JoP Journal of Pharmacopuncture
Journal of Pharmacopuncture 2024;27(2):70-81
pISSN: 2093-6966 • eISSN: 2234-6856
https://doi.org/10.3831/KPI.2024.27.2.70
Review Article
Check for updates

Preclinical Evidence and Underlying Mechanisms of *Polygonum multiflorum* and Its Chemical Constituents Against Cognitive Impairments and Alzheimer's Disease

Jihyun Cha[1], Ji Hwan Yun[1], Ji Hye Choi[1], Jae Ho Lee[2,3], Byung Tae Choi[1,2,3]*, Hwa Kyoung Shin[1,2,3]*

[1]Department of Korean Medicine, School of Korean Medicine, Pusan National University, Yangsan, Republic of Korea
[2]Department of Korean Medical Science, School of Korean Medicine, Pusan National University, Yangsan, Republic of Korea
[3]Graduate Training Program of Korean Medical Therapeutics for Healthy Aging, Pusan National University, Yangsan, Republic of Korea

Received February 15, 2024
Reviewed February 16, 2024
Accepted March 5, 2024

***Corresponding Author**
Hwa Kyoung Shin
Department of Korean Medicine, School of Korean Medicine, Pusan National University, Yangsan 50612, Republic of Korea
Tel: +82-51-510-8476
E-mail: julie@pusan.ac.kr

Byung Tae Choi
Department of Korean Medicine, School of Korean Medicine, Pusan National University, Yangsan 50612, Republic of Korea
Tel: +82-51-510-8475
E-mail: choibt@pusan.ac.kr

Objectives: Cognitive impairments, ranging from mild to severe, adversely affect daily functioning, quality of life, and work capacity. Despite significant efforts in the past decade, more than 200 promising drug candidates have failed in clinical trials. Herbal remedies are gaining interest as potential treatments for dementia due to their long history and safety, making them valuable for drug development. This review aimed to examine the mechanisms behind the effect of *Polygonum multiflorum* on cognitive function.
Methods: This study focused primarily on the effects of *Polygonum multiflorum* and its chemical constituents on cognitive behavioral outcomes including the Morris water maze, the passive avoidance test, and the Y maze, as well as pathogenic targets of cognitive impairment and Alzheimer's disease (AD) like amyloid deposition, amyloid precursor protein, tau hyperphosphorylation, and cognitive decline. Additionally, a thorough evaluation of the mechanisms behind *Polygonum multiflorum*'s impact on cognitive function was conducted. We reviewed the most recent data from preclinical research done on experimental models, particularly looking at *Polygonum multiflorum*'s effects on cognitive decline and AD.
Results: According to recent research, *Poligonum multiflorum* and its bioactive components, stilbene, and emodin, influence cognitive behavioral results and regulate the pathological target of cognitive impairment and AD. Their mechanisms of action include reducing oxidative and mitochondrial damage, regulating neuroinflammation, halting apoptosis, and promoting increased neurogenesis and synaptogenesis.
Conclusion: This review serves as a comprehensive compilation of current experiments on AD and other cognitive impairment models related to the therapeutic effects of *Polygonum multiflorum*. We believe that these findings can serve as a basis for future clinical trials and have potential applications in the treatment of human neurological disorders.

Keywords: Alzheimer's disease, cognitive function, emodin, stilbene, dementia, *Polygonum multiflorum*

INTRODUCTION

Dementia-related cognitive impairment can make performing daily tasks and participating in family and community activities difficult [1]. Cognitive impairment can range from mild to severe. A clinical diagnosis of dementia is marked by significant cognitive dysfunction that impairs social and daily functioning. Many cognitive domains, such as memory, language, problem-solving, and executive function, are affected by dementia. Alzheimer's disease (AD) is the most prevalent cause of dementia, affecting more than 10% of those aged ≥ 65 years. Among the several types of dementia, AD accounts for the majority of cases. In contrast, mild cognitive impairment (MCI) is a stage between dementia and normal aging. It is characterized by mild impairment in one or more cognitive domains that do not substantially affect daily independence. Epidemiological

studies have indicated that MCI is a high-risk illness with the potential to develop into AD, emphasizing the importance of early detection and intervention to maximize treatment benefits [2]. AD is one of the leading causes of death in old age. Recently, the diminished immune system and decreased physical activity in patients with terminal dementia have garnered considerable social attention [3].

To date, the most practical treatment method is to identify dementia early and initiate medication. In the past 10 years, more than 200 potential therapeutic ideas have failed in clinical trials despite tremendous efforts to address the complexity of the disease and its many causes. AD appears to include a range of disorders with comparable levels of amyloid precursor protein (APP) and tau abnormalities, caused by several factors [4]. This neuropathological heterogeneity in dementia may have important implications for future therapeutic approaches to this disease [5]. New approaches to treat dementia by addressing the complex neuropathological heterogeneity are necessary.

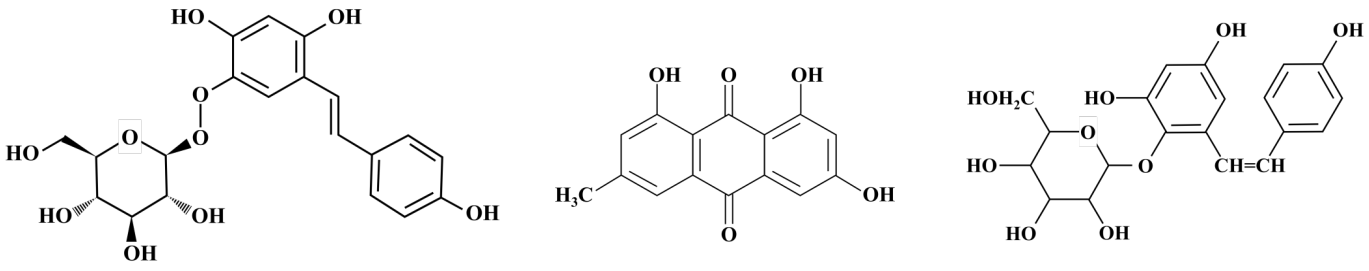
Traditional herbs and herbal medicines have been used for a long time and are recognized as safe and effective. However, herbs and herbal medicines do not have sufficient scientific research evidence to support their use [6]. However, complementary and alternative interventions are gaining increasing interest as valuable sources for developing drug candidates for dementia [7]. Heshouwu (何首乌), or *Polygonum multiflorum* Thunb., is a traditional Chinese herb of low toxicity that is renowned for its ability to blacken hair, tone the liver and kidneys, and prevent aging [8]. The therapeutic potential of *Polygonum multiflorum* extracts and its bioactive constituents in the treatment of neurological diseases has been the subject of numerous investigations [9, 10]. This study aimed to describe the preclinical evidence and the underlying molecular mechanisms of action of *Poligonum multiflorum*, especially its bioactive components, stilbene, and emodin, and their effectiveness in addressing cognitive impairment and preventing AD.

