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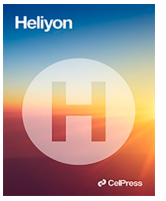

Review article

Advancements in research on the effects of panax notoginseng saponin constituents in ameliorating learning and memory disorders

Shusen Liu [a,b,c], Min Wang [a,b], Haiyan Xiao [a,b], Jingxue Ye [a,b], Li Cao [a,b], Wenlan Li [c,*], Guibo Sun [a,b,**]

[a] Beijing Key Laboratory of Innovative Drug Discovery of Traditional Chinese Medicine (Natural Medicine) and Translational Medicine, Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, 100193, China
[b] Key Laboratory of Bioactive Substances and Resources Utilization of Chinese Herbal Medicine, Ministry of Education, Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100193, China
[c] School of Pharmacy, Harbin University of Commerce, Harbin, 150076, China

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ABSTRACT

Learning and memory disorder is a cluster of symptoms caused by neuronal aging and other diseases of the central nervous system (CNS). Panax notoginseng saponins (PNS) are a series of saponins derived from the natural active ingredients of traditional Chinese medicine (TCM) that have neuroprotective effects on the central nervous system. In this paper, we review the ameliorative effects and mechanisms of Panax notoginseng saponin-like components on learning and memory disorders to provide valuable references and insights for the development of new drugs for the treatment of learning and memory disorders. Our summary results suggest that Panax ginseng saponins have significant effects on improving learning and memory disorders, and these effects and potential mechanisms are mediated by their anti-inflammatory, anti-apoptotic, antioxidant, β-amyloid lowering, mitochondrial homeostasis in vivo, neuronal structure and function improving, neurogenesis promoting, neurotransmitter release regulating, and probiotic homeostasis in vivo activities. These findings suggest the potential of Panax notoginseng saponin-like constituents as drug candidates for improving learning and memory disorders.

1. Introduction

Learning and memory, as advanced cognitive functions of the brain, play essential roles in human survival, development, and cognition. Neuroscience has primarily focused on researching the mechanisms involved in the formation and degeneration of learning and memory. This line of inquiry is of paramount importance in the treatment of neurodegenerative diseases and enhancing the quality of human life. Specifically, learning refers to the cognitive process of adapting to the external environment, while memory encompasses neural activity that preserves and reproduces learned behaviors through interactions among neurons and synapses [1]. Current

* Corresponding author.
** Corresponding author. Beijing Key Laboratory of Innovative Drug Discovery of Traditional Chinese Medicine (Natural Medicine) and Translational Medicine, Institute of Medicinal Plant Development, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, 100193, China.
E-mail addresses: lwldzd@163.com (W. Li), sunguibo@126.com (G. Sun).

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research has indicated that neuroinflammation [2], neuronal apoptosis [3], and altered synaptic plasticity [4] have significant impacts on learning and memory capacity. Moreover, neuronal injury resulting from normal aging or various diseases associated with the central nervous system (CNS) - including Alzheimer's disease (AD) [5], vascular cognitive impairment and dementia (VCID) [6], malnutrition dementia [7], depression [8], traumatic brain injury [8], post-traumatic stress disorder (PTSD) [9], and Kosakov syndrome [10], can lead to cognitive impairment with a decline in learning and memory ability.

Recently, medicinal plants have gained much attention, with Panax notoginseng, a well-known and popular Chinese medicine, being found to have potential as a neuroprotective agent [11]. Notoginseng Radix et Rhizoma, commonly referred to as Tianqi or Sanqi in East Asian nations, denotes the dried root and rhizome of Panax notoginseng (Burk.) F. H. Chen, a member of the Panax species within the Araliaceae family Panax notoginseng boasts a long-standing medicinal legacy that spans over four centuries. Saponins, as a widely present compound in medicinal plants, have pharmacological activities such as anti-inflammatory, antioxidant, and the inhibition of abnormal autophagy and apoptosis in hippocampal neurons [12–14]. These properties make them have a significant pharmacological effect in improving learning and memory. The main components isolated from Notoginseng Radix et Rhizoma are PNS, which have antioxidant, anti-apoptotic, and anti-endoplasmic reticulum stress effects [15–17]. Different anatomical parts (root, stem, leaf, bud, and seed) of Notoginseng Radix et Rhizoma contain various saponins, including ginsenoside (Rb1, Re, Rg1, Rg2, Rh1), notoginsenoside (R1-R6), and aescin (VII) [18]. The five saponins with the highest content in Notoginseng – notoginsenoside R1 (7%–10%), ginsenoside Rb1 (30%–36%), Rg1 (20%–40%), Rd (5%–8.4%), and Re (3.9%–6%) constitute up to 90% of the total PNS and are the most studied components in pharmaceutical experiments by far [19](Fig. 1).

