Chinese Journal of Natural Medicines

Research progress of small–molecule natural medicines for the treatment of ischemic stroke

Kui Liu, Ling Wang, Tao Pang

Citation: Kui Liu, Ling Wang, Tao Pang, Research progress of small–molecule natural medicines for the treatment of ischemic stroke, Chinese Journal of Natural Medicines, 2025, 23(1), 21–30. doi: 10.1016/S1875–5364(25)60801–6.

View online: https://doi.org/10.1016/S1875–5364(25)60801–6

Related articles that may interest you

Traditional Chinese medicines derived natural inhibitors of ferroptosis on ischemic stroke

Chinese Journal of Natural Medicines. 2024, 22(8), 746–755 https://doi.org/10.1016/S1875–5364(24)60603–5

Danshen–Chuanxiongqin Injection attenuates cerebral ischemic stroke by inhibiting neuroinflammation *via* the TLR2/ TLR4–MyD88–NF–κB Pathway in tMCAO mice

Chinese Journal of Natural Medicines. 2021, 19(10), 772–783 https://doi.org/10.1016/S1875–5364(21)60083–3

A naturally derived small molecule compound suppresses tumor growth and metastasis in mice by relieving p53–dependent repression of CDK2/Rb signaling and the Snail–driven EMT

Chinese Journal of Natural Medicines. 2024, 22(2), 112–126 https://doi.org/10.1016/S1875–5364(24)60550–9

Traditional Chinese medicine enables the development of small–molecule inhibitors of HSP47, future therapeutic implication in venous thromboembolism

Chinese Journal of Natural Medicines. 2023, 21(9), 641–642 https://doi.org/10.1016/S1875–5364(23)60479–0

Research progress on naturally–occurring and semi–synthetic ocotillol–type ginsenosides in the genus *Panax L.* (*Araliaceae*)

Chinese Journal of Natural Medicines. 2021, 19(9), 648–655 https://doi.org/10.1016/S1875–5364(21)60089–4

Recent progress on anti–*Candida* natural products

Chinese Journal of Natural Medicines. 2021, 19(8), 561–579 https://doi.org/10.1016/S1875–5364(21)60057–2

Wechat

Chinese Journal of Natural Medicines 23 (2025) 21-30

Contents lists available at ScienceDirect

Chinese Journal of Natural Medicines

journal homepage: www.cjnmcpu.com/

Review

Research progress of small-molecule natural medicines for the treatment of ischemic stroke

Kui Liu, Ling Wang, Tao Pang*

State Key Laboratory of Natural Medicines, New Drug Screening and Pharmacodynamics Evaluation Center, China Pharmaceutical University, Nanjing 210009, China

ARTICLE INFO

Article history:
Received 16 June 2024
Revised 18 August 2024
Accepted 21 September 2024
Available online 20 January 2025

Keywords:
Natural medicines
Small molecule
Ischemic stroke
Antioxidants
Neuroinflammation.

ABSTRACT

Stroke is the second leading cause of disability and mortality worldwide, imposing a substantial socioeconomic burden on individuals and healthcare systems. Annually, approximately 14 million people experience stroke, with ischemic stroke comprising nearly 85% of cases, of which 10% to 20% involve large vessel occlusions. Currently, recombinant tissue plasminogen activator (tPA) remains the only approved pharmacological intervention. However, its utility is limited due to a narrow therapeutic window and low recanalization rates, making it applicable to only a minority of patients. Therefore, there is an urgent need for novel therapeutic strategies, including pharmacological advancements and combinatory treatments. Small-molecule natural medicines, particularly those derived from traditional Chinese herbs, have demonstrated significant therapeutic potential in ischemic stroke management. These compounds exert multiple neuroprotective effects, such as antioxidation, anti-inflammatory action, and inhibition of apoptosis, all of which are critical in mitigating stroke-induced cerebral damage. This review comprehensively examines the pathophysiology of acute ischemic stroke (AIS) and highlights the recent progress in the development of small-molecule natural medicines as promising therapeutic agents for cerebral ischemic stroke.

1. Introduction

Strokes are classified into two major categories: ischemic and hemorrhagic [1]. Ischemic strokes constitute approximately 85% of all stroke cases, while hemorrhagic strokes account for the remaining 15% [2]. Hemorrhagic strokes are predominantly caused by chronic hypertension and the rupture of atherosclerotic plaques, with secondary causes including vascular malformations, tumors, and hemorrhagic transformation of ischemic stroke or venous thrombosis [3]. Ischemic stroke, on the other hand, results primarily from reduced cerebral blood flow due to arterial occlusion, although venous occlusion in cerebral veins or sinuses can also contribute to tissue ischemia and neuronal injury. Neurological deficits following stroke typically involve hemiparesis, sensory impairments, balance disturbances, and ptosis [2]. Given that ischemic stroke is the most prevalent form, this review focuses on ischemic cerebral infarction and the emerging role of small-molecule natural compounds in its treatment.

Ischemic stroke has three primary etiologies: (1) cerebrovascular atherosclerosis and plaque rupture, responsible for approximately 50% of cases; (2) lacunar infarctions due to small vessel disease, causing 25% of cases; and (3) cardiogenic embolism, which accounts for 20% [4]. Additionally, vascular inflammation and other less common factors contribute to the occurrence of ischemic stroke. Extensive research has highlighted three major mechanisms of neuronal injury during ischemia: 1) direct neuronal necrosis due to oxygen and glucose deprivation; 2) excessive generation of reactive oxygen species (ROS) during reperfusion, which exacerbates oxidative stress and neuronal injury; and 3) ischemia-induced inflammation, which exacerbates neuronal apoptosis and extends the zone of tissue damage [5-7].

The principal therapeutic goal in managing ischemic stroke is to restore cerebral blood flow by recanalizing occluded vessels and preventing the progression of tissue injury in the ischemic penumbra. The ischemic penumbra, a region of hypoperfused but salvageable tissue surrounding the infarct core, is highly vulnerable to irreversible damage if reperfusion is not achieved promptly. The focus of acute ischemic stroke (AIS) treatment is thus centered on preserving the penumbra by mitigating pathophysiological processes such as oxidative stress, inflammation, and apoptosis. Recent advancements in the development of small-molecule therapeutic agents have opened new avenues for the treatment of ischemic stroke, providing a promising foundation for novel treatment strategies [8-11]. This review aims to explore the underlying pathogenesis of ischemic stroke and assess the clinical and experimental progress in utilizing small-molecule natural drugs as therapeutic agents for ischemic stroke.

2. Pathophysiology of ischemic stroke

Ischemic stroke results in a sudden and significant reduction of cerebral blood flow, which diminishes the supply of oxygen and glucose to neurons, tissues highly dependent on these substrates for survival. The loss of neurons directly compromises brain function, leading to significant neurological deficits. There-

---

* Corresponding author.
E-mail address: tpang@cpu.edu.cn

https://doi.org/10.1016/S1875-5364(25)60801-6

fore, protecting neurons from ischemic injury and promoting their regeneration are essential therapeutic goals. Strategies for neuroprotection include mitigating neuronal injury, promoting repair, and fostering neurogenesis. For example, the natural product 4,10-aromadendranediol has been shown to induce neurogenesis in neurons through activation of the ERK signaling pathway [12]. Several interrelated mechanisms drive neuronal death following ischemic stroke, including excitotoxicity [2], oxidative [13] and nitrosative stress, and inflammatory responses [14]. These factors not only damage neurons but also compromise the function of glial cells and endothelial cells, creating a deleterious feedback loop that accelerates neurodegeneration. The integrity of the blood-brain barrier (BBB) is crucial for maintaining central nervous system (CNS) homeostasis, and its disruption following ischemic stroke exacerbates brain injury [15]. A variety of protein molecules are involved in maintaining the integrity of BBB, such as occludin, claudins, ZO proteins, and JAM proteins [16]. In addition, BBB interaction with immune cells is involved in neuroprotection and neuronal injury as well as pro-inflammatory and anti-inflammatory responses. In conclusion, ischemic stroke is driven by a multifactorial pathophysiology. Understanding these complex processes is critical for developing targeted interventions. Therefore, elucidating the pathogenesis of ischemic stroke supports the development of effective treatments based on these natural compounds (Fig. 1).

2.1. Neuroexcitotoxicity

The brain is the most metabolically active organ in the body, relying on mitochondrial oxidative phosphorylation to sustain its high ATP demand. During ischemia, the interruption of ATP production results in a rapid energy deficit, which severely impairs the function of the Na^+/K^+ ATPase pump. This disruption causes membrane depolarization, promoting the efflux of potassium ions and the influx of sodium ions In addition, the failure of Ca^{2+}-ATPase pumps results in a significant rise in intracellular Ca^{2+} levels. Elevated intracellular Ca^{2+} activates calcium-dependent enzymes, including proteases, lipases, and DNases, which leads to cell death in the ischemic core. One of the key contributors to ischemic brain injury is neuroexcitotoxicity, driven by excessive glutamate release [2]. In the CNS, there are several glutamate receptors involved in the regulation of neuroexcitatory toxicity. Glutamate is an important major factor in neuroexcitatory toxicity, and neurons and astrocytes are two major players in glutamate metabolism. Glutamate binds to its receptors to transmit action signals [17, 18]. Activation of glutamate receptors leads to prolonged membrane depolarization and a massive influx of Ca^{2+} into neurons, which also greatly promotes neuronal excitatory toxicity after ischemia-reperfusion (I/R) [19]. The resultant calcium overload further exacerbates neuronal injury and promotes widespread neurodegeneration. Astrocytes play a critical role in mitigating neuroexcitotoxicity by regulating extracellular glutamate levels. Astrocytes maintain low synaptic glutamate concentrations, preventing excessive receptor activation. Research by Zhang et al. demonstrated that astrocytes can significantly protect cortical neurons from glutamate-induced acute damage in ischemic conditions [20]. Therefore, maintaining glutamate homeostasis in the extracellular space is essential for preventing excitotoxicity and reducing neuronal injury.

