Review Article

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Therapeutic Potential of Active Components from *Acorus gramineus* and *Acorus tatarinowii* in Neurological Disorders and Their Application in Korean Medicine

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Neurological disorders represent a substantial healthcare burden worldwide due to population aging. *Acorus gramineus* Solander (AG) and *Acorus tatarinowii* Schott (AT), whose major component is asarone, have been shown to be effective in neurological disorders. This review summarized current information from preclinical and clinical studies regarding the effects of extracts and active components of AG and AT (e.g., α-asarone and β-asarone) on neurological disorders and biomedical targets, as well as the mechanisms involved. Databases, including PubMed, Embase, and RISS, were searched using the following keywords: asarone, AG, AT, and neurological disorders, including Alzheimer's disease, Parkinson's disease, depression and anxiety, epilepsy, and stroke. Meta-analyses and reviews were excluded. A total of 873 studies were collected. A total of 89 studies were selected after eliminating studies that did not meet the inclusion criteria. Research on neurological disorders widely reported that extracts or active components of AG and AT showed therapeutic efficacy in treating neurological disorders. These components also possessed a wide array of neuroprotective effects, including reduction of pathogenic protein aggregates, antiapoptotic activity, modulation of autophagy, anti-inflammatory and antioxidant activities, regulation of neurotransmitters, activation of neurogenesis, and stimulation of neurotrophic factors. Most of the included studies were preclinical studies that used *in vitro* and *in vivo* models, and only a few clinical studies have been performed. Therefore, this review summarizes the current knowledge on AG and AT therapeutic effects as a basis for further clinical studies, and clinical trials are required before these findings can be applied to human neurological disorders.

Keywords: alzheimer's disease, asarone, depression, epilepsy, parkinson's diseases, stroke

INTRODUCTION

Neurological disorders are the main cause of death and disability, and these diseases have risen rapidly due to the increasing elderly population worldwide. These disorders, particularly Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy, and stroke, encompass diseases of the nervous system, cause irreversible damage, are difficult to treat, and show a wide range of sequelae [1]. These factors lead to poor prognosis, prolonged illness, and limited ability to perform personal and social roles during the disease period. Moreover, many of these disorders show only a minimal response to conventional therapies, thus necessitating the identification or development of innovative treatment modalities.

Recently, drugs of natural origin have attracted increasing interest in treating neurological disorders because of their

potential efficacy and limited or nonexistent side effects. Traditional Korean medicines, which use natural raw materials, have a high potential for developing new constituents and conventional medicines. In Korean medicine, *Acorus gramineus* Solander (AG) and *Acorus tatarinowii* Schott (AT), which is widely known as "Shi Chang Pu," have been commonly used alone or in combination with other herbs. These herbs have been used in Korean medicine to improve mental, cognitive, and learning capacities, thus suggesting that they may be effective against neurological disorders, such as meningitis and dementia [1]. These herbs have also attracted the attention of researchers because they have shown therapeutic efficacy against cognitive impairment, anxiety, gastritis, and gastric ulcers and have shown sedative activity in preclinical studies [2]. Among the bioactive phytochemicals of AG and AT, α-asarone and β-asarone are the most widely studied components in the treatment of various diseases (Fig. 1) [3].

Asarone plays a broad role in the nervous system and has shown antiepileptic, sedative, antidepressant, and neuroprotective effects in different neurological disease models [4]. Molecular investigations have shown that asarone may have antiapoptotic, anti-inflammatory, and antioxidant effects and may modulate neurotransmitter production and neurotrophic factor regulation in AD, PD, epilepsy, and stroke. In addition, asarone is able to cross the blood-brain barrier (BBB), thus increasing its potential as a therapeutic drug for neurological disorders.

In this study, we aimed to review the molecular mechanisms of extracts or active components of AG and AT (e.g., α-asarone and β-asarone) in neurological disorders, such as AD, PD, depression and anxiety, epilepsy, and stroke. This study also discusses the pharmacological potential and basis of the molecular mechanism of α-asarone and β-asarone in neurological disorders discussed in pre-clinical and clinical studies.

METHODS

1. Search strategy

Experimental studies focused on evaluating asarone in treating neurological disorders were identified in PubMed (https://pubmed.ncbi.nlm.nih.gov), Embase (https://www.embase.com), and RISS (http://www.riss.kr). The keywords used were as follows: asarone ("extract" OR "tang" OR "san" OR "wan" OR "decoction" OR "powder" OR "ball" OR "pill") AND ("*Acorus gramineus*"[tiab] OR "*Acorus tatarinowii*"[tiab] OR "shi chang pu"[tiab]).

2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) studies on asarone, AG or AT extracts, and herbal formulas containing AG or AT; (2) preclinical *in vitro*, *in vivo*, and clinical trials; and (3) studies that mainly focused on neurological disorders. The exclusion criteria were as follows: (1) non-English studies; (2) studies that showed no efficacy for neurological disorders; and (3) editorials, abstracts, comments, and reviews.

3. Data extraction

All data were drawn independently by two reviewers from the included studies (TK and MB). The following details were extracted from each study: (1) compounds used, (2) species and experimental model studied, and (3) results and outcome measures.
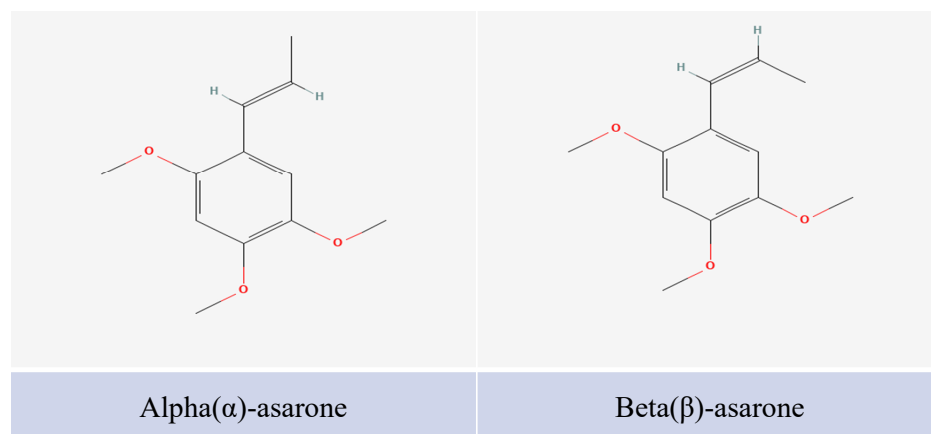

Figure 1. Alpha (α)-asarone (1,2,4-trimethoxy-5-[(E)-prop-1-enyl]benzene; PubChem CID: 636822) and beta (β)-asarone (1,2,4-trimethoxy-5-[(Z)-prop-1-enyl]benzene; PubChem CID: 5281758).

RESULTS

1. Study selection

Among the results obtained in the database search, 873 studies were collected after excluding duplicates. Among these studies, 715 were excluded on the basis of the exclusion criteria. Sixty-eight of the remaining 158 studies were excluded after reviewing their full texts. Thus, 89 studies were included for review, and the distribution of these studies by disease was as follows: AD and dementia (29); PD (12); depression and anxiety (10); epilepsy and seizure (12); stroke (10); herbal medicine (16) (Fig. 2).