PATHOPHYSIOLOGY OF AD AND COGNITIVE IMPAIRMENT

Alzheimer's disease (AD) is a neurological illness that causes memory loss and progressive cognitive deterioration. Its pathogenesis entails the build-up of neurofibrillary tangles made up of hyperphosphorylated tau proteins and amyloid beta (Aβ) plaques, which cause cell death and neuronal dysfunction. Neuronal injury is made worse by neuroinflammation, which is typified by the activation of astrocytes and microglia. Cognitive decline is also associated with glutamatergic excitotoxicity and deficiencies in the cholinergic system. All these processes combine to cause synaptic dysfunction and neuronal loss, eventually leading to clinical symptoms, such as the cognitive abnormalities linked to AD [3, 4]. Consequently, medications that can regulate these pathophysiological processes hold great promise for treating AD.

Poligonum multiflorum Thunb AND ITS CHEMICAL CONSTITUENTS

Polygonum multiflorum Thunb. or Heshouwu, is a traditional Chinese herb that has been renowned for its potential health benefits, including anti-aging, neuroprotection, and hair growth-promoting effects [8]. The extract from *Polygonum multiflorum* contains various bioactive components including flavones, quinones, and stilbenes that contribute to its pharmacological properties. These bioactive components work synergistically to exert various pharmacological effects including antioxidant, anti-inflammatory, and neuroprotective activities [8]. Of the bioactive components, 2,3,5,4'-tetrahydroxystilbene-2-O-β-D-glucoside (TSG) and emodin (Fig. 1) may be potentially effective for treating AD and cognitive impairment.



2,3,5,4′-Tetrahydroxystilbene 2-O-β-D-glucoside | Emodin | Natural TSG

Figure 1. Chemical structures of stilbenes, emodin, and natural TSG. TSG, 2,3,5,4′-tetrahydroxystilbene-2-O-β-D-glucoside.

Table 1. Neuroprotective effects of *Poligonum multiflorum* extract and bioactive components in Alzheimer's disease and cognitive impairment models

Model	Intervention (drug, routine, dose, duration)	Outcomes behavioral test	Outcomes pathology	Reference
$A\beta_{1-42}$-injected SD rats	50 mg/kg/day TSG intragastric administration for 4 weeks	- Morris water maze: escape latency ↓, time spent in the target quadrant ↑, the number of crossing times ↑	Src and p-NR2B ↑	[11]
$A\beta_{1-42}$-induced mice	30, 60, and 120 mg/kg TSG ICV injection for 5 days	- Morris water maze: escape latency ↓, time staying in the target quadrant ↑, cross platform times ↑ - Passive avoidance: latency time to enter the dark compartment ↑	MDA and GSSG ↓	[12]
APP695V717I Tg mice	100 mg/kg/day TSG intragastric administration for 1 month	- Morris water maze: escape latency ↓, swimming distance ↓, time taken to cross the former platform location ↑ - Y-maze electric shock: the number of electric-stimulus escapes ↓	LC3-II and Beclin-1 ↓	[13]
PDAPPV717I Tg mice	120 and 240 μmol/kg/day TSG intragastric administration for 6 months	- Morris water maze: escape latency ↓, time spent in the target quadrant ↑ - Object recognition: discrimination index ↑	-	[14]
Aged SD rats (1-, 3-, 6-, 18- and 24-month-old)	30 and 60 mg/kg/day TSG intragastric administration for 3 months	- Morris water maze: escape latency ↓, swimming distance ↓ - Passageway water maze: error times ↓	Synapses and synaptic vesicles ↑ SYP ↑	[15]
Aged mice (4- and 20-month-old)	50, 100 and 200 mg/kg/day TSG intragastric administration for 3 months	- Step-through passive avoidance: latency ↑, error times ↓	Synaptophysin, p-synapsin I and PSD95 ↑, α-synuclein ↓	[16]
TBI mice	60 mg/kg/day TSG intragastric administration for 21 days	- Morris water maze: swimming distance to find the platform ↓, time staying in correct quadrant ↑	Brain lesion volume ↓ Neuronal apoptosis ↓, Immature neurons ↑	[17]
C57BL6J mice	20, 40 and 80 mg/kg/day TSG intragastric administration for 4 weeks	- Fear conditioning: contextual fear memory ↑ - Novel object recognition: preference for the novel object ↑	Hippocampal LTP ↑, dendrite spine density ↑ p-CREB and BDNF ↑, SIRT1 ↑ and miR-134 ↓	[18]
HCY-injected rats	0, 20, 40 and 80 mg/kg/day Emodin intragastric administration for 2 weeks	- Morris water maze: escape latency ↓, times crossing the platform ↑ - Novel object recognition: recognition index ↑	Aβ, BACE1 and tau phosphorylation ↓ Synaptophysin, synapsin1, neuron, p-CREB, GluR1, NR1, NR2B ↑ IL-6, TNF-α ↓	[19]
$A\beta_{25-35}$-induced mice	0.5 and 1% PWE oral administration for 4 weeks	- Morris water maze: escape latency ↓, error frequency ↓ - Passive avoidance: step-through latency ↑	TBARS level ↓, GPx activity ↑	[20]
SAMP8 mice (1-month-old)	PM extract (50% and 95% ethanol and water) oral administration for 18 weeks	- Shuttle avoidance: number of successful active avoidance ↑	Vacuole number, lipofuscin, and MDA concentration ↓	[9]
SAMP8 mice (1-and 7-month-old)	50% ethanol PM extract oral administration for 18 weeks	- Shuttle avoidance: number of successful active avoidance ↑	Spongy degeneration, lipofuscin, and MDA concentrations ↓	[10]

 https://doi.org/10.3831/KPI.2024.27.2.70

Table 1. Continued

Model	Intervention (drug, routine, dose, duration)	Outcomes behavioral test	Outcomes pathology	Reference
C57BL/6 mice	100 and 500 mg/kg/day PMC–12 oral administration for 2 weeks	- Morris water maze: latency time ↓	BDNF, p-CREB, and synaptophysin ↑	[21]
Focal cerebral ischemia	100 and 500 mg/kg/day PMC-12 oral administration for 3 weeks	- Morris water maze: escape latency time ↓	Neuronal apoptosis ↓, BDNF and p-CREB ↑	[22]
$A\beta_{25-35}$-induced mice	100 and 500 mg/kg/day PMC-12 oral administration for 3 weeks	- Morris water maze: escape latency time ↓, swimming distance in target quadrant ↓	Aβ, Iba-1, and GFAP ↓	[23]
APP/PS1 Tg mice	50 mg/kg/day TSG intragastric administration for 12 months		APP–KPI inclusion and Aβ plaque ↓	[24]
NaN_3-induced mitochondrial dysfunction rat	60 and 120 mg/kg/day TSG intragastric administration for 27 days		$A\beta_{1-42}$, APP, BACE1 and PS1 ↓ Mitochondrial COX ↑ NGF, BDNF ↑	[25]
$AlCl_3$-treated rat	4 g/kg TSG oral administration for 5 months	- Passive avoidance: step-through latency ↑	APP ↓	[26]
APP/PS1 Tg mice	60, 120 and 180 mg/kg TSG oral administration for 2 months, every other day		Cell survive ↑ Aβ plaque ↓ Ferroptosis ↓	[27]
APPV717I Tg mice	120 and 240 μmol/kg/day TSG intragastric administration for 6 months		α-Synuclein ↓	[28]
MPTP-induced PD mice	20 and 40 mg/kg/day TSG intragastric administration for 14 days		TH positive cells ↑ Dopamine, DOPAC, and HVA ↑	[29]

