REVIEW
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Advances in the study of senegenin in vascular cognitive impairment

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Author contributions

Lu YT conceived and designed the study, provided administrative support, collected, analyzed and interpreted data, wrote the manuscript. Chen ZY provided conception and design, administrative support, analyzed and interpreted data, wrote manuscript. Cao XM and He L provided study materials, wrote manuscript. Xiang YY provided administrative support, wrote manuscript. Wang ZX, Yu TR, and Yin XP wrote manuscript. All the authors approved the final version.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

VCI, vascular cognitive impairment; TCM, traditional Chinese medicine; VD, vascular dementia; AD, Alzheimer's disease; VCIND, vascular cognitive impairment no dementia; MRI, magnetic resonance imaging; BBB, blood-brain barrier; IL-6, interleukin-6; NF-κB, nuclear factor kappa B; ROS, reactive oxygen species; Bcl-2, B-cell lymphoma 2; Bax, Bcl-2-associated X protein; mTOR, mechanistic target of rapamycin; Aβ, amyloid beta; NO, nitric oxide; LPS, lipopolysaccharide; GluR1, glutamate receptor 1; GluR2, glutamate receptor 2; 5-HT, serotonin (5-hydroxytryptamine); Parkin, Parkin RBR E3 ubiquitin protein ligase; TNF-α, tumor necrosis factor alpha; SVD, small vessel disease; CCH, chronic cerebral hypoperfusion; NLRP3, NOD-like receptor family pyrin domain containing 3; BACE, β-secretase.

Citation

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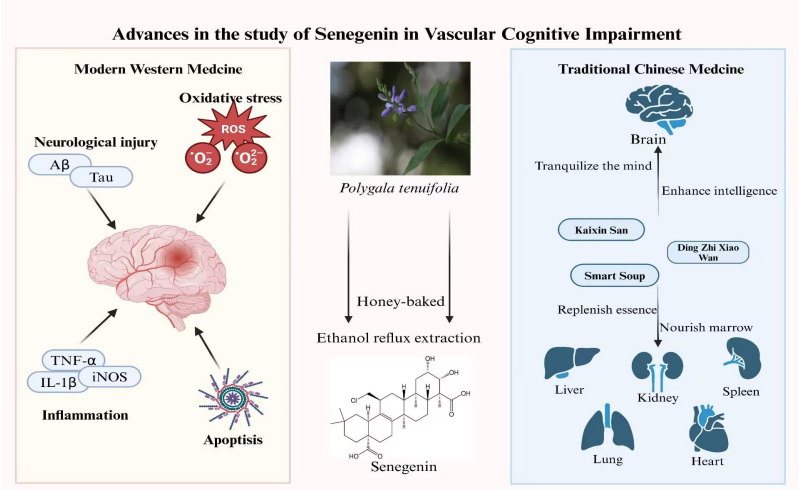
Abstract

Vascular cognitive impairment (VCI) denotes a condition marked by parenchymal brain damage resulting from vascular issues, ultimately culminating in cognitive deterioration that spans from mild cognitive impairment to vascular dementia. Senegenin is a saponin extract obtained from *Polygala tenuifolia*, a traditional Chinese medicinal herb known for its significant neuroprotective properties. The review analyzes the impact of senegenin on VCI from the viewpoints of traditional Chinese medicine (TCM) and contemporary medical practices. From the standpoint of TCM, we examine three notable traditional Chinese medicine formulations: Kaixin San, Dingzhi Xiaowan, and Smart Soup. We extensively examine the neuroprotective effects, antioxidant capabilities, and anti-inflammatory actions of senegenin from a contemporary medical standpoint. Additionally, we perform a retrospective review of the extraction and formulation techniques of senegenin. The aim of this review is to summarize the particular mechanisms of senegenin's multi-targeting and to offer novel insights into clinical therapy strategies for VCI.

Keywords: Senegenin; vascular cognitive impairment; vascular dementia; *Polygala tenuifolia*; traditional Chinese medicine; modern medicine



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Highlights

1. This review bridges traditional Chinese medicine and modern medicine to systematically elucidate senegenin's multi-target mechanisms against vascular cognitive impairment.
2. Senegenin exhibits synergistic neuroprotective, antioxidant, and anti-inflammatory effects through key pathways including Bcl-2/Bax, PI3K/Akt, and NLRP3.
3. The article highlights optimized extraction methods that enhance bioavailability while reducing toxicity, providing crucial insights for clinical translation.

Medical history of objective

Senegenin, a key bioactive compound from *Polygala tenuifolia*, was first documented in the *Shennong Bencao Jing* (compiled in 1st century B.C.–2nd century C.E.) as a superior herb for treating cognitive disorders. Its use was further detailed in Hongjing Tao's *Bencao Jingji Zhu* (compiled in 420 C.E.–589 C.E.) and Shizhen Li's *Compendium of Materia Medica* (compiled in 1596 C.E.), emphasizing its role in calming the spirit and enhancing memory. Modern pharmacological effects show that senegenin possesses excellent action in the central nervous system, especially for the treatment of VCI, through its neuroprotective, anti-inflammatory, and antioxidant properties.

