DOI: 10.66069/ojspub.27450743

Neural Remodeling After Ischemic Stroke from the Perspective of Qi-Blood-Neurovascular Unit Coupling: A Narrative Review

Yuxin Liu, Haizhe Zhou*

Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
**Correspondence Author*

Abstract: ***Neurological recovery after ischemic stroke is closely associated with successful reperfusion and preservation of the neurovascular unit (NVU). Traditional Chinese medicine (TCM) concepts such as disharmony of qi and blood and intermingling of phlegm and blood stasis show conceptual parallels with blood-brain barrier disruption, glial dysregulation, inflammatory activation, and other pathological changes recognized in modern medicine. From the perspective of qi-blood-NVU coupling, this review summarizes NVU injury, neural remodeling, and the potential mechanisms of TCM interventions after ischemic stroke. It further discusses how therapeutic approaches that replenish qi, activate blood circulation, resolve blood stasis, and unblock the collaterals may influence neurotrophic factor expression, inflammatory microenvironments, microcirculation, and synaptic plasticity. Current evidence suggests that TCM may modulate post-stroke neural repair through multicomponent, multitarget, and multipathway actions. However, major limitations remain, including the lack of standardized disease-syndrome animal models, insufficient validation of key causal mechanisms, and limited high-quality clinical evidence. Future studies should integrate multi-omics, artificial intelligence-assisted analysis, advanced disease models, and rigorously designed clinical trials to clarify the modern biological basis of qi-blood-NVU coupling and to provide a stronger foundation for neural repair and integrative treatment after ischemic stroke.***

Keywords: Neural plasticity, Ischemic stroke, Neurovascular unit, Multi-omics, Traditional Chinese medicine**.**

1. Introduction

Ischemic stroke is a cerebrovascular disorder associated with high rates of disability and mortality. It is generally caused by cerebral arterial stenosis or occlusion and related hemodynamic disturbances, resulting in cerebral ischemia, hypoxia, and neuronal injury. Although intravenous thrombolysis and endovascular treatment can restore blood flow, their use is constrained by narrow therapeutic windows, and many patients continue to experience persistent neurological deficits. Consequently, the development of effective strategies to promote neural repair has become a major clinical and research priority. The NVU is composed of neurons, vascular endothelial cells, astrocytes, pericytes, and the extracellular matrix [1]. Its structural and functional integrity is essential for normal brain activity. Neural remodeling refers to the brain's capacity for self-repair through processes such as axonal sprouting, synaptic regeneration, and circuit reorganization [2]. Therefore, modulation of the NVU to facilitate neural remodeling is increasingly recognized as a key route to functional recovery. With the modernization of TCM research, the potential role of TCM in post-stroke neural repair has attracted growing attention. TCM pathophysiological concepts, including disharmony of qi and blood and toxic injury to the brain collaterals, show theoretical convergence with modern descriptions of NVU injury. Therapeutic strategies aimed at harmonizing qi and blood have also shown potential in clinical rehabilitation, although their biological basis remains incompletely defined. This review examines the relationship between NVU injury and qi-blood disharmony within a qi-blood-NVU framework, with the aim of providing a mechanistic basis and clinical reference for integrative approaches to post-stroke neural repair.

2. The Pathophysiological Bridge Between Neurovascular Unit Injury and Qi-Blood Disharmony

2.1 Mechanisms of Neurovascular Unit Injury in Modern Medicine

After cerebral ischemia, NVU injury is driven mainly by three interrelated processes. First, the blood-brain barrier (BBB) is disrupted. Experimental work suggests that HIF-1alpha/ VEGF/MMP-9 signaling contributes to BBB injury after cerebral ischemia-reperfusion, with MMP-9-mediated degradation of tight-junction and basement- membrane components [3]. This compromises barrier structure, increases permeability, and promotes vasogenic edema [4]. A clinical association study reported that serum NOX4 and AQP4 may have predictive value for malignant cerebral edema after endovascular treatment, whereas preclinical research has implicated the counter-regulatory renin-angiotensin axis in ischemic injury [5,6]. Their causal roles in edema formation remain uncertain. Functional impairment accompanies structural barrier failure. Changes in P-glycoprotein expression have been reported in neurons during acute cerebral ischemia [7]; whether analogous endothelial changes alter drug efflux requires BBB-specific evidence. Under ischemic or hypoxic conditions, reduced GLUT1 expression can impair endothelial glucose handling [8], and GLUT1 downregulation in the cerebral microvasculature has also been associated with neurocognitive dysfunction in aged mice [9]. Separately, cerebral ischemia can downregulate the neuroprotective GDNF-Ret signaling pathway in hippocampal neurons [10]. Enhanced endothelial transcytosis and mitochondrial dysfunction further facilitate the entry of harmful substances

into the brain and disturb metabolic homeostasis [11].

