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Review Article

Panax Ginseng in the treatment of Alzheimer's disease and vascular dementia

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ABSTRACT

Dementia has become one of the most important diseases threatening human health. Alzheimer's disease (AD) and vascular dementia (VaD) have the highest incidence rates among the types of dementia, but until now, therapeutic methods have been limited. *Panax ginseng* has been used in China for thousands of years to treat dementia, and modern medical studies have found that it contains multiple active components, such as ginsenosides, polysaccharides, amino acids, volatile oils and polyacetylenes, many of which have therapeutic effects in treating AD and VaD. Studies have found that ginsenosides have multitarget therapeutic effects in treating dementia, such as regulation of synaptic plasticity and the cholinergic system, inhibition of Aβ aggravation and tau hyperphosphorylation, anti-neuroinflammation, anti-oxidation effects and anti-apoptosis effects. Other active components of *Panax ginseng*, such as gintonin, oligosaccharides, polysaccharides and ginseng proteins, also have therapeutic effects on AD and VaD. The effectiveness of ginseng-containing Chinese medicine compounds has also been confirmed by clinical and basic investigations in treating AD and VaD. In this review, we summarized the potential therapeutic effects and related mechanisms of *Panax ginseng* in treating AD and VaD to provide some examples for further studies.

1. Introduction

With the aging population and the increase in the average life expectancy, the incidence of dementia has dramatically increased. In 2015, there were approximately 47 million dementia patients worldwide, and this number is expected to triple by 2050 [1]. Patients with dementia experience impairments in memory, executive function, and other cognitive functions, accompanied by a decline in their daily living abilities, imposing a heavy burden on families and society. Alzheimer's disease (AD) and vascular dementia (VaD) are the most common types of dementia, accounting for approximately 80% of all dementia patients [2]. In China, the estimated prevalence of dementia is 6% in people aged 60 years or older, 3.9% for AD, and 1.6% for VaD [3]. Despite the high incidence and serious social impact, until now, the treatment methods and curative effects have been very limited, and new treatment strategies need to be urgently addressed [4].

Panax ginseng, considered “The Lord of Herbs”, is a perennial herb that belongs to the Araliaceae family and has been used for more than 4000 years in China, Korea and Japan. It was first described as a Chinese herbal medicine in China's earliest pharmacy work “Sheng Nong's herbal classic” and has the effects of calming the spirit and soul and enhancing happiness and intelligence, and it can be used in dementia treatment [5]. Modern pharmacological studies have identified nearly 200 active components of ginseng, including ginsenosides, polysaccharides and monosaccharides, vitamins, amino acids, organic acids and non-saponin water-soluble glycosides [6]. Active components of *Panax ginseng* have a variety of pharmacological activities in many diseases, such as heart failure, myocardial ischemia, type II diabetes, Parkinson's disease, depression, cancer, and dementia [7]. Chinese herbs can be used in combination, so as to form traditional Chinese medicine compounds to treat diseases, and they have multi-ingredient and multi-target therapy synergistic effects, making them appropriate for individualized treatment schemes [8]. Many ginseng-containing Chinese medicinal compounds have been

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developed to treat dementia, such as the Huannao Yicong formula, Dengzhan Shengmai capsule and Shenma Yizhi formula [9–11].

In this review, we focused on the pharmacological effects and clinical efficacy of the active components of *Panax ginseng* and *Panax ginseng*-containing Chinese medicine compounds in the treatment of AD and VaD.

2. Ginsenosides

Ginseng saponins, namely, ginsenosides, are the most important active components of *Panax ginseng*, a type of triterpene glycoside. To date, approximately 30 types of ginsenosides have been identified from ginseng root and processed ginseng products, which are usually classified into three categories: protopanaxadiol, such as Rb1, Rb2, Rc, Rd, Rg3 and Rh2; protopanaxtriol, such as Re, Rf, Rg1, Rg2 and Rh1; and oleanolic acid (OA), such as Ro and Ri. All share a similar basic structure, but the first two belong to the dammarane family, consisting of a four-ring structure, and the latter belongs to the oleanane family, consisting of a five-ring structure (Table 1) [12–14]. Many ginsenosides produce AD and VaD treatment effects through various mechanisms. In this literature review, these mechanisms are summarized (Table 2).

2.1. Anticholinergic effects

Cholinergic neurons exist widely in the brain, especially in the thalamus, striatum, limbic system, and neocortex, and are closely related to cognition and other higher brain functions [15]. The cholinergic hypothesis is one of the most important hypotheses related to the pathogenesis of AD. Cholinergic lesions emerge in the early stages of AD, and cholinesterase inhibitors such as donepezil and galantamine are recommended for mild-to-moderate AD [15,16]. In VaD, ischemic infarction may directly damage cholinergic neurons or interrupt the lateral cholinergic pathway, and a meta-analysis showed that cholinesterase inhibitors may have beneficial effects in VaD patients, improve the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) score, and increase the clinical global impression scale [17,18].

