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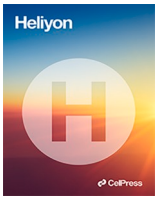

Review article

Targeting the neurovascular unit: Therapeutic potential of traditional Chinese medicine for the treatment of stroke

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ABSTRACT

Stroke poses a significant global health challenge due to its elevated disability and mortality rates, particularly affecting developing nations like China. The neurovascular unit (NVU), a new concept encompassing neurons, brain microvascular endothelial cells, pericytes, astrocytes, microglia, and the extracellular matrix, has gained prominence in recent years. Traditional Chinese medicine (TCM), deeply rooted in Chinese history, employs a combination of acupuncture and herbal treatments, demonstrating significant efficacy across all stages of stroke, notably during recovery. The holistic approach of TCM aligns with the NVU's comprehensive view of treating stroke by addressing neurons, surrounding cells, and blood vessels collectively. This review examines the role of NVU in stroke and endeavors to elucidate the mechanisms through which traditional Chinese medicine exerts its anti-stroke effects within the NVU framework. The NVU contributes to neuroinflammation, immune infiltration, blood-brain barrier permeability, oxidative stress, and Ca^{2+} overload during stroke occurs. Additionally, TCM targeting the NVU facilitates nerve repair post-stroke through various pathways and approaches. Specific herbs, including *panax notoginseng*, *ginseng*, and *borneol*, alleviate brain injury by enhancing brain-derived neurotrophic factor expression and targeting astrocytes and microglia to yield anti-inflammatory and antioxidant effects. Acupuncture, another facet of TCM, promotes brain injury repair by augmenting cerebral blood flow and improving circulation. This exploration aims to assess the viability of stroke treatment by directing TCM interventions toward the NVU, thus paving the way for its broader clinical application.

1. Introduction

A stroke is an acute cerebral vascular injury characterized by sudden weakness on one side (arm, face, or leg), slurred speech, blurred vision, sudden difficulty walking, and an abrupt severe headache. It is commonly categorized into hemorrhagic and ischemic strokes, with the latter, including ischemia/reperfusion injury, being more prevalent [1]. And according to the etiology and incidence area of ischemic stroke, it can be subdivided into atherothrombotic infarct, cardioembolic stroke, lacunar infarct, infarction with unknown etiology, and primary cerebral infarction [2]. Globally, stroke ranks as the second leading cause of mortality and morbidity, imposing a substantial burden on families and society [3].

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Various mechanisms contribute to stroke, encompassing excitotoxicity, mitochondrial death pathways, release of free radicals, protein misfolding, apoptosis, necrosis, autophagy, and inflammation. The impact of stroke extends beyond neuronal cells to include astrocytes and other cerebral white matter [4]. However, prior research has often focused predominantly on neurons, neglecting other crucial components. To address this limitation, the concept of the neurovascular unit (NVU) has been introduced, offering a novel target for the clinical treatment of stroke [5]. The NVU is a complex, multicellular network that organizes neural networks and blood vessels, comprising neurons, brain microvascular endothelial cells (BMECs), pericytes, astrocytes (AS), microglia (MG), and the extracellular matrix (EM) [6]. These components function as a unified, single-functional unit. It is worth noting that hematological diseases such as primary thrombocytosis, polycythemia vera and thrombotic thrombocytopenic purpura may also lead to stroke. However, the treatment and recurrence risk of stroke caused by hematological diseases are different from those we usually call stroke. Our research only involves stroke in the ordinary sense, and we should strictly distinguish between the two [7]. Current stroke treatments predominantly involve thrombolytics, plasminogen activators, mechanical thrombolysis, ion channel blockers (such as calcium and sodium channel blockers), and antioxidants. However, the effectiveness of most drugs is limited, exhibiting efficacy within a narrow therapeutic range [8].

Considering the multi-component, multi-target, multi-pathway, and overall regulatory effects of traditional Chinese medicine (TCM) [9], our approach goes beyond exploring the role of the neurovascular unit in stroke. We also analyze how TCM modulates stroke through the neurovascular unit, aiming to offer a fresh perspective on stroke treatment.

2. Structure of NVU

In our brain, neurons establish a network for signal transmission and communication, connecting through dendrites and axons. These neurons are enveloped by glial cells, serving to prevent direct contact with vascular cells and buffering the impact of blood-borne substances. Among these glial cells, astrocytes (AS) are noteworthy, with long-extending processes that wrap around arterioles and neural synapses [10]. Astrocytes act as a crucial bridge, linking the neuroglial part with the vascular part and facilitating neuron-glial crosstalk [11]. Microglia, another type of glial cell, contribute to regulating brain function by eliminating dying neurons and pruning nonfunctional synapses [12]. The BMECs, pericytes, and AS endfeet are all constituents of blood-brain barrier (BBB). Among of them, BMECs constitute the largest proportion [13], while pericytes are embedded in the basement membrane of blood microvessels between BMECs and AS endfeet [14]. Both the pericytes and BMECs produce extracellular matrix (ECM), forming the basal lamina of central nervous system (CNS) capillaries [11].

The NVU plays an important role in regulating the functional integrity of BBB and the cerebral blood flow (CBF), thereby maintaining a homeostasis of the brain microenvironment [15]. For instance, the microvasculature dilation normally occurs after neural activity triggers a series of chemical and electrical reactions in adjacent AS in order to meet the increased demand for blood flow [10]. Furthermore, pericytes around capillaries can induce vasodilation [16]. Additionally, the MG can express complement 3 receptor (C3R), interacting with the complement factors in the CNS to eliminate the necrotic neurons [17].

3. Pathogenesis of ischemic stoke

The pathogenesis of ischemic stroke is intricate, involving a multitude of factors. Typically, ischemic stroke arises from the occlusion of cerebral arteries, resulting in significant deprivation of glucose and oxygen in the affected brain tissue. This deprivation initiates a cascade of injuries to cerebral cells and tissues. Various types of cell death are implicated, encompassing autophagy, apoptosis, necroptosis, and pyroptosis. Apoptosis can follow two pathways: the intrinsic apoptotic pathway, mediated by mitochondria, and the extrinsic pathway, mediated by receptors [18]. Generally, apoptosis and necroptosis become the predominant modes of cell death in cases of mild and severe cerebral injuries, respectively [19]. Moreover, inflammation, immune infiltration, and excitotoxicity are intricately connected to the mechanisms of cell injury in ischemic stroke. In the subsequent sections, we will provide a summary of the pathophysiology underlying ischemic stroke (Fig. 1.).

