

[Review]

## Natural Compounds Preventing Neurodegenerative Diseases Through Autophagic Activation

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**Abstract :** Neurodegenerative diseases (NDDs) are a group of intractable diseases that significantly affect human health. To date, the pathogenesis of NDDs is still poorly understood and effective disease-modifying therapies for NDDs have not been established. NDDs share the common morphological characteristic of the deposition of abnormal proteins in the nervous system, including neurons. Autophagy is one of the major processes by which damaged organelles and abnormal proteins are removed from cells. Impairment of autophagy has been found to be involved in the pathogenesis of NDDs, and the regulation of autophagy may become a therapeutic strategy for NDDs. In recent years, some active compounds from plants have been found to regulate autophagy and exert neuroprotection against NDDs, including Alzheimer's disease, Parkinson's disease, Huntington's disease, spinal and bulbar muscular atrophy, spinocerebellar ataxia 3, and amyotrophic lateral sclerosis, via activating autophagy. In this paper, we review recent advances in the use of active ingredients from plants for the regulation of autophagy and treatment of NDDs.

**Keywords :** autophagy, neurodegenerative diseases, natural compounds.

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### Introduction

Autophagy refers to self-phagocytosis and is a process by which cells remove a large amount of proteins with long half-lives as well as damaged organelles. The mechanism of autophagy involves double-membraned autophagic vacuoles encapsulating the cytoplasm and organelles, and their fusion with lysosomes, resulting in the degradation of intracellular components. There are 3 types of autophagy: macroautophagy, microautophagy, and chaperone-mediated autophagy [1]. The pathway of autophagy can be divided into a series of steps, including induction, vesicle nucleation, phagophore elongation, closure, and completion, docking

and fusion, followed by degradation and recycling. There are 4 complexes involved in autophagy, including the autophagy-related gene 1 (Atg1)/unc-51-like kinase (ULK) complex, Atg6 (Beclin 1)/class III phosphatidylinositol triphosphate kinase (class III PI3K) complex, transmembrane Atg9/vacuole membrane protein 1(VMP1) complex and ubiquitin-like protein complex (Atg12 and Atg8/microtubule-associated protein 1 light chain 3 (LC3)). These complexes are regulated by intracellular stress-related pathways and function in different stages of autophagy. The Atg1/ULK complex is regulated by the Adenosine monophosphate (AMP)-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), whereas Be-

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clin1/class III PI3K) is regulated by c-Jun N-terminal kinase (JNK) [2].

The degradation of proteins with long half-lives, organelles, and aggregated proteins is crucial for the maintenance of cell homeostasis. Studies have shown that autophagy is closely associated with normal growth and development, as well as the occurrence and development of cardiovascular diseases, cancers and neurodegenerative diseases (NDDs). The formation of aggregated proteins is a major pathological feature of NDDs. In normal neurons, these abnormal proteins in the cytoplasm are cleared via autophagy, but an impairment of autophagy leads to the failure to remove these proteins, resulting in the accumulation of abnormally aggregated proteins [3–5]. Thus, the identification of compounds that are able to regulate autophagy is pivotal for the prevention and treatment of NDDs [6–8]. In recent years, various studies have demonstrated that some active ingredients of natural products, such as plants, can regulate and activate autophagy, and thus may be useful for the treatment and prevention of NDDs.

### Alzheimer's disease

Alzheimer's disease (AD) is an NDD characterized by progressive dementia, slowly progressive focal cortical atrophy, and formation of senile plaques containing  $\beta$ -amyloid ( $A\beta$ ) and neurofibrillary tangles (NFT) composed of hyperphosphorylated tau protein in neurons. In the brain of AD patients, swollen and malnourished neurites are observed containing a large amount of autophagic vacuoles with  $A\beta$  deposition, suggesting that autophagy is associated with the pathogenesis of AD [9]. In a cell model of AD and transgenic mice, arctigenin, a lignan found in certain plants of the Asteraceae, including the greater burdock (*Arctium lappa*) and *Saussurea heteromalla*, was found to reduce the expression level of amyloid precursor protein cleaving enzyme 1 and to inhibit the production of  $A\beta$ . Moreover, arctigenin may also enhance autophagy to clear amyloid precursor proteins, in which the activation of autophagy is dependent on inhibition of the Rho-GTPase family (RAC)-alpha serine/threonine kinases (Akt)/mTOR pathway and activation of the AMPK/Raptor pathway [10]. Resveratrol is a phytoalexin extracted from grapes and has

