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# The mechanism of microglia-mediated immune inflammation in ischemic stroke and the role of natural botanical components in regulating microglia: A review

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Ischemic stroke (IS) is one of the most fatal diseases. Neuroimmunity, inflammation, and oxidative stress play important roles in various complex mechanisms of IS. In particular, the early proinflammatory response resulting from the overactivation of resident microglia and the infiltration of circulating monocytes and macrophages in the brain after cerebral ischemia leads to secondary brain injury. Microglia are innate immune cells in the brain that constantly monitor the brain microenvironment under normal conditions. Once ischemia occurs, microglia are activated to produce dual effects of neurotoxicity and neuroprotection, and the balance of the two effects determines the fate of damaged neurons. The activation of microglia is defined as the classical activation (M1 type) or alternative activation (M2 type). M1 type microglia secrete pro-inflammatory cytokines and neurotoxic mediators to exacerbate neuronal damage, while M2 type microglia promote a repairing anti-inflammatory response. Fine regulation of M1/M2 microglial activation to minimize damage and maximize protection has important therapeutic value. This review focuses on the interaction between M1/M2 microglia and other immune cells involved in the regulation of IS phenotypic characteristics, and the mechanism of natural plant components regulating microglia after IS, providing novel candidate drugs for regulating microglial balance and IS drug development.

## KEYWORDS

ischemic stroke, microglia/macrophages, neuroimmune inflammation, natural botanical components, botanicals

# 1 Introduction

Ischemic stroke (IS) is one of the common cerebrovascular diseases, which seriously affects national health due to its high morbidity and lethality (1). It is characterized by the pathological changes of the cerebral arteries or the carotid arteries that innervate the brain, causing cerebral blood circulation disorders, which in turn lead to acute or subacute brain damage. It often causes patients to have varying degrees of language, motor and sensory dysfunction (2). Among them, focal rapid-onset cerebral ischemia-hypoxia (or hemispherical in the case of coma) persists for more than 24 hours or results in death (3). IS constitutes 87% of strokes, including cryptogenic, lacunar and thromboembolic strokes (4). The risk factors for IS include age, smoking, diabetes, high blood pressure and obesity (5). The pathological mechanism is that ischemia and hypoxia in the brain can lead to a series of events including calcium overload, excitatory amino acid neurotoxicity, free radical generation, activation of apoptotic genes, and immune inflammation (6). In fact, recent studies have found that the inflammatory response plays a dual key role in neuroprotection and neurotoxicity in IS (6). Activation of resident cells, such as microglia, astrocytes and endothelial cells promotes both brain regeneration and recovery. It also recruits immune cells that express inflammatory mediators, leading to blood-brain barrier (BBB) disruption, neuronal death, brain edema, and hemorrhagic transformation (6). In this case, clinical treatment options for acute ischemic stroke remain limited. Intravenous injection of tissue-type plasminogen activator (t-PA) restores cerebral perfusion through thrombolysis, which to a certain extent rescues dying cells in the ischemic penumbra (7). However, the treatment time window of 3-4.5 hours is too narrow for practical use of thrombolytics in most parts of the world. Once the therapeutic window is exceeded, the benefits of t-PA are outweighed by its risks, with a dramatic increase in the chance of hemorrhagic transformation (8). Meanwhile, the choice of medical devices for intra-arterial thrombectomy can be used as an alternative to clinical thrombolysis, but it may also cause other complications, so it has great limitations (9). The current study shows that the regulation of immune cells after stroke is the key to regulating inflammation and repairing vascular neural units after stroke (10). As the main body of neuroimmune inflammation in the brain after stroke, microglia play functions such as immune recruitment, regulation, inflammation, phagocytosis, and vascular repair, which in turn become the key to the development of stroke drugs (11). This review focuses on the interaction between classical activation (M1 type) or alternative activation (M2 type) microglia and other immune cells involved in the regulation of IS phenotypic characteristics. Meanwhile, Our previous studies have found that natural compounds and multi-component herbs may treat IS by regulating microglia (12-16); other teams also explored the

mechanism by which natural plant active ingredients regulate microglia after IS (17). Therefore, this review also summarizes the natural plant compounds that regulate M1/M2 microglia after IS, in order to provide candidate or lead compounds for the development of drugs that regulate neuroimmune inflammation after IS.

## 2 Pathological mechanisms of immune inflammation in IS

### 2.1 Pathological mechanism of IS

Following an ischemic attack, a series of events involving the central nervous system (CNS) is triggered (18). The pathogenesis of IS begins in the blood vessels, in part due to arterial occlusion leading to hypoxia, reactive oxidative species production, and changes in shear stress on the luminal wall (19, 20). During hypoxia, shear stress on the vascular endothelium due to changes in rheology and blood flow stagnation causes activation of platelets, the complement system and the coagulation cascade, resulting in endothelial cell destruction and microvascular occlusion (21). The combined effect of oxidative stress, inflammatory mediators (such as IL-1 $\beta$ , TNF- $\alpha$ ), down-regulated endothelin, and up-regulated leukocyte- or vascular-derived proteases increases BBB permeability (22). Endothelial cell-derived prostaglandins and chemoattractants also promote leukocyte entry into the infarct site (22). The increased surface affinity of leukocytes, the activation of integrin molecules and the up-regulated expression of corresponding ligands on endothelial cells further promote the infiltration of neutrophils, macrophages and other leukocytes. Activated leukocytes produce reactive oxidative species, proteolytic enzymes, cytokines, platelet-activating factor, which promote vasoconstriction, platelet aggregation and further neurotoxicity (19). In the perivascular space, activated macrophages secrete numerous pro-inflammatory cytokines, leading to the release of histamine, proteases and TNF- $\alpha$ , and further reducing the integrity of the BBB (18).