Following oxygen-glucose deprivation in the brain, a substantial accumulation of the excitatory neurotransmitter glutamate occurs,

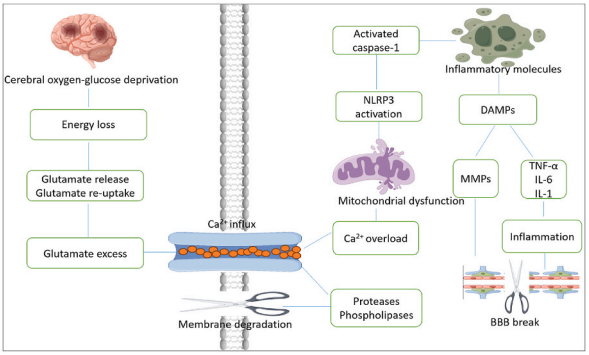

Fig. 1. The pathogenesis of ischemic stroke.

leading to an overload. This, in turn, results in the influx of Ca2+, releasing phospholipase and protease, ultimately causing damage to the cell membrane. Simultaneously, the Ca2+ overload from this influx disrupts mitochondrial function, activating NLRP3 and initiating a cascade of inflammatory reactions. Eventually, this sequence of events culminates in the breakdown of the blood-brain barrier (BBB).

3.1. Excitatory toxicity

Ischemic stroke induces the depletion of energy stores, resulting in ionic imbalance. This, in turn, leads to the release of neurotransmitters and the inhibition of the reuptake of excitatory neurotransmitters like glutamate. The elevated glutamate levels can stimulate excessive calcium influx upon binding to ionotropic N-methyl-D–aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. This cascade of events triggers the downstream activation of numerous phospholipases and proteases, leading to the degradation of essential cellular membranes and proteins crucial for maintaining cellular integrity [20].

3.2. Inflammation and immune infiltration

Following cerebral ischemia, Ca2+ overload can result in mitochondrial dysfunction, subsequently activating the NOD-like receptor protein 3 (NLRP3) inflammasome. This activation converts pro-caspase-1 into caspase-1, leading to the cleavage of both pro-IL-1 and pro-IL-18 into active pro-inflammatory cytokines. These cytokines are released into the extracellular environment, further triggering autophagy and pyroptosis, thereby releasing damage-associated molecular patterns (DAMPs) [21]. DAMPs, in turn, stimulate various inflammatory signaling pathways in innate immune cells, releasing inflammatory mediators such as interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), ultimately causing central inflammatory events. Concurrently, up-regulation of matrix metalloproteinases (MMPs) poses a detrimental effect by impairing the integrity of the BBB [22].

The central nervous system (CNS) differs from the peripheral nervous system as it lacks conventional lymphatic vasculature, and barriers restrict the presence of peripheral immune cells [23]. However, in the context of stroke injury, endogenous CNS antigens gain access to activated lymphocytes through the compromised BBB. This activation prompts endothelial cells within the BBB to recruit peripherally circulating leukocytes, facilitating their infiltration into the brain parenchyma [24].

3.3. Autophagy

Autophagy is a cellular catabolic pathway designed for self-protection, with its primary function being the degradation of long-lived or misfolded proteins and damaged organelles. This process breaks down these components into metabolic elements, recycling them to sustain cellular homeostasis [25]. Autophagy-related signaling pathways are known to be activated in neurons, glial cells, and brain microvascular cells. However, autophagy is considered a double-edged sword for cell survival. Moderate autophagy is thought to be neuroprotective, while excessive autophagy can lead to neuronal cell death. Various pathways participate in the regulation of autophagy, including mammalian target of rapamycin (mTOR), Mitogen-activated protein kinase (MAPK), 5′-AMP-activated protein kinase (AMPK), Beclin-1, p53, Rab7, among others [26].

3.4. Apoptosis

During an ischemic stroke, various factors contribute to an elevated cellular Ca^{2+} level, leading to the activation of calpains. Calpains, in turn, mediate the cleavage of BH3-interacting domain death agonist (BID) into its truncated form (tBID). Upon receiving death signals, tBID translocates to the mitochondrial membrane, where it interacts with other resident proapoptotic members of the Bcl-2 family, including BCL2-Associated X (Bax), Bak, Bad, and Small molecular protein of Bcl-X (Bcl-XS). This interaction induces changes in mitochondrial permeability, triggering the release of cytochrome *c* and contributing to apoptosome formation through binding with Apoptotic protease activating factor-1 (Apaf-1). Subsequently, procaspase-9 is activated, initiating a caspase cascade that propels the cell toward apoptosis. The aforementioned process represents the intrinsic apoptotic pathway [25].

On the other hand, the receptor apoptosis pathway is typically initiated by external stimulations. The ligands include TNF-α, TNF-related apoptosis-inducing ligand (TRAIL). It is now understood that ligands like the first apoptosis signal ligand (FasL) bind to receptors such as Fas/CD95 and TNF receptor 1 (TNFR1), recruiting cytoplasmic adapter proteins like tumor necrosis factor receptor type-1–associated death domain (TRADD) and Fas-associated death domain protein (FADD) to form the death-induced signaling complex (DISC). DISC catalyzes the proteolytic breakdown and autocatalytic activation of procaspase-8, leading to the activation of initiator caspase-8. Ultimately, activated caspase-8 triggers the downstream cleavage of executioner procaspase-3, resulting in apoptotic cell death through a further downstream cascade [27].

3.5. Necroptosis

Following cerebral ischemia, oxygen-glucose deprivation leads to a rapid depletion of adenosine triphosphate (ATP), causing the depolarization of plasma membranes. This depolarization activates voltage-dependent calcium channels, resulting in the release of glutamate. Subsequently, glutamate activates N-methyl-D–aspartate (NMDA) receptors, leading to calcium (Ca^{2+}) overload. This excess Ca^{2+} triggers the activation of calcium/calmodulin-dependent protein kinase II (CaMKII), which directly phosphorylates receptor-interacting protein kinase (RIPK1). Once activated, RIPK1 would recruits various downstream components to form complex I.

The crucial kinase's activation state is initiated through de-ubiquitination of RIPK1, causing RIPK1 to translocate into the cytoplasm, forming cytosolic complex IIa or complex IIb. In this active state, RIPK1 subsequently binds to caspase-8, inducing apoptosis. When caspase-8 is inhibited, RIPK1 recruits RIPK3, forming the necrosome (complex IIb). Ultimately, necroptosis is executed through the phosphorylation and oligomerization of mixed-lineage kinase domain-like pseudokinase (MLKL) [28].

3.6. Pyroptosis

Pyroptosis is a recently identified inflammation-associated programmed cell death characterized by cell swelling, plasma membrane lysis, chromatin condensation, and DNA fragmentation. It is typically categorized into the canonical inflammasome pathway and the noncanonical inflammasome pathway [29].

The noncanonical inflammasome pathway is usually triggered by lipopolysaccharide (LPS) stimulation, and its primary execution involves caspase-4/5. Differently, the canonical pathway is initiated by caspase-1. Mature caspase-1 converts pro-interleukin-1β (pro-IL-1β) and pro-IL-18 into their active forms, IL-1β and IL-18, respectively. These cytokines are then released outside the cell through membrane pores formed by Gasdermin D (GSDMD), leading to the recruitment of more inflammatory cells and the induction of a cascade inflammatory response, ultimately resulting in cell death [30].