Second, glial polarization and function become dysregulated. Abnormal expression of aquaporin-4 (AQP4), which is densely distributed in astrocytic endfeet, is closely associated with cytotoxic edema and impaired fluid and metabolic homeostasis [12,13]. Structural and molecular coupling between astrocytes and cerebral vessels is essential for BBB maintenance [14,15]. It is therefore plausible that disruption of this interface after ischemia compromises NVU integrity, although direct evidence for ischemia-induced astrocytic endfoot detachment remains limited. Microglia tend to shift toward a pro-inflammatory M1-like phenotype and release inflammatory mediators that damage neurons and amplify inflammatory cascades [16]. Importantly, astrocytic and microglial responses are not independent; their reciprocal signaling may create a self-perpetuating cycle of neuroinflammation [17].

Third, pericyte dysfunction contributes to microvascular failure. During the early phase of ischemia, oxidative-nitrative stress and calcium-dependent contraction can produce capillary constriction and persistent microcirculatory impairment even after arterial recanalization [18]. Disruption of platelet-derived growth factor B/platelet-derived growth factor receptor-beta signaling, basement-membrane integrity, and endothelial-pericyte communication further destabilizes the microvasculature [19,20]. Pericyte loss and dysfunction intersect with oxidative stress and inflammatory signaling [19,20]. Ferroptosis and NLRP3 inflammasome activation are implicated more broadly in stroke-related cell death and neuroinflammation [21,48], but pericyte-specific causal roles remain insufficiently established. Thus, post-ischemic NVU injury results from interacting vascular, glial, and neuronal mechanisms that amplify tissue damage. Multicomponent strategies targeting several elements of this network have therefore attracted increasing interest.

2.2 TCM Pathogenesis of Qi-blood Disharmony

In TCM, ischemic stroke is classified within the category of zhongfeng (stroke syndrome). Its core pathogenesis is commonly summarized as deficiency in origin and excess in manifestation, with disharmony of qi and blood [22]. Deficiency in origin primarily includes liver-kidney yin deficiency and qi deficiency. Liver-kidney yin deficiency may permit hyperactivity of liver yang and internal wind, whereas qi deficiency weakens the propulsion of blood and disrupts circulation. Excess in manifestation is particularly evident during the acute phase and is characterized by wind, fire, phlegm, and blood stasis, which disturb the clear orifices and obstruct the brain collaterals [22].

The disease often develops on a background of systemic deficiency. Liver-kidney yin deficiency and qi deficiency are understood in TCM to impede blood flow and promote blood stasis. In contemporary clinical research, the qi-deficiency and blood-stasis pattern has been operationalized in a randomized trial protocol using syndrome criteria and neurological outcomes [24]. Contemporary theoretical research also discusses candidate mechanisms and biomarkers, but validation remains preliminary [25]. Persistent blood stasis may impair the distribution of body fluids and contribute to phlegm accumulation, producing the pattern of intermingled phlegm and blood stasis and further obstructing the brain collaterals. With prolonged disease, retained phlegm and stasis may transform into heat and toxin, giving rise to the concept of toxic injury to the brain collaterals [25]. In collateral-disease literature, some authors have proposed, mainly in cognitive impairment and Alzheimer's disease contexts, that the brain-collateral concept may be interpreted alongside elements of the modern NVU [26]. Experimental studies of TCM formulas in CSVD-related cognitive impairment have targeted NVU injury [27], but these findings do not establish a one-to-one equivalence between the TCM construct of toxic injury and a defined biomedical mechanism.

2.3 A multi-omics Bridge Between Qi-blood Dysregulation and Neural Plasticity

Network pharmacology and molecular docking have been used to screen active constituents of Chinese medicinal materials, including Gastrodia elata-related studies, and to construct component-target-pathway networks [28]. Predictive studies in other neuropsychiatric contexts have linked herbal constituents to BDNF/TrkB/CREB signaling [29]. These findings are hypothesis-generating rather than direct evidence of post-stroke neural remodeling, but they support the broader possibility that Chinese medicines may act through coordinated multitarget and multipathway mechanisms.

Metabolomic and gut microbiome studies provide additional systems-level evidence. In Alzheimer's disease-like experimental models, Chinese herbal interventions have been reported to modulate the microbiota-gut-brain axis and short-chain fatty-acid metabolism [30,31]. A systematic review describes broader associations between gut microbiota and Alzheimer's disease [32]. Separately, experimental work indicates that GABAergic signaling can modulate neuroinflammatory responses [33], although that study did not test a Chinese medicine intervention. Other experimental studies of a TCM formula and a natural flavonoid have reported modulation of microglial polarization and synaptic-plasticity pathways [34,35], while a review discusses BDNF/TrkB as a candidate pathway in TCM treatment of ischemic stroke [36]. These sources provide indirect or preclinical support and should not be treated as clinical proof of the qi-blood-NVU framework.