multiple bioactivities, including antioxidative activity. Studies on  $A\beta$  transgenic nematodes found that their incubation in medium with 100  $\mu$ M resveratrol attenuated their paralysis caused by abnormal  $A\beta$  deposition, which was found to be a result of resveratrol inducing the activation of autophagosome formation. This suggests that resveratrol can activate autophagy to mitigate  $A\beta$  toxicity [11]. Triptolide is an active ingredient extracted from the plant tripterygium and has antioxidative and neuroprotective activities. A study on a PC12 cell (derived from a pheochromocytoma of the rat adrenal medulla) model of AD showed that triptolide attenuates  $A\beta$  toxicity in cells and reduces their apoptosis, which was associated with the induction of autophagy by triptolide [12]. In an amyloid precursor protein/presenilin1 (APP/PS1) transgenic mouse model, immunohistochemistry of brain sections demonstrated that curcumin, the principal curcuminoid of turmeric, inhibited  $A\beta$  production, and immunofluorescence staining and western blot analysis showed that the expression of the autophagy-related LC3 protein was increased, however the expression of phosphatidylinositol 3-kinase, phosphorylated Akt, and phosphorylated mTOR was significantly reduced. Thus, the investigators speculated that the curcumin-induced inhibition of  $A\beta$  production is associated with the activation of autophagy via the PI3K/Akt/mTOR signaling pathway [13].

### Parkinson's disease

Parkinson's disease (PD) is a NDD characterized by the progressive and diffuse loss of dopaminergic neurons in the substantia nigra and the accumulation of Lewy bodies (inclusions containing  $\alpha$ -synuclein ( $\alpha$ -syn)) in cells. PD patients usually present resting tremor, muscle rigidity, bradykinesia and ataxia. The loss of dopaminergic neurons in the substantia nigra is associated with the accumulation of  $\alpha$ -syn in Lewy bodies.  $\alpha$ -syn is the main component of Lewy bodies and may act as a toxic factor mediating the pathology of PD [14]. Studies have demonstrated that autophagy is involved in the pathogenesis of PD, the overproduction of  $\alpha$ -syn may inhibit autophagy, suggesting that autophagy is a potential target in the pharmacotherapy of PD [15]. Isorhynchophylline is an active ingredient

extracted from *Uncaria*, a genus of flowering plants in the family Rubiaceae. A study showed that in neuronal cells, treatment with isorhynchophylline at 12.5, 25, and 50  $\mu\text{M}$  for 24 h increased the expression of LC3-II in different neuronal cells N2a cell (Neuro-2a, mouse neuroblastoma cell line), PC12 cell, SH-SY5Y cell (human neuroblastoma cell line), and primary cortical neurons [16]. Furthermore, the treatment of N2a cells stably expressing green fluorescent protein (GFP)-LC3 with isorhynchophylline at 6.25, 12.5 and 25  $\mu\text{M}$ , as well as the treatment of primary neurons from E17 embryonic mouse brain with isorhynchophylline at 50  $\mu\text{M}$  for 24 h induced the accumulation of punctate structures of LC3 in the cytoplasm, which was inhibited by 3-methyladenine (3-MA). These results suggested that isorhynchophylline induces autophagy in neurons [16]. In rotenone-induced PD animals, resveratrol was found to activate autophagy and reduce neuronal apoptosis; experiments in genetic PD animal models [17], confirmed that resveratrol attenuates rotenone-induced neuronal injury and increases LC3 expression, which were associated with the activation of autophagy [18].

