

Review Article

Catapol: a promising natural neuroprotective agent for neurologic disorders

Wenting Li^a and Xidan Zhou^{b,*}

^aDepartment of Pharmacy, The Eighth Affiliated Hospital, Sun Yat-Sen University, Shenzhen 518033, China

^bThe Brain Cognition and Brain Disease Institute, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, China

*Correspondence: xd.zhou@siat.ac.cn (X. Zhou)

Received: 30 December 2024; Revised: 5 April 2025; Accepted: 2 May 2025

Published online: 22 May 2025

DOI 10.15212/AMM-2024-0097

ABSTRACT

Neurologic disorders are the leading cause of illness and disability as a result of increased life expectancy and global population aging, highlighting the urgent need and great challenge for discovering neuroprotective agents with better efficacy and minimal side-effects. Catalpol, an iridoid glycoside derived from *Rehmanniae Radix*, has therapeutic potential in neurologic diseases due to its diverse biological activities. This review summarizes the research advances and therapeutic potential of catalpol for a wide range of neurologic disorders, including depression, cognitive impairment, stroke, Parkinson's disease, and multiple sclerosis. A comprehensive discussion of experimental models used, dosages, duration of treatment, and mechanisms involved is provided. The common mechanisms underlying the neuroprotective effects of catalpol on these neurologic disorders are closely related to antioxidant, anti-neuroinflammatory, and anti-apoptotic properties, as well as the capacity to promote neuroplasticity and neurogenesis. Despite the promising results from experimental studies, there are still challenges to be addressed, such as identifying direct binding targets, assessing toxicologic effects, and understanding pharmacokinetics. Furthermore, well-designed and controlled clinical trials should be conducted to validate the efficacy and safety for treating various neurologic conditions. This review provides compelling evidence supporting catalpol as a promising natural neuroprotective agent.

Keywords: catalpol, *Rehmanniae Radix*, neurologic disorders, mechanisms, signaling pathways

1. INTRODUCTION

Neurologic disorders have become the leading cause of illness and disability and the second leading cause of death due to global population aging in the past 30 years [1]. From 1990 to 2017 the number of people affected by various neurologic disorders in the US has increased substantially and has imposed a substantial burden on the healthcare system and society [2]. Neurologic diseases often stem from the structural, biochemical, or electrical abnormalities in the brain, spinal cord, peripheral nerves, or autoimmune system. These disorders encompass a wide range of conditions, including neurodevelopmental, neurodegenerative, neuropsychiatric, cerebrovascular, neuroimmunologic, and neuromuscular disorders, traumatic injuries, Alzheimer's disease (AD) and other dementias, Huntington's disease (HD), Parkinson's disease (PD), stroke, epilepsy, anxiety, depression, multiple sclerosis (MS), traumatic brain

injury (TBI), spinal cord injury (SCI), amyotrophic lateral sclerosis (ALS), headaches, and migraines, and neuropathic pain [3, 4].

Although the specific etiologies of these neurologic diseases vary greatly, genome-wide association study (GWAS) analysis revealed the shared genetic susceptibility and molecular connection among major psychiatric and neurodegenerative diseases, such as immune function, mitochondrial processes, and synaptic transmission [5]. Neuroinflammation is considered one of the most common pathogenic factors in various neurologic disorders [6] with inflammasome activation contributing to the pathophysiologic progression [7]. In addition, central nervous system (CNS) vulnerability to reactive oxygen species (ROS)-mediated damage makes oxidative stress another key factor in the pathogenesis of neurologic conditions [8]. Oxidative stress-induced ferroptosis has also emerged as a pivotal mechanism underlying the occurrence and progression of these disorders [9]. Given

the high energy demands of the brain, disruptions in energy metabolism commonly accompanies neurologic diseases, highlighting a new “neuroenergetics” perspective [10]. Mitophagy, the selective elimination of damaged mitochondria, is essential for regulating the number of mitochondria and maintaining energy metabolism in the CNS. Because neuronal cells primarily rely on mitochondrial oxidative phosphorylation for ATP production, dysfunctional mitophagy is closely linked to neurologic disorders [11]. Moreover, differentiation of oligodendrocyte precursor cells (OPCs) into mature myelinating oligodendrocytes also requires high metabolic and mitochondrial activity. Therefore, disrupted OPC differentiation is increasingly recognized as a contributor to neurodegenerative disorders, which are characterized by elevated oxidative and carbonyl stress [12]. Furthermore, changes in synaptic plasticity are another hallmark of many neurologic conditions. For example, microglia-mediated synaptic elimination via the complement cascade is implicated in AD [13, 14]. Neurotransmitters, which are responsible for synaptic connection forming and information processing, often exhibit dysregulated homeostasis in neurologic disorders, further contributing to the pathophysiology [15]. The recently acknowledged gut-brain axis underscores the role in connecting gut microbiota and the immune system to brain function and the development of neurologic disorders [16].

In the past decade a wide range of therapeutic options for neurologic disorders has emerged, including mesenchymal stem cell (MSC) transplantation [17], adeno-associated virus (AAV)-based gene therapy [18], RNA-based therapeutics [19], brain stimulation [20], and fecal microbiota transplantation [21]. However, most of these approaches are still in the preclinical stages and the translation to clinical applications may take years. Currently, while some first-line pharmacologic treatments are available to alleviate symptoms, such as selective serotonin reuptake inhibitors (SSRIs) for depression, diazepam for anxiety, memantine for AD, and levodopa for PD [22–24], concerns about adverse effects and safety assessments limit use [25]. Therefore, natural medicinal herbs and ethnopharmacologic prescriptions have gained increasing attention in recent years due to historical use and reported therapeutic benefits, including reduced side effects compared to synthetic drugs.

Lily bulb and *Rehmannia* decoction (LBRD), a commonly-used classic traditional Chinese medicine (TCM) formula, was documented in *the Synopsis of Prescriptions of the Golden Chamber*, written by Zhongjing Zhang for treating “emotional disorders.” This well-known formula, which consists of *Lilium henryi* Baker (Liliaceae) and *Rehmannia glutinosa* (Gaertn) DC (Plantaginaceae), has demonstrated antidepressant effects in preclinical experiments and clinical trials via multiple pathways [26], as follows: correction of neurotransmitter deficits and inflammation imbalance [27]; regulating glycerophospholipid metabolism and glutamatergic synapses

based on metabolomics studies and network pharmacology [28]; altering the expression of a variety of microRNAs [29]; and inhibiting neuroinflammation and intestinal permeability via the gut microbiota-brain axis [30]. In our previous studies Lily bulb and *Rehmannia* Radix extract were shown to have ameliorative effects on menopausal neuropsychiatric disorders by modulating neurotransmitters, neurotrophins, and estrogen receptors [31, 32]. The pharmacologic effects of *Rehmannia* Radix have been extensively studied, including antioxidative, anti-inflammatory, anti-tumor, antidepressant, neuroprotective, immunomodulatory, and anti-aging effects, and protective roles against diabetes, bone metabolism, cardiovascular and cerebrovascular diseases, spinal cord injuries, and liver and kidney injuries [33, 34].

Iridoids, a class of naturally occurring compounds found in a variety of plants, are known for diverse biological activities, including neuroprotective effects. Recent studies have highlighted the potential of iridoids in protecting neural cells from damage, making neural cells a promising therapeutic target for neurodegenerative diseases. Specifically, eight iridoid components in *R. glutinosa* reversed an imbalanced metabolic state and harmonized the level of oxidized substances to exhibit neuroprotective effects against corticosterone-induced injury in PC12 cells [35]. Similarly, several iridoids from *Valeriana jatamansi* have shown moderate neuroprotective effects against CoCl_2 -induced neuronal cell death in PC12 cells [36, 37]. An early review further supported the neuroprotective effects of iridoids, in which the antioxidant and anti-inflammatory properties have been shown to attenuate neuronal damage [38]. Another review emphasized the therapeutic potential of iridoids for AD and PD [39]. Taken together, these studies suggested that iridoids may represent a promising class of compounds in the development of therapeutic strategies for neurodegenerative diseases.

Catalpol, an iridoid glycoside derived from *Rehmannia* Radix, has a central role in many of these pharmacologic activities [33, 40]. The plant source (*R. glutinosa*) and chemical structure of catalpol are shown in Figure 1. While earlier studies have summarized the therapeutic potentials of catalpol in AD and depression [41, 42], this review provides a comprehensive overview of the effects on a broad spectrum of neurologic disorders and related mechanisms, including depression, AD, stroke, PD, MS, Duchenne muscular dystrophy (DMD), epilepsy, TBI, neuropathic pain, and attention deficit hyperactivity disorder (ADHD). The mechanisms underlying each neurologic condition are also discussed, providing robust evidence for catalpol as a promising natural neuroprotective agent for future clinical applications.

2. METHODOLOGY

We conducted a literature search on catalpol and neurologic disorders using PubMed, Elsevier, ScienceDirect,

Review Article

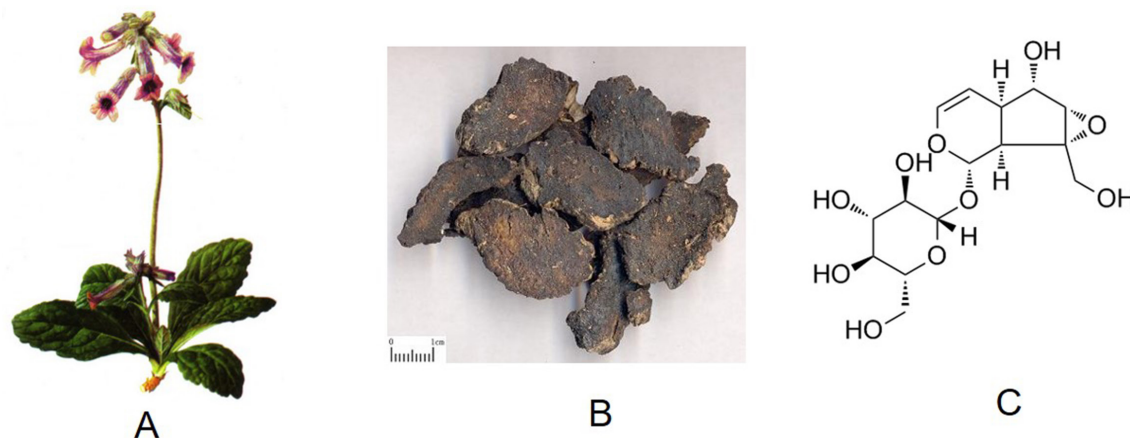


Figure 1 | Representative images of *Rehmannia glutinosa* and the chemical structure of catalpol.

A: Original plant of *Rehmannia glutinosa*; B: Medicinal material derived from *Rehmannia glutinosa*; C: Chemical structure of catalpol.

SpringerLink, Web of Science, Chinese National Knowledge Infrastructure (CNKI), and Scopus databases with publications up to April 2025 included. The searched keywords included "catalpol," "neurologic disorders," "depression," "Alzheimer's disease" or "memory" or "cognitive impairment," "ischemic stroke," "Parkinson's disease," "multiple sclerosis," "neuromuscular disease," "epilepsy," "traumatic brain injury," "neuropathic pain," "attention deficit hyperactivity disorder," and "post-traumatic stress disorder." The inclusion criteria were as follows: (1) original studies on the neuroprotective activity of catalpol and the mechanism of action; and (2) *in vivo* and *in vitro* studies. The exclusion criteria: (1) duplicate articles; and (2) studies with an unclear dose of catalpol. A total of 50 articles were included in this study.

3. NEUROPROTECTIVE ACTIVITIES AND RELATED MECHANISMS OF ACTION

3.1 Depression

Depression is a prevalent mental disorder primarily manifested as anhedonia, low mood, loss of interest in everything, exhaustion, and worthlessness, affecting approximately 3.8% of the global population according to a survey from the World Health Organization (<https://www.who.int/news-room/fact-sheets/detail/depression>). Multiple hypotheses have been proposed to explain the pathogenesis of depression, including genetic factors, environmental stress factors, hypothalamus-pituitary-adrenal (HPA) axis hyperactivity, monoamine neurotransmitter deficiency or dysfunction, oxidative stress, neuroinflammation, neurogenesis, and synaptic plasticity [43, 44]. As a result, a variety of animal models have been developed to gain deeper insight into neurobiological basis of depression, including the learned helplessness, olfactory bulbectomy, unpredicted chronic mild stress, early life stress, social defeat, chronic

restraint stress, glucocorticoid/corticosterone, physical pain, and genetic or transgenic models [45, 46]. While the existing rodent models of depression have limitations, such as an inability to fully reflect feelings (sadness, guilt, or suicidal thoughts), these models are valuable tools for studying molecular, genetic, epigenetic, and environmental risk factors involved in the pathogenesis of depression [45].

Catalpol has been extensively studied for antidepressant effects in various experimental models with the most widely investigated model being depression induced by chronic unpredictable mild stress (CUMS) lasting for at least 3 weeks, as shown in Table 1. The mechanisms underlying CUMS-induced depression are generally attributed to anti-oxidant effects via the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme-oxygenase-1 (HO-1) signaling pathway [47, 48], inhibition of HPA axis hyperactivity [49], neuroinflammation [48, 50, 51], and regulation of synaptic plasticity [52, 53]. The antidepressant effects of catalpol inhibit HPA axis hyperactivity and enhance central antioxidant defense via the dual regulation of nuclear factor kappa-B (NF-κB) and Nrf2 in corticosterone (CORT)-induced depression [54]. Furthermore, catalpol has been reported to ameliorate depression-like behavior in mice with streptozotocin-induced hyperglycemia [55] and post stroke [56], the underlying mechanisms of which are partly attributed to restoration of the balance between oxidation and antioxidation, and promotion of phosphoinositide 3-kinase (PI3K)-mediated adult hippocampal neurogenesis, respectively. Additionally, catalpol increases serotonin (5-HT) and 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) levels in the brains of mice, suggesting that the antidepressant effects of catalpol may be mediated by the central serotonergic system [57].

Notably, the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT or PKB) signaling pathway has been implicated in the antidepressant effects of catalpol [47,

Table 1 | Effects of catalpol in experimental models of depression.

Animal	Models	Doses/duration	Mechanisms/effects	Refs
Rats-male	CUMS (5 weeks)	10 mg/kg, 5 weeks, i.g.	Upregulating the PI3K/Akt/Nrf2/HO-1 signaling pathway, improving the hippocampal neurotrophic, neuroprotective, and antioxidant levels	[47]
Rats-male	CUMS (3 weeks)	10 mg/kg, 3 weeks, i.g.	Enhancing anti-oxidation and neurotrophs and inhibiting neuroinflammation via activation of HO-1	[48]
Rats-male	CUMS (5 weeks)	5, 10, and 20 mg/kg, 5 weeks, i.g.	Restoring HPA axis dysfunction, upregulating BDNF expression and its cognate receptor (TrkB), and downregulating COX-2 expression	[49]
Rats-female	CUMS (5 weeks)	10 mg/kg, 4 weeks, i.p.	Inhibiting the NLRP3 inflammasome via the TLR4/ MAPK/NF-κB pathway	[50]
Mice-male	CUMS (5 weeks)	20 mg/kg, 4 weeks, i.p.	Via oxidative stress-mediated regulation of NLRP3 and neuroinflammation	[51]
Rats-male	CUMS (5 weeks)	10 mg/kg, 5 weeks, i.g.	Regulating TrkB signaling-mediated synaptic plasticity	[52]
Mice-male and female	CUMS (13 weeks)	20 mg/kg, 8 weeks, i.g.	Improving hippocampal SIRT1-mediated synaptic plasticity and neurogenesis	[53]
Mice-male	CORT for 21 days	20 mg/kg, 21 days, 30 min prior to CORT injection, i.g.	Inhibiting HPA axis hyperactivity, central inflammation, and oxidative damage through dual regulation of NF-κB and Nrf2	[54]
Mice-male	Streptozotocin-induced hyperglycemia	5, 10, and 20 mg/kg, 3 weeks, i.g.	Upregulating the PI3K/Akt/Nrf2/HO-1 signaling pathway	[55]
Mice-male	Post-stroke depression (MCAO combined with CORT feeding)	5 and 20 mg/kg, 2 weeks, i.p.	Promoting PI3K-mediated adult neurogenesis	[56]

55, 56]. As an upstream signaling cascade, the PI3K/AKT pathway has a crucial role in neuronal survival, proliferation, and apoptosis. A recent review has systematically summarized the regulatory effects of the PI3K/AKT signaling pathway on neuroinflammation, hippocampal neurogenesis, neurotransmitter imbalance, and synaptic plasticity impairment in depression [58]. Furthermore, PI3K/AKT signaling is essential for modulating redox balance by mediating the transcription factor Nrf2/HO-1 pathway combined with the antioxidant-response element (ARE), thereby protecting cells from oxidative stress (Figure 2) [59]. In addition, NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasomes and the toll-like receptor 4 (TLR4)/mitogen-activated protein kinase (MAPK)/nuclear factor-κB (NF-κB) pathway have been implicated in the neuroinflammatory properties of catalpol (Figure 3), which contribute to the antidepressant effects [50]. As a transmembrane transduction receptor, TLR4 directly binds to lipopolysaccharide (LPS), which activates the NF-κB and MAPK signaling pathways, leads to the synthesis and release of various inflammatory mediators, and ultimately triggers and amplifies the inflammatory response [60]. NF-κB is a transcription factor that promotes the transcription of genes encoding proinflammatory cytokines, such as interleukin-1 beta (IL-1β), IL-6, and tumor necrosis factor alpha (TNF-α) [60]. Co-administration of catalpol has been shown to alleviate fluoxetine-induced hepatic

injury while potentiating the antidepressant effects of fluoxetine, the detoxification mechanism of which has been attributed to the inhibition of ferroptosis via activation of the transcription factor 3 (ATF3)/ferroptosis suppressor protein 1 (FSP1) signaling [61].