4. The NVU in pathogenesis of ischemic stroke

4.1. Neuron

Neurons in the brain consist primarily of four components: dendrites, cell body, axon, and presynaptic terminals of the axon. Their function involves collecting information from the environment, integrating this information, and generating output that can modify the environment [31]. Impairment of neuronal plasticity is often a contributing factor in major neurological disorders, as neuronal plasticity is a fundamental process underlying learning and memory [32]. Additionally, certain mental illnesses, such as depression and anxiety, may develop after a stroke, potentially linked to disruptions in neuronal plasticity [33]. Traditionally, neurons have been the primary focus of ischemic stroke treatment. However, it should be recognized that neurons are not isolated entities; they interact with other neurocytes [34]. For instance, microglia can establish direct contact with different compartments of neurons, playing a role in fine-tuning neuronal responses and fate [35].

4.2. Pericytes

The brain, receiving 1/5 of the cardiac output and consuming 1/5 of the body's oxygen and glucose, emphasizes the importance of cerebral blood flow for brain homeostasis [36]. Pericytes have been shown to regulate capillary diameter and cerebral blood flow by releasing various vasoactive molecules and neurotransmitters during ischemic stroke, exacerbating tissue hypoxia [37]. Studies have indicated that neighboring pericytes expand their processes to prevent vascular dilatation after pericyte ablation [38].

The BBB, a protective barrier between the central nervous system and its surrounding vasculature, hinders the movement of pathogens and toxins from the blood to the brain while allowing the passage of essential nutrients [39]. Comprising brain microvascular endothelial cells, astrocytes endfeet, neurons, and pericytes, the BBB's integrity is crucial. Loss and degeneration of pericytes can lead to BBB opening, neuronal uptake of blood-derived neurotoxic products, reduced microcirculation, and capillary flow, causing tissue hypoxia and subsequent chronic neuronal dysfunction and degenerative changes [40]. After cerebral ischemic stroke, pericytes secrete hypoxia-inducible factor-1 (HIF-1), vascular growth factor, and matrix metalloproteinase (MMP). HIF-1 plays a dual role in nerve protection and enhancing vascular permeability [41], vascular endothelial growth factor (VEGF) increases BBB permeability, and MMP can compromise BBB integrity [42]. It is now understood that pericyte recruitment is integral to the BBB repair process, activated by the upregulation of platelet-derived growth factor receptor β (PDGFRβ) in peri-infarct areas [43]. PDGF-β positive

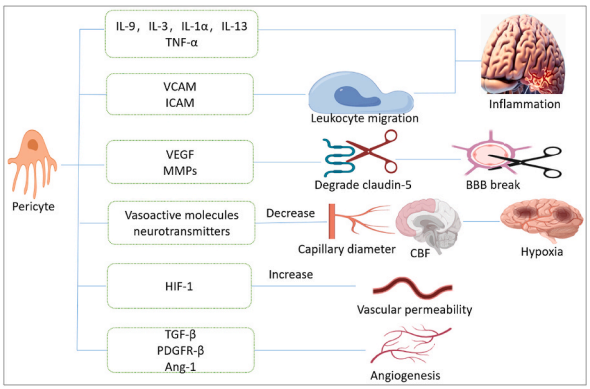

Fig. 2. The pericytes in ischemic stroke.

pericytes subsequently recruit macrophages to infarct areas, aiding in the clearance of necrotic tissue and promoting cell survival [44].

Experiments have demonstrated that cultured pericytes expressing PDGF-β exhibit anti-apoptotic responses and induce cell growth by expressing nerve growth factor (NGF) and neurotrophin-3 (NT-3) through the Akt pathway [45,46].

Pericytes play a crucial role in the neuroinflammation and immune infiltration associated with cerebral ischemic injury. They enhance leukocyte exosmosis and recruitment by expressing various mediators, and they also express adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) to guide leukocyte migration and crawling. Additionally, pericytes release pro-inflammatory cytokines such as IL-1α, TNF-α, IL-3, IL-9, and IL-13, contributing to cell injury exacerbation [47].

Pericytes exhibit angiogenic properties in ischemic stroke, mediating the formation and maturation of new blood vessels through signaling molecules such as PDGFRβ, transforming growth factor (TGF-β), VEGF, and Angiotensin 1 (Ang-1) [48].

In the brain, pericytes can function as microglia-generating multi-potent vascular stem cells, potentially acquiring a microglial phenotype following ischemic stroke [49,50]. A few researches demonstrated that pericytes contribute to scar formation and organ fibrosis as well as glial cells, but it still needs further study [51]. The roles of pericytes in ischemic stroke encompass various aspects (Fig. 2.).

Pericytes exert a bidirectional impact on ischemic stroke. Firstly, they release ICAM and VCAM, promoting the migration of leukocytes, and also release inflammatory factors such as IL-3 and IL-9, contributing to brain inflammation. Secondly, pericytes degrade claudin-5 by releasing VEGF and MMPs, ultimately leading to the breakdown of the BBB. Additionally, pericytes can reduce cerebral blood flow (CBF) and worsen cerebral ischemia by releasing various vasoactive factors while enhancing vascular permeability through the release of HIF-1. All these actions collectively exacerbate brain injury following cerebral ischemia. However, concurrently, pericytes play a role in promoting angiogenesis by releasing TGF-β, PDGFR-β, and Ang-1.

4.3. Astrocytes

The functions of astrocytes are diverse and crucial, encompassing the formation and maintenance of the blood-brain barrier, involvement in neuroinflammation and CNS immunity, clearance of excessive glutamate, participation in the formation of glial scar, and contribution to neuroangiogenesis (Fig. 3.).

AS have dual effects on the BBB. On one side, they secrete the basal lamina to restrict lymphocyte access to the parenchyma in a healthy brain [52]. In ischemic stroke, they upregulate Pentraxin 3 (PTX3) in peri-infarct areas, potentially supporting BBB integrity by regulating vascular endothelial growth factor-related mechanisms [53]; On the other side, astrocytes express VEGF-A, MMP-9, and HIF-1α, inducing BBB breakdown by disrupting the expression of claudin-5 in ischemic stroke [54]. Dysregulation of BBB tightness after brain injury can lead to inflammation and secondary brain damage [55].

AS express leukocyte adhesion molecules such as intercellular adhesion molecules and vascular cell adhesion molecules, attracting immune cells specifically to the injured region and facilitating their infiltration from vasculature into CNS tissue. Activated AS can release proinflammatory cytokines (IFN-γ, TNF-α, and IL-17) as well as anti-inflammatory cytokines (IL-10 and TGF-β) [56].

The balance of astrocytic γ-aminobutyric acid (GABA) and glutamate is crucial, as excessive GABA causes cortical hypometabolism, and overexpressed astrocytic glutamate induces neurotoxicity. Astrocytes play a role in maintaining the homeostasis of GABA and glutamate [57–59], regulating glutamate clearance during stroke to prevent brain injury caused by neurotoxicity [60,61].

