



Panax notoginseng saponins and their applications in nervous system disorders: a narrative review

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Abstract: Panax notoginseng saponins (PNS), also called “sanqi” in Chinese, are the main active ingredients which are extracted from the root of *Panax notoginseng* (Burk.) F. H. Chen., and they have been traditionally used as a medicine in China for hundreds of years with magical medicinal value. PNS have varied biological functions, such as anti-inflammatory effects, anti-cancer effects, anti-neurotoxicity, and the prevention of diabetes. Nervous system disorders, a spectrum of diseases originating from the nervous system, have a significant impact on all aspects of patients' lives. Due to the dramatic gains in global life expectancy, the prevalence of nervous system disorders is growing gradually. Even if the mechanism of these diseases is still not clear, they are mainly characterized by neuronal dysfunction and neuronal death. Consequently, it is essential to find measures to slow down or prevent the onset of these diseases. At present, traditional Chinese medicines, as well as their active components, have gained widespread popularity in preventing and treating these diseases because of their merits, especially PNS. In this review, we predominantly address the recent advances in PNS researches and their biological functions, and highlight their applications in nervous system disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), and stroke.

Keywords: Panax notoginseng saponins (PNS); nervous system disorders; Alzheimer's disease (AD); Parkinson's disease (PD); stroke

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Introduction

Traditional Chinese medicine has gained widespread popularity in recent years. Furthermore, a myriad of studies have confirmed the effectiveness of these medicines for treating nervous system diseases. Among the wide variety of traditional Chinese medicines, *Panax notoginseng* (Burk.) F. H. Chen is one of the most commonly used products, and panax notoginseng saponins (PNS) are the main active compounds which are extracted from the

root of *Panax notoginseng*. PNS contain about 20 different kinds of saponin constituents, among which ginsenoside Rb1, ginsenoside Rg1, notoginsenoside R1, ginsenoside Rd, and ginsenoside Re are the top five saponins, which constitute up to 90% of total PNS (1,2). Among these saponins, Rb1 and Rd are classified as protopanaxadiol-type saponins (PDS), while Rg1, R1, and Re are classified as protopanaxatriol-type saponins (PTS) (3). Compared with other traditional Chinese medicine, PNS have more advantages, including long history and various

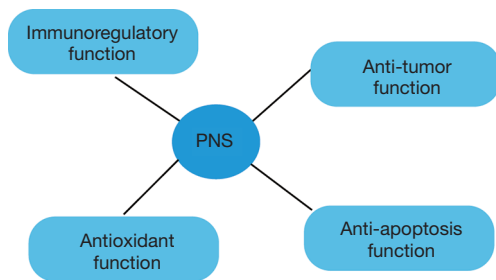


Figure 1 The biological functions of Panax notoginseng saponins (PNS), including immunoregulatory effects, antioxidant capacity, anti-apoptotic effects and anti-tumor properties.

pharmacological effects. Because these various beneficial effects, for example the inhibition of inflammatory responses, reduction of oxidative stress, and the inhibition of apoptosis, they are widely used therapeutically for the treatment of nervous system diseases.

Nervous system diseases, for example Alzheimer's disease (AD), Parkinson's disease (PD) and stroke, significantly disrupt patients' lives. Nowadays, the prevalence of nervous system disorders is growing, partly due to the dramatic increase in life expectancy. However, effective treatments are still lacking. Even if the etiology of these disorders remains elusive, they share common pathological features, including neuronal dysfunction and neuronal death. Therefore, it is urgent to seek novel approaches to slow down or prevent these diseases. In recent years, PNS have gained widespread popularity because of their various beneficial effects. As a kind of traditional Chinese medicines, the research hotspots and potential advantages of the pharmacological effects of PNS on nervous system diseases are the neuroprotection effects. This review provides an update on the applications of PNS in nervous system diseases. We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/atm-20-6909>).

The biological functions of PNS

Immunoregulatory function

The inflammatory response is a complex biological process which occurs when healthy tissues are invaded by physical stimuli, toxins, bacteria or viruses. It plays a significant role in the pathological processes of multiple diseases by releasing inflammatory cytokines, reactive oxygen free radicals, nuclear transcription factors, anti-inflammatory

neuropeptides and so on (4).