Interestingly, in the abovementioned studies, depression models were primarily developed using male rodents, despite epidemiologic evidence clearly showing that women are significantly more susceptible to stress-related mental health disorders and that depression is at least twice as prevalent in women as in men [62]. The physiology and reproductive experiences of females are linked to changes in the brain, behavior, and endocrine profiles, which may affect both the stress levels and the response to treatment [63]. It is highly encouraging that catalpol has greater antidepressant activity in female mice than in male mice, and the mechanism underlying this gender difference may be attributed to the higher sensitivity of catalpol in enhancing hippocampal SIRT1-mediated synaptic plasticity and neurogenesis in females [53].

3.2 AD or cognitive impairment

AD is a neurodegenerative disorder that primarily affects the elderly population worldwide and is characterized by a progressive decline in cognitive function. Although the well-established pathologic hallmarks of AD include amyloid-beta (Aβ) plaque aggregation

Review Article

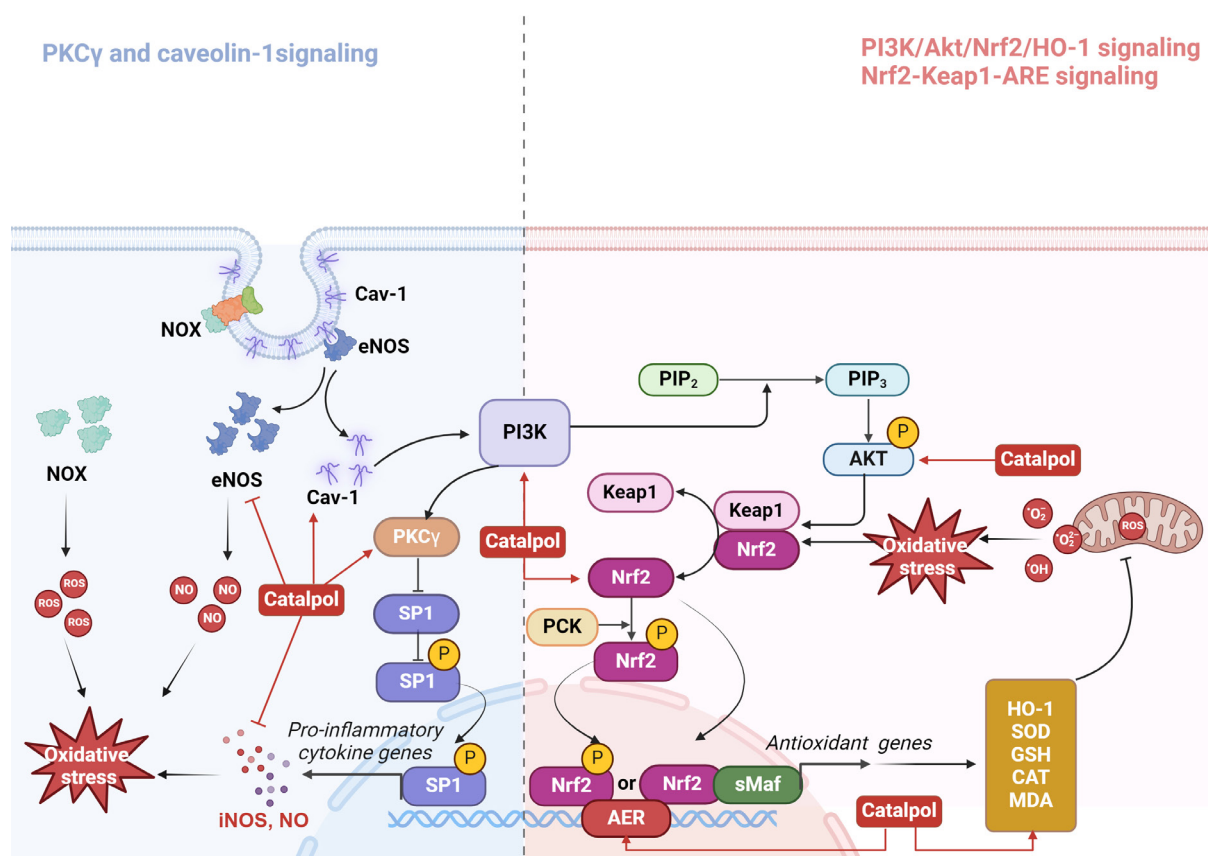


Figure 2 | Molecular pathways involved in the antioxidant mechanism underlying catalpol.

Catalpol exerts antioxidant effects by modulating the PKC γ /caveolin-1, PI3K/AKT/Nrf2/HO-1, and Nrf2/Keap1/ARE signaling pathways. (1) Catalpol activates PKC γ and promotes caveolin-1, which suppresses SP1 phosphorylation and nuclear translocation and inhibits oxidant gene expression, such as iNOS. In contrast, catalpol facilitates Nrf2 nuclear translocation and enhances antioxidant gene expression, including GSH, SOD, CAT, and MDA (left). (2) Catalpol promotes PI3K/AKT signaling, which phosphorylates and releases Nrf2 from Keap1, allowing Nrf2 to translocate to the nucleus and bind to the antioxidant response element (ARE), which induces the expression of HO-1 and other antioxidant enzymes. (3) Catalpol also directly modulates the Nrf2/Keap1/ARE pathway by dissociating Nrf2 from Keap1, enabling nuclear translocation and enhancing transcription of antioxidant genes, thereby mitigating oxidative stress and protecting cells from damage (right). The arrows indicate activation and the blunt lines indicate inhibition.

and hyperphosphorylated tau and neuronal loss, accumulating evidence has suggested the importance of other factors in the pathogenesis of AD, such as gliosis, inflammation, mitochondrial dysfunction, oxidative stress, and ferroptosis [64]. Among these newly recognized factors, oxidative stress has emerged as a central factor that interconnects various pathologic manifestations of AD because oxidative stress can damage neurons and induce mitochondrial dysfunction [65, 66]. Oxidative stress can regulate the activities of amyloid precursor protein (APP) and the related secretase, such as β -secretase (BACE1) via oxidants and oxidative products, leading to the aggregation of A β [65]. Moreover, the excessive production of ROS under oxidative stress results in redox imbalance, neurotoxicity, genomic instability, pro-inflammatory gene transcription, and cytokine release, including IL-1 β , IL-6, and TNF- α [66]. In addition to the abovementioned hypotheses, loss

of cholinergic neurons has been identified as a major correlate of cognitive impairment in patients with AD. Specifically, early neurotoxicity caused by A β oligomers impacts the cholinergic synapses, which is manifested by a reduction in choline acetyltransferase (ChAT) activity [67]. Modulation of the cholinergic signaling pathway, including inhibition of acetylcholinesterase (AChE), activation of ChAT, and promotion of acetylcholine (ACh) synthesis, has been reported as a strategy for improving memory function in AD [67]. Furthermore, brain-derived neurotrophic factor (BDNF)/tropomyosin-related kinase B receptor (TrkB) neurotrophic signaling has been shown to influence endogenous A β production and tau aggregation through the Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling and CCAAT-enhancer binding protein β (C/EBP β [an age-dependent transcription factor])/AEP (δ -secretase [an asparagine endopeptidase]) pathways

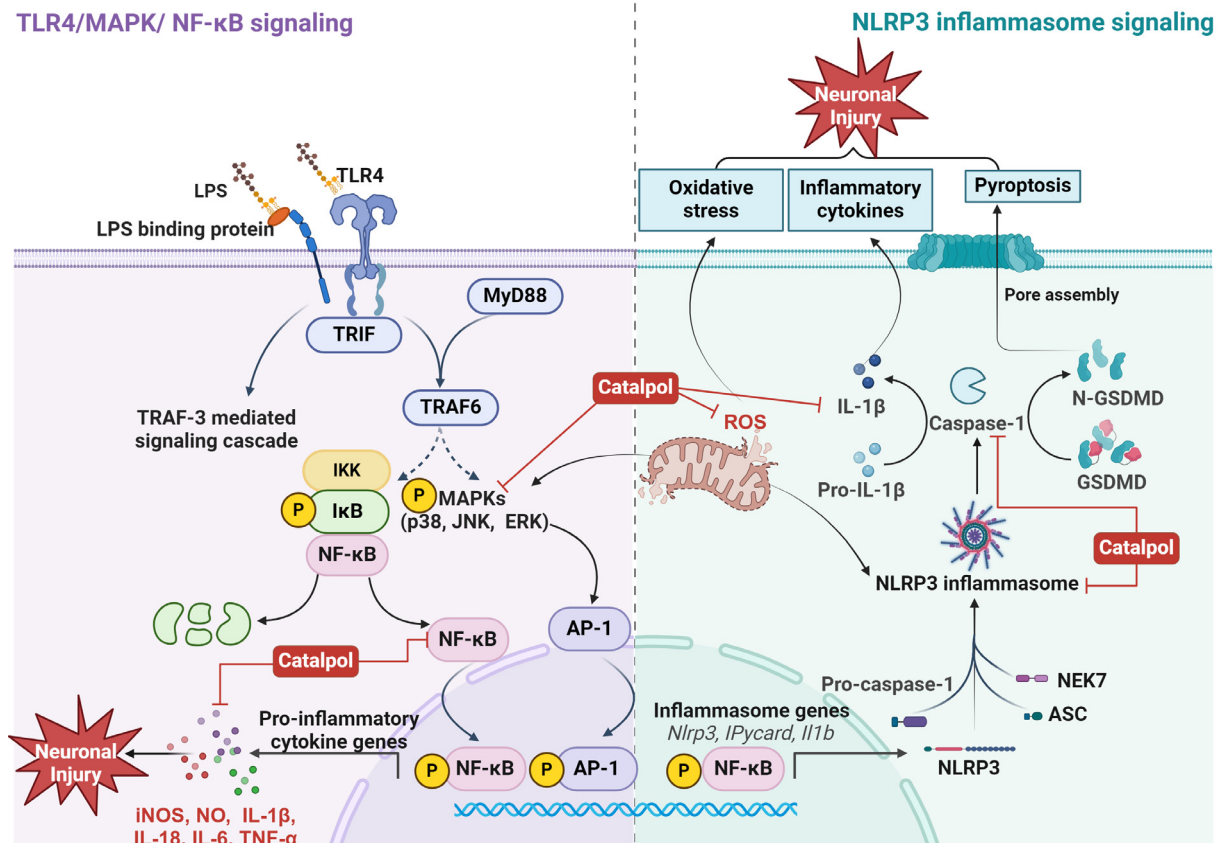


Figure 3 | Molecular pathways involved in the anti-neuroinflammatory mechanism of catalpol.

Catalpol exerts anti-neuroinflammatory effects by modulating the TLR4/MAPK/NF-κB signaling pathway and inhibiting NLRP3 inflammasome activation. Catalpol suppresses the activation of TLR4-mediated MAPK signaling cascades, including ERK, JNK, and p38. This inhibition prevents NF-κB nuclear translocation and suppresses the transcription of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α (left). Catalpol inhibits NLRP3 inflammasome assembly by reducing the activation of upstream signals, preventing caspase-1 activation and the subsequent maturation and release of IL-1β. Catalpol reduces ROS production and attenuates mitochondrial damage (right). Catalpol mitigates neuroinflammation and protects against neuronal damage via these pathways. The arrows indicate activation and the blunt lines indicate inhibition.

[68, 69]. Multiple transgenic mouse models of AD have been developed through knock-in/knock-out or CRISPR gene editing techniques of familial and sporadic AD risk genes, such as Tg2576, TgCRND8, APP/PS1, 5xFAD, and 3xTg-AD [70, 71]. Additionally, cognitive impairment may commonly arise as a complication of various diseases, including schizophrenia, chronic pain, stroke, and diabetes [72].

Catalpol exerts memory-enhancing effects in various experimental models of cognitive impairment, including the effects induced by D-galactose (or Aβ₂₅₋₃₅, LPS, or post stroke), as follows: APP/PS1 transgenic mice; natural-aged rats; streptozotocin-induced diabetic encephalopathy; and hypoxia ischemia-induced brain damage (Table 2). Catalpol increases the levels of ChAT and muscarinic muscarinic acetylcholine receptor (AChR) subtype expression, especially M₁ [73, 74], thereby contributing to neuroprotection and memory enhancement. In contrast, catalpol was reported to elevate ChAT expression and activity in

another study without affecting M receptor affinity [75]. Nevertheless, the memory-enhancing effects of catalpol may be attributed to regulation of the cholinergic nerve system. Multiple lines of evidence also suggest that catalpol mitigates memory dysfunction by significantly attenuating oxidative stress that is specifically mediated by regulation of reactive oxygen species (ROS)-associated enzymes, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) [76-79]. Catalpol mitigates cognitive impairment in D-galactose-induced senescent mice by restoring energy metabolism through upregulation of key enzymes, including lactate dehydrogenase (LDH), glutathione S-transferase (GSH-ST), glutamine synthetase (GS), and creatine kinase (CK) [80]. Catalpol reduces apoptosis, alleviates mitochondrial injury, and decreases Aβ generation via AKT/GSK3β (glycogen synthase kinase-3β) signaling pathway in N2a/APP695swe cells and APP/PS1 transgenic mice, thereby improving neuronal function and cognitive performance [81]. The

Review Article

Table 2 | Effects of catalpol in experimental models of cognitive impairment.

Animal	Models	Doses/duration	Mechanisms/effects	Refs
Mice-male and female	D-galactose-induced senescence	2.5, 5, and 10 mg/kg, 2 weeks, i.c.	Improving cholinergic function and reducing inflammatory cytokines	[73]
Mice-male and female	Post-stroke cognitive impairment (MCAO)	1, 3, and 9 mg/kg, 3 days, i.p.	Via the central cholinergic system	[74]
Rats-male	A β_{25-35} -induced memory defect	5 and 10 mg/kg, 7 days, i.p.	Regulating the cholinergic nerve system function	[75]
Mice-male and female	D-galactose-induced senescence	5 and 10 mg/kg, 2 weeks, i.c.	Enhancing endogenous antioxidant enzymatic activities and inhibiting free radical generation	[76]
Mice-male	Induced by D-galactose and sodium nitrite	20 mg/kg, 30 days, i.g.	Reducing the levels of oxidative stress and soluble A β_{40} and A β_{42}	[77]
Rats-male	Streptozotocin-induced diabetic encephalopathy	5 mg/kg, 2 weeks, i.p.	Attenuating oxidative stress and upregulating PKC γ and caveolin-1	[78]
Rats-male	Streptozotocin-induced diabetic encephalopathy	10, 50 and 100 mg/kg, 6 weeks, i.g.	Attenuating oxidative stress	[79]
Mice-male and female	D-galactose-induced senescence	2.5, 5, and 10 mg/kg, 2 weeks, i.c.	Promoting the activities of enzymes related to energy metabolism	[80]
Mice-not mentioned	APP/PS1 transgenic	200 μ M, every other day for 4 weeks, i.g.	Reducing apoptosis, alleviating mitochondrial injury, relieving A β generation, and regulating PTMs	[81]
Mice-male and female	APP/PS1 transgenic	5 mg/kg, 30 days, i.p.	Regulating ferroptosis with upregulation of HSPA5 and GPX4	[82]
Mice-not mentioned	LPS-induced cognitive deficits	10 mg/kg, 10 days, i.p.	Attenuating NF- κ B activation and protecting mitochondrial function	[83]
Mice-male	LPS-induced post-sepsis cognitive impairment	2.5, 5, and 10 mg/kg, 13 days, i.p.	Blocking the NF- κ B pathway, upregulating TrkB-mediated BDNF secretion, and preserving BBB integrity	[84]
Mice-female	A β_{25-35} and ibotenic acid-induced memory deficits	50 mg/kg, 60 days, i.g.	Elevating BDNF expression	[85]
Mice-female	A β_{25-35} and ibotenic acid-induced memory defect	5, 15, and 45 mg/kg, 3 months, i.g.	Elevating BDNF mRNA and protein levels	[86]
Rats-male	Aged (22–24 months)	5 mg/kg, 10 days, i.p.	Increasing hippocampal neuroplasticity and upregulating PKC and BDNF	[87]
Rats-male	Aged (23–24 months)	15 mg/kg, 2 months, i.g.	Increasing the expression of synaptic proteins	[88]
Neonatal Rats-not mentioned	Hypoxia ischemia-induced brain damage	2.5, 5, 10, and 20 mg/kg, 21 days, i.g.	Inhibiting ferroptosis and ameliorating oxidative stress	[89]

neuroprotective effects of catalpol in APP/PS1 mice were shown to be partially mediated by upregulation of ferroptosis-associated proteins (HSPA5 and GPX4) in the hippocampus [82]. Catalpol alleviates memory impairment in LPS-induced cognitive deficits by inhibiting NF- κ B activation and protecting mitochondrial function in the cerebral cortex and hippocampus [83]. Additionally, catalpol upregulates BDNF/TrkB neurotrophic signaling (Figure 4) and preserves blood-brain barrier (BBB) integrity, further contributing to the memory-enhancing effects in LPS-induced cognitive deficits [84]. The neuroprotective effects of catalpol have been attributed to elevated BDNF expression in A β_{25-35} and

glutamate receptor agonist-induced memory defects [85, 86]. Catalpol promotes hippocampal neuroplasticity in natural-aged rats by increasing presynaptic proteins, such as synaptophysin and growth-associated protein (GAP-43) [87]. Catalpol also protects synaptic proteins (dynamin 1, PSD-95, and synaptophysin) from A β -induced primary neuron injury, which markedly improves cognitive function in aged rats [88]. Catalpol was shown to improve learning and memory abilities in neonatal rats with hypoxia ischemia-induced brain damage by inhibiting neuronal ferroptosis through regulation of ferroptosis-related proteins and amelioration of oxidative stress [89].