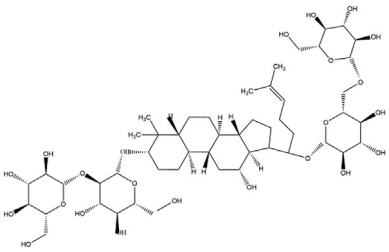
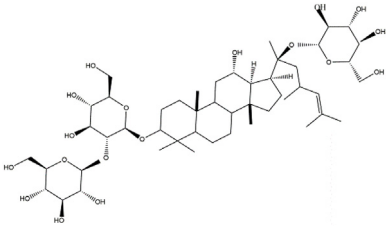
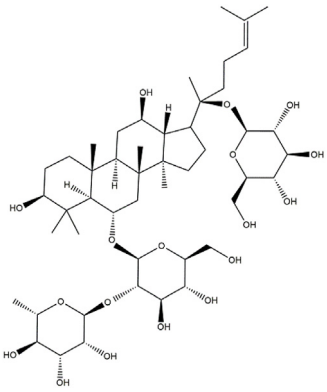
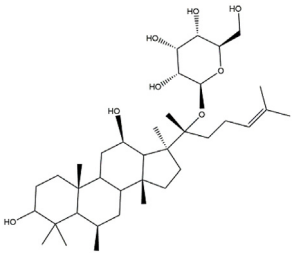
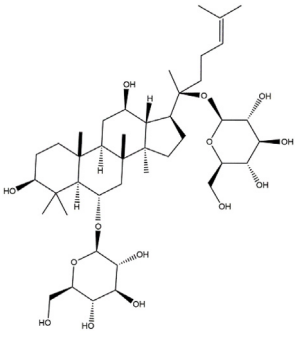
Some ginsenosides have anticholinergic activity, thus improving cognitive function. Ginsenoside Rb1 elevates acetylcholine (Ach) levels, increases choline acetyltransferase (ChAT) activity, reduces acetylcholinesterase (AChE) activity in the hippocampus of rats with cognitive impairment, and rescues cisplatin-induced memory impairment; ginsenoside Rg5 could also improve cognitive functions by regulating AChE and ChAT activities in streptozotocin-induced memory-impaired rats [19,20]. Ginsenoside Rd and Re can enhance ChAT and vesicular Ach transporter (VAChT) expression and increase ACh production in neuro-2a (N2a) cells. Ginsenoside Re also shows a dose-dependent increase in extracellular levels of ACh in the hippocampus and medial prefrontal cortex of SD rats [21,22]. Another ginsenoside, OA, could increase ACh levels in mice with cholinergic blockade-induced cognitive deficits [23].

2.2. Regulation of synaptic plasticity

Neuroplasticity is considered the internal mechanism of learning, memory, thoughts, feelings and other behaviors, and synaptic plasticity is thought to play key roles in this process [24,25]. Synaptic damage in the hippocampus and cerebral cortex has been established as an early event and a major brain structural change in AD and VaD, which is directly related to cognitive impairments [25,26]. Restoring synaptic function in AD and VaD may be a viable therapeutic method [27].

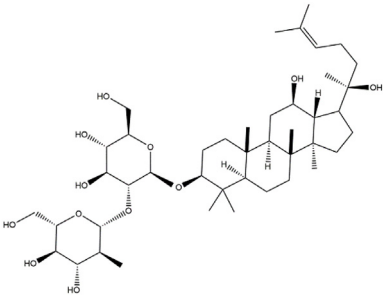
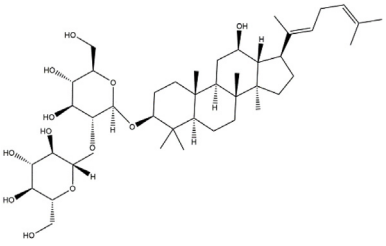
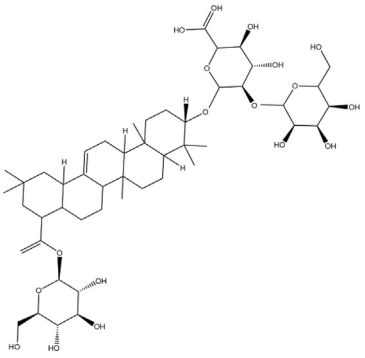
Long-term potentiation (LTP) is a persistent strengthening of signal transmission between two neurons and is closely related to

Table 1
Chemical structural formula of ginsenosides

Ginsenoside	Molecular formula	Structural formula
Rb1	C54H92O23	
Rd	C48H82O18	
Re	C48H82O18	
F1	C36H62O9	
Rg1	C42H72O14	

(*continued on next page*)

Table 1 (*continued*)

Ginsenoside	Molecular formula	Structural formula
Rg3	C42H72O13	
Rg5	C42H70O12	
Ro	C48H76O19	

learning, memory and behavior [28]. Synaptic proteins and dendritic spines are common indicators of synaptic plasticity [25]. Ginsenoside Rg1 can facilitate LTP and increase the density of dendritic spines in the hippocampus of aged mice, thus increasing memory function [29]. Other studies found that ginsenosides Rg1 and Rb1 could promote the expression of synaptic vesicles and postsynaptic membrane-associated proteins such as postsynaptic density protein 95 (PSD-95), thus improving the learning and memory abilities of dementia mice [30,31].