2. Alzheimer's disease and dementia (Table 1)

AD is a degenerative brain disease that shows clinical features of slowly progressing cognitive decline and behavioral disorders [5]. One specific pathogenesis of AD is an amyloid cascade characterized by the excessive formation of amyloid-beta (Aβ) plaques due to an abnormal degradation pathway of amyloid precursor protein (APP), which usually stabilizes microtubules, maintains neuronal shape, and reduces axonal transmission. A representative example is the Tau hypothesis, which explains the hyperphosphorylation of helper Tau proteins [5]. In addition, neuron damage due to the inflammatory

Figure 2. Flow diagram.

response [5], oxidative stress [5], cholinergic neurotransmitter imbalance [6], and vascular-related factors, including hypercholesterolemia and hyperhomocysteinemia [5], have also been shown to mediate AD and dementia pathology.

The essential oil of AT has been shown to ameliorate Aβ-induced toxicity via an autophagy pathway in a *Caenorhabditis elegans* model [7]. β-Asarone can ameliorate cognitive function by inhibiting Aβ accumulation, apoptotic neuronal death, and autophagy. In addition, β-asarone has been shown to decrease senile plaque formation and Aβ40 and Aβ42 levels in the hippocampus [8] and inhibit Beclin-1-dependent autophagy via PI3K/Akt/mTOR signaling in APP/PS1 mice [9]. Moreover, β-asarone has been shown to decrease apoptosis by activating calcium/calmodulin-dependent protein kinase II (CaMKII)/cAMP response element-binding protein (CREB)/B-cell lymphoma 2 (Bcl-2), thereby inducing an improvement in the cognitive function of APS/PSI mice [10]. In an Aβ-induced neurotoxicity in vitro study, β-asarone was shown to inhibit apoptotic neuronal death by inhibiting the proapoptotic Bax protein, activating the antiapoptotic Bcl protein [11] and c-Jun N-terminal kinase (JNK) pathway, and regulating Bcl-2 family proteins in PC12 cells [12]. After the *in vivo* Aβ injection in the rat hippocampus, β-asarone was shown to improve cognitive function by suppressing apoptotic neuronal death via the activation of Bcl-2 and Bcl-w and β-asarone reversed the downregulation of JNK phosphorylation [13]. In addition, β-asarone was shown to activate p-c-Jun and decrease the activation of Bcl-2-associated agonist of cell death (Bad), Bax, and caspase-9 [14]. The effects of β-asarone on autophagy are controversial. For instance, this component has been reported to promote autophagy, which is involved in the removal of harmful proteins, *in vitro* [15] and in an animal model of AD [16]. However, β-asarone has also been reported to decrease Rho-kinase expression, reduce autophagy, influence synaptic damage [17], and attenuate Aβ-induced autophagy via the induction of the Akt-mTOR pathway [18].

The antioxidant and anti-inflammatory effects of asarone are also well-studied in the context of AD. β-Asarone has been shown to delay inflammatory responses and autophagy by inhibiting the induction of tumor necrosis factor α (TNF-α), interleukin (IL)-6, and interleukin-1 beta (IL-1β) in Aβ-treated SH-SY5Y cells [19]. β-Asarone has also been shown to improve spatial learning and memory by reducing TNF-α and IL-1β production and aquaporin-4 (AQP4) expression and by protecting astrocytes [20]. α-Asarone has been shown to modulate the dynamics of microglial morphology and decrease
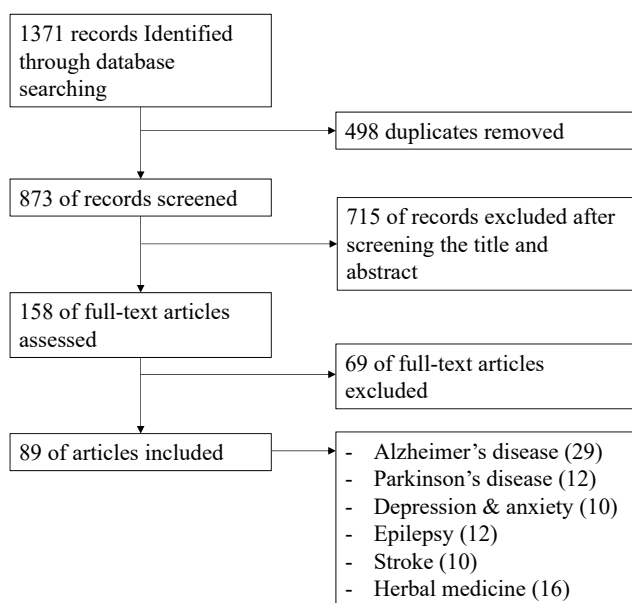
Table 1. Therapeutic potential of *Acorus gramineus* Solander and *Acorus tatarinowii* Schott in Alzheimer's disease

Effect	Compound	Species	Experimental model	Experiment result	Mechanisms	Ref.
Anti-Aβ accumulation	SCP-Oil	Worm	*Caenorhabditis elegans* model	Serotonin sensitivity and olfactory learning skill ↑	Misfolded Aβ and polyQ proteins ↓	[7]
	β-asarone	Mouse	APP/PSI double transgenic mice	Senile plaques in the hippocampus & Aβ ↓↑	Levels of Aβ40 and Aβ42 in hippocampus ↓	[8]
	β-asarone	Mouse	APP/PSI transgenic mice	Learning and memory function ↑	Beclin-1-dependent autophagy (the PI3K/Akt/mTOR pathway) ↓	[9]
Anti-apoptosis	β-asarone	Mouse	APP/PSI double transgenic mice	Cognitive function ↑	CaMKII-α/p-CREB/Bcl-2 pathway ↑	[10]
	β-asarone	Cell	Aβ42 injury cells	Neuronal apoptosis ↓	Bax ↓, Bcl-2 ↑	[11]
	β-asarone	CellΩ	Aβ-induced PC12 cells	Neuronal apoptosis ↓	JNK activation ↓ Bcl-w and Bcl-xL in a JNK-dependent manner ↑ Cytochrome c and activation of caspase-3 ↑	[12]
	β-asarone	Rat	AD induced rats	Spatial memory ↑	JNK activation ↓, caspase-3 activation & Bcl-w, and Bcl-2 ↑	[13]
	β-asarone	Rat	AD induced rats	Neuronal apoptosis ↓	Bad expression & p-c-Jun activation, Bax expression ↓ Activation of caspase-9 ↑	[14]
Autophagy regulation	β-asarone	Cell	Aβ1~42-induced PC12 cells	Aβ ↓ Autophagy ↑	APP, PS1, Aβ, and BACE1 expression ↓ PINK1, Parkin & Autophagy ↑	[15]
	β-asarone + Icariin	Cell, mouse	Aβ-induced PC12 cells, APP/PS1 mice	Mitochondrial damage ↓	Clearance of toxic proteins & the formation of autophagosomes ↑ Beclin-1, PINK1, and p/Parkin ↑	[16]
	β-asarone	Mouse	SAMP8 mice	Cognitive function ↑	ROCK expression ↓, autophagy and synaptic loss ↓	[17]
	β-asarone	Cell	Aβ-induced PC12 cells	Neuronal apoptosis ↓	Beclin-1 expression ↓ p-Akt and p-mTOR ↑	[18]
Anti-inflammation	β-asarone	Cell	Human neuroblastoma cells SH-SY5Y cells	Autophagy ↓ Inflammation ↓	Toxic effect of Aβ25-35 in SH-SY5Y cells ↓ Pro-inflammatory cytokines (IL-6, IL-1β and TNF-α) ↓	[19]
	β-asarone	Mouse, cell	Aβ1~42 injected rats Aβ1-42 induced astrocytes	Spatial learning and memory ↑	TNF-α, IL-1β & AQP4 expression ↓	[20]
	α-asarone	Cell	LPS-induced BV2 cells	Microglial, morphological dynamics ↑	Activated microglia ↓ MCP-1 ↓	[21]
Antioxidant-oxidant	α-asarone	Rat	Aβ-injected rats	Spatial memory ↑	NO production & activation of astrocytes ↓	[22]
	β-asarone	Mouse	Aβ-infused mice	Cell loss in the cerebral cortex and hippocampus ↓	GPX and SOD ↑	[23]
	β-asarone	Cell	Aβ-induced PC12 cells	Aβ-induced damage ↓	ROS, MDA ↓, SOD, CAT, GSH-PX ↑, P13K/Akt/Nrf2 signaling pathway ↑, HO-1 ↑	[24]
	β-asarone	Rat	Aβ-infused rats	Learning and memory ability ↑	Oxidative stress ↓ Pro-inflammatory cytokine ↓ Neurotransmitter and AChE activity ↑	[25]