While all of the above processes occur in the vascular and perivascular spaces, ischemia can also affect the brain parenchyma. Following the impact of ischemia, a series of interrelated cytoplasmic and nuclear events, including bioenergetic exhaustion, excitotoxicity, Ca<sup>2+</sup> overload, oxidative stress, and inflammatory responses, begin to occur at the damaged site, culminating in neuronal cell death (20). Excitotoxicity and Ca<sup>2+</sup> overload are the main factors leading to the early stage of ischemic cell death (23). Glutamate overload results in prolonged activation of AMPA and NMDA ionotropic receptor subtypes, resulting in an enhanced influx of calcium, sodium and water to neurons (23). A large influx of calcium activates protease, lipase and nuclease-mediated catabolic

processes (24). Increased calcium influx from glutamate receptor hyperactivation, Ca<sup>2+</sup> release from mitochondria, and failure of Ca<sup>2+</sup> efflux mechanisms are known to explain the irreversible accumulation of intracellular Ca<sup>2+</sup> following excitotoxic stimulation. Meanwhile, oxidative and nitrosative stress are also potent mediators of ischemic injury. Under normal physiological conditions, there is a balance between the production and decomposition of reactive oxygen species (ROS), but IS disrupts this balance and leads to an increase in its production (25). The metabolic activity of ROS and reactive nitrogen species is rapid, and the antioxidant defense capacity of the brain is limited, so the brain is sensitive to damage caused by oxidative and nitrosative stress (26). Damage-associated molecular patterns (DAMPs) released by dying neurons contribute to a new phase of the inflammatory response (27, 28). Among them, heat shock proteins, high mobility group-binding protein 1 (HMGB1), mitochondria-derived N-formyl peptides and peroxidases, activate brain-native immune cells through pattern recognition receptors (29–31). DAMPs lead to an inflammatory environment by stimulating immune cells to produce cytokines, chemokines, adhesion molecules and many immune effector molecules (32–34).

## 2.2 Key events and pathways of immune biological modules involved in the IS pathological progression

After the occurrence of IS, the immune system starts rapidly, participates in all aspects of the occurrence, development and prognosis of stroke, and plays a corresponding role in different stages of stroke (35). Intracerebral inflammation after IS is not limited to the surrounding ischemic foci, but spreads to the whole brain and persists for a long time, continuously affecting the pathophysiological changes of brain tissue after stroke (36). Therefore, understanding the changes and roles of immune responses in different stages of stroke has important guiding significance for further research on neuroprotection and neuroreparation in stroke. Previous studies have shown that in the early stage of IS, various inflammatory cells and factors are involved in the development of inflammation in the brain and aggravate secondary brain injury (21, 37). In the subacute phase, brain injury can remodel the immune system, turning immune system function from activation to suppression, but it leads to an increase in post-stroke infections (21, 38). Moreover, the spread of neuroinflammation in the whole brain after IS can lead to delayed brain tissue changes (39).

### 2.2.1 Immune activation after IS

After the occurrence of IS, with the occurrence of intravascular hypoxia and changes in hemodynamics, platelets, coagulation and complement systems are activated, and the inflammatory response first occurs in the blood vessels (40).

The oxidative stress response and activated complement system caused by hypoxia directly damage the local vascular system, leading to necrosis and dissociation of vascular endothelial cells, destruction of BBB integrity, and exposure of antigens under the vascular endothelium (41). Immune cells in the blood adhere to the vessel wall and upregulate the expression of adhesion factors and chemokines. Innate immune cells such as neutrophils, monocytes, and macrophages are activated, migrate to ischemic sites under the action of chemokines and extravasate into the extravascular space through the damaged BBB (42). Subsequently, macrophages in the ischemic brain tissue are activated to further release inflammatory factors and aggravate the chemotaxis and extravasation of innate immune cells (43). Meanwhile, immune cells such as neutrophils and mast cells at the site of ischemic injury release intracellular MMPs, destroy vascular basement membrane and tight junction proteins, accelerate the destruction of BBB, and lead to an increase in cerebral infarct size (44). Neurons are extremely sensitive to ischemia, hence, ischemia leads to rapid neuronal necrosis. Necrotic neurons release endogenous factors, called DAMPs. DAMPs increase the release of chemokines from immune cells through Toll-like receptors (TLRs) on the surface of immune cells such as microglia