Stroke leads to severe reactive AS proliferation [62]. In the acute phase of ischemic stroke, the proliferation and hypertrophy of AS is beneficial to restore injury by sealing the site of injury, remodeling the tissue, and controlling the local immune response both spatially and temporally. However, the formation of glial scarring by excessive astrocyte proliferation may limit recovery of CNS function in the chronic stage [63].

Research found that Chemogenetic ablation of a subset of reactive astrocytes after stroke dramatically impairs vascular and ECM remodeling, suggesting that reactive astrocytes may play a critical role in vascular remodeling during neural repair [64]. Additionally, astrocytic cytochrome P450 4A/20-hydroxyeicosatetraenoic acid has been implicated in angiogenesis in ischemic stroke [65], suggesting that astrocytes may promote neurovascular regeneration after ischemic injury.

Astrocytes possess multiple functions, acting as key modulators of brain edema due to the high expression of Aquaporin 4 (AQP4)

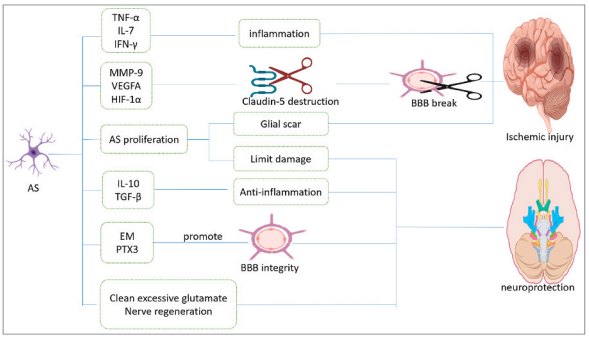

Fig. 3. The astrocytes in ischemic stroke.

on astrocyte endfeet [66]. Reactive astrocytes produce multiple neurotrophic factors such as glial derived neurotrophic factor, to protect neurons [67]. Study have shown that AS provide energy to neurons during ischemic stroke [68]. They can also be directly programmed into induced neurons (iNeurons) by the master neuronal transcription factor NeuroD1 (Neurogenic differentiation factor) [69]. Moreover, AS provide a robust neuroprotection against ischemic injury through mediating ischemic tolerance [70]. Interestingly, astrocytes play a role in rendering memory flexible and may contribute to memory loss after stroke [71]. Additionally, astrocytes are direct targets of hormone action in CNS, indicating that drugs for stroke may work through them [72].

AS play a dual role in cerebral ischemia. On the one hand, it induces inflammation by releasing inflammatory mediators such as TNF-α and IL-17, and contribute to BBB disruption through the release of VEGFA and MMP-9, thereby exacerbating brain injury. Conversely, on the other hand, AS alleviate brain injury by releasing anti-inflammatory factors such as IL-10 and enhancing BBB integrity through the release of extracellular matrix (EM) and pentraxin 3 (PTX3). Furthermore, astrocytes actively participate in the removal of overloaded glutamate and promote nerve regeneration following brain injury. It is important to note that a moderate proliferation of astrocytes can limit brain injury; however, excessive proliferation leading to the formation of a glial scar may exacerbate brain injury.

4.4. Microglia

MG primarily play a significant role in neuroinflammation following cerebral ischemia, and persistent inflammation in the brain is known to impact neuronal plasticity, impair memory, and is generally considered a typical driver of tissue damage in cerebral disorders [73] (Fig. 4.).

As the brain resident cells, microglia rapidly acquire properties of reactive species generation, antigen presentation, phagocytosis in response to cerebral ischemia. They produce a series of inflammatory mediators, including IL-1β, TNF-α, IL-6, and MMPs. Conversely, MG produce anti-inflammatory factors such as IL-4 and IL-10 in the resolution phase of brain inflammation [74]. The former type of microglia, exhibiting pro-inflammatory properties, is defined as M1, while the latter type, with anti-inflammatory characteristics, is defined as M2. Research has indicated that M1-type microglia disrupt the blood-brain barrier by upregulating pro-inflammatory cytokines, while M2-type microglia may enhance BBB integrity by increasing the expression of TJ proteins [75]. Moreover, MG may play a dual role in vascular disintegration and angiogenesis during stroke. They also participate in synaptic remodeling and are of great significance in promoting neural circuit refinement [76]. Notably, the enzyme glutaminase (GLS), which catalyzes the hydrolysis of glutamine to produce glutamate, is significantly upregulated in activated MG under pathological conditions, suggesting a potential link between microglia and neuroexcitotoxicity in cerebral ischemia [77]. In recent years, researchers have explored strategies to promote the expression of the M2 type of microglia to treat ischemic stroke [78].

Microglia (MG) can be classified into two types: M1 and M2, each playing contrasting roles in the acute and recovery stages of cerebral ischemia. The M1 type promotes inflammation by releasing cytokines such as IL-6 and IL-1β and secretes matrix metalloproteinases (MMPs) that contribute to the disruption of the blood-brain barrier (BBB). Conversely, the M2 type exerts an anti-inflammatory effect during the recovery period by releasing anti-inflammatory factors such as IL-4 and IL-10. Additionally, M2 microglia enhance the integrity of the BBB by reinforcing TJs.

4.5. BMECs and ECM

BMECs play a crucial role in the blood-brain barrier, gaining their specialized functions through interactions with supporting cells such as neurons, pericytes, and astrocytes [79]. Key proteins that modulate BBB integrity, including claudin-5, occludin, and zonula occludens-1 (ZO-1), are present in BMECs [80]. BMECs perform complex functions that require considerable energy [81], such as

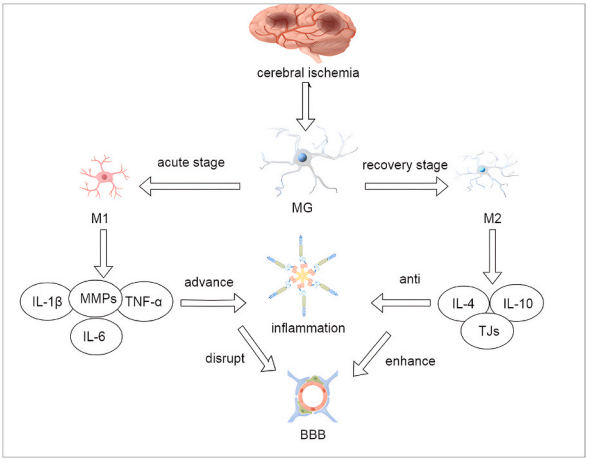

Fig. 4. The microglia in ischemic stroke.

facilitating the entry of nutrients and exogenous drugs into brain tissue through specific transport proteins. They also produce enzymes that degrade harmful molecules, providing a metabolic barrier to the brain. BMECs are involved in platelet activation and adhesion, the generation and balance of endothelin-1 (ET-1) and nitric oxide (NO), and the secretion of neurotrophins such as brain-derived neurotrophic factor (BDNF) and VEGF [82]. During ischemic stroke, excessive VEGF can cause BBB breakdown by increasing endothelial permeability. The Insulin-like growth factor (IGF)-1 expressed in BMECs can reduce neuronal loss and infarct volume, increase glial proliferation in brain, prevent neurons from damage caused by oxidative stress and apoptosis, and promote nerve repair [83]. Additionally, BMECs can contribute to BBB breakdown by secreting MMPs [84] during stroke. The cerebral microvascular endothelial glycocalyx (eGC), a part of brain microvascular endothelial cells, has anticoagulant and anticlotting properties, potentially slowing down the formation of cerebral thrombosis. Damage to the eGC could indicate the development of vascular inflammation by decreasing NO release and increasing leukocyte adhesion [85].