Aβ, amyloid β; SD, Sprague-Dawley; TSG, 2,3,5,4′-tetrahydroxystilbene-2-O-β-D-glucoside; NR2B, N-methyl D-aspartate receptor subtype 2B; ICV, intracerebroventricular; MDA, malondialdehyde; GSSG, oxidized glutathione; Tg, transgenic; LC3, microtubule-associated proteins 1A/1B light chain 3; SYP, synaptophysin; PSD95, postsynaptic density protein 95; CaMKII, calcium/calmodulin-dependent protein kinase II; TBI, traumatic brain injury; LTP, long-term potentiation; CREB, cAMP-response element-binding protein; BDNF, brain-derived neurotrophic factor; SIRT, sirtuin; miR, microRNA; HCY, Homocysteine; GluR1, glutamate receptor 1; NR, N-methyl-D-aspartate receptor; IL-6, Interleukin-6; TNF-α, Tumor necrosis factor alpha; PWE, *Polygonum multiflorum* Thunb. water extract; TBARS, thiobarbituric acid reactive substances; GPx, glutathione peroxidase; SAMP8, senescence-accelerated mice; PM, *Polygonum multiflorum* Thunb.; PMC-12, *Polygonum multiflorum* Thunberg complex composition-12; Iba-1, ionized calcium-binding adapter molecule-1; GFAP, glial fibrillary acidic protein; APP, amyloid precursor protein; PS1, presenilin-1; KPI, Kunitz protease inhibitor; NaN_3, sodium azide; BACE1, beta-site APP cleaving enzyme 1; COX, cytochrome c oxidase; NGF, nerve growth factor; $AlCl_3$, aluminum chloride; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetra-hydropypridine; PD, Parkinson's disease; TH, tyrosine hydroxylase; DOPAC, 3,4-dihydroxyphenylacetic acid; HVA, homovanillic acid.

THE NEUROPROTECTIVE EFFECTS OF *Poligonum multiflorum* EXTRACT AND THE BIOACTIVE COMPONENTS IN AD AND COGNITIVE IMPAIRMENT MODELS

Behavioral outcomes

TSG has demonstrated notable improvements in spatial learning and memory deficits in various experimental models (Table 1). In Aβ-injected rats, TSG reduced escape latency time and enhanced overall performance in the Morris water maze test [11]. Additionally, TSG increased swimming time in the target quadrant through the Morris water maze experiment, and the number of avoidances was increased in the passive avoidance experiment in $A\beta_{1-42}$-induced mice [12]. Studies on APP transgenic mice and aged rats/mice confirmed TSG's posi-

tive impact on learning and memory by demonstrating shortened escape latency and improved memory function in various tests [13-16]. Following TBI, TSG administration improved neurological outcomes and cognitive function, as evidenced by a reduced swimming distance in the Morris water maze task and improved spatial memory in the probe test [17]. Additionally, TSG-treated mice exhibited significantly improved contextual fear memory and a stronger preference for the novel object during the test phase than non-treated normal mice [18].

In another study that focused on the effect of emodin on homocysteine-induced dementia, emodin-treated rats showed increased interest in a novel object and improved cognitive deficits in the Morris water maze test [19].

Polygonum multiflorum Thunb. water extract (PWE) has also been shown to significantly improve cognitive deficits in A_{25-35}-injected mice, as observed in the Morris water maze and passive avoidance tests [20]. Furthermore, *Polygonum multiflorum* Thunb. extracts enhance active shuttle avoidance responses in mice, indicating improved learning and memory [9, 10]. Furthermore, the use of *Polygonum multiflorum* Thunb. complex composition-12 (PMC-12) in normal mice led to enhanced spatial learning and memory abilities, and when used in Aβ-injected mice, restored damaged functions, in a focal cerebral ischemia mice model that involved the Morris water maze test [21-23].

Pathological outcomes

TSG offers potential benefits for treating AD by reducing amyloid plaques in APP/PS1 transgenic (Tg) mice [24], decreasing $Aβ_{1-42}$ content in NaN_3-infused rat brains [25], and suppressing APP overexpression induced by chronic aluminum exposure in rats [26]. It has also been shown to be effective in addressing ferroptosis, oxidative stress, and Aβ production in APP/PS1 mice [27]. In aged animals, TSG showed promising effects by reversing synaptic deficits, inhibiting α-synuclein overexpression, and improving memory and movement functions. The effects were associated with TSG's time-dependent suppression of APP overexpression [15, 16]. Furthermore, TSG has the potential to prevent and/or treat AD by preventing α-synuclein overexpression and aggregation in APPV717I Tg AD mice [28]. Its protective effects extend to synaptic ultrastructure, synapse-related protein levels, and inhibition of α-synuclein overexpression in aged mice. These findings suggest that TSG may be potentially effective in treating various aging-related neurodegenerative diseases [16]. In PD, TSG protected dopaminergic neurons and partially restored dopamine levels in a dose-dependent manner [29].

Emodin demonstrated neuroprotective effects, counteracting AD-like features, including Aβ overproduction, tau hyperphosphorylation, neuron loss, synaptic damage, cerebral microvascular damage, inflammation, and oxidative stress in a rat model. These observations suggest that emodin may be effective in addressing hyperhomocysteinemia-induced cognitive deficits [19].

NEUROPROTECTIVE MECHANISMS OF *Poligonum multiflorum* EXTRACTS AND ITS BIOACTIVE COMPONENTS IN AD AND COGNITIVE IMPAIRMENT MODELS

Ameliorating mitochondrial and oxidative damage

As mentioned, TSG has neuroprotective effects (Table 2). Specifically, TSG suppresses MPTP-induced p38 and caspase-3, -6, and -9, suggesting that it regulates the ROS-mediated JNK, P38, and mitochondrial pathways [29]. Furthermore, TSG attenuates 1-methyl-4-phenyl pyridium (MPP^+)-induced apoptosis in PC12 cells by suppressing reactive oxygen species (ROS) generation and modulating c-Jun N-terminal kinase (JNK) activation [30]. In the broader context of oxidative stress, TSG slows intracellular ROS and nitric oxide (NO) accumulation, and simultaneously reduces protein-bound 3-nitrotyrosine levels [31]. Furthermore, TSG concentration-dependently increased Nrf2 and HO-1 expression, while decreasing Keap1 protein expression in $Aβ_{1-42}$-treated mice involved in the Keap1/Nrf2 antioxidant pathway [12]. TSG has also shown its ability to protect against cerebral ischemia/reperfusion injury through the JNK, SIRT1, and NF-κB pathways, inhibiting intracellular ROS/reactive nitrogen species and reducing brain infarct volume in the oxygen-glucose deprivation followed by reperfusion (OGD-R) and MCAO model [32]. These results highlight the protective effects of TSG against oxidative stress-induced neurodegenerative disorders.

