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Article

Study on the regulatory mechanism of Panax notoginseng saponins on the mechanical response of glial cells after cerebral ischemia

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Abstract: Neuroglial cells, especially microglia and astrocytes, are crucial in the brain's recovery process after ischemic injury. Recent studies have shown that Panax notoginseng saponins (PNS) have potential therapeutic effects on the mechanical responses of neuroglial cells and their related regulatory mechanisms after cerebral ischemia. This study investigated the regulatory effects of PNS on neuroglial cells after cerebral ischemia, with a focus on its impact on microglial activation and cellular mechanical responses. Experimental results demonstrated that PNS significantly enhanced the mechanical stiffness of microglial cells (Young's modulus increased by 27.65%), a mechanism involving the scavenging of reactive oxygen species (ROS levels reduced, $P < 0.01$), stabilization of the cytoskeleton, and modulation of membrane tension, thereby suppressing the release of inflammatory factors and pathological activation. Additionally, LPNS pretreatment effectively protected the membrane integrity of astrocytes (LDH release decreased by 18.05%–29.54%), attributed to the synergistic effects of antioxidation, membrane stabilization, and anti-apoptosis. In the ischemia-reperfusion model, PNS markedly reduced leukocyte adhesion in cerebral blood vessels (72 h) by inhibiting endothelial adhesion molecule expression, improving nitric oxide (NO) production, and alleviating oxidative stress.

Keywords: Panax notoginseng saponins; cerebral ischemia; neuroglial cells; mechanical response; cytoskeleton

1. Introduction

Cerebral ischemia refers to a pathological condition where the brain tissue experiences oxygen and nutrient deprivation due to insufficient blood supply, usually caused by blockages or narrowing of the cerebral blood vessels. It is one of the most common causes of stroke (cerebrovascular accident), and its pathogenesis is complex. The main mechanisms of cerebral ischemia include reduced blood flow, insufficient oxygen supply, metabolic disturbances, and inflammatory responses. Ischemic brain injury triggers a series of physiological changes, such as neuronal cell death, intracellular calcium ion accumulation, free radical production, and cell membrane rupture, ultimately leading to brain dysfunction [1–3].

Epidemiological data shows that cerebral ischemia is one of the leading causes of death and long-term disability worldwide. According to the World Health Organization (WHO), stroke is the third leading cause of death globally, with higher incidence and mortality rates in elderly populations. In China, stroke has become the leading cause of death, and the incidence of ischemic stroke is rising annually, closely linked to chronic conditions such as hypertension, diabetes, and hyperlipidemia [4].

Early diagnosis and treatment of cerebral ischemia remain a challenge in clinical

medicine. Although there are effective treatment options, such as thrombolysis and mechanical thrombectomy, clinical outcomes are still limited due to time window constraints and the risks of complications. Current research is focused on exploring new drug targets, neuroprotective mechanisms, and early intervention strategies to improve patient prognosis [5].

Panax notoginseng saponins (PNS) have attracted considerable attention in recent years [6–10]. Panax notoginseng possesses a variety of pharmacological properties, such as antioxidant and the ability to enhance microcirculation. PNS is considered one of its main active components, with significant biological activity, particularly in neuroprotection and neural repair. Research has shown that PNS has multiple beneficial effects after cerebral ischemia, specifically in regulating glial cell functions, inhibiting neuroinflammatory responses, and promoting neural repair.

Regarding the regulation of glial cells, PNS exhibits strong anti-inflammatory effects. During cerebral ischemia, microglia become activated and release significant amounts of pro-inflammatory factors, including TNF-α and IL-1β. The excessive release of these factors exacerbates brain damage [11–15]. PNS reduces the overactivation of microglia, thus alleviating the inflammatory response triggered by cerebral ischemia. Additionally, PNS can regulate the proliferation and differentiation of astrocytes, promote their normal function in the repair process after cerebral ischemia, and reduce the formation of glial scars, providing a better microenvironment for neuronal regeneration.