Several representative formulas illustrate this potential. A 2024 dissertation reported that Shenma Yizhi Formula promoted M2-like microglial polarization and BDNF/TrkB signaling in an experimental vascular-dementia model [37]. Naoluoxintong and its component formulas increased hippocampal expression of GluR1, calcium/calmodulin-dependent protein kinase II (CaMKII), and protein kinase A (PKA) in rats subjected to middle cerebral artery occlusion and reperfusion, supporting a role in synaptic plasticity [38]. The neuroprotective effects of Shenrong Guben Huanshao Pill have been explored through multi-omics analysis [39]; however, their relevance to post-stroke neural remodeling remains to be established. Further application of integrated omics to disease-syndrome models may define more precisely the molecular networks through which qi-blood dysregulation

influences neural plasticity and may identify new targets for therapies based on the principle of simultaneously regulating qi and blood.

Overall, the relationship between post-stroke NVU injury and TCM patterns such as qi-blood disharmony, intermingling of phlegm and blood stasis, and toxic injury to the brain collaterals should not be interpreted as a simple one-to-one correspondence. Rather, these concepts intersect at multiple levels, including microcirculatory dysfunction, BBB disruption, inflammation, glial polarization, and impaired neural plasticity. Table 1 summarizes the proposed pathological and therapeutic associations within the qi-blood-NVU framework.

Table 1: Proposed Pathogenesis-Pathology Relationships in Post-Stroke Neural Remodeling Within the Qi-Blood-NVU Framework

TCM pattern	Modern pathological correlate	Relevant NVU components	Potential biomarkers	Potential therapeutic approach
Qi deficiency and blood stasis	Microcirculatory dysfunction; insufficient energy metabolism	Endothelial cells, pericytes, neurons	GLUT1, VEGF, BDNF, lactate metabolism	Replenish qi and activate blood circulation
Intermingling of phlegm and blood stasis	Inflammation, oxidative stress, and BBB disruption	Microglia, astrocytes, endothelial cells	MMP-9, AQP4, TNF-alpha, IL-1beta	Activate blood, resolve stasis and phlegm, and unblock collaterals
Toxic injury to brain collaterals	Hypothesized inflammatory cascades; possible ferroptosis and NLRP3 involvement	Microglia, pericytes, neurons	NLRP3, ROS, GPX4, IL-6	Potential adjunctive strategy: clear heat and toxins and unblock collaterals
Liver-kidney deficiency	Insufficient neurotrophic support and reduced synaptic plasticity	Neurons, astrocytes	BDNF/TrkB	Tonify the kidney, replenish essence and qi, and nourish blood

Based on these proposed relationships, interventions for neural repair after ischemic stroke should not be restricted to a single target. Instead, they should address BBB protection, inflammatory microenvironment regulation, improvement of microcirculation, and promotion of synaptic plasticity. Integrative treatment may therefore offer stage-specific advantages through coordinated, multitarget regulation.

3. Evidence-Informed Integration of Therapeutic Strategies

3.1 Modern Medical Strategies: Multitarget Regulation of the Neurovascular Unit

Modern therapeutic research is gradually shifting from single-target neuroprotection toward multicomponent regulation of the NVU. MMP-9 is a major mediator of BBB disruption and hemorrhagic transformation after ischemic stroke, and preclinical inhibition can reduce barrier breakdown and edema [40,41]. However, no MMP-9-specific intervention has established routine clinical efficacy. Contemporary work therefore emphasizes stage-specific protection of the BBB and the multiple cellular mechanisms that drive ischemic brain edema [42].

Regulation of glial responses is another emerging strategy. Microglia can exert both injury-promoting and repair-supporting functions after ischemic stroke, so therapeutic modulation must account for phenotype, timing, and cellular context [43]. Experimental depletion studies have sometimes worsened inflammation, leukocyte accumulation, and lesion evolution, cautioning against indiscriminate suppression of microglia or colony-stimulating factor 1 receptor signaling [44,45]. Regulation of AQP4 in astrocytic endfeet is also being investigated as a means of modulating cytotoxic and vasogenic edema, although the direction and timing of intervention are critical because AQP4 has phase-dependent roles in water influx and clearance [46,47]. In parallel, strategies targeting pericyte contraction, microvascular obstruction, and ferroptotic cell death are being investigated as components of NVU protection [48].