In addition to its neuroprotective properties, the ethyl acetate extract of *Polygonum multiflorum* (EEPM) alleviates extracellular regulated kinase (ERK) and p38 activation while increasing cAMP-responsive element-binding protein (CREB) activation under glutamate-induced oxidative toxicity in HT22 hippocampal cells [33]. PWE demonstrated antioxidant prop-

 https://doi.org/10.3831/KPI.2024.27.2.70

Table 2. Therapeutic potential of *Poligonum multiflorum* in Alzheimer's disease and cognitive impairment models

Effect	Species	Experimental model	Intervention	Mechanisms	Experiment result	Reference
Ameliorating mitochondrial and oxidative damage	Mouse	MPTP-induced PD	TSG	ROS ↓ and JNK and p38 activation ↓ Bax/Bcl-2 ration ↓ Cytochrome c, smac and cleaved caspase-3, -6, and -9 ↓	Neuroprotection Controlling ROS-mediated JNK, P38 and mitochondrial function	[29]
	PC12 cell	MPP+-induced apoptosis	TSG	ROS ↓ and JNK activation ↓	Apoptotic cell death ↓ Oxidative damage ↓	[30]
	PC12 cell	6-OHDA-induced apoptosis	TSG	ROS and NO ↓ Protein-bound 3-nitrotyrosine ↓	Apoptotic cell death ↓ Oxidative stress ↓	[31]
	Mouse	$A\beta_{1-42}$-treated AD	TSG	MDA and GSSG ↓ GSH, CAT and SOD ↑ Nrf2 & HO-1↑ and Keap1 ↓	Keap1/Nrf2 antioxidant pathway	[12]
	SD rat	OGD-R-induced neuronal injury and MCAO	TSG	ROS and MMP dissipation ↓ JNK and Bcl-2 family-related apoptotic signaling pathway ↓ SIRT1 activation ↑ NF-κB activation and iNOS ↓	Ischemic/reperfusion injury ↓ Brain infarct volume ↓	[32]
	HT22 cell	Glutamate-induced oxidative toxicity	EEPM	p-ERK, p-JNK, p-p38↓ p-CREB↑	Neuroprotection Antioxidant activity ↑	[33]
	Mice	$A\beta_{25-35}$-treated AD	PWE	TBARS level ↓ GPx activity ↑	Cognitive deficit ↓ Antioxidant effect ↑	[20]
	Mice	SAMP8 mice	PM	Vacuole number, lipofuscin, and MDA concentration ↓	Brain pathological change ↓ Learning and memory ↑	[9]
	Mice	SAMP8 mice	PM	Spongy degeneration, lipofuscin, and MDA concentrations ↓	Brain pathological change ↓ Learning and memory ↑	[10]
	HT22 cell	Glutamate-induced apoptosis	PMC-12	ROS ↓ p38 MAPK and PI3K signal ↓ BDNF/p-CREB ↑	- Neuroprotection ↑ - Spatial memory ability ↑	[22]
Neuroinflammation modulation	Rat	NaN_3-induced mitochondrial dysfunction	TSG	$A\beta_{1-42}$, APP, BACE1 and PS1 ↓ Mitochondrial COX ↑ NGF, BDNF, TrkB ↑	- Neuroinflammation ↓ - Mitochondrial function ↑	[25]
	Mouse	APP695V717I Tg	TSG	LC3-II and Beclin-1 ↓	- Autophagy pathway ↓	[13]
	Mouse	APP/PS1 Tg	TSG	GSH/GPX4/ROS and Keap1/Nrf2/ARE signal ↑ Lipid peroxidation and NLRP 3 ↓	- Cell survival ↑ - Ferroptosis ↓ - Oxidative stress ↓ - Neuroinflammation ↓	[27]

https://doi.org/10.3831/KPI.2024.27.2.70

Table 2. Continued

Effect	Species	Experimental model	Intervention	Mechanisms	Experiment result	Reference
	BV2 cell	LPS/ATP and $A\beta_{25-35}$-induced inflammation	TSG	NLRP3 inflammasome ↓ AMPK/PINK1/Parkin-dependent mitophagy ↑	- Mitophagy ↑ - Neuroinflammation ↓	[34]
	N9 and BV2 cell	Aβ-induced inflammation	TSG	iNOS, NO, COX-2, PGE2 ↓ IL-1β, IL-6, and TNFα ↓ IL-10, BDNF, GDNF, arginase-1 ↑	- Microglial activation ↓ - Polarizing microglia toward M2 phenotype ↑	[35]
	BV2 cell	LPS-induced inflammation	TSG	TNFα, IL-1β, NO ↓ NADPH oxidase, ROS ↓ NF-κB signaling pathway ↓	- Microglial activation ↓ - Neuroinflammation ↓	[36]
	Mouse primary microglia	LPS-induced inflammation	Emodin	- p-LKB1, p-CaMKII, p-AMPK ↑ HO-1, NQO1 ↑ NO, PGE2, iNOS, COX-2 ↓ TNF-α, IL-6, p-IκBα ↓ p-STAT, p-JNK, p-p38 MAPK ↓	- Regulation of AMPK/Nrf2 signaling - Neuroinflammation ↓	[37]
	Mouse primary microglia	LPS-induced inflammation	CRPE56IGIH	PGE2 and NO ↓ NF-κB activation ↓ MAPK and JAK-STAT signaling ↓ HO-1 and NQO-1 ↑	- Phase II antioxidant enzyme ↑ - Neuroinflammation ↓	[38]
	Mouse primary microglia	LPS-induced inflammation	CRPE55IB	PGE2 and NO ↓ TNF-α and IL-6 ↓ MAPK and JAK-STAT signaling ↓ Nrf2/ARE activation ↑ HO-1 and NQO1 ↑	- Regulation of AMPK/Nrf2 signaling - Neuroinflammation ↓	[39]
Anti-apoptosis	HT22 cell	Glutamate-induced oxidative toxicity	TSG	ROS and HO-1 ↓, active form of caspase-3 and calpain-1 proteases ↓ VDAC-1 ↓, Bax ↓, Bcl-2 ↑ MMP stabilization ↑	Cell viability ↑ Apoptotic cell death ↓	[40]
	SH-SY5Y cell	MPP+-induced cytotoxicity	TSG	ROS ↓, MMP disruption ↓ Bax/Bcl-2 ratio and caspase-3 activity ↓	Mitochondrial function ↑ Oxidative stress ↓ Apoptosis ↓	[41]
	PC12 cell	MPP+-induced apoptosis	TSG	ROS ↓ and JNK activation ↓	Apoptotic cell death ↓ Oxidative stress ↓	[30]
	PC12 cell	MPP+-induced apoptosis	TSG	LDH release ↓ PI3K/Akt signaling pathway ↑	Neuroprotection Apoptosis ↓	[42]
	HT22 cell Mouse	Glutamate-induced oxidative stress MCAO	PWE	ROS ↓ P-CREB and BDNF ↑	Neuroprotection	[43]

