

# Neuroprotective mechanisms of 3-n-butylphthalide in neurodegenerative diseases (Review)

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**Abstract.** Since 3-n-butylphthalide (NBP) was approved by the China Food and Drug Administration for the treatment of acute ischemia stroke in 2002, a number of studies have investigated NBP worldwide. In recent years, NBP has also demonstrated potential as treatment of several neurodegenerative diseases, which has increased the interest in its mechanisms of protection and action. Clinical studies and studies that used cell or animal models, have directly demonstrated neuroprotective effects of NBP via the following mechanisms: i) Inhibiting the inflammatory reaction; ii) reducing mitochondrial oxidative stress; iii) regulating apoptosis and autophagy; iv) inducing resistance to endoplasmic reticulum stress; and v) decreasing abnormal protein deposition. Therefore, NBP may be a potential drug for neurodegenerative diseases, and it is particularly important to identify the mechanism of NBP as it may assist with the development of new drugs for neurodegeneration. The present review summarizes the neuroprotective mechanisms of NBP and discusses new perspectives and prospects. The aim of the current review is to provide a new summary regarding NBP and its associated mechanisms.

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## 1. Introduction

3-n-butylphthalide (NBP), approved by the China Food and Drug Administration for the treatment of acute ischemic stroke, is a type of compound isolated from the seeds of Chinese celery (1). The molecular structure of NBP is presented in Fig. 1. Therapy using NBP has been recommended by Chinese guidelines for acute ischemic stroke (2). A randomized double-blind trial (clinical trial no. ChiCTR-TRC-09000483) reported that NBP significantly improves clinical outcomes, including the modified Rankin Scale (3) and National Institute of Health Stroke Scale scores (4), of patients who experienced ischemic stroke (5). In addition, a study demonstrated that NBP therapy persistently increases the level of endothelial progenitor cells in peripheral blood, ameliorate cerebral blood flow and improve neuronal functions (6). Furthermore, NBP has been reported to be a safe treatment for cerebral ischemia stroke (5-7). A study has indicated that NBP exhibits protective effects in several neurodegenerative diseases (8). However, to the best of our knowledge, the neuroprotective mechanism of NBP remains unclear. Therefore, the present review discusses the potential mechanism of neuroprotective effects of NBP. The aim of the current review is to provide further understanding regarding the advances of NBP.

## 2. NBP inhibits the inflammatory reaction

Inflammation, a complex biological response to injury, is associated with neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease (PD), multiple sclerosis, amyotrophic lateral sclerosis, traumatic brain injury (TBI) and more (9-11). NBP has exhibited anti-inflammatory effects in various models of these diseases and certain mechanisms have been identified. NBP has been reported to reduce

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the inflammatory reaction by inhibiting nucleotide binding oligomerization domain like receptor protein 3-inflammasome microglia activation and mitigating the Alzheimer's-like pathology via the nuclear factor erythroid-2-related factor 2-thioredoxin-interacting protein-TXNIP-thioredoxin axis in an APP/PS1 mouse model (12,13). Furthermore, NBP inhibited the inflammatory reaction in lipopolysaccharide (LPS)-induced rats via inhibition of c-Jun N-terminal kinase activation and the NF- $\kappa$ B pathway (14,15). NBP was reported to improve dyskinesia in a LPS-induced PD mouse model via a reduction in the loss of dopaminergic neurons, activation of mouse microglia, an increase in TNF- $\alpha$  levels and  $\alpha$ -synuclein deposition in the black substantia of the mouse midbrain (16). Additionally, NBP-treatment reduces NF- $\kappa$ B activation following TBI (17), and NBP also inhibits the inflammatory reaction via the same pathway in spontaneously hypertensive rats (18). Notably, a number of studies have indicated that NBP inhibits the inflammatory reaction in other neuroassociated experimental models, such as an experimental model of autoimmune encephalomyelitis of microglia or autoimmune myositis in guinea pigs (19,20). In addition, NBP-treatment has been demonstrated to significantly ameliorate cerebral ischemia reperfusion-induced brain injury of Sprague-Dawley (SD) rats by inhibiting toll like receptor 4/NF- $\kappa$ B-associated inflammation (21). NBP attenuates advanced glycation end products-induced endothelial dysfunction by ameliorating inflammatory responses (22). In summary, there is some understanding regarding the mechanism of NBP in the inhibition of inflammation.