2.2. Oxidative stress

During ischemia, multiple mechanisms contribute to the excessive generation of ROS and reactive nitrogen species (RNS), including glutamate-mediated excitotoxicity, elevated intracellular Ca^{2+} levels, mitochondrial dysfunction, and the release of pro-inflammatory cytokines. Increased Ca^{2+} influx triggers the opening of the mitochondrial permeability transition pore (MPTP) and the release of cytochrome C, which accelerates ROS production [21]. Due to their high oxygen demand, abundant polyunsaturated lipid content, and limited endogenous antioxidant defenses, neurons are particularly vulnerable to oxidative damage. Excess ROS accumulation leads to widespread protein oxidation, lipid peroxidation, mitochondrial DNA damage, and the activation of signaling cascades that promote inflammation, apoptosis, and necrosis [22]. ROS and RNS production is concentrated in the ischemic penumbra. Inhibition of ROS production is beneficial for preserving neuronal viability in this area [23]. Several antioxidant defense mechanisms are activated in response to oxidative stress, including pathways regulated by nuclear factor E2-related factor 2 (Nrf2). Under oxidative stress, Nrf2 dissociates from its cytoplasmic inhibitor, Kelch-like ECH-associated protein 1 (KEAP1), and translocates to the nucleus, where it induces the expression of antioxidant response elements. Enhancing Nrf2 activity by modulating its interaction with KEAP1 offers a promising approach to bolstering cellular antioxidant defenses [24]. Mitochondria, the primary source of intracellular ROS [25], are particularly susceptible to damage under sustained oxidative stress. Disruptions in the electron transport chain cause electron leakage, leading to the generation of superoxide, a major byproduct of mitochondrial respiration [26]. Protecting mitochondrial function is essential for reducing ROS production and mitigating neuronal injury.

2.3. Immunoinflammation

The immune system plays a pivotal role in the pathophysiological progression of stroke. The excessive inflammatory response caused by stroke includes increased levels of inflammatory cells, cytokines, and chemokines in the circulating blood. Damaged or dead cells release endogenous dangerous molecules through damage-associated molecular patterns (DAMPs), which activate the innate immune system by interacting with pattern recognition receptors (PRRs). These DAMPs, such as adenosine, histones, heat shock proteins, and high mobility group box-1 (HMGB1), are recognized by pattern recognition receptors (PRRs) on immune cells. Activation of these receptors triggers intracellular signaling pathways, such as the NF-κB pathway, leading to the initiation of a robust inflammatory cascade. Once activated, the innate immune system recruits a variety of peripheral and central immune cells, including neutrophils, microglia, macrophages, and lymphocytes [27, 28]. These immune cells secrete pro-inflammatory cytokines, chemokines, and interferons, which amplify the inflammatory response within the brain. The increased expression of adhesion molecules such as P-selectin, E-selectin, ICAM-1, ICAM-2, and VCAM-1 on endothelial cells facilitates the adhesion and infiltration of leukocytes across the blood-brain barrier, further promoting inflammation and exacerbating neuronal injury [29].

2.3.1. Microglia-mediated inflammation

The initial inflammatory response after ischemic injury is mediated by the activation of microglia, the resident immune cells of the CNS. Microglia rapidly detect ischemic injury, transitioning into a phagocytic state in which they release a variety of cytotoxic and/or cytoprotective substances. During ischemia, activated microglia release pro-inflammatory cytokines, including tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). However, sustained or excessive microglial activation can shift this balance toward a harmful inflammatory response, ultimately exacerbating neuronal damage and increasing the risk of cell death. Microglial activation in ischemic stroke is regulated by several key receptors, with toll-like receptor 4 (TLR4) playing a central role. TLR4 is expressed on microglia [30], and experimental evidence has shown that inhibiting TLR4 signi-

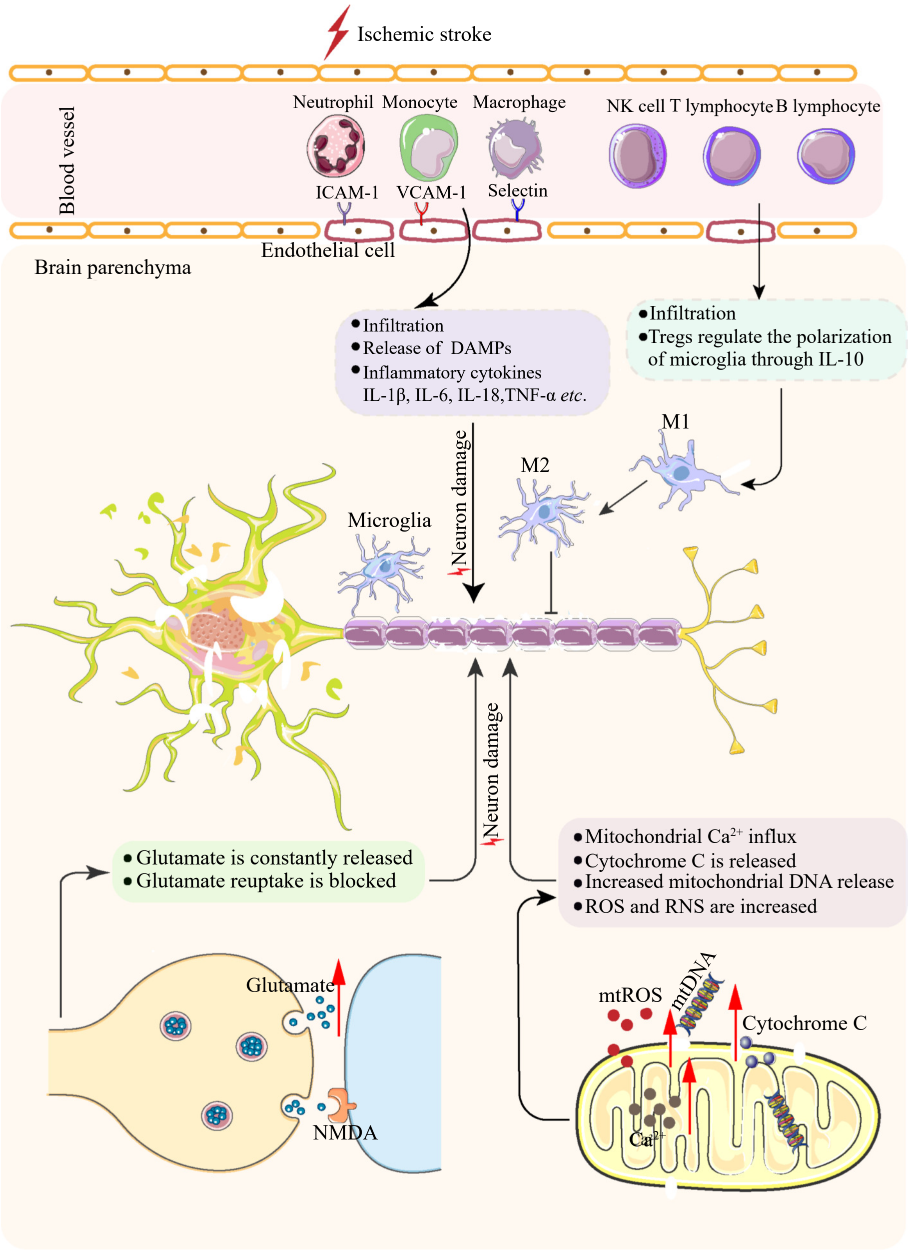

Fig. 1 The pathophysiological mechanism of ischemic stroke. During cerebral I/R injury, endothelial cells are activated and express selectin, ICAM-1, and VCAM-1, which contribute to peripherally infiltrated immune cells. With the breakdown of the BBB, neutrophils, monocytes, and macrophages migrate to the brain parenchyma and regulate the inflammatory response by releasing inflammatory cytokines IL-1β, IL-6, IL-18, and TNF-α. Tregs interact with microglia in the ischemic brain and regulate the polarization of microglia from the M1 phenotype to the M2 phenotype through IL-10. During the pathological process of ischemic stroke, glutamate release is increased, reuptake is hindered, and glutamate binding with its receptor *N*-methyl-D-aspartic acid (NMDA) results in a sustained excitatory signal. Reperfusion injury exacerbated mitochondrial Ca^{2+} influx excess, MPTP opening, and cytochrome C and mitochondrial DNA (mtDNA) release, which promote ROS and RNS production. These events finally promote neuronal damage in ischemic stroke.

ficantly limits LPS-induced activation of microglia and production of ROS [31, 32]. Notably, microglial activation is highly dynamic, with an early M2-like phenotype transitioning chronologically to the pathological M1 subgroup [33].

2.3.2. Leukocyte-mediated inflammation

Immediately after ischemic stroke, innate immune responses are initiated. Necrotic cells resulting from focal cerebral ischemia release DAMPs, which activate resident brain immune cells, such as microglia, and are also released into the bloodstream. This signaling cascade recruits peripheral immune cells to the brain, contributing to both acute injury and subsequent tissue repair processes [33]. A key step in leukocyte recruitment is the increased expression of endothelial adhesion molecules, including intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1). These molecules serve as ligands for leukocyte integrins, promoting the adhesion and transmigration of immune cells across the BBB, leading to its breakdown. This disruption allows for further infiltration of immune cells, exacerbating inflammation and neuronal injury. Neutrophils are among the first responders to the ischemic brain. Upon infiltration, neutrophils release a host of cytotoxic substances, including elastase, matrix metalloproteinase-9 (MMP-9), cathepsin G, reactive oxygen species (ROS), RNS, and pro-inflammatory cytokines like interleukin-1β (IL-1β). Neutrophils also form neutrophil extracellular traps (NETs), structures that amplify tissue damage and inflammation [34]. Monocytes and bone marrow-derived macrophages (MDMs) are normally absent from the brain parenchyma, but during the acute phase of stroke, their numbers in circulation rise significantly, largely driven by the CXCL12/CXCR4 axis. Between days 3 and 5 of the subacute phase MDMs with a pro-inflammatory phenotype accumulate at the infarct site. By day 7, these MDMs undergo a phenotypic shift to a reparative state, aiding tissue regeneration [35]. In summary, targeting endothelial cell activation and regulating leukocyte infiltration are critical strategies for mitigating stroke-induced damage.