BDNF/TrkB neurotrophic signaling

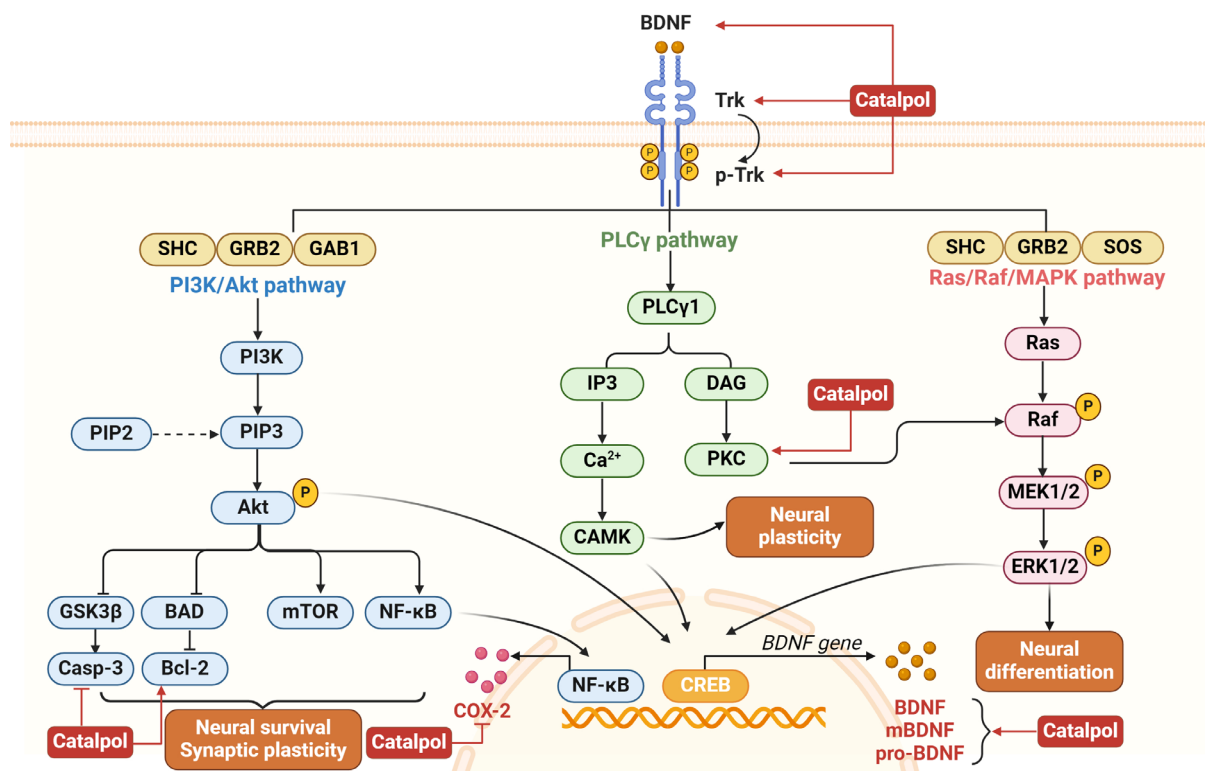


Figure 4 | Molecular pathways involved in the neurogenesis mechanism underlying catalpol.

Catalpol promotes neurogenesis by modulating the BDNF/TrkB signaling pathway and the BDNF/TrkB signaling pathway downstream cascades, including the PI3K/Akt, PLC γ , and Ras pathways. (1) Catalpol enhances BDNF expression and activates TrkB, leading to downstream activation of PI3K/Akt signaling, which promotes neuronal survival and growth through inhibition of apoptosis-related proteins, such as Bcl-2, caspase-3, and COX-2. (2) Catalpol activates the PLC γ pathway, resulting in increased intracellular calcium levels and activation of cAMP response element-binding protein (CREB), which enhances *BDNF* gene expression and facilitates neuronal synaptic plasticity. (3) Catalpol stimulates the Ras/Raf/MAPK pathway, which promotes neuronal proliferation and differentiation. These coordinated signaling events contribute to enhanced neurogenesis and neural repair. The arrows indicate activation and the blunt lines indicate inhibition.

It is worth noting that AD also demonstrates a gender bias, with females being at higher risk than males [90]. Synaptic plasticity and associative memory impairments are more severe in female than male APP/PS1 mice, which supports the faster progression of AD noted in females [91]. Furthermore, the microglial heterogeneity that occurs in aging and AD has a crucial role in the gender differences because current evidence indicates that male and female microglia might use alternative strategies to respond to the microenvironment under healthy and diseased conditions [90]. Male and female rodents were equally used in the studies that evaluated the effects of catalpol on cognitive impairment. No significant differences were observed between male and female mice with respect to the effects of catalpol on AChE and ChAT activities, mAChR1 expression, or pro-inflammatory cytokine production [73].

3.3 Ischemic stroke

Ischemic stroke is the most common type of stroke and is characterized by a sudden blockage of blood flow to brain regions due to cerebrovascular occlusion [92]. Disruption in cerebral blood flow deprives the brain of oxygen and glucose, which leads to energy deficiency and impaired ion homeostasis, and ultimately results in various neuropathologic changes, including neuronal cell death (apoptosis, autophagy, and necroptosis), oxidative stress, mitochondrial dysfunction, neuroinflammation, BBB breakdown, excitotoxicity, and calcium overload [93]. Notably, angiogenesis has a protective mechanism by promoting nerve regeneration and functional recovery during stroke, which can be initiated and regulated via angiogenic factors, such as vascular endothelial growth factor (VEGF) [94]. VEGF binding to the VEGF receptor (vascular endothelial growth factor receptor 2 [VEGFR2], also known as KDR)

Review Article

triggers autophosphorylation of tyrosine residues and activation of downstream signaling pathways, such as PI3K/AKT and phospholipase-C γ /protein kinase C/mitogen-activated extracellular signal-regulated kinase/extracellular signal-regulated kinase (PLC γ /PKC/MEK/ERK) signaling, and regulates endothelial cell survival, proliferation, migration, and vasodilatation permeability [95]. Animal models of ischemic stroke can be categorized into global, focal, and multifocal ischemia. Global ischemia refers to the gross reduction of blood flow throughout the entire brain, thus impacting cerebral metabolism and neuronal function. In contrast, focal ischemia involves a more specific and localized obstruction of blood flow in a particular brain region, which is known as the ischemic core. Multifocal ischemia is characterized by multiple, scattered areas of reduced blood flow within the brain [96]. Currently, focal ischemia induced by middle cerebral artery occlusion (MCAO) is the most widely used model in rats and mice because focal ischemia closely mimics human ischemic stroke and produces a penumbra like that observed in humans with strokes.

The most common experimental model used for ischemic stroke is MCAO in rats, in which a filament is utilized to block cerebral blood flow from the middle cerebral artery to induce a transient occlusion (Table 3) [93]. An oxygen and glucose deprivation/reperfusion (OGD/R) model is frequently used for *in vitro* studies [93]. Network pharmacology and molecular docking analysis have suggested that the catalpol signaling pathways are involved in angiogenic remodeling, such as VEGF,

neurotrophic factors, and inflammation [107]. Several studies have confirmed that catalpol alleviates ischemic stroke by promoting neurogenesis and angiogenesis through several signaling pathways (Figure 5), such as the VEGF-A/KDR [97], VEGF-PI3K/AKT and VEGF-MEK1/2/ERK1/2 [98], VEGF and erythropoietin (EPO) [99], stromal cell-derived factor-1 (SDF-1) and the SDF-1 receptor (CXCR4) [100], and JAK2-STAT3 signaling pathways [101]. Additionally, catalpol has been shown to enhance neurogenesis in infarcted brain regions and promote survival of newborn neurons by inhibiting apoptosis through activation of BDNF [102]. In both *in vivo* and *in vitro* stroke models, Catalpol promotes neuronal cell activity and axonal regeneration via the PI3K/AKT/mammalian target of rapamycin (mTOR) signaling axis [103]. Furthermore, catalpol upregulates transcription of methyltransferase-like 3 (METTL3) by activating nuclear respiratory factor 1 (NRF1) and lysine acetyltransferase 2A (KAT2A), thereby regulating the m⁶A level of Beclin-1 (a major regulator of autophagy) and protecting against neuronal injury and excessive autophagy after ischemic stroke [104]. Catalpol also improves the ultrastructural morphology of neuronal cells and protects hippocampal neuron function after ischemic stroke [105]. In agreement with the above-mentioned discussion, the anti-oxidative and -apoptotic effects of catalpol have been further substantiated, contributing to the protective role of catalpol against ischemic stroke via the Nrf2/HO-1 and B-cell lymphoma-2 (Bcl-2)/Bcl-2 associated X protein (Bax) pathways, respectively [106].

Table 3 | Effects of catalpol in experimental models of ischemic stroke.

Animal	Models	Doses/duration	Mechanisms/effects	Refs
Rats-male	MCAO	5 mg/kg, 2 weeks, i.p.	Promoting angiogenesis and NSC proliferation and differentiation via the VEGF-A/KDR pathway	[97]
Rats-male	MCAO	2.5, 5, and 10 mg/kg, 14 days, i.v.	Protecting the neurovascular unit in ischemic region via VEGF-PI3K/AKT and VEGF-MEK1/2/ERK1/2 signaling	[98]
Rats-male	MCAO	5 mg/kg, 7 days, i.p.	Increasing brain angiogenesis and upregulating VEGF and EPO	[99]
Rats-male	MCAO	5 mg/kg, 7 days, i.p.	Promoting neurogenesis and angiogenesis via the SDF-1 α /CXCR4 pathway	[100]
Rats-male	MCAO	5 mg/kg, 7 days, i.p.	Stimulating angiogenesis via the JAK2/STAT3 pathway	[101]
Rats-male	MCAO	5 and 10 mg/kg, 7 days, i.p.	Enhancing neurogenesis and promoting the survival of newborn neurons by activating BDNF	[102]
Rats-male and female	MCAO	2.5, 5, and 7.5 mg/kg, 7 days, i.p.	Promoting internal neuronal cell activity and axonal regeneration via the PI3K/AKT/mTOR pathway	[103]
Rats-male	MCAO	5 mg/kg, 7 days, i.p.	Relieving neuronal injury and excessive autophagy via the NRF1/KAT2A/METTL3/Beclin-1 axis	[104]
Rats-male	MCAO	30 mg/kg, 14 days, i.p.	Improving the ultrastructural morphology of neuronal cells and protecting hippocampal neuron function	[105]
Rats-male	MCAO	2.5, 5, and 10 mg/kg, 3 days, intranasal	Anti-oxidative and -apoptotic mechanisms	[106]

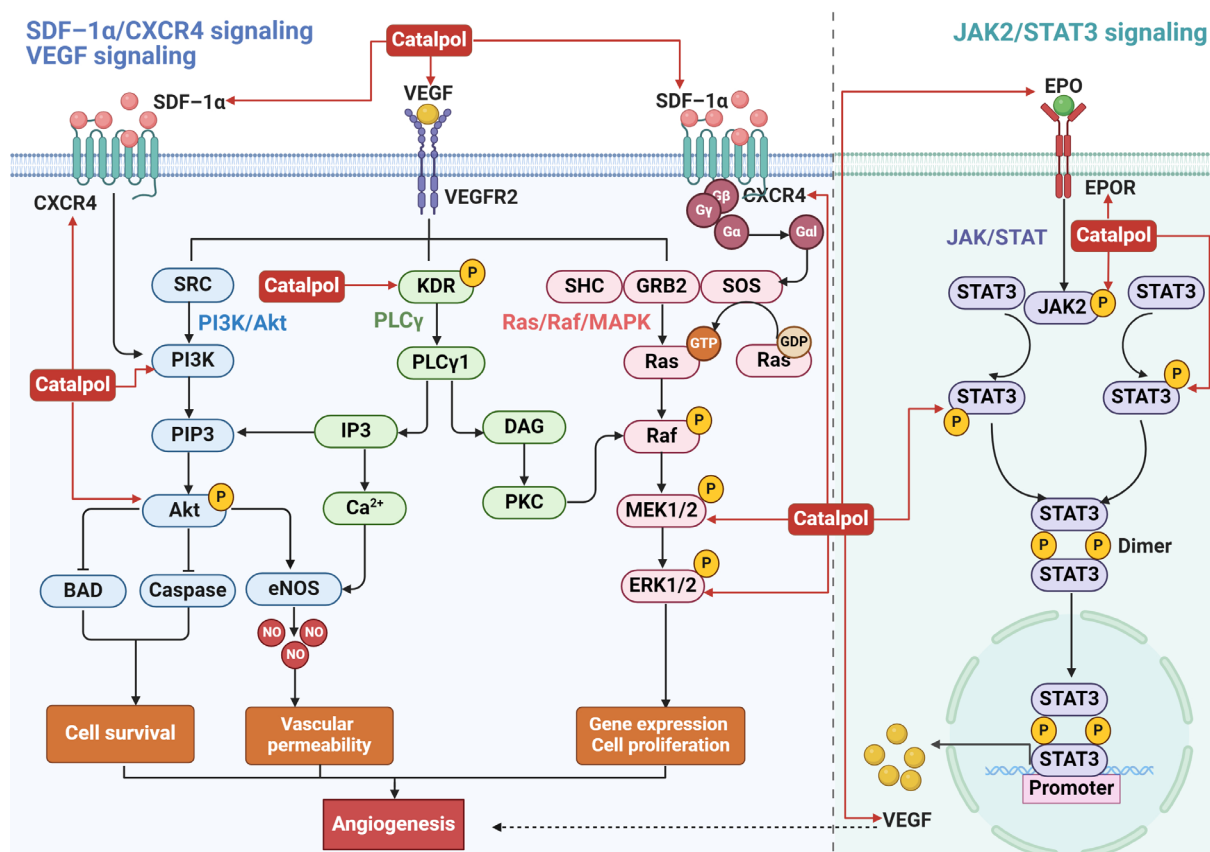


Figure 5 | Molecular pathways involved in the angiogenesis mechanism underlying catalpol.

Catalpol promotes angiogenesis by regulating the JAK2/STAT3, SDF-1α/CXCR4, and VEGF signaling pathways. (1) Catalpol upregulates VEGF expression and enhances VEGF receptor (VEGFR) activation, enhancing kinase insert domain receptor (KDR) phosphorylation and activating the PLCγ signaling pathway, thereby promoting endothelial cell proliferation, survival, and vascular permeability. (2) Catalpol enhances the SDF-1α/CXCR4 axis, activating PI3K/Akt signaling with upregulation of PI3K and Akt phosphorylation and Ras/Raf/MAPK signaling with increased ERK1/2 phosphorylation (left). (3) Catalpol elevates EPO, activates the EPO receptor (EPOR) and downstream JAK2, which leads to phosphorylation and activation of STAT3. Then, STAT3 translocates to the nucleus to induce the expression of pro-angiogenic genes, including VEGF (right). These coordinated pathways contribute to enhanced angiogenesis. The arrows indicate activation and the blunt lines indicate inhibition.

Another model used for transient global ischemia was bilateral occlusion of the common carotid arteries in gerbils. Catalpol inhibits apoptosis by modulating the expression of Bcl-2 and Bax [108], reduces free radicals, and inhibits lipid peroxidation by regulating the activity of SOD and MDA [109] in gerbils after ischemia-reperfusion injury, which offers a potential explanation for the protective effects of catalpol. In addition, catalpol increases Na⁺-K⁺-ATPase and Ca²⁺-ATPase activity, thus inhibiting cellular calcium overload and excitotoxicity [110]. Administration of catalpol 0, 12, 24, 48, and 72 h after reperfusion rescues neurons in the hippocampal CA1 region and reduces working errors in the Y maze. Interestingly, the neuroprotective efficacy of catalpol was still apparent after short (12 d) and long intervals (35 d) after ischemia [111], even when the first treatment occurred 3 h after ischemia. These findings suggest that catalpol has potential therapeutic benefits in the treatment of global cerebral ischemia.

Similarly, gender differences in stroke pathophysiology, treatment, and outcomes have been observed in epidemiologic studies [112]. Women, especially postmenopausal women, have a higher number of stroke-related deaths and worse outcomes. Moreover, women are more frequently institutionalized and permanently disabled compared to men, which is primarily attributed to longer life expectancy and older age at the time of stroke onset [113]. Although stroke predominantly affects the aging female population, most animal models for experimental stroke rely almost universally on young adult male rodents to evaluate neuropathologic, neurologic, and behavioral outcomes after stroke [114], as shown in Table 3. Therefore, incorporating both genders in preclinical studies and enhancing the correlation between these studies and clinical trials is crucial for evaluating potential stroke therapies and identifying neuroprotective or therapeutic agents [115].