Apart from regulating glial cells, PNS also promotes neural repair by improving the mechanical response of brain tissue. The communication between glial cells and neurons is crucial for recovery following cerebral ischemia [16–20]. PNS regulates the mechanical behavior of glial cells, enhances their ability to adapt to injury, and improves the membrane tension and cytoskeletal stability of these cells. This helps promote neuronal survival and regeneration, further accelerating the repair process of brain tissue.

Moreover, PNS has significant antioxidant effects, which can reduce oxidative stress caused by ischemia and protect glial cells from oxidative damage. After cerebral ischemia, free radicals and reactive oxygen species increase in brain tissue, and these substances have direct toxic effects on neurons. PNS reduces cellular damage after cerebral ischemia by boosting antioxidant enzyme activity and lowering oxidative stress.

In conclusion, PNS regulates the function of glial cells through multiple pathways, not only reducing the inflammatory response after cerebral ischemia but also improving the microenvironment, enhancing antioxidant capacity, promoting neuronal regeneration, and supporting the repair of brain tissue. This makes PNS a promising potential drug for the repair of cerebral ischemia. With further research into its molecular mechanisms, PNS holds promise as a potential new treatment for cerebral ischemia in clinical practice. Future research should further explore the combination of PNS with other therapies, its clinical effectiveness, and safety to promote its practical application in the treatment of cerebral ischemia.

2. Experimental methods

2.1. Cells

Microglial cells BV2 were purchased from Shandong Kesheng Biotechnology Co., Ltd. The cells were grown in DMEM/F-12 medium (Gibco, USA) with 10% fetal bovine serum (Gibco, USA) and 1% penicillin-streptomycin (HyClone, USA). The cells were maintained in a 37 ℃, 5% CO_2 incubator (Gibco, USA) for static cultivation. When the cells reached the logarithmic growth phase (80%–90% confluence), they were used for experiments.

2.2. Measurement of Young's modulus

Based on the cone-sphere model [21], we used Atomic Force Microscopy (AFM) to calculate the Young's modulus of all samples. The spring constant is calibrated to 0.38 ± 0.02 N/m using thermal tuning method. The scanning speed is set to 0.5 Hz, corresponding to a line speed of 10 μm/s, and the sampling frequency is 512 pixels/line. All measurements were conducted in a constant temperature environment of 25 ℃, with relative humidity controlled below 40% to reduce environmental interference. The surface treatment steps for the sample are as follows: (a) Cleaning steps: immerse the sample in ethanol and deionized water for ultrasonic cleaning for 10 min each to remove surface contaminants; (b) drying treatment: After drying with high-purity nitrogen, place it in a vacuum drying oven (25 ℃, 10 kPa) and let it stand for 12 h; (c) substrate fixation: Paste the processed sample onto the silicon wafer substrate and use conductive adhesive to ensure surface flatness.

To measure the Young's modulus of the sample using AFM, it is first necessary to ensure that the sample surface is flat and clean to avoid contamination that may affect the measurement results. Next, an appropriate AFM probe is selected, usually based on the sample's hardness and the expected range of the Young's modulus. The instrument is calibrated before measurement to ensure the probe stiffness is accurate. Then, AFM scanning parameters, including scan speed, scan range, and sampling frequency of the force-distance curve, are set, and contact mode is typically used for the measurement. During the scanning process, the AFM probe contacts the sample surface and generates a force-displacement response. By collecting force-distance curves, local elastic information of the sample is obtained. Afterward, the force-displacement data are processed using an appropriate mechanical model to calculate Young's modulus at each measurement point. Finally, by analyzing data from multiple measurement points, a distribution map of Young's modulus is created, thus obtaining the overall mechanical properties. This entire process allows for highly accurate measurement of its Young's modulus and provides detailed local mechanical property data.

3. Effects of PNS on the mechanical response of glial cells

In brain ischemia, glial cells, especially microglia and astrocytes, play important roles. During ischemia, microglia become activated and release inflammatory factors, which may trigger neuronal damage. Excessive activation of the inflammatory response can exacerbate brain injury, so controlling the activation level of these cells

is crucial. Additionally, the function of glial cells is influenced by mechanical properties, such as cell membrane tension, cytoskeletal structure, and changes in the extracellular matrix. Regulating these mechanical characteristics can help improve the function and repair of glial cells.