3.2 TCM Strategies: Syndrome Differentiation and Available Evidence

Within the framework of syndrome differentiation, TCM has developed a set of interventions centered on harmonizing qi and blood. For blood stasis, blood-activating and stasis-resolving therapy is generally considered a core approach. Sodium tanshinone IIA sulfonate has stroke-specific evidence, including a randomized single-center trial and a recent meta-analysis, but study quality and generalizability remain concerns [49,50]. Tetramethylpyrazine (ligustrazine) has extensive mechanistic and preclinical literature, with proposed antioxidant, anti-inflammatory, endothelial-protective, and microcirculatory effects, whereas high-quality stroke-specific clinical evidence remains limited [51,52]. Accordingly, the evidence base varies substantially across preparations, and potential herb-drug interactions should be evaluated carefully when these agents are combined with antithrombotic or cardiovascular drugs [53].

When a pattern of intense heat-toxin is identified during the acute phase, heat-clearing, detoxifying, and consciousness-restoring therapies may be considered as adjunctive approaches, but clinical recommendations require stronger evidence. A review has summarized active ingredients and pharmacological effects of Angong Niuhuang Pill in acute stroke [54]. A small clinical study of Shexiang Sihuang Decoction combined with rt-PA reported NIHSS and serum MMP-9 outcomes [55]; it did not directly establish effects on consciousness or excitotoxicity. During recovery, a clinical-experience report has described yin-nourishing and collateral-unblocking therapy [23], and experimental work has examined Shenma Yizhi Formula [37]. Reviews of BDNF/TrkB-related TCM mechanisms in ischemic stroke and post-stroke depression provide additional mechanistic hypotheses [36,56]. These sources do not support a standardized clinical recommendation for a specific formula.

3.3 Integrative Evidence and Clinical Practice

Integrative Chinese and Western medicine may be most useful when disease mechanisms and TCM patterns are

jointly considered. During the acute phase, thrombolysis or thrombectomy should remain the standard reperfusion treatment. A 2025 meta-analysis evaluated Xingnaojing combined with alteplase and reported intracranial blood-flow and safety outcomes [57]; it does not establish efficacy after thrombectomy or justify generalization to all TCM adjuncts. During recovery, a small study combined external herbal immersion with rehabilitation training in older patients with stroke [58]. Evidence for additive or synergistic benefit remains limited.

Experimental research on triterpenoid saponins from Ilex pubescens has reported regulation of sphingolipid metabolism and PI3K/AKT/eNOS signaling in a blood-stasis model [59]. Separately, MMP-9-related nanomedicines have been reviewed in tumors and vascular diseases [60]. These two literatures do not demonstrate convergence on a shared signaling network in ischemic stroke. Metabolomic studies provide a systems-level basis for hypothesis generation and may help explain why different TCM strategies are used for patients with the same biomedical diagnosis but different syndrome patterns [61]. These developments indicate a gradual shift from isolated vascular recanalization or single-target neuroprotection toward combined regulation of NVU integrity, microenvironmental homeostasis, and qi-blood balance. Nevertheless, claims of synergy require confirmation in rigorously designed comparative trials.

4. Current Controversies and Challenges

4.1 Theoretical Controversies and Methodological Limitations

Current research faces both conceptual and methodological limitations. Traditional NVU models do not fully describe the early infiltration of peripheral immune cells, their interactions with resident glia, or the spatiotemporal evolution of tissue injury and recovery [62,63]. The proposed correspondence between TCM concepts such as toxic injury to the brain collaterals and modern biomedical mechanisms remains conceptual and controversial [64-66]. The available TCM literature articulates collateral and toxin-related theories, but an anatomical or molecular equivalence between the collateral system and the NVU has not been validated.

Animal models do not fully reproduce the complexity of human stroke, and standardized models that combine biomedical disease features with TCM syndrome characteristics are lacking [67]. Integration of multi-omics data is limited by differences among platforms, inconsistent normalization procedures, and the absence of computational frameworks capable of resolving dynamic pathological networks [68]. Outcome assessment is another obstacle. A review of outcome measures in acupuncture trials for post-stroke spasticity illustrates heterogeneity in endpoint selection [69]. Similar problems may affect broader integrative stroke research, although this requires direct systematic evaluation.

4.2 Controversies in Intervention and Gaps in Evidence

Target identification for complex Chinese medicines remains methodologically difficult, and newer approaches attempt to resolve multicomponent and multitarget networks [70]. Candidate blood markers, including uric acid, gamma-glutamyl transferase, and YKL-40, have been associated with short-term prognosis after acute cerebral infarction [71], but such association studies do not establish a validated biomarker for time-window-based individualized treatment. It is also difficult to define the optimal balance between suppressing harmful inflammation and preserving later repair processes [72]. Standardizing individualized syndrome differentiation within clinical pathways remains a practical challenge [24,69]. The optimal form of integrative treatment also remains uncertain, and herb-drug interactions are incompletely characterized [53].

Technical limitations also constrain the field. BBB research lacks in vitro models that fully reproduce the cellular and hemodynamic complexity of the in vivo environment [73]. The clinical evidence base for many Chinese herbal preparations is also incomplete. Large, adequately powered, methodologically rigorous trials are uncommon, and reproducible biomarkers that link TCM syndrome patterns with NVU function and clinical outcomes have not yet been established.