Review Article

3.4 PD

PD is a progressive neurodegenerative disorder that is primarily characterized by motor dysfunction due to impairment of the dopaminergic nigrostriatal system with clinical symptoms of tremor at rest, bradykinesia, rigidity, and postural instability [116]. In addition to the selective degeneration of dopaminergic neurons, the main pathologic changes that occur in PD also involve reduced expression of tyrosine hydroxylase (TH) in the substantia nigra pars compacta (SNpc) and decreased density of dopamine transporter (DAT) and dopamine (DA) content in the striatum [117]. The most relevant animal models for studying PD include neurotoxin-induced models, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), 6-hydroxydopamine (6-OHDA), and agricultural pesticides (rotenone or paraquat), pharmacologic models treated with reserpine or haloperidol, and genetic models with manipulation of PD risk genes, including α -synuclein, leucine-rich repeat kinase 2 (LRRK2), DJ-1, PINK-1, and Parkin [118, 119]. MPTP-induced mouse models have been used most widely in PD research due to practical ease, cost-effectiveness, fewer ethical concerns, and stronger clinical correlation compared to other toxin-based models [120]. Moreover, increasing evidence suggests gender-specific differences in the development and phenotypic expression of PD, with men being twice as likely than women to develop the disease, although women have a higher mortality rate and more rapid disease progression [121].

In a classic PD model of MPTP-induced neurotoxicity, catalpol was shown to increase DA and the DA metabolite, DOPAC, levels as well as the density of TH receptor-positive neurons [122]. Another study showed that catalpol improves locomotor ability and elevates DA levels, along with increasing TH and DAT density in the same PD model. These effects were likely mediated by upregulating glial cell-derived neurotrophic factor (GDNF) expression in the striatum [123]. Mitochondrial dysfunction and oxidative stress are also well-established as key pathologic mechanisms in PD [116, 124]. Dopaminergic neurons are particularly susceptible to mitochondrial ROS and loss of mitochondrial complex I activity has been shown to exacerbate dopaminergic neuron death with microtubule dysfunction in PD models [124, 125]. The anti-oxidant and -apoptotic effects of catalpol have been shown to relieve MPTP-induced oxidative stress by inhibiting the mitogen-activated protein kinase kinase (MKK) 4/c-Jun N-terminal kinase (JNK)/c-Jun signaling pathway (Figure 6), which prevents dopaminergic neurons from degeneration in PD models [126].

3.5 MS

MS is a chronic inflammatory disease of the CNS that is characterized by extensive oligodendrocyte damage and demyelination [127, 128]. Disruption in oligodendrocyte maturation and regeneration contributes to axonal degeneration and neuronal death, thereby

classifying MS as an inflammatory and neurodegenerative disease [128]. Several molecular mechanisms have been proposed to explain neurodegeneration, disease progression, and chronic disability in MS, including immune effector mechanisms (clonal expansion of B cells, Epstein-Barr virus [EBV]-infected B cells, CD8⁺ cytotoxic T lymphocytes, and microglia or astrocyte activation), and mechanisms related to neurodegeneration and axonal dysfunction (mitochondrial injury, anomalous distribution of ion channels, glutamate excitotoxicity, and loss of myelin-derived trophic support) [128]. Experimental autoimmune encephalomyelitis (EAE), a widely used animal model of MS, exhibits pathologic and clinical features like human MS [129]. Substantial evidence reveals striking gender differences in the development and progression of human MS [130, 131]. Females are twice as likely to develop MS as males, while males tend to experience more rapid disease progression and greater disability compared to females [132]. This finding is primarily attributed to the regulatory effects of hormonal and genetic factors on the inflammatory processes involved in the pathogenesis of autoimmune disorders, such as regulating T cell effector function [133, 134].

Catalpol has been reported to regulate oligodendrocyte differentiation, inhibit inflammatory cell infiltration, increase the proportion of regulatory T (Treg) cells, and suppress demyelination in EAE mice. The underlying mechanisms are closely related to activation of the Rho-family GTPase Cdc42/Rac1 signaling pathway, which facilitates the transition of OPCs from migration to radial membrane extension (a critical step in myelination), thereby promoting the differentiation of OPCs into mature oligodendrocytes [135]. Furthermore, catalpol exerts neuroprotective effects in EAE mice by increasing the tyrosine hydroxylase expression and noradrenaline levels in the spinal cord and locus coeruleus [136].

3.6 Duchenne muscular dystrophy (DMD)

DMD is a progressive neuromuscular disease caused by mutations in the chromosome X-linked gene encoding dystrophin, a cytoskeletal protein crucial for maintaining muscle integrity. Dystrophin connects the cytoskeleton of muscle fibers to the underlying basal lamina; absence of dystrophin leads to excessive calcium influx across the cell membrane [137]. As a result, affected skeletal muscles undergo atrophy, mitochondrial dysfunction, and necrosis with the transforming growth factor- β (TGF- β)/transforming growth factor- β -activated kinase 1 (TAK1) signaling pathway having a crucial role in muscle fibrosis [137]. DMD affects 1 in 3500–5000 males globally, making DMD the most prevalent inherited neuromuscular disorder [138]. The dystrophin-deficient (mdx) mouse, which carries a nonsense point mutation in exon 23 that prevents full-length dystrophin expression, is the most common animal model used in DMD research, and provides a foundational platform for preclinical gene therapy studies in DMD [139].

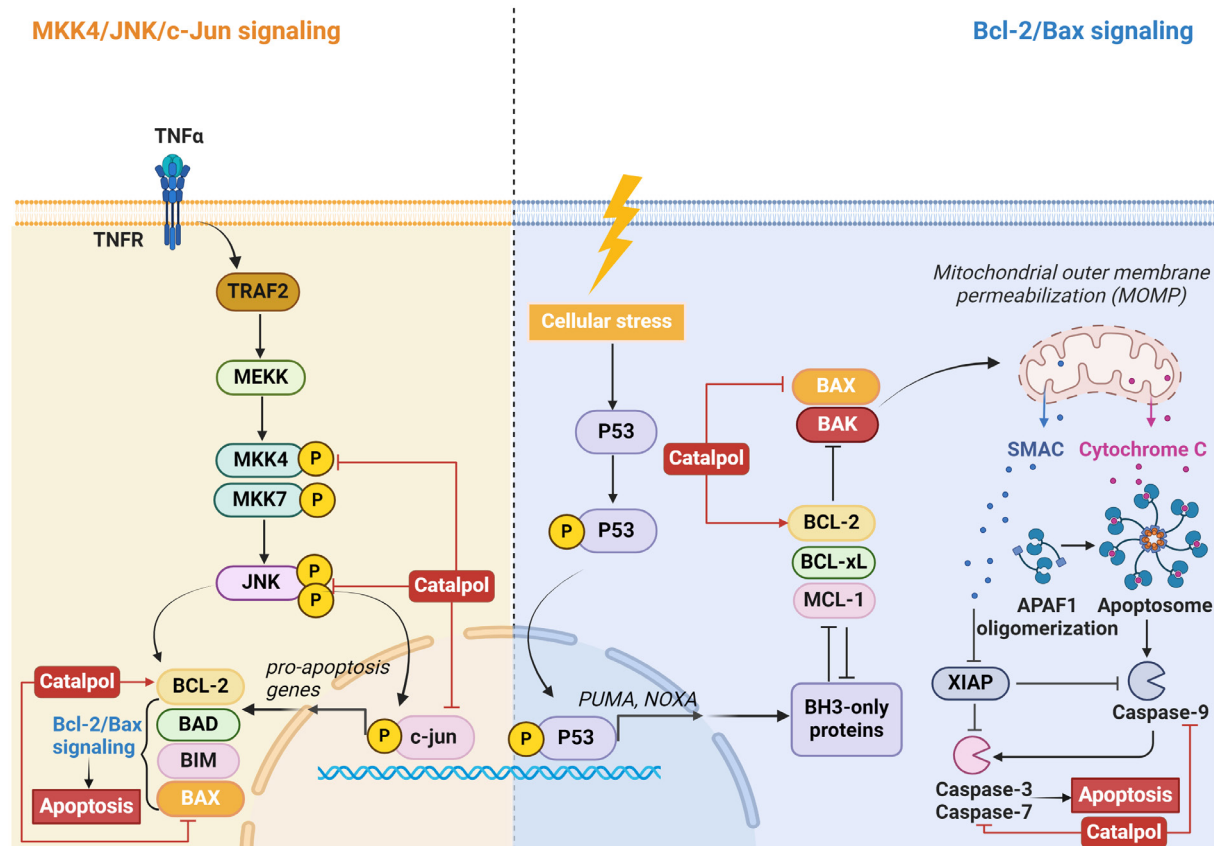


Figure 6 | Molecular pathways involved in the anti-apoptotic mechanism underlying catalpol.

Catalpol exerts anti-apoptotic effects through modulation of the MKK4/JNK/c-Jun and Bcl-2/Bax signaling pathways. Catalpol inhibits MKK4 phosphorylation, which prevents downstream activation of JNK and the JNK target transcription factor, c-Jun. Suppression of c-Jun phosphorylation reduces the transcription of pro-apoptotic genes and regulates Bcl-2/Bax signaling, mitigating apoptosis (left). Catalpol upregulates the expression of the anti-apoptotic protein, Bcl-2, while downregulating the pro-apoptotic protein, Bax, thereby maintaining mitochondrial membrane potential, inhibiting cytochrome c release, and suppressing the expression of caspase-7 and -9 (right). This modulation of the Bcl-2:Bax ratio prevents mitochondrial dysfunction and activation of the intrinsic apoptotic pathway, ultimately protecting cells from apoptosis. The arrows indicate activation and the blunt lines indicate inhibition.

Catalpol has been shown to restore skeletal muscle strength and alleviate skeletal muscle damage and fibrosis in aged dystrophin-deficient mice by inhibiting the TGF- β 1/TAK1 signaling pathway [137]. Additionally, catalpol directly binds to TAK1, suppressing TAK1 phosphorylation and improving overall muscle health and function in dystrophic skeletal muscles [140].

3.7 Epilepsy

Epilepsy is a prevalent neurologic disease characterized by recurrent and unpredictable seizures [141]. One of the most severe and refractory forms of epilepsy is status epilepticus (SE), which is defined as repeated seizures with unconsciousness or persistent seizures lasting > 30 min [142]. Sustained neuronal electrical activity and prolonged seizures can result in neuronal injury or death, largely due to excessive production of ROS [142]. Over the past 40 years, numerous animal models have been

developed, such as the phenytoin- or lamotrigine-resistant kindled rat, the 6-Hz mouse model of partial seizures, the intrahippocampal kainate model in mice, and the lithium-chloride/pilocarpine, kainic acid, pentylene-tetrazol (PTZ)-induced seizure, and electric shock-induced seizure models [143]. Electroshock-induced and acute pentylenetetrazol (PTZ)-injected seizure models are often used to discover antiepileptic drugs and assess seizure susceptibility or threshold in response to pharmacologic interventions [144]. Gender differences in epilepsy are well-recognized, with men generally exhibiting a higher susceptibility and incidence compared to women. Additionally, changes in seizure sensitivity are notable during puberty, pregnancy, and menopause, which are characterized by substantial fluctuations in reproductive hormones and behavioral patterns [144].

Catalpol significantly reduces seizure severity and prolongs after-discharge duration by modulating the

Review Article

Nrf2-Keap1-ARE signaling pathway, thereby mitigating oxidative stress [142]. Additionally, catalpol has anticonvulsant effects in models of seizures induced by electroshock and the GABA antagonist, pentylenetetrazol (PTZ), likely via regulation of the GABA_A receptor [141].

3.8 Other neurologic diseases

TBI is a leading cause of mortality and disability and is defined by disruption of brain function due to external physical forces [145]. Oxidative stress and neurovascular inflammation are prominent hallmarks of TBI pathogenesis [146]. Animal models of TBI can be classified into focal, diffuse, and mixed injuries. Focal injury, represented by animal models of controlled cortical impact, is frequently used due to strong clinical relevance, controllable severity of injury, and high reproducibility across laboratories [13]. Epidemiologic studies have demonstrated gender-dependent differences in the outcomes after TBI, although there is still some debate regarding these results [147]. A review of 50 studies examining TBI in both genders indicated that females exhibit a protective advantage in behavioral outcomes and pathology after TBI despite preclinical injury models primarily focusing on adult male animals [147]. Studies have demonstrated that catalpol effectively reduces ROS generation, inhibits posttraumatic microglial activation and neutrophil infiltration, and ameliorates neuronal apoptosis, thereby improving neurologic outcomes after TBI [148].

Neuropathic pain, a chronic pain condition often resulting from severe somatosensory nerve injury, has been increasingly linked to heightened spinal neuroimmune and neuroinflammatory activities in experimental models [149]. Currently, surgical methods, including peripheral nerve ligation or transection, are well-validated models for producing neuropathic pain and inducing long-lasting behavioral and functional disorders in rodents [150]. Numerous extensive studies have emphasized gender differences in the magnitude of pain hypersensitivity, the neuroanatomy and cell biology of pain, the neurochemistry of pain, and pain transcriptomics [151]. Catalpol exerts significant antinociceptive effects on neuropathic pain, primarily through modulation of neuroinflammatory responses in the spinal cord [152].

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in childhood that is marked by persistent symptoms of inattention, hyperactivity, and impulsivity. It is believed that environmental factors interact with a genetic predisposition, thereby increasing susceptibility to ADHD. The most widely used genetic model for ADHD is the spontaneous hypertensive rat, which closely resembles ADHD symptoms in humans [153]. ADHD exhibits a strong male bias in incidence and notable gender-specific differences in behavioral phenotypes, which might be attributed to gender-specific responses to juvenile stress on the dopaminergic system [154]. Catalpol has been reported to

effectively ameliorate hyperactive and impulsive behavior by inhibiting neuronal apoptosis, enhancing myelination, and upregulating key regulatory proteins in the prefrontal cortex development [155].

Post-traumatic stress disorder (PTSD) is a chronic mental disorder that is characterized by cognitive dysfunction after exposure to traumatic stressors. Therefore, many of the current animal models of PTSD emphasize the type of trauma, such as stress-enhanced fear learning, single-prolonged stress, a single exposure to severe stress, and predator/predator odor exposure [156]. Gender differences have also been demonstrated in PTSD resilience and susceptibility because women are twice as likely as men to develop PTSD [157]. Abnormal hippocampal neural plasticity is a significant contributor to PTSD progression [158]. Catalpol has been shown to promote the therapeutic effects of physical exercise, reducing hyper-responsiveness to threatening stimuli and improving brain function by promoting hippocampal neurogenesis [159]. The detailed information about catalpol in PD, MS, DMD, epilepsy, TBI, pain, ADHD, and PTSD is listed in Table 4.

4. PHARMACODYNAMIC (PD_y) AND PHARMACOKINETIC (PK) PROFILES

4.1 Pharmacologic properties

Successful clinical translation of catalpol requires a comprehensive understanding of the PD_y and PK profiles. Catalpol, a bioactive iridoid glycoside derived predominantly from *Rehmanniae Radix*, exhibits a broad range of PD_y effects, including antioxidant, anti-inflammatory, neuroprotective, and anti-apoptotic properties, making catalpol a promising therapeutic candidate for neurologic disorders.

Catalpol exerts potent antioxidant effects primarily through activation of the Nrf2/Keap1/ARE pathway, which promotes transcription of antioxidant enzymes, such as HO-1, NAD(P)H quinone oxidoreductase-1 (NQO1), and SOD. Catalpol facilitates Nrf2 phosphorylation and nuclear translocation through Keap1 dissociation or via PI3K/AKT signaling, which reinforces cellular antioxidant defenses. Catalpol reduces amyloid-β generation and neuronal oxidative stress by activating the Keap1-Nrf2/ARE signaling pathway in immortalized lymphocytes from patients with late-onset AD and the SKNMC cell co-culture model [160]. Catalpol reduces ROS production, lowers malondialdehyde (MDA) levels, and upregulates antioxidant enzymes via the Nrf2/PI3K/AKT signaling in ischemic stroke models, thereby mitigating oxidative damage and inhibiting neuronal ferroptosis [89].

Catalpol reduces inflammatory responses by suppressing the NF-κB signaling pathway and NLRP3 inflammasome. Catalpol reduces the expression of pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) and chemokines (CXCL8 and CXCL5) in LPS-induced endometritis models by inhibiting the TLR4/NF-κB signaling

Table 4 | Effects of catalpol in experimental models of other neurologic disorders.