Introduction

Vascular cognitive impairment (VCI) has a wide-ranging definition that includes mild cognitive impairment (VCIND) with vascular dementia (VD), as well as mixed cognitive impairment in which vascular factors are combined with neurodegenerative diseases [1]. About 20% of dementia globally is predominantly cerebrovascular, and another 20% is mixed (vascular + Alzheimer's disease). By 2050, there will be a significant increase in patients with vascular-related dementia, especially in low- and middle-income countries [2]. What's more, pure VCI is not rare: in the elderly population without neurodegenerative lesions, 20.9% had significant cerebrovascular lesions, of which 42.3% developed cognitive impairment, confirming that pure VD can exist independently [3]. VD as the world's second most prevalent type of dementia besides Alzheimer's disease (AD) can be subdivided into post-stroke dementia, subcortical ischemic vascular dementia, multiple infarct dementia, and mixed dementia [4]. But, the diagnosis of purely vascular dementia is uncommon in clinical studies and autopsies, whereas mixed dementia is more common in the elderly patient population, with up to 75% of dementia patients having evidence of vascular pathology among their autopsy findings [5]. However, in epidemiologic studies, many VDs due to non-stroke vascular brain injury with mixed dementia tend to be misdiagnosed as AD in the absence of imaging and neuropathologic The probability of small-vessel disease in these patients is more than 80%, especially microinfarcts, which can be difficult to detect on normal-intensity MRI and autopsy, the gold standard for studying the pathologic correlates of dementia, often has a therapeutic lag, although small infarcts, which are difficult to detect on MRI, can be observed [6]. In past studies, it has been shown that approximately two-fifths of patients with VCIND will progress to VD within two years, and in the process of progression, patients will experience irreversible neurological damage by expanding the scope of their cognitive impairment, with extensive damage to the cognitive domains, which will severely affect their quality of survival [7]. Therefore, earlier intervention for VCIND patients to slow down the course of the disease or even not develop VD will be the main research direction for the treatment of VCI nowadays and in the future. So, risk factor control by some effective medications with few side effects is very important [8]. Systemic microenvironmental alterations as well as cerebrovascular aging are the main causes of VCI and AD; focusing on specific factor modulation in the microenvironment (e.g., IGF-1/CCL11 balance) and BBB-targeted delivery strategies will provide new strategies for VCI treatment [9].

Drugs such as Galantamine, Donepezil, Memantine and Rivastigmine are already in clinical use for the treatment of VC, and cholinesterase inhibitors often lead to serious side effects along with their effectsI [10–14]. Therefore, the selection of multi-target drugs would be a potentially effective strategy for the treatment of VCI. Some active extracts or ingredients from TCM have therapeutic properties for neurological disorders due to their multi-component and multi-target properties and low toxicity. *Polygala tenuifolia* is a kind of traditional Chinese medicine (TCM) with a long history of more than 2,000 years in the treatment of cognitive disorders and dementia [15]. The genomics of *Polygala tenuifolia* has been analyzed in previous studies to elucidate the gene expression of senegenin, which has a chemical formula of $C_{30}H_{45}ClO_6$ (Figure 1) [16]. In the existing studies, it has been proven to be safe in specific populations, as well as having important roles in neuroprotection and anti-inflammation [17–19].

Studies in traditional Chinese medicine

Research on vascular cognitive impairment in TCM

In TCM, VCI is often manifested as forgetfulness, slowed reaction, poor concentration, decreased calculation ability, and unclear speech [20]. A national cross-sectional study showed that the overall prevalence of vascular dementia was 1.6 percent, representing 3.92 million Chinese adults aged 60 years old or even older with vascular dementia [21].

TCM believes the kidneys are the key to linking the brain with the heart, liver, lungs, and other organs. If kidney essence is deficient and phlegm and blood stasis block the channels, the normal functioning of the brain will be affected, leading to cognitive disorders and even dementia [22]. Therefore, research on the application of Chinese herbal medicines for kidney tonification in both the prevention and treatment of dementia is still in progress, and some early studies have proved that the linkage between the brain and the kidneys in traditional Chinese medicine can be compared with the pothalamic-pituitary-thyroid/gonadal axis and the hypothalamic-pituitary-adrenal axis (Figure 2) [23–25].

Currently, most conventional pharmaceuticals are based on controlling risk factors or improving symptoms, and the choice of efficacy is limited with the development of the disease. In recent years, clinical studies on Chinese materia medica in treating VCI have shown an incremental trend, which confirms that Chinese materia medica has certain advantages in controlling the progression of cognitive disorders, improving the cognitive function of patients, managing vascular risk factors, etc [26]. Nonetheless, the data supporting the use of Chinese materia medica for the prevention and treatment of dementia necessitates enhancement through more comprehensive and high-quality research, especially to clarify the exact mechanisms involved [27].