5. Future Directions

Research on cerebral ischemia is entering a multidisciplinary phase in which methodological innovation and integrative theory may jointly address current limitations. The NVU should be studied as a dynamic network rather than as a collection of isolated targets. Organoids, advanced BBB models, spatial and single-cell omics, and nanoscale or imaging-based sensors may help overcome barriers in disease modeling, spatiotemporal observation, and minimally invasive monitoring. Future clinical studies should include rigorously designed, adequately powered randomized controlled trials that evaluate both efficacy and safety, with particular attention to the potential benefits and risks of combining Chinese herbal medicines with standard stroke treatments.

Integrated multi-omics and computational or artificial intelligence-assisted analysis may be used to deconvolute the multicomponent and multitarget networks of classical formulas and to connect these networks with measurable pathological indicators and TCM syndrome features [68,70]. A standardized outcome framework tailored to integrative stroke research is also needed. Such a framework should combine neurological function, imaging, circulating biomarkers, patient-reported outcomes, safety data, and reproducible syndrome measures. These advances may facilitate a transition from isolated target discovery toward network-level therapeutic design.

6. Conclusion

This review proposes qi-blood-NVU coupling as a cross-disciplinary framework for interpreting neural remodeling after ischemic stroke. The framework is not intended to imply a simple equivalence between TCM theory and NVU biology. Rather, it highlights potentially intersecting processes involving microcirculatory dysfunction, BBB disruption, neuroinflammation, glial responses, neurotrophic support, and synaptic plasticity. Examples

include the proposed association of toxic injury to the brain collaterals with neuroinflammatory injury and the association of qi deficiency and blood stasis with impaired microcirculation and energy metabolism.

At the therapeutic level, integrative treatment should extend beyond the simple addition of separate therapies. In principle, acute interventions may prioritize reperfusion and stabilization of the post-ischemic microenvironment, whereas recovery-phase strategies may focus on rehabilitation, vascular support, and plasticity-promoting mechanisms. The scientific value of the qi-blood-NVU framework will depend on whether its proposed relationships can be operationalized, experimentally tested, and clinically validated. Further basic and clinical research is therefore required before this framework can guide standardized treatment or drug development.

References

[1] Seo S, Choi CH, Yi KS, et al. An engineered neurovascular unit for modeling neuroinflammation. Biofabrication. 2021;13(3):035039.

[2] Dong S, Luo E. Research progress on acupuncture-induced neural remodeling after intracerebral hemorrhage. Chinese Journal of Comparative Medicine. 2025;35(9):122-133.

[3] Liao T, Wang Y, Li S, et al. Effects of electroacupuncture on the blood-brain barrier in rats with cerebral ischemia-reperfusion injury through regulation of the HIF-1alpha/VEGF/MMP-9 signaling pathway. Acupuncture Research. 2025;50(6):613-623.

[4] Michinaga S, Koyama Y. Pathogenesis of brain edema and investigation into anti-edema drugs. Int J Mol Sci. 2015;16(5):9949-9975.

[5] Geng W, He X, Zheng X, et al. Predictive value of serum NOX4, Kal, and AQP4 for malignant cerebral edema after endovascular treatment of acute anterior-circulation large-vessel occlusion. Journal of Molecular Diagnostics and Therapy. 2025; 17(10): 1889-1892.

[6] McFall A, Nicklin SA, Work LM. The counter-regulatory axis of the renin-angiotensin system in the brain and ischemic stroke: insight from preclinical stroke studies and therapeutic potential. Cell Signal. 2020;76:109809.

[7] Li X, Bai R, Wang Y, et al. Regulatory mechanisms of P-glycoprotein overexpression in neurons during the acute phase of cerebral ischemia. Chinese Journal of Clinical Pharmacology. 2023;39(9):1242-1246.

[8] Li M, Gao S, Liu Z, et al. Regulation of human umbilical vein endothelial cell function by glucose transporter 1 under ischemic and hypoxic conditions. Journal of Sun Yat-sen University (Medical Sciences). 2025; 46(3): 444-455.

[9] Chen Y, Joo J, Chu JMT, et al. Downregulation of the glucose transporter GLUT1 in the cerebral microvasculature contributes to postoperative neurocognitive disorders in aged mice. J Neuroinflammation. 2023; 20(1): 237.

[10] Curcio M, Salazar IL, Inacio AR, et al. Brain ischemia downregulates the neuroprotective GDNF-Ret signaling pathway by a calpain-dependent mechanism in cultured hippocampal neurons. Cell Death Dis. 2015;6(2):e1645.

[11] Jiang X, Andjelkovic AV, Zhu L, et al. Blood-brain barrier dysfunction and recovery after ischemic stroke. Prog Neurobiol. 2018;163-164:144-171.