Previous studies have suggested an anti-inflammatory role of PNS both *in vitro* and *in vivo* (Figure 1). Rhule *et al.* found Rb1 suppressed the production of tumor necrosis factor- α (TNF- α) and interleukin 6 (IL-6) induced by lipopolysaccharide (LPS) in cultured macrophages in a dose-dependent manner *in vitro* (5). Rh1 inhibited histamine release from mast cells and the IgE-mediated passive cutaneous anaphylaxis reaction *in vivo* (6). In addition, PNS modulated the proliferation and differentiation of Th17 cells by downregulating the levels of inflammatory cytokines and cell cycle genes (1). Hence, PNS could be potentially applied as an anti-inflammatory agent.

Antioxidant function

Oxidative stress is produced by a series of reactions caused by various stimuli, bacteria, viruses or toxins. It is related to an increase in reactive oxygen species production or a decrease in the effectiveness of antioxidant defenses (7). Oxidative stress from oxidative metabolism can cause base damage and strand breaks in DNA. Base damage is mainly caused by the generation of reactive oxygen species, such as O_2^- , OH^- and H_2O_2 . Some of these reactive oxygen species act as cellular messengers in redox signaling, hence, oxidative stress can cause disruptions to the normal mechanisms of cellular signaling, and lead to many pathophysiological conditions in the body, such as nervous system disorders (8).

PNS have been shown to have protective properties via enhancing antioxidant enzyme activity, such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GSHPX) in senescence-accelerated mouse-prone 8 (SAMP8) mice and mouse melanoma B16 cells (9,10). In addition, PNS had protective effects on oxidative stress-induced brain cell damage, which was associated with a reduction in reactive oxygen species (ROS) levels and an upregulation in antioxidant mediators, such as heme oxygenase-1 (HO-1) and glutathione S-transferase pi 1 (11). Furthermore, Rb1 protected cells from oxidative injury induced by H_2O_2 , which was related to inhibiting endoplasmic reticulum stress (12). Hence, PNS could be potentially applied as an antioxidative agent.

Anti-apoptotic function

Apoptosis, or programmed cell death, is a mechanism which occurs in multicellular organisms when stimulated

by various triggers (13). Apoptotic cell death is a neat, orderly process. The characteristics of apoptosis include a reduction in the volume of cells and their nuclei, the loss of connections to adjacent cells, the formation of blebs on the cell surface, the dissection of chromatin into fragments, and the rapid engulfment of the cell corpse by phagocytosis. It is well known that the progress of apoptosis can be regulated by the expression of B-cell lymphoma protein 2 (Bcl-2, an anti-apoptotic gene) and Bcl-2 associated X protein (Bax, a pro-apoptotic gene) (14). Caspase-3, downstream to Bcl-2 and Bax, also plays a key role in the execution phase of apoptosis (15). Apoptosis has recently been the focus of investigations into the mechanisms underlying multisystem diseases.

Cao *et al.* found PNS could suppress the abnormal apoptosis and autophagy of hippocampal neurons in mice with learning and memory impairment, which was associated by re-activating phosphoinositide 3-kinase/Akt/mammalian target of rapamycin signaling transduction (16). Yuan *et al.* found that PNS had a protective effect against avascular necrosis of the femoral head induced by steroids through the inhibition of apoptosis and caspase-3 activation (17). In addition, PNS also reversed decreases in Bcl-2 expression and increases in Bax and caspase-3 expression induced by H₂O₂ in bone marrow stromal cells (18). Hence, PNS could be potentially used as an anti-apoptotic agent.

Anti-tumor functions

Tumor, or cancer, involves abnormal cell growth of tissue with the potential to spread or invade to other healthy parts of the body (19). The possible signs and symptoms of cancer include the formation of a lump, abnormal bleeding, prolonged cough, unexplained weight loss and a change in bowel movements. Presently, over 100 types of cancers can affect human beings, highlighting it is a serious threat to human health. In recent years, traditional Chinese medicines have caught people's attention to treat cancers, including PNS.