Treatment of vascular cognitive impairment by traditional Chinese medicine and its clinical progress

In TCM, the treatment of VCI is divided into pharmacological and non-pharmacological treatments, of which non-pharmacological treatments are Shiatsu and electro-acupuncture, together with the guidance of correct living habits, such as suitable diet, Aerobic exercise and efficient sleep [28–32].

Regarding pharmacological treatment, TCM experts propose a therapeutic strategy of "invigorating blood circulation, resolving phlegm, and dredging collaterals" to address acute manifestations, combined with "tonifying the kidney, replenishing essence, and nourishing marrow" for fundamental regulation. Historical frequency analysis of herbal applications reveals the predominant use of tonifying medicinals, mostly warm-natured, primarily entering the

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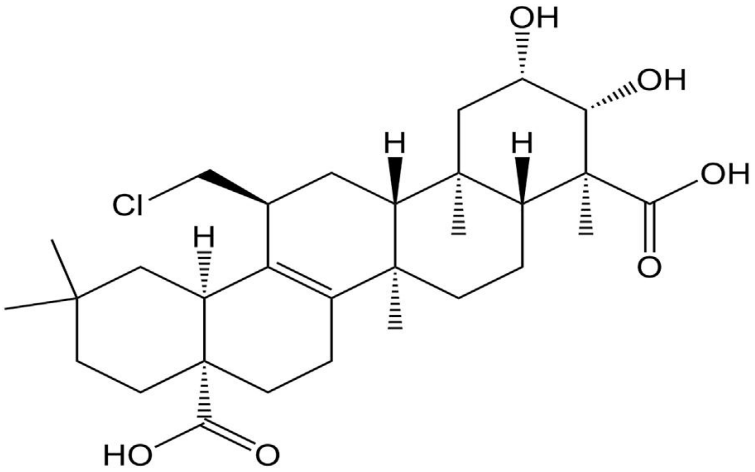

Figure 1 Chemical formula of senegenin

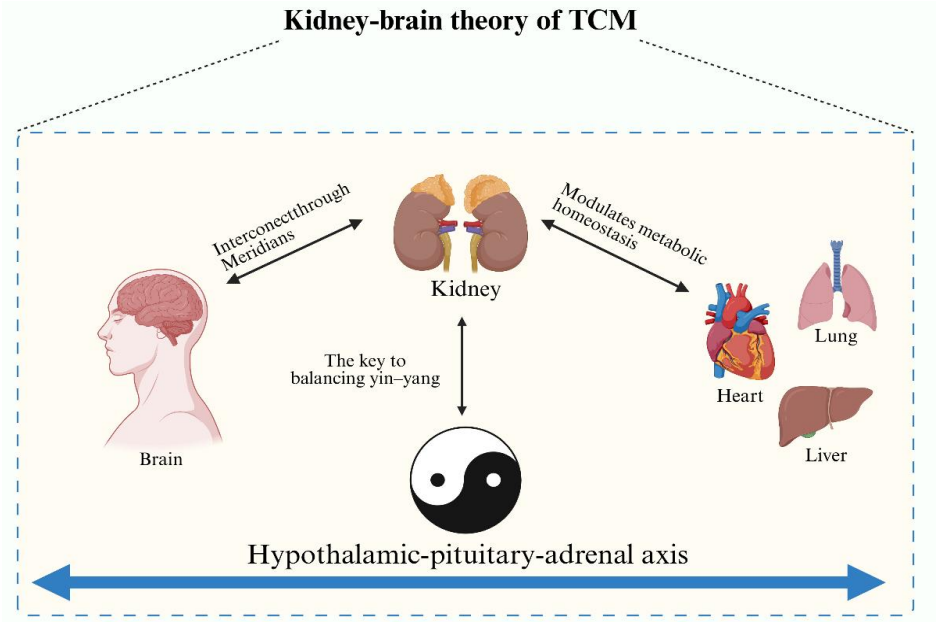

Figure 2 The key effect of kidney in brain.

This diagram illustrates the Kidney-brain theory in TCM, where the kidneys play a critical role in harmonizing up-down regulatory functions. Research suggests that the renal-brain connection mirrors the activity of the hypothalamic-pituitary-adrenal axis. A large number of TCM treatments for encephalopathy not only concentrate on localized brain therapy but also pertain to the entire body's organs, with the kidneys being the most critical.

liver, kidney, spleen, and heart meridians. The most frequently employed categories include "shen-calming" (keep mental tranquility), "blood-invigorating" (promote blood circulation), and "orifice-opening medicinals" (sensory and mental clarity by removing blockages) [33]. *Polygala tenuifolia* is the most utilized shen-calming medicinal in VCI management [34]. Studies indicate that Polygala tenuifolia is frequently coupled with Ligusticum chuanxiong and Acorus tatarinowii in numerous TCM formulations, significantly contributing to dementia treatment [35, 36]. Senegenin, the primary bioactive compound in Polygala, has been shown to preserve its neurotherapeutic effects on the central nervous system. Classical formulas documented in historical texts, subsequently modified by renowned TCM practitioners, consistently highlight Polygala's therapeutic significance.