2.3.3. T cell-mediated inflammation

The adaptive immune system contributes to both neuroinflammation and tissue repair following ischemic stroke. Peripheral immune cells, including T cells, B cells, natural killer (NK) cells, and dendritic cells (DCs), infiltrate the brain in response to ischemic injury, affecting both acute and chronic phases of stroke [36]. T cells enter the brain within the first week post-ischemia, with different subsets playing distinct roles in stroke pathology. Pro-inflammatory T cell subtypes, such as $CD4^+$ Th1 and Th17 cells, aggravate stroke damage by expanding infarct size and promoting neuroinflammation through cytokines like interferon-γ (IFN-γ) and interleukin-17 (IL-17) [33]. For instance, depletion of $CD4^+$ or $CD8^+$ T cells in experimental models has been shown to significantly reduce infarct volume, highlighting their pathological role [37]. Conversely, regulatory T cells (Tregs) exert a protective effect by limiting excessive neuroinflammation. Tregs secrete anti-inflammatory cytokines such as IL-10, which suppresses pro-inflammatory responses and facilitates tissue repair [38]. Zhou et al. demonstrated that Tregs directly interact with microglia, shifting their activation from a pro-inflammatory M1 phenotype to a reparative M2 phenotype *via* IL-10 signaling, thereby promoting neuroprotection [39]. This microglial polarization is crucial for reducing neuronal injury and fostering recovery. T cells also patrol the cerebrospinal fluid (CSF), where they search for CNS-specific antigens and trigger localized immune responses. During inflammation, these interactions, particularly in secondary lymphoid tissues, affect T cell trafficking, leading to increased BBB permeability [40, 41]. Understanding the role of T cells in ischemic stroke is vital for the development of targeted therapies.

3. Clinical application of natural medicines

Thrombolytic therapy remains the cornerstone of treatment for ischemic stroke and cerebral infarction. The fundamental objective of thrombolysis is to restore cerebral perfusion by using pharmacological thrombolytic agents or mechanical devices to recanalize occluded vessels, thereby promoting partial recovery of brain function and neurological outcomes. Time from stroke onset to intervention is the most critical determinant of treatment efficacy in AIS [42]. Recent advancements in intravenous thrombolysis and mechanical thrombectomy for large vessel occlusions have significantly reduced mortality and disability rates in AIS patients. Intravenous thrombolytic therapy is most effective when administered within 4.5 h of stroke onset. However, a substantial proportion of patients present with conditions such as proximal arterial occlusion, delayed admission beyond 4.5 h, recent major surgeries, or active bleeding, rendering them ineligible for systemic thrombolytic therapy. For these patients, mechanical thrombectomy has become the preferred treatment option, particularly in cases of large artery occlusion confirmed *via* clinical or imaging evaluations [43]. Mechanical thrombectomy offers distinct advantages over intravenous thrombolysis, including an extended treatment window of up to 24 h and superior recanalization rates. This broader therapeutic window allows for treatment in a greater number of patients. Nevertheless, pre-hospital delays, especially in low- and middle-income countries, remain a significant obstacle to timely intervention. Addressing these delays and developing new therapeutic approaches to extend the treatment window for AIS are critical unmet needs in stroke management. In recent years, natural medicines have shown considerable promise in the treatment of ischemic stroke, particularly for their potential to address these therapeutic gaps [44]. We have summarized the clinical application of several natural medicines in the table (Supplementary Table 1).

4. Research of natural medicines in the treatment of ischemic stroke

Natural medicines have a long-standing tradition in the treatment of cerebral ischemia and remain a key area of research for developing novel therapeutic strategies for ischemic stroke. Over the years, extensive theoretical knowledge has been accumulated regarding their pharmacological effects. Numerous herbal extracts have been shown to exert therapeutic effects in stroke by modulating mechanisms such as anti-inflammation, antioxidation, neurogenesis promotion, and preservation of BBB integrity. Representative compounds include salvianolic acid A [45], astragaloside IV [46], ginkgolide B [47, 48], and nordihydroguaiaretic acid [32]. The nuclear factor kappa B (NF-*κ*B) pathway is a central regulator of inflammatory responses. NF-*κ*B controls the transcription of genes responsible for inflammation, apoptosis, and cell survival. Research by Liu et al. confirmed that Kudiezi Injection (KDZ), a traditional Chinese medicine formulation, exerts potent anti-inflammatory effects by inhibiting the TLR4/NF-*κ*B signaling pathway, which significantly mitigates brain injury in acute focal ischemia [49]. In addition, Chinese herbal preparations such as Jieyudan [50], Di-Tan Decoction (DTD) [9, 51, 52], and Danshen Decoction [53] have shown promising clinical efficacy in managing stroke symptoms and enhancing recovery. Screening active ingredients from traditional Chinese medicine is an essential strategy for discovering novel therapeutic agents. This review mainly introduces and discusses the research progress on several representative active compounds from natural sources that hold the potential for treating ischemic stroke (Fig. 2).

4.1. Research of natural medicines in neuroprotection

Over recent decades, research has elucidated multiple mechanisms of neuronal death in AIS, including apoptosis, necroptosis, autophagic cell death, and ferroptosis [54]. Targeting key proteins involved in these cell death processes can enhance neuronal survival and regeneration. Many herbal medicines have been traditionally used to treat stroke, with growing evidence supporting their neuroprotective effects across various pathological conditions. Advances in proteomics and network pharmacology have helped to clarify the molecular targets and regulatory mechanisms of active compounds and traditional Chinese medicinal formulations, providing a stronger scientific basis for their application in treating ischemic brain injury [55]. Here, we discuss key pharmacological effects and molecular mechanisms of several representative natural compounds that exhibit neuroprotective properties.

4.1.1. Astragaloside IV (AST)

AST is one of the primary bioactive components of *Astragalus membranaceus* var. *mongholicus* and *A. membranaceus* [56]. AST exerts multiple beneficial effects on brain protection, including anti-ischemic, anti-oxidative, and anti-apoptotic actions. The brain-derived neurotrophic factor (BDNF) is a critical neurotrophic factor involved in neurogenesis and neuronal survival [57]. Ni et al. demonstrated that AST improves neurobehavioral outcomes and promotes neurogenesis in middle cerebral artery occlusion (MCAO) rat models by regulating the BDNF-TrkB signaling pathway [58]. In addition, angiogenesis is crucial for brain repair following ischemic stroke [59], and the phosphatidylinositol 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) pathway plays a significant role in this process [60]. AST has been shown to promote angiogenesis by activating the PI3K/Akt/mTOR signaling pathway, enhancing long-term recov-

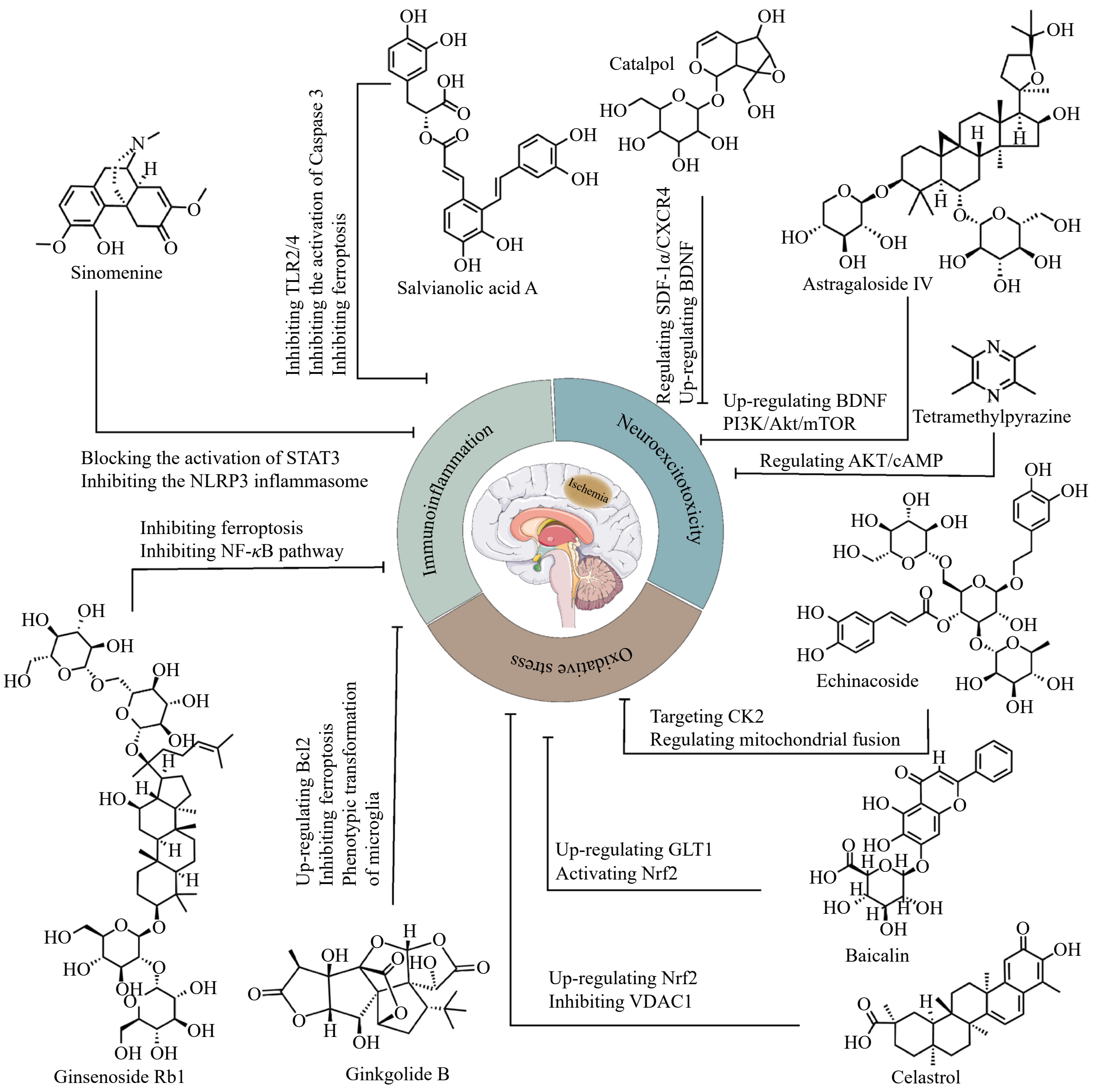

Fig. 2 The pathological mechanism of stroke and the chemical structure formula of natural medicines. VDAC1: voltage-dependent anion-selective channel protein 1; TLR2/4: toll-like receptor 2/4; SDF-1α: stromal cell-derived factor 1 alpha; CXCR4: CXC chemokine receptor 4; PI3K: phosphatidylinositol 3-kinase; Akt: protein kinase B; mTOR: mammalian target of rapamycin; cAMP: cyclic adenosine monophosphate; NF-κB: nuclear factor kappa B; GLT1: glutamate transporter 1; Nrf2: nuclear factor-erythroid factor 2; Bcl2: B-cell lymphoma-2; CK2: casein kinase 2.

ery and reducing histological damage in ischemic models [61]. Mitochondrial dysfunction, a major contributor to neuronal death [26], is closely associated with ischemic injury. AST has also been shown to protect mitochondrial function by preserving hexokinase II (HK-II), which prevents the opening of the mPTP [62], thereby promoting neuronal survival [63].