PNS was able to halt SW480 human colorectal cancer cells in the S and G2/M phases (20). Moreover, PNS showed an anti-proliferative effect in hepatoma Hep3B cells, which was indicated by reduced tumor volume and weight (21). PNS had an inhibitory effect on metastatic breast carcinoma cell line 4T1 migration and invasion (22). PNS could also attenuate lung cancer growth by modulating the protein levels of Met/miR-222 axis (23). Furthermore, R1 inhibited human colorectal cancer HCT116 cell metastasis

by inhibiting cell migration, adhesion, and invasion through regulating the expression of metastasis-associated signaling molecules (24). Hence, PNS could be potentially applied as an anti-tumor agent.

In summary, PNS have a wide range of functions, such as anti-inflammatory, anti-oxidative, anti-apoptotic, and anti-tumor effects.

The applications of PNS in nervous system diseases

Nervous system diseases encompass over 600 different disorders, from neurodegenerative diseases such as AD and PD, to stroke. Along with an aging society, these diseases have attracted worldwide medical attention because of their widespread prevalence. Therefore, it is urgent to find novel approaches to slow down or prevent these diseases. Recently, traditional Chinese medicines, including PNS, have attracted worldwide attention because of their clinical efficacy in a wide spectrum of diseases, including nervous system diseases.

PNS and AD

AD, characterized by progressive cognitive impairment and memory impairment, is a neurodegenerative disease affecting 30 million patients worldwide. Along with the general increase in human life span, it is gradually becoming a heavy burden and challenge. The main hypotheses of the pathogenesis of AD are cholinergic theory and β -amyloid peptide (A β) theory (25,26). Treatment of AD is targeted towards the formation and deposition of A β , tau protein phosphorylation, and the cholinergic system.

Effects of PNS on A β formation and deposition

Amyloid precursor protein (APP) is widely found in the cell membrane of many tissues. Normal APP is shredded by α -secretase to produce soluble APP, which is important for cell nutrition. In addition, APP is cleaved by γ -secretase and γ -secretase to produce A β , which mainly exists in two forms—A β 1-40 and A β 1-42. A β 1-42 is easily oligomerized, which has a toxic effect on neurons. A small amount of A β can also be degraded by extracellular enzymes, including neprilysin (NEP) and insulin degrading enzyme (IDE).

Studies show that PNS can downregulate the expression of the APP gene in the brain, upregulate the expression of ADAM9 mRNA, then promote APP to be shredded by α -secretase and inhibit the cleavage of APP by β -site