[12] Zheng X, Song W, Zhang Y, et al. Baicalin alleviates cerebral edema induced by ischemia-reperfusion in rats by inhibiting TRPV4 and AQP4 in astrocytes. China Journal of Chinese Materia Medica. 2022; 47(4): 1031-1038.

[13] Wu X, Peng L, Li K, et al. Role and regulatory mechanisms of aquaporin-4 after ischemic stroke: a review. Chinese Journal of Cerebrovascular Diseases. 2024;21(10):693-699.

[14] Lorin C, Guiet R, Chiaruttini N, et al. Structural and molecular characterization of astrocyte and vasculature connectivity in the mouse hippocampus and cortex. Glia. 2024;72(11):2001-2021.

[15] Guerit S, Fidan E, Macas J, et al. Astrocyte-derived Wnt growth factors are required for endothelial blood-brain barrier maintenance. Prog Neurobiol. 2021;199:101937.

[16] Chao B, Ren J, Guo R, et al. Role and mechanism of IQGAP1 in oxygen-glucose deprivation / reoxygenation - induced microglial polarization. Journal of Anhui Medical University. 2025; (11):2011-2018.

[17] Yang S, Chen Y, Tang J, et al. Microglia-astrocyte crosstalk following ischemic stroke. Mol Brain. 2025; 18(1):75.

[18] Yemisci M, Gursoy-Ozdemir Y, Vural A, et al. Pericyte contraction induced by oxidative-nitrative stress impairs capillary reflow despite successful opening of an occluded cerebral artery. Nat Med. 2009; 15(9): 1031-1037.

[19] Zhou SY, Li YX, Gao RL, et al. The role of pericytes in ischemic stroke: from cellular functions to therapeutic targets. Front Mol Neurosci. 2022;15:866700.

[20] Gautam J, Yao Y. Roles of pericytes in stroke pathogenesis. Cell Transplant. 2018;27(12):1798-1808.

[21] Xu W, Huang Y, Zhou R. NLRP3 inflammasome in neuroinflammation and central nervous system diseases. Cell Mol Immunol. 2025;22(4):341-355.

[22] Zhong LLD, Kun W, Shi N, et al. Evidence-based Chinese Medicine Clinical Practice Guideline for Stroke in Hong Kong. Chin Med. 2020;15(1):116.

[23] Lin Y, Qin Z, Xu Y. Clinical experience with yin-nourishing and collateral-unblocking therapy for ischemic stroke during the recovery period. China Modern Doctor. 2025;63(13):79-81.

[24] Wang Y, Zhang L, Pan Y, et al. Investigation of invigorating qi and activating blood circulation prescriptions in treating qi deficiency and blood stasis syndrome of ischemic stroke patients: study protocol for a randomized controlled trial. Front Pharmacol. 2020;11:892.

[25] Wang H, Sun L, Hu X, et al. Pathogenesis of cerebral ischemia-reperfusion injury based on the theory that qi and blood interact in the vessels and the preventive mechanisms of qi-replenishing and blood-activating medicines. Practical Journal of Cardiac Cerebral Pneumal and Vascular Disease. 2025;33(12):99-103.

[26] Xu X, Wang J, Shao W. Prevention and treatment of Alzheimer's disease from the perspective of improving neurovascular unit function based on collateral disease