Types	Animal	Models	Doses/duration	Mechanisms/effects	Refs
PD	Mice-not mentioned	MPTP-induced neurotoxicity	1.5 and 15 mg/kg, 7 days, i.p.	Protecting dopaminergic neurons	[122]
	Mice-male	MPTP-induced neurotoxicity	50 mg/kg, 8 weeks, i.g.	Elevating the striatal GDNF expression	[123]
	Mice-male	MPTP-induced neurotoxicity	15 mg/kg, 14 days, i.p.	Attenuating inflammation and reducing oxidative stress and inhibiting apoptosis via MKK4/JNK/c-Jun signaling	[126]
MS	Mice-female	Induced MOG ₃₅₋₅₅ and CFA	40 mg/kg, 40 days, i.g.	Regulating oligodendrocyte regeneration and remyelination via the GEF-Cdc42/Rac1 pathway	[135]
	Mice-female	Induced by MOG ₃₅₋₅₅ and CFA	10 mg/kg, 40 days, i.p.	Increasing the level of noradrenaline in the locus coeruleus	[136]
DMD	Mice-male	Aged dystrophin-deficient mice (12 months old)	100 and 200 mg/kg, 6 weeks, i.g.	Inhibiting the TGF- β 1/TAK1 signaling pathway	[137]
	Mice-male	Dystrophin-deficient	200 mg/kg, 6 weeks, i.g.	Inhibiting the phosphorylation of TAK1 by binding to TAK1, reducing fibrosis, and increasing myoblast differentiation	[140]
Epilepsy	Mice-male	Electroshock (or PTZ or strychnine) –induced seizures	10 mg/kg at 30 min before modeling, s.c.	Regulating GABA _A receptor activity	[141]
Status epilepticus	Rats-male	Induced by LiCl-pilocarpine	5 mg/kg at 30 min before modeling, i.p.	Regulating the Nrf2-Keap1-ARE signaling pathway to inhibit the oxidative stress response	[142]
TBI	Rats-male	Controlled cortical impact	10 mg/kg, 3 days, i.v.	Providing neuroprotection against oxidative stress and neuroinflammation	[148]
Pain	Rats-male	Chronic constriction injury model	1, 5, 25 and 125 mg/kg, 5 days, i.p.	Modulating neuroinflammation in spinal cord	[152]
ADHD	Rats-male	Spontaneously hypertensive rats	50 mg/kg, 4 weeks, i.g.	Inhibiting neuronal apoptosis and increasing myelination and BDNF expression	[155]
PTSD	Mice-male	Unconditional stimulation combined with conditional stimulation (US-CS)	20 mg/kg, 2 weeks, i.p.	Promoting adult hippocampal neurogenesis	[159]

pathway in a dose-dependent fashion [161]. Catalpol attenuates microglial activation, reduces production of nitric oxide (NO) and ROS, and downregulates pro-inflammatory cytokines with alleviation of NLRP3 inflammasome activation [162] and TLR4/NF- κ B signaling [161] in LPS-stimulated BV2 microglial cells. Given the key encephalitic role of microglia in neuroinflammation, the anti-inflammatory effect of catalpol suggests the potential for neurologic disorder treatment.

Catalpol prevents neuronal apoptosis by regulating the JNK/c-Jun and Bcl-2/Bax pathways. Catalpol increases the expression of anti-apoptotic Bcl-2 while downregulating pro-apoptotic Bax and attenuating H₂O₂-induced apoptosis in endothelium [163]. Catalpol reduces JNK and p38 phosphorylation, which prevents the transcription of pro-apoptotic genes and CaMKII-dependent apoptosis in LPS-stimulated neuronal PC12 cells [164]. Catalpol was shown to reduce neuronal apoptosis by modulating Bcl-2/Bax and inhibiting cytochrome c release in an ischemic stroke model [106]

and by suppressing the JNK/c-Jun pathway in an MPTP-induced PD model [126].

Catalpol exerts neuroprotective effects by reducing oxidative stress, alleviating inflammatory responses, and inhibiting neuronal apoptosis [165]. Additionally, catalpol upregulates BDNF expression and activates TrkB, leading to downstream activation of PI3K/Akt, PLC γ , and Ras/ERK pathways, which promotes neuronal survival, differentiation, and synaptic plasticity. Catalpol has been reported to increase BDNF and TrkB levels in a model of ischemia-induced cognitive impairment, which enhances hippocampal neurogenesis and cognitive recovery [98]. Catalpol restores synaptic plasticity and improves memory deficits in LPS-induced cognitive impairment model by activating the BDNF/TrkB pathway [84]. The multifaceted PDy effects of catalpol, especially the antioxidant, anti-inflammatory, neuroprotective, and anti-apoptotic properties, highlight the potential for treating neurologic disorders.

Review Article

4.2 PK characteristics

Most natural products are administered orally but bioavailability is often limited due to gastrointestinal degradation and hepatic first-pass metabolism. The PK properties of these compounds significantly impact efficacy and safety, making it essential to understand absorption, distribution, metabolism, and excretion during drug development.

Catalpol has been shown to undergo rapid absorption with high oral bioavailability (50–65%). The following LC/MS/MS PK parameters were reported in rats administered catalpol (50 mg/kg orally): $t_{1/2}$ (1.212 ± 0.388 h); $V_{1/F}$ (1.428 ± 0.681 L/kg); $AUC_{0-\infty}$ ($69,520 \pm 22,927$ ng h/mL); $MRT_{0-\infty}$ (3.273 ± 0.365 h); T_{max} (1.333 ± 0.408 h); and C_{max} ($23,318 \pm 10,468$ ng/mL) [166]. Further studies examined different oral doses of catalpol (50, 100, and 200 mg/kg), which revealed the following: T_{max} values of 1.3 ± 0.4 , 1.6 ± 0.8 , and 2.3 ± 0.8 h; $t_{1/2}$ values of 1.8 ± 1.3 , 1.7 ± 1.0 , and 2.6 ± 1.5 h; and C_{max} values of 23 ± 10 , 35 ± 14 , and 36 ± 9 μ g/mL, respectively [167]. These findings indicated rapid absorption, although the plasma concentration did not increase in a dose-dependent manner. The absolute bioavailability of catalpol at 50 mg/kg was 66.7%, suggesting the efficacy of oral administration. Another comparative study showed higher bioavailability via intramuscular injection (71.63%) than oral administration (49.38%), indicating catalpol instability in the gastrointestinal tract.

Catalpol or metabolites were distributed in different tissues following absorption. A recent PsK study involving [^{3} H] catalpol (intragastric administration of 30 mg/kg) in rats showed that catalpol-related substances are primarily concentrated in the stomach, large intestine, bladder, and kidneys. Catalpol metabolism is mainly mediated by the intestinal flora, resulting in an aglycone-containing hemiacetal hydroxyl structure [168]. Moreover, intravenous administration of catalpol (6 mg/kg) showed brain penetration, as evidenced by a CSF/plasma AUC ratio of 5.8% with a shorter plasma elimination half-life (~ 0.7 h) compared to CSF (~ 1.5 h) [169]. This finding suggested potential therapeutic implications for neurologic disorders. Additionally, catalpol and its metabolites are primarily excreted through the renal route with a rapid clearance. Oral administration of catalpol (50 mg/kg) exhibits a short elimination half-life (1.212 ± 0.388 h), indicating faster elimination that is likely due to the hydrophilic nature [166]. Further PK assessments in rats confirmed the predominant renal excretion of catalpol, as evidenced by a mean recovery of the total catalpol dose with $57.52\% \pm 12.50\%$ in the urine [168].

The PKs of catalpol vary under different disease models. In streptozotocin-induced diabetic rats, the $AUC_{(0-t)}$, C_{max} , and $t_{1/2}$ were higher, while the T_{max} was lower compared to normal rats. The corresponding $AUC_{(0-t)}$, C_{max} , T_{max} , and $t_{1/2}$ values were 92.4 ± 38.2 and 214.1 ± 79.03 μ g/mL·L, 11.82 ± 6.79 vs. 37.41 ± 13.01 μ g/mL, 3.1 ± 1.7 vs. 2.4 ± 1.1 h, and 4.0 ± 1.0 vs. 11.6 ± 4.2 h, respectively

[170]. Furthermore, the PK parameters for catalpol (8.0 mL/kg) revealed higher absorptivity and a longer elimination half-life in doxorubicin-induced chronic kidney disease rats, as indicated by an $AUC_{(0-t)}$ 1627.83 ± 241.40 and 439.71 ± 42.34 μ g/min·mL, and $t_{1/2}$ 118.28 ± 39.13 and 84.00 ± 13.42 min, respectively, when compared to normal rats [171]. The altered PKs of catalpol under various conditions are influenced by the gastrointestinal microenvironment, liver enzymes (CYP), drug transporters (P-glycoprotein), and plasma protein binding (glucuronidation and sulfation). These findings highlight the complex metabolism and PKs of catalpol, which are important considerations for therapeutic development. Furthermore, clinical trials are essential to validate efficacy and safety.

5. CLINICAL APPLICATIONS AND TOXICITY

The LBRD has been validated to have significantly therapeutic effects on depression and diminish the incidence of adverse reactions [172]. A study combining metabolomics and network pharmacology revealed that LBRD significantly improves the psychological suboptimal health state, primarily through regulating pyruvate and phenylalanine metabolism [173]. However, there are currently few reports about the clinical use of catalpol for neurologic disorders. In a preliminary study involving patients following surgical resection for locally advanced colon cancer, treatment with catalpol (10 mg/kg, twice a day for 12 weeks, i.p.) showed benefits in clinical outcome without severe complications and was cost-effective [174].

To date studies have demonstrated that catalpol is relatively safe for rodents with nearly no side effects reported. ICR mice received a maximum catalpol dose of 1000 mg/kg within 1 day via gavage in an animal study to evaluate the acute toxicity of catalpol and showed no noticeable poisoning symptoms or any abnormalities in life activity after 2 weeks of continuous observation [175]. Another acute toxicity test of catalpol in Kunming mice revealed that the median lethal dose (LD_{50}) of intraperitoneal administration was 206.5 mg/kg with a 95% confidence interval between 190.7 and 223.6 mg/kg [176]. Wistar rats received a 90-d intravenous injection of catalpol (10, 20, and 40 mg/kg) in an assessment of long-term toxicity and displayed no abnormalities in appearance, the blood biochemistry profile, or toxicity involving major organs [176]. A phase-1 trial (ChiCTR1900028589) also investigated the safety of catalpol in healthy subjects. Well-designed clinic trials inspired by the established safety profile from pre-clinical and clinical trials are warranted to further evaluate efficacy in neurologic disease for future research.

6. CONCLUSION AND FUTURE PERSPECTIVES

This review summarized the research advances on the therapeutic potentials of catalpol for a wide range

of neurologic disorders. The neuroprotective effects of catalpol are primarily mediated through the following common mechanisms (**Figure 7**): (1) antioxidant effects via modulating the PI3K/Akt/Nrf2/HO-1, PKC γ , caveolin-1, and Nrf2-Keap1-ARE pathways; (2) anti-neuroinflammatory actions by suppressing the NLRP3 inflammasome and TLR4/MAPK/NF- κ B pathway; (3) anti-apoptotic properties through regulation of the MKK4/JNK/c-Jun and Bcl-2/Bax cascade pathways; and (4) promotion of synaptic plasticity and neurogenesis by activating BDNF/TrkB neurotrophic signaling pathway. In addition, catalpol exerted its neuroprotective effects through disorder-specific mechanisms. For example, catalpol inhibited HPA axis in depression, improved cholinergic function, and reduced A β production in AD. Catalpol promoted angiogenesis via the VEGF-A/KDR, VEGF-PI3K/AKT, VEGF-MEK1/2/ERK1/2, SDF-1 α /CXCR4, and JAK2/STAT3 signaling pathways in ischemic stroke, and mitigated excessive autophagy via the NRF1/KAT2A/METTL3/Beclin-1 pathway. Catalpol protects dopaminergic neurons in PD and enhances oligodendrocyte regeneration and remyelination in MS via the GEF-Cdc42/Rac1

pathway. Catalpol promotes myoblast differentiation in DMD via the TGF- β 1/TAK1 signaling pathway and regulates GABA $_A$ receptor activity in epilepsy. Despite the indication of these signaling pathways in many of the included studies, it is essential to note that much of the existing research relies on broad techniques, such as western blotting, quantitative polymerase chain reaction (qPCR), or immunostaining to observe changes at the molecular level. More detailed investigations, including the use of antagonists or inhibitors, knock-out mice, and other advanced methodologies, such as electrophysiologic recording, are necessary to further elucidate the precise molecular mechanisms underlying catalpol.

As global life expectancy increases and population aging accelerates, neurologic diseases have become a considerable global health burden due to the high incidence, disability, and mortality rates. Unfortunately, most first-line drugs for these conditions only alleviate symptoms and often come with obvious side effects in clinical practice. Natural compounds, sourced from plants, animals, and microorganisms provide a rich

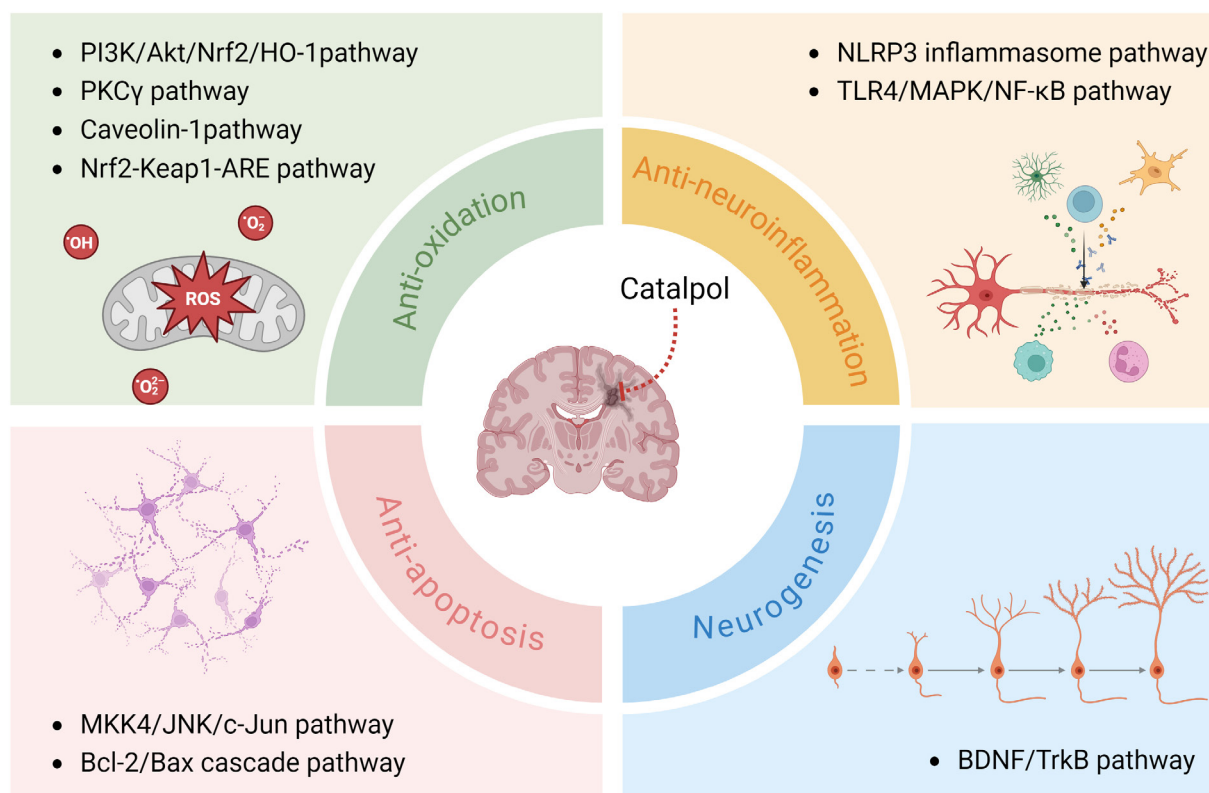


Figure 7 | The common mechanism underlying catalpol against neurologic disorders.

Catalpol exerts neuroprotective effects through four key mechanisms, as follows: (1) anti-oxidation by activating PKC γ /caveolin-1, PI3K/AKT/Nrf2/HO-1, and Nrf2/Keap1/ARE pathways to enhance antioxidant defense; (2) anti-neuroinflammation by inhibiting TLR4/MAPK/NF- κ B and NLRP3 inflammasome signaling and reducing inflammatory cytokine production; (3) promoting neurogenesis by activating BDNF/TrkB signaling and enhancing neuronal survival, differentiation, and plasticity; and (4) anti-apoptosis by suppressing MKK4/JNK/c-Jun signaling and modulating the Bcl-2:Bax ratio to maintain mitochondrial integrity and inhibit apoptosis.

Review Article

reservoir of chemical structures that can serve as the foundation for innovative therapeutic agents. While natural compounds are widely acknowledged as valuable potential precursors for drug discovery and development due to potent biological activities, it is essential to recognize the possible risks and limitations associated with natural compound use. Therefore, there is an urgent need to identify some natural and low-toxicity neuroprotective agents for the prevention and intervention of neurologic disorders. In this context, the TCM formulas (LBRD and *Rehmanniae Radix*) have been extensively studied for neuroprotective effects in preclinical and clinical settings. Catalpol, a major active compound from *Rehmanniae Radix*, exhibits pharmacologic efficacy comparable to the extract, particularly in the effects on the CNS. This review comprehensively discussed the therapeutic potential of catalpol for a wide range of neurologic disorders, detailing experimental models, dosages, duration, and mechanisms of action. The neuroprotective effects of catalpol, rooted in the common mechanisms of anti-oxidation, anti-neuroinflammation, anti-apoptosis, and promotion of neuroplasticity and neurogenesis, make catalpol a promising candidate for neurologic disorders.

Despite the encouraging efficacy of catalpol in experimental investigations, there are still challenges to be addressed in preclinical research, including the identification of direct binding targets, evaluation of toxicologic effects, and PKs. Advanced techniques, such as cryo-electron microscopy (cryo-EM), X-ray crystallography, and nuclear magnetic resonance (NMR) spectroscopy, can be used to determine the precise molecular structures and binding sites of catalpol. Additionally, the interactions between catalpol and its targets can be predicted with high accuracy using computational methods, such as molecular docking and virtual screening. Although current studies have shown that catalpol is highly safe for rodents, more extensive research is needed to further validate these findings and ensure safety. Furthermore, comprehensive PK evaluations should be given more attention, including absorption, distribution, metabolism, and excretion (ADME) studies to provide a thorough understanding of how catalpol interacts within biological systems. These rigorous evaluations will be beneficial to validate the efficacy and safety of catalpol, reduce the risk of potential adverse effects, and further enhance the potential for translation into clinical use.

More importantly, there is a lack of clinical trials investigating the neuroprotective effects of catalpol. To bridge the gap between preclinical and clinical research, the appropriate selection and utilization of animal models should be prioritized to ensure congruency with neurologic disorders in humans. Many variables, especially gender and age, must be carefully considered because these factors may affect the susceptibility, progression, and manifestation of neurologic disorders, as well as the efficacy and safety of therapeutic interventions.