### 3. NBP reduces mitochondrial oxidative stress

Mitochondria, the site of oxidative metabolism in eukaryotes, produce energy through the oxidation of carbohydrates, fats and amino acids (23). Therefore, mitochondrial dysfunction in the form of oxidative stress may contribute to the pathogenesis of various neurodegenerative diseases (24). Oxidative stress is considered a condition that is caused by an imbalance between pro- and antioxidant factors, which leads to molecular and cellular damage (25). Oxidative stress serves an essential role in the development of age-related diseases (26). NBP exhibits a cumulative beneficial effect on the process of mitochondrial damage (27). This section will discuss the mechanisms involved in mitochondrial oxidative stress.

Recently, NBP exhibited a powerful effect on antioxidant stress in some different models. NBP inhibited oxidative stress in K141N-induced SH-SY5Y cells and in LPS-induced rats through activation of the Kelch-like ECH-associating protein 1 Nrf2-related factor 2-antioxidant response element signaling pathway (15,28). Similarly, NBP reduced oxidative damage to provide neuroprotection in mice following TBI and in rats following carbon monoxide poisoning (29,30). In addition, NBP protects against cerebral ischemia-reperfusion injury by decreasing antioxidant stress via the ERK signaling pathway (31). NBP also protects against H<sub>2</sub>O<sub>2</sub>-induced injury in neural stem cells by activation of the PI3K/Akt and the Mash1 signaling pathways (32). Furthermore, NBP has been reported to increase superoxide dismutase and catalase activity, and reduce malondialdehyde activity in the experimental autoimmune myositis (EAM) model, NBP directly protects muscle

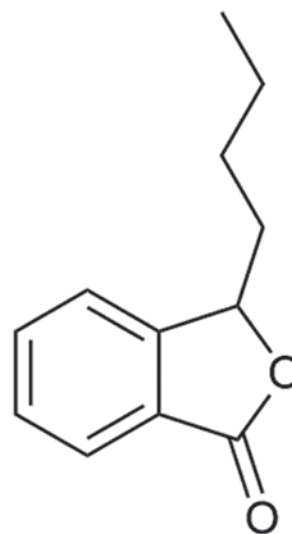


Figure 1. Molecular structure of 3-n-butylphthalide.

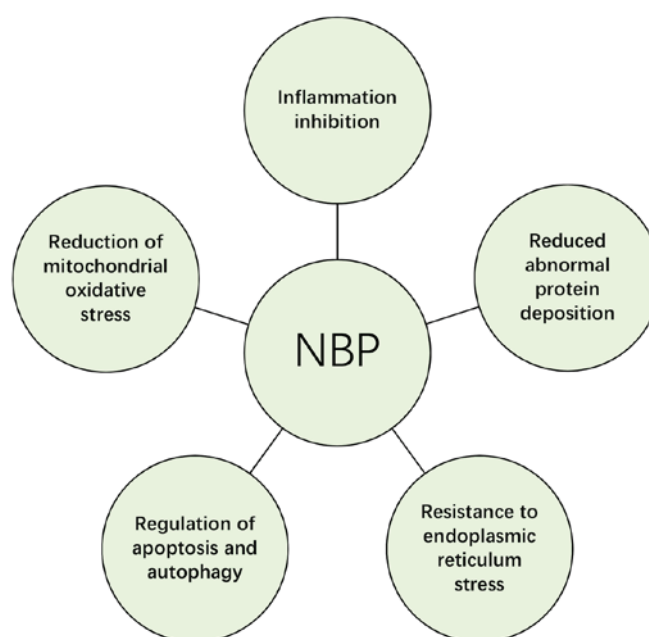


Figure 2. Neuroprotective mechanisms of NBP. NBP, 3-n-butylphthalide.