2.3. Targeting amyloid β (Aβ) and tau

The deposition of amyloid plaques by Aβ and the assembly of neurofibrillary tangles by hyperphosphorylated tau are the most important pathological changes in brains with AD [32]. Anti-amyloid therapy and anti-tau therapy for AD have been studied for years, including secretase inhibitors, Aβ aggregation inhibitors, Aβ immunotherapy, phosphatase modifiers, tau-aggregation inhibitors, microtubule stabilizers and others, which are expected to become a new breakthrough in AD treatment [33]. Cerebral amyloid angiopathy is an important pathological feature of VaD [34].

Ginsenoside Rg1 decreases amyloid precursor protein (APP) expression, Aβ deposition and hyperphosphorylated Tau levels, alleviates neuronal damage in the hippocampus and cortex of AD model mice, and improves cognitive functions tested by the Morris water maze test and open field experiments [35]. Ginsenoside F1, a metabolite of Re and Rg1 deglycosylated by intestinal microflora, can protect against $A\beta_{1-42}$-induced cytotoxicity, reduce the secretion of $A\beta_{1-42}$ in mouse neuroblastoma N2a and human neuroblastoma SH-SY5Y cells and decrease Aβ plaque formation in APP/PS1 mice. The mechanisms may be related to the increase in the levels of insulin-degrading enzyme (IDE) and neprilysin (NEP), which play important roles in Aβ catabolism [36]. Ginsenoside Rg3 promotes microglial activity and Aβ uptake by promoting the expression of scavenger receptor class A (SRA), clathrin and caveolin, accelerating the degradation of Aβ by increasing the levels of NEP and IDE, and further increasing the nonamyloid degradation mode of amyloid precursor protein (APP) in APP-Swe-transfected N2a cells [37,38]. Ginsenoside Compound K (CK) (Fig. 1), the main metabolite and final absorption form of protopanaxadiol-type ginsenosides in the human intestine by gut microbiota, induced a decrease in $A\beta_{1-42}$ deposition in the hippocampus of VaD rats and protected against learning and memory impairments by enhancing the phosphorylation of GSK-3β and IDE expression [39]. Ginsenoside Rd decreased the levels of hyperphosphorylated tau in the olfactory bulb, telencephalon and spinal cord of AD model mice by inhibiting the activities of GSK 3β and cyclin-dependent kinase 5, thereby ameliorating cognitive impairment [40].

2.4. Anti-inflammation and antioxidative stress

Inflammation and oxidative stress play critical roles in the initiation and development of AD and VaD. Inflammation is usually essential for the repair process; however, once it is prolonged or overactivated, it may cause detrimental effects. In AD and VaD, risk factors and pathological products may activate microglia, astrocytes and lymphocytes, leading to the production and release of inflammatory cytokines and inflammasomes such as interleukin-1 (IL-1), IL-8, tumor necrosis factor-α (TNF-α) and nucleotide-binding oligomerization domain-like receptors (NLRs), which in turn aggravate Aβ and tau pathologies, promote endothelial damage and vascular dysfunction, and ultimately accelerate cognitive decline [41–43]. Excessive oxidative stress has been detected in the brains of patients with AD and VaD and may promote the production of Aβ, induce mitochondrial and neural cell damage, synaptic loss and hyperphosphorylation of tau, reduce nitric oxide bioavailability, and damage endothelial function [42,44,45].

Ginsenoside Rg1 significantly decreased the levels of ROS, NADPH oxidase 2 (NOX2), p47-phox, NLRP1, IL-1β and NF-κB in lipopolysaccharide (LPS)-induced HT22 cells [46]. Ginsenoside Rg1 and Rb1 could decrease the levels of TNF-α, caspase-1, inducible nitric oxide synthase (iNOS), and other indices in the cerebral cortex and peripheral blood; inhibit the activity of microglia and astrocytes; and reduce nerve cell loss in SAMP8 mice, alleviating spatial learning and memory deficits [47]. CK could target both neuroinflammation and oxidative stress, improve cognitive function, promote the expression of low-density lipoprotein receptor-related protein 1 and inhibit the NF-κB pathway in $A\beta_{42}$ oligomer-damaged BV2 cells. It can also decrease the levels of TNF-α, IL-1β, IL-6, the NOD-like receptor protein 3 (NLRP3) inflammasome and malonaldehyde (MDA) and enhance the activities of superoxide dismutases (SOD), glutathione peroxidases (GSH-Px), and endoplasmic reticulum (ER) stress in the hippocampus of diabetic model mice [48,49]. OA inhibited caspase-3 activity, decreased ROS, MDA, Bax and Aβ levels, and increased Bcl2 levels in N2a/APP695swe cells via the regulation of stanniocalcin-1 (STC-1) and uncoupling protein-2 (UCP2) signaling [50]. OA can also decrease neuroinflammation by regulating the activity of astrocytes and decreasing the levels of IL-1β, IL-6 and TNF-α in AD model rats and cell lines [51].