Moreover, well-designed clinical trials should be conducted to evaluate the efficacy, safety, and optimal dosing of catalpol in human subjects. In addition, a comparative analysis of catalpol with other neuroprotective agents should be conducted in future preclinical and clinical research, providing a broader perspective on the effectiveness and safety profile of catalpol. Based on clinical validity, the optimization of chemical structure and investigations of precise molecular targets and mechanisms should be performed to lay the foundation for further research and development of a promising neuroprotective agent.

ABBREVIATIONS

5-HIAA, 5-hydroxyindoleacetic acid; 5-HT, serotonin; AAV, adeno-associated virus; ACC, acetyl-CoA carboxylase; Ach, acetylcholine; AD, Alzheimer's disease; ADHD, attention deficit hyperactivity disorder; AEP, asparagine endopeptidase; AGE, advanced glycation end product; AKT, protein kinase B; ALS, amyotrophic lateral sclerosis; AMPK, adenosine 5'-monophosphate-activated protein kinase; APP, amyloid precursor protein; ARE, antioxidant-response element; ATF3, activating transcription factor 3; ATP, adenosine triphosphate; A β , amyloid-beta; BACE1, β -secretase; Bax, Bcl-2 associated X protein; BBB, blood brain barrier; Bcl-2, B-cell lymphoma-2; C/EBP β , CCAAT-enhancer binding protein beta; CAT, catalase; ChAT, choline acetyltransferase; CK, creatine kinase; CNKI, Chinese national knowledge infrastructure; CNS, central nervous system; CORT, corticosterone; CUMS, chronic unpredictable mild stress; CVD, cardio-cerebrovascular diseases; ER, estrogen receptor; CXCR4, C-X-C motif chemokine receptor 4; DA, dopamine; DAT, dopamine transporter; DMD, Duchenne muscular dystrophy; EAE, experimental autoimmune encephalomyelitis; EBV, Epstein-Barr virus; EPO, erythropoietin; ER, estrogen receptor; ERK, extracellular signal-regulated kinase; FSP1, ferroptosis suppressor protein 1; GAP-43, growth-associated protein 43; GDNF, glial cell derived neurotrophic factor; GRP78, glucose-regulated protein 78; GS, glutamine synthetase; GSH-Px, glutathione peroxidase; GSH-ST, glutathione S-transferase; GSK3 β , glycogen synthase kinase-3 β ; GWAS, genome-wide association study; HD, Huntington's disease; HO-1, hemeoxygenase-1; HPA, hypothalamus-pituitary-adrenal; IL-1 β , interleukin-1 beta; IL-6, interleukin-6; JAK2, Janus kinase 2; JNK, c-Jun N-terminal kinase; KAT2A, lysine acetyltransferase 2A; LBRD, Lily bulb and *Rehmannia* decoction; LDH, lactate dehydrogenase; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MCAO, middle cerebral artery occlusion; MDA, malondialdehyde; MEK, mitogen-activated extracellular signal-regulated kinase; METTL3, methyltransferase-like 3; MKK4, mitogen-activated protein kinase kinase 4; MS, multiple sclerosis; MSCs, mesenchymal stem cells; mTOR, mammalian target of rapamycin; NF- κ B, nuclear factor kappa-B; NO, nitric oxide; NOX4, NADPH oxidase 4; NQO1, NAD(P)H quinone oxidoreductase-1; NRF1, nuclear respiratory factor 1; Nrf2, nuclear factor erythroid 2-related factor 2; OGD/R, oxygen and glucose deprivation/reperfusion; OPCs, oligodendrocyte precursor cells; PD, Parkinson's disease; PERK, protein kinase RNA-like endoplasmic reticulum kinase; PGC-1 α , peroxisome proliferators-activated receptor gamma coactivator 1-alpha; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PLC γ , phospholipase-C γ ; PPAR, peroxisome proliferators-activated receptor; PTSD, post-traumatic stress

disorder; PTZ, pentylenetetrazol; RAGE, receptor for advanced glycation end product; ROS, reactive oxygen species; SCI, spinal cord injury; SDF-1, stromal cell-derived factor-1; SE, status epilepticus; SIRT1, silent information regulator factor 2-related enzyme 1; SNpc, substantia nigra pars compacta; SOD, superoxide dismutase; SSRIs, selective serotonin reuptake inhibitors; STAT3, signal transducer and activator of transcription 3; TAK1, transforming growth factor- β -activated kinase 1; TBI, traumatic brain injury; TCM, traditional Chinese medicine; TERT, telomerase reverse transcriptase; TGF- β , transforming growth factor- β ; TH, tyrosine hydroxylase; TLR4, toll-like receptor 4; TNF- α , tumor necrosis factor alpha; VEGF, vascular endothelial growth factor; VEGFR2, vascular endothelial growth factor receptor 2

ACKNOWLEDGEMENTS

This work was financially supported by the Basic and Applied Basic Research Foundation of Guangdong Province (2020A1515110993), Shenzhen Medical Research Fund (A2303004), the National Natural Science Foundation of China (No. 82004079), the Excellent Technology Innovation Cultivation Program of Shenzhen (No. RCB520200714115000364), the Natural Science Foundation of Guangdong Province (No. 2022A1515012330), and the Excellent Medical Innovation Foundation of the Eighth Affiliated Hospital, Sun Yat-sen University (No. YXYXCRC202108). **Figures 2–7** and the Graphical Abstract were created using BioRender. Huang, S. (2025).

CONFLICTS OF INTEREST

The authors have no conflicts of interest regarding the publication of this paper. Figures were created using BioRender software (<https://www.biorender.com/>).

REFERENCES

- [1] Feigin VL, Vos T, Nichols E, Owolabi MO, Carroll WM, Dichgans M, et al.: The Global Burden of Neurological Disorders: Translating Evidence into Policy. *The Lancet. Neurology* 2020, 19:255–265.
- [2] Collaborators GUND, Feigin VL, Vos T, Alahdab F, Amit AML, Barnighausen TW, et al.: Burden of Neurological Disorders Across the US From 1990–2017: A Global Burden of Disease Study. *JAMA Neurology* 2021, 78:165–176.
- [3] GBD 2021 Nervous System Disorders Collaborators: Global, Regional, and National Burden of Disorders Affecting the Nervous System, 1990–2021: A Systematic Analysis for the Global Burden of Disease Study 2021. *The Lancet. Neurology* 2024, 23:344–381.
- [4] Svendsen SP, Svendsen CN: Cell Therapy for Neurological Disorders. *Nature Medicine* 2024, 30:2756–2770.
- [5] Wingo TS, Liu Y, Gerasimov ES, Vattathil SM, Wynne ME, Liu J, et al.: Shared Mechanisms Across the Major Psychiatric and Neurodegenerative Diseases. *Nature Communication* 2022, 13:4314.
- [6] Mishra A, Bandoopathyay R, Singh PK, Mishra PS, Sharma N, Khurana N: Neuroinflammation in Neurological Disorders: Pharmacotherapeutic Targets from Bench to Bedside. *Metabolic Brain Disease* 2021, 36:1591–1626.
- [7] Ravichandran KA, Heneka MT: Inflammasomes in Neurological Disorders – Mechanisms and Therapeutic Potential. *Nature Reviews. Neurology* 2024, 20:67–83.
- [8] Hassan W, Noreen H, Rehman S, Kamal MA, da Rocha JBT: Association of Oxidative Stress with Neurological Disorders. *Current Neuropharmacology* 2022, 20:1046–1072.
- [9] Li J, Jia B, Cheng Y, Song Y, Li Q, Luo C: Targeting Molecular Mediators of Ferroptosis and Oxidative Stress for Neurological Disorders. *Oxidative Medicine and Cellular Longevity* 2022, 2022:3999083.
- [10] Korczowska-Lacka I, Hurla M, Banaszek N, Kobylarek D, Szymanowicz O, Kozubski W, et al.: Selected Biomarkers of Oxidative Stress and Energy Metabolism Disorders in Neurological Diseases. *Molecular Neurobiology* 2023, 60:4132–4149.
- [11] Zhang L, Dai L, Li D: Mitophagy in Neurological Disorders. *Journal of Neuroinflammation* 2021, 18:297.
- [12] Spaas J, van Veggel L, Schepers M, Tiane A, van Horsen J, Wilson DM 3rd, et al.: Oxidative Stress and Impaired Oligodendrocyte Precursor Cell Differentiation in Neurological Disorders. *Cellular and Molecular Life Sciences* 2021, 78:4615–4637.
- [13] Cardozo PL, de Lima IBQ, Maciel EMA, Silva NC, Dobransky T, Ribeiro FM: Synaptic Elimination in Neurological Disorders. *Current Neuropharmacology* 2019, 17:1071–1095.
- [14] Martella G, Bonsi P, Johnson SW, Quartarone A: Synaptic Plasticity Changes: Hallmark for Neurological and Psychiatric Disorders. *Neural Plasticity* 2018, 2018: 9230704.
- [15] Nimgampalle M, Chakravarthy H, Sharma S, Shree S, Bhat AR, Pradeepkiran JA, et al.: Neurotransmitter Systems in the Etiology of Major Neurological Disorders: Emerging Insights and Therapeutic Implications. *Ageing Research Reviews* 2023, 89:101994.
- [16] Suganya K, Koo BS: Gut-Brain Axis: Role of Gut Microbiota on Neurological Disorders and How Probiotics/Prebiotics Beneficially Modulate Microbial and Immune Pathways to Improve Brain Functions. *International Journal of Molecular Sciences* 2020, 21:7551.
- [17] Andrzejewska A, Dabrowska S, Lukomska B, Janowski M: Mesenchymal Stem Cells for Neurological Disorders. *Advanced Science* 2021, 8:2002944.
- [18] Ling Q, Herstine JA, Bradbury A, Gray SJ: AAV-based In Vivo Gene Therapy for Neurological Disorders. *Nature Reviews. Drug Discovery* 2023, 22:789–806.
- [19] Anthony K: RNA-based Therapeutics for Neurological Diseases. *RNA Biology* 2022, 19:176–190.
- [20] Camacho-Conde JA, Gonzalez-Bermudez MDR, Carretero-Rey M, Khan ZU: Brain Stimulation: A Therapeutic Approach for the Treatment of Neurological Disorders. *CNS Neuroscience & Therapeutics* 2022, 28:5–18.
- [21] Vendrik KEW, Ooijevaar RE, de Jong PRC, Laman JD, van Oosten BW, van Hilten JJ, et al.: Fecal Microbiota Transplantation in Neurological Disorders. *Frontiers in Cellular and Infection Microbiology* 2020, 10:98.
- [22] Strawn JR, Mills JA, Poweleit EA, Ramsey LB, Croarkin PE: Adverse Effects of Antidepressant Medications and their Management in Children and Adolescents. *Pharmacotherapy* 2023, 43:675–690.
- [23] McShane R, Westby MJ, Roberts E, Minakaran N, Schneider L, Farrimond LE, et al.: Memantine for Dementia. *The Cochrane Database of Systematic Reviews* 2019, 3:CD003154.
- [24] Pirker W, Katzenschlager R, Hallett M, Poewe W: Pharmacological Treatment of Tremor in Parkinson's

Review Article

- Disease Revisited. *Journal of Parkinson's Disease* 2023, 13:127–144.
- [25] McFarland D, Merchant D, Khandai A, Mojtahedzadeh M, Ghosn O, Hirst J, et al.: Selective Serotonin Reuptake Inhibitor (SSRI) Bleeding Risk: Considerations for the Consult-Liaison Psychiatrist. *Current Psychiatry Reports* 2023, 25:113–124.
- [26] Chi X, Wang S, Baloch Z, Zhang H, Li X, Zhang Z, et al.: Research Progress on Classical Traditional Chinese Medicine Formula Lily Bulb and Rehmannia Decoction in the Treatment of Depression. *Biomedicine & Pharmacotherapy* 2019, 112:108616.
- [27] Pan J, Lu Y, Wang S, Ma T, Xue X, Zhang Z, et al.: Synergistic Neuroprotective Effects of Two Natural Medicinal Plants Against CORT-induced Nerve Cell Injury by Correcting Neurotransmitter Deficits and Inflammation Imbalance. *Phytomedicine* 2023, 121:155102.
- [28] Chi X, Xue X, Pan J, Wu J, Shi H, Wang Y, et al.: Mechanism of Lily Bulb and Rehmannia Decoction in the Treatment of Lipopolysaccharide-induced Depression-like Rats Based on Metabolomics Study and Network Pharmacology. *Pharmaceutical Biology* 2022, 60:1850–1864.
- [29] Zhang H, Xue X, Pan J, Song X, Chang X, Mao Q, et al.: Integrated Analysis of the Chemical-material Basis and Molecular Mechanisms for the Classic Herbal Formula of Lily Bulb and Rehmannia Decoction in Alleviating Depression. *Chinese Medicine* 2021, 16:107.
- [30] Mao Q, Zhang H, Zhang Z, Lu Y, Pan J, Guo D, et al.: Co-decoction of Lili Bulbus and Radix Rehmannia Recens and Its Key Bioactive Ingredient Verbascoside Inhibit Neuroinflammation and Intestinal Permeability Associated with Chronic Stress-induced Depression via the Gut Microbiota-brain Axis. *Phytomedicine* 2024, 129:155510.
- [31] Zhou XD, Shi DD, Wang HN, Tan QR, Zhang ZJ: Aqueous Extract of Lily Bulb Ameliorates Menopause-like Behavior in Ovariectomized Mice with Novel Brain-uterus Mechanisms Distinct from Estrogen Therapy. *Biomedicine & Pharmacotherapy* 2019, 117:109114.
- [32] Zhou XD, Shi DD, Zhang ZJ: Ameliorative Effects of Radix Rehmanniae Extract on the Anxiety- and Depression-like Symptoms in Ovariectomized Mice: A Behavioral and Molecular Study. *Phytomedicine* 2019, 63:153012.
- [33] Jia J, Chen J, Wang G, Li M, Zheng Q, Li D: Progress of Research into the Pharmacological Effect and Clinical Application of the Traditional Chinese Medicine Rehmanniae Radix. *Biomedicine & Pharmacotherapy* 2023, 168:115809.
- [34] Wang Z, Wang X, Mou X, Wang C, Sun Y, Wang J: Rehmannia Glutinosa DC.-*Lilium lancifolium* Thunb. in the Treatment of Depression: A Comprehensive Review and Perspectives. *Frontiers in Pharmacology* 2024, 15:1471307.
- [35] Zhang B, Zhou N, Zhang Z, Wang R, Chen L, Zheng X, et al.: Study on the Neuroprotective Effects of Eight Iridoid Components Using Cell Metabolomics. *Molecules* 2024, 29:1497.
- [36] Wang RJ, Chen HM, Yang F, Deng Y, Ao H, Xie XF, et al.: Iridoids from the Roots of *Valeriana jatamansi* Jones. *Phytochemistry* 2017, 141:156–161.
- [37] Tan Y-Z, Yong Y, Dong Y-H, Wang R-J, Li H-X, Zhang H, et al.: A New Secoiridoid Glycoside and a New Sesquiterpenoid Glycoside from *Valeriana jatamansi* with Neuroprotective Activity. *Phytochemistry Letters* 2016, 17:177–180.
- [38] Dinda B, Dinda M, Kulsi G, Chakraborty A, Dinda S: Therapeutic Potentials of Plant Iridoids in Alzheimer's and Parkinson's Diseases: A Review. *European Journal of Medicinal Chemistry* 2019, 169:185–199.
- [39] Wang C, Gong X, Bo A, Zhang L, Zhang M, Zang E, et al.: Iridoids: Research Advances in Their Phytochemistry, Biological Activities, and Pharmacokinetics. *Molecules* 2020, 25:287.
- [40] Bhattamisra SK, Yap KH, Rao V, Choudhury H: Multiple Biological Effects of an Iridoid Glucoside, Catalpol, and Its Underlying Molecular Mechanisms. *Biomolecules* 2019, 10:32.
- [41] Kou Y, Li Z, Yang T, Shen X, Wang X, Li H, et al.: Therapeutic Potential of Plant Iridoids in Depression: A Review. *Pharmaceutical Biology* 2022, 60:2167–2181.
- [42] Chen H, Deng C, Meng Z, Meng S, Pan W: Effects of Catalpol on Alzheimer's Disease and Its Mechanisms. *Evidence-Based Complementary and Alternative Medicine* 2022, 2022:1–12.
- [43] Jesulola E, Micalos P, Baguley IJ: Understanding the Pathophysiology of Depression: From Monoamines to the Neurogenesis Hypothesis Model - Are We There Yet? *Behavioural Brain Research* 2018, 341:79–90.
- [44] Duman RS, Aghajanian GK, Sanacora G, Krystal JH: Synaptic Plasticity and Depression: New Insights from Stress and Rapid-acting Antidepressants. *Nature Medicine* 2016, 22:238–249.
- [45] Wang Q, Timberlake II MA, Prall K, Dwivedi Y: The Recent Progress in Animal Models of Depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 2017, 77:99–109.
- [46] Song J, Kim YK: Animal Models for the Study of Depressive Disorder. *CNS Neuroscience & Therapeutics* 2021, 27:633–642.
- [47] Wang J, Chen R, Liu C, Wu X, Zhang Y: Antidepressant Mechanism of Catalpol: Involvement of the PI3K/Akt/Nrf2/HO-1 Signaling Pathway in Rat Hippocampus. *European Journal of Pharmacology* 2021, 909:174396.
- [48] Wu X, Liu C, Wang J, Guan Y, Song L, Chen R, et al.: Catalpol Exerts Antidepressant-Like Effects by Enhancing Anti-oxidation and Neurotrophs and Inhibiting Neuroinflammation via Activation of HO-1. *Neurochemical Research* 2022, 47:2975–2991.
- [49] Wang J-M, Yang L-H, Zhang Y-Y, Niu C-L, Cui Y, Feng W-S, et al.: BDNF and COX-2 Participate in Anti-depressive Mechanisms of Catalpol in Rats Undergoing Chronic Unpredictable Mild Stress. *Physiology & Behavior* 2015, 151:360–368.
- [50] Liang X, Zhao Y, Xu T, Wang W, Sun W, Wang R: Catalpol Alleviates Depression by Inhibiting NLRP3 Inflammasome via TLR4/MAPK/NF-Kb Pathway. *Iranian Journal of Public Health* 2023, 52:722–731.
- [51] Wang Y-L, Wu H-R, Zhang S-S, Xiao H-L, Yu J, Ma Y-Y, et al.: Catalpol Ameliorates Depressive-like Behaviors in CUMS Mice via Oxidative Stress-mediated NLRP3 Inflammasome and Neuroinflammation. *Translational Psychiatry* 2021, 11:353.
- [52] Wu X, Liu C, Wang J, Zhang Y, Li Y, Wang Y, et al.: The Role of TrkB Signaling-mediated Synaptic Plasticity in the Antidepressant Properties of Catalpol, the Main Active Compound of Rehmannia Glutinosa Libosch. *Journal of Ethnopharmacology* 2024, 333:118448.
- [53] Wu X, Zhang Y, Wang J, Qin L, Li Y, He Q, et al.: Role of SIRT1-mediated Synaptic Plasticity and Neurogenesis:

- Sex-differences in Antidepressant-like Efficacy of Catalpol. *Phytomedicine* 2024, 135:156120.
- [54] Song L, Wu X, Wang J, Guan Y, Zhang Y, Gong M, et al.: Antidepressant Effect of Catalpol on Corticosterone-induced Depressive-like Behavior Involves the Inhibition of HPA Axis Hyperactivity, Central Inflammation and Oxidative Damage Probably via Dual Regulation of NF- κ B and Nrf2. *Brain Research Bulletin* 2021, 177:81–91.
- [55] Wu X, Wang J, Song L, Guan Y, Cao C, Cui Y, et al.: Catalpol Weakens Depressive-like Behavior in Mice with Streptozotocin-induced Hyperglycemia via PI3K/AKT/Nrf2/HO-1 Signaling Pathway. *Neuroscience* 2021, 473:102–118.
- [56] Li B, Zhou X, Zhen L, Zhang W, Lu J, Zhou J, et al.: Catalpol Reduced the Cognitive and Mood Dysfunctions in Post-stroke Depression Mice via Promoting PI3K-mediated Adult Neurogenesis. *Aging* 2023, 15:8433–8443.
- [57] Wang J, Cui Y, Feng W, Zhang Y, Wang G, Wang X, et al.: Involvement of the Central Monoaminergic System in the Antidepressant-like Effect of Catalpol in Mice. *BioScience Trends* 2014, 8:248–252.
- [58] Guo N, Wang X, Xu M, Bai J, Yu H, Le Z: PI3K/AKT Signaling Pathway: Molecular Mechanisms and Therapeutic Potential in Depression. *Pharmacological Research* 2024, 206:107300.
- [59] Yang K, Cao F, Qiu S, Jiang W, Tao L, Zhu Y: Metformin Promotes Differentiation and Attenuates H₂O₂-Induced Oxidative Damage of Osteoblasts via the PI3K/AKT/Nrf2/HO-1 Pathway. *Frontiers in Pharmacology* 2022, 13:829830.
- [60] Zhou W, Hong J, Liu T, Li M, Jin H, Wang X, et al.: Polygonatum Polysaccharide Regulates Macrophage Polarization and Improves LPS-Induced Acute Lung Injury through TLR4-MAPK/NF- κ B Pathway. *Canadian Respiratory Journal* 2022, 2022:1–11.
- [61] Wu X, Guan Y, Wang J, Song L, Zhang Y, Wang Y, et al.: Co-catalpol Alleviates Fluoxetine-Induced Main Toxicity: Involvement of ATF3/FSP1 Signaling-mediated Inhibition of Ferroptosis. *Phytomedicine* 2024, 126:155340.
- [62] Czeh B, Fuchs E, Wiborg O, Simon M: Animal Models of Major Depression and Their Clinical Implications. *Progress in Neuro-psychopharmacology & Biological Psychiatry* 2016, 64:293–310.
- [63] Lima S, Sousa N, Patricio P, Pinto L: The underestimated sex: A review on female animal models of depression. *Neuroscience and Biobehavioral Reviews* 2022, 133:104498.
- [64] Monteiro AR, Barbosa DJ, Remião F, Silva R: Alzheimer's Disease: Insights and New Prospects in Disease Pathophysiology, Biomarkers and Disease-modifying Drugs. *Biochemical Pharmacology* 2023, 211:115522.
- [65] Bai R, Guo J, Ye X-Y, Xie Y, Tian X: Oxidative Stress: The Core Pathogenesis and Mechanism of Alzheimer's Disease. *Ageing Research Reviews* 2022, 77:101619.
- [66] Ionescu-Tucker A, Cotman CW: Emerging Roles of Oxidative Stress in Brain Aging and Alzheimer's Disease. *Neurobiology of Aging* 2021, 107:86–95.
- [67] Ferreira-Vieira TH, Guimaraes IM, Silva FR, Ribeiro FM: Alzheimer's Disease: Targeting the Cholinergic System. *Current Neuropharmacology* 2016, 14:101–115.
- [68] Wang Z-H, Xiang J, Liu X, Yu SP, Manfredsson FP, Sandoval IM, et al.: Deficiency in BDNF/TrkB Neurotrophic Activity Stimulates δ -Secretase by Upregulating C/EBP β in Alzheimer's Disease. *Cell Reports* 2019, 28:655–669.
- [69] Liao J, Chen C, Ahn EH, Liu X, Li H, Edgington-Mitchell LE, et al.: Targeting Both BDNF/TrkB Pathway and Delta-secretase for Treating Alzheimer's Disease. *Neuropharmacology* 2021, 197:108737.
- [70] Tai LM, Maldonado Weng J, LaDu MJ, Brady ST: Relevance of Transgenic Mouse Models for Alzheimer's disease. *Progress in Molecular Biology and Translational Science* 2021, 177:1–48.
- [71] Zhong MZ, Peng T, Duarte ML, Wang M, Cai D: Updates on Mouse Models of Alzheimer's Disease. *Molecular Neurodegeneration* 2024, 19:23.
- [72] Henry JD: Prospective Memory Impairment in Neurological Disorders: Implications and Management. *Nature Reviews Neurology* 2021, 17:297–307.
- [73] Zhang X, Jin C, Li Y, Guan S, Han F, Zhang S: Catalpol Improves Cholinergic Function and Reduces Inflammatory Cytokines in the Senescent Mice Induced by D-galactose. *Food and Chemical Toxicology* 2013, 58:50–55.
- [74] Wan D, Xue L, Zhu H, Luo Y: Catalpol Induces Neuroprotection and Prevents Memory Dysfunction through the Cholinergic System and BDNF. *Evidence-Based Complementary and Alternative Medicine* 2013, 2013:1–9.
- [75] Wang J-H, Xie H, Zhao T-K, Kang B: Catalpol Regulates Cholinergic Nerve System Function Through Effect on Choline Acetyl-transferase not M Receptor Affinity. *Biomedicine & Pharmacotherapy* 2015, 69:291–296.
- [76] Zhang X, Jiang B, Li Z, Hao S, An L: Catalpol Ameliorates Cognition Deficits and Attenuates Oxidative Damage in the Brain of Senescent Mice Induced by D-galactose. *Pharmacology Biochemistry and Behavior* 2007, 88:64–72.
- [77] Huang J-Z, Wu J, Xiang S, Sheng S, Jiang Y, Yang Z, et al.: Catalpol Preserves Neural Function and Attenuates the Pathology of Alzheimer's Disease in Mice. *Molecular Medicine Reports* 2016, 13:491–496.
- [78] Zhou H, Liu J, Ren L, Liu W, Xing Q, Men L, et al.: Relationship with Spatial Memory in Diabetic Rats and Protein Kinase C γ , Caveolin-1 in the Hippocampus and Neuroprotective Effect of Catalpol. *Chinese Medical Journal* 2014, 127:916–923.
- [79] Wang C-F, Li D-Q, Xue H-Y, Hu B: Oral Supplementation of Catalpol Ameliorates Diabetic Encephalopathy in Rats. *Brain Research* 2010, 1307:158–165.
- [80] Zhang X-L, An L-J, Bao Y-M, Wang J-Y, Jiang B: D-galactose Administration Induces Memory Loss and Energy Metabolism Disturbance in Mice: Protective Effects of Catalpol. *Food and Chemical Toxicology* 2008, 46:2888–2894.
- [81] Du J, Liu J, Huang X, Li Y, Song D, Li Q, et al.: Catalpol Ameliorates Neurotoxicity in N2a/APP695swe Cells and APP/PS1 Transgenic Mice. *Neurotoxicity Research* 2022, 40:961–972.
- [82] Tian L, Li H, Xiong W, Li X, Duan S, Yang C, et al.: Proteomic Alteration in Catalpol Treatment of Alzheimer's Disease by Regulating HSPA5/GPX4. *European Journal of Pharmacology* 2025, 987:177075.
- [83] Zhang A, Hao S, Bi J, Bao Y, Zhang X, An L, et al.: Effects of Catalpol on Mitochondrial Function and Working Memory in Mice After Lipopolysaccharide-induced Acute Systemic Inflammation. *Experimental and Toxicologic Pathology* 2009, 61:461–469.
- [84] Hu W, Zou L, Yu N, Wu Z, Yang W, Wu T, et al.: Catalpol Rescues LPS-induced Cognitive Impairment via Inhibition of NF-Kb-regulated Neuroinflammation and

Review Article

- Up-regulation of TrkB-mediated BDNF Secretion in Mice. *Journal of Ethnopharmacology* 2024, 319:117345.
- [85] Wang Z, Liu Q, Zhang R, Liu S, Xia Z, Hu Y: Catalpol Ameliorates Beta Amyloid-induced Degeneration of Cholinergic Neurons by Elevating Brain-derived Neurotrophic Factors. *Neuroscience* 2009, 163:1363–1372.
- [86] Xia Z, Zhang R, Wu P, Xia Z, Hu Y: Memory Defect Induced by Beta-amyloid Plus Glutamate Receptor Agonist is Alleviated by Catalpol and Donepezil Through Different Mechanisms. *Brain Research* 2012, 1441:27–37.
- [87] Liu J, He Q-J, Zou W, Wang H-X, Bao Y-M, Liu Y-X, et al.: Catalpol Increases Hippocampal Neuroplasticity and Up-regulates PKC and BDNF in the Aged Rats. *Brain Research* 2006, 1123:68–79.
- [88] Xia Z, Wang F, Zhou S, Zhang R, Wang F, Huang JH, et al.: Catalpol Protects Synaptic Proteins from Beta-amyloid Induced Neuron Injury and Improves Cognitive Functions in Aged Rats. *Oncotarget* 2017, 8:69303–69315.
- [89] Lin J, Deng L, Qi A, Jiang H, Xu D, Zheng Y, et al.: Catalpol Alleviates Hypoxia Ischemia-Induced Brain Damage by Inhibiting Ferroptosis Through the PI3K/NRF2/system Xc-/GPX4 Axis in Neonatal Rats. *European Journal of Pharmacology* 2024, 968:176406.
- [90] Delage CL, Šimončičová E, Tremblay M-È: Microglial Heterogeneity in Aging and Alzheimer's Disease: Is Sex Relevant? *Journal of Pharmacological Sciences* 2021, 146:169–181.
- [91] Navakkode S, Gaunt JR, Pavon MV, Bansal VA, Abraham RP, Chong YS, et al.: Sex-Specific Accelerated Decay in Time/Activity-dependent Plasticity and Associative Memory in an Animal Model of Alzheimer's Disease. *Aging Cell* 2021, 20:13502.
- [92] Shehjar F, Maktabi B, Rahman ZA, Bahader GA, James AW, Naqvi A, et al.: Stroke: Molecular Mechanisms and Therapies: Update on Recent Developments. *Neurochemistry International* 2023, 162:105458.
- [93] Qin C, Yang S, Chu Y-H, Zhang H, Pang X-W, Chen L, et al.: Signaling Pathways Involved in Ischemic Stroke: Molecular Mechanisms and Therapeutic Interventions. *Signal Transduction and Targeted Therapy* 2022, 7:215.
- [94] Fang J, Wang Z, Miao CY: Angiogenesis After Ischemic Stroke. *Acta Pharmacologica Sinica* 2023, 44:1305–1321.
- [95] Melincovici CS, Boşca AB, Şuşman S, Mărginean M, Mărginean C, Istrate M, et al.: Vascular Endothelial Growth Factor (VEGF) – Key Factor in Normal and Pathological Angiogenesis. *Romanian Journal of Morphology and Embryology* 2018, 59:455–467.
- [96] Kumar A, Aakriti, Gupta V: A Review on Animal Models of Stroke: An Update. *Brain Research Bulletin* 2016, 122:35–44.
- [97] Sun S, Xu Y, Yu N, Zhang M, Wang J, Wan D, et al.: Catalpol Alleviates Ischemic Stroke Through Promoting Angiogenesis and Facilitating Proliferation and Differentiation of Neural Stem Cells via the VEGF-A/KDR Pathway. *Molecular Neurobiology* 2023, 60:6227–6247.
- [98] Wang H-J, Ran H-F, Yin Y, Xu X-G, Jiang B-X, Yu S-Q, et al.: Catalpol Improves Impaired Neurovascular Unit in Ischemic Stroke Rats via Enhancing VEGF-PI3K/AKT and VEGF-MEK1/2/ERK1/2 Signaling. *Acta Pharmacologica Sinica* 2021, 43:1670–1685.
- [99] Zhu H-F, Wan D, Luo Y, Zhou J-L, Chen L, Xu X-Y: Catalpol Increases Brain Angiogenesis and Up-Regulates VEGF and EPO in the Rat after Permanent Middle Cerebral Artery Occlusion. *International Journal of Biological Sciences* 2010, 6:443–453.
- [100] Zhang MF, Wang JH, Sun S, Xu YT, Wan D, Feng S, et al.: Catalpol Attenuates Ischemic Stroke by Promoting Neurogenesis and Angiogenesis via the SDF-1 α /CXCR4 Pathway. *Phytomedicine* 2024, 128:155362.
- [101] Dong W, Xian Y, Yuan W, Huifeng Z, Tao W, Zhiqiang L, et al.: Catalpol Stimulates VEGF Production via the JAK2/STAT3 Pathway to Improve Angiogenesis in Rats' Stroke Model. *Journal of Ethnopharmacology* 2016, 191:169–179.
- [102] Zhu H-F, Shao Y, Qin L, Wang J-H, Feng S, Jiang Y-B, et al.: Catalpol Enhances Neurogenesis And Inhibits Apoptosis Of New Neurons Via BDNF, But Not The BDNF/Trkb Pathway. *Drug Design, Development and Therapy* 2019, 13:4145–4157.
- [103] Wang J, Wan D, Wan G, Wang J, Zhang J, Zhu H: Catalpol Induces Cell Activity to Promote Axonal Regeneration via the PI3K/AKT/mTOR Pathway In Vivo and In Vitro Stroke Model. *Annals of Translational Medicine* 2019, 7:756–756.
- [104] Liu K, Yao X, Gao J, Wang J, Qi J: A Study on the Mechanism of Beclin-1 m6A Modification Mediated by Catalpol in Protection Against Neuronal Injury and Autophagy Following Cerebral Ischemia. *Molecular Medicine* 2024, 30:65.
- [105] Xie S, Zhi Y, Zeng B: Protective Effects of Catalpol on Limb Motor Function and Ultrastructure of Hippocampal Neurons in Rats with Cerebral Ischemia. *Molecular Biotechnology* 2021, 64:213–219.
- [106] Wang J, Zhang Y, Zhang M, Sun S, Zhong Y, Han L, et al.: Feasibility of Catalpol Intranasal Administration and Its Protective Effect on Acute Cerebral Ischemia in Rats via Anti-Oxidative and Anti-Apoptotic Mechanisms. *Drug Design, Development and Therapy* 2022, 16:279–296.
- [107] Wang J, Zhang M, Sun S, Wan G, Wan D, Feng S, et al.: Network Pharmacology-Based Prediction of Catalpol and Mechanisms Against Stroke. *Evidence-Based Complementary and Alternative Medicine* 2021, 2021:1–14.
- [108] Li D-Q, Bao Y-M, Li Y, Wang C-F, Liu Y, An L-J: Catalpol Modulates the Expressions of Bcl-2 and Bax and Attenuates Apoptosis in Gerbils after Ischemic Injury. *Brain Research* 2006, 1115:179–185.
- [109] Liu Y-R, Li P-W, Suo J-J, Sun Y, Zhang B-A, Lu H, et al.: Catalpol Provides Protective Effects Against Cerebral Ischaemia/Reperfusion Injury in Gerbils. *Journal of Pharmacy and Pharmacology* 2014, 66:1265–1270.
- [110] Liu Y-R, Lei R-Y, Wang C-E, Zhang B-A, Lu H, Zhu H-C, et al.: Effects of Catalpol on ATPase and Amino Acids in Gerbils with Cerebral Ischemiareperfusion Injury. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* 2014, 35:1229–1233.
- [111] Li D-Q, Li Y, Liu Y, Bao Y-M, Hu B, An L-J: Catalpol Prevents the Loss of CA1 Hippocampal Neurons and Reduces Working Errors in Gerbils After Ischemia-reperfusion Injury. *Toxicon* 2005, 46:845–851.
- [112] Haast RAM, Gustafson DR, Kiliaan AJ: Sex Differences in Stroke. *Journal of Cerebral Blood Flow & Metabolism* 2012, 32:2100–2107.
- [113] Ahnstedt H, McCullough LD, Cipolla MJ: The Importance of Considering Sex Differences in Translational Stroke Research. *Translational Stroke Research* 2016, 7:261–273.
- [114] Zhang H, Lin S, Chen X, Gu L, Zhu X, Zhang Y, et al.: The Effect of Age, Sex and Strains on the Performance and