Notoginseng and Ginseng both belong to the Araliaceae Juss. family. They contain chemical components with a high degree of similarity [20]. In terms of pharmacological effects, Ginseng has a relatively good effect on improving learning and memory, and at the same time, there are also many studies proving the potential of Notoginseng and its saponins in improving learning and memory disorders [21]. Although some articles summarize the effects of Ginseng and ginsenoside on cognition [22] and the central nervous system [23], no review comprehensively summarizes the effects of Notoginseng and its saponins on improving learning and memory disorders. We searched the PubMed and China National Knowledge Infrastructure databases via using "Panax notoginseng saponins", "Notoginseng saponins","Ginsenoside","Notoginsenoside" and "Learning and memory disorders" as search terms. The PubMed database was comprehensively searched up to August 2022, and it showed 85 pieces of literature; we excluded some irrelevant ones and searched for other potential and relevant references. and there were no limitations in the language of all publications. Therefore, this article provides a comprehensive review of the improvement effects and mechanisms of PNS in learning and memory disorders, aiming to provide a beneficial reference for future research.

2. Research on the etiology of learning and memory disorders

The ability to learn and form memories is crucial for organisms to adapt strategically to changing environmental demands [24]. Whether it depends on the learning and memory of the hippocampus, non-hippocampal memory, or non-neuronal immune memory, it requires a complete neuronal structure and a healthy brain physiological environment [25–27]. Learning and memory disorders are symptom clusters that can manifest in many diseases, such as Alzheimer's disease (AD) [5], vascular cognitive impairment and dementia (VCID) [6], malnutrition dementia [7], depression [8], traumatic brain injury (TBI) [28], post-traumatic stress disorder (PTSD) [9], and Korsakov syndrome (KS) [10] and so on.

There are direct or indirect relationships between these aforementioned disorders and learning and memory disorders. The main reason for the learning and memory impairments in AD patients is due to the accumulation of extracellular β-amyloid (Aβ), which

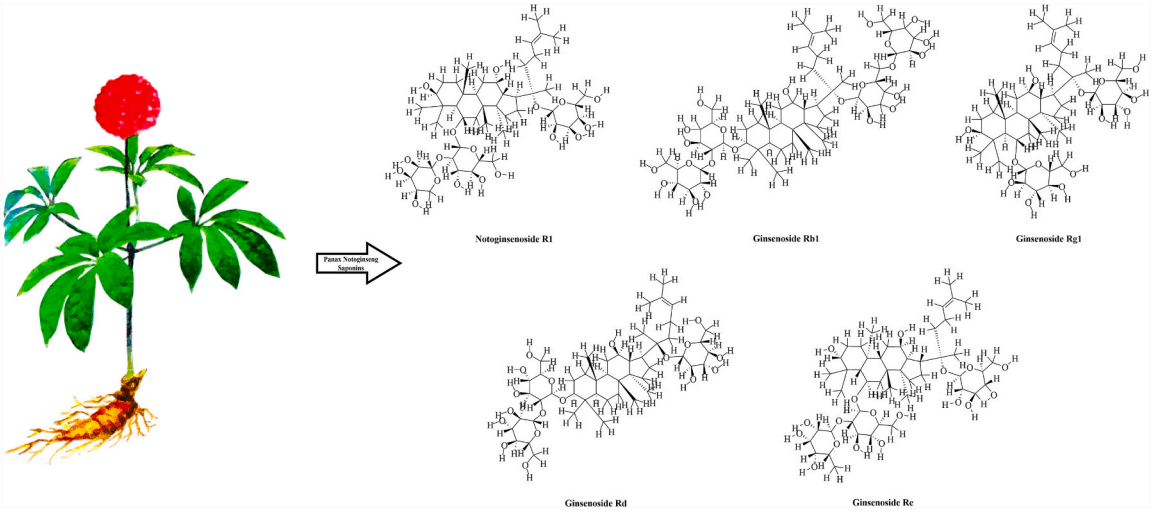

Fig. 1. The chemical structures of the five saponins with the highest content in Panax notoginseng.