Table 2
Ginsenosides in the treatment of AD and VaD

Ginsenoside	Subject	Targets	Actions	Reference
Rb1	Wistar rats	Ach, ChAt, AChes	Anticholinergic	[19]
	C57BL/6 mice	Synaptophysin	Synaptic regulation	[30]
	SAMP8 mice	TNF-α, ASC and caspase-1, iNOS	Anti-inflammation	[47]
	SD rats	Bax, bcl-2, caspase-3	Anti-apoptosis	[53]
	PC12 cells	LC3II/I, p62	Regulate autophagy	[57]
	C57BL/6N mice	Blood glucose, NMDAR1, IDE, Cdk5/p35	Alleviate insulin resistance	[61]
Rd	Neuro-2a cells	ChAT, VAChT, ACh	Anticholinergic	[21]
	APP mice	p-Tau, GSK-3β	Targeting tau	[40]
Re	Neuro-2a cells, SD rats	ChAT, VAChT, ACh	Anticholinergic	[21,22]
Rg1	C57BL/6J mice	LTP, dendritic spines	Synaptic regulation	[29]
	C57BL/6 mice	Synaptophysin, PSD95, GLuN1, CaMKIIα	Synaptic regulation	[30,31]
	APP/PS1 mice	APP, Aβ, p-Tau	Targeting Aβ and tau	[35]
	HT22 cells, SAMP8 mice	ROS, iNOS, NOX2, p22phox, p47phox, NLRP1, caspase-1, IL-1β, NF-κB and p−NF−κB	Anti-inflammation and anti-oxidation	[46,47]
	C57BL/6J mice	Bcl-2/Bax	Anti-apoptosis	[54]
	Tree shrews	Gut microbiota	Regulate the gut microbiota	[59,60]
Rg3	Nuro-2a cells,HM06 microglial cells, BALB/c mice	Aβ, sAPPα, NEP, IDE	Targeting Aβ	[37,38]
Rg5	Wistar rats	ChAt, AChes	Anticholinergic	[20]
F1	N2a and SH-SY5Y cells, APP/PS1 mice	Aβ, IDE, NEP	Targeting Aβ	[36]
Oleanolic acid	ICR mice	Ach	Anticholinergic	[23]
	N2a/APP695swe cells	ROS, MDA, Aβ, Bax, Bcl-2, caspase-3	Anti-inflammation and anti-apoptosis	[50]
	SD rats, primary rat neurons, DI-TNC1, SH-SY5Y cells	IL-6, TNF-α, and IL-1β	Anti-inflammation	[51]
Compound K	2VO-SD rats	Aβ, pSer9-GSK-3β, IDE	Targeting Aβ	[39]
	db/db mice	TNF-α, IL-6, IL-1β, NLRP3, MDA, SOD, GSH-Px, BiP, CHOP, p-PERK, p-IRE1α, ATF6	Anti-inflammation and anti-oxidation	[48]
	BV2 cells	NF-κB, LRP1, IL-6, TNF-α	Anti-inflammation	[49]
	Primary astrocytes (C57 mice)	LC3, mTOR, P70S6K, P62, ULK1, Aβ	Regulate autophagy	[56]

Note: Ach: acetylcholine; ChAt: cholineacetyltransferase; Aches: acetylcholinesterases; TNF-α: tumor necrosis factor-α; ASC: apoptosis-associated speck-like protein containing a CARD; iNOS: inducible nitric oxide synthase; LC3: Microtubule-associated protein 1A/1B-light chain 3; IDE: insulin-degrading enzyme; NMDAR1: N-methyl-d-aspartate receptor type 1; CDK5: Cyclin-dependent kinase; IL-1β: interleukin-1β; IL-6: interleukin-6; NF-κB: nuclear factor-κB; VAChT: vesicular acetylcholine transporter; GSK: Glycogen synthase kinase; LTP: long-term potentiation; PSD95: postsynaptic density-95; GLuN1: N-methyl-d-aspartate receptor subunit 1; CaMKIIα: calcium/calmodulin-dependent protein kinase II alpha; APP: amyloid precursor protein; Aβ: amyloid β; ROS: reactive oxygen species; NOX2: NADPH oxidase 2; NLRP1: NLR family, pyrin domain containing 1; NEP: neprilysin; IDE: insulin-degrading enzyme; MDA: malonaldehyde; NLRP3: NOD-like receptor protein 3; SOD: superoxide dismutases; GSH-Px: glutathione peroxidases; PERK: proteins kinase R-liked endoplasmic reticulum kinases; IRE1: inositol-requiring kinases 1; ATF6: activation of transcription factors 6; BiP: binding immunoglobulin proteins; CHOP: transcription factors C/EBP homologous proteins; LRP1: low-density lipoprotein receptor-related protein 1; mTOR: mammalian target of rapamycin; ULK1: Unc-51 Like Autophagy Activating Kinase 1.