Table 2. Continued

Effect	Species	Experimental model	Intervention	Mechanisms	Experiment result	Reference
	Rat primary hippocampal neuron	STS-induced cytotoxicity	TSG	BDNF ↑ TrkB/Akt signaling ↑ Bcl-2 ↑ and cleaved-Caspase-3 ↓	Regulation of BDNF/TrkB/Akt signaling Neuroprotection	[44]
Neurogenesis & synaptogenesis	Rat	Aged SD rats	TSG	Synapses & synaptic vesicles ↑ SYP ↑	Hippocampal synapse ↑ Learning and memory ability ↑	[15]
	Mouse	C57BL6J	TSG	- Hippocampal LTP ↑, dendrite spine density ↑ SIRT1 ↑ and miR-134 ↓ ERK1/2/CaMKII/CREB phosphorylation ↑ BDNF ↑	Hippocampal synaptic plasticity ↑ Memory ability ↑	[18]
	Mouse	C57BL/6	PMC-12	BDNF and p-CREB ↑ Synaptophysin ↑	- Hippocampal neurogenesis ↑ - Learning memory ↑	[21]
	Mouse	TBI-induced C57BL/6	TSG	DNA fragmentation ↓ Immature neuron ↑	- Glial and neuronal cell death ↓ - Neurogenesis ↑ - Motor and cognitive function ↑	[17]
	PC12 cell Rat primary hippocampal neuron		TSG	Cell differentiation ↑ Intracellular calcium level ↑ p-ERK1/2 and pCaMKII ↑ HFS-induced LTP ↑	Hippocampal synaptic plasticity ↑	[45]

MPTP, 1-methyl-4-phenyl-1,2,3,6-tetra-hydropypridine; PD, Parkinson's disease; TSG, 2,3,5,4′-tetrahydroxystilbene-2-O-β-D-glucoside; ROS, reactive oxygen species; JNK, c-Jun N-terminal kinase; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; PC12, pheochromocytoma 12; MPP+, 1-methyl-4-phenylpyridinium; 6-OHDA, 6-hydroxydopamine; NO, nitric oxide; Aβ, amyloid β; MDA, malondialdehyde; GSSG, oxidized glutathione; GSH, glutathione; CAT, catalase; SOD, superoxide dismutase; Nrf2, nuclear factor erythroid 2-related factor 2; HO-1, heme oxygenase; Keap1, Kelch-like ECH-associated protein 1; SD, Sprague-Dawley; OGD/R, oxygen-glucose deprivation/reperfusion; MCAO, middle cerebral artery occlusion; MMP, mitochondrial membrane potential; SIRT1, sirtuin 1; NF-κB, nuclear factor-kappa B; iNOS, inducible nitric oxide synthase; EEPM, Ethyl acetate extract from *Polygonum multiflorum*; ERK, extracellular regulated kinase; CREB, cAMP-response element-binding protein; PWE, *Polygonum multiflorum* Thunb. water extract; TBARS, thiobarbituric acid reactive substances; GPx, glutathione peroxidase; SAMP8, senescence-accelerated mice; PM, *Polygonum multiflorum* Thunb.; MAPK, mitogen activated protein kinase; PI3K, phosphoinositide 3-kinase; BDNF, brain-derived neurotrophic factor; NaN_3, sodium azide; APP, amyloid precursor protein; BACE1, beta-site APP cleaving enzyme 1; PS1, presenilin-1; COX, cytochrome c oxidase; NGF, nerve growth factor; TrkB, Tropomyosin receptor kinase B; Tg, transgenic; LC3-II, microtubule-associated protein 1 light chain 3; GPX, glutathione peroxidase; LPS, lipopolysaccharide; ATP, adenosine triphosphate; AMPK, adenosine monophosphate-activated protein kinase; PINK1, PTEN-induced putative kinase 1; PGE2, prostaglandin E2; IL, interleukin; TNF-α, tumor necrosis factor alpha; GDNF, glial cell-derived neurotrophic factor; LKB1, liver kinase B1; CaMKII, Ca2+/calmodulin-dependent protein kinase II; NQO1, NADPH dehydrogenase quinone-1; IκBα, NF-κB inhibitor α; STAT, signal transducer and activator of transcription protein; VDAC, voltage-dependent anion channel; LDH, lactate dehydrogenase; PWE, *Polygonum multiflorum* Thunb water extract; STS, staurosporine; SYP, synaptophysin; LTP, long-term potentiation; miR, microRNA; HFS, high frequency stimulation.

erties in AD, potentially limiting Aβ accumulation by reducing acetylcholinesterase activity and increasing glutathione peroxidase activity [20]. Furthermore, *Polygonum multiflorum* extracts have been shown to improve cognitive performance by lowering lipofuscin and lipid peroxidation in SAMP8 and $A\beta_{25-35}$-induced cognitive deficit mice, suggesting potential antioxidant properties [9, 10, 20].

Modulation of neuroinflammation

TSG increased mitochondrial cyclooxygenase-2 (COX-2) activity and neurotrophic factors, and reduced Aβ content, suggesting a multimodal therapeutic strategy in a rat model of mitochondrial dysfunction induced by NaN_3 infusion [25]. Moreover, TSG reduced the damage to the endoplasmic reticulum caused by Aβ neurotoxicity in Tg animals by stimulating the hippocampus to generate autophagy-related proteins [13]. Furthermore, TSG delivery in APP/PS1 Tg mice decreased indicators associated with ferroptosis, such as elevated lipid peroxidation and increased neuroinflammation, including NLRP3 [27]. By inhibiting LPS/ATP and Aβ-induced inflammation in microglia and neurons, TSG demonstrated anti-inflammatory properties [34]. In Aβ-induced microglia, TSG suppresses β-amyloid-induced activation, thereby, inhibiting NO and prostaglandin E2 (PGE2), while promoting anti-inflammatory factors, such as IL-10, BDNF, GDNF, and Arg-1. TSG also attenuates PU.1 protein expression, polarizes microglia toward the M2 phenotype, and regulates PU.1 signaling [35]. Furthermore, TSG reduces LPS-induced proinflammatory factors including TNF-α, IL-1β, and NO, NADPH oxidase activation, ROS production, and NF-κB signaling, thus, mediating neuroinflammation by inhibiting microglial activation [36].