affects neuronal functions [29–32]. Meanwhile, Aβ promotes the abnormal phosphorylation of tau protein, leading to its aggregation into neurofibrillary tangles and generates toxic effects on neurons [33–35]. VCID is an age-related mental disability caused by a range of cerebrovascular disorders involving neurovascular dysfunction, blood-brain barrier (BBB) disruption, white matter damage, microRNA, oxidative stress, neuroinflammation, and gut microbiota alterations [6,36,37]. Malnutrition can lead to learning and memory disorders, and elderly people with dementia are at an increased risk of malnutrition due to various nutritional problems [38–41]. While the mechanism of how depression leads to learning and memory impairments remains unclear [42,43], several studies have demonstrated that treating and repairing neurons in the hippocampus can improve cognitive disorders caused by depression [8, 44,45]. Traumatic brain injuries can induce not only acute learning and memory disorders but also a number of neurodegenerative diseases [46–50]. Post-traumatic stress disorder (PTSD) can lead to dysregulation in multiple biological systems. These dysregulations include immune system dysregulation, heightened inflammation, oxidative stress, mitochondrial dysfunction, renin-angiotensin system dysregulation, and accelerated biological aging. These various dysregulations collectively contribute to an elevated risk of subsequent learning and memory disorders [9,51–53]. Korsakov syndrome (KS) is a severe neurological disorder characterized by anterograde amnesia [10] that results from alcoholism [53,54].

In current clinical trials (Phase III and Phase IV), drugs targeting learning and memory disorders include agonists or inhibitors of central nervous system receptors, including N-Methylaspartate and Memantine; opioids like Meperidine and Morphine; sleep aids and tranquilizers such as Suvorexant and Melatonin; Calcium channel blockers like Nilvadipine and Amlodipine; Hormones, for instance, Estradiol; Non-steroidal anti-inflammatory drugs (NSAIDs), such as Indomethacin; Anesthetics including Benzocaine and Cadexomer iodine; Anti-anxiety drugs and antidepressants including Opipramol and Buspirone; anticonvulsant medications like Topiramate and Lamotrigine; neuroprotectants such as 3-N-butylphthalide and Cerebrolysin; along with vitamins like Nicotinamide and B group vitamins. In addition, certain herbal-related drugs such as Black cohosh, Valerian, Piper methysticum, Chamomile, Passionflower, Erythrina mulungu, and Yohimbe have either entered or completed Phase III and Phase IV clinical trials alongside others [55,56]. (Fig. 2 for associated disorders as well as the main drug types).

3. The improvement of learning-memory disorder by notoginseng saponins

3.1. Notoginsenoside R1

Notoginsenoside R1 (R1) is a distinctive saponin found in the root of Panax notoginseng, comprising approximately 7–10% of its saponins [57,58]. Studies have shown that R1 can increase the membrane excitability of CA1 pyramidal neurons in hippocampal slices by lowering the spike threshold, possibly through a mechanism involving the inhibition of voltage-gated K (+) currents, thereby preventing Aβ-induced synaptic dysfunction and improving hippocampal-based memory performance in an AD mouse model [59]. Furthermore, voltage-gated sodium channels (Nav) play a crucial role in regulating cell excitability and the initiation and transmission of action potentials (APs) [60]. R1 modulates the abundance and/or spatial arrangement of voltage-gated sodium channels (Nav). Furthermore, R1 enhanced the viability of neurons damaged by Aβ1-42. The reduction of neuronal hyperexcitability caused by R1 could be associated with the inhibition of Navβ2 cleavage, resulting in the partial restoration of the aberrant localization of Nav 1.1α [61]. In addition, it has been demonstrated that R1 can alleviate impaired learning and memory in SD mice by regulating the Melatonin receptor type 1A (MTNR1A)-mediated phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) signaling pathway, thereby reducing excessive autophagy and apoptosis of hippocampal neurons [62]. Moreover, it protects