Kaixin San. Kaixin San consists of *Polygalae Radix*, *Poria*, *Ginseng Radix et Rhizoma*, and *Acori Tatarinowii Rhizoma*, and was originally derived from Simiao Sun's ancient book *Beiji Qianjin Yaofang*, which is a classical prescription for the treatment of cognitive impairment and morbid forgetfulness [37]. Early-phase clinical trials have confirmed its favorable safety profile with no severe adverse events reported at therapeutic doses (3–6 g/day) [38]. Kaixin San attenuated Tau hyperphosphorylation via AKT/GSK3β inhibition, suppressed neuroinflammation through TLR4/NF-κB blockade, to reduced neuronal apoptosis, synergistically improving cognitive deficits in SAMP8 mice [39]. It also counters Aβ-induced synaptic deficits by enhancing AMPAR (GluR1/2), anchoring proteins (ABP/GRIP1/NSF), and GluR1-Ser845 phosphorylation, reducing GluR2-Ser880/PKCδ, restoring LTP and memory in mice [40]. Kaixin San is also known to relieve depression and improve memory.

Dingzhi Xiaowan. Dingzhi Xiaowan is derived from Kaixin San, but compared with Kaixin San, Dingzhi Xiaowan has increased the proportion of *Polygalae Radix* and *Acori Tatarinowii Rhizoma*. Highlight its therapeutic efficacy in the treatment of dementia [41]. Phytochemical analysis of the traditional Chinese formulation Dingzhi Xiaowan revealed that *Polygalae Radix*, a principal bioactive component, exhibits dual pharmacological properties: significant nootropic effects through modulation of neurotransmitter pathways, and pharmacokinetic enhancement through facilitated absorption and bioavailability optimization of co-formulated herbal constituents [42]. Dingzhi Xiaowan alleviates depressive behaviors by upregulating TPH

to enhance 5-Hydroxytryptamine(5-HT) synthesis and suppressing 5-Hydroxytryptamine Transporter (5-HTT)-mediated reuptake, elevating brain 5-HT levels in CMS rats without monoamine oxidase inhibition, demonstrating improved safety [43].

Smart soup. *Polygalae Radix*, together with *Poria* and *Acori Tatarinowii Rhizoma*, make up the formula Smart Soup in the ancient book *Yixin Fang*, in which *Polygala tenuifolia* accounts for about one-third of the ingredients.

Polygala tenuifolia accounts for about one-third of the ingredients in this formula, playing a role in "replenishing Qi and blood" (replenishes vital energy and nourishes blood to enhance overall vitality) filling in essence, and tonifying the marrow. Smart soup plays an important role in eliminating Aβ protein in dementia [44]. Two-year retrospective cohort research included 14 moderate-to-severe AD patients. The combination group (Aricept + Smart Soup, n = 7) showed significantly less worsening in ADAS-cog scores (+3.65 ± 1.99) compared to the Aricept-only group (+18.00 ± 5.08, $P < 0.05$) [45].

Due to the distinctive theoretical framework of TCM, senegenin exhibits significant therapeutic potential for the treatment of VCI. Nonetheless, the specific molecular pathways that account for its efficacy deserve additional clarification. Consequently, employing contemporary research methodologies to systematically examine the molecular foundation of senegenin's neuroprotective, antioxidant, and anti-inflammatory properties is essential. This method offers scientific support for TCM insights and clearly defines senegenin's multi-target processes in addressing VCI pathology, establishing a foundation for innovative therapeutics. This section outlines significant advancements from a contemporary medical perspective.

Research in the perspective of modern western medcine

Risk factors and biomarkers associated with vascular cognitive impairment

The fundamental pathology of VCI includes cerebrovascular injuries (macrovascular atherosclerosis, small vessel disease, chronic hypoperfusion), resulting in neuronal injury through white matter disruption, hidden microinfarcts, and blood-brain barrier (BBB) leaking [46–48]. BBB disruption (e.g., pericyte impairment) constitutes a terminal common pathway, with CypA-EMMPRIN-MMP9 processes involved in amyloid-associated subtypes [49, 50]. Modifiable risk factors (hypertension, dyslipidemia, and diabetes) exacerbate damage by disrupting neurovascular coupling and nitric oxide signaling, resulting in hypoperfusion and oxidative stress [51–53]. Biomarkers encompass IL-6/sTNFR1 for systemic inflammation [54, 55]. Cerebrospinal fluid/serum albumin ratio (QAlb) for blood-brain barrier permeability, and MRI cerebrovascular reactivity for hemodynamic reserve [56, 57]. The clinical identification of vascular dementia will remain a significant problem; thus, determining its related biomarkers will be crucial for accurate diagnosis (Table 1) [50, 55, 56, 58, 59–73]. Dependable biomarkers are essential for the early diagnosis, classification, prognostic evaluation, and therapeutic surveillance of VCI (particularly non-stroke and mixed kinds), representing a significant focus and challenge in contemporary research.