Emodin induces HO-1 and NQO1 via AMPK/Nrf2, thus, decreasing LPS-induced proinflammatory factors in microglia [37]. Additionally, CRPE56IGIH, a novel compound of *Polygonum multiflorum*, inhibits neuroinflammation by regulating NF-κB/MAPK, JAK-STATs activation and upregulating the AMPK/Nrf2 pathways in LPS-stimulated microglia [38, 39].

Anti-apoptosis

TSG inhibits ROS production, oxygenase-1 expression, caspase-3 activation, and calpain-1 proteases in HT22 cells exposed to glutamate. TSG also prevents glutamate-induced disruption of mitochondrial membrane potential (MMP) and voltage-dependent anion channel-1 [40]. Moreover, in SH-SY5Y cells, TSG reduces the Bax to Bcl-2 ratio, indicating mitochondrial dysfunction-induced apoptosis, while inhibiting intracellular ROS elevation, MMP disruption, and caspase-3 activation induced by MPP+ [41]. Furthermore, TSG reduces MPP+-induced damage in PC12 cells by inhibiting ROS generation, modulating JNK activation, and regulating the PI3K/Akt signaling pathway, resulting in decreased cell viability and apoptosis [30, 42]. TSG after TBI exerts neuroprotective effects by reducing the volume of brain lesions, enhancing neuronal death, and increasing the number of immature neurons in the hippocampus [17]. In HT22 cells and the hippocampus of the MCAO mouse model, PWE suppressed ROS generation and cellular Ca^{2+} levels. These findings indicate potential benefits on hippocampal neurons and contribution to reducing apoptotic cell death [43]. In particular, neurons pretreated with PWE demonstrate resistance to staurosporine-induced toxicity, preserving BDNF and TrkB/Akt signaling, and restoring the expression of Bcl-2 and caspase-3 [44].

Neurogenesis and synaptogenesis

TSG enhanced the expression of the synaptic vesicle membrane protein SYP in the hippocampus of aged rats, indicating a protective effect on neural synaptic structures [15]. Furthermore, in normal mice, TSG enhances memory by upregulating SIRT1, downregulating miR-134, and promoting the phosphorylation of ERK1/2, CaMKII, CREB, and BDNF expression in the hippocampus [18]. The neuroprotective and neurogenic effects of TSG in TBI occur as a result of reducing glutamate-induced excitotoxicity, lowering TUNEL+/NeuN+ cells, and increasing the number of DCX-positive neuronal precursor cells [17]. Moreover, TSG promotes the differentiation of PC12 cells, elevates intracellular Ca2+ levels in hippocampal neurons, and enhances hippocampal long-term potentiation (LTP) and dendritic spine density [18, 45]. In another context, PMC-12 enhanced hippocampal neurogenesis and cognitive function in focal cerebral ischemia and normal mice [21, 22]. The results correlated with increased levels of BDNF, p-CREB, and synaptophysin associated with neural plasticity, suggesting a regulatory process through mature BDNF expression and CREB phosphorylation.

 https://doi.org/10.3831/KPI.2024.27.2.70

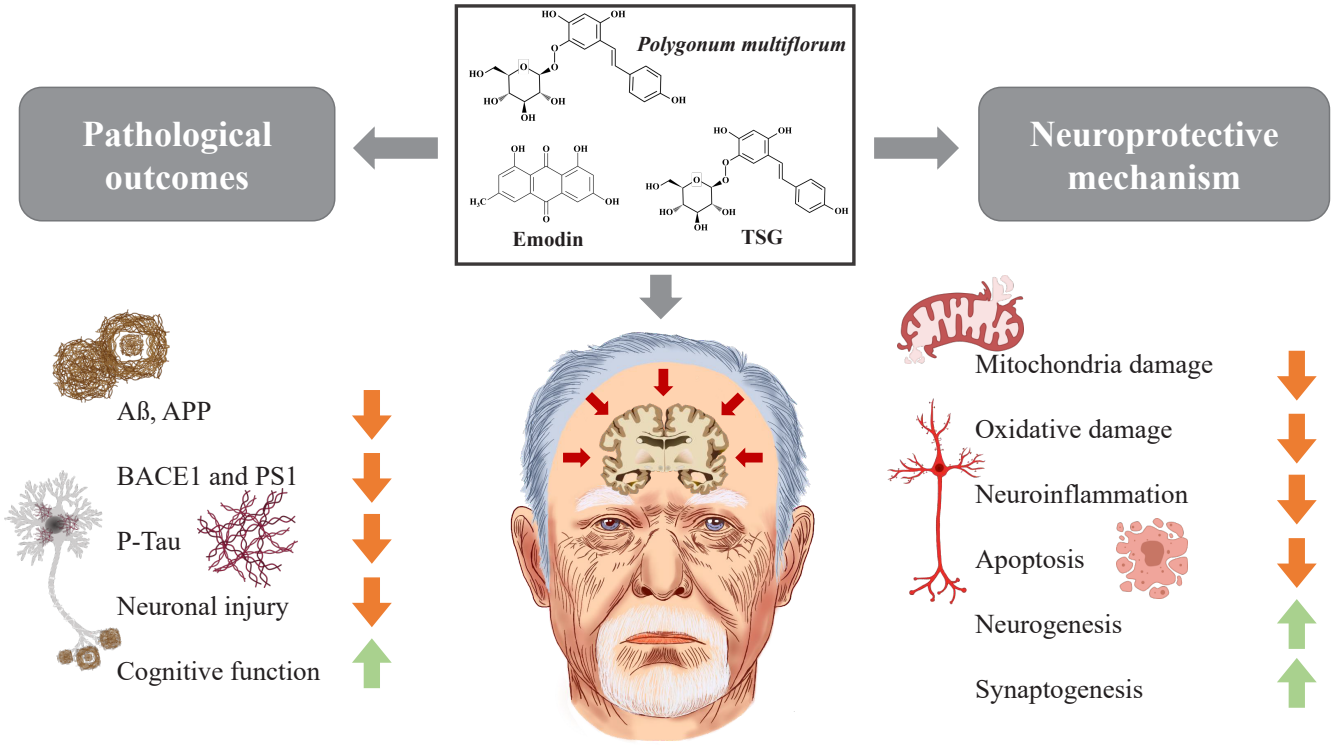


Figure 2. Diagrammatic effects of *Poligonum multiflorum* Thunb. and its bioactive components on therapeutic target for Alzheimer's disease and cognitive impairment. TSG, 2,3,5,4′-tetrahydroxystilbene-2-O-β-D-glucoside; Aβ, amyloid β; APP, amyloid precursor protein; BACE1, beta-site APP cleaving enzyme 1; PS1, presenilin-1; P-Tau, phosphor-tau; AD, Alzheimer's disease.