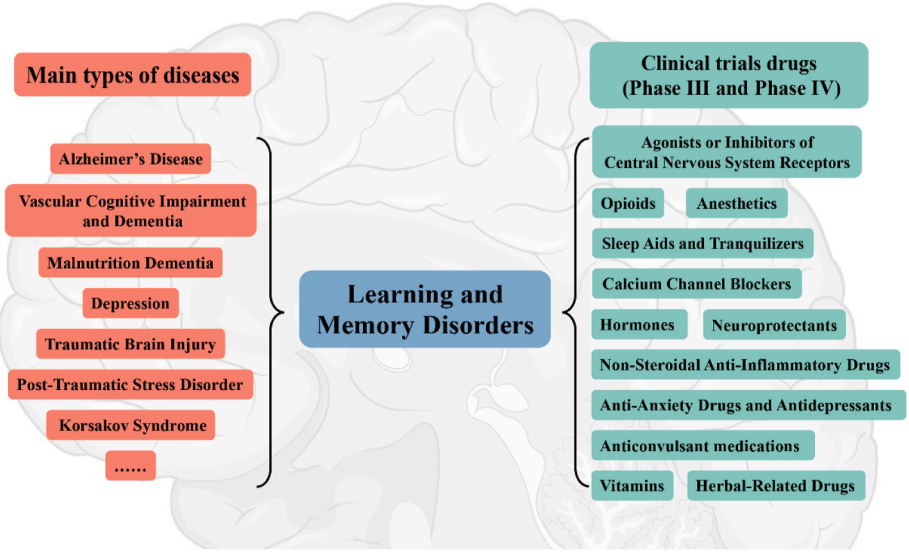

Fig. 2. Associated disorders causing learning and memory disorders and the main types of drugs entering phase III and IV clinics.

against isoflurane-induced learning and cognitive dysfunction by promoting the expression of miR-29a and preventing inflammatory responses [63]. R1 promotes post-stroke angiogenesis by activating the Nicotinamide phosphoribosyltransferase- Nicotinamide adenine dinucleotide- Sirtuin 1 (NAMPT-NAD-SIRT1) cascade, which helps to improve vascular cognitive impairment and dementia [57].

3.2. Ginsenoside Rg1

Ginsenoside Rg1 (Rg1) has the highest content among PNS, accounting for approximately 20%–40% of PNS [58]. Studies targeting Rg1 to improve learning and memory disorder have also been conducted at a relatively early stage; an earlier study found that Rg1 can improve performance in a passive avoidance learning paradigm and enhance cholinergic metabolism [64].

Several studies have illustrated the efficacy of Rg1 in alleviating learning and memory deficits associated with Alzheimer's disease.

Table 1
Effects and mechanisms of ginsenoside Rg1 in ameliorating learning and memory impairment as reported and evidenced.