4.1.2. Tetramethylpyrazine (TMP)

TMP, an alkaloid derived from *Ligusticum chuanxiong* Hort [64], has been widely studied for its neuroprotective effects in ischemic stroke. TMP exerts its effects through antioxidant activity [65], anti-inflammatory actions [66], and preservation of the BBB integrity [67]. However, TMP has limited clinical application due to its rapid metabolism, short half-life, and poor bioavailability [64, 68]. To address these limitations, Nie et al. synthesized a derivative, tetramethylpyrazine nitrone (TBN), with improved pharmacokinetics [69]. Guo et al. demonstrated that TBN enhances BDNF expression by activating the AKT/cAMP response element-binding (CREB) pathway, leading to reduced cerebral infarct volume, improved neurogenesis, and enhanced functional recovery in MCAO models [70].

4.1.3. Catalpol

Catalpol, an iridoid glucoside isolated from *Rehmannia glutinosa*, exhibits potent neuroprotective properties [71]. One of its key mechanisms of action involves the chemokine stromal cell-derived factor 1 alpha (SDF-1α) and its receptors, CXCR4 and CXCR7, which play essential roles in brain homeostasis and neurogenesis [72]. Zhang et al. found that catalpol promotes neurogenesis and angiogenesis through the SDF-1α/CXCR4 pathway, contributing to neuroprotection [73]. Moreover, catalpol increases brain levels of BDNF and enhances the formation of new neurons, further supporting neural recovery after stroke [74].

4.2. Research of natural medicines in antioxidation

Oxidative stress plays a central role in the pathogenesis of ischemic stroke [75]. Vascular recanalization beyond the time window produces large quantities of ROS and RNS. Overproduction of ROS and RNS initiates a cascade of cellular signaling events that compromise the integrity of the BBB, promote brain edema, trigger inflammatory responses, and induce neuronal death. Previous studies have shown that ROS levels increase significantly after cerebral I/R in experimental models, and inhibiting ROS production can effectively reduce cerebral infarct volume [76, 77]. Thus, targeting signaling pathways involved in ROS/RNS production represents a promising therapeutic approach for ischemic stroke. This section highlights several key natural antioxidant compounds that have demonstrated neuroprotective effects by mitigating ROS/RNS-mediated injury in ischemic stroke.

4.2.1. Baicalin

Baicalin, a natural flavonoid extracted from the root of *Scutellaria baicalensis*, has been extensively studied for its wide range of pharmacological properties, including antitumor [78], antiviral [79], anti-inflammatory [80], antioxidant [81] effects. Baicalin has demonstrated the ability to protect the BBB and reduce ischemic brain injury [82]. During cerebral I/R, the reverse transmission in the mitochondrial electron transport chain leads to succinate dehydrogenase activation, which in turn results in excessive ROS production. ROS accumulation degrades glutamine synthetase in astrocytes, a key enzyme involved in glutamate metabolism. Song et al. confirmed that baicalin significantly reduces oxidative stress and preserves glutamine synthetase levels, thereby protecting neurons from I/R and the subsequent loss of glutaminase [83, 84]. Termination of glutamate neurotransmission *via* glutamate transporter 1 (GLT1) is essential to maintain low glutamate concentration in extracellular space and avoid excitatory toxicity [85]. Zhou et al. confirmed that baicalin upregulates GLT1 *via* activation of the PI3K/Akt signaling pathway, thus protecting neonatal rat brains from hypoxic-ischemic injury [86]. Moreover, baicalin activates the Nrf2 signaling pathway, which is key in modulating the cellular antioxidant response. Upon oxidative stress, Nrf2 dissociates from Keap1 and translocates to the nucleus, where it binds to antioxidant response elements (AREs) to promote the transcription of antioxidant genes [87]. Wang et al. reported that baicalin alleviates lipopolysaccharide (LPS)-induced BBB damage by activating the Nrf2-mediated antioxidant pathway, further emphasizing its neuroprotective potential [88].

4.2.2. Celastrol (Cel)

Cel is a triterpenoid extracted from *Tripterygium wilfordii* [89]. Hong et al. identified that Cel inhibits the degradation of Nrf2 by targeting the E3 ubiquitin ligase NEDD4, thereby enhancing antioxidant defenses, and reducing ROS production in astrocytes during ischemia [90]. This regulation of Nrf2 stabilizes the cellular antioxidant response, reducing oxidative damage in the ischemic brain. Li et al. further revealed that Cel exerts its neuroprotective effects by interacting with the cyclic adenosine monophosphate (cAMP)/exchange protein activated by the cAMP (EPAC-1) signaling pathway. Cel binds to EPAC-1, preventing its interaction with the voltage-dependent anion-selective channel protein 1 (VDAC1), which in turn blocks the opening of the mPTP. Interestingly, the neuroprotective effects of Cel were diminished in neuron-specific EPAC1 knockout models [91], which preserves mitochondrial function and mitigates ischemia-induced neuronal death.

4.2.3. Echinacoside (ECH)

ECH, a natural phenylethanoid glycoside, was first isolated from *Echinacea angustifolia* DC [92]. Mitochondria are the primary energy-producing organelles in cells. The regulation of mitochondrial homeostasis is thus of great significance for mitigating ischemic injury [26, 93]. Mitochondria are highly dynamic organelles that undergo continuous cycles of fusion and fission, which are essential for adapting to changes in the physiological environment. Mitochondrial fusion helps restore mitochondrial function by combining the components of damaged mitochondria [94]. Zeng et al. demonstrated that ECH promotes mitochondrial fusion in PC12 cells and protects against oxygen-glucose deprivation/reoxygenation (OGD/R)-induced injury. In a mouse model of MCAO, ECH was found to enhance mitochondrial fusion and reduce brain injury by targeting the casein kinase 2α (CK2α') subunit, thereby improving mitochondrial function [95]. Mechanistically, ECH recruits basic transcription factor 3 (BTF3) to form a CK2α'/BTF3 complex, which promotes the nuclear translocation of *β*-catenin. This activates TCF/LEF transcription factors, leading to the upregulation of mitofusin-2 (Mfn2), a key gene involved in mitochondrial fusion [95].

4.3. Research of natural medicines in anti-inflammation

Neuroinflammation plays a central role throughout the progression of ischemic stroke and is triggered by the release of DAMPs from injured or necrotic cells [33]. These DAMPs activate various immune cells, which release inflammatory mediators that disrupt the integrity of the BBB, leading to brain edema and exacerbating neuronal injury [96]. Inflammatory processes are mediated by multiple signaling pathways, such as the TLR/NF-*κ*B signaling pathway [97]. Activation of receptors such as tumor necrosis factor receptors (TNFR), interleukin-1 receptors (IL-1R), and TLRs triggers a signaling cascade that ultimately activates I*κ*B kinase-β (IKKβ), a key step in the classical NF-*κ*B pathway [24]. Since NF-*κ*B is active in numerous immune cells, targeting this pathway represents a promising therapeutic strategy to modulate neuroinflammation in ischemic stroke.

4.3.1. Salvianolic acid A (SAA)

SAA is an active ingredient extracted from *Salviae miltiorrhizae* Bunge (Danshen). Ling et al. demonstrated that SAA attenuates cerebral edema and reduces ischemic injury in a rat model of I/R by inhibiting the TLR2/4-mediated inflammatory response, leading to decreased levels of pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α) [98]. In addition to its anti-inflammatory actions, SAA exerts neuroprotective effects through other mechanisms, including the regulation of Bcl-2 and the inhibition of caspase-3 activation. Yang et al. found that SAA improved cognitive function and reduced hippocampal damage in a transient middle cerebral artery occlusion (tMCAO) rat model, highlighting its broader neuroprotective role [99]. Furthermore, SAA inhibits ferroptosis by activating the Akt/GSK-3β/Nrf2 signaling pathway, as shown by Shi et al. [100]. These findings suggest that SAA's multi-target effects may offer significant neuroprotective benefits in ischemic stroke.

4.3.2. Sinomenine (SN)

SN is an alkaloid extracted from *Sinomenium acutum*. The signal transducer and activator of transcription 3 (STAT3) pathway plays a critical role in regulating inflammation, and its activation is associated with increased expression of cytokines such as TNF-α and IL-6 [101, 102]. Qiu et al. demonstrated that SN inhibits the activation of STAT3 in primary astrocytes, which in turn reduces the production of pro-inflammatory cytokines and alleviates cerebral infarction and neuronal apoptosis in a mouse model of MCAO [103]. Studies have shown that Ca^{2+}-permeable acid-sensing ion channels (ASIC) are proton-gated volt-independent ion channels prevalent in the nervous system [104], which can directly induce Ca^{2+} entry and provide additional Ca^{2+} entry pathways in ischemic neurons [105]. Wu et al. confirmed that the pharmacological characteristics of SN involved in neuroprotection may include the co-inhibition of ASIC1a and L-type calcium channels [105]. Inflammasome plays a key role in the initiation and development of inflammation in the CNS, specifically NLRP3. Activation of the NLRP3 inflammasome promotes the release of several pro-inflammatory cytokines, including IL-1β, IL-18, and TNF-α [106]. Qiu et al. confirmed that SN inhibited the NLRP3 inflammasome through the AMPK pathway and played a neuroprotective role in ischemic stroke [107].