CONCLUSION

Polygonum multiflorum and its bioactive components, TSG, and emodin, have shown promising neuroprotective effects in various preclinical models of cognitive impairment and AD. The multifaceted mechanisms involve the mitigation of oxidative damage, modulation of neuroinflammation, prevention of apoptosis, and the promotion of neurogenesis and synaptogenesis. These findings indicate the potential of using *Polygonum multiflorum* for the development of dementia treatment. More research is needed to elucidate the underlying molecular mechanisms and translate the available preclinical findings into effective treatment for cognitive impairment and AD in humans (Fig. 2).

CONFLICTS OF INTEREST

Hwa Kyoung Shin has been an editorial board member of Journal of Pharmacopuncture since 2022 but has no role in the decision to publish this article. No other potential conflicts of interest relevant to this aricle were reported.

FUNDING

This work was supported by a 2-Year Research Grant of Pusan National University.

ORCID

Jihyun Cha, https://orcid.org/0009-0003-2578-3590
Ji Hwan Yun, https://orcid.org/0009-0000-4084-7327
Ji Hye Choi, https://orcid.org/0009-0000-8971-0831
Jae Ho Lee, https://orcid.org/0009-0003-8543-5774
Byung Tae Choi, https://orcid.org/0000-0002-5965-4346
Hwa Kyoung Shin, https://orcid.org/0000-0002-8061-6782

REFERENCES

1. Poulos CJ, Bayer A, Beaupre L, Clare L, Poulos RG, Wang RH, et al. A comprehensive approach to reablement in dementia. Al-

zheimers Dement (N Y). 2017;3(3):450-8.
2. Hugo J, Ganguli M. Dementia and cognitive impairment: epidemiology, diagnosis, and treatment. Clin Geriatr Med. 2014; 30(3):421-42.
3. Gonzales MM, Garbarino VR, Pollet E, Palavicini JP, Kellogg DL Jr, Kraig E, et al. Biological aging processes underlying cognitive decline and neurodegenerative disease. J Clin Invest. 2022; 132(10):e158453.
4. Serý O, Povová J, Míšek I, Pešák L, Janout V. Molecular mechanisms of neuropathological changes in Alzheimer's disease: a review. Folia Neuropathol. 2013;51(1):1-9.
5. Bondi MW, Edmonds EC, Salmon DP. Alzheimer's disease: past, present, and future. J Int Neuropsychol Soc. 2017;23(9-10):818-31.
6. Rao RV, Descamps O, John V, Bredesen DE. Ayurvedic medicinal plants for Alzheimer's disease: a review. Alzheimers Res Ther. 2012;4(3):22.
7. Gregory J, Vengalasetti YV, Bredesen DE, Rao RV. Neuroprotective herbs for the management of Alzheimer's disease. Biomolecules. 2021;11(4):543.
8. Lin L, Ni B, Lin H, Zhang M, Li X, Yin X, et al. Traditional usages, botany, phytochemistry, pharmacology and toxicology of Polygonum multiflorum Thunb.: a review. J Ethnopharmacol. 2015;159:158-83.
9. Chan YC, Cheng FC, Wang MF. Beneficial effects of different Polygonum multiflorum Thunb. extracts on memory and hippocampus morphology. J Nutr Sci Vitaminol (Tokyo). 2002;48(6): 491-7.
10. Chan YC, Wang MF, Chang HC. Polygonum multiflorum extracts improve cognitive performance in senescence accelerated mice. Am J Chin Med. 2003;31(2):171-9.
11. Zhou L, Hou Y, Yang Q, Du X, Li M, Yuan M, et al. Tetrahydroxystilbene glucoside improves the learning and memory of amyloid-$\beta_{(1-42)}$-injected rats and may be connected to synaptic changes in the hippocampus. Can J Physiol Pharmacol. 2012; 90(11):1446-55.
12. Xie M, Zhang G, Yin W, Hei XX, Liu T. Cognitive enhancing and antioxidant effects of tetrahydroxystilbene glucoside in Aβ1-42-induced neurodegeneration in mice. J Integr Neurosci. 2018;17(3-4):355-65.
13. Luo H, Li Y, Guo J, Liu Z, Zhang Z, Wang Y, et al. Tetrahydroxy stilbene glucoside improved the behavioral disorders of APP695V717I transgenic mice by inhibiting the expression of Beclin-1 and LC3-II. J Tradit Chin Med. 2015;35(3):295-300.
14. Zhang L, Xing Y, Ye CF, Ai HX, Wei HF, Li L. Learning-memory deficit with aging in APP transgenic mice of Alzheimer's disease and intervention by using tetrahydroxystilbene glucoside. Behav Brain Res. 2006;173(2):246-54.
15. Wang R, Tang Y, Feng B, Ye C, Fang L, Zhang L, et al. Changes in hippocampal synapses and learning-memory abilities in age-increasing rats and effects of tetrahydroxystilbene glucoside in aged rats. Neuroscience. 2007;149(4):739-46.
16. Shen C, Sun FL, Zhang RY, Zhang L, Li YL, Zhang L, et al. Tetrahydroxystilbene glucoside ameliorates memory and movement functions, protects synapses and inhibits α-synuclein aggregation in hippocampus and striatum in aged mice. Restor Neurol Neurosci. 2015;33(4):531-41.
17. Chen YH, Chen YC, Chin YT, Wang CC, Hwang LL, Yang LY, et al. 2, 3, 5, 4'-tetrahydroxystilbene-2-O-beta-D-glucoside protects against neuronal cell death and traumatic brain injury-induced pathophysiology. Aging (Albany NY). 2022;14(6):2607-27.
18. Chen T, Yang YJ, Li YK, Liu J, Wu PF, Wang F, et al. Chronic administration tetrahydroxystilbene glucoside promotes hippocampal memory and synaptic plasticity and activates ERKs, CaMKII and SIRT1/miR-134 in vivo. J Ethnopharmacol. 2016; 190:74-82.
19. Zeng P, Shi Y, Wang XM, Lin L, Du YJ, Tang N, et al. Emodin rescued hyperhomocysteinemia-induced dementia and Alzheimer's disease-like features in rats. Int J Neuropsychopharmacol. 2019;22(1):57-70.
20. Um MY, Choi WH, Aan JY, Kim SR, Ha TY. Protective effect of Polygonum multiflorum Thunb on amyloid beta-peptide 25-35 induced cognitive deficits in mice. J Ethnopharmacol. 2006; 104(1-2):144-8.
21. Park HR, Kim JY, Lee Y, Chun HJ, Choi YW, Shin HK, et al. PMC-12, a traditional herbal medicine, enhances learning memory and hippocampal neurogenesis in mice. Neurosci Lett. 2016;617:254-63.
22. Ahn SM, Kim YR, Kim HN, Choi YW, Lee JW, Kim CM, et al. Neuroprotection and spatial memory enhancement of four herbal mixture extract in HT22 hippocampal cells and a mouse model of focal cerebral ischemia. BMC Complement Altern Med. 2015;15:202.
23. Park MY, Jung YS, Park JH, Choi YW, Lee J, Kim CM, et al. PMC-12, a prescription of traditional Korean medicine, improves amyloid β-induced cognitive deficits through modulation of neuroinflammation. Evid Based Complement Alternat Med. 2015;2015:768049.
24. Yin X, Chen C, Xu T, Li L, Zhang L. Tetrahydroxystilbene glucoside modulates amyloid precursor protein processing via activation of AKT-GSK3β pathway in cells and in APP/PS1 transgenic mice. Biochem Biophys Res Commun. 2018;495(1):672-8.
25. Zhang RY, Zhang L, Zhang L, Wang YL, Li L. Anti-amyloidgenic and neurotrophic effects of tetrahydroxystilbene glucoside on a chronic mitochondrial dysfunction rat model induced by so-