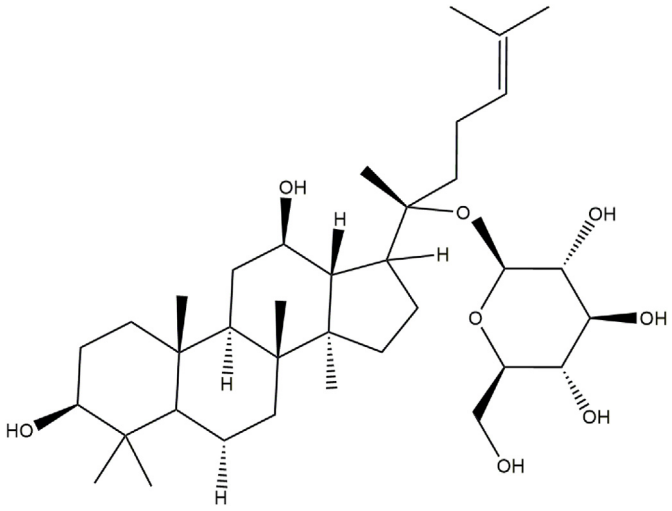


Fig. 1. Chemical structure of compound K.

2.5. Other effects

Apoptosis is one of the important mechanisms in maintaining homeostasis of the internal environment in the body and in the development of neurodegenerative diseases, and ginsenosides can regulate these processes [52]. Ginsenoside Rb1 targets apoptosis-associated Bax, caspase-3 and bcl-2 in the hippocampus of $A\beta_{1\text{-}40}$-induced rats and prevents cognitive deficits [53]. Ginsenoside Rg1 increased the ratio of Bcl-2/Bax expression and decreased neuronal loss in the hippocampus of VaD model mice [54]. Autophagy is a critical cellular process that is responsible for the disintegration of misfolded proteins and damaged organelles by lysosomes and has been shown to be involved in the pathological changes of neurodegenerative diseases [55]. Studies have found that CK and ginsenoside Rb1 have therapeutic potential for AD by regulating autophagy. CK could enhance autophagy in primary astrocytes by promoting the expression of LC3 proteins and inhibiting the mTOR signal pathway, which promote Aβ clearance [56]. Ginsenoside Rb1 could improve the LC3II/Iratio and decrease p62 protein expression by activating the PINK1/parkin signaling pathway in Aβ-damaged PC12 cells [57].

Changes in the gut microbiota are associated with various diseases, including dementia [58]. Ginsenoside Rg1 could regulate the gut microbiota to achieve a neuroprotective effect by altering the abundance of Bacteroidetes, Proteobacteria and Verrucomicrobia in the gut and increasing the energy requirement in the hippocampus [59,60]. Diabetes mellitus (DM), which is characterized by impairment in insulin signaling, is thought to be strongly associated with cognitive dysfunction. A study found that ginsenoside Rb1 could improve the memory and cognition of streptozotocin (STZ)-lesioned mice by improving glucose tolerance and alleviating insulin resistance. These mechanisms may be related to the suppression of Cdk5/p35 activity and upregulation of N-methyl-D-aspartate receptor type 1 (NMDAR1) and IDE expression [61,62].

3. Other active components of *Panax ginseng*

In addition to ginsenosides, other active components of *Panax ginseng* have also been found to have potential in the treatment of dementia (Table 3). Gintonin, a glycolipoprotein derived from ginseng, contains G-protein-coupled lysophosphatidic acids and has the potential to treat AD and other cognitive impairment-related diseases [63]. Studies have found that gintonin can treat dementia through multiple mechanisms, including antioxidant and anti-inflammatory effects, decrease β-amyloid deposition, ameliorate functional damage to the blood–brain barrier (BBB), promote hippocampal neurogenesis, decrease ACh levels and ChAT activity, increase AChE activity and regulate synaptic function [64–67].

Ginseng oligosaccharides, a class of active components extracted from ginseng, comprise polymers of 2-14 D-glucose molecules, which can inhibit the expression of IL-1β and IL-6 and the activity of astrocytes in the hippocampus of scopolamine-treated mice and protect cognitive function, as demonstrated by the Morris water maze task and novel object recognition tasks [68]. Shin and colleagues [69] identified the curative effect of a nonsaponin fraction with rich polysaccharides (NFP) in the treatment of AD and found that NFP could inhibit Aβ accumulation and microglial activity, improve mitochondrial function, neurogenesis and neuron proliferation in the brains of 5XFAD mice and HT22 cells, and alleviate cognitive impairment in AD model mice.