Effect	Mechanism and Descriptions	Cited references
Improving learning and memory disorder; improving performance in a passive avoidance learning paradigm	Enhancing cholinergic metabolism	[64]
Effective in improving learning and memory disorders caused by Alzheimer's disease	Reducing the amount of Abeta detected in the brains of mice; reducing the level of amyloid beta; regulating the activity of PKA/CREB; improving cognitive performance in SAMP8 mice	[65,66]
Inducing neuroprotection and ameliorating learning and memory disorders	Ameliorating amyloid pathology; modulating the amyloid precursor protein process; improving cognition; activating PKA/CREB signaling	[67]
Attenuating the generation of Aβ; improving learning and memory	Enhancing the binding of PPARγ to the BACE1 promoter; suppressing the activity of BACE1; increasing the expression of IDE	[81,82]
Reducing okadaic acid-induced spatial memory impairment; preventing Aβ formation	Through the GSK3β/tau signaling pathway	[68]
Restoring hippocampal long-term potentiation and memory	Promoting the clearance of AD-related proteins; activating the BDNF-TrkB pathway	[69]
Improving behavioral deficits in AD mice	By regulating the expression of CPLX2, SYN2, and SNP25 proteins	[83]
In response to the senescence of neuronal cells; ameliorating learning disabilities in aged rats	Reversing *tert*-butyl hydroperoxide-induced morphological changes; promoting expression of synaptic plasticity-related proteins; regulating the PI3K/AKT pathway	[70–72]
Protecting against neural stem cell senescence	Ameliorating D-galactose-induced cognitive impairment; reducing oxidative stress; downregulating the Akt/mTOR signaling pathway	[73]
Ameliorating cognitive deficits in aging mice induced by D-galactose and AlCl3	Restoring FGF2-Akt and BDNF-TrkB signaling axis; inhibiting apoptosis	[74]
Alleviating learning and memory impairments induced by painkillers and other chemicals	Improving spatial learning capacity impaired by morphine; restoring morphine-inhibited long-term potentiation	[84]
Effectively improving memory impairment induced by scopolamine		[85]
Inhibiting mitochondrial dysfunction; exerting antioxidant, anti-inflammatory, and anti-apoptotic effects	Ameliorating isoflurane-induced caspase-3 activation; attenuating isoflurane/surgery induced neurocognitive impairment and Sirt3 dysfunction	[86–88]
Ameliorating lipopolysaccharide-induced cognitive impairment	Through regulation of the cholinergic system	[89]
Protecting against neuronal degeneration induced by chronic dexamethasone	By inhibiting mouse NLRP1 inflammatory cytokines	[90]
Ameliorating cognitive deficits induced by repeated alcohol intoxication	Modulating NR2B-containing NMDARs and excitotoxic signaling	[91]
Rg1 showed good effects against neurological functions, neural structures, and neurophysiological aspects affecting learning and memory	Ameliorated chronic restraint stress-induced learning and memory deficits by reducing reactive oxygen species (ROS) production, reducing neuronal oxidative damage in mouse frontal cortex and hippocampal cornu ammonis 1 (CA1), inhibiting the expression of NADPH oxidase 2 (NOX2), neutrophil cytosol factor 1 (p47phox), and ras-related c3 botulinum toxin substrate 1 (RAC1).	[92]
Modulated firing in the medial prefrontal cortex of rats and inhibited hippocampo-medial prefrontal cortical long-term potentiation.	Rg1 ameliorated the learning and memory deficits induced by chronic restraint stress in rats by mediating the BDNF/TrkB/extracellular signal-regulated kinase (Erk) pathway in the prefrontal cortex.	[93,94]
Rg1 acts similarly to growth factors in promoting the proliferation and differentiation of neural stem cells.	May reduce cognitive impairment induced by cardiac arrest by regulating neuroinflammation and hippocampal plasticity.	[95,96]
Promotes remyelination and functional recovery in demyelinating diseases by enhancing oligodendrocyte progenitor cell-mediated remyelination, improving spatial memory, motor function, and anxiety-like behavior in mice.	Promotes glutamate release, possibly through a Ca2+/calmodulin-dependent protein kinase II (CaMKII)-dependent pathway, to regulate central nervous system neurotransmitters to enhance learning and memory.	[97,98]
Reduces PTSD-like behaviors in mice by reducing corticosterone and corticotrophin-releasing hormone levels.	Has a protective effect on PTSD-like behavior in mice by promoting synaptic proteins and reducing inward rectifying potassium channel 4.1 (Kir4.1) and tumor necrosis factor alpha (TNF-α) in the hippocampus.	[79,80,99]
Potential application in the treatment of learning and memory disorders in postmenopausal women.	Can prevent cognitive impairment and hippocampal neuronal apoptosis in vascular dementia mice, probably by promoting g protein-coupled receptor 30 (GPR30) expression.	[75–77]

This is attributed to its capacity to reduce amyloid-beta levels [65,66], modulate the activity of protein kinase A (PKA) and cAMP response element-binding protein (CREB) [67], as well as promote neuroprotection and memory enhancement through various pathways [68,69]. Moreover, Rg1 has demonstrated the ability to enhance cognitive abilities in aged mice, hinder Aβ formation, suppress inflammatory responses, regulate neurotransmitters, and boost neural stem cell proliferation, significantly improving stress-induced learning and memory impairments [70–74]. Furthermore, Rg1 exhibits potential therapeutic applications in treating learning and memory impairments in perimenopausal women [75,76], vascular cognitive impairment [77], sepsis-associated encephalopathy [78], and post-traumatic stress disorder [79,80]. For details, refer to Table 1.

3.3. Ginsenoside Rb1

Ginsenoside Rb1(Rb1) accounts for 30–36% of the total saponins found in Notoginseng Radix et Rhizoma and has been studied extensively [58]. In vitro studies have demonstrated that Rb1 enhances choline uptake into nerve endings and promotes the release of acetylcholine (ACh) from hippocampal slices. This indicates that the potential of Rb1 to mitigate memory deficits may be linked to its facilitation of ACh metabolism in the central nervous system [78]. Further research reveals that Rb1 can increase the expression of phosphorylated Akt (P-Akt) and phosphorylated mTOR (P-mTOR), reduce the effect of phosphorylated phosphatase and tensin homolog (P-PTEN), and alleviate memory impairment, pyramidal cell necrosis, and apoptosis in the hippocampal CA1 region of rats after L-glutamate and Ca2+ microperfusion, in a dose-dependent manner [100]. In addition, intravenous administration of Rb1 can up-regulate the expression of B-cell lymphoma-extra large (Bcl-x(L)) and prevent the death of ischemic neurons. Intravenous administration of gRb1 exhibits a greater range of effective doses than intracerebroventricular injection, possibly because the blood-brain barrier regulates the central adsorption of Rb1 from the bloodstream, allowing for an optimal amount of Rb1 to be transported into the ischemic brain [101]. Furthermore, metabolite M1 of Rb1 has been shown to improve Aβ(25–35)-induced memory impairment, axonal atrophy, and synaptic loss [102]. The metabolite compound K of Rb1 may also improve learning and memory disorders by resisting inflammation and oxidation, promoting neurotransmitter release, and reducing Aβ deposition through various mechanisms [103–108].