3.1. Activation and mechanical response of microglia

Figure 1 shows the force-displacement curve of microglia. From the figure, it can be seen that as displacement increases, the force decreases. This may be related to the cell's elastic modulus, viscosity, or inherent rheological properties. As displacement increases, microglial cells may undergo a transition from elastic deformation to viscous flow, or the cell membrane may experience some degree of damage or structural adjustment. This reduction in force could also be due to the rearrangement of the cytoskeleton (such as microtubules and actin filaments), resulting in changes in the mechanical strength and deformation capacity of the cells. Microglia are rapidly activated following brain ischemia such as TNF-α and IL-1β. PNS may regulate the mechanical response of microglia and inhibit their excessive activation. Some studies have found that PNS can modulate the membrane tension of microglial cells, improving membrane fluidity. Additionally, PNS regulates the dynamic changes in microtubules and actin filaments in the cytoskeleton, reducing excessive migration and expansion of microglia, further inhibiting their activation.

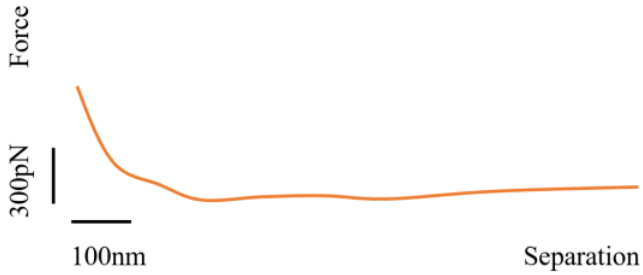

Figure 1. Force-displacement curve of microglia.

Figure 2 shows the precise statistical results of Young's modulus for each group. The Young's modulus value of normal microglia is 14.21 kPa. When comparing the modulus of the PNS-treated microglia group with the normal microglia group, the results indicate that PNS treatment for 24 h can increase the Young's modulus of the cell without affecting the cell morphology. The sample has a repetition rate of 10, a *t*-value of 3.45, and a *p*-value less than 0.01. The Young's modulus of the PNS-treated microglia group is 18.14 kPa, which is a 27.65% increase compared to the 14.21 kPa of the normal microglia group. This suggests that PNS can effectively prevent the reduction in cell modulus caused by oxidative stress damage, thereby enhancing cell survival. The increase in Young's modulus in the PNS-treated microglia group can be attributed to several mechanisms, which involve the regulation of cellular mechanical properties in response to oxidative stress and inflammatory stimuli. Here are some possible reasons for the observed increase in modulus: (1) Oxidative stress protection: Oxidative stress typically leads to the degradation of cellular components, including proteins, lipids, and the cytoskeleton, which can reduce cell stiffness and mechanical strength. **Figure 3** shows the effects of PNSs on intracellular POS level. Compared

with the control group, when the cells were pretreated with PNSs, the ROS level was significantly reduced ($P < 0.01$). A significant change in ROS level was observed, indicating severe oxidative stress in the cells. PNS has antioxidant properties, which may reduce the accumulation of reactive oxygen species (ROS) and prevent the damage to the cytoskeleton, thereby maintaining or even enhancing cell stiffness. By reducing oxidative stress, PNS helps preserve or restore the structural integrity of the microglia, reflected in the increase in Young's modulus; (2) cytoskeletal stabilization: The cytoskeleton, composed of microtubules and actin filaments, plays a crucial role in maintaining cellular shape and mechanical properties. The mechanical strength of cells is largely determined by the organization and integrity of the cytoskeletal network. PNS has been shown to modulate cytoskeletal dynamics by stabilizing microtubules and actin filaments. This stabilization could lead to a more robust cytoskeletal framework, thus contributing to the increase in the Young's modulus. The enhanced organization of the cytoskeleton may reduce cellular deformation and improve the ability of the cell to resist external mechanical forces; (3) membrane tension modulation: Cell membrane tension is an important factor influencing cellular mechanics. By improving membrane fluidity, PNS may reduce the membrane's susceptibility to damage under stress, contributing to an increase in the cell's overall stiffness. This modulation of membrane properties may be a key factor in the observed increase in Young's modulus, as membrane tension directly influences the mechanical properties of the cell surface.