Effects of senegenin on vascular cognitive impairment

Recent studies have shown that cardiovascular and cerebrovascular risk factors are strongly associated with cognitive impairment and dementia [74]. Atherosclerosis, small vessel disease, cerebral microhemorrhage, and cerebral atrophy often lead to neurological damage such as apoptosis (Bcl-2/Bax), inflammation (IL-6, α-globin, NLRP3), oxidative stress (H_2O_2, NO, O_2^-), and loss of neurons, which leads to a series of cognitive impairment and dementia [75–78].These mechanisms are often associated with pathways such as Aβ/Tau and RhoGDIα, PI3KAkt, NF-κB, and others [79–80]. Mixed cases are common in patients with VCI [81], and the use of multi-targeted drugs may be of more excellent help in the treatment of VCI. Senegenin demonstrates neuroprotective properties via many mechanisms in neuronal cells. It mitigates neuroinflammation, diminishes oxidative stress, and curtails apoptosis. Senegenin, a natural chemical, exhibits considerable effectiveness in reducing neuronal damage while limiting side effects. Nonetheless, the data supporting the utilization of Chinese materia medica for the prevention and treatment of dementia necessitates enhancement through more comprehensive and high-quality research, especially to clarify the exact mechanisms involved. Moreover, some tential signaling pathways of senegenin have been elucidated (Figure 3) [82, 83].

Neuroprotective and trophic effects

The accumulation of highly phosphorylated microtubule-associated proteins tau and Aβ in the brain is highly relevant to the development of cognitive impairment and even dementia in both AD and VD. Biochemical evidence of cerebral hypoperfusion associated with SVD, Aβ levels, plaque load, EDN1 levels, and Braak tangle stage has been found in AD, VD, and mixed dementia and is most widespread in mixed dementia [84]. A clinical study by Hyemin Jang, et al. applying the AT (Aβ/tau) classification system to patients with SVCI provided evidence of the influence of AT on cognitive function in patients with VCI and also demonstrated that the accumulation of highly phosphorylated microtubule-associated proteins tau and tau in brain is highly correlated with cognitive impairment and even dementia. Evidence indicates that AT influences cognitive function and that cerebral SVD may independently contribute to cognitive impairment, irrespective of Aβ [85]. Elevated TGF-β1 induces angiotensin II (AngII), which elevates blood pressure, reduces hippocampal blood flow, and impairs synaptic and cognitive function [86]. In the study conducted by Jesky et al., PC12 cells were pretreated with different

Table 1 Biomarkers associated with cerebrovascular disease and their function

Biomarker	Function	Reference
oxLDL, MMP-9	Atherosclerotic lesions	[59]
PIGF	cerebral small vessel pathology	[60]
QAlb	Increased BBB permeability	[56]
fMRI BOLD	Cerebral amyloid angiopathy	[61]
VCAM-1, HCY	endothelial dysfunction and atherosclerosis	[62]
hsa-miR-1972, hsa-miR-3141, hsa-miR-26b-5p	WMLs	[63]
mTOR	AD, age-related cerebrovascular dysfunction	[64]
MCP-1, IL-18, GDF-15, myeloperoxidase, IL-6, TNF-α,NLRP3	Inflammation, cerebrovascular disease	[55], [65], [66]

Table 1 Biomarkers associated with cerebrovascular disease and their function (*continued*)

Biomarker	Function	Reference
Aβ, CRP	large artery atherosclerosis, ischemic stroke, Alzheimer dementia	[67]
Aβ, tau, clusterin	CMBs, CSVD	[68]
PCT, MR-proANP	SBI, SCVD	[69]
Plasma osteopontin	Cerebral Atrophy, AD, VCI	[70]
ARTS	SVD	[71]
C1QA, C1QB, C1QC, CD163, FCGR2A	VCI	[72]
NfL, GFAP	VCI, SVD, white matter injury, neuroaxonal injury, AD	[73]
CypA, EMMPRIN, MMP-2, MMP-9	VD, white matter hyperintensities, lacunar infarcts, cortical infarcts	[50]

PIGF, plasma placental growth factor; Qalb, cerebrospinal fluid/serum albumin ratio; fMRI BOLD, functional MRI blood oxygen level–dependent; VCAM-1, vascular cell adhesion molecule 1; HCY, homocysteine; mTOR , mechanistic/mammalian target of rapamycin; Aβ, β-amyloid; CRP, C-reactive protein; PCT, Procalcitonin; MR-proANP, midregional pro-atrialnatriuretic peptide; ARTS, an in vivo MRI-based classifier of arteriolosclerosis; NfL, plasma neurofilament light chain; GFAP, glial fibrillary acidic protein; CypA, Cyclophilin A; WMLs, White matter lesions; AD, Alzheimer's disease; CMBs, Cerebral microbleeds; CSVD, small vessel disease; SBI, silent brain infarcts; SCVD, subclinical cerebrovascular damage; SVD, small vessel disease.