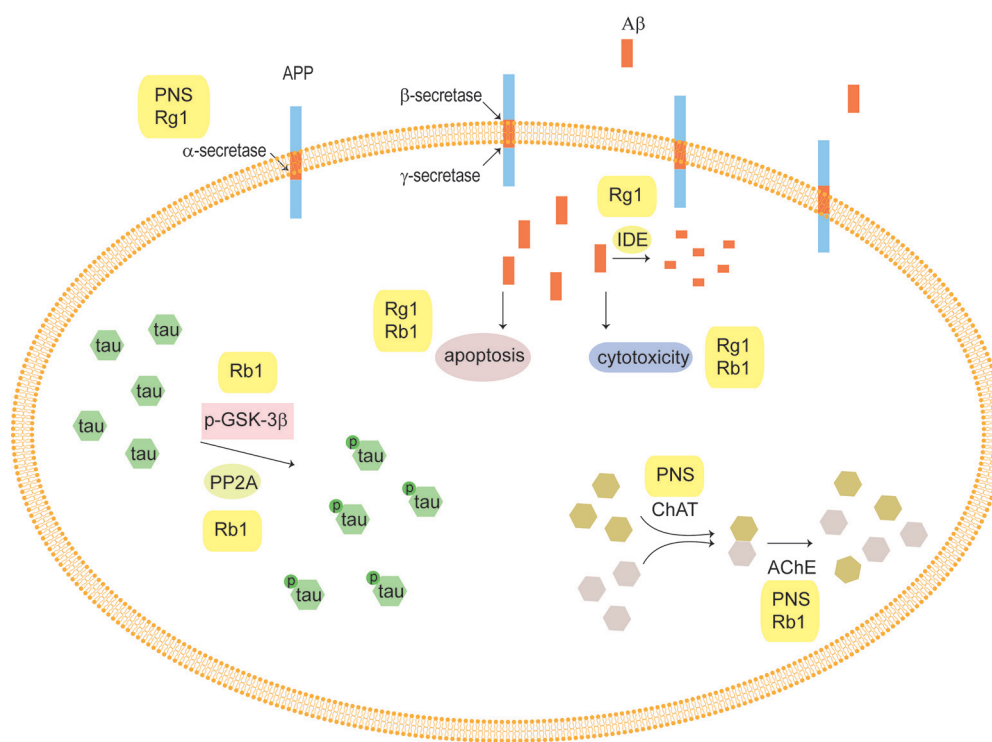


Figure 2 Panax notoginseng saponins (PNS) and Alzheimer's disease (AD). Amyloid precursor protein (APP) is shredded by α -secretase to produce soluble APP, and cleaved by β -secretase and γ -secretase to produce β -amyloid ($A\beta$) which has toxic effects on neurons. PNS could promote APP shearing by α -secretase, and attenuate the cytotoxicity of neurons induced by $A\beta$. The hyperphosphorylation of tau plays a key role in the pathogenesis of AD. PNS can regulate p-GSK-3 β and PP2A levels to prevent tau hyperphosphorylation. Acetylcholine (ACh) is an important neurotransmitter which promotes learning and improves memory ability. PNS can increase the content and activity of choline acetyltransferase (ChAT), and inhibit acetylcholinesterase (AChE) activity.

amyloid precursor protein cleaving enzyme 1 (BACE1). This downregulated the production of $A\beta$, which ameliorated learning and memory ability in mice (27) (Figure 2). More precisely, Rg1 increased the expression of ADAM10 mRNA and promoted APP shearing by α -secretase (28), and inhibited APP sheared by β -secretase and γ -secretase (29), which decreased the production of BACE1. Rg1 also activated peroxisome proliferator-activated receptor gamma (PPAR γ) to upregulate the expression of IDE and enhance $A\beta$ degradation in an AD rat model (30).

Wu *et al.* found that Rg1 could attenuate the cytotoxicity of neurons induced by $A\beta_{25-35}$ and protect primary rat cerebrocortical neurons by upregulating ERK1/2 phosphorylation and reducing nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) nuclear translocation (31) (Figure 2). In addition, they also found Rg1 could inhibit the apoptosis induced by $A\beta_{25-35}$ in human endothelial cells through downregulation

of the tyrosine nitration initiated by hypoxia-inducible transcription factor 1 alpha (HIF-1 α), and inhibiting mitochondrial apoptosis (32).

In addition, Rb1 could inhibit the production of ROS, increase Bcl-2/Bax ratio and decrease caspase-3 activity, which resisted cell damage induced by $A\beta$ (33) (Figure 2).

Effects of PNS on the phosphorylation of tau protein

Tau protein is a microtubule-associated protein, and its hyperphosphorylation performs central roles in the pathogenic mechanisms of AD (34). The high phosphorylation of tau protein is associated with glycogen synthase kinase-3 (GSK-3) and protein phosphatase 2A (PP2A) (35).

It was found that Rb1 could protect mice against toxicity induced by a neurotoxin through blocking the hyperphosphorylation of tau via regulating the levels of p-GSK-3 β and PP2A. Therefore, Rb1 might be used as a

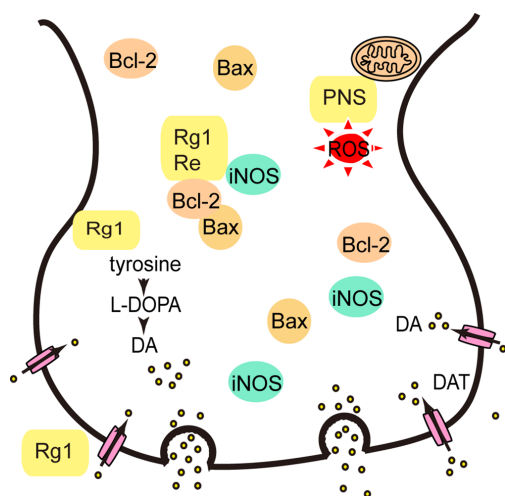


Figure 3 Panax notoginseng saponins (PNS) and Parkinson's disease (PD). PNS can inhibit neurotoxicity through enhancing antioxidant activity [reactive oxygen species (ROS), inducible nitric oxide synthase (iNOS)], modulating inflammation, and inhibiting mitochondria-mediated apoptosis (Bcl-2, Bax). PNS demonstrates neuroprotective effects on dopaminergic neurons by regulating tyrosine hydroxylase (TH), and dopamine transporter (DAT).

potential preventive drug candidate for AD as well as other tau pathology-associated disorders (36,37) (Figure 2).