Ginseng protein, which is a protein isolated from ginseng, also improves cognitive functions. Li and colleagues [70,71] found that ginseng protein could increase the expression of Bcl-2 and the activity of SOD, decrease the expression of Bax and levels of MDA, NO, total nitric oxide synthase and iNOS, decrease the levels of $A\beta_{1\text{-}42}$ and p-tau in D-galactose/$AlCl_3$-induced rats, and alleviate Aβ and H_2O_2-induced primary cortical neuron damage; the mechanisms may be related to the activation of the PI3K/Akt and CREB signaling pathways. Polyacetylene, another active component of ginseng, can inhibit the activities of AChE, butyrylcholinesterase and β-secretase [72].

4. *Panax ginseng*-containing Chinese medicine compounds

Chinese medicine compounds are a unique feature of traditional Chinese medicine in treating diseases. Through the combination of different drugs, multitarget therapeutic effects can be exerted, and side effects can be significantly reduced [73]. Based on syndrome differentiation and treatment, ginseng alone or in combination with other Chinese herbal medicines to form a Chinese medicine compound has been used in China for thousands of years for the treatment of dementia [74]. Using modern medical technology, the mechanisms underlying the treatment of dementia have been partially analyzed (Table 4).

A single Chinese herbal medicine is a unique form of Chinese medicine, and red ginseng or white ginseng alone have therapeutic effects on dementia. Red ginseng, a processed form of ginseng obtained by steaming and drying, reduces Aβ deposition, inhibits the activity of astrocytes and microglia, improves neurogenesis in 5XFAD mice, and promotes mitochondrial function in HT22 cells [75]. Another study found that red ginseng could increase the expression of the BBB tight-junction proteins claudin-5 and occludin, restore the diversity of the gut microbiota, increase the population of Lactobacillus species, reduce Aβ accumulation and microglial activation, and improve the cognitive function of Tg2576 transgenic mice [76]. White ginseng, which is dried ginseng without steam, was reported to have anti-AD effects by alleviating neuronal damage, inhibiting microglial activity and synaptic loss, and increasing ChAT-positive cells in the $A\beta_{1\text{–}42}$-injected mouse hippocampus [77].

Qi Fu Yin, a classic prescription of the Ming Dynasty, consists of *Panax ginseng, Rehmannia glutinosa, Angelica sinensis, Glycyrrhiza uralensis, Atractylodes macrocephala, Polygala tenuifolia* and *Semen ziziphi spinosae*. A meta-analysis of 697 AD and VaD patients found that Qi Fu Yin could increase the scores of cognitive function assessment scales such as the Hasegawa Dementia Scale (HDS) and Mini-Mental State Examination (MMSE) [78]. Basic experimental studies found that Qi Fu Yin could downregulate iNOS expression in LPS-challenged BV-2 cells, and network pharmacology analysis found that Qi Fu Yin may have an AD therapeutic effect by alleviating tau hyperphosphorylation by inhibiting GSK3β [79,80]. Shenqi Yizhi granules consist of *Panax ginseng, Radix astragali, and Radix scutellariae*, which can inhibit astrocyte and microglia activities, and the cognitive improvement function may be related to the regulation of energy metabolism, stress response, amino acid metabolism and other pathological processes in 5XFAD mice [81]. The Huannao Yicong formula (HYF) consists of *Radix ginseng*, *Rhizoma chuanxiong*, *Radix polygoni multiflora*, *Rhizoma coptidis* and *Rhizoma acori tatarinowii*, could increase the scores of the Montreal Cognitive Assessment (MoCA) and MMSE and could decrease the scores of the Chinese Medicine Symptom Scale (CM-SS) and ADAS-

Table 3
Other active components of *Panax ginseng* in the treatment of AD and VaD

Component	Subject	Targets	Actions	Reference
Gintonin	C57BL/6J mice, HT22 cells	LPO, ROS, NRF-2, HO-1, PARP-1, NF-κB, TNF-α, APP, Aβ, BACE-1, ADAM-10, PSD95, syntaxin, SNAP-25, SNAP-23	Anti-inflammation, anti-oxidation and anticholinergic	[64]
	APPswe/PSEN-1 mice	Aβ, BBB integrity, occludin, claudin-5, claudin-3, ZO-1, ICAM-1, VCAM-1	Targeting Aβ and microvascular protection	[65]
	APPswe/PSEN-1 mice, primary cortical astrocytes	glial fibrillary acidic protein, NeuN, LPA1 receptor	Promotion of hippocampal neurogenesis	[66]
	AβPPswe/PSEN1dE9 mice, hippocampal neural progenitor cell	Acetylcholine, ChAT, AChE	Anticholinergic	[67]
Oligosaccharides	ICR mice	IL-1β, IL-6	Anti-inflammation	[68]
Polysaccharides	5XFAD mice, HT22 cells	Aβ, microglia	Targeting Aβ and anti-inflammation	[69]
Ginseng protein	Wistar rats	Bcl-2/Bax, PI3K, Akt	Targeting Aβ and tau	[70]
	primary cortical neurons; Wistar rats	Bcl-2, Bax, caspase-3, Aβ, p-Tau, SOD, MDA, T-NOS, iNOS, NO, CREB	Anti-oxidation	[71]
Polyacetylene	Biochemical methods	Ache, butyrylcholinesterase, β-secretase	Anticholinergic	[72]