3.4. Ginsenoside Rd

Ginsenoside Rd (Rd) accounts for 5%–8.4% of the total saponins present in Notoginseng [58]. In vitro and in vivo studies suggest that Rd promotes the proliferation of neural stem cells (NSCs) without affecting their differentiation, which could explain how ginseng enhances intelligence [109].

Inflammation and apoptosis severity are highly correlated with cognitive decline. Rd has been shown to alleviate inflammation induced by β-amyloid peptide 1–40 and attenuate cognitive dysfunction in a rat model of Alzheimer's disease [110]. Moreover, subsequent studies confirmed that Rd can reduce tau phosphorylation and sequential cognition impairment after ischemic stroke [111]. Furthermore, another study found that Rd increases the expression of α-secretase and soluble amyloid precursor protein α while decreasing the expression of β-secretase and amyloid β by activating estrogen-like activity, thereby enhancing the learning and memory function of ovariectomized rats [112]. Another study revealed that Rd improves learning and memory ability in amyloid β-protein precursor transgenic mice, possibly through inhibiting the transcription activity of nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) [113].

Administration of Rd has also been shown to ameliorate cognitive dysfunction induced by chronic cerebral hypoperfusion in mice, with induction of BDNF responsible for Rd-mediated neuroprotection both in vivo during chronic cerebral hypoperfusion and in vitro during oxygen-glucose deprivation/reperfusion [114]. Additionally, treatment with Rd reversed the decrease in phosphorylated PI3K, CREB, BDNF, and TrkB expression in the hippocampus caused by chronic restraint stress. The findings suggest that Rd can improve cognitive impairment in chronically stressed mice by mitigating oxidative stress and inflammation while upregulating the hippocampal BDNF-mediated CREB signaling pathway [115].

Finally, a study found that Rd can reduce anxiety and depression in mice by improving gut dysbiosis caused by alterations in intestinal microorganisms [116].

3.5. Ginsenoside Re

Ginsenoside Re(Re) is a minor component of the main saponins found in Panax notoginseng, accounting for 3.9%–6% of their total content [58]. Previous studies have shown that administration of Re before brake stress significantly improves helpless behavior and cognitive impairment by modulating the central noradrenergic system in rats [117]. Moreover, Re has been demonstrated to protect against chronic restraint stress-induced cognitive deficits by regulating NACHT, LRR and PYD domains-containing protein 3(NLRP3) and nuclear factor-erythroid 2-related factor 2 (Nrf2) pathways in mice [118]. Chronic treatment with Re can also reduce the levels of TNF-α and malondialdehyde (MDA) in both cerebral regions of diabetic rats and significantly improve their cognitive function [119].

A combined pharmacokinetic and pharmacodynamic study of Re suggested that increased levels of dopamine and acetylcholine outside the cells, particularly in the hippocampus, may contribute to its anti-dementia activity [120]. Additionally, Re can protect against phencyclidine-induced behavioral changes and mitochondrial dysfunction in the dorsolateral cortex of mice. This protective effect is achieved through the interactive modulation of glutathione peroxidase-1 and NADPH oxidase [121].

Furthermore, other studies have confirmed that Re can inhibit the interaction between platelet-activating factor receptor (PAFR), NF-κB, and microglia proliferation in the hippocampus and reduce memory impairment in aged Klotho-deficient mice through the

mutual regulation of angiotensin II iiAT1 receptor, Nrf2, and glutathione peroxidase-1 (GPx-1) genes [122,123].

3.6. Other panax notoginseng saponins

In addition to the five main components of PNS mentioned above, other saponins comprise approximately 9.8% of PNS [58]. Although their content is relatively low, they exhibit significant pharmacological effects on learning and memory disorders that cannot be ignored, and their actions and mechanisms are shown in Table 2.