4.3.3. Ginsenoside Rb1 (GsRb1)

GsRb1, a prominent bioactive component isolated from *Panax ginseng* root, has been widely recognized for its pharmacological properties [8, 108]. Astrocytes are the most abundant glial cells that protect and support neuronal function. GsRb1 inhibits NADH dehydrogenase in mitochondrial complex I in astrocytes to block reverse electron transport-derived ROS produced by complex I, thereby exerting a neuroprotective effect [109]. Ferroptosis, a form of regulated cell death, is a key driver of neuronal death in ischemic stroke. Targeting the molecular regulators of ferroptosis is conducive to neuronal survival [110]. Zhang et al. proved that GsRb1, like ferroptosis inhibitors, significantly restores antioxidant levels and inhibits ischemic brain damage in neonatal rats subjected to hypoxic-ischemic injury. Additionally, GsRb1 inhibits lipid oxidation and decreases inflammatory markers in the oxygen-glucose deprivation (OGD) model of PC12 cells *in vitro* [111]. The PI3K/Akt signaling pathway regulates inflammation, oxidative stress, apoptosis, autophagy, and vascular endothelial homeostasis after cerebral ischemia [112]. Liu et al. confirmed that GsRb1 inhibits amyloid-induced neuronal apoptosis and significantly increases neurite outgrowth in hippocampal neurons by upregulating the expressions of phosphorylated Akt and phosphorylated extracellular signal-regulated kinase 1/2(ERK1/2). These effects are eliminated by inhibitors of the signaling proteins Akt and MEK, API-2, and PD98059 [113]. Mitochondria play a key role in a variety of cellular processes, including ATP production, Ca^{2+} regulation, ROS production, and apoptosis. In ischemic stroke, the reduction in blood supply leads to mitochondrial dysfunction. The selective removal of damaged mitochondria, or mitophagy, is crucial for maintaining neuronal viability [114]. Li et al. reported that GRb1 inhibits astrocyte pyroptosis by regulating mitochondrial phagocytosis and the NF-*κ*B pathway, thereby maintaining neurohomeostasis by inhibiting inflammation and enhancing synaptic plasticity [115].

4.3.4. Ginkgolide B (GB)

GB is a major bioactive component derived from *Ginkgo biloba* [47]. Pre-clinical studies by Hui et al. have demonstrated that GB has a protective effect [116]. Ongoing clinical trials are investigating the efficacy and safety of GB-based formulations in the prevention and treatment of cerebrovascular diseases, such as ischemic stroke [117]. Cao et al. confirmed that GB prevents neuronal loss and significantly reduces apoptosis 72 h after MCAO in rats by up-regulating the expression of B-cell lymphoma-2 (Bcl2) and phosphorylated AMPK [118]. Nuclear receptor coactivator 4 (NCOA4) facilitates ferritinophagy, the autophagic degradation of ferritin through lysosomes, which promotes ferroptosis [119]. Yang et al. confirmed that GB can inhibit ferroptosis by disrupting the NCOA4-ferritin heavy chain 1 (FTH1) interaction, thus protecting against I/R injury [120]. Additionally, Shu et al. demonstrated that GB promotes the shift of microglia/macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, so as to alleviate cerebral ischemic injury in mice and improve the neurological outcomes of mice [121].

5. Conclusion

AIS remains a leading cause of mortality and long-term disability, primarily due to its sudden onset and the challenges associated with timely medical intervention. Delays in hospital admission often prevent early thrombolytic therapy, worsening neurological damage and leading to poor prognosis. Chinese herbal medicine, with a long history in the prevention and treatment of ischemic stroke, offers significant potential for therapeutic development. Numerous studies have demonstrated that bioactive compounds and extracts from Chinese herbal medicine can protect against ischemic injury by preserving BBB integrity, reducing excitotoxicity, enhancing antioxidant and anti-inflammatory responses, and promoting neurogenesis and angiogenesis. However, several limitations that restrict the clinical application of natural products in stroke treatment: 1) One of the primary obstacles is the difficulty of many natural compounds in crossing the BBB. To address this, drug delivery systems such as liposomes, nanoparticles, and structural modifications of compounds have been explored. For instance, 9-aminoacridine (9-AA), a compound shown to alleviate ischemic brain injury in tMCAO and reperfusion rats, has limited bioavailability due to poor water solubility. The development of 9-AA-loaded liposomes (9-AA/L) significantly improved BBB permeability and brain tissue targeting, reducing infarct size and enhancing neurological recovery in a rat model of tMCAO [122]. 2) Despite promising preclinical findings, the molecular mechanism of action of natural products is not clear. Elucidating the structure-activity relationships (SARs) and precise mechanisms of action is essential for optimizing their therapeutic applications. The development of network pharmacology [123], RNA sequencing [124], proteomics, and bio-orthogonal chemistry [125] has significantly advanced the discovery of natural drug targets. For example, the SAR of the benzoxepane scaffold, a common motif in bioactive natural products, led to the identification of pyruvate kinase M2 (PKM2) as a key anti-inflammatory target through photoaffinity labeling (PAL) [126]. 3) Chinese herbal medicines are often characterized by their multi-component, multi-target nature [127], which can both enhance their therapeutic potential and introduce challenges. A deeper understanding of SARs is necessary to refine these compounds for clinical use, minimizing side effects, and improving safety profiles. 4) Most preclinical studies on stroke employ young, healthy animal models, while the majority of clinical stroke patients are middle-aged or elderly and often have comorbidities such as hypertension and diabetes. These conditions can significantly alter drug efficacy, leading to a disparity between preclinical findings and clinical outcomes. Developing animal models that better mimic the clinical population is crucial for accurately assessing the efficacy of natural products in stroke therapy. This refinement in preclinical research is essential for advancing drug development and improving the translation of natural products from bench to bedside.

Funding

This work was supported by the National Natural Science Foundation of China (Nos. 82174010 and 81973512).

Declaration of competing interest

These authors have no conflict of interest to declare.

References

1 Benesch C, Glance LG, Derdeyn CP, et al. Perioperative neurological evaluation and management to lower the risk of acute stroke in patients undergoing noncardiac, nonneurological surgery: a scientific statement from the American Heart Association/American Stroke Association. *Circulation*. 2021;143(19):e923-e946. https://doi.org/10.1161/CIR.0000000000000968..

2 Khoshnam SE, Winlow W, Farzaneh M, et al. Pathogenic mechanisms following ischemic stroke. *Neurol Sci*. 2017;38(7):1167-1186. https://doi.org/10.1007/s10072-017-2938-1.

3 Magid BJ, Girard R, Polster S, et al. Cerebral hemorrhage: pathophysiology, treatment, and future directions. *Circ Res*. 2022;130(8):1204-1229. https://doi.org/10.1161/CIRCRESAHA.121.319949.

4 Diener HC, Easton JD, Hart RG, et al. Review and update of the concept of embolic stroke of undetermined source. *Nat Rev Neurol*. 2022;18(8):455-465. https://doi.org/10.1038/s41582-022-00663-4.

5 Martín-Montañez E, Valverde N, Ladrón de GMD, et al. Insulin-like growth factor II prevents oxidative and neuronal damage in cellular and mice models of Parkinson's disease. *Redox Biol*. 2021;46:102095. https://doi.org/10.1016/j.redox.2021.102095.

6 Okarmus J, Agergaard JB, Stummann TC, et al. USP30 inhibition induces mitophagy and reduces oxidative stress in parkin-deficient human neurons. *Cell Death Dis*. 2024;15(1):52. https://doi.org/10.1038/s41419-024-06439-6.

7 Zhao Y, Zhang X, Chen X, et al. Neuronal injuries in cerebral infarction and ischemic stroke: from mechanisms to treatment (Review). *Int J Mol Med*. 2021;49(2):15. https://doi.org/10.3892/ijmm.2021.5070.

8 Liston TE, Holstein D, Solt D, et al. Lack of interactions between alteplase/tenecteplase and the adenosine A1R/A3R agonist AST-004. *Stroke*. 2024;55(7):1923-1926. https://doi.org/10.1161/STROKEAHA.124.046688.

9 Zhen Z, Xue DJ, Chen YP, et al. Decoding the underlying mechanisms of Di-Tan-Decoction in treating intracerebral hemorrhage based on network pharmacology. *BMC Complement Med Ther*. 2023;23(1):23-44. https://doi.org/10.1186/s12906-022-03831-7.

10 Hergenreder E, Minotti AP, Zorina Y, et al. Combined small-molecule treatment accelerates maturation of human pluripotent stem cell-derived neurons. *Nat Biotechnol*. 2024;42(10):1515-1525. https://doi.org/10.1038/s41587-023-02031-z.

11 de Rus JA, Layé S, Calon F. How nutrients and natural products act on the brain: beyond pharmacology. *Cell Rep Med*. 2023;4(10):101243. https://doi.org/10.1016/j.xcrm.2023.101243.

12 Chang S, Ruan WC, Xu YZ, et al. The natural product 4,10-aromadendranediol induces neuritogenesis in neuronal cells *in vitro* through activation of the ERK pathway. *Acta Pharmacol Sin*. 2017;38(1):29-40. https://doi.org/10.1038/aps.2016.115.

13 Guo JD, Zhao X, Li Y, et al. Damage to dopaminergic neurons by oxidative stress in Parkinson's disease (Review). *Int J Mol Med*. 2018;41(4):1817-1825. https://doi.org/10.3892/ijmm.2018.3406.

14 Kierdorf K, Wang Y, Neumann H. Immune-mediated CNS damage. *Results Probl Cell Differ*. 2010;51:173-196. https://doi.org/10.1007/400.

15 Sweeney MD, Zhao Z, Montagne A, et al. Blood-brain barrier: from physiology to disease and back. *Physiol Rev*. 2019;99(1):21-78. https://doi.org/10.1152/physrev.00050.2017.

16 Zheng X, Ren B, Gao Y. Tight junction proteins related to blood-brain barrier and their regulatory signaling pathways in ischemic stroke. *Biomed Pharmacother*. 2023;165:115272. https://doi.org/10.1016/j.biopha.2023.115272.