theory. Journal of Anhui University of Chinese Medicine. 2023;42(2):4-7.
[27] Hu Y, Han Z, Wang Y, et al. Protective effect and mechanism of Jiannao Guben Formula on the neurovascular unit in rats with cognitive impairment due to cerebral small-vessel disease. China Journal of Traditional Chinese Medicine and Pharmacy. 2024; 39(11): 6032-6036.
[28] Yang S, Liu S, Han W, et al. Mechanism of the antidepressant effect of Gastrodia elata based on network pharmacology and in vitro experiments. Central South Pharmacy. 2024;22(3):647-653.
[29] Song M, Yang Q, Zhong Q, et al. Mechanisms of the antidepressant effects of Citrus medica and Citrus bergamia based on network pharmacology and the BDNF/TrkB/CREB pathway. World Science and Technology-Modernization of Traditional Chinese Medicine. 2025;27(4):1136-1149.
[30] Du L, Chen J, Yan J, et al. Lingguizhugan decoction ameliorates cognitive impairment in AD-like mice by influencing the microbiome-gut-brain axis mediated by short-chain fatty acids. Phytomedicine. 2024; 133: 155942.
[31] Gu X, Fan M, Zhou Y, et al. Intestinal endogenous metabolites affect neuroinflammation in 5xFAD mice by mediating the gut-brain axis and the intervention with Chinese medicine. Alzheimers Res Ther. 2024; 16(1): 222.
[32] Zhou XP, Sun LB, Liu WH, et al. The complex relationship between gut microbiota and Alzheimer's disease: a systematic review. Ageing Res Rev. 2025;104:102637.
[33] Jiang J, Tang B, Wang L, et al. Systemic LPS-induced microglial activation results in increased GABAergic tone: a mechanism of protection against neuroinflammation in the medial prefrontal cortex in mice. Brain Behav Immun. 2022;99:53-69.
[34] Ou Z, Zhao M, Xu Y, et al. Huangqi Guizhi Wuwu decoction promotes M2 microglial polarization and synaptic plasticity via the Sirt1/NF-kappaB/NLRP3 pathway in MCAO rats. Aging (Albany NY). 2023; 15(19):10031-10056.
[35] Li L, Jiang W, Yu B, et al. Quercetin improves cerebral ischemia/reperfusion injury by promoting microglia/macrophage M2 polarization through regulation of PI3K/Akt/NF-kappaB signaling. Biomed Pharmacother. 2023;168:115653.
[36] Wang Q, Liu F, Zhang Y. Traditional Chinese medicine treats ischemic stroke by regulating the BDNF/TrkB signaling pathway: a review. Chinese Journal of Experimental Traditional Medical Formulae. 2026; 32(5): 312-321.
[37] Zhang Z. Mechanism by which Shenma Yizhi Formula regulates microglial polarization to improve synaptic plasticity in vascular dementia [dissertation]. Beijing: China Academy of Chinese Medical Sciences; 2024.
[38] Qin X, Li P, Shi X, et al. Effects of Naoluoxintong and its component formulas on learning, memory, and synaptic plasticity in rats subjected to right middle cerebral artery occlusion and reperfusion. Journal of Traditional Chinese Medicine. 2022;63(12):1163-1169.
[39] Cui W, Wang Y, Shao Y, et al. Exploring the neuroprotective effect and potential mechanism of Shenrong Guben Huanshao Pill based on multi-omics analysis. Phytomedicine. 2025;143:156861.
[40] Chaturvedi M, Kaczmarek L. MMP-9 inhibition: a therapeutic strategy in ischemic stroke. Mol Neurobiol. 2014;49(1):563-573.
[41] Turner RJ, Sharp FR. Implications of MMP-9 for blood-brain barrier disruption and hemorrhagic transformation following ischemic stroke. Front Cell Neurosci. 2016;10:56.
[42] Han W, Song Y, Rocha M, Shi Y. Ischemic brain edema: emerging cellular mechanisms and therapeutic approaches. Neurobiol Dis. 2023;178:106029.
[43] Shui X, Chen J, Fu Z, et al. Microglia in ischemic stroke: pathogenesis insights and therapeutic challenges. J Inflamm Res. 2024;17:3335-3352.
[44] Jin WN, Shi SXY, Li Z, et al. Depletion of microglia exacerbates postischemic inflammation and brain injury. J Cereb Blood Flow Metab. 2017;37(6):2224-2236.
[45] Otxoa-de-Amezaga A, Miro-Mur F, Pedragosa J, et al. Microglial cell loss after ischemic stroke favors brain neutrophil accumulation. Acta Neuropathol. 2019; 137(2): 321-341.
[46] Mamtilahun M, Tang G, Zhang Z, et al. Targeting water in the brain: role of aquaporin-4 in ischemic brain edema. Curr Drug Targets. 2019;20(7):748-755.
[47] Zador Z, Stiver S, Wang V, Manley GT. Role of aquaporin-4 in cerebral edema and stroke. Handb Exp Pharmacol. 2009;(190):159-170.
[48] Wang Y, Wu S, Li Q, et al. Pharmacological inhibition of ferroptosis as a therapeutic target for neurodegenerative diseases and strokes. Adv Sci (Weinh). 2023;10(24):e2300325.
[49] Liu F, Zhao Q, Sun L, et al. A systematic review and meta-analysis of randomized controlled trials on the efficacy and safety of tanshinone IIA sodium sulfonate injection as adjunctive therapy for stroke. J Ethnopharmacol. 2025;353(Pt B):120413.
[50] Ji B, Zhou F, Han L, et al. Sodium tanshinone IIA sulfonate enhances the effectiveness of rt-PA treatment in acute ischemic stroke patients by ameliorating blood-brain barrier damage. Transl Stroke Res. 2017; 8(4):334-340.
[51] Liu Y, Yang G, Cui W, Zhang Y, Liang X. Regulatory mechanisms of tetramethylpyrazine on central nervous system diseases: a review. Front Pharmacol. 2022; 13:948600.
[52] Lin J, Wang Q, Zhou S, et al. Tetramethylpyrazine: a review of its mechanisms and functions. Biomed Pharmacother. 2022;150:113005.
[53] Shen Q, Chen W, Wang W, et al. Drug interactions between traditional Chinese medicines and cardiovascular drugs. Eur J Drug Metab Pharmacokinet. 2024;49(5):559-582.
[54] Wang X, Cheng Z, Yao K, et al. Active ingredients and pharmacological effects of Angong Niuhuang Pill in the acute phase of stroke: a review. Journal of Anhui University of Chinese Medicine. 2025:1-8.
[55] Xie J, Zhang T, Liu T, et al. Effects of Shexiang Sihuang Decoction combined with rt-PA on NIHSS scores and serum MMP-9 levels in patients with acute ischemic stroke. Chinese Journal of Integrative Medicine on Cardio-/Cerebrovascular Disease. 2018;16(7):937-939.