mitochondria and muscle cells from oxidative damage (33). However, the protective effect of NBP on mitochondrial function is not only limited to neurodegeneration, but also appears in cardiovascular diseases. A study suggested that NBP exerts a cardioprotective effect on cardiac ischemic injury via the regulation of mitochondrial function both using *in vivo* and *in vitro* experiments (34). In summary, the antioxidant effect of NBP has been widely recognized.

### 4. NBP regulates apoptosis and autophagy

Apoptosis and autophagy are basic biological phenomena of cells, which serve essential roles in removing abnormal cells in multicellular organisms. Disorders in the apoptosis and autophagy processes may cause the occurrence of neuropathy (35). The neuroprotective effect of NBP via the regulation

Table I. Neuroprotective mechanisms of 3-n-butylphthalide.

A, Inflammation inhibition				
Author, year	Study subject	Method	Molecular mechanism	Refs.
Wang <i>et al</i> , 2018	APP/PS1 mice A172, SH-SY5Y	Transgenic LPS induced	NLRP3 inflammasome activation inhibition NLRP3 inflammasome activation inhibition	(13)
Yang <i>et al</i> , 2018	SD rats	LPS induced	NF- $\kappa$ B pathway inhibition	(14)
Zhao <i>et al</i> , 2016	C57BL/6 mice	LPS induced	Downregulation of JNK activation	(15)
Zhao <i>et al</i> , 2017	C57BL/6 mice	Traumatic brain injury	NF- $\kappa$ B pathway inhibition	(17)
Wang <i>et al</i> , 2018	EAE	Neuroantigen-specific proinflammatory T cells induced	Suppression of PGAM5	(19)
Zhang <i>et al</i> , 2016	SD rats	Cerebral ischemia reperfusion induced	Increased HGF expression	(21)
Liu <i>et al</i> , 2017	HUVECs	Advanced glycation end product induced	RAGE/NF- $\kappa$ B pathway inhibition	(22)
B, Reduction of mitochondrial oxidative stress				
Author, year	Study subject	Method	Molecular mechanism	Refs.
Yang <i>et al</i> , 2017	SH-SY5Y	Missense mutations	Increased Nrf2 expression	(28)
Liu <i>et al</i> , 2017	ICR mice	Traumatic brain injury	Nrf2-ARE pathway activation	(29)
Li <i>et al</i> , 2015	SD rats	Carbon monoxide poisoned	Keap1/Nrf2 pathway activation	(30)
Zhu <i>et al</i> , 2018	ICR mice	Cerebral ischemia reperfusion injury	ERK signaling inhibition	(31)
Wang <i>et al</i> , 2018	NSCs from SD rats	Hydrogen peroxide induced	PI3K/Akt and Mash1 pathway activation	(32)
Chen <i>et al</i> , 2017	Guinea pigs	Experimental autoimmune myositis	Enhanced Na <sup>+</sup> -K <sup>+</sup> and Ca <sup>2+</sup> -Mg <sup>2+</sup> ATPase activities	(33)
Tian <i>et al</i> , 2017	H9C2	Hydrogen peroxide induced	Enhanced Nrf-1 and TFAM expression	(34)
C, Regulation of apoptosis and autophagy				
Author, year	Study subject	Method	Molecular mechanism	Refs.
Zhao <i>et al</i> , 2017	C57BL/6 mice	Traumatic brain injury	Downregulated caspase-3 and -9 expression	(17)
Liu <i>et al</i> , 2017	HUVECs	Advanced glycation end product induced	Regulation of Bcl-2 expression	(22)
Lei <i>et al</i> , 2014	SH-SY5Y	$\beta$ -amyloid induced	Regulation of Bcl-2, caspase-3 and -9 expression	(37)
Xu <i>et al</i> , 2017	C57BL/6 mice	Repeated cerebral ischemia reperfusion	Bcl-2/Bax elevation	(38)
Xiang <i>et al</i> , 2014	APP/PS1 mice	Transgenic	BDNF/TrkB/PI3K/Akt pathway regulation	(39)
D, Resistance to endoplasmic reticulum stress				
Author, year	Study subject	Method	Molecular mechanism	Refs.
Liao <i>et al</i> , 2018	SD rats	Doxorubicin induced	GRP78, CHOP and caspase-12 expression regulation	(41)
Niu <i>et al</i> , 2018	SD rats	Bilateral surgical ligation of common carotid arteries	GRP78, CHOP and caspase-12 expression regulation	(42)
Zheng <i>et al</i> , 2017	SD rats	Laminectomy performed at T9	ATF-4, ATF-6, XBP-1, PDI, GRP78, CHOP and cleaved-caspase 12 attenuation	(43)
	HBMECs	Thapsigargin induced	ATF-4, ATF-6, XBP-1, PDI, GRP78, CHOP and cleaved-caspase 12 attenuation	