- Outcome in Animal Models of Stroke. *Neurochemistry International* 2019, 127:2–11.
- [115] Matur AV, Candelario-Jalil E, Paul S, Karamyan VT, Lee JD, Pennypacker K, et al.: Translating Animal Models of Ischemic Stroke to the Human Condition. *Translational Stroke Research* 2022, 14:842–853.
- [116] Pajares M, I Rojo A, Manda G, Boscá L, Cuadrado A: Inflammation in Parkinson's Disease: Mechanisms and Therapeutic Implications. *Cells* 2020, 9:1687.
- [117] Gopinath A, Mackie P, Hashimi B, Buchanan AM, Smith AR, Bouchard R, et al.: DAT and TH Expression Marks Human Parkinson's Disease in Peripheral Immune Cells. *NPJ Parkinson's Disease* 2022, 8:72.
- [118] Dovonou A, Bolduc C, Soto Linan V, Gora C, Peralta Ili MR, Lévesque M: Animal Models of Parkinson's Disease: Bridging the Gap Between Disease Hallmarks and Research Questions. *Translational Neurodegeneration* 2023, 12:36.
- [119] Lal R, Singh A, Watts S, Chopra K: Experimental Models of Parkinson's Disease: Challenges and Opportunities. *European Journal of Pharmacology* 2024, 980:176819.
- [120] Mustapha M, Mat Taib CN: MPTP-induced Mouse Model of Parkinson's Disease: A Promising Direction of Therapeutic Strategies. *Bosnian Journal of Basic Medical Sciences* 2020, 21:422–433.
- [121] Cerri S, Mus L, Blandini F: Parkinson's Disease in Women and Men: What's the Difference? *Journal of Parkinson's Disease* 2019, 9:501–515.
- [122] Jiang B, Zhang H, Bi J, Zhang XL: Neuroprotective Activities of Catalpol on MPP+/MPTP-Induced Neurotoxicity. *Neurological Research* 2013, 30:639–644.
- [123] Xu G, Xiong Z, Yong Y, Wang Z, Ke Z, Xia Z, et al.: Catalpol Attenuates MPTP Induced Neuronal Degeneration of Nigral-striatal Dopaminergic Pathway in Mice Through Elevating Glial Cell Derived Neurotrophic Factor in Striatum. *Neuroscience* 2010, 167:174–184.
- [124] Raza C, Anjum R, Shakeel NUA: Parkinson's Disease: Mechanisms, Translational Models and Management Strategies. *Life Sciences* 2019, 226:77–90.
- [125] Choi WS, Palmiter RD, Xia Z: Loss of Mitochondrial Complex I Activity Potentiates Dopamine Neuron Death Induced by Microtubule Dysfunction in a Parkinson's Disease Model. *The Journal of Cell Biology* 2011, 192:873–882.
- [126] Wang L-Y, Yu X, Li X-X, Zhao Y-N, Wang C-Y, Wang Z-Y, et al.: Catalpol Exerts a Neuroprotective Effect in the MPTP Mouse Model of Parkinson's Disease. *Frontiers in Aging Neuroscience* 2019, 11:316.
- [127] Dobson R, Giovannoni G: Multiple Sclerosis – A Review. *European Journal of Neurology* 2019, 26:27–40.
- [128] Correale J, Gaitán MI, Ysraelit MC, Fiol MP: Progressive Multiple Sclerosis: From Pathogenic Mechanisms to Treatment. *Brain* 2017, 140:527–546.
- [129] Muñoz-Jurado A, Escribano BM, Túniz I: Animal Model of Multiple Sclerosis: Experimental Autoimmune Encephalomyelitis. *Methods in Cell Biology* 2024, 188:35–60.
- [130] Zeydan B, Rangachari M, Kantarci OH: Editorial: Understanding Sex-specific Issues in MS and Its Animal Models: Natural History, Management and Mechanisms. *Frontiers in Neurology* 2024, 15:1366126.
- [131] McCombe PA, Greer JM: Effects of Biological Sex and Pregnancy in Experimental Autoimmune Encephalomyelitis: It's Complicated. *Frontiers in Immunology* 2022, 13:1059833.
- [132] Ryan L, Mills KHG: Sex Differences Regulate Immune Responses in Experimental Autoimmune Encephalomyelitis and Multiple Sclerosis. *European Journal of Immunology* 2021, 52:24–33.
- [133] Ramien C, Taenzer A, Lupu A, Heckmann N, Engler JB, Patas K, et al.: Sex Effects on Inflammatory and Neurodegenerative Processes in Multiple Sclerosis. *Neuroscience & Biobehavioral Reviews* 2016, 67:137–146.
- [134] Umair M, Fazazi MR, Rangachari M: Biological Sex As a Critical Variable in CD4⁺ Effector T Cell Function in Preclinical Models of Multiple Sclerosis. *Antioxidants & Redox Signaling* 2022, 37:135–149.
- [135] Wu M, Kang Q, Kang Y, Tong Y, Yang T, Fan Y, et al.: Catalpol Regulates Oligodendrocyte Regeneration and Remyelination by Activating the GEF-Cdc42/Rac1 Signaling Pathway in EAE Mice. *Evidence-Based Complementary and Alternative Medicine* 2022, 2022:7074157.
- [136] Li Q, Yang T, Guo A-C, Fan Y-P: Role of Catalpol in Ameliorating the Pathogenesis of Experimental Autoimmune Encephalomyelitis by Increasing the Level of Noradrenaline in the Locus Coeruleus. *Molecular Medicine Reports* 2018, 17:4163–4172.
- [137] Xu D-Q, Zhao L, Li S-J, Huang X-F, Li C-J, Sun L-X, et al.: Catalpol Counteracts the Pathology in a Mouse Model of Duchenne Muscular Dystrophy by Inhibiting the TGF- β 1/TAK1 Signaling Pathway. *Acta Pharmacologica Sinica* 2020, 42:1080–1089.
- [138] Lim KRQ, Nguyen Q, Dzierlega K, Huang Y, Yokota T: CRISPR-Generated Animal Models of Duchenne Muscular Dystrophy. *Genes* 2020, 11:342.
- [139] McGreevy JW, Hakim CH, McIntosh MA, Duan D: Animal Models of Duchenne Muscular Dystrophy: From Basic Mechanisms to Gene Therapy. *Disease Models & Mechanisms* 2015, 8:195–213.
- [140] Xu D, Zhao L, Jiang J, Li S, Sun Z, Huang X, et al.: A Potential Therapeutic Effect of Catalpol in Duchenne Muscular Dystrophy Revealed by Binding with TAK1. *Journal of Cachexia, Sarcopenia and Muscle* 2020, 11:1306–1320.
- [141] Kim M, Acharya S, Botanas CJ, Custodio RJ, Lee HJ, Sayson LV, et al.: Catalpol and Mannitol, Two Components of Rehmannia Glutinos, Exhibit Anticonvulsant Effects Probably via GABAA Receptor Regulation. *Biomolecules & Therapeutics* 2020, 28:137–144.
- [142] Gao J, An L, Xu Y, Huang Y: Catalpol Exerts an Anti-Epileptic Effect, Possibly by Regulating the Nrf2-Keap1-ARE Signaling Pathway. *Medical Science Monitor* 2018, 24:9436–9441.
- [143] Löscher W: Animal Models of Seizures and Epilepsy: Past, Present, and Future Role for the Discovery of Antiseizure Drugs. *Neurochemical Research* 2017, 42:1873–1888.
- [144] Reddy DS: The Neuroendocrine Basis of Sex Differences in Epilepsy. *Pharmacology Biochemistry and Behavior* 2017, 152:97–104.
- [145] Khellaf A, Khan DZ, Helmy A: Recent Advances in Traumatic Brain Injury. *Journal of Neurology* 2019, 266:2878–2889.
- [146] Abdul-Muneer PM, Chandra N, Haorah J: Interactions of Oxidative Stress and Neurovascular Inflammation in the Pathogenesis of Traumatic Brain Injury. *Molecular Neurobiology* 2015, 51:966–979.

Review Article

- [147] Rubin TG, Lipton ML: Sex Differences in Animal Models of Traumatic Brain Injury. *Journal of Experimental Neuroscience* 2019, 13:1179069519844020.
- [148] Ni H, Rui Q, Kan X, Gao R, Zhang L, Zhang B: Catalpol Ameliorates Oxidative Stress and Neuroinflammation after Traumatic Brain Injury in Rats. *Neurochemical Research* 2022, 48:681–695.
- [149] Cavalli E, Mammana S, Nicoletti F, Bramanti P, Mazzon E: The Neuropathic Pain: An Overview of the Current Treatment and Future Therapeutic Approaches. *International Journal of Immunopathology and Pharmacology* 2019, 33:2058738419838383.
- [150] Guida F, De Gregorio D, Palazzo E, Ricciardi F, Boccella S, Belardo C, et al.: Behavioral, Biochemical and Electrophysiological Changes in Spared Nerve Injury Model of Neuropathic Pain. *International Journal of Molecular Sciences* 2020, 21:3396.
- [151] Mogil JS, Parisien M, Esfahani SJ, Diatchenko L: Sex Differences in Mechanisms of Pain Hypersensitivity. *Neuroscience & Biobehavioral Reviews* 2024, 163:105749.
- [152] Wang Y, Zhang R, Xie J, Lu J, Yue Z: Analgesic Activity of Catalpol in Rodent Models of Neuropathic Pain, and Its Spinal Mechanism. *Cell Biochemistry and Biophysics* 2014, 70:1565–1571.
- [153] Regan SL, Williams MT, Vorhees CV: Review of Rodent Models of Attention Deficit Hyperactivity Disorder. *Neuroscience & Biobehavioral Reviews* 2022, 132:621–637.
- [154] Jung DH, Lee HJ, Choi YW, Shin HK, Choi BT: Sex-specific Responses to Juvenile Stress on the Dopaminergic System in an Animal Model of Attention-deficit Hyperactivity Disorder. *Biomedicine & Pharmacotherapy* 2023, 160:114352.
- [155] Yuan H, Ni X, Zheng M, Han X, Song Y, Yu M: Effect of Catalpol on Behavior and Neurodevelopment in an ADHD Rat Model. *Biomedicine & Pharmacotherapy* 2019, 118:109033.
- [156] Richter-Levin G, Stork O, Schmidt MV: Animal Models of PTSD: A Challenge to be Met. *Molecular Psychiatry* 2018, 24:1135–1156.
- [157] Shansky RM: Sex Differences in PTSD Resilience and Susceptibility: Challenges for Animal Models of Fear Learning. *Neurobiology of Stress* 2015, 1:60–65.
- [158] Jowf GIA, Ahmed ZT, Reijnders RA, Nijs LD, Eijssen LMT: To Predict, Prevent, and Manage Post-Traumatic Stress Disorder (PTSD): A Review of Pathophysiology, Treatment, and Biomarkers. *International Journal of Molecular Sciences* 2023, 24:5238.
- [159] Sun L, Zhang W, Ye R, Liu L, Jiang L, Xi C: Catalpol Enhanced Physical Exercise-Mediated Brain Functional Improvement in Post-traumatic Stress Disorder Model via Promoting Adult Hippocampal Neurogenesis. *Aging* 2021, 13:18689–18700.
- [160] Xiang C, Lu Y, Hao R, Wei Y, Hu Y, Yu G: Catalpol Alleviates Amyloid- Generation and Neuronal Oxidative Stress Injury via Activating the Keap1-Nrf2/ARE Signaling Pathway in the Immortalized Lymphocytes from Patients with Late-onset Alzheimer's Disease and SKNMC Cells Co-culture Model. *Iranian Journal of Basic Medical Sciences* 2024, 27:1547–1557.
- [161] Zhang H, Wu ZM, Yang YP, Shaukat A, Yang J, Guo YF, et al.: Catalpol Ameliorates LPS-Induced Endometritis by Inhibiting Inflammation and TLR4/NF-kappaB Signaling. *Journal of Zhejiang University. Science B* 2019, 20:816–827.
- [162] She Y, Shao CY, Liu YF, Huang Y, Yang J, Wan HT: Catalpol Reduced LPS Induced BV2 Immunoreactivity Through NF-kappaB/NLRP3 Pathways: An In Vitro and In Silico Study. *Frontiers in Pharmacology* 2024, 15:1415445.
- [163] Hu L, Sun Y, Hu J: Catalpol Inhibits Apoptosis in Hydrogen Peroxide-induced Endothelium by Activating the PI3K/Akt Signaling Pathway and Modulating Expression of Bcl-2 and Bax. *European Journal of Pharmacology* 2010, 628:155–163.
- [164] Chen W, Li X, Jia LQ, Wang J, Zhang L, Hou D, et al.: Neuroprotective Activities of Catalpol Against CaMKII-dependent Apoptosis Induced by LPS in PC12 Cells. *British Journal of Pharmacology* 2013, 169:1140–1152.
- [165] Yang C, Shi Z, You L, Du Y, Ni J, Yan D: Neuroprotective Effect of Catalpol via Anti-Oxidative, Anti-Inflammatory, and Anti-Apoptotic Mechanisms. *Frontiers in Pharmacology* 2020, 11:690.
- [166] Lu R, Gu Y, Si D, Liu C: Quantitation of Catalpol in Rat Plasma by Liquid Chromatography/Electrospray Ionization Tandem Mass Spectrometry and Its Pharmacokinetic Study. *Journal of Chromatography. B, Analytical Technologies in the Biomedical and Life Sciences* 2009, 877:3589–3594.
- [167] Wu L-n, Lu R, Gu Y, Liu C-x, Si D-y: Pharmacokinetics and Bioavailability of Catalpol in Rats. *Chinese Journal of Clinical Pharmacology and Therapeutics* 2012, 17:126–130.
- [168] Ge X, Zheng Y, He Y, Chen C, Yang C, Lu S, et al.: Pharmacokinetics, Mass Balance, Tissue Distribution, and Metabolism of [³H]Catalpol in Rats: The Main Bioactive Component of *Rehmannia glutinosa* for the Treatment of Ischemic Stroke. *Current Drug Metabolism* 2023, 24:448–457.
- [169] Wang Q, Xing M, Chen W, Zhang J, Qi H, Xu X: HPLC-APCI-MS/MS Method for the Determination of Catalpol in Rat Plasma and Cerebrospinal Fluid: Application to an In Vivo Pharmacokinetic Study. *Journal of Pharmaceutical and Biomedical Analysis* 2012, 70:337–343.
- [170] Feng Y, Liu Z, Peng Y, Zhang L, Ju P, Bi K, et al.: Validated LC-MS Method for Simultaneous Quantitation of Catalpol and Harpagide in Rat Plasma: Application to a Comparative Pharmacokinetic Study in Normal and Diabetic Rats After Oral Administration of Zeng-Ye-Decoction. *Biomedical Chromatography* 2013, 27:1503–1510.
- [171] Zhao M, Qian D, Liu P, Shang EX, Jiang S, Guo J, et al.: Comparative Pharmacokinetics of Catalpol and Acteoside in Normal and Chronic Kidney Disease Rats After Oral Administration of *Rehmannia Glutinosa* Extract. *Biomedical Chromatography* 2015, 29:1842–1848.
- [172] Peng L, Zhang XF, Guo DY, Zhai BT, Liang YJ, Chen ZZ, et al.: Evaluation of the Clinical Efficacy of the Classic Prescription "Baihe Dihuang Decoction" Based on Meta-Analysis. *Evidence-based Complementary and Alternative Medicine: eCAM* 2022, 2022:8559176.
- [173] Tian JS, Meng Y, Wu YF, Zhao L, Xiang H, Jia JP, et al.: A Novel Insight into the Underlying Mechanism of Baihe Dihuang Tang Improving the State of Psychological Suboptimal Health Subjects Obtained from Plasma Metabolic Profiles and Network Analysis. *Journal*

- of *Pharmaceutical and Biomedical Analysis* 2019, 169:99–110.
- [174] Fei B, Dai W, Zhao S: Efficacy, Safety, and Cost of Therapy of the Traditional Chinese Medicine, Catalpol, in Patients Following Surgical Resection for Locally Advanced Colon Cancer. *Medical Science Monitor* 2018, 24:3184–3192.
- [175] Dong W, Xu J, Chen L: Separation and Identification of Catalpol from *Rehmannia* and its Acute Toxicity Test. *Journal of Fudan University (Natural Science)* 2009, 48:3.
- [176] Jiang T, Zhang A, Zhao R, Jiang B: Protective Effect of Catalpol in Mice Injuries Induced by Rotenone and Evaluation of the Safety of Catalpol. *Progress in Modern Biomedicine* 2008, 8:1039–1045.