17 Shen Z, Xiang M, Chen C, et al. Glutamate excitotoxicity: potential therapeutic target for ischemic stroke. *Biomed Pharmacother*. 2022;151:113125. https://doi.org/10.1016/j.biopha.2022.113125.

18 Wang J, Tan S, Zhang Y, et al. Set7/9 aggravates ischemic brain injury *via* enhancing glutamine metabolism in a blocking Sirt5 manner. *Cell Death Differ*. 2024;31(4):511-523. https://doi.org/10.1038/s41418-024-01264-y.

19 Smith HL, Chaytow H, Gillingwater TH. Excitotoxicity and ALS: new therapy targets an old mechanism. *Cell Rep Med*. 2024;5(2):101423. https://doi.org/10.1016/j.xcrm.2024.101423.

20 Zhang LN, Wang Q, Xian XH, et al. Astrocytes enhance the tolerance of rat cortical neurons to glutamate excitotoxicity. *Mol Med Rep*. 2019;19(3):1521-1528. https://doi.org/10.3892/mmr.2018.9799.

21 Qin C, Yang S, Chu YH, et al. Signaling pathways involved in ischemic stroke: molecular mechanisms and therapeutic interventions. *Signal Transduction Targeted Ther*. 2022;7(1):215. https://doi.org/10.1038/s41392-022-01064-1.

22 Chamorro Á, Dirnagl U, Urra X, et al. Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. *Lancet Neurol*. 2016;15(8):869-881. https://doi.org/10.1016/S1474-4422(16)00114-9.

23 Meng W, Ma Z, Ye H, et al. Polyphenolic oligomer-derived multienzyme activity for the treatment of ischemic stroke through ROS scavenging and blood-brain barrier restoration. *J Mater Chem B*. 2024;12(8):2123-2138. https://doi.org/10.1039/d3tb02676k.

24 Sivandzade F, Prasad S, Bhalerao A, et al. NRF2 and NF-*κ*B interplay in cerebrovascular and neurodegenerative disorders: molecular mechanisms and possible therapeutic approaches. *Redox Biol*. 2019;21:101059. https://doi.org/10.1016/j.redox.2018.11.017.

25 Wang Y, Guan X, Gao CL, et al. Medioresinol as a novel PGC-1α activator prevents pyroptosis of endothelial cells in ischemic stroke through PPARα-GOT1 axis. *Pharmacol Res*. 2021;169:105640. https://doi.org/10.1016/j.phrs.2021.105640.

26 Yang JL, Mukda S, Chen SD. Diverse roles of mitochondria in ischemic stroke. *Redox Biol*. 2018;16:263-275. https://doi.org/10.1016/j.redox.2018.03.002.

27 Levard D, Buendia I, Lanquetin A, et al. Filling the gaps on stroke research: focus on inflammation and immunity. *Brain Behav Immun*. 2021;91:649-667. https://doi.org/10.1016/j.bbi.2020.09.025.

28 Wang L, Bai Y, Tao Y, et al. Bear bile powder alleviates Parkinson's disease-like behavior in mice by inhibiting astrocyte-mediated neuroinflammation. *Chin J Nat Med*. 2023;21(9):710-720. https://doi.org/10.1016/S1875-5364(23)60449-2.

29 Li YF, Ren LN, Guo G, et al. Endothelial progenitor cells in ischemic stroke: an exploration from hypothesis to therapy. *J Hematol Oncol*. 2015;8:33. https://doi.org/10.1186/s13045-015-0130-8.

30 García-Culebras A, Durán-Laforet V, Peña-Martínez C, et al. Myeloid cells as therapeutic targets in neuroinflammation after stroke: specific roles of neutrophils and neutrophil-platelet interactions. *J Cereb Blood Flow Metab*. 2018;38(12):2150-2164. https://doi.org/10.1177/0271678X18795789.

31 Parada E, Casas AI, Palomino-Antolin A, et al. Early toll-like receptor 4 blockade reduces ROS and inflammation triggered by microglial pro-inflammatory phenotype in rodent and human brain ischaemia models. *Br J Pharmacol*. 2019;176(15):2764-2779. https://doi.org/10.1111/bph.14703.

32 Guan X, Zhu S, Song J, et al. Microglial CMPK2 promotes neuroinflammation and brain injury after ischemic stroke. *Cell Rep Med*. 2024;5(5):101522. https://doi.org/10.1016/j.xcrm.2024.101522.

33 Endres M, Moro MA, Nolte CH, et al. Immune pathways in etiology, acute phase, and chronic sequelae of ischemic stroke. *Circ Res*. 2022;130(8):1167-1186. https://doi.org/10.1161/CIRCRESAHA.121.319994.

34 Iadecola C, Buckwalter MS, Anrather J. Immune responses to stroke: mechanisms, modulation, and therapeutic potential. *J Clin Invest*. 2020;130(6):2777-2788. https://doi.org/10.1172/JCI135530.

35 Blank-Stein N, Mass E. Macrophage and monocyte subsets in response to ischemic stroke. *Eur J Immunol*. 2023;53(10):e2250233. https://doi.org/10.1002/eji.202250233.

36 Machhi J, Kevadiya BD, Muhammad IK, et al. Harnessing regulatory T cell neuroprotective activities for treatment of neurodegenerative disorders. *Mol Neurodegener*. 2020;15(1):32. https://doi.org/10.1186/s13024-020-00375-7.

37 Liesz A, Zhou W, Mracskó É, et al. Inhibition of lymphocyte trafficking shields the brain against deleterious neuroinflammation after stroke. *Brain*. 2011;134(Pt 3):704-720. https://doi.org/10.1093/brain/awr008.

38 Lei TY, Ye YZ, Zhu XQ, et al. The immune response of T cells and therapeutic targets related to regulating the levels of T helper cells after ischaemic stroke. *J Neuroinflamm*. 2021;18(1):25. https://doi.org/10.1186/s12974-020-02057-z.

39 Zhou K, Zhong Q, Wang YC, et al. Regulatory T cells ameliorate intracerebral hemorrhage-induced inflammatory injury by modulating microglia/macrophage polarization through the IL-10/GSK3β/PTEN axis. *J Cereb Blood Flow Metab*. 2017;37(3):967-979. https://doi.org/10.1177/0271678X16648712.

40 Engelhardt B, Vajkoczy P, Weller RO. The movers and shapers in immune privilege of the CNS. *Nat Immunol*. 2017;18(2):123-131. https://doi.org/10.1038/ni.3666.

41 Korn T, Kallies A. T cell responses in the central nervous system. *Nat Rev Immunol*. 2017;17(3):179-194. https://doi.org/10.1038/nri.2016.144.

42 Saini V, Guada L, Yavagal DR. Global epidemiology of stroke and access to acute ischemic stroke interventions. *Neurology*. 2021;97(20 Supplement 2):S6-S16. https://doi.org/10.1212/WNL.0000000000012781.

43 Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet*. 2016;387(10029):1723-1731. https://doi.org/10.1016/S0140-6736(16)00163-X.

44 Luo Z, Yin F, Wang X, et al. Progress in approved drugs from natural product resources. *Chin J Nat Med*. 2024;22(3):195-211. https://doi.org/10.1016/S1875-5364(24)60582-0.

45 Jiang M, Wang XY, Zhou WY, et al. Cerebral protection of salvianolic acid A by the inhibition of granulocyte adherence. *Am J Chin Med*. 2011;39(1):111-120. https://doi.org/10.1142/S0192415X11008683.

46 Wei X, He Y, Wan H, et al. Integrated transcriptomics, proteomics and metabolomics to identify biomarkers of astragaloside IV against cerebral ischemic injury in rats. *Food Funct*. 2023;14(8):3588-3599. https://doi.org/10.1039/D2FO03030F.

47 Li Y, Zhang M, Li S, et al. Selective ischemic-hemisphere targeting ginkgolide B liposomes with improved solubility and therapeutic efficacy for cerebral ischemia-reperfusion injury. *Asian J Pharm Sci*. 2023;18(2):100783. https://doi.org/10.1016/j.ajps.2023.100783.

48 Zhou J, Fan Q, Cai X, et al. *Ginkgo biloba* extract protects against depression-like behavior in mice through regulating gut microbial bile acid metabolism. *Chin J Nat Med*. 2023;21(10):745-758. https://doi.org/10.1016/S1875-5364(23)60496-0.

49 Liu X, Zhang X, Wang F, et al. Improvement in cerebral ischemia–reperfusion injury through the TLR4/NF-*κ*B pathway after Kudiezi Injection in rats. *Life Sci*. 2017;191:132-140. https://doi.org/10.1016/j.lfs.2017.10.035.

50 Zhang T, Wu X, Cao S, et al. Efficacy of the oriental herbal medicine, Jie Yu Dan, for alleviating post-stroke aphasia: a systematic review and meta-analysis of randomized clinical trials. *Eur J Integr Med*. 2018;24:35-48. https://doi.org/10.1016/j.eujim.2018.10.012.

51 Chua KK, Wong A, Kwan PW, et al. The efficacy and safety of the Chinese herbal medicine Di-Tan Decoction for treating Alzheimer's disease: protocol for a randomized controlled trial. *Trials*. 2015;16:199. https://doi.org/10.1186/s13063-015-0716-z.

52 Xu A, Wen ZH, Su SX, et al. Elucidating the synergistic effect of multiple Chinese herbal prescriptions in the treatment of post-stroke neurological damage. *Front Pharmacol*. 2022;13:784242. https://doi.org/10.3389/fphar.2022.784242.

53 Ren L, Luo L, Hu Z, et al. Functional characterization of CYP81C16 involved in the tanshinone biosynthetic pathway in *Salvia miltiorrhiza*. *Chin J Nat Med*. 2023;21(12):938-949. https://doi.org/10.1016/S1875-5364(23)60484-4.

54 Fricker M, Tolkovsky AM, Borutaite V, et al. Neuronal cell death. *Physiol Rev*. 2018;98(2):813-880. https://doi.org/10.1152/physrev.00011.2017.

55 Li X, Liu Z, Liao J, et al. Network pharmacology approaches for research of traditional Chinese medicines. *Chin J Nat Med*. 2023;21(5):323-332. https://doi.org/10.1016/S1875-5364(23)60429-7.