Perlecan, a component of the ECM, has a beneficial effect on the ischemic brain by enhancing pericyte recruitment through cooperative action with PDGFRβ. Recombinant perlecan domain V has been reported to reduce infarct volume, attenuate neuronal death, and promote angiogenesis in ischemic stroke [86]. Moreover, ECM regulates various cerebral functions such as learning, memory, synaptogenesis, and plasticity. It may be related to the dementia after stroke [87]. Additionally, ECM regulates several aspects of cell behavior, including cell migration and adhesion, survival, gene expression and differentiation [88].

5. Pathogenesis of cerebral ischemia/reperfusion injury

Cerebral ischemia/reperfusion injury involves multiple mechanisms, with Ca^{2+} overload and oxidative stress being broadly accepted as key contributors [89] (Fig. 5.).

When cerebral ischemia occurs, anaerobic respiration increases so that the intracellular pH decreases; once reperfusion, the Na +/H + exchanger (NHE) would be acitivated and brings about a large amount of influx of Na + to maintain acid-base balance. At the same time, the low level of ATP resulted from cerebral ischemia also weakened the activity of energy-dependent Na + pump, and induced a higher level of intracellular Na +. When the oxygen supply is restored, the imbalance in intracellular Na^+ initiates the Na^+/Ca^{2+} exchanger, sensitive to Na^+, resulting in Ca^{2+} influx. Ca^{2+} overload disrupts mitochondrial function and promotes the overproduction of reactive oxygen species (ROS) [90]. A substantial quantity of ROS, including hydrogen peroxide (H_2O_2), induces oxidative stress [91]. This occurs through various mechanisms, such as the Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase system and the NO synthase system, ultimately leading to cell death and tissue necrosis by triggering DNA damage, lipid peroxidation, cytoskeletal structural injury, and chemotaxis [92]. In the context of cerebral ischemia/reperfusion injury (CIRI), cell death patterns encompass not only tissue necrosis but also autophagy, apoptosis, and necroptosis [93–95], as mentioned above.

The primary role of mitochondria is to generate intracellular energy production (ATP) through the oxidative phosphorylation pathway [96]. Dysfunctional mitochondria play a crucial role in Ca^{2+} overload and oxidative stress in CIRI. Consequently, mitophagy becomes imperative for cell survival, selectively eliminating damaged and dysfunctional mitochondria to prevent cell death. Mitophagy patterns generally involve both ubiquitin-mediated and receptor-mediated pathways [97].

Furthermore, the Nucleotide oligomerization domain (NOD)-like receptor family pyrin domain-containing 6 (NLRP6) has been implicated in cerebral ischemia-reperfusion injury, underscoring inflammation as one of its pathogenic factors [98]. Research indicates that certain microRNAs may serve as critical regulators of cerebral ischemia-reperfusion, although their feasibility requires further investigation [99,100].

During cerebral ischemia, the intracellular pH decreases due to increased anaerobic respiration. However, during the reperfusion process, the activation of NHE results in an influx of a large amount of Na+, leading to intracellular overload. Subsequently, the NCE is activated, causing an influx and overload of Ca2+. This, in turn, leads to mitochondrial destruction, generating a substantial amount of reactive oxygen species (ROS) and inducing oxidative stress. The cascade effect includes DNA damage, lipid peroxidation, cytoskeleton

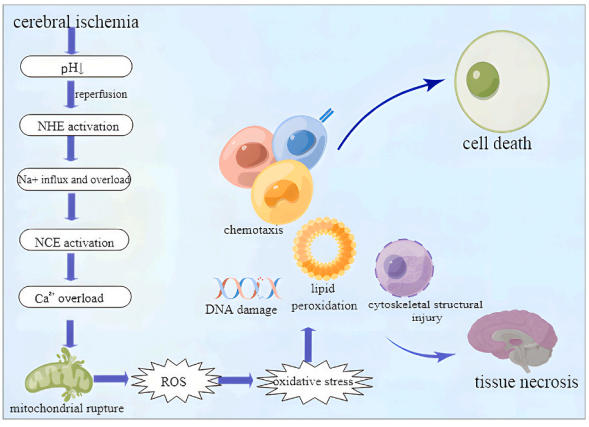

Fig. 5. The pathogenesis of ischemia/reperfusion injury.

structure damage, and chemotaxis, ultimately culminating in cell death and tissue necrosis.

6. NUV in ischemia/reperfusion injury

Pericyte contractility is intricately regulated by intracellular Ca^{2+} concentration, making them more susceptible during Ca^{2+} overload. Notably, pericytes exhibit large elongated mitochondria along the central core, potentially serving as a significant source of ROS in ischemia/reperfusion injury. ROS, in turn, leads to an augmented influx of calcium ions [101]. Studies have elucidated that ROS induces sustained pericyte contraction, may contributing to the "no-reflow phenomenon" [102]. Inhibiting oxidative stress has been demonstrated to mitigate ischemia and reperfusion-induced pericyte contraction, positively influencing tissue survival [51]. Additionally, under ischemia/reperfusion injury, pericytes may impede the delivery of substrates and drugs to tissues, negati0vely impacting survival [103].

The excessive accumulation of calcium ions in cerebral ischemia-reperfusion injury can impact astrocytic Ca^{2+} signaling, given that astrocytes' excitability is characterized by this phenomenon [104]. Astrocytic sustenance against oxidative stress and promotion of neuronal survival involves the release of antioxidants like glutathione (GSH) and an increase in the expression of transcription factors such as NF-E2-related factor 2 (Nrf2) [105]. Notably, GSH, acting directly as a reactive oxygen species scavenger, originates mainly from astrocytes. Astrocyte-released Nrf2 coordinates the expression of genes crucial for free radical scavenging. Additionally, astrocytes release the antioxidant molecule ascorbic acid, which can be absorbed by neurons, thereby modifying local energy metabolism [106].

MG predominantly contribute to neuroinflammation in ischemia/reperfusion injury. Activated Toll-like receptors (TLRs) stimulate the production of IL-23, triggering the generation of IL-17 from microglia, ultimately leading to neuroinflammation [107].

BMECs exhibit a dual action in ischemia/reperfusion. On one hand, brain endothelial Atg7 has been implicated in contributing to brain damage during ischemia/reperfusion by modulating the expression of pro-inflammatory cytokines [108]. On the other hand, BMECs' autophagy proves beneficial for maintaining BBB integrity [109]. Additionally, the endothelial glycocalyx has a protective role, preventing BBB injuries caused by oxidative stress [110].