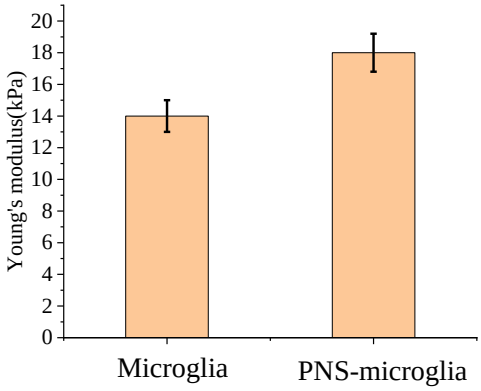

Figure 2. Young's modulus of microglia for each group ($p < 0.01$).

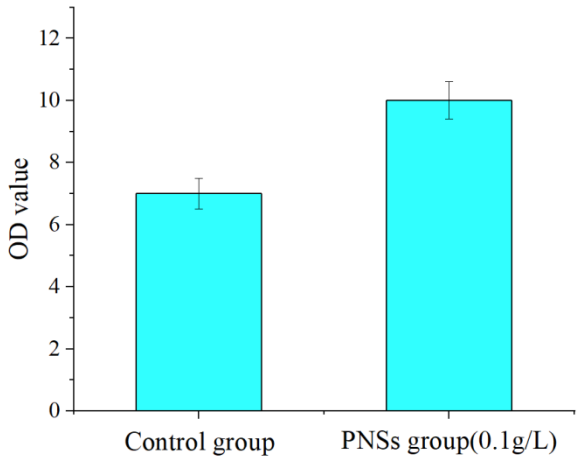

Figure 3. Effects of PNSs on intracellular POS level ($p < 0.01$ for PNSs group).

3.2. LDH release observed in LPNS-treated astrocytes

Lactate dehydrogenase (LDH) release is commonly used as an indicator of cell membrane damage and cell death, as it is released into the culture medium when the integrity of the cell membrane is compromised. In this study, pre-treatment with LPNS (Lipoid nanoparticles) at concentrations of 2.5 μg/mL and 5 μg/mL for 24 h significantly reduced the release of LDH in astrocytes compared to the control group (injury induced by H_2O_2 treatment). The sample has a repetition rate of 10, a *t*-value of 3.57, and a *p*-value less than 0.01.

LPNS may have a potential impact on cell viability. LPNS are commonly used in drug delivery systems, and their particle size, surface properties, and composition can affect the permeability of cell membranes, leading to cell uptake or toxic reactions. Properly formulated LPNS can enhance drug delivery into cells, boost cell activity, or trigger biological responses. However, excessive or inappropriate LPNS may have negative effects on cells, such as inducing cellular stress, inflammatory responses, or apoptosis. Therefore, studying the impact of LPNS on cells is crucial to ensuring their safety and efficacy. Specifically, the LDH release was decreased by 18.05% and 29.54%, respectively, indicating that LPNS treatment may help to protect astrocytes from membrane damage and potentially reduce cell death. These results suggest that LPNS could exert a protective effect on astrocyte cells, possibly through mechanisms that stabilize the cell membrane, reduce oxidative stress, or prevent apoptotic pathways. Further investigation into the molecular mechanisms behind this protective effect would help to clarify how LPNS influences astrocyte viability and cellular integrity. The reduction in LDH release observed in astrocytes pre-treated with Lipoid nanoparticles (LPNS) at concentrations of 2.5 μg/mL and 5 μg/mL for 24 h highlights the potential protective effects of LPNS on cell membrane integrity. The fact that LPNS treatment resulted in a significant decrease in LDH release suggests that LPNS may act to stabilize the cell membrane and protect against cell death, which is particularly important in the context of astrocyte function in the brain. Several possible mechanisms could explain how LPNS treatment helps to reduce LDH release and protect astrocytes from membrane damage: (1) Membrane stabilization: LPNS may directly interact with the cell membrane, promoting its stability and reducing membrane permeability. This could prevent the leakage of intracellular components, such as LDH, and reduce cellular damage. The lipid composition of LPNS could play a role in integrating into the cell membrane, thereby reinforcing its structural integrity and making it more resistant to external stressors; (2) antioxidant properties: Many types of nanoparticles, including lipid-based ones like LPNS, have been shown to have antioxidant properties. Oxidative stress is a significant contributor to cell membrane damage, so by minimizing ROS production, LPNS could protect astrocytes from oxidative damage and the resulting release of LDH; (3) reduction of apoptotic pathways: LPNS treatment may help modulate signaling pathways related to apoptosis. Apoptosis, or programmed cell death, is often triggered by cellular stress or damage, leading to the activation of caspases and other pro-apoptotic proteins. By mitigating the stress signals that lead to apoptosis, LPNS could help to reduce cell death and the consequent release of LDH. This could involve the inhibition of pro-apoptotic molecules or the activation of survival pathways that preserve cell integrity.

