in ischemic damage. It was reported that NBP markedly elevated SOD activity and the GSH/GSSG ratio in MCAO rat models, while reducing the levels of TNF-*α*, IL-6 and malondialdehyde (MDA) [21]. Additionally, NBP demonstrated antioxidant properties by activating Nrf2, boosting HO-1 and NQO1 expression, enhancing SOD activity and curbing the production of MDA and 8-iso PGF2*α* in the hippocampus of mice with repeated cerebral ischemia reperfusion (RCIR). The ameliorating effect of NBP on neuroinflammation caused by RCIR injury involves Nrf2 on TLR4/MyD88/NF-*κ*B pathway [22].

In addition, the therapeutic efficacy of NBP is related to the amelioration of mitochondrial dysfunction. NBP augments the activity of mitochondrial $Na^{(+)}$ / $K^{(+)}$-ATPase and $Ca^{(2+)}$-ATPase in rats with middle cerebral artery occlusion (MCAO) and in cultured neurons [23]. Research indicates that NBP enhances the activity of cytochrome C oxidase 7c (Cox7c) and increases mitochondrial levels of SOD and ATP [24]. Concurrently, NBP inhibits the mitochondria-dependent apoptosis pathway, modulating the expression of apoptotic proteins such as cytochrome c (Cyto-C) and apoptosis-inducing factor (AIF), Caspase-3, Bax and Bcl-2, thereby reducing neuronal apoptosis [25,26]. A clinical trial shows that NBP's effectiveness in treating ischemic cerebrovascular disease is high, reaching 74.7%, and the incidence of adverse reactions is low, indicating that NBP has good clinical safety [15]. The effect of NBP on IS is shown in Fig. 2.

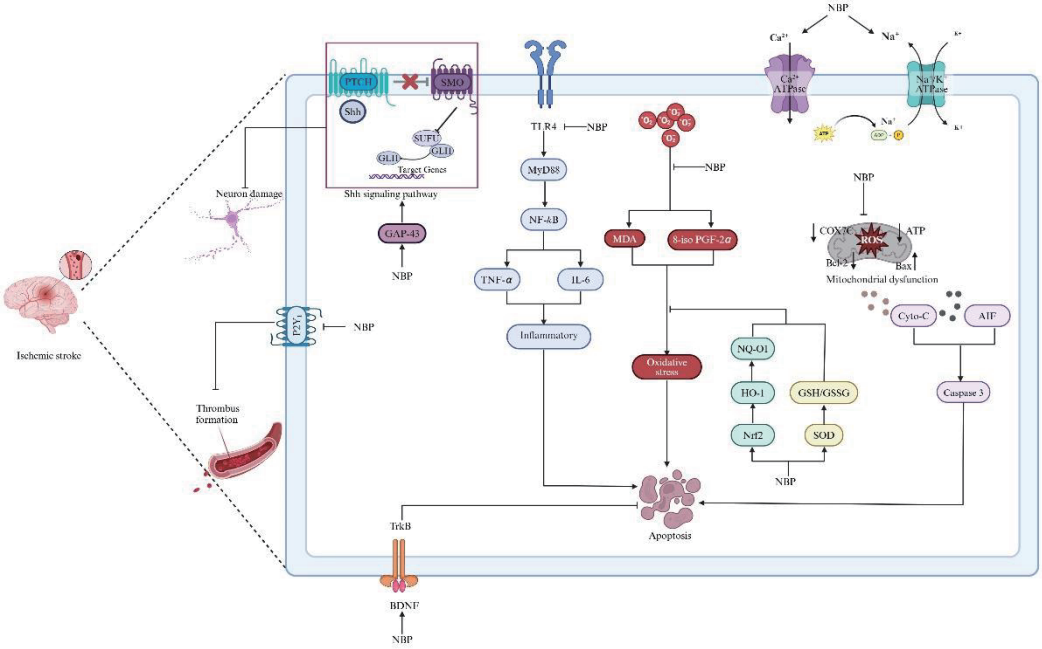


Fig. 2 Effect of NBP on IS

2.2 Anti-AD Effect

AD, a complex neurodegenerative disease resulting from multiple factors, is the leading cause of senile dementia. The brain of AD patients exhibit two classic neuropathological signs: senile plaques composed of progressive accumulation of amyloid-β peptide (Aβ) and neurofibrillary tangles (NFTs). NFTs are formed by the aggregation of paired helical filaments (PHFs) composed of truncated and hyperphosphorylated microtubule-associated protein tau [27]. Currently, the small molecular drugs available for clinical treatment of AD are cholinesterase inhibitors that enhance cholinergic system function and *N*-methyl-D-aspartate (NMDA) receptor antagonists that attenuate glutamate excitotoxicity [28]. However, cholinesterase inhibitors have significant hepatotoxicity, while NMDA receptor antagonists can only temporarily improve symptoms, failing to halt or slow down disease progression. Therefore, inhibiting the production of Aβ or eliminating the existing Aβ at the source is the important research direction for the treatment of AD.