7. The pathogenesis of hemorrhagic stroke

Cerebral hemorrhage can result from various causes, among which hypertension and small vessel disease are the most common factors. The former mostly causes deep subcortical hemorrhage with sensory–motor deficits as the main clinical feature, while the latter mostly causes acute spontaneous cerebral lobe hemorrhage with headaches and seizures as the main clinical features, and the latter presents a more severe early prognosis than the former [111,112]. Additionally, hemorrhagic transformation stands out as a significant complication of acute ischemic stroke [113]. Factors such as atrial fibrillation, prior use of oral anticoagulants and antiplatelet medications, as well as low total and LDL cholesterol, are closely associated with hemorrhagic transformation [114]. The secondary injury following cerebral hemorrhagic stroke manifests through processes such as inflammation, apoptosis, and disruption of the BBB [115].

Heme released from blood serves as an activator of the inflammatory mediator NLRP3. Studies have indicated that IL-1β, TNF-α, and NLRPs contribute to the damage caused by cerebral hemorrhage, establishing a clear link between cerebral hemorrhage and neuroinflammation. IL-1β induces neutrophil infiltration and BBB disruption, while TNF-α is implicated in BBB breakdown and apoptosis [116]. Furthermore, thrombin activation post-cerebral hemorrhage can lead to neuronal injury through the complement cascade, TNF-α, or activation of MMP in endothelial cells, exacerbating BBB disruption and contributing to cerebral edema [117].

Cerebral hemorrhage primarily induces cell death through apoptosis and autophagy, with appropriate autophagic activity serving as a pro-survival mechanism, while excessive self-digestion has the opposite effect [118]. Additionally, it is thought that there is an association between ischemia/reperfusion and hemorrhagic transformation mediated by free radicals, although this hypothesis requires further confirmation [119].

8. NVU in hemorrhagic stroke

Lipocalin-type prostaglandin D2 Synthase (LPGDS), a significant cerebrospinal fluid (CSF) protein capable of scavenging biliverdin in patients with subarachnoid hemorrhage (SAH), is significantly expressed in ischemic pericytes, suggesting a potential association between pericytes and the clearance of biliverdin in CSF among SAH patients [120]. Furthermore, global ischemia following SAH leads to a significant constriction of pericytes and triggers programmed cell death [121], potentially exacerbating brain injury by impeding vessels and causing reduced capillary density, leading to microcirculation shut down [122]. Additionally, it is thought that pericyte loss after hemorrhagic stroke may be linked to early brain injury through the promotion of microthrombosis [123].

Thrombin released from intracerebral hemorrhage (ICH) has been shown to enhance the activation of Tie2, promoting pericytes and brain microvascular endothelial cell coverage to facilitate neurological repair [124,125]. The endothelial glycocalyx plays a role in rejecting red blood cells from the endothelium, potentially limiting the spread of hematoma [110]. After ICH, iron released from the hematoma accumulates in pericytes and BMECs, contributing to secondary brain injury [126].

MG are among the first non-neuronal cells to respond during the innate immune response to ICH. Their positive role is primarily reflected in promoting the phagocytosis of red blood cells and tissue debris, clearing hematoma [127] by activating M1 type. However, over-expression of the M1 type tends to amplify the inflammatory response in the acute phase, releasing various inflammatory factors that can further damage neurons [128]. Conversely, M2-type MG often exert an anti-inflammatory effect, preventing brain tissue

injury in the later stages of hemorrhagic stroke [129]. Additionally, MG has been implicated in post-stroke pain (PSP) [129].

9. Traditional Chinese medicine treat stroke through NVU

TCM has a rich history of being employed to treat stroke in China for thousands of years, and it is highly conceivable that an increasing number of traditional Chinese medicines will be subjected to verification through animal experiments in the future [130]. In TCM, the etiology of stroke is classified into categories such as "wind", "phlegm", and "blood stasis." Accordingly, the therapeutic approach in TCM typically involves dispelling wind, eliminating phlegm, and promoting blood circulation. TCM treatments commonly encompass the use of herbs and acupuncture.

9.1. Single herb and active ingredients of herbs

Borneol demonstrates the capability to downregulate the expression of inflammatory and oxidative stress proteins in microglia and astrocytes, effectively alleviating pain induced by stroke. Additionally, *borneol* can selectively bypass astrocytes and directly target neurons, facilitating the targeted delivery of drugs to the brain and enhancing the neuronal targeting ability of drugs by opening TJs in the BBB. For instance, *borneol* can enhance the ability of resveratrol to effectively penetrate the BBB and inhibit oxidative stress. Furthermore, *borneol* contributes to neuronal nourishment by elevating BDNF levels and protects BMECs from damage caused by oxygen and glucose deprivation [131].

Panax notoginseng demonstrates the ability to mitigate neuronal damage resulting from cerebral ischemia by suppressing inflammatory mediators released by MG and elevating the levels of the anti-inflammatory cytokine IL-10. Additionally, it exerts antioxidative effects through the estrogen receptor (ER)-dependent activation of the Akt/Nrf2/heme oxygenase-1 (HO-1) pathway, known for its robust antioxidant properties. This activation leads to the promotion of various antioxidants such as superoxide dismutase (SOD), catalase (CAT), and thioredoxin-1 (Trx-1), among others. Furthermore, *Panax notoginseng* protects neurons against injuries induced by cerebral ischemia/reperfusion by manifesting anti-apoptotic effects, inhibiting amino acid excitotoxicity, and mitigating calcium overload. Moreover, it plays a crucial role in repairing the BBB by enhancing the survival of BMECs [132].

A study revealed that *Ginseng* could reduce the levels of cytokines, such as TNF-α, IL-1β, and IL-6, in the context of cerebral ischemia. This effect was achieved by downregulating MG M1 activation while concurrently upregulating MG M2 activation [133].