Note: LPO: lipid peroxidation; ROS: reactive oxygen species; NRF-2: nuclear factor erythroid-2 related factor-2; HO-1: heme oxygenase-1; PARP-1: poly(ADP-ribose) polymerase-1; NF-κB: nuclear factor-κB; TNF-α: tumor necrosis factor-α; APP: amyloid precursor protein; Aβ: amyloid β; BACE-1: beta-amyloid cleaving enzyme-1; ADAM-10: a disintegrin and metalloproteinase domain-containing protein 10; PSD95: postsynaptic density protein-95; SNAP: synaptosomal-associated protein; BBB: brain-blood barrier; ICAM: intercellular cell adhesion molecule; VACM: vascular cell adhesion molecule; NeuN: neuronal nuclear protein; LPA1: lysophosphatidic acid-1; ChAT: choline acetyltransferase; AChE: Acetylcholinesterase; IL-1β: interleukin-1β; IL-6: interleukin-6; PI3K: phosphatidylinositol-3 kinase; AKT: serine/threonine protein kinase B; SOD: superoxide dismutases; MDA: malonaldehyde; T-NOS: total nitric oxide synthase; iNOS: inducible nitric oxide synthase; CREB: cAMP response element binding protein.

Table 4
Panax ginseng-containing Chinese medicine compounds in the treatment of AD and VaD

Compound	Subject	Targets	Actions	Reference
Red ginseng	HT22 Cells, 5XFAD mice	Aβ, astrocytes, microglia, neurogenesis	Anti-inflammation	[75]
	Tg2576 mice	Aβ, Iba-1, Claudin-5, Occludin, Laminin, CD13, gut microbiota	Regulation of gut-brain axis	[76]
White Ginseng	ICR mice	Iba-1, Synaptophysin, ChAT	Anticholinergic	[77]
Qi Fu Yin	AD and VaD patients	MMSE, HDS	Cognition improving	[78]
	BV-2 cells	iNOS	Anti-inflammation	[79]
Shenqi Yizhi granules	5XFAD mice	Iba-1, 2-DE, GFAP	Anti-inflammation, energy metabolism, synaptic transmission and so on	[81]
Huannao Yicong Formula	mild to moderate AD patients	ADAS-Cog, CM-SS, MMSE, MoCA	Cognition improving	[82]
	SD rats, APP/PS1 mice, APP695V717I mice	IL-1, TNF-α, APP, Aβ, caspase-3, -8, -9, -12, Bcl-2/Bax, γ-secretase, p-Tau, TTBK1, GSK-3β, CDK-5, PKC, TrkA	Anti-inflammation, anti-apoptosis, targeting Aβ and tau	[83–86]
Shenzhi Jiannao formula	2VO-SD rats, PC12 cells, wistar rats,	Clathrin, RAB5B, NMDAR1, calcium, ROS, superoxide, INS, pAKT1, caspase-3	Synaptic protection, anti-apoptosis and anti-oxidation	[87–89]
Sailuotong	mild-to-moderate VaD patients	VaDAS-cog, ADCS-CGIC, MMSE, ADCS-ADLs,	Cognition improving	[90]
	SD rats, hCMEC/D3 cells, EA.hy926 Cells	IL-1α, IL-6, IL-12, CXCL10, LCN2, p-STAT3, p-JAK2, GFAP, Claudin-1, Occludin, Nrf2, HO-1, ROS, SOD, Bax/Bcl-2, caspase-3	Anti-inflammation, anti-oxidation and anti-apoptosis	[91–93]
Shenma YIzhi Formula	mild-to-moderate VaD patients	MMSE, NIHSS, CM-SS	Cognition improving	[94]
	SD rats	SOD, GSH-Px, GSH, MDA, ATP5A, ChAT, AChE	Anti-oxidation and anticholinergic	[95,96]