In summary, the reduction in LDH release observed in LPNS-treated astrocytes suggests that LPNS may protect against membrane damage and cell death through several potential mechanisms, including membrane stabilization, antioxidant activity, modulation of apoptotic signaling, regulation of inflammation, and enhancement of energy metabolism and autophagy. Additional studies are required to identify the molecular pathways through which LPNS exerts its protective effects, offering potential insights for developing treatments for neurological disorders related to astrocyte damage.

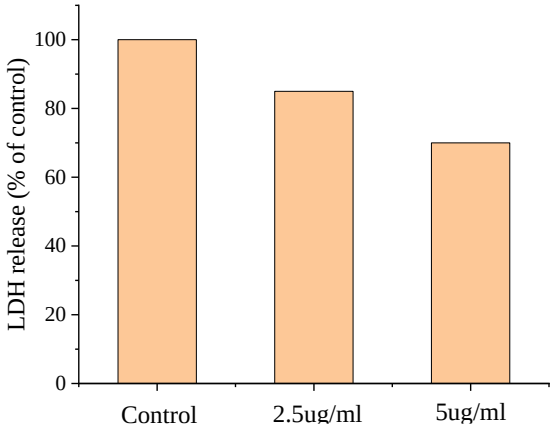

Figure 4. Effect of LPNS on release of lactate dehydrogenase (LDH) ($p < 0.01$).

3.3. PNS-induced improvement in leukocyte adhesion

Figure 5 shows the effect of PNS on leukocyte adhesion. The figure shows that PNS treatment reduced leukocyte adhesion in the cerebral vascular cortex of mice 72 h after ischemia-reperfusion (I/R). PNS treatment may reduce leukocyte adhesion in the cerebral vascular cortex after ischemia-reperfusion (I/R) at 72 h through the following mechanisms:

The treatment with PNS (which may refer to a specific compound like ginsenosides or other anti-inflammatory agents) for ischemia-reperfusion (I/R) injury in the cerebral vascular cortex has multifaceted effects, each contributing to the reduction of leukocyte adhesion. Let's further expand on the mechanisms mentioned above and explore their potential interactions in greater detail:

1) Inhibition of inflammatory response

Pro-inflammatory Mediators: During ischemia, there is a rapid depletion of oxygen and nutrients, leading to tissue injury and activation of inflammatory pathways. Ischemia-reperfusion injury causes a cascade of events including the activation of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6. These adhesion molecules play a crucial role in leukocyte recruitment and attachment to the blood vessel wall.

PNS Inhibition: PNS treatment could attenuate the production of these inflammatory cytokines, which is a central regulator of inflammation, or by modulating the activity of other inflammatory mediators. By reducing the release of pro-inflammatory cytokines and inhibiting the expression of adhesion molecules, PNS can decrease the recruitment and adhesion of leukocytes to the endothelial surface, ultimately reducing the degree of tissue damage.