Ginkgo biloba extract has been identified as a protective agent against ischemic brain injury by inhibiting astrogliosis and suppressing neuroinflammation through the LCN2-JAK2/STAT3 pathway [134]. *Resveratrol*, extracted from *rhizoma polygoni cuspidati*, was found to yield neuroprotective effects by modulating various pathways, inhibiting neuroinflammation by influencing the Th17/Tregs and Th1/Th2 polarity shift in the small intestinal lamina propria (SI-LP) [135]. Additionally, *resveratrol* was found to promote M2 polarization of MG [136]. An increasing body of evidence suggests that resveratrol inhibits the NLRP3/IL-1β axis and the Silent mating type information regulation 2 homolog-1 (Sirt1)/AMPK pathway in microglia [137,138]. *Resveratrol* also inhibits C-reactive protein (CRP) production from astrocytes, represses reactive astrocyte proliferation, and activates the deactivation of the STAT3 pathway [139,140]. *Xanthohumol,* derived from *Humulus Lupulus*, demonstrated protective effects by preventing oxidative stress injury by inhibiting the phosphorylation of p38-MAPK and mediating nuclear Nrf2 activation in CIRI [141]. Additionally, it was found to relieve neuroinflammation through NRF2-ARE signaling in microglial BV2 cells [142]. *Apigenin,* extracted from *celery*, alleviates CIRI by resisting oxidative stress and apoptosis [143]. *Sinomenine*, extracted from *sinomenium acutum*, activates astrocytic dopamine D2 receptors, alleviating neuroinflammatory injury via the CRYAB/STAT3 pathway and Nrf2 signaling pathway in ischemic stroke [144,145]. *Sinomenine* also protects neurons against ROS-induced oxidative stress through a ROS-dependent upregulation of the endogenous antioxidant system in CIRI [146]. Furthermore, *Sinomenine* restrains the release of inflammatory molecules in M1 microglia, such as TNF-α, IL-1β, and IL-6, and enhances microglia M2 polarization, thereby relieving brain injury in intracerebral hemorrhage [147,148]. *Ferulic acid*, extracted from *Rhizoma Ligustici*, protects neurons against ischemia/reperfusion (I/R)-induced ROS generation and apoptosis by inhibiting Ca^{2+} influx, superoxide anion (O_2^-) production, malondialdehyde (MDA) production, and glutathione peroxidase (GSH-Px). This protective effect may be related to the inactivation of the TLR/MyD88 pathway [149]. *Ferulic acid* also protects neurons from ischemic damage by inhibiting microglia-mediated pro-inflammatory responses and downregulating the expression of NO production and inducible nitric oxide synthase (iNOS) in astrocytes [150,151]. *Calycosin,* extracted from *Astragalus*, has been demonstrated to resist cerebral ischemia/reperfusion injury by suppressing the toll-like receptor, PI3K-AKT, TNF, MAPK, and VEGF signaling pathways [152]. *Astragaloside* IV, another extract from *Astragalus*, has shown the ability to facilitate brain remodeling and repair by downregulating IL-17 expression via the Wnt pathway after ischemic stroke [153]. *Tetramethylpyrazine*, derived from *Rhizoma Ligustici*, is widely thought to protect neurons from ischemic injury by inhibiting TRPC6, promoting the production of BDNF [154], and protect BMECs by suppressing the PKCδ (protein kinase C)/MARCKS (myristoylated alanine-rich C-kinase substrate) Pathway and Rho/Rho-kinase (Rho-associated kinases, ROCK) Signaling Pathway in CIRI [155,156]. *Anthocyanin*, extracted from *Caulis Perillae*, has been proven to alleviate neuronal apoptotic injury by regulating Bcl-2 family proteins and reducing inflammatory molecules such as TNF-α, IL-1β, and IL-6. Additionally, *Anthocyanin* ameliorates cerebral edema by inhibiting MMP-9 [157,158]. *Cordycepin*, extracted from *Cordyceps*, and Polysaccharides, extracted from longan flesh, have been indicated to inhibit oxidative stress induced by ischemia/reperfusion [159,160]. *Curcumin*, extracted from *Turmeric*, has been found to protect astrocytes from oxidative stress [161]. *Salvianolic Acid*, derived from *Salvia*, alleviates injuries resulting from cerebral ischemia/reperfusion in various ways. For example, it can inhibit apoptosis in pericytes [162], suppress astrocyte activation to reserve microvascular integrity through the down-regulation of TNF-α [163], and enhance cerebral angiogenesis and neurological recovery by activating JAK2(Janus Kinase 2)/STAT3(Signal Transducer and Activator of Transcription 3) signaling pathway [164]. Additionally, it relieves

neuroinflammation by inhibiting the activation of TLR2/4 [165]. It also demonstrates the ability to modulate M1/M2 phenotypes, inhibit the NLRP3 inflammasome/pyroptosis axis in MG [166], and directly repress microglial activation [167]. *Puerarin*, an extract from *Puerariae*, has been demonstrated to provide neuroprotection against transient cerebral ischemia by attenuating autophagy in neurons at the ischemic penumbra [168]. It exerts a protective effect on astrocytes after CIRI by inhibiting pro-apoptosis factors, upregulating BDNF secretion in astrocytes, and regulating the transcriptome [169,170]. *Gastrodin*, extracted from *Gastrodia*, has been proven to prevent neuronal injury during cerebral ischemia/reperfusion by resisting oxidative stress, reversing increased MDA content, and reducing the expression of TNF-α and IL-1β. It increases SOD activity and the expression of HO-1 and SOD1; *Gastrodin* has also been reported to decrease neuronal apoptosis by preserving the expression of Bcl-2 and suppressing the expression of Bax protein and cleaved caspase3. Additionally, *Gastrodin* protects astrocytes against I/R injury by inhibiting the expression of NOS and relieving NO-induced neurotoxicity [171]. *Isorhynchophylline*, extracted from *Uncaria*, has been shown to reduce the level of AQP4, attenuating cerebral edema. It also alleviates neuroinflammation by restraining microglial M1 expression and promoting M2 levels [172]. *Breviscapine*, an extract from *Erigeron*, has been proven to ameliorate CIRI through the Nrf2 and HO-1 pathways [173]. *Hydroxysafflor yellow* A, extracted from *Carthamus*, and *daucosterol palmitate*, extracted from *Alpinia*, were found to protect BMECs against ischemic injury by inhibiting autophagy via the PI3K/Akt/mTOR signaling pathway [174,175]. *Oridonin*, extracted from *rabdosia rubescens*, has been shown to relieve CIRI by suppressing the activation of the NLRP3 inflammasome induced in BV2 microglia cells by inhibiting NF-κB signaling [176]. Current evidence suggests that *celastrol*, extracted from *thunder god vine*, exerts protective effects against ischemic injury, possibly through the downregulation of p-JNK, p-c-Jun, and NF-κB expression [177]. *Syringin*, extracted from *Acanthopanax*, was found to shield neurons from CIRI by inhibiting neuroinflammation and the TLR4 signaling pathway [178]. *Galuteolin*, extracted from *honeysuckle*, exerts neuroprotective effects against CIRI by inhibiting apoptosis, oxidation, and inflammation [179]. *Quercetin*, extracted from *Chinese Thorowax*, *Yulangsan polysaccharide*, extracted from *Yulangsan*, and *Licochalcone B*, extracted from *Licorice*, have been found to mitigate CIRI through resistance to oxidative stress and apoptosis [180–182]. A study suggested that *Shikonin*, extracted from *Asian puccoon*, yielded protective effects on neuronal cells by promoting the absorption of hematoma in cerebral hemorrhage, enhancing the ability of microglia to phagocytize erythrocytes [183].

However, certain active components in herb decoctions face challenges such as low solubility and stability. Studies have revealed that utilizing neutral charge nano-liposomes (NPS) as a carrier can substantially enhance these limitations, making it a promising approach that merits further promotion [184,185].