Note: Aβ: amyloid β; ChAT: choline acetyltransferase; MMSE: mini-mental state examination; HDS: Hastgawa Dementia Scale; iNOS: inducible nitric oxide synthase; 2-DE: two-dimensional gel electrophoresis; GFAP: glial fibrillary acidic protein, the astrocyte marker; ADAS-Cog: Alzheimer's Disease Assessment Scale- Cognitive Subscale; CM-SS: Chinese Medicine Symptom Scale; MoCA: Montreal Cognitive Assessment; IL-1: interleukin-1; TNF-α: tumor necrosis factor-α; APP: amyloid precursor protein; TTBK1: total tau protein kinase; GSK-3β: glycogen synthase kinase-3β; CDK-5: cyclin-dependent kinase-5; PKC: protein kinase C; TrkA: tyrosine amyloid protein kinase; RAB5B: member RAS oncogene family; NMDAR1: N-methyl-d-aspartic acid receptor 1; ROS: reactive oxygen species; INS: insulin; pAKT1: protein kinase B; VaDAS-cog: vascular dementia assessment scale—cognitive subscale; ADCS-CGIC: Alzheimer's disease cooperative study-clinical global impression of change; ADCS-ADLs: Alzheimer's Disease Cooperative Study ADL Scale; CXCL10: C-X-C motif chemokine ligand 10; LCN2: lipocalin-2; p-STAT3: phosphorylated signal transducer and activator of transcription 3; p-JAK2: Janus kinase-2; Nrf2: nuclear factor erythroid 2—related factor 2; HO-1: anti—heme oxygenase-1; SOD: superoxide dismutases; NIHSS: National Institutes of Health Stroke Scale; GSH-Px: glutathione peroxidases; GSH: glutathione; MDA: malonaldehyde; ATP5A: a mitochondrial marker; AChE: Acetylcholinesterase.

Cog of mild-to-moderate AD patients, which may be related to the reduction of the serum levels of AchE and $A\beta_{42}$, anti-inflammation and anti-apoptosis functions, regulation of γ-secretase activity, inhibition of Aβ aggravation and tau hyperphosphorylation [82–86].

Shenzhi Jiannao (SZJN) formula consists of *Panax ginseng*, *Rhizoma Anemarrhenae*, and *Radix Paeoniae Rubra* and can treat VaD by promoting clathrin-mediated endocytosis and cell proliferation and inhibiting apoptosis and oxidative stress. The SZJN formula could increase clathrin and RAB5B expression, reduce NMDAR1 expression, increase the proportion of G0/G1 and G2/M phase cells, reduce Ca2+, ROS and superoxide expression, increase the expression of insulin and phosphorylated-AKT1 (pAKT1), and inhibit caspase-3 expression in the hippocampus of VaD model rats and PC12 cells [87–89].

Sailuotong consists of *Panax ginseng, Ginkgo biloba, and Crocus sativus*, and clinical studies found that Sailuotong could significantly decrease the VaD Assessment Scale—cognitive subscale scores (VaDAS-cog), increase the scores of Alzheimer's disease cooperative study-clinical global impression of change (ADCS-CGIC), MMSE and Alzheimer's Disease cooperative study-activities of daily living (ADCS-ADLs), improve the cognitive function and daily life ability of mild-to-moderate VaD patients, and prevent some amount of adverse events [90]. The mechanisms of Sailuotong in treating VaD may be related to its antineuroinflammation, antioxidation, antiapoptosis and brain microvascular endothelial cell (BMEC) protection effects [91–93]. The Shenma YIzhi formula (SYF) consists of *Panax ginseng*, *Ramulus euonymi, Rhizoma chuanxiong* and *Rhizoma gastrodiae*. A clinical trial found that SYF could significantly improve the MMSE, National Institutes of Health Stroke Scale (NIHSS), and CM-SS scores in VaD patients, which may be related to the improvement of vascular endothelial functions, mitochondrial structure, energy metabolism and hippocampal cholinergic dysfunction [94–96].

5. Conclusion and perspective

As the most common types of dementia, AD and VaD have aroused widespread concern worldwide. Although there are many hypotheses regarding their pathogenesis, their therapeutic methods need to be further explored. The use of *Panax ginseng* in AD and VaD treatment has been studied for years. *Panax ginseng* alone, ginsenosides and other active components of *Panax ginseng* and *Panax ginseng*-containing Chinese medicine compounds have therapeutic effects on AD and VaD through multiple mechanisms, such as anti-neuroinflammation, antioxidation and anti-apoptosis; inhibition of Aβ aggravation and tau hyperphosphorylation, targeting the cholinergic system; and regulation of gut microflora, synaptic plasticity and autophagy. Most of these compounds target multiple therapeutic effects, and as there has been no breakthrough in the research of single target drugs in the treatment of dementia, *Panax ginseng* could be a potential treatment. The therapeutic effects of Rb1, Rg1 and Compound K on AD and VaD have been widely studied and deserve more attention. Although the compatibility law and mechanism of Chinese medicine compounds need to be further clarified, many randomized controlled clinical studies have confirmed the effectiveness and safety of *Panax ginseng*-containing Chinese medicine compounds in the treatment of AD and VaD. Considering the complexity of the pathogenesis of dementia, Chinese medicine compounds may be a feasible treatment approach. Based on the above analysis and summary, we believe that *Panax ginseng* has great potential in AD and VaD treatment and warrants further research and development.

Declaration of competing interest

All authors have no conflicts of interest to declare.

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