2) Improvement of endothelial function

Endothelial dysfunction: Ischemia-reperfusion injury results in endothelial dysfunction, which includes the loss of endothelial integrity, increased vascular permeability, and impaired ability to regulate blood flow. Under normal circumstances, endothelial cells maintain a barrier that prevents excessive leukocyte adhesion. However, ischemic damage leads to the upregulation of adhesion molecules, which facilitates leukocyte rolling, firm adhesion, and subsequent transmigration into the tissue.

PNS's role in repair and recovery: PNS may help in the repair and restoration of endothelial function by promoting the proliferation and migration of endothelial cells, facilitating their recovery from damage. Additionally, PNS may enhance the synthesis of nitric oxide (NO), a vasodilator produced by endothelial cells that also exerts anti-inflammatory effects. By improving endothelial integrity and functionality, PNS prevents the excessive adhesion of leukocytes, maintaining the vascular barrier and promoting tissue protection after ischemia-reperfusion injury.

3) Regulation of immune response

Immune cell activation: In the aftermath of ischemia-reperfusion, immune cells such as macrophages, neutrophils, and *T* lymphocytes are activated. These cells release various pro-inflammatory cytokines, reactive oxygen species (ROS), and proteolytic enzymes that further exacerbate vascular injury and tissue damage. Moreover, the overactivation of the immune system can lead to a prolonged and excessive inflammatory response, making leukocyte adhesion persist even after the initial insult.

Modulation by PNS: PNS may help modulate the immune response by regulating the activation and function of immune cells. By modulating the immune response, PNS can reduce the overall burden of inflammation, thus preventing the excessive accumulation of immune cells (and leukocytes) in the vascular and tissue spaces.

4) Antioxidant effects

Oxidative stress in I/R injury: A key result of ischemia-reperfusion is the generation of reactive oxygen species (ROS). This oxidative stress is a key contributor to endothelial dysfunction, leukocyte activation, and tissue damage.

PNS's Antioxidant Potential: PNS has been shown to possess antioxidant properties and glutathione peroxidase. By scavenging ROS and reducing oxidative stress, PNS can protect endothelial cells from damage, thereby preserving their ability to maintain vascular integrity and inhibit leukocyte adhesion. Moreover, the reduction of oxidative damage to leukocytes themselves may also reduce their activation and adhesion to the blood vessel walls.

5) Additional mechanisms

Molecular pathways involved in leukocyte adhesion: Leukocyte adhesion to the endothelial cells is a complex process that involves several key molecular pathways. PNS may interfere with the signaling pathways that regulate these molecules, inhibiting the molecular interactions that lead to leukocyte adhesion.

Balance of pro- and anti-inflammatory mediators: A critical aspect of PNS's role could involve its ability to modulate the balance between pro-inflammatory and anti-inflammatory signals.

6) Potential synergistic effects

Combination of mechanisms: The mechanisms outlined above are likely

interrelated and may act synergistically. For example, the inhibition of inflammatory cytokines and the enhancement of antioxidant capacity could complement each other in reducing endothelial damage and preventing leukocyte adhesion. Furthermore, the improvement in endothelial function and immune modulation might be linked, as both contribute to a less permeable and more resilient blood-brain barrier.

PNS treatment may reduce leukocyte adhesion in the cerebral vascular cortex after ischemia-reperfusion injury by a combination of mechanisms: inhibiting the inflammatory response, promoting endothelial function, modulating immune responses, and exerting antioxidant effects. These actions not only limit the immediate leukocyte adhesion but also contribute to long-term protection and recovery of the vascular and tissue integrity, providing a multifaceted therapeutic approach for ischemia-reperfusion injuries.