The therapeutic effects of NBP on cognitive deficits have been validated in various AD models, encompassing APP/PS1 mice, P301S transgenic mice, senescence-accelerated prone mice (SAMP8), Aβ intracerebrally injected rats and aged rats [29-33]. Research indicates NBP notably inhibits the hyperphosphorylation of tau protein at the Ser262 site and reduces the activity of MARK4 associated with tau protein at the Ser262 site [30]. In addition, NBP improves amyloid-induced learning and memory deficits by reducing $STEP_{61}$ levels and increasing phosphorylated (p)-ERK1/2 and p-CREB levels [34]. Synaptophysin (SYN) and postsynaptic density 95 (PSD-95) serve as markers for presynaptic and postsynaptic terminals, respectively, representing the structural foundation of synaptic plasticity underlying learning and memory. After three months of NBP administration to SAMP8 mice, the levels of SYN and PSD-95 increased significantly [35].

With its chiral carbon atom, NBP exists in two enantiomeric forms: *l*-NBP (**2**) and *d*-NBP (**3**) (Fig. 1). According to literature reports, *l*-NBP exhibits a stronger ability to alleviate cognitive deficits compared to *d*-NBP and *dl*-NBP [36]. In Aβ PP/PS1 mice, *l*-NBP also decreased tau hyperphosphorylation and inhibited cyclin-dependent kinase and glycogen synthase kinase 3β (GSK-3β) to improve cognitive deficits [37]. Furthermore, a study revealed that *l*-NBP significantly reduced the total deposition of Aβ plaques in the brain of transgenic mice with Alzheimer's disease by redirecting the processing of amyloid precursor protein to non-amyloidogenic pathways and lowering Aβ levels in brain homogenates [38].

Lei et al. examined the impact of *l*-NBP on neurogenesis both *in vitro* and *in vivo*, discovering that *l*-NBP promoted the proliferation and migration of neural stem cells *in vitro*, inducing neuronal differentiation. These findings suggest that *l*-NBP may stimulate the proliferation, migration and differentiation of hippocampal neural stem cells, thereby reversing cognitive deficits in APP/PS1 mice. Consistent with the study by Yang et al., the mechanism may involve the Akt/CREB/BDNF/TrkB signaling pathway [39,40]. The effect of NBP on AD is shown in Fig. 3.

2.3 Anti-PD Effect

PD, the second most common neuro degenerative disease. With the aging of the population, the incidence rate is gradually increasing. Currently, clinical studies indicate that the primary pathological features of PD patients include the apoptosis of dopaminergic neurons in the substantia nigra and striatum, as well as the abnormal folding of α-synuclein, which leads