4. Conclusion and remarks

PNS are a series of natural compounds that improve learning-memory disorders and cognition through their effects on the central nervous system. In this review, we summarize the therapeutic effects and molecular mechanisms by which various Panax ginseng saponin-like constituents improve learning-memory disorders (Fig. 3). The available data and our summarized results suggest that Panax ginseng saponins may improve learning-memory impairment through various pharmacological activities, such as their anti-inflammatory, anti-apoptotic, and antioxidant properties, reduction of amyloid beta levels, maintenance of mitochondrial homeostasis, improvement of neuronal structure and function, promotion of neurogenesis, modulation of neurotransmitter release, and maintenance of probiotic homeostasis. Based on these findings, Panax notoginseng saponin-like components, as a series of specific natural compounds, hold promising potential for improving learning and memory disorders.

In ameliorating the learning-memory impairment associated with AD, PNS-like components play a role in improving learning-memory impairment by modulating the PKA/CREB pathway [65,66], GSK3β/tau pathway [67], regulating PPARγ [82], NFκB [123], and reducing amyloid β levels.

In enhancing the hippocampus, neurons, and their structure and function, PNS-like components have been shown to promote the value-added of neural stem cells [94,109], regulate the PI3K/Akt/mTOR pathway, reduce excessive autophagy and apoptosis of hippocampal neurons [62,100], regulate neuronal structure and function [61,97,140], and modulate neurotransmitters in the central nervous system [78,98,111]to improve learning and memory disorders.

In response to learning and memory disorders caused by chemicals such as anesthetics, painkillers, and alcohol, PNS-like components improve mitochondrial function [86,129] through anti-inflammation [63,84,90,131,144], reduce Sirt3 dysfunction 75, modulate the PI3K/AKT/GSK-3β signaling pathway [88], modulate the NF-κB signaling pathway [133], and modulate the ERK/-CREB/BDNF signaling pathway [141].

In stroke and vascular dementia-induced learning and memory disorder, PNS-like components play ameliorative roles by promoting angiogenesis [57], reducing hippocampal neuronal apoptosis [77,101,130], and providing neuroprotection [114].

In neuronal cell aging, PNS-like components have been effective in ameliorating learning and memory disorder by improving morphological changes in cell aging [70], regulating the PI3K/AKT/mTOR pathway [71–73], and regulating the FGF2/Akt and BDNF/TrkB signaling pathways [73].

Due to post-traumatic stress disorder, depression, and external physical stimuli that lead to learning and memory disorder, PNS-like components may play a role in the amelioration of learning and memory disorder by reducing neuronal inflammation and oxidative damage [80,92,115,136], modulating the BDNF/TrkB/Erk signaling pathway [93,115,134,142], regulating the NLRP3/Nrf2 signaling pathway [118], regulating neurotransmitter and hormone levels [79,117,124,128,136], and regulating intestinal flora dysbiosis[115].

In addition to the above, PNS also plays a role in the treatment of learning and memory disorder in postmenopausal women [75,76], ameliorating cognitive dysfunction in mice with sepsis-related encephalopathy [145], and improving cognitive function in diabetic rats [119].

Table 2
Effects and Mechanisms of other Panax notoginseng saponins in Ameliorating Learning and Memory Impairment as Reported and Evidenced.

Chemical Component	Effects	Mechanism and Descriptions	Cited references
Ginsenoside Rb3	Antidepressant-like effects, modulates neurotransmitters		[124]
Ginsenoside Rf	Improves spatial learning and memory in AD mice		[125]
Ginsenoside Rg2	Enhances cognitive behavior; protects against memory impairment; anti-apoptotic effects	Autophagy induction, protein aggregate clearance, protective effects	[126–130]
Ginsenoside Rg3	Attenuates learning and memory disorders; controls fear memory regression	Anti-inflammatory activity, Aβ42 uptake and degradation, HPA axis, BDNF-TrkB pathway	[131–134]
Ginsenoside Rg5	Ameliorates cognitive dysfunction, prevents apoptosis, impacts gene expression related to cognitive impairment	Neuroinflammatory attenuation, decreases β-amyloid accumulation, HO-1/Nrf2 signaling pathway, gene expression modulation	[135,136]
Ginsenoside Rh1	Improves memory in mouse models, increases cell survival	Cell survival, upregulates BDNF expression	[137,138]
Ginsenoside Rh2	Reverses cognitive impairment from sleep deprivation, promotes spatial learning, protects against memory impairment, exhibits antidepressant effects	Cholinergic transmission regulation, reduction of oxidative stress, ERK-CREB-BDNF signaling pathway modulation	[139–142]
Ginsenoside Rk3	Cognitive improvement	Improves spatial learning and memory deficits in double transgenic mouse models of APP/PS1	[143]