### Huntington's disease

Huntington's disease (HD) is a fatal NDD characterized by motor, cognitive, and behavioral impairment. HD patients have an expansion of trinucleotide (CAG) repeat in exon 1 of the gene encoding huntingtin (Htt), which results in an increase of the polyglutamine domain within the protein's N-terminus. HD is associated with accumulation of the mutant Htt protein in aggregates and inclusions. In a HD cell model, activation of autophagy not only reduced the number of Htt aggregates, but decreased the expression level and toxicity of the mutant Htt protein, suggesting that autophagy may become a new target for the therapy of HD [19]. Onjisaponin B derived from *Radix Polygalae* was found to regulate autophagy in PC12 cells via Atg7 and the AMPK-mTOR signaling pathway, and was also found to increase the clearance of the mutant Htt protein and mutant of  $\alpha$ -synuclein (at position 53, changing an Ala to Thr (A53T)) [20]. This study indicates the potential of therapies for NDDs via the activation of autophagy to clear mutant proteins and to reduce neurotoxicity. Trehalose is a recently identified inducer of autophagy.

It is a non-reducing disaccharide identified in different non-mammals, and acts as a chaperone that assists protein folding and protects cells against environmental stress. In addition, trehalose may also promote the clearance of mutant Htt protein and  $\alpha$ -synuclein via an mTOR independent pathway [21]. In animal studies, results showed that trehalose could inhibit accumulation of the mutant Htt protein and reduce its toxicity, thus attenuating the pathology of HD in mice [22]. In addition, trehalose may also protect cells against mutant Htt-induced cell death [23]. The neuroprotective effects of trehalose have been demonstrated in various NDD models expressing different pathological proteins [24], suggesting its potential as a clinical therapy for NDDs. Epigallocatechin gallate (EGCG) is a catechin extracted from tea and is an active ingredient of polyphenol. Studies have shown that EGCG induces autophagy [25–28]. In a HD cell model, EGCG inhibited accumulation of the Htt protein and attenuated its cytotoxicity, which was associated with the activation of autophagy [29]. In HD cell and mouse models, berberine, a quaternary ammonium salt from the protoberberine group of isoquinoline alkaloids, was found to inhibit mutant Htt protein accumulation, mitigate HD symptoms, and activate autophagy [30].

### Spinal and bulbar muscular atrophy

Spinal and bulbar muscular atrophy (SBMA), which is also known as Kennedy disease, is an X-linked motor neuron disease that usually occurs in adulthood. It is caused by trinucleotide (CAG) repeat expansion in the first exon of the androgen receptor (AR) gene on the X chromosome [31]. Some studies have shown that autophagy is closely associated with the pathogenesis of SBMA [32, 33]. In SBMA cells and transgenic animal models, the activation of autophagy was found to reduce aggregation of the abnormal AR protein, leading to a delay in disease progression [34–36]. Paeoniflorin, the principal active ingredient extracted from the roots of *Paeonia* plants, including *Paeonia alba* and *Paeonia lactiflora*, has neuroprotective activity and was found to increase LC3 expression and activate autophagy to protect PC12 cells against 1-methyl-4-phenylpyridinium (MPP<sup>+</sup>)-induced injury [37]. Paeoniflorin was also found to increase the expression of transcription factor

EB (TFEB) to activate autophagy, reduce aggregation of the mutant AR protein, alleviate disease phenotypes, and delay disease progression [38].

### **Spinocerebellar ataxia 3**

Spinocerebellar ataxia 3 (SCA3) is a type of spinocerebellar ataxia and has a high incidence in the Asian population. It is caused by an ataxin-3 protein with an abnormally elongated polyglutamine stretch. Autophagy is involved in the clearance of the abnormal ataxin-3 protein, and hence impaired autophagy may cause the abnormal aggregation of the mutant ataxin-3 protein, causing toxicity to cells and subsequent cell death. Thus, treating SCA3 via targeting autophagy may become a new therapeutic strategy [39]. Trehalose is an inducer of autophagy that acts independently of mTOR. After treatment with the trehalose analogs lactulose and melibiose, aggregation of the abnormal ataxin-3 (75 repeats of glutamine (Q75)) protein was significantly reduced in a cell model, which was associated with the activation of autophagy as well as a reduction in free radical production [40].