Table I. Continued.

D, Resistance to endoplasmic reticulum stress				
Author, year	Study subject	Method	Molecular mechanism	Refs.
He <i>et al</i> , 2017	SD rats	Laminectomy performed at T9	ATF-4, ATF-6, XBP-1, PDI, GRP78, CHOP and cleaved-caspase 12 attenuation	(44)
	PC12	Thapsigargin induced	ATF-4, ATF-6, XBP-1, PDI, GRP78, CHOP and cleaved-caspase 12 attenuation	
E, Reduced abnormal protein deposition				
Author, year	Study subject	Method	Molecular mechanism	Refs.
Peng <i>et al</i> , 2010	3xTg-AD mice	Transgenic	Direction of APP processing towards a non-amyloidogenic pathway	(47)
Peng <i>et al</i> , 2012	AβPP/PS1 mice	Transgenic	Tau hyperphosphorylation inhibition	(48)
Chen <i>et al</i> , 2018	C57BL/6 mice	LPS induced	Reduction of α-synuclein deposition	(16)
Huang <i>et al</i> , 2010	PC12	MPP <sup>+</sup> toxicity induced	Reduction of α-synuclein deposition	(49)
LPS, lipopolysaccharide; SD, Sprague Dawley; JNK, c-Jun N-terminal kinase; HGF, hepatocyte growth factor; PGAM5, PGAM family member 5; RAGE, receptor for advanced glycation end-product; Nrf, nuclear respiratory factor; ARE, antioxidant response element; Keap1, Kelch-like ECH-Associating protein 1; Mash1, mammalian achaete scute homolog-1; TFAM, human mitochondrial transcription factor A; ICR, Institute of Cancer Research; NSC, neural stem cell; BDNF, brain derived neurotrophic factor; TrkB, Tyrosine receptor kinase B; GRP78, glucose regulated protein 78; XBP-1, X-box-binding protein 1; PDI, protein disulfide isomerase; APP, amyloid precursor protein; ATF, activating transcription factory; CHOP, CCAAT-enhancer binding protein homologous protein; MPP <sup>+</sup> , 1-methyl-4-phenylpyridinium.				

of apoptosis and autophagy has been demonstrated. Treatment with NBP has been reported to reduce apoptotic cell death by increasing the levels of cleaved caspase-3 and caspase-9 following TBI (17). Furthermore, NBP blocks neural apoptosis in areas surrounding cortical contusions on the brain that are induced by TBI (29). The neuroprotective mechanism of NBP involves the mitochondrial apoptotic pathway. NBP inhibits HSPB8 K141N mutation-induced neurotoxicity, attenuates  $\beta$ -amyloid-induced toxicity in SH-SY5Y cells, and protects rat cardiomyocytes from ischemia or reperfusion through regulating mitochondrion-mediated apoptosis (28,36,37). Furthermore, certain studies have demonstrated the inhibition of apoptosis by NBP via the Akt pathway. One study reported that NBP activates Akt/mTOR signaling to inhibit neuronal apoptosis and autophagy in mice with repeated cerebral ischemia reperfusion injury (38). Another study demonstrated that NBP improves cognitive impairment of APP/PS1 mice by inhibiting apoptosis via the PI3K/AKT pathway (39). Additionally, NBP reduces the number of apoptotic cells by regulating Bcl-2 in HUVECs and an EAM model (22,33).