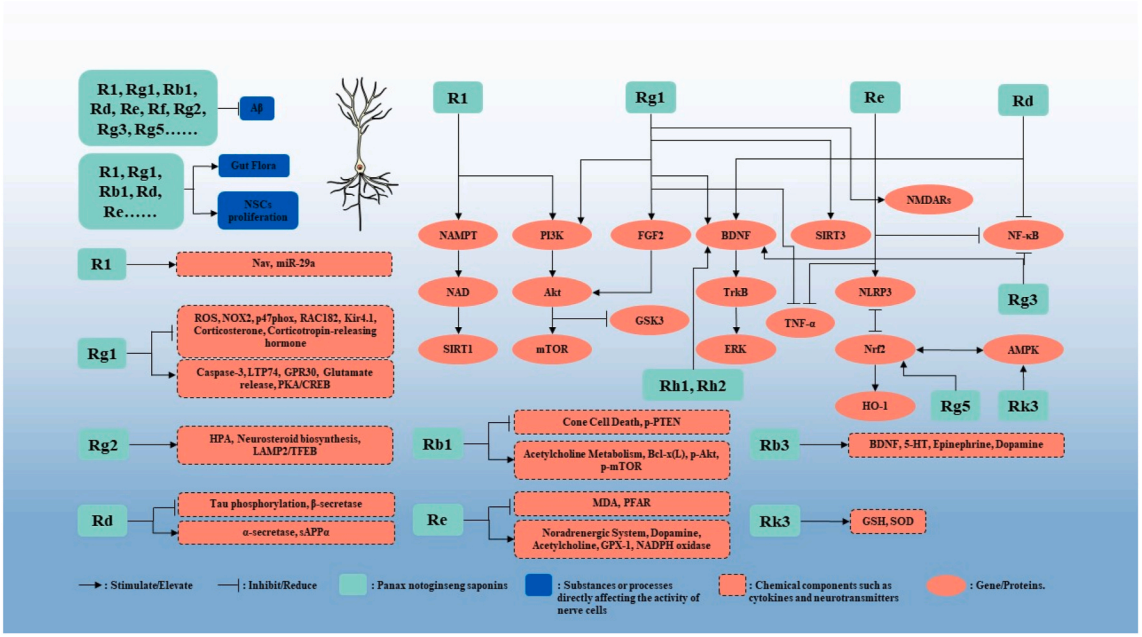

Fig. 3. Mechanism of improving learning and memory impairments by PNS.

PNS have been extensively studied for the treatment of cardiovascular and cerebrovascular diseases, yielding abundant results. As research in human brain science, behavior, and brain-related diseases, such as Alzheimer's disease, has progressed, there has been a gradual increase in studies exploring the potential of PNS in treating learning and memory disorders. In comparison to ongoing or completed clinical trials examining pharmacological interventions for learning and memory disorders, PNS have exhibited broader and more effective therapeutic effects. However, due to factors such as the cost and availability of PNS, there is a lack of comprehensive clinical research examining their efficacy in improving learning and memory disorders. With the advancement of professional expertise and technical capabilities, it is anticipated that future studies will contribute to a more thorough understanding of the role of PNS in treating and improving learning and memory disorders.

In conclusion, this review was conducted by discussing the ameliorative effects of PNS-like constituents on learning and memory disorders due to various causes. The summarized results and analyses suggest that Panax notoginseng saponin-like constituents hold promise as a series of natural active ingredients for improving learning and memory disorders.

Data availability statement

Data availability is not applicable to this article as no new data were created or analyzed in this study.

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CRediT authorship contribution statement

Shusen Liu: Writing – original draft, Data curation. **Min Wang:** Writing – review & editing. **Haiyan Xiao:** Writing – review & editing, Data curation. **Jingxue Ye:** Writing – review & editing, Resources. **L.I. Cao:** Writing – review & editing, Project administration. **Wenlan Li:** Writing – review & editing, Visualization, Funding acquisition, Conceptualization. **Guibo Sun:** Writing – review & editing, Visualization, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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