### **Amyotrophic lateral sclerosis**

Amyotrophic lateral sclerosis (ALS) is a chronic, progressive NDD characterized by the progressive degeneration of motor neurons. The accumulation of proteins (including Cu-Zn superoxide dismutase (SOD1) and transactive response (TAR) DNA binding protein 43 kDa (TDP-43)) and injured mitochondria in the motor neurons are the major pathological features of ALS. In the disease pathogenesis of ALS, motor neurons become unable to effectively clear proteins and organelles, which indicates an impairment of autophagy [41]. Treatment with trehalose was found to attenuate the motor dysfunction and prolong the survival time of a mutant SOD1 mouse model, and pathologi-

cal examination showed that the expression of mutant SOD1 and p62 (an adaptor protein that binds to ubiquitin and LC3 in the autophagic degradation pathway) was reduced significantly, however LC3-II expression was markedly increased after trehalose treatment, suggesting that the protective effects of trehalose are associated with the activation of autophagy. In an SOD1 cell model, trehalose promoted the degradation of mutant SOD1 in an autophagy-dependent manner, and upregulated the mRNA expression levels of autophagy-related proteins (LC3, Beclin1, p62/SQSTM1 and Atg5) and enhanced the nuclear translocation of forkhead box protein O1 (FOXO1), which indicates the activation of autophagy. These findings demonstrate that trehalose may be applicable for the treatment of ALS [42, 43].

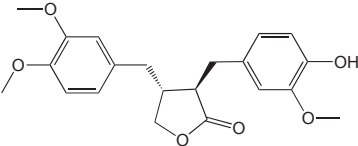
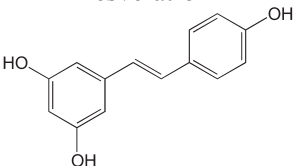
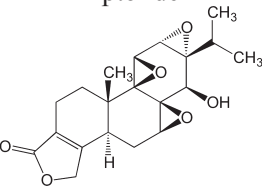
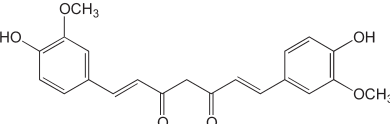
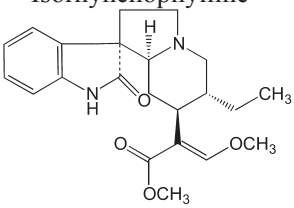
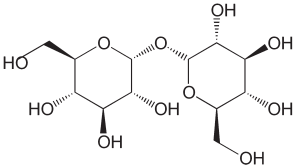
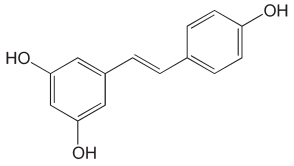
### **Conclusion**

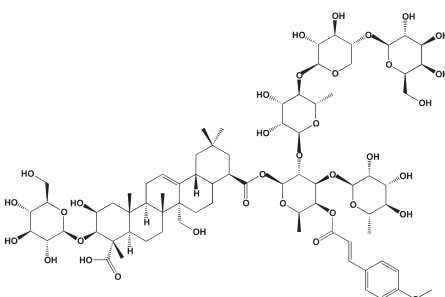
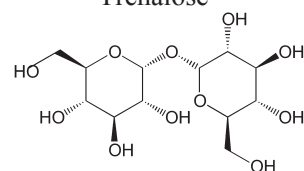
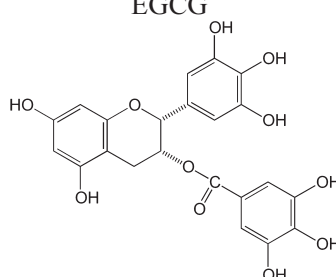
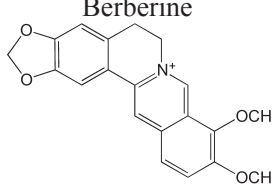
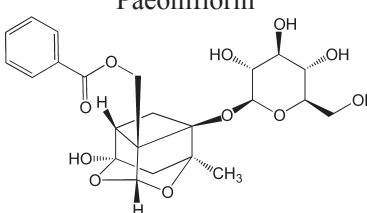
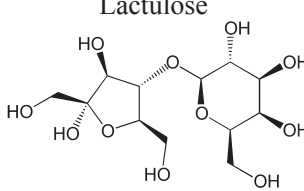
To date, many studies have been performed to investigate the regulation of autophagy by the active ingredients of plants. These ingredients may regulate autophagy via various pathways, including PI3K-Akt, mTOR, extracellular signal-regulated kinase (ERK)1/2 and JNK pathways. The mTOR signaling pathway is the most extensively studied, whereas the formation of autophagosomes, the docking of autophagosomes to lysosomes and autophagosome-lysosome formation are less well studied (Table 1). To investigate strategies for the prevention and treatment of NDDs and to elucidate their potential mechanisms of action, we should screen new compounds that affect autophagy and identify key targets of as well as the interaction network involved in the regulation of autophagy.