Effect of PNS on acetylcholine

Acetylcholine (ACh) is one of the important neurotransmitters in the central cholinergic system, and its main function is to promote learning and improve memory ability. ACh is synthesized by choline acetyltransferase (ChAT), and decomposed by acetylcholinesterase (AChE). The balance of ACh is maintained by ChAT and AChE (38). If the activities of ChAT and AChE are abnormal, it will cause the decompensation of ACh, which leads to biochemical changes in the central cholinergic system.

PNS have a strong protective effect on cholinergic neurons in AD rat models (Figure 2). PNS can repair and improve damaged neurons to increase the quantity and quality of surviving cells, and increase the content and activity of ChAT, which protects and improves the function of the central cholinergic system.

Previous studies have demonstrated that both Rb1 and Rg1 can alleviate cognitive deficits, and are also effective in boosting neuron survival in the spinal cord. Furthermore, Wang *et al.* compared the effects of Rg1 and Rb1 on dementia in a mouse model. They found that both Rb1

and Rg1 ameliorated cognitive impairment using step-down passive avoidance (SD) and Morris water maze (MWM) tests, thereby increasing the levels of ACh in the hippocampus. However, they found Rg1 inhibited the activity of AChE while Rb1 had no effect on AChE activity. In addition, both Rb1 and Rg1 also prevented a decrease in 5-HT caused by scopolamine, but Rb1 was more active than Rg1 at the same dose (39).

In conclusion, PNS have been demonstrated to inhibit A β formation and deposition, prevent tau hyperphosphorylation, and maintain ACh balance, suggesting that PNS might be a potential treatment strategy for AD (Figure 2).

PNS and PD

PD, the second most common neurodegenerative disorder, affects 1% of individuals over 60 years old. It is defined by symptoms of motor impairment, including resting tremor, postural instability, bradykinesia, and rigidity. PD is characterized by the selective loss of dopaminergic neurons in the substantia nigra pars compacta (40). At present, 6-hydroxydopamine (6-OHDA), 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and its active metabolite 1-methyl-4-phenylpyridinium ion (MPP⁺) are used in models to induce PD.

Luo *et al.* found that PNS increased the expression of thioredoxin-1 (Trx-1) and attenuated MPP⁺-induced neurotoxicity *in vitro* (41) (Figure 3). Subsequently, they found PNS inhibited neurotoxicity induced by MPTP *in vivo* through enhancing antioxidant activity, modulating inflammation and inhibiting mitochondria-mediated apoptosis (42). Rb1 had neuroprotective effects on dopaminergic neurons via stimulating estrogen receptors with consequent activation of ERK1/2 and Akt, as well as inhibiting the levels of SAPK/JNK and p38 (43). Apart from Rb1, Rg1 also had neuroprotective effects on dopaminergic cells in a rat model of PD induced by 6-OHDA, which might be associated with the activation of the insulin-like growth factor receptor (IGF-IR) pathway. The authors found that Rg1 significantly antagonized the decrease in tyrosine hydroxylase (TH), dopamine transporter (DAT), and Bcl-2 in the substantia nigra induced by 6-OHDA (44). Re prevented apoptosis of substantia nigra neurons in a mouse model of PD induced by MPTP, which could be related to the upregulation of Bcl-2, the downregulation of Bax and inducible nitric oxide synthase (iNOS) levels, and the inhibition of caspase-3 activation (45).

Overall, PNS have demonstrated neuroprotective effects on dopaminergic cells, which suggests that PNS might be a potential treatment strategy for PD (Figure 3).

PNS and stroke

Cerebral ischemia is characterized by ischemia and hypoxia of brain tissue caused by cerebral blood flow supply. If cerebral ischemia is not completely blocked for 0.5 hours, cerebral blood flow will return to normal again, and will lead to ischemia-reperfusion injury (46). The treatment of cerebral ischemia mainly involves protecting neurons, reducing the infarct size, and decreasing neuronal death (46,47). Ischemic stroke, especially permanent occlusions, accounts for the overwhelming majority of strokes worldwide. Apart from artery occlusion, apoptosis, inflammatory responses, oxidative stress, angiogenesis, and neural plasticity play pivotal roles in the severity of cerebral ischemia injury and clinical prognosis.