Table 1. Continued

Effect	Compound	Species	Experimental model	Experiment result	Mechanisms	Ref.
Neurotransmitter	β-asarone	Cell	APS/PSI double transgenic mice	Learning and memory ability ↑	Aβ neurotoxicity ↓ SYP and GluR1 ↑	[26]
	α-asarone	Rat	Aged rats	Cognitive function ↑	Aβ neurotoxicity ↓ GABA receptors ↑	[27]
	α-asarone, β-asarone	Cell	NMDA or Glu-exposed cortical cells of rat	Neuronal apoptosis ↓	NMDA receptor function ↓	[28]
	β-asarone + tenuigenin	Human	93 AD patients	Therapeutic effect ↑	MMSE, ADL score ↑	[29]
	β-asarone + tenuigenin	Human	152 AD patients	Therapeutic effect ↑	MMSE, ADL score ↑	[30]
	β-asarone	Rat	AD induced rats	Memory impairment ↓	rCBF of right parietal lober & the activity of NA-K-ATP ↑ ET-1 mRNA expression in hippocampus & pyruvic acid ↓	[31]
Others	Volatile oil fraction of AT	Mouse	Aβ-infused mice	Cognitive function ↑ Spatial memory ↑	Doublecortin and nestin ↓	[32]
	α-asarone, β-asarone	Mouse	APS/PSI transgenic mice	Hippocampal neurogenesis ↑ NPCs ↑	ERK pathway & neurogenesis ↑	[33]
	α-asarone, β-asarone	Cell	Primary astrocytes from rats	NGF, BDNF & GDNF ↑	Neuronal action of AT ↑ Neurotrophic factors in astrocytes ↑	[34]
	α-asarone, β-asarone	Cell	PC12 cells	NGF ↑	Neurofilaments ↑	[35]

SCP, Shi Chang Pu in Chinese; Aβ, amyloid-beta; polyQ, polyglutamine; APP, amyloid precursor protein; PS1, presenilin-1; P13K, phosphoinositide 3-kinases; Akt, protein kinase B; mTOR, mammalian target of rapamycin; CaMKII-α, calcium/calmodulin-dependent protein kinase II-alpha; p-CREB, phosphor-cAMP response element-binding protein; Bcl-2, B-cell lymphoma 2; Bax, BCL2-associated X; JNK, c-Jun N-terminal kinases; AD, Alzheimer's disease; BACE, beta-secretase 1; PINK, PTEN-induced kinase 1; SAMP8, senescence accelerated mouse-prone 8; ROCK, Rho-associated protein kinase; IL-, interleukin-; TNF-α, tumor necrosis factor-α; AQP4, aquaporin4; LPS, lipopolysaccharide; MCP-1, monocyte chemoattractant protein-1; NO, nitric oxide; GPX, glutathione peroxidase; SOD, superoxide dismutase; ROS, reactive oxygen species; MDA, malondialdehyde; CAT, catalase; GSH-Px, glutathione peroxidase; Nrf2, nuclear factor erythroid-2-related factor 2; HO-1, heme oxygenase 1; AChE, acetylcholinesterase; SYP, synaptophysin; GluR1, glutamatergic receptor 1; GABA, γ-aminobutyric acid type; NMDA, N-methyl-D-aspartate; MMSE, Mini-mental State Examination; ADL, activities of daily living; rCBF, regional cerebral blood flow; NA-K-ATP, sodium-potassium adenosine triphosphatase, sodium–potassium pump; ET, endothelin; AT, *Acorus tatarinowii*; NPC, neural progenitor cell; ERK, extracellular signal-regulated kinase; NGF, nerve growth factor; BDNF, brain-derived neurotrophic factor; GDNF, glial-derived neurotrophic factor.

the expression of monocyte chemoattractant protein in lipo-polysaccharide (LPS)-induced BV2 cells [21]. Assessments of asarone's antioxidant activity showed that nitrite levels in the temporal cortex and hippocampus of rats were significantly reduced with the improvement in spatial memory after α-asarone administration [22]. Moreover, the activities of glutathione peroxidase (GPX) and antioxidant enzymes superoxide dismutase (SOD) were induced after β-asarone administration in rats [23]. β-Asarone has also been shown to reduce reactive oxygen species and malondialdehyde expression, induce SOD, catalase (CAT), and GPX activities, and promote nuclear fac-

tor erythroid-2-related factor 2 (Nrf2) and heme oxygenase 1 expression by upregulating P13K/Akt/Nrf2 signaling in Aβ-induced PC12 cells [24].

Asarone improves cognitive function by modulating neurotransmitters. β-Asarone has been shown to improve cognitive function by restoring the levels of hippocampal neurotransmitters, such as dopamine (DA), serotonin, γ-aminobutyric acid (GABA), and norepinephrine, and acetylcholinesterase activity and reducing oxidative and neuroinflammatory damage in Aβ-infused rats [25]. β-Asarone was also shown to have neuroprotective efficacy for AD via the modulation of synaptic plasticity

by inducing the expression of synaptophysin and glutamatergic receptor 1 [26]. In addition, α-asarone was shown to ameliorate cognitive dysfunction by reducing neuronal excitotoxicity via GABA A (GABAA) receptors in aged rats [27]. Both α-asarone and β-asarone showed neuroprotective activity against excitotoxicity due to N-methyl-d-aspartate (NMDA) or glutamate (Glu) blocking NMDA receptor function [28]. In a clinical study, a combined prescription of β-asarone and tenuigenin in AD patients was shown to increase clinical scores, which indicates the improvement in AD symptoms [29, 30].

Asarone has also been shown to have cerebrovascular protective and neurogenesis effects. Treatment with β-asarone was shown to improve cerebral metabolism and blood flow and to downregulate the mRNA expression of endothelin 1 in the hippocampus of AD rats [31]. Treatment with volatile oil fractions or water extracts of AG in Aβ1-42-injected mice was shown to ameliorate cognitive impairment and hippocampal neurogenesis via the upregulation of nestin and doublecortin in the hippocampus [32]. The extracts of AT and its major constituents, namely, α-asarone and β-asarone, have been shown to promote the proliferation of neural progenitor cells with activated extracellular signal-regulated kinase (ERK) in hippocampus-derived progenitor cells [33] and potentiate neuronal differentiation via nerve growth factor (NGF) in PC12 cells [34]. The volatile oil fractions from AG, which contain α-asarone and β-asarone, stimulate neurotrophic factor secretion, namely, brain-derived neurotrophic factor (BDNF), NGF, and glial-derived neurotrophic factor, via the PKA signaling pathway [35].

3. Parkinson's disease (Table 2)

PD is a common chronic neurodegenerative disease and characteristically associated with dopaminergic neuronal loss in the substantia nigra and pars compacta [36]. Motor symptoms, such as bradykinesia, resting tremors, and stiffness, are the main dysfunctions exhibited by patients with PD. The treatment of motor symptoms in PD is primarily based on DA regulation; therefore, DA metabolites (levodopa and ʟ-dopa), DA-degrading enzyme inhibitors (monoamine oxidase-B and MAO-B), and DA agonists are the drugs of choice for the initial treatment.