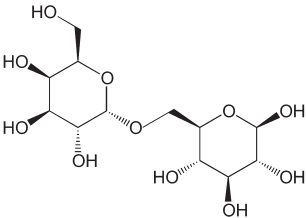
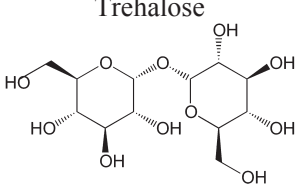
### **Conflict of Interest**

The authors declare no conflict of interest.

**Table 1. Effect of natural compounds on induction of autophagy in neurodegenerative diseases**

Diseases	compounds	function	references
AD	<p>Arctigenin</p> 	Akt/mTOR ↓ AMPK/Raptor ↑	[10]
	<p>Resveratrol</p> 	flux of autophagy ↑	[11]
	<p>Triptolide</p> 	autophagy ↑	[12]
	<p>Curcumin</p> 	PI3K/Akt/mTOR ↓	[13]
	PD	<p>Isorhynchophylline</p> 	beclin1 dependent autophagy ↑
<p>Trehalose</p> 		LC3 II ↑ autophagy ↑	[17]
<p>Resveratrol</p> 		HO-1 ↑ flux of autophagy ↑	[18]

Diseases	compounds	function	references
HD	<p>Onjisaponin B</p> 	AMPK-mTOR dependent autophagy ↑	[20]
	<p>Trehalose</p> 	mTOR independent autophagy ↑ chemical chaperone	[21]
	<p>EGCG</p> 	Sirt 1 ↑ AMPK/ULK ↑ flux of autophagy ↑	[25, 26, 29]
	<p>Berberine</p> 	LC3 II ↑ p62 ↓ autophagy ↑	[30]
SBMA	<p>Paeoniflorin</p> 	TFEB ↑ flux of autophagy ↑	[38]
SCA3	<p>Lactulose</p> 	autophagy ↑ ROS ↓	[40]

Diseases	compounds	function	references
	<p>Melibiose</p> 	<p>autophagy ↑ ROS ↓</p>	[40]
ALS	<p>Trehalose</p> 	<p>SOD1 ↓ p62 ↓ LC3 II ↑ autophagy ↑</p>	[42,43]

AD: Alzheimer's disease, PD: Parkinson's disease, HD: Huntington's disease, SBMA: spinal and bulbar muscular atrophy, SCA3: spinocerebellar ataxia 3, ALS: amyotrophic lateral sclerosis

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## オートファジー活性化天然化合物による神経変性疾患の治療

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**要 旨**：神経変性疾患はその発症メカニズムがまだ明確にされていない難治性疾患の一群である。罹患率は高く根本的な病態抑制治療法が確立されていない。神経変性疾患における形態学的病変では、病因となる蛋白質が神経細胞内で異常な凝集体を形成して蓄積しており、それらが細胞毒性を発揮して神経細胞死に至ると考えられている。オートファジーは、細胞内でこれらの異常蛋白質を分解するシステムとして重要な役割を果たしており、神経変性疾患の発病に強く関わっていることが知られている。従って、オートファジーは神経変性疾患の新しい治療ターゲットになっており、植物由来の天然化合物によるオートファジー活性化機構およびその機序に基づいた神経変性疾患の治療法開発研究が盛んに行われている。本稿では、アルツハイマー病、パーキンソン病、ハンチントン病、球脊髄性筋萎縮症、脊髄小脳変性症3型、筋萎縮性側索硬化症などの神経変性疾患について、オートファジー経路を活性化する作用のある天然化合物を用いた治療法の開発に関して概説する。

**キーワード**：オートファジー, 神経変性疾患, 天然化合物.