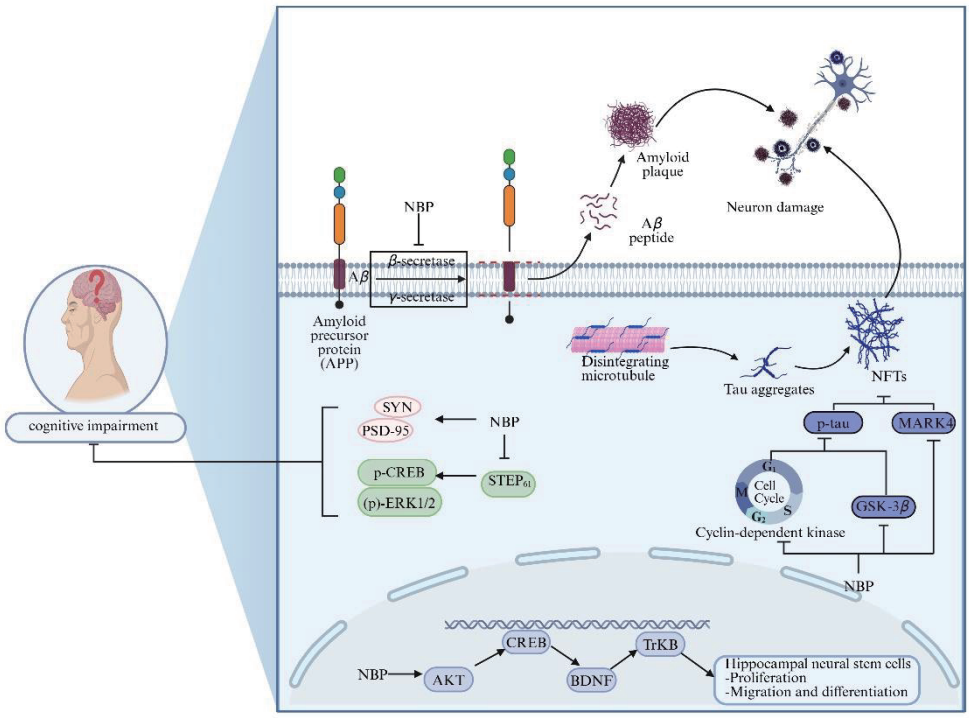


Fig. 3 Effect of NBP on AD

to the formation of Lewy bodies (LB) [41]. In terms of clinical treatment, neurotransmitter drugs such as Madopar are usually prescribed. However, these drugs fail to inhibit neuronal apoptosis, and long-term use will result in adverse effects [42].

Studies have indicated that neuroinflammation, induced by excessive activation of microglia, is closely related to the occurrence and progression of PD [43]. Researchers have utilized a rotenone-induced oxidative stress model in BV2 microglia to examine the role of NBP in reducing oxidative stress and its underlying mechanism. The results showed that NBP inhibited rotenone's effect on mitochondrial membrane depolarization in BV2 microglia, thereby preserving mitochondrial function and reducing intracellular reactive oxygen species (ROS) levels. This indicates that NBP exhibits neuroprotective properties against PD, and may inhibit oxidative stress via the Keap1-Nrf2-HO-1 signaling pathway [44]. The NLRP3 inflammasome, a cytoplasmic protein complex comprising NLRP3, ASC and Caspase-1, plays a crucial role in the pathogenesis and development of inflammatory and immune responses by enhancing the release of IL-1β and IL-18 [45]. Research has demonstrated that the activation of NLRP3 inflammasome is related to the pathogenesis of PD. It has been discovered that NBP inhibits neuroinflammation, mitigates mitochondrial damage and alleviates MPTP-induced behavioral impairments and dopaminergic neuron damage in mice by suppressing the activation of NLRP3 inflammasome, PARP1 and p-α-Syn aggregation. Furthermore, NBP significantly enhances the survival rate of 6-OHDA-induced SH-SY5Y cells, inhibits apoptosis, decreases ROS production and activates the expression of TH and Nurr1, thus exerting neuroprotective effects [46]. The effect of NBP on PD is shown in Fig. 4.