PNS have been shown to reduce infarct volumes and neurological damage in a rat model of middle cerebral artery occlusion (MCAO) by downregulating the expression of TNF- α and IL-1 β , upregulating the expression of IL-10 (2), attenuating TUNEL-positive cells, and decreasing the levels of caspase-1 and caspase-3 (48). Moreover, PNS were able to enhance angiogenesis in ischemic boundary zones, increase capillary densities, and increase the expression of vascular endothelial growth factor (VEGF) as well as angiopoietin-1 (Ang-1) (49). In addition, PNS also promoted stroke recovery by downregulating the expression of neural plasticity-associated proteins, such as nogo-A, NgR and neurotrophic factor, ROCK2, in MCAO rats and in SH-SY5Y cells induced by oxygen-glucose deprivation/reperfusion (OGD/R) (50,51).

Rb1 induced neuroprotection in rats with cerebral ischemia by inhibiting the gene levels of TNF- α , IL-1 β , IL-6, as well as the activation of the NF- κ B pathway, and increasing the level of brain-derived neurotrophic factor (BDNF) (52,53). Additionally, Liang *et al.* found that after Rb1 treatment, SH-SY5Y cells resisted apoptosis induced by OGD/R, which was associated with the protection of mitochondrial function through inhibiting the release of apoptosis inducing factor (AIF) and cytochrome c (Cyt_c) (54).

Rg1 also had a protective effect on ischemia-reperfusion injury which was related to inhibiting the apoptosis of hippocampal neurons, and regulating the expression of phospho-JunN-terminal kinase (p-JNK) and p-ERK1/2 (30). Additionally, R1 had protective effects on

injury induced by cerebral ischemia-reperfusion *in vivo* and *in vitro*. Its mechanism was associated with the activation of the Akt/Nrf2 pathway to inhibit the activity of NADPH oxidase and the defunctionalization of mitochondria (55).

In brief, PNS have been demonstrated to reduce infarct volumes and neurological damage, as well as regulate neural plasticity, suggesting that PNS shows potential as a treatment strategy for stroke (Figure 4).

PNS and other nervous system diseases

The N-methyl-D-aspartic acid (NMDA) receptor can regulate neuronal survival, dendrite and axon structural development, synaptic plasticity, neuronal circuit formation, and learning and memory activity (3,56). An imbalance in NMDA receptor activity may contribute to the development of nervous system diseases (57,58). R1 was shown to have a protective effect on mouse neurons exposed to glutamate (Glu) *in vitro* by acting on NMDA receptors, which indicated R1 might be a candidate in patients who were diagnosed neurodegenerative diseases related with Glu excitotoxicity (59).

Neurotrophic factors are proteins which play key roles in the development, survival and apoptosis of neurons. Nerve growth factor (NGF), an important neurotrophic factor, is a potential drug target for the treatment of nerve injury. Rb1 and Rg1 have been shown to increase the expression of NGF in Schwann cells, the glial cells in the peripheral nervous system, which suggests they could exert neuroprotective effects in peripheral nerve injuries (60).

Microglia, the brain's innate immune cells, can transition to an activated phenotype during an inflammatory response. Reactive microglia not only protect neurons, but also secrete cytotoxic factors to damage neurons. The activation of microglia plays an important role in nervous system diseases (61,62). PNS have been shown to have an inhibitory effect on hippocampal microglia activation in SAMP8 mice, as Rg1 inhibited the activation of microglia by activating the PLC- γ signaling pathway (63).

Ion channels, including sodium (Na⁺), potassium (K⁺), calcium (Ca²⁺), play important roles in nervous system disorders. PNS could significantly inhibit ion channel currents in a dose- and voltage-dependent manner (64,65). It can be inferred PNS might be useful agents for regulation of ion channel current, which could be used for the treatment of neuron system diseases. And the neuroprotection mechanism of PNS is via the mechanism of regulating channels and receptors (66,67).