Dopaminergic neuron damage due to neurotoxicity, oxidative stress, and inflammation is considered the underlying pathogenesis of PD. β-asarone can improve motor function by inhibiting α-synuclein (α-syn) aggregation, dopaminergic

cell death, and autophagy. The administration of β-asarone improves behavioral symptoms and elevates tyrosine hydroxylase (TH) levels via JNK/Bcl-2/Beclin-1 signaling in 6-hydrooxydopamine (6-OHDA)-treated rats and SN4741 cells [37]. β-Asarone has also shown a neuroprotective effect by modulating metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), which induces neuronal death and α-syn expression in a 1-methyl-4 phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mouse model and in 1-methyl-4-phenylpyridinium (MPP+)-treated SH-SY5Y cells, as the corresponding in vitro model [38].

Asarone has also been shown to attenuate behavioral deficits in PD animal models via its anti-inflammatory and antioxidant effects. α-Asarone attenuated microglia-mediated neuroinflammation by inhibiting the activation of NF-κB in LPS-treated BV2 cells and mitigated PD-like behavioral impairments in an MPTP-treated mouse model [39]. Moreover, β-asarone reduced autophagy and endoplasmic reticulum (ER) stress by inhibiting the protein kinase RNA-like ER kinase (PERK)/C/EBP homologous binding protein (CHOP)/Bcl-2/Beclin-1 pathway [40] and the inositol-requiring enzyme 1 (IRE1)/X-box binding protein 1 (XBP1) pathway [41] and by modulating the heat-shock protein 70 (Hsp70)/mitogen-activated protein kinase (MAPK)/myocyte enhancer factor 2D (MEF2D)/Beclin-1 pathway [42] in a 6-OHDA-treated rat model. The aqueous extract of AG has been reported to inhibit neuroinflammation via the modulation of MAPKs, nuclear factor kappa B (NF-κB), and TIR domain-containing adapter-inducing interferon-β (TRIF) dependent signaling in LPS-stimulated BV2 cells and prevent neurotoxicity in an MPTP-treated mouse model [43]. In a recent study, β-asarone reduced neuron damage by decreasing α-syn and inhibiting oxidative stress, inflammatory reactions, and cell apoptosis in a 6-OHDA-treated parkinsonism rat model [44].

Asarone has been shown to further induce the efficacy of ʟ-dopa via the co-treatment with ʟ-dopa. This coadministration increased DA in the striatum of naive rats [45] and 6-OHDA rats [46-48]. Furthermore, β-asarone affected the transformation of ʟ-dopa to DA by modulating catechol-O-methyltransferase (COMT) and DA metabolism [45], inhibiting autophagy activity via the downregulation of microtubule-associated protein light chain 3B (LC3B) and Beclin-1 expression and the upregulation of p62 expression [48], and promoting ʟ-dopa into the brain via the modulation of tight junction proteins and P-glycoprotein in the BBB [47] and via the regulation of dopa decarboxylase, TH, COMT, MAO-B, and DA transporter levels [46].

Table 2. Therapeutic potential of *Acorus gramineus* Solander and *Acorus tatarinowii* Schott in Parkinson's disease

Effect	Compound	Species	Experimental model	Results	Mechanisms	Ref.
Anti-cell death	β-asarone	Rat, cell	6-OHDA-induced rats SN4741 cells	Motor function ↑ (OFT, RRT, forelimb akinesia)	*In vitro*: LC3-II ↓ *In vivo*: HVA, Dopacl, 5-HIAA, Bcl-2 ↑ Beclin-1, JNK, p-JNK ↓, Bcl-2 ↑	[37]
	β-asarone	Mouse, cell	MPTP-induced mice SH-SY5Y cells	Motor function ↑ (RRT)	*In vitro*: TH+ cell ↑, MALAT1, α-syn, CHX, MG132 ↓ *In vivo*: MALAT1 ↓	[38]
Antioxidant	α-asarone	Mouse, cell	MPTP-induced mice BV-2 cells	Motor function ↑ (Y-maze test and pole test)	*In vitro*: NO, iNOS, COX-2, TNF-α, IL-6, IL1β, NF-κB, IκB ↓ *In vivo*: Mac-1, CD-68, Iba-1, iNOS, COX-2, DOPAC ↓	[39]
	β-asarone	Rat	6-OHDA-induced rats	ER stress ↓	GRP78, p-PERK, CHOP, Beclin-1 ↓ Bcl-2 ↑	[40]
	β-asarone	Rat	6-OHDA-induced rats	ER stress ↓	IRE1, p-IRE1, XBP1 ↓	[41]
	β-asarone	Rat	6-OHDA-induced rats	CMA↑, Autophagy ↓	HSC70, HSP70, MEF2D, LAMP-2A level ↑ α-Syn ↓	[42]
Anti-inflammation	AG extract	Mouse	MPTP-induced mice BV-2 cells	Cell death ↓ Neuroinflammation ↓	TH+ cell ↑ NO, iNOS, TNF-α, IL-6, IL1β, NF-κB, IκB ↓	[43]
	β-asarone	Rat	6-OHDA-induced rats	Motor function ↑ (OFT, RRT, forelimb activity)	α-Syn, Il-1β, TNF-α, NO, IL-6, BAX, Caspase ↓ TH, SOD, CAT, GSH-Px, Bcl-2 ↑	[44]
Coordination with levodopa	β-asarone + L-dopa	Rat	SD rat	L-Dopa, DA ↑	DA ↑, COMT ↓	[45]
	β-asarone + L-dopa	Rat	6-OHDA-induced rats	Motor function ↑ (OFT, ST, RRT)	DDC level, DA level, MAO-B, COMT, DOPAC/DA, HVA/DA, TH, DAT ↑	[46]
	β-asarone + L-dopa	Rat	6-OHDA-induced rats	L-Dopa BBB permeability ↑	L-dopa, DA, DOPAC, HVA ↑ S100β ↑ NSE, P-gp, ZO-1, occludin, actin, claudin-5 ↓	[47]
	β-asarone + L-dopa	Rat	6-OHDA-induced rats	Autophagy activity ↓	Beclin-1, LC3B ↓ p62 expression ↑	[48]

SD, Sprague Dawley; 6-OHDA, 6-hydroxydopamine; OFT, open-field test; RRT, rotarod test; LC3-II, light chain 3-II; HVA, homovanillic acid; Dopacl, 3,4-dihydroxyphenylacetic acid; 5-HIAA, 5-hydroxyindole acetic acid; JNK, c-Jun *N*-terminal kinase; Bcl-2, B-cell lymphoma; MPTP, 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine; TH, tyrosine hydroxylase; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; α-syn, α-synuclein; CHX, cycloheximide; MG132, a proteasome inhibitor; NO, nitric oxide; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; TNF-α, tumor necrosis factor-alpha; IL-, interleukin-; NF-κB, nuclear factor kappa B; IκB, NF-κB inhibitor; Mac-1, macrophage Ag complex-1; CD-68, cluster of differentiation 68; Iba-1, ionized calcium-binding adapter molecule 1; DOPAC, 3, 4-dihydroxyphenylacetic acid; GRP78, glucose-regulated protein 78; p-PERK, phosphorylated protein kinase RNA-like endoplasmic reticulum kinase; CHOP, C/EBP homologous binding protein; ER, endoplasmic reticulum; IRE1, inositol-requiring enzyme 1; p-IRE1, phosphorylated IRE1; XBP1, X-box binding protein 1; CMA, chaperone-mediated autophagy; HSC70, heat-shock cognate protein 70; HSP70, heat-shock protein 70; MEF2D, myocyte enhancer factor 2D; LAMP-2A, lysosomal membrane protein receptor type 2A; BAX, B-cell lymphoma 2-associated X protein; TH, thyrosine hydroxylase; SOD, superoxide dismutase; CAT, catalase; GSH-Px, glutathione peroxidase; ʟ-dopa, levodopa; DA, dopamine; COMT, catechol-O-methyltransferase; DAT, dopamine transporter; ST, stepping test; DDC, dopa decarboxylase; MAO-B, monoamine oxidase-B; BBB, blood–brain barrier; S100β, S100 calcium-binding protein β; NSE, neuron-specific enolase; P-gp, P-glycoprotein; ZO-1, zonula occludens-1; LC3B, microtubule-associated protein light chain 3B.