56 Wang F, Qian H, Kong L, et al. Accelerated bone regeneration by astragaloside IV through stimulating the coupling of osteogenesis and angiogenesis. *Int J Biol Sci*. 2021;17(7):1821-1836. https://doi.org/10.7150

/ijbs.57681.

57 Longo V, Barbati SA, Re A, et al. Transcranial direct current stimulation enhances neuroplasticity and accelerates motor recovery in a stroke mouse model. *Stroke*. 2022;53(5):1746-1758. https://doi.org/10.1161/STROKEAHA.121.034200.

58 Ni GX, Liang C, Wang J, et al. Astragaloside IV improves neurobehavior and promotes hippocampal neurogenesis in MCAO rats though BDNF-TrkB signaling pathway. *Biomed Pharmacother*. 2020;130:110353. https://doi.org/10.1016/j.biopha.2020.110353.

59 Cai H, Ma Y, Jiang L, et al. Hypoxia response element-regulated MMP-9 promotes neurological recovery *via* glial scar degradation and angiogenesis in delayed stroke. *Mol Ther*. 2017;25(6):1448-1459. https://doi.org/10.1016/j.ymthe.2017.03.020.

60 Zhang M, Zhu R, Zhang L. Triclosan stimulates human vascular endothelial cell injury *via* repression of the PI3K/Akt/mTOR axis. *Chemosphere*. 2020;241:125077. https://doi.org/10.1016/j.chemosphere.2019.125077.

61 Shi G, Chen J, Zhang C, et al. Astragaloside IV promotes cerebral angiogenesis and neurological recovery after focal ischemic stroke in mice *via* activating PI3K/Akt/mTOR signaling pathway. *Heliyon*. 2023;9(12):e22800. https://doi.org/10.1016/j.heliyon.2023.e22800.

62 Nederlof R, Eerbeek O, Hollmann MW, et al. Targeting hexokinase II to mitochondria to modulate energy metabolism and reduce ischaemia-reperfusion injury in heart. *Br J Pharmacol*. 2014;171(8):2067-2079. https://doi.org/10.1111/bph.12363.

63 Li Y, Yang Y, Zhao Y, et al. Astragaloside IV reduces neuronal apoptosis and parthanatos in ischemic injury by preserving mitochondrial hexokinase-II. *Free Radic Biol Med*. 2019;131:251-263. https://doi.org/10.1016/j.freeradbiomed.2018.11.033.

64 Qi M, Su X, Li Z, et al. Bibliometric analysis of research progress on tetramethylpyrazine and its effects on ischemia-reperfusion injury. *Pharmacol Ther*. 2024;259:108656. https://doi.org/10.1016/j.pharmthera.2024.108656.

65 Chang CY, Wu CC, Pan PH, et al. Tetramethylpyrazine alleviates mitochondrial abnormality in models of cerebral ischemia and oxygen/glucose deprivation reoxygenation. *Exp Neurol*. 2023;367:114468. https://doi.org/10.1016/j.expneurol.2023.114468.

66 Feng XF, Li MC, Lin ZY, et al. Tetramethylpyrazine promotes stroke recovery by inducing the restoration of neurovascular unit and transformation of A1/A2 reactive astrocytes. *Front Cell Neurosci*. 2023;17:1125412. https://doi.org/10.3389/fncel.2023.1125412.

67 Jin Z, Liang J, Kolattukudy PE. Tetramethylpyrazine preserves the integrity of blood-brain barrier associated with upregulation of MCPIP1 in a murine model of focal ischemic stroke. *Front Pharmacol*. 2021;12:710358. https://doi.org/10.3389/fphar.2021.710358.

68 Marco-Contelles J. Recent advances on nitrones design for stroke treatment. *J Med Chem*. 2020;63(22):13413-13427. https://doi.org/10.1021/acs.jmedchem.0c00976.

69 Nie L, He K, Qiu C, et al. Tetramethylpyrazine nitrone alleviates D-galactose-induced murine skeletal muscle aging and motor deficits by activating the AMPK signaling pathway. *Biomed Pharmacother*. 2024;173:116415. https://doi.org/10.1016/j.biopha.2024.116415.

70 Guo B, Zheng C, Cao J, et al. Tetramethylpyrazine nitrone exerts neuroprotection *via* activation of PGC-1α/Nrf2 pathway in Parkinson's disease models. *J Adv Res*. 2024;64:195. https://doi.org/10.1016/j.jare.2023.11.021.

71 Li S, Tian Z, Xian X, et al. Catalpol rescues cognitive deficits by attenuating amyloid β plaques and neuroinflammation. *Biomed Pharmacother*. 2023;165:115026. https://doi.org/10.1016/j.biopha.2023.115026.

72 Wiciński M, Górski K, Walczak M, et al. Neuroprotective properties of linagliptin: focus on biochemical mechanisms in cerebral ischemia, vascular dysfunction and certain neurodegenerative diseases. *Int J Mol Sci*. 2019;20(16):4052. https://doi.org/10.3390/ijms20164052.

73 Zhang MF, Wang JH, Sun S, et al. Catalpol attenuates ischemic stroke by promoting neurogenesis and angiogenesis *via* the SDF-1α/CXCR4 pathway. *Phytomedicine*. 2024;128:155362. https://doi.org/10.1016/j.phymed.2024.155362.

74 Zhu HF, Shao Y, Qin L, et al. Catalpol enhances neurogenesis and inhibits apoptosis of new neurons *via* BDNF, but not the BDNF/Trkb pathway. *Drug Des Devel Ther*. 2019;13:4145-4157. https://doi.org/10.2147/DDDT.S223322.

75 Chen H, He Y, Chen S, et al. Therapeutic targets of oxidative/nitrosative stress and neuroinflammation in ischemic stroke: applications for natural product efficacy with omics and systemic biology. *Pharmacol Res*. 2020;158:104877. https://doi.org/10.1016/j.phrs.2020.104877.

76 Chouchani ET, Pell VR, Gaude E, et al. Ischaemic accumulation of succinate controls reperfusion injury through mitochondrial ROS. *Nature*. 2014;515(7527):431-435. https://doi.org/10.1038/nature13909.

77 Huang G, Zang J, He L, et al. Bioactive nanoenzyme reverses oxidative damage and endoplasmic reticulum stress in neurons under ischemic stroke. *ACS Nano*. 2022;16(1):431-452. https://doi.org/10.1021/acsnano.1c07205.

78 Zhao H, Li C, Li L. Baicalin alleviates bleomycin-induced pulmonary fibrosis and fibroblast proliferation in rats *via* the PI3K/AKT signaling pathway. *Mol Med Rep*. 2020;21(6):2321-2334. https://doi.org/10.3892/mmr.2020.11046.

79 Huang Q, Wang M, Wang M, et al. *Scutellaria baicalensis*: a promising natural source of antiviral compounds for the treatment of viral diseases. *Chin J Nat Med*. 2023;21(8):563-575. https://doi.org/10.1016/S1875-5364(23)60401-7.

80 Wei Z, Gao R, Sun Z, et al. Baicalin inhibits influenza A (H1N1)-induced pyroptosis of lung alveolar epithelial cells *via* caspase-3/GSDME pathway. *J Med Virol*. 2023;95(5):e28790. https://doi.org/10.1002/jmv.28790.

81 Wang Z, Ma L, Su M, et al. Baicalin induces cellular senescence in human colon cancer cells *via* upregulation of DEPP and the activation of Ras/Raf/MEK/ERK signaling. *Cell Death Dis*. 2018;9(2):217. https://doi.org/10.1038/s41419-017-0223-0.

82 Long Y, Liu S, Wan J, et al. Brain targeted borneol-baicalin liposome improves blood-brain barrier integrity after cerebral ischemia-reperfusion injury *via* inhibiting HIF-1α/VEGF/eNOS/NO signal pathway. *Biomed Pharmacother*. 2023;160:114240. https://doi.org/10.1016/j.biopha.2023.114240.

83 Song X, Gong Z, Liu K, et al. Baicalin combats glutamate excitotoxicity *via* protecting glutamine synthetase from ROS-induced 20S proteasomal degradation. *Redox Biol*. 2020;34:101559. https://doi.org/10.1016/j.redox.2020.101559.

84 Liu K, Zhou Y, Song X, et al. Baicalin attenuates neuronal damage associated with SDH activation and PDK2-PDH axis dysfunction in early reperfusion. *Phytomedicine*. 2024;129:155570. https://doi.org/10.1016/j.phymed.2024.155570.

85 Fontana AC. Current approaches to enhance glutamate transporter function and expression. *J Neurochem*. 2015;134(6):982-1007. https://doi.org/10.1111/jnc.13200.

86 Zhou ZQ, Li YL, Ao ZB, et al. Baicalin protects neonatal rat brains against hypoxic-ischemic injury by upregulating glutamate transporter 1 *via* the phosphoinositide 3-kinase/protein kinase B signaling pathway. *Neural Regen Res*. 2017;12(10):1625-1631. https://doi.org/10.4103/1673-5374.217335.

87 George M, Tharakan M, Culberson J, et al. Role of Nrf2 in aging, Alzheimer's and other neurodegenerative diseases. *Ageing Res Rev*. 2022;82:101756. https://doi.org/10.1016/j.arr.2022.101756.

88 Wang X, Yu JY, Sun Y, et al. Baicalin protects LPS-induced blood-brain barrier damage and activates Nrf2-mediated antioxidant stress pathway. *Int Immunopharmacol*. 2021;96:107725. https://doi.org/10.1016/j.intimp.2021.107725.

89 Liu M, Guo J, Zhao J, et al. Activation of NRF2 by celastrol increases antioxidant functions and prevents the progression of osteoarthritis in mice. *Chin J Nat Med*. 2024;22(2):137-145. https://doi.org/10.1016/S1875-5364(24)60586-8.

90 Hong Z, Cao J, Liu D, et al. Celastrol targeting Nedd4 reduces Nrf2-mediated oxidative stress in astrocytes after ischemic stroke. *J Pharm Anal*. 2023;13(2):156-169. https://doi.org/10.1016/j.jpha.2022.12.002.