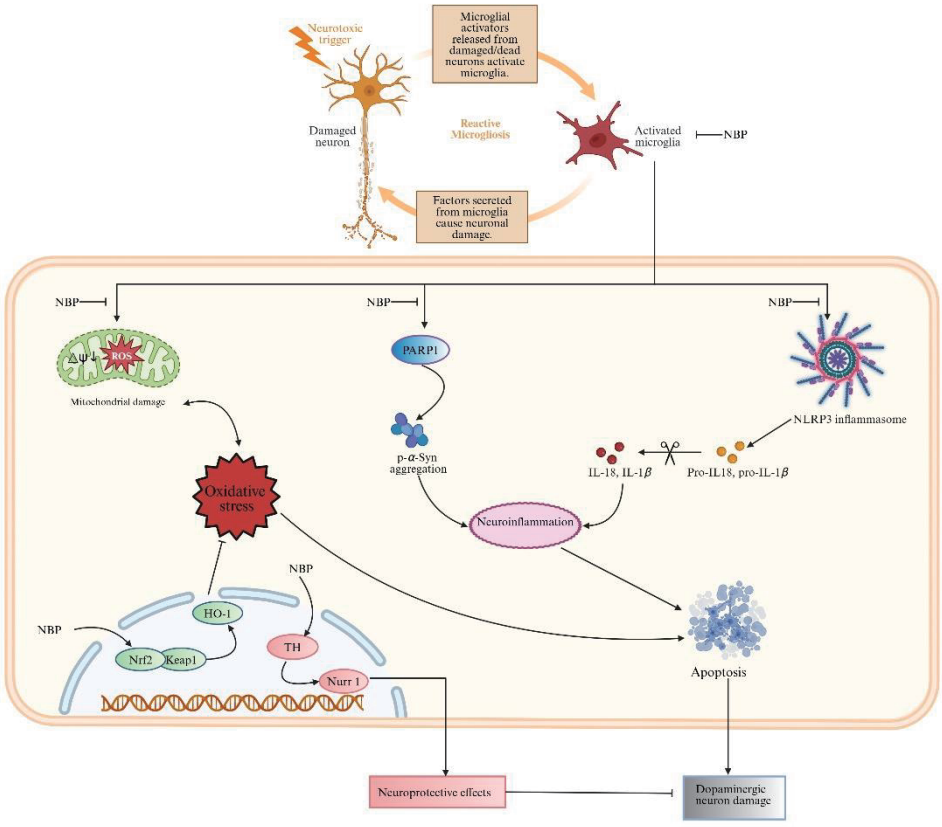


Fig. 4 Effect of NBP on PD

2.4 Anti-ALS Effect

ALS is a rare neurodegenerative disease. Usually, patients with ALS experience damage to both upper and lower motor neurons, resulting in progressive weakness, atrophy and paralysis of muscles in the trunk, limbs, chest and abdomen. Eventually, ALS can lead to dyspnea, respiratory failure and ultimately death [47,48]. Currently, the factors that trigger ALS and its pathogenesis remain unclear. There is a lack of effective drugs to treat the disease. Recently, NBP and its derivatives have been used to treat ALS. In 2018, NBP was approved as orphan drug for ALS by the US Food and Drug Administration (FDA). Research has indicated that NBP possesses the capability to improve delayed motor nerve function, reduce motor units and mitigate motor neuron loss. It significantly restores motor function in SOD1-G93A mice and extends their survival time. Furthermore, NBP significantly downregulates glial and autophagy activation in the spinal cord of SOD1-G93A mice, while mildly upregulating Nrf-2 and HO-1 and suppressing the activation of NF-κB p65 and TNF-α. Meanwhile, the immunoreactivity of CD11b and glial fibrillary acidic protein (GFAP) was significantly reduced [49]. The effect of NBP on ALS is shown in Fig. 5

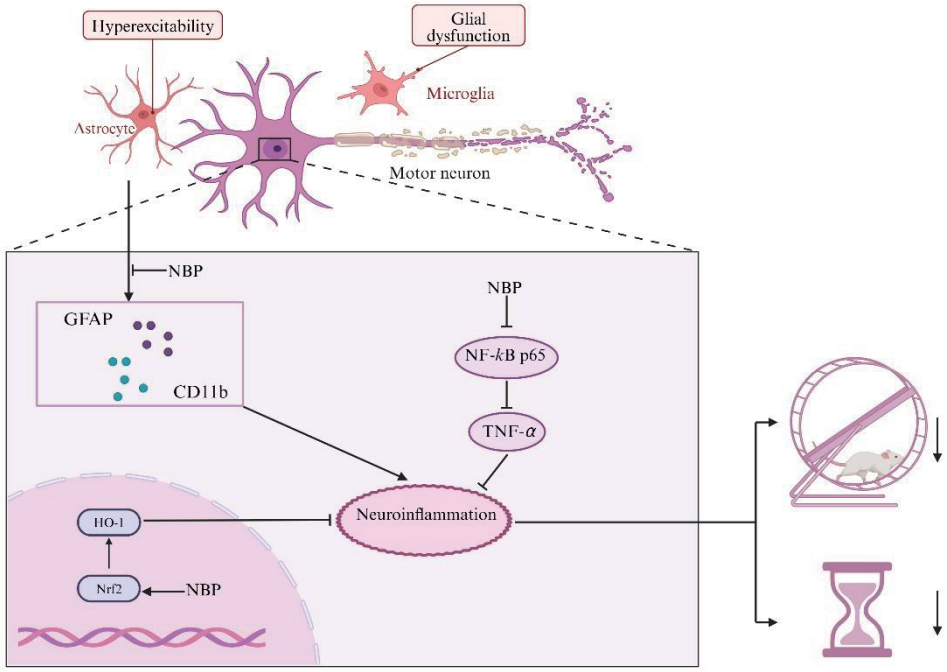


Fig. 5 Effect of NBP on ALS

3 Conclusion

Current research shows that NBP, as multi-target neuroprotective agent, can improve neurological diseases such as IS, AD, PD and ALS through various mechanisms, making it a promising compound in the field of pharmaceutical research for treating CNSDs. However, the development of new drugs is often a lengthy and intricate process, requiring rigorous pharmacological studies to ensure precise clinical positioning. NBP has been approved for clinical use in China for about 20 years, and its efficacy in treating IS has been extensively validated. Furthermore, research on NBP in treating CNSDs has further validated its extensive neuroprotective effects. However, the roles of NBP in the treatment of neurodegenerative disease remain to be elucidated. As the global population with CNSDs continues to grow, the demand for new drugs to treat these diseases is also increasing. Therefore, intensifying research on NBP will help to further establish its significant potential clinical value in neurological diseases, offering more prospects for discovering novel therapeutic agents.

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