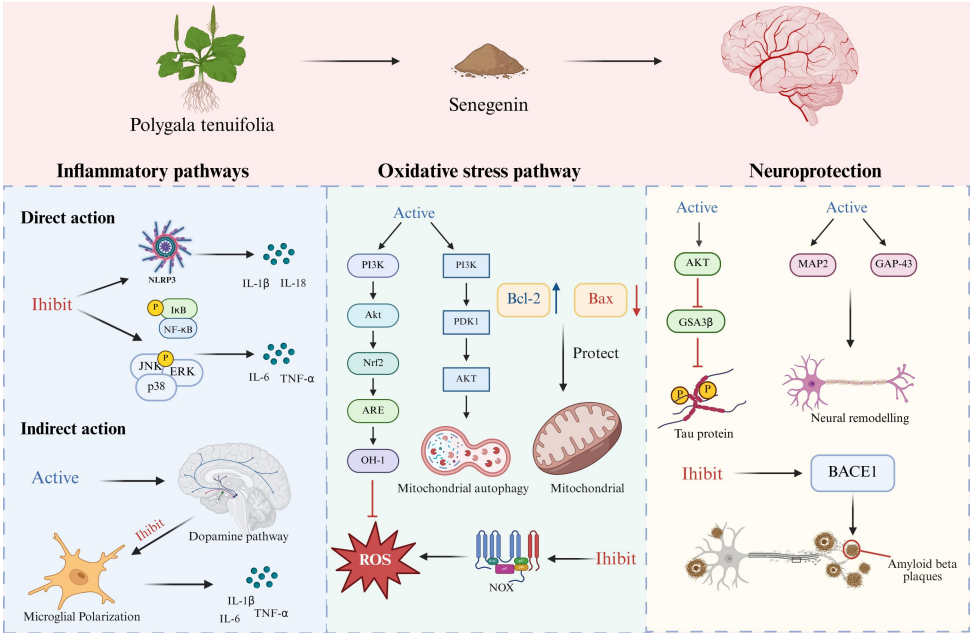

Figure 3 Molecular mechanism of senegenin in the nervous system.

This figure primarily elucidates the key mechanisms of senegenin in VCI through three pathways: the inflammatory pathway, the oxidative stress pathway, and neuroprotection. Demonstrates the significant role of senegenin in VCI treatment. ROS, reactive oxygen species; VCI, vascular cognitive impairment.

concentrations of senegenin before exposure to Aβ(25–35). Principal discoveries encompass Pretreatment with 20 μg/mL senegenin enhanced cell viability by 34% ($P < 0.001$ compared to the Aβ-only group). Pretreatment with 40 μg/mL senegenin enhanced survival by 23% ($P < 0.001$). Senegenin also markedly enhanced the expression of neurite development proteins MAP2 and GAP-43. This molecular reaction was directly associated with increased neurite outgrowth, as confirmed morphologically and by immunofluorescence [87]. This experiment presents evidence of the potential of senegenin to promote neurite growth and increase cell survival. In addition, Chen, et al. found that senegenin increased the proportion of Tuj-1 (neuronal marker) and GFAP (astrocyte marker) positive cells and increased the proportion of astrocytes in neuronal cells [88]. The increased frequency of mEPSCs in senegenin was blocked by BAPTA-AM, an intracellular calcium chelator, which regulated intracellular calcium levels and enhanced presynaptic neurotransmitter release [89]. The inhibitory effect of senegenin on β-secretase (BACE) activity was assessed using a BACE activity assay kit. Senegenin reduced Aβ production by inhibiting BACE activity (up to 76.1%) without affecting the expression of the C99 fragment [90]. The root extract PSM-04 (similar to senegenin) reduced 10 neurotoxicity induced by L-glutamate or Aβ oligomers and reduced amyloid plaques and glial cell proliferation in the hippocampus in in vitro experiments [91].

Whether senegenin trophoblasts by increasing proteins such as MAP2 or by down-regulating Ub so that Aβ proteins are inhibited and Tau phosphorylation is reduced, these phenomena suggest that senegenin significantly improves cognitive function.