91 Li X, Liu W, Jiang G, et al. Celastrol ameliorates neuronal mitochondrial dysfunction induced by intracerebral hemorrhage *via* targeting cAMP-activated exchange protein-1. *Adv Sci (Weinh)*. 2024;11(19):e2307556. https://doi.org/10.1002/advs.202307556.

92 Wang W, Jiang S, Zhao Y, et al. Echinacoside: a promising active natural products and pharmacological agents. *Pharmacol Res*. 2023;197:106951. https://doi.org/10.1016/j.phrs.2023.106951.

93 Guan R, Zou W, Dai X, et al. Mitophagy, a potential therapeutic target for stroke. *J Biomed Sci*. 2018;25(1):87. https://doi.org/10.1186/s12929-018-0487-4.

94 Youle RJ, van der Bliek AM. Mitochondrial fission, fusion, and stress. *Science*. 2012;337(6098):1062-1065. https://doi.org/10.1126/science.1219855.

95 Zeng KW, Wang JK, Wang LC, et al. Small molecule induces mitochondrial fusion for neuroprotection *via* targeting CK2 without affecting its conventional kinase activity. *Signal Transduct Target Ther*. 2021;6(1):71. https://doi.org/10.1038/s41392-020-00447-6.

96 Gao C, Xu Y, Liang Z, et al. A novel PGAM5 inhibitor LFHP-1c protects blood-brain barrier integrity in ischemic stroke. *Acta Pharm Sin B*. 2021;11(7):1867-1884. https://doi.org/10.1016/j.apsb.2021.01.008.

97 Li S, Fan G, Li X, et al. Modulation of type I interferon signaling by natural products in the treatment of immune-related diseases. *Chin J Nat Med*. 2023;21(1):3-18. https://doi.org/10.1016/S1875-5364(23)60381-4.

98 Ling Y, Jin L, Ma Q, et al. Salvianolic acid A alleviated inflammatory response mediated by microglia through inhibiting the activation of TLR2/4 in acute cerebral ischemia-reperfusion. *Phytomedicine*. 2021;87:153569. https://doi.org/10.1016/j.phymed.2021.153569.

99 Yang R, Hu N, Liu TY, et al. Salvianolic acid A provides neuroprotective effects on cerebral ischemia-reperfusion injury in rats *via* PKA/CREB/c-Fos signaling pathway. *Phytomedicine*. 2024;124:155326. https://doi.org/10.1016/j.phymed.2023.155326.

100 Shi Y, Yan D, Nan C, et al. Salvianolic acid A inhibits ferroptosis and protects against intracerebral hemorrhage. *Sci Rep*. 2024;14(1):12427. https://doi.org/10.1038/s41598-024-63277-4.

101 Zhu H, Jian Z, Zhong Y, et al. Janus kinase inhibition ameliorates ischemic stroke injury and neuroinflammation through reducing NLRP3 inflammasome activation *via* JAK2/STAT3 pathway inhibition. *Front Immunol*. 2021;12:714943. https://doi.org/10.3389/fimmu.2021.714943.

102 Jin W, Zhao J, Yang E, et al. Neuronal STAT3/HIF-1α/PTRF axis-mediated bioenergetic disturbance exacerbates cerebral ischemia-reperfusion injury *via* PLA2G4A. *Theranostics*. 2022;12(7):3196-3216. https://doi.org/10.7150/thno.71029.

103 Qiu J, Yan Z, Tao K, et al. Sinomenine activates astrocytic dopamine D2 receptors and alleviates neuroinflammatory injury *via* the CRYAB/STAT3 pathway after ischemic stroke in mice. *J Neuroinflammation*. 2016;13(1):263. https://doi.org/10.1186/s12974-016-0739-8.

104 Cherninskyi A, Storozhuk M, Maximyuk O, et al. Triggering of major brain disorders by protons and ATP: the role of ASICs and P2X receptors. *Neurosci Bull*. 2023;39(5):845-862. https://doi.org/10.1007/s12264-022-00986-8.

105 Wu WN, Wu PF, Chen XL, et al. Sinomenine protects against ischaemic brain injury: involvement of co-inhibition of acid-sensing ion channel 1a and L-type calcium channels. *Br J Pharmacol*. 2011;164(5):1445-1459. https://doi.org/10.1111/j.1476-5381.2011.01487.x.

106 Wang S, Lei P, Feng Y, et al. Jinyinqingre Oral Liquid alleviates LPS-induced acute lung injury by inhibiting the NF-κB/NLRP3/GSDMD pathway. *Chin J Nat Med*. 2023;21(6):423-435. https://doi.org/10.1016/S1875-5364(23)60397-8.

107 Qiu J, Wang M, Zhang J, et al. The neuroprotection of sinomenine against ischemic stroke in mice by suppressing NLRP3 inflammasome *via* AMPK signaling. *Int Immunopharmacol*. 2016;40:492-500. https://doi.org/10.1016/j.intimp.2016.09.024.

108 Wu Y, Du J, Wu Q, et al. The osteogenesis of ginsenoside Rb1 incorporated silk/micro-nano hydroxyapatite/sodium alginate composite scaffolds for calvarial defect. *Int J Oral Sci*. 2022;14(1):10. https://doi.org/10.1038/s41368-022-00157-5.

109 Ni XC, Wang HF, Cai YY, et al. Ginsenoside Rb1 inhibits astrocyte activation and promotes transfer of astrocytic mitochondria to neurons against ischemic stroke. *Redox Biol*. 2022;54:102363. https://doi.org/10.1016/j.redox.2022.102363.

110 Alim I, Caulfield JT, Chen Y, et al. Selenium drives a transcriptional adaptive program to block ferroptosis and treat stroke. *Cell*. 2019;177(5):1262-1279.e25. https://doi.org/10.1016/j.cell.2019.03.032.

111 Zhang M, Lin W, Tao X, et al. Ginsenoside Rb1 inhibits ferroptosis to ameliorate hypoxic-ischemic brain damage in neonatal rats. *Int Immunopharmacol*. 2023;121:110503. https://doi.org/10.1016/j.intimp.2023.110503.

112 Liu T, Wang W, Li X, et al. Advances of phytotherapy in ischemic stroke targeting PI3K/Akt signaling. *Phytother Res*. 2023;37(12):5509-5528. https://doi.org/10.1002/ptr.7994.

113 Liu J, He J, Huang L, et al. Neuroprotective effects of ginsenoside Rb1 on hippocampal neuronal injury and neurite outgrowth. *Neural Regen Res*. 2014;9(9):943-950. https://doi.org/10.4103/1673-5374.133137.

114 Tang YC, Tian HX, Yi T, et al. The critical roles of mitophagy in cerebral ischemia. *Protein Cell*. 2016;7(10):699-713. https://doi.org/10.1007/s13238-016-0307-0.

115 Li Y, Li J, Yang L, et al. Ginsenoside Rb1 protects hippocampal neurons in depressed rats based on mitophagy-regulated astrocytic pyroptosis. *Phytomedicine*. 2023;121:155083. https://doi.org/10.1016/j.phymed.2023.155083.

116 Hui W, Huang W, Zheng Z, et al. *Ginkgo biloba* extract promotes Treg differentiation to ameliorate ischemic stroke *via* inhibition of HIF-1α/HK2 pathway. *Phytother Res*. 2023;37(12):5821-5836. https://doi.org/10.1002/ptr.7988.

117 Zhao H, Guo Q, Li B, et al. The efficacy and safety of ginkgo terpene lactone preparations in the treatment of ischemic stroke: a systematic review and meta-analysis of randomized clinical trials. *Front Pharmacol*. 2022;13:821937. https://doi.org/10.3389/fphar.2022.821937.

118 Cao Y, Yang L, Cheng H. Ginkgolide B protects against ischemic stroke *via* targeting AMPK/PINK1. *Front Pharmacol*. 2022;13:941094. https://doi.org/10.3389/fphar.2022.941094.

119 Zhou B, Liu J, Kang R, et al. Ferroptosis is a type of autophagy-dependent cell death. *Semin Cancer Biol*. 2020;66:89-100. https://doi.org/10.1016/j.semcancer.2019.03.002.

120 Yang Y, Wu Q, Shan X, et al. Ginkgolide B attenuates cerebral ischemia-reperfusion injury *via* inhibition of ferroptosis through disrupting NCOA4-FTH1 interaction. *J Ethnopharmacol*. 2024;318(Pt B):116982. https://doi.org/10.1016/j.jep.2023.116982.

121 Shu ZM, Shu XD, Li HQ, et al. Ginkgolide B protects against ischemic stroke *via* modulating microglia polarization in mice. *CNS Neurosci Ther*. 2016;22(9):729-739. https://doi.org/10.1111/cns.12577.

122 Wang H, Xu X, Guan X, et al. Liposomal 9-aminoacridine for treatment of ischemic stroke: from drug discovery to drug delivery. *Nano Lett*. 2020;20(3):1542-1551. https://doi.org/10.1021/acs.nanolett.9b04018.

123 Luo W, Deng J, He J. Integration of molecular docking, molecular dynamics and network pharmacology to explore the multi-target pharmacology of fenugreek against diabetes. *J Cell Mol Med*. 2023;27(14):1959-1974. https://doi.org/10.1111/jcmm.17787.

124 Zheng P, Zhang N, Ren D, et al. Integrated spatial transcriptome and metabolism study reveals metabolic heterogeneity in human injured brain. *Cell Rep Med*. 2023;4(6):101057. https://doi.org/10.1016/j.xcrm.2023.101057.

125 Zhang C, Wu J, Zhang Y, et al. Click chemistry and natural products. *Chin J Nat Med*. 2024;22(2):97-99. https://doi.org/10.1016/S1875-5364(24)60557-1.

126 Gao CL, Hou GG, Liu J, et al. Synthesis and target identification of benzoxepane derivatives as potential anti-neuroinflammatory agents for ischemic stroke. *Angew Chem Int Ed*. 2020;59(6):2429-2439. https://doi.org/10.1002/anie.201912489.

127 Duan Y, Du W, Song Z, et al. Functional characterization of a cycloartenol synthase and four glycosyltransferases in the biosynthesis of cycloastragenol-type astragalosides from *Astragalus membranaceus*. *Acta Pharm Sin B*. 2023;13(1):271-283. https://doi.org/10.1016/j.apsb.2022.05.015.