dium azide. J Nat Med. 2018;72(3):596-606.
26. Luo HB, Yang JS, Shi XQ, Fu XF, Yang QD. Tetrahydroxy stilbene glucoside reduces the cognitive impairment and overexpression of amyloid precursor protein induced by aluminum exposure. Neurosci Bull. 2009;25(6):391-6.
27. Gao Y, Li J, Wu Q, Wang S, Yang S, Li X, et al. Tetrahydroxy stilbene glycoside ameliorates Alzheimer's disease in APP/PS1 mice via glutathione peroxidase related ferroptosis. Int Immunopharmacol. 2021;99:108002.
28. Zhang L, Yu S, Zhang R, Xing Y, Li Y, Li L. Tetrahydroxystilbene glucoside antagonizes age-related α-synuclein overexpression in the hippocampus of APP transgenic mouse model of Alzheimer's disease. Restor Neurol Neurosci. 2013;31(1):41-52.
29. He H, Wang S, Tian J, Chen L, Zhang W, Zhao J, et al. Protective effects of 2,3,5,4'-tetrahydroxystilbene-2-O-β-D-glucoside in the MPTP-induced mouse model of Parkinson's disease: involvement of reactive oxygen species-mediated JNK, P38 and mitochondrial pathways. Eur J Pharmacol. 2015;767:175-82.
30. Li X, Li Y, Chen J, Sun J, Li X, Sun X, et al. Tetrahydroxystilbene glucoside attenuates MPP+-induced apoptosis in PC12 cells by inhibiting ROS generation and modulating JNK activation. Neurosci Lett. 2010;483(1):1-5.
31. Tao L, Li X, Zhang L, Tian J, Li X, Sun X, et al. Protective effect of tetrahydroxystilbene glucoside on 6-OHDA-induced apoptosis in PC12 cells through the ROS-NO pathway. PLoS One. 2011;6(10):e26055.
32. Wang T, Gu J, Wu PF, Wang F, Xiong Z, Yang YJ, et al. Protection by tetrahydroxystilbene glucoside against cerebral ischemia: involvement of JNK, SIRT1, and NF-kappaB pathways and inhibition of intracellular ROS/RNS generation. Free Radic Biol Med. 2009;47(3):229-40.
33. Kim HN, Kim YR, Jang JY, Choi YW, Baek JU, Hong JW, et al. Neuroprotective effects of Polygonum multiflorum extract against glutamate-induced oxidative toxicity in HT22 hippocampal cells. J Ethnopharmacol. 2013;150(1):108-15.
34. Gao Y, Li J, Li J, Hu C, Zhang L, Yan J, et al. Tetrahydroxy stilbene glycoside alleviated inflammatory damage by mitophagy via AMPK related PINK1/Parkin signaling pathway. Biochem Pharmacol. 2020;177:113997.
35. Jiao C, Gao F, Ou L, Yu J, Li M, Wei P, et al. Tetrahydroxystilbene glycoside antagonizes β-amyloid-induced inflammatory injury in microglia cells by regulating PU.1 expression. Neuroreport. 2018;29(10):787-93.
36. Zhang F, Wang YY, Yang J, Lu YF, Liu J, Shi JS. Tetrahydroxystilbene glucoside attenuates neuroinflammation through the inhibition of microglia activation. Oxid Med Cell Longev. 2013;2013:680545.
37. Park SY, Jin ML, Ko MJ, Park G, Choi YW. Anti-neuroinflammatory effect of emodin in LPS-stimulated microglia: involvement of AMPK/Nrf2 activation. Neurochem Res. 2016;41(11):2981-92.
38. Park SY, Jin ML, Kang NJ, Park G, Choi YW. Anti-inflammatory effects of novel polygonum multiflorum compound via inhibiting NF-κB/MAPK and upregulating the Nrf2 pathways in LPS-stimulated microglia. Neurosci Lett. 2017;651:43-51.
39. Park SY, Jin ML, Chae SY, Ko MJ, Choi YH, Park G, et al. Novel compound from Polygonum multiflorum inhibits inflammatory response in LPS-stimulated microglia by upregulating AMPK/Nrf2 pathways. Neurochem Int. 2016;100:21-9.
40. Lee SY, Ahn SM, Wang Z, Choi YW, Shin HK, Choi BT. Neuroprotective effects of 2,3,5,4'-tetrahydoxystilbene-2-O-β-D-glucoside from Polygonum multiflorum against glutamate-induced oxidative toxicity in HT22 cells. J Ethnopharmacol. 2017;195:64-70.
41. Sun FL, Zhang L, Zhang RY, Li L. Tetrahydroxystilbene glucoside protects human neuroblastoma SH-SY5Y cells against MPP+-induced cytotoxicity. Eur J Pharmacol. 2011;660(2-3):283-90.
42. Qin R, Li X, Li G, Tao L, Li Y, Sun J, et al. Protection by tetrahydroxystilbene glucoside against neurotoxicity induced by MPP+: the involvement of PI3K/Akt pathway activation. Toxicol Lett. 2011;202(1):1-7.
43. Ahn SM, Kim YR, Kim HN, Shin HK, Choi BT. Beneficial effects of Polygonum multiflorum on hippocampal neuronal cells and mouse focal cerebral ischemia. Am J Chin Med. 2015;43(4):637-51.
44. Ren TT, Fan SR, Lang XY, Yu Y, Lan R, Qin XY. 2,3,5,4'-tetrahydoxystilbene-2-O-β-D-glucoside eliminates staurosporine-induced cytotoxicity by restoring BDNF-TrkB/Akt signaling axis. Int J Med Sci. 2020;17(14):2207-13.
45. Wang T, Yang YJ, Wu PF, Wang W, Hu ZL, Long LH, et al. Tetrahydroxystilbene glucoside, a plant-derived cognitive enhancer, promotes hippocampal synaptic plasticity. Eur J Pharmacol. 2011;650(1):206-14.