4. Depression and anxiety (Table 3)

Depression is a representative mental illness that is accompanied by symptoms in the areas of mood, cognitive, and motor functions. Biological and psychosocial factors are involved in different ways during depression. However, the best-known theory for the biological etiology of depression is the monoamine hypothesis since monoamine neurotransmitters, such as serotonin, noradrenaline, and DA, are known to be involved in mood regulation. This theory is supported by the fact that selective serotonin-, norepinephrine-DA-, and serotonin-norepinephrine-reuptake inhibitors, which are drugs that act on these substances, are currently being used as antidepressants [49].

However, many studies describing the effects of asarone in improving depression are related to the improvement of brain functions, mainly by increasing the production of BDNF and other neurotrophic factors rather than the production of neurotransmitters. The administration of β-asarone reversed depression-like behaviors in an unpredictable chronic mild stress (UCMS)-treated model, which is related to enhanced neurogenesis and decreased neuronal cell death in the hippocampus [50-52]. In addition to these therapeutic effects, β-asarone increased BDNF by enhancing ERK1/2, CREB phosphorylation, tropomyosin receptor kinase B (Trk-B), and Bcl-2 and by reducing Bad and mitogen-activated protein kinase phosphatase-1 (MKP-1) [50-52]. In addition, α-asarone also attenuated depression-like behavior via the modulation of hippocampal pCREB levels in a nicotine-withdrawn mouse model of depression [53].

The antidepressant results of asarone are also demonstrated

Table 3. Therapeutic potential of *Acorus gramineus* Solander and *Acorus tatarinowii* Schott in depression and anxiety

Effect	Compound	Species	Experimental model	Results	Mechanisms	Ref.
Anti-depression	β-asarone	Rat	CUMS exposed rats	Depressant-like behavior ↓ (SPT, FST)	BDNF ↑, ERK1/2 and CREB phosphorylation ↑	[50]
	β-asarone	Rat	CUMS exposed rats	Depressant-like behavior ↓ (SPT, OFT, FST)	Apoptosis ↓, CREB ↑, BDNF ↑, Trk-B ↑, Bcl-2 ↑, Bad ↓, ERK ↑	[51]
	β-asarone	Rat	CUMS exposed rats	Body weight ↑ Depressant-like behavior ↓ (SPT, OFT)	MKP-1 ↓, p-ERK1/2 ↑, BDNF ↑	[52]
	α-asarone	Mouse	Nicotine withdrawal induced mice	Depressant-like behavior ↓ (FST)	p-CREB ↓	[53]
	EO from AT, α-asarone, β-asarone	Mouse	Normal mice	Depressant-like behavior ↓ (FST, TST)		[54]
	α-asarone	Mouse	Normal mice	Depressant-like behavior ↓ (TST)		[55]
Anti-anxiety	α-asarone	Mouse	Normal mice	Anxiolytic-like behavior ↑ (EPM, LDT, NFC, MBT)		[56]
	α-asarone	Rat	Sleep deprived rats	Anxiolytic-like behavior ↑ (EPM, OFT)	MDA ↓, CAT ↑, GSH-R ↑, GSH-Px ↑	[57]
	α-asarone	Mouse	CFA-induced chronic Inflammatory pain mice	Anxiolytic-like behavior ↑ (EPM, OFT)	AMPARs ↓, NMDARs ↓, GABAARs ↑, hyper-excitability of pyramidal neurons ↓	[58]
	α-asarone	Rat	Corticosterone-induced anxiety rats	Anxiolytic-like behavior ↑ (EPM, HBT)	TH ↓, BDNF ↓, TrkB ↓	[59]

CUMS, chronic unpredictable mild stress; SPT, sucrose-preference test; FST, forced-swimming test; BDNF, brain-derived neurotrophic factor; ERK, extracellular signal-regulated kinases; CREB, cAMP response element-binding protein; OFT, open-field test; Trk-B, tropomyosin receptor kinase B; Bcl, B-cell lymphoma; Bad, Bcl-2-associated death promoter; MKP-1, mitogen-activated protein kinase phosphatase-1; p-ERK, phosphorylated extracellular signal-regulated kinases; p-CREB, phosphorylated cAMP response element-binding protein; EO, essential oil; AT, *Acorus tatarinowii*; TST, tail-suspension test; EPM, elevated plus maze; LDT, light/dark-transition test; NFC, novel–food-consumption test; MBT, marble-burying test; CFA: complete Freund's adjuvant; MDA, malondialdehyde; CAT, catalase; GSH-R, glutathione reductase; GSH-Px, glutathione peroxide; AMPARs, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors; NMDARs, NR2A-containing *N*-methyl-ᴅ-aspartate recpetors; GABAAs, γ-aminobutyric acid type A receptors; HBT, hole-board test; TH, tyrosine hydroxylase.

in normal mouse models. The major essential oil components from AT (essential oils and asarone) have shown antidepressant-like efficacy in normal mice [54], and the effects of α-asarone promoted mediation via the noradrenergic and serotonergic systems [55].

The effects of asarone on anxiety symptoms have also been studied. In particular, α-asarone alleviated anxiety in various experimental animal models. First, the anxiolytic potential of α-asarone has been observed in normal mice using various behavioral tests, and the effects of α-asarone were similar to that of diazepam [56]. The administration of α-asarone improved insomnia-associated anxiety and cognitive functions by inhibiting lipid peroxidation and enhancing the activities of CAT and glutathione reductase (GSH-R) in a sleep-deprived rat model [57]. α-Asarone has also shown an anxiolytic-like activity in a chronic pain-related anxiety model because of the maintenance of the stability between excitatory and inhibitory communications and the attenuation of the hyperexcitability of excitatory neurons in the basolateral amygdala [58]. Moreover, the administration of α-asarone prior to corticosterone treatment improved anxiety. This effect was related to the regulation of the noradrenergic system and BDNF via the modulation of the Trk-B signaling process in rats [59].

5. Epilepsy (Table 4)

Epilepsy is a chronic neurological disorder that is characterized by persistent seizures despite the absence of physical abnormalities [60]. The antiepileptic and anticonvulsive effects of α-asarone have been investigated in various rodent seizure models [61, 62]. Decoctions and volatile oils extracted from AT prevented convulsions associated with convulsion-induced GABAergic neuron injury in a pentylenetetrazole (PTZ)-treated model [63]. The water extracts and essential oils of AG acted on the central nervous system via the GABAergic system [64, 65] and exhibited neuroprotective effects by blockading NMDA receptor activity [66]. Moreover, α-asarone modulated neurotransmitters, thereby suppressing the seizures caused by intense abnormal excitability. However, the antiepileptic action of α-asarone was mediated by GABAergic regulation and not by the antagonism of acetylcholine receptors [67-70].