Reduction of oxidative stress

Reactive oxygen species (ROS) are by-products of normal oxygen metabolism and play an important role in signaling, eliminating foreign microorganisms, promoting immune responses, etc. They play an important role in various systemic diseases, such as tumors, cardiovascular diseases, and neurological disorders [92–94]. However, excessive ROS can lead to oxidative stress in the organism, resulting in neuronal damage and disease progression. ROS can activate intracellular ROS can activate intracellular signaling pathways such as mTOR, AMPK, and Sirtuins, affecting cellular metabolism and stress responses [95]. Mitochondria are important sites for ROS production and, therefore, play an important role in human health and disease, and their dysfunction has been linked to various aging-related diseases. Expression of Parkin-induced mitochondrial autophagy in Drosophila will reduce proteotoxicity and slow aging [96]. Previous studies showed that mitochondrial dysfunction in patients with VCIND is associated with oxidative stress and activation of the ERK-Mfn2 signaling axis [97]. Bcl-2, as an antioxidant, plays an important role in the control of oxidative stress as well as apoptosis and can protect the cells from H_2O_2 and menaquinone-induced oxidative cell death. In the case of Bcl-2 overexpression, it can ultimately inhibit lipids. In the Bcl-2/Bax dimer, high expression of Bcl-2 inhibits apoptosis, while high expression of Bax promotes apoptosis [98].

In previous studies, it was found that senegenin could inhibit the JNK signaling pathway, increase the expression of Bcl-2 and inhibit the expression of Bax, increase the Bcl-2/Bax ratio, protect the mitochondrial structure and eventually inhibit the apoptosis of PC12 cells, and also up-regulate the expression of RhoGDIα protein to inhibit the apoptosis of H/R-induced neurons [99]. In addition, it was also found that senegenin from *Polygala tenuifolia* could increase the protein expression of Nrf2 and HO-1 and activate the PI3K/Akt signaling pathway, reflecting its excellent antioxidant effect and anti-apoptotic ability [100]. Meanwhile, senegenin from *Polygala tenuifolia* reduced the production of ROS by inhibiting NOX activity [101]. Moreover, senegenin induced PINK1/Parkin-mediated mitochondrial autophagy for neuroprotection and elucidated that senegenin could alleviate the neurological damage caused by the activation of mitochondrial autophagy by Aβ(1–42) [102].

Senegenin ultimately controls oxidative stress and protects neuronal cells by controlling the ratio of Bcl-2/Bax, reducing the production of ROS, and up-regulating the expression of RhoGDIα protein.

Inhibition of inflammation

Chronic cerebral ischemia (CCH) causes 80% of all brain injuries; therefore, cellular inflammation due to CCH is also common in brain injuries, and inflammatory factors can act as a bridge between CCH and brain injury [103]. Specifically, some early neuroinflammatory conditions can influence the development of other mechanisms leading to brain injury, such as increased microglia immunoreactivity or white matter lesions in older adults due to blood-brain barrier damage [104]. Elevated inflammatory factors such as TNF-α, IL-6, and IL-23 due to obstructive sleep apnea syndrome will lead to cognitive decline [105]. Activation of NF-κB and P65 predisposes to damage of the blood-brain barrier, and severe immune cell infiltration occurs, causing significant cognitive decline [106]. Na^+, Ga^+, and ROS activate inflammatory vesicles such as NLRP3, which promotes the onset of inflammatory cell death by cellular pyroptosis [107]. IL-1β, TNF-α, IFN-γ, IL-4, IL-5, and G-CSF levels were significantly higher in VD patients compared to AD. In addition, levels of two chemokines, MCP-1 and MIP-1β, were substantially lower in patients with VD, and cellular prion proteins in cerebrospinal fluid or serum served as cellular markers to differentiate between the two and correlated with inflammatory factors [108]. It has been mentioned in previous studies on VCI that microglia activate in VD, releasing pro-inflammatory cytokines such as TNF-α and IL-1β, which are associated with neuronal loss and contribute to the development of dementia [109]. When NO is overproduced, or cells are in a pro-oxidative state, NO can react with superoxide anion to generate peroxynitrite, a strongly oxidizing anion that causes protein nitration and leads to damage to cellular components. NO also activates cyclooxygenase, which produces free radicals and prostaglandins in the catalytic process, and both are closely associated with the development of neuroinflammation [110].

Senegenin plays a role in inhibiting NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation, caspase-1 fragmentation, and IL-1β secretion by decreasing ROS and inhibits NLRP3 inflammasome activation by increasing dopamine levels in the striatum and decreasing lipopolysaccharide (LPS) [111]. Basal therapy targeting NLRP3 may become a new strategy [66]. And the corresponding drugs are being actively developed [112]. In addition, fenugreek saponins inhibited the activation of these pro-inflammatory signaling pathways by reducing the phosphorylation of JNK1/2, ERK1/2, p38, and NF-κB (p65) and by preventing the phosphorylation and degradation of IκBα [113]. In addition, senegenin attenuates inflammatory responses and improves cognitive deficits by inhibiting microglia M1-type activation and modulating microglia polarity [114].

Cognitive impairment is often accompanied by inflammation, and effective anti-inflammatory drugs are urgently needed. Senegenin inhibits inflammation from multiple angles by reducing ROS, inhibiting LPS signaling, and modulating dopamine levels. Therefore, senegenin contributes significantly to treating VCI in the anti-inflammatory pathway.