### 5. NBP resists endoplasmic reticulum stress

ERS is characterized by incorrect folding and aggregation of unfolded proteins in the endoplasmic reticulum lumen and a disturbance of the calcium balance, which can activate the unfolded protein response and lead to disturbance of the cell function and cell death (40). In recent years, certain studies have reported an anti-ERS effect of NBP. One study demonstrated that NBP inhibits doxorubicin-induced ERS in SD rats (41).

In addition, NBP alleviates vascular cognitive impairment by regulating ERS and the Sonic hedgehog/Patched homolog 1 signaling pathway in SD rats (42). Both of these studies agreed that NBP attenuates ERS through regulating the expression of 78-kDa glucose-regulated protein (GRP78), CCAAT-enhancer binding protein homologous protein (CHOP) and caspase-12. Furthermore, NBP also inhibits ERS by attenuating activating transcription factory (ATF)-4, ATF-6, X-box binding protein 1, protein disulfide isomerase, GRP78, CHOP and cleaved-caspase-12 in a spinal cord injury (SCI) model, which may improve functional recovery and prevent disruption of the blood-spinal cord barrier (43,44). However, this mechanism has only recently been identified; therefore, there is limited literature about it. Further research on this mechanism may lead to new findings.

### 6. NBP decreases abnormal protein deposition

Abnormal protein deposition is closely associated with numerous neurodegenerative diseases (45), such as Alzheimer's disease, which is associated with amyloid- $\beta$  (A $\beta$ ) and tau proteins; and PD, which is associated with  $\alpha$ -synuclein (46). A study has demonstrated that NBP significantly reduces total cerebral A $\beta$  plaque deposition and lowers A $\beta$  levels in brain homogenates in a triple-transgenic mouse model of Alzheimer's disease via directing amyloid precursor protein processing toward a non-amyloidogenic pathway (47). Furthermore, NBP treatment inhibited tau hyperphosphorylation in A $\beta$ PP/PS1 mice, which may improve cognitive impairment (48). NBP enhances a 1-methyl-4-phenylpyridini-

union-induced cellular model and a LPS-induced mice model of PD via reducing the accumulation of  $\alpha$ -synuclein (16,49). However, the molecular mechanisms of how NBP reduces the accumulation of  $\alpha$ -synuclein and inhibits tau hyperphosphorylation remain unclear. Furthermore, to the best of our knowledge, there is no associated study that provides the clinical evidence that NBP is effective in multiple sclerosis or Lewy body dementia via attenuating abnormal protein deposition. Potentially, new findings can be revealed in additional neurodegenerative diseases.

## 7. Conclusion

In summary, current studies suggest that NBP serves a neuroprotective role through inhibiting inflammation, protecting mitochondrial function, alleviating oxidative stress, regulating apoptosis, resisting ERS and decreasing the abnormal protein deposition (Fig. 2). Details on specific molecular mechanisms are presented in Table I. Taken together, it is suggested that NBP provides a promising therapeutic strategy for neurodegenerative diseases. In further studies, the mechanism of action of NBP may be further clarified, and the understanding regarding its potential uses may be expanded.

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## Availability of data and materials

All data generated or analyzed during this study are included in this published article.

## Authors' contributions

RL was a major contributor in writing the manuscript. RL, RW, LZ and WB contributed to researching data, discussing content and editing the manuscript. All authors read and approved the final version of the manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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