In addition, α-asarone modulated neuronal excitability in rat hippocampal cell cultures and suppressed the epileptic symptoms of mice in a PTZ or kainate seizure animal model, presumably based on the activation of GABAA receptors [67].

Furthermore, α-asarone produced antiepileptic effects in a lithium-pilocarpine-treated rat model via modulating GABAergic homeostasis, decreasing GABA degradation by lowering the activity of GABA-T, increasing GABA levels by increasing the expression of glutamic acid decarboxylase 67 (GAD67), and increasing GABA-mediated inhibition by increasing the expression of GABAA receptor [69]. α-Asarone has also been shown to block the Na^+ channel and activate GABAA receptors in the mitral cells of the olfactory bulb in mice brain slices [70]. According to a recent study, α-asarone pretreatment prolonged the onset time of nicotine-treated mice seizures but not the relationship to nicotinic acetylcholine receptors [68].

In addition to these effects, α-asarone has been shown to have antioxidant and anti-inflammatory effects; therefore, it could provide protection from brain damage. Treatment with α-asarone delayed the onset time of clonic and tonic seizures in various animal seizure models and induced antioxidant enzymes, such as SOD, GPX, and GSH-R, in the brain, particularly in the cortex, striatum, and hippocampus [71]. α-Asarone has also been shown to arrest the inflammatory process via the transcriptional level regulation of NF-κB by inhibiting the degradation pathways of NF-κB inhibitor (IκB) alpha (IκBα) and IκB beta (IκBβ) in pilocarpine-treated status epilepticus rats and LPS-treated microglial cells [72].

6. Stroke (Table 5)

Stroke is a neurological disorder wherein the blood vessels supplying blood to the brain become blocked or rupture, thus causing damage to the brain. Pathophysiological events arise in stroke, including energy deprivation, glutamate-induced excitotoxicity, oxidative stress, inflammation, and BBB breakdown [73].

Asarone has been shown to provide neuroprotective effects against stroke-induced damage by inhibiting autophagy and neuronal cell death. Both α-asarone and β-asarone attenuate ischemia-induced injury by inhibiting autophagy [74-76]. β-Asarone has previously been shown to attenuate Beclin-1-dependent autophagy in PC12 cells after oxygen-glucose deprivation followed by reperfusion [74] and ischemia-reperfusion-induced autophagy by regulating Bcl-2, Beclin 1, JNK, and p-JNK in a middle cerebral artery occlusion (MCAO) rat model [75]. α-Asarone treatment has also been shown to reduce the infarct volume, improve neurological functions, decrease the expression of ionized calcium-binding adaptor molecule-1 (IBA1) and

Table 4. Therapeutic potential of *Acorus gramineus* Solander and *Acorus tatarinowii* Schott in epilepsy

Effect	Compound	Species	Experimental model	Results	Mechanisms	Ref.
	α-asarone	Mouse, rat	MES-induced seizure mice scPTZ-induced seizure mice LI-PILO-induced epilepsy rats	Seizure incidence, severity, frequency ↓, latency ↑		[61]
	α-asarone	Mouse, rat	MES-induced seizure mice PTZ-induced seizure mice LI-PILO-induced SE rats SRS induced rats	Seizure onset, incidence, latency, severity, mortality, frequency ↓		[62]
Neurotransmitter	Decoction and volatile oil of AT	Mouse, rat	MES-induced seizure mice PTZ-induced seizure mice Prolonged PTZ-induced seizure rats	Convulsant ↓, mortality ↓, seizure latency ↑, seizure intensity ↓	GABA-IR neurons ↑, GABA-IR neuron damage ↓	[63]
	Water extract of AG	Mouse	PTZ-induced seizure mice	Onset of seizure and death ↓	GABA agonist	[64]
	EO of AG	Mouse	PTZ-induced seizure mice	Convulsion ↓	GABA transaminase ↓, GABA ↑, glutamate content ↓	[65]
	EO of AG	Cell	Glutamate-induced excitotoxicity in primary rat cortical cells	Excitotoxicity ↓, neuroprotection ↑	NMDAR antagonist	[66]
	α-asarone	Rat	PTZ-induced epilepsy rats Kainate-induced epilepsy rats	Latency of seizures ↑, Susceptibility to seizure ↓	Firing rate of spontaneous spiking ↓, tonic GABAergic inhibition ↑, inducing inward currents when picotoxin and bicuculline together ↓	[67]
	α-asarone	Mouse	Nicotine-induced seizure mice	LCA and BT ↓, onset time of seizures ↑		[68]
	α-asarone	Rat	LI-PILO-induced TLE rats	GABAergic modulation	GABA ↑, GAD67 ↑, GABAAR-mRNA ↑, GABA-T ↓	[69]
	α-asarone	Cell	CNaIIA cell line	Spontaneous firing of mitral cells and Na$^+$ channel ↓	Spontaneous firing of output neurons, mitral cells ↓, Nav1.2 currents ↓	[70]
Antioxidant	α-asarone	Mouse	PTZ-induced seizure mice Picrotoxin-induced seizure mice NMDA-induced seizure mice PILO-induced seizure mice MES-induced seizure mice	Treadmill performance and LCA ↓, hypothermia ↑, sleep ↑, onset of seizures ↓	Antioxidant enzymes ↑	[71]
Anti-inflammation	α-asarone	Rat	PILO-induced TLE rats	Cognitive function ↑ (WMT), behavioral score of SRSs ↓, frequency of seizures ↓	Microglial activation ↓, proinflammatory cytokine ↓, LPS-stimulated neuroinflammatory responses ↓, NF-κB ↓	[72]

MES, maximal electroshock; scPTZ, subcutaneous pentylenetetrazol seizure; LI-PILO, lithium-pilocarpine; PTZ, pentylenetetrazol; SE, status epilepticus; SRS, spontaneous recurrent seizures; AT, *Acorus tatarinowii*; GABA-IR, GABA-like immunoreactivity; AG, *Acorus gramineus*; GABA, γ-aminobutyric acid; EO, essential oil; NMDAR, *N*-methyl-d-aspartate receptor; LCA, locomotor activity; BT, body temperature; nAChRs, nicotinic acetylcholine receptor; TLE, temporal lobe epilepsy; GAD67, glutamic acid decarboxylase 67; GABAAR, γ-aminobutyric acid type A receptor; GABA-T, GABA transaminase; CNaIIA, type IIA Na$^+$ channel; Nav1.2 channel, a dominant rat brain Na$^+$ channel subtype; NMDA, *N*-methyl-d-aspartate; WMT, water maze test; LPS, lipopolysaccharide; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells.