Extraction and pharmacological toxicity of senegenin

In modern research, more than 140 compounds have been extracted from senegenin, mainly three major groups: triterpene saponins, ketones, and sugar esters; senegenin is a hydrolysis product of triterpene saponins through the hydrolysis of the sugar group, the total saponins are converted to senegenin, which reduces toxicity in senegenin and reduces the molecular weight so that it can pass through the blood-brain barrier to play a role in nerve cells with ease [115].

In previous studies, different extraction methods significantly influenced the efficacy of *Polygala tenuifolia* extracts. Ultrasound-assisted extraction (UAE) produced higher saponin content (DISS and PolyIII) compared to other techniques. The optimal conditions were: Temperature: 48 ˚C, Time: 32 min, Liquid-to-solid ratio: 10 mL/g, Ethanol concentration: 70%. The extract was filtered using a Buchner funnel and a 0.2 μm membrane, then adjusted to a volume of 25 mL. The predicted saponin content reached 5.60 mg/mL, outperforming other methods. Experimental results aligned closely with predictions. The LS-SVM model demonstrated superior extraction efficiency and antioxidant activity compared to RSM [116].

Processing methods have a significant impact on Chinese herbal medicines. Various adjuvants, such as wine, honey, and brine, are usually used in the processing to enhance the efficacy and reduce the toxicity of crude drugs [117]. The main preparation methods for *Polygala tenuifolia* include the preparation of *Polygala tenuifolia*, honey *Polygala tenuifolia*, and raw *Polygala tenuifolia*. After controlled experiments and statistics, it was found that the efficacy of honey *Polygala tenuifolia* in relieving cough, resolving phlegm and sedation would be better than that of the other methods of preparation, perhaps because of the use of honey in the preparation of honey, which has specific moisturizing effect itself, so that the combination of both of them would yield more desirable results. However, different concoctions can uniquely trigger other aspects of the efficacy of *Polygala tenuifolia*, thus achieving better concoction results [118]. Research has shown that honey *Polygala tenuifolia* not only has lower intestinal toxicity than raw *Polygala tenuifolia*, but also improves the bioavailability of certain components (e.g., Sibiricose A5, Sibiricose A6, 3,6-disinapoyl sucrose) [119].

Experiments with isolated intestinal motility and PGE2 and TNF-α levels revealed that glycosylated total senegenin caused significant intestinal contraction and decreased PGE2, attenuated gastric mucosal protection, but did not affect TNF-α. In contrast, senegenin had less effect on these indices, demonstrating lower gastrointestinal toxicity

[120]. However, some studies have shown that gastrointestinal flatulence and thinning of the intestinal wall can still occur with prolonged use or high concentrations of senegenin [121, 122]. Some research is still needed to determine how to determine the dosage of senegenin as well as the dosing cycle. Extraction and processing are critical to the efficacy of senegenin: honey-processing reduces toxicity while preserving efficacy, whereas modern methods face standardization and BBB delivery challenges. Future advancement requires activity-guided quality control, elucidating processing-induced structure-activity relationships, and nano-delivery strategies to unlock therapeutic potential.

Conclusion

This study consolidates information endorsing senegenin, extracted from *Polygala tenuifolia*, as a potential multi-target therapeutic for VCI. Preclinical studies convincingly illustrate its neuroprotective, antioxidant, and anti-inflammatory properties – regulating critical pathways such as Bcl-2/Bax, PI3K/Akt, NLRP3, and Aβ/Tau. Its congruence with TCM principles (e.g., "tonifying kidney essence") further emphasizes therapeutic potential. Existing clinical studies have been able to demonstrate the safety and efficacy of senegenin, but more in-depth and extensive research is needed to mature its clinical use (e.g., clarifying the purity of senegenin extraction and clinical dosage), and the existing laboratory models are difficult to fully simulate the complexity of the human VCI condition, which has led to an obstacle in the translation from the laboratory to the clinic. Therefore, multi-stage and multi-center clinical studies are a priority for the future. At the same time, we will integrate cutting-edge technologies (single-cell genomics, spatial genomics) and carry out multidisciplinary cross-collaboration (computer science, nanotechnology) to finely analyze the mechanism of action and network of senegenin at the molecular, cellular, and loop levels and to identify its core targets and biomarkers so as to validate it in a model that is more closely related to the human body. Meanwhile, connecting Chinese and Western medical theories and combining senegenin with existing therapeutic strategies aims to achieve better efficacy.

In conclusion, senegenin represents a strong candidate from TCM for the treatment of VCI. To fully realize its therapeutic potential, coordinated interdisciplinary efforts focused on generating robust clinical evidence and deepening mechanistic insights are required. The success of these efforts is expected to provide a novel, multi-targeted therapeutic strategy to reduce the burden of VCI on patients and society.

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