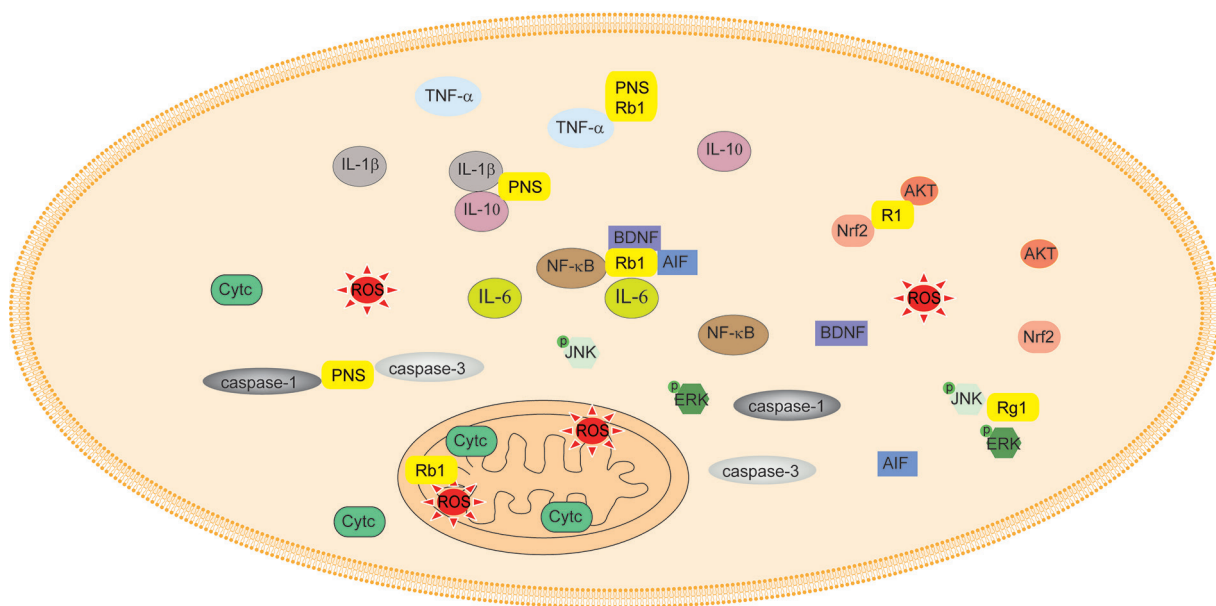


Figure 4 Panax notoginseng saponins (PNS) and stroke. PNS had protective effects on ischemia-reperfusion injury by regulating the genes involved in the inflammatory response, including TNF- α , IL-1 β , IL-6, and IL-10, and apoptosis-related genes caspase-1, caspase-3, as well as p-JNK, p-ERK, Akt, Nrf2, AIF and Cytc.

Conclusions and perspectives

In recent years, PNS have become one of the most popular healthcare products, especially for many older adults who have hypertension, hyperlipidemia, hyperglycemia, and nervous system diseases. PNS contain about 20 different kinds of saponin constituents, among which Rb1, Rg1, R1, Rd and Re are the top five saponins, which constitute up to 90% of total PNS. In this review, we focused on the significant roles of the main components of PNS on the prevention and treatment of nervous system diseases.

The bioactive components of PNS can slow vascular aging through anti-inflammatory, anti-oxidative, anti-apoptotic, and anti-tumor effects. Due to these merits, PNS exert protective effects on numerous diseases, such as nervous system disorders, cancer (68), coronary artery diseases (69), hyperlipidemia and obesity (70), osteoarthritic chondrocytes (71) and diabetes (72). With a dramatic increase in life expectancy, most countries have an aging society, meaning that nervous system disorders, including neurodegenerative disorders, have attracted worldwide attention. Therefore, it is urgent to find novel approaches to prevent or slow down these nervous system disorders. Based on demonstrated findings, traditional Chinese medicines, especially PNS, are promising natural agents highly needed as alternatives effective and safe for the management of

nervous system disorders, such as AD, PD and stroke, which suggests PNS might be potential neuroprotective drugs. However, the effects of PNS on peripheral nervous system diseases are not clear. The clinical applications and research value of PNS are of great significance, however, the mechanisms underlying its various therapeutic effects need to be further studied.

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Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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