Table 5. Therapeutic potential of *Acorus gramineus* Solander and *Acorus tatarinowii* Schott in stroke

Effect	Compound	Species	Experimental model	Results	Mechanisms	Ref.
Neuroprotection	β-asarone	Cell	PC12 cells (OGD/R)	Cell viability ↑, autophagy ↓	MMP ↑, Beclin-1 ↓, [Ca$_2$$^+$]$_i$ ↓	[74]
	β-asarone	Rat	MCAO	Autophagy ↓	Beclin1 ↓, JNK ↓, p-JNK ↓, Bcl-2 ↑	[75]
	α-asarone	Rat	MCAO	Infarct volume ↓ Epilepsy ↓ Neurological function ↑	Apoptosis ↓, GFAP ↓, Iba-1 ↓, LC3II/LC3I ↓, p62 ↑	[76]
	β-asarone	Cell	Hypoxia induced PC12 cells	Cell viability ↑	SOD ↑, MMP ↑, apoptosis ↓, LDH ↓, ROS ↓, RPPH1 ↓	[77]
	α-asarone	Rat	4-Vessel occlusion	Neuroprotection ↑	Cell death ↓, damaged pyramidal neurons ↓	[78]
	β-asarone	Rat	MCAO	Infarction volume ↓	Apoptosis ↓, PAPs ↓, AAPs ↑, Nrf2-ARE pathway-related proteins ↑	[79]
Antioxidant	β-asarone	Rat	MCAO	Motor function ↑	LDH ↓, GSH ↑, LPO ↓, GPx ↑, GR ↑, CAT ↑, GST ↑	[80]
Anti-inflammation	β-asarone	Cell	LPS-stimulated BV-2 microglial cells	Anti-inflammatory effects ↑	NO ↓, iNOS ↓, COX-2 ↓, NF-κB ↓	[81]
BBB protection	AT extract	Rat	MCAO	Infarct size, edema ↓ BBB permeability ↓ Neurological function ↑	Astrocytic NKCC1/AQP4 ↓ JNK/iNOS-mediated ICAM-1/MMP-9 signaling ↓	[82]
Neurogenesis	α-asarone	Mouse	MCAO	Motor function ↑	Differentiation of transplanted NPCs ↑	[83]

OGD/R, 2 hours of oxygen-glucose deprivation followed by 24 hours of reperfusion; LPS, lipopolysaccharide; MMP, mitochondrial membrane potential; MCAO, middle cerebral artery occlusion; JNK, c-Jun *N*-terminal kinase; p-JNK, phosphorylated c-Jun *N*-terminal kinase; Bcl-2, B-cell lymphoma 2; GFAP, glial fibrillary acidic protein; Iba-1, ionized calcium-binding adaptor molecule-1; LC3, microtubule-associated protein light chain 3; SOD, superoxide dismutase; LDH, lactate dehydrogenase; MDA, malondialdehyde; ROS, reactive oxidative species; RPPH1, ribonuclease P RNA component H1; PAPs, pro-apoptotic proteins; AAPs, antiapoptotic proteins; Nrf2, nuclear factor erythroid 2-related factor 2; ARE, antioxidant response elements; NPC, neural progenitor cell; CIR, cerebral ischemia-reperfusion; GSH, glutathione; LPO, lipid peroxidation; GPx, glutathione peroxidase; GR, glutathione reductase; CAT, catalase; GST, glutathione S transferase; LPS, lipopolysaccharides; NO, nitric oxide; iNOS, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; NF-κB, nuclear factor-κB; BBB, blood–brain barrier; AT, *Acorus tatarinowii*; NKCC1, Na-K-Cl cotransporter; AQP4, aquaporin 4; ICAM, Na-K-Cl cotransporter-1; MMP-9, matrix metallopeptidase 9.

LC3, and increase the expression of p62 in MCAO rats, thus suggesting that α-asarone attenuates ischemic brain injury by modulating the activation of glia and autophagy [76]. Asarone has also been shown to play a role in inhibiting neuronal cell death [77, 78]. Treatment with β-asarone mitigated neuronal death by negatively regulating the ribonuclease P RNA component H1 (H1RNA)/MiR-542-3p/death effector domain (DED)-containing 2 signaling pathway in hypoxia-treated PC12 cells [77]. β-Asarone also decreased the infarction volume and apoptotic cell death via the activation of Nrf2-antioxidant response element signaling in MCAO rats [79]. Additionally, α-asarone reduced neuronal death in the hippocampus in a study using a four-vessel occlusion model of rats [78].

Asarone has also been shown to improve brain function via antioxidant, anti-inflammatory, and BBB-protecting activities in ischemic models. β-Asarone treatment increased glutathione (GSH) levels by decreasing lipid peroxidation and restoring the activity of endogenous antioxidant enzymes involving GPX, GSH-R, CAT, and GSH S transferases, thus indicating that β-asarone might have antioxidant activity against MCAO ischemic rats [80]. In addition, AG ethanolic extract and its active component, β-asarone, exhibited anti-inflammatory outcomes by suppressing proinflammatory mediators via NF-κB and JNK signaling in LPS-treated BV2 microglia cells [81]. Furthermore, AT extract reduced brain edema by alleviating astrocytic swelling and BBB breakdown, which are associated with the down-regulation of astrocytic Na-K-Cl cotransporter 1 (NKCC1)/AQP4 and JNK/inducible nitric oxide synthase (iNOS)-mediated NKCC1/mitochondrial membrane potential 9 signaling [82].

A recent report suggested that α-asarone influences primary cultured NPCs and an ischemic stroke mouse model [83]. α-Asarone promoted the proliferation of NPCs and the dif-

ferentiation of neuron-lineage cells via the activation of ERK, β-catenin, and cyclin D1, thereby facilitating neurofunctional recovery after NPC transplantation and ischemic brain injury.

7. Effects of formulas and decoctions, including *A. gramineus* and *A. tatarinowii* on neurological disorders (Table 6)

The therapeutic potentials of nine AG- and AT-containing herbal formulas and decoctions against neurological disorders were reviewed. The composition of each formula is listed in Table 7. The most studied prescription is Kai Xin San, an herbal formula composed of *Radix ginseng*, poria, *R. polygalae*, and *A. tatarinowii rhizome*. This formula has been used to improve memory, cognition, depression, and other neurological symptoms for thousands of years in China [84-90]. Kai Xin San

ameliorated cognitive dysfunction in Aβ-treated mice [85] and rats [90], scopolamine-induced mice [88], and multi-infarct dementia rats [87]. In addition, Kai Xin San has also been shown to have an antidepressant effect in rat models with chronic mild stress [84] and UCMS [86, 89].

Kaixin Jieyu decoction is an herbal medicine preparation from Sini powder and Kai Xin San. This preparation has been shown to reduce depression-like behavior via the production of monoamines in a UCMS rat model [91] and the expression of glial fibrillary acidic protein (GFAP) and BDNF in the hippocampus [92]. In addition, other studies have reported that the Qisheng Wan formula [93]; Bushen Tiansui decoction [94]; GPCRAC with extracts from *Polygala tenuifolia*, *Rehmannia lutinosa*, *Gastrodia elata*, *Cistanche deserticola*, AG, and *Curcuma longa* [95]; Bazhu decoction [96]; and Chong Myung Tang [97] ameliorated the cognitive impairment of AD animals.

Table 6. Therapeutic potential of formulas including *Acorus gramineus* Solander and *Acorus tatarinowii* Schott in neurological disorders

Component	Disorders	Species	Results	Ref.
Kai Xin San	Depression	CUMS exposed rats	Antidepressant-like behavior ↑ (SPT, NIH, Two-Way Active Avoidance Test)	[84]
	AD	Aβ-injected rats	Memory ↑ (SDT)	[85]
	Depression	CUMS exposed rats	Antidepressant-like behavior ↑ (SPT, OFT, FST)	[86]
	Stroke	ICA embolic rats	Cognitive function ↑ (MWM)	[87]
	Dementia	SCOP induced mice	Cognitive function ↑ (MWM, Y-maze)	[88]
	Depression	CUMS exposed rats	Antidepressant-like behavior ↑ (SPT, OFT), weight ↑	[89]
	AD	Aβ-injected rats	Cognitive function ↑ (NOR), injured neurons ↓, Aβ level ↓, IDE expression ↑	[90]
Kaixin Jieyu	Depression	CUMS exposed rats	Antidepressant-like behavior ↑ (SPT, OFT)	[91]
	Stroke	CCA ligation rats	Antidepressant-like behavior ↑ (SPT, OFT)	[92]
Qisheng Wan formula	AD	Aβ-injected rats	Cognitive function ↑ (MWM)	[93]
Bushen Tisansui Decoction	AD	Aβ-injected rats	Cognitive function ↑ (MWM)	[94]
GPCRAC	Dementia	SCOP induced mice	Memory ↑ (SDT) Cognitive function ↑ (MWM)	[95]
Bazhu Decoction	AD	5×FAD transgenic mice	Cognitive function ↑ (OFT, Y-maze, MWM)	[96]
Chong Myung Tang	Dementia	SCOP induced mice	Cognitive & memory function ↑ (passive avoidance test, MWM)	[97]
Yishen Huazhuo Decoction	AD	AD patient (human)	Cerebral activity ↑ [supramarginal gyrus (BA 40), superior temporal gyrus (BA 22)]	[98]
Yeolda Hanso Tang	PD	MPP+ -induced cells MPTP-induced mice	Cell viability ↑ (survival ratio of TH-IR cell ↑)	[99]