9.2. Prescriptions

The *Naoxintong Capsule*, a Chinese patent drug derived from *Buyang Huanwu Decoction*, has been reported to inhibit apoptotic responses by protecting cells from the oversecretion and overexpression of proapoptotic cytokines. Simultaneously, it restrains oxidative stress by increasing the SOD level in CIRI [186]. Additionally, the *Xiaoshuan enteric-coated capsule*, also derived from *Buyang Huanwu Decoction*, has demonstrated a neuroprotective function in ischemic stroke by regulating neuronal/glial metabolism and re-establishing cerebral blood flow [187]. The *Dan-Deng-Tong-Nao capsules*, a proprietary medicine consisting of *Salvia*, *Erigeron*, *Rhizoma Ligustici*, and *Puerariae*, were found to alleviate CIRI by protecting brain microvascular endothelial cells [188]. Research indicates that *Xiao-Xu-Ming Decoction* relieves CIRI through the PI3K/Akt pathway [189]. The *Danhong injection*, composed of *Salvia* and *Carthamus*, has been demonstrated to diminish inflammation during cerebral ischemia/reperfusion by maintaining the integrity of the BBB and regulating the TLR4-related signaling pathway [190]. *Taohong Siwu Decoction* and *Xuefu Zhuyu Decoction* were proven to ameliorate CIRI by repressing inflammatory factors such as TNF-α and iNOS, and inhibiting apoptosis through inactivating caspase-3 [191]. *Kaixinjieyu*, consisting of Kaixin and Sini powder, improves cerebral perfusion by up-regulating neurogenesis and enhancing the TJ of the BBB [192]. *Qiancao naomaitong mixture*, made up of *Madder* and *Loosestrife,* is widely thought to possess the bioactivities of anti-apoptosis, antioxidation, and neuronal nutrition [193]. A variable formula of *Angong Niuhuang Pills* was demonstrated to exert neuroprotective effects against cerebral ischemic reperfusion by improving mitochondrial function [194].

In addtion, *Liangxue tongyu* prescription can treat hemorrhagic stroke via various pathways. *Liangxue tongyu* prescription could prevent neurons from excitotoxicity via the PI3K/Akt signal pathway and exert its comprehensive therapeutic effects by ameliorating BBB permeability, reducing secondary brain edema, promoting hematoma absorption, alleviating neuroinflammation, and reducing neurological damage [195].

9.3. Acupuncture

Acupuncture, a method rooted in Chinese medicine theory, involves penetrating needles into specific parts of patients' bodies and is commonly used as a supplementary and auxiliary treatment for various clinical diseases. Acupuncture exhibits diverse functions in stroke management through the NVU. Yue Zhuo et al. demonstrated that acupuncture can expedite the establishment of cerebral collateral circulation, enhancing cerebral blood flow and improving cerebral oxygen metabolism, ultimately preventing cerebral neurons from undergoing apoptosis [196]. Rong Liu et al. discovered that electroacupuncture attenuates inflammation post-ischemic stroke by inhibiting NF-κB-mediated activation of microglia, leading to a decrease in the expression of inflammatory factors such as IL-1β and TNF-α [197]. Additionally, Xing Lin et al. reported that electroacupuncture suppresses M1 microglia and enhances M2 microglial activation in the peri-ischemic cortex, thereby alleviating neuroinflammation [198]. Haijun Zhao et al. found that electroacupuncture contributes to the recovery of neurological deficits by activating astrocytes [199]. Wen-biao Wang et al. indicated that electroacupuncture at Baihui and Shuigou exerts neuroprotective effects in CIRI by increasing the serum level of TGF-β1 [200]. Furthermore, acupuncture has been demonstrated to promote the repair of neurovascular units after cerebral ischemia by activating

the PI3K/AKT signaling pathway [201]. Moreover, acupuncture activates the inherent antioxidant enzyme system and inhibits the excessive generation of ROS, thus relieving CIRI [202].

In addition to acupuncture, TCM plays a significant role in preventing and treating risk factors associated with stroke, including obesity, hypertension, diabetes, hyperlipidemia, and atrial fibrillation [203–205]. For instance, aloe vera demonstrates significant effects on obese rats [206]. Emodin, the active component of rhubarb, alleviates lipid metabolism disorders by enhancing LDL-C uptake and inhibiting cholesterol synthesis. Resveratrol exhibits a notable hypoglycemic effect [207], while hawthorn extract has anti-platelet aggregation and rhythm control properties, offering a certain effect on atrial fibrillation [208]. In the treatment of hypertension, TCM acts on the renin/angiotensin/aldosterone system and calcium channels, effectively lowering blood pressure [209].

10. Comparison between modern medicine and TCM in treating stroke

At present, the treatment of ischemic stroke in modern medicine includes thrombolysis, embolectomy, intracranial angioplasty and stenting, prevention of infection, anti-platelet aggregation, lipid regulation, blood pressure control, etc [210,211]. Some studies also showed that chloroquine and octreotide may improve the injury caused by ischemic stroke through different ways [212,213], and the selective activation of estrogen receptor and endothelial progenitor cells may become new targets for ischemic stroke treatment [214,215]. And the treatment of hemorrhagic stroke in modern medicine includes surgical removal of intracranial hematoma, reduction of intracranial pressure, elimination of brain edema, control of blood pressure, prevention of infection and prevention of complications such as deep vein thrombosis and aspiration pneumonia. It is worth noting that studies have confirmed that corticosteroids and glycerol, which were frequently used for post-stroke treatment before, are not beneficial to the treatment [216].

There are great differences between TCM and modern medicine in the treatment of stroke. TCM focuses on the whole, inferring and summarizing the causes from the overall symptoms of patients, and then treating them according to syndrome differentiation [217]. However, modern medicine tends to be scattered locally, and tends to find out the specific pathological changes first and then treat them according to the pathological mechanism. On the whole, the effect of modern medical treatment is better in the acute stage of stroke, and the treatment of TCM is more suitable in the rehabilitation stage. In addition, the treatment of stroke in modern medicine is still developing [218], while the treatment of stroke in TCM has been basically finalized.

11. Conclusion and perspectives

Stroke has emerged as a critical global health concern due to its high mortality and disability rates. Despite numerous therapeutic interventions, their efficacy remains limited. This article comprehensively reviews the pathogenesis of stroke, underscores the role of the neurovascular unit in stroke pathology, and explores the potential of TCM in stroke treatment. The examination of these aspects offers valuable insights into the application of TCM for stroke. However, certain limitations persist in our study. One notable drawback is the absence of effective methods for evaluating the curative effects of TCM in the research studies included in our article. Additionally, the role of the extracellular matrix in the pathology of stroke has not been fully elucidated, and the mechanisms through which TCM treats stroke via the ECM remain unclear. Currently, the application of TCM in stroke treatment is more prevalent in China, and there is a need for further exploration and research to facilitate its international adoption.

11.1. Medical ethics with laws and regulations

The literature included in this study conforms to the principles of medical ethics and the system of medical ethics norms including respect, benefit and harmlessness [219]. Among them, the use of Chinese medicine conforms to China's health administrative regulations and Chinese medicine management law [220,221].

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Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Bingxin Wu: Writing – review & editing, Writing – original draft, Formal analysis, Data curation. **Dabiao Zhou:** Writing – original draft, Data curation. **Zhigang Mei:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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