[56] Li X, Wang D, Zhao D. Mechanisms of traditional Chinese medicine for post-stroke depression based on the BDNF/TrkB signaling pathway. Acta Chinese Medicine. 2025:1-12.
[57] Zhao T, Hu Y, Jin Z, et al. Effects and safety of Xingnaojing combined with alteplase on intracranial blood-flow velocity in acute ischemic stroke: a meta-analysis. Clinical Medication Journal. 2025; 23(10): 80-86.
[58] Mi H, Gao X, Meng J, et al. Effects of alternating hot and cold Chinese herbal immersion combined with rehabilitation training on upper-limb function in older patients with stroke. Chinese Journal of Multiple Organ Diseases in the Elderly. 2025;24(10):769-773.
[59] Chen J, Cao D, Jiang S, et al. Triterpenoid saponins from Ilex pubescens promote blood circulation in blood stasis syndrome by regulating sphingolipid metabolism and the PI3K/AKT/eNOS signaling pathway. Phytomedicine. 2022;104:154242.
[60] Li X, Xu Z. Applications of matrix metalloproteinase-9-related nanomedicines in tumors and vascular diseases. Pharmaceutics. 2025;17(4):479.
[61] Cui F, Yang J, Wang Z, et al. Applications and prospects of metabolomics in traditional Chinese medicine. Chinese Traditional and Herbal Drugs. 2022; 53(14): 4512-4526.
[62] Cai W, Zhang K, Li P, et al. Dysfunction of the neurovascular unit in ischemic stroke and neurodegenerative diseases: an aging effect. Ageing Res Rev. 2017;34:77-87.
[63] Eldahshan W, Fagan SC, Ergul A. Inflammation within the neurovascular unit: focus on microglia for stroke injury and recovery. Pharmacol Res. 2019;147:104349.
[64] Liu H, Shen W, Wei J, et al. Clinical application of toxin pathogen causing disease in common nervous system diseases: a review. Chinese Journal of Experimental Traditional Medical Formulae. 2022;28(24):244-252.
[65] Lu G, Xiong C, Wang R, et al. Cerebral small-vessel disease based on the xuanfu-collateral theory. Asia-Pacific Traditional Medicine. 2025;21(2):215-219.
[66] Fan X, Li A. Integrated Chinese and Western medical treatment of stroke under the guidance of the theory of toxic injury to the brain collaterals. Yunnan Journal of Traditional Chinese Medicine and Materia Medica. 2018;39(11):8-11.
[67] Pan L, Deng X, Luo Y. Advances in integrative translational research on animal models of ischemic stroke in traditional Chinese and Western medicine. Laboratory Animal and Comparative Medicine. 2026;46(3):344-356.
[68] He X, Liu H, Zhao B, Zhang L, Yuan H. Recent advances in mass spectrometry-based single-cell multidimensional multi-omics analysis. Journal of Chinese Mass Spectrometry Society. 2025; 46(6): 729-750. doi:10.7538/zpxb.2025.0089.
[69] Song J, Mao W, Liu J. Current use and considerations regarding outcome measures in clinical trials of acupuncture for post-stroke spasticity. Journal of Practical Traditional Chinese Internal Medicine. 2025; 39(9): 31-35,144.
[70] Zhang Q, Xu J, Lu X, et al. New methods for target identification of complex components in Chinese medicines and their applications. Chinese Pharmacological Bulletin. 2025;(11):2001-2008.
[71] Yan Y, Zhang Q, Liu Y, et al. Associations of peripheral blood uric acid, gamma-glutamyl transferase, and YKL-40 levels with short-term prognosis in patients with acute cerebral infarction. Translational Medicine Journal. 2025;14(7):52-57.
[72] Chen Y, Liu Q, Wei Q, et al. Roles of inflammatory-immune regulatory pathways in microglial polarization and neural repair after stroke. Stroke and Nervous Diseases. 2025;32(5):537-542.
[73] Zhang H, Zhang R, Wang Q. Research and applications of in vitro blood-brain barrier models. Journal of International Neurology and Neurosurgery. 2021; 48(3): 303-306.