CUMS, chronic unpredictable mild stress; SPT, sucrose-preference test; NIH, novelty-induced hypophagia; AD, Alzheimer's disease; Aβ, amyloid-beta; SDT, step-down test; OFT, open-field test; FST, forced-swim test; ICA, internal carotid artery; MWM, Morris water maze; SCOP, scopolamine; NOR, novel-object recognition; IDE, insulin-degrading enzyme; CCA, common carotid artery; GPCRAC, the combination of *Gastrodia elata*, *Polygala tenuifolia*, *Cistanche deserticola*, *Rehmannia lutinosa*, *Acorus gramineus*, *Curcuma longa*; BA, broaden area; PD, Parkinson's disease; MPP+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4 phenyl-1, 2, 3, 6-tetrahydropyridine; TH-IR, tyrosine hydroxylase-immunoreacting.

Table 7. Compositions of the formulas including *Acorus gramineus* Solander and *Acorus tatarinowii* Schott

Formula	Composition
Kai-Xin-San	*Panax ginseng, Poria cocos, Polygala tenuifolia, and Acori Tatarinowii*
Kaixin-jieyu	*Radix Ginseng, Radix Paeoniae rubra, Acorus Gramineus soland, Fructus Aurantii immaturus, Radix Polygalae, Poria, Morinda Officinalis and Glycyrrhiza*
Qisheng Wan Formula	*Poria cocos, Cinnamomum cassia, Polygala tenuifolia, Panax ginseng, Asparagus cochinchinensis, Acorus tatarinowii, Lycium chinense*
Bushen Tiansui	*Epimedium brevicornum, Polygonum multiflorum, Chinemys reevesii, Fossilia Ossis Mastodi, Polygala, Acorus tatarinowii*
GPCRAC	*Gastrodia elata, Polygala tenuifolia, Cistanche deserticola, Rehmannia lutinosa, Acorus gramineus, Curcuma longa*
Yishen Huazhuo Decoction	*Epimedium, Fructus ligustri, Psoralea fruit, Radix polygoni multiflori, Radix astragali, Ligusticum wallichi franchat, Acorus gramineus*
Bazhu Decoction	*Radix Morindae Officinalis, Asiatic Cornelian Cherry Fruit, Grassleaf Sweetflag Rhizome, Earth Worm, Arisaema Cum Bile*
Yeolda-Hanso Tang	*Pueraria lobata, Angelica tenuissima, Scutellaria baicalensis, Platycodon grandiflorum, Angelicae Dahurica, Cimicifuga heracleifolia, Raphanus sativa, Polygala tenuifolia, Acorus gramineus, Dimocarpus longan*
Chong-Myung Tang	*Acorus gramineus, Polygala tenuifolia, Poria cocos*
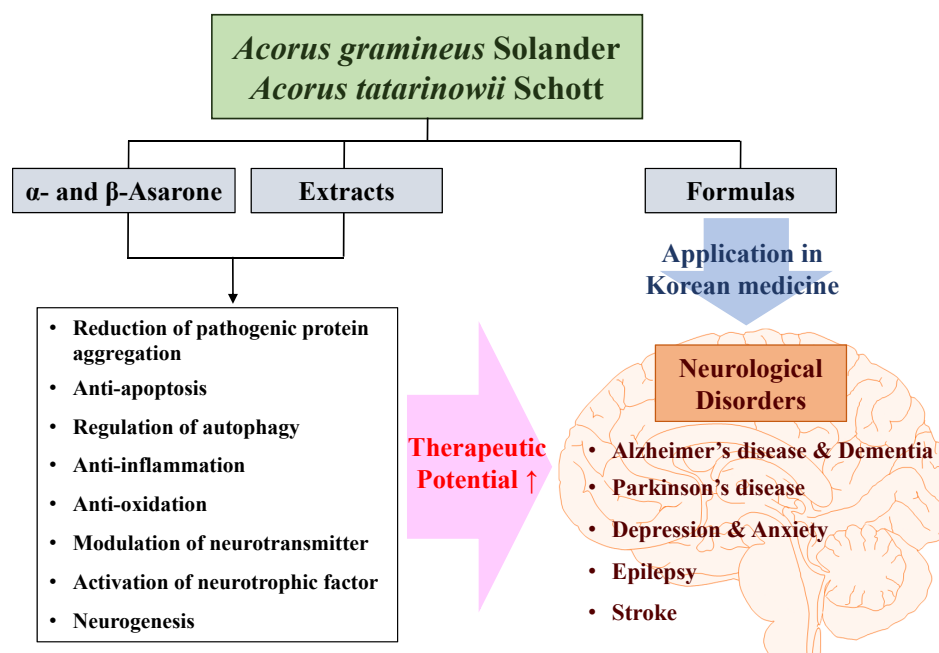
Figure 3. Mechanism of action of extracts or active components of *Acorus gramineus* Solander and *Acorus tatarinowii* Schott in neurological disorders.

Moreover, a study reported that the Yishen Huazhuo decoction improved brain activity in AD patients [98]. The curative potential of Yeolda Hanso Tang in the prevention and treatment of PD has been studied using a PC12 cell model and an MPTP-treated PD mouse model [99].

CONCLUSION

AG and AT, which is commonly referred to as "Shi Chang Pu," have been widely used for improving mental, cognitive, and learning capacities in Korean medicine, and α- and β-asarone, which are the bioactive phytochemicals of AG and AT, are the most studied agents in the treatment of various diseases. In this review, 73 studies showed the potential neuroprotective func-

tion of the extracts and the compounds of AG or AT (α-asarone and β-asarone) in neurological disorders. They improved behavioral functions and neuronal cell survival, and their effects were associated with several potential mechanisms of action, including reduction of pathogenic protein aggregates, antiapoptotic activity, regulation of autophagy, anti-inflammatory and antioxidant activities, modulation of neurotransmitters, and activation of neurotrophic factors and neurogenesis (Fig. 3).

These neuroprotective features make asarones from AG or AT a potential therapeutic for treating neurological disorders, such as AD, PD, depression, anxiety, epilepsy, and stroke. These results can also explain the therapeutic effects of traditional Korean medicines, including Shi Chang Pu, on neurological diseases. However, the most studied AG- and AT-containing formulas and decoctions against neurological disorders were of Chinese traditional medicine origin. Therefore, more research is needed on the therapeutic potentials of the Korean medical formulas and decoctions, including Shi Chang Pu, against neurological disorders. In this review, several limitations of this study also require consideration. First, we searched only databases written in English, and the exclusion of studies published in non-English languages may lead to some selection bias. Second, many studies evaluated the neuroprotective effects on neurological diseases by employing preclinical *in vitro* and *in vivo* studies, which differ greatly from human patients. Therefore, we hope this review will encourage clinical trials on AG and AT, as well as their active components, in patients with neurological disorders.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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