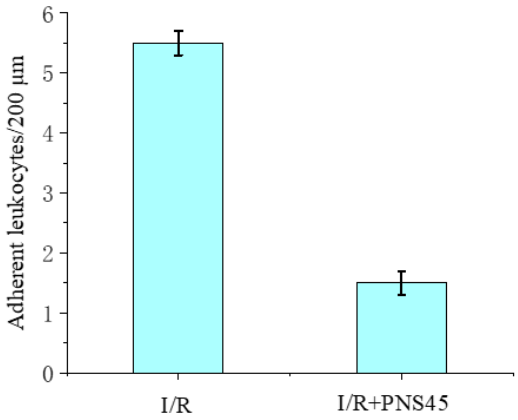

Figure 5. Effect of PNS on leukocyte adhesion.

4. Discussion

The experimental results of this study indicate that PNS plays a significant role in regulating the physiological functions of microglia and astrocytes. Specifically, PNS significantly enhanced the mechanical stiffness of microglia (with a 27.65% increase in Young's modulus), and its mechanism of action may be related to clearing reactive oxygen species (ROS), stabilizing the cytoskeleton, and regulating membrane tension. These effects collectively inhibit the release of inflammatory factors and pathological activation, indicating that PNS can exert anti-inflammatory effects through regulation of the intracellular environment.

In further experiments, we found that PNS pretreatment can effectively protect the membrane integrity of astrocytes. The specific manifestation is a decrease in the release of lactate dehydrogenase (LDH) (18.05%–29.54%), which supports the synergistic effect of PNS in antioxidant, membrane structure stabilization, and anti-apoptosis. PNS reduces cellular oxidative damage by clearing ROS, thereby slowing down membrane damage and death. This mechanism demonstrates great potential for PNS in cell protection, especially in the context of neurological damage, with significant clinical application prospects.

In the ischemia-reperfusion model, PNS significantly reduced the adhesion of white blood cells in cerebral blood vessels (72 h), which may be related to PNS inhibiting the expression of endothelial cell adhesion molecules, improving nitric

oxide (NO) synthesis, and alleviating oxidative stress. White blood cell adhesion is one of the key factors leading to ischemia-reperfusion injury. Therefore, PNS effectively reduces the inflammatory response caused by ischemia-reperfusion through its anti-inflammatory and antioxidant effects.

Although this study provides multifaceted evidence on PNS, demonstrating its potential in neuroprotection and anti-inflammatory fields, there is still a lack of direct evidence on these mechanisms. Future research should further explore the specific molecular mechanisms of PNS on cell membrane tension, antioxidant effects, and cytoskeleton stability, in order to better elucidate its biological role. In addition, the efficacy and safety of PNS in clinical applications still need to be validated through more animal experiments and clinical trials.

5. Conclusion

This study thoroughly explores the potential of Panax notoginseng saponins (PNS) in the treatment of brain ischemia, particularly its unique advantages in modulating the mechanical responses of glial cells. The results indicate that PNS can significantly improve the functional state of glial cells by regulating the cytoskeleton, membrane tension, and extracellular matrix remodeling. This helps inhibit excessive activation of glial cells, reduce inflammatory responses, and promote neural repair. The reactive changes in microglia and astrocytes after brain ischemia are closely related to the occurrence and progression of brain injury. By modulating the mechanical properties of these cells, PNS holds promise as a therapeutic strategy for alleviating neuroinflammation, inhibiting cell death, and promoting the recovery of neural function.

Furthermore, the regulation of membrane tension, extracellular matrix remodeling, and cytoskeletal dynamics by PNS provides a possible mechanistic basis for its role as a neuroprotective agent. These mechanisms not only help reduce the excessive activation of glial cells following brain ischemia but also may promote the repair of damaged neural tissue, thereby improving neurological function. By reducing inflammatory responses and enhancing the neural repair process, PNS offers new insights and theoretical foundations for clinical treatment of brain ischemic injury.

Future research should further investigate the mechanisms of action of PNS in different types of glial cells, especially in different stages of brain injury and pathological environments. Additionally, optimizing the administration method and dosage of PNS, as well as its long-term safety and efficacy, are important areas for further study. These findings may provide more effective treatment options for the clinical management of brain ischemic injury and offer theoretical support and practical guidance for the development of novel neuroprotective drugs.

Conflict of interest: The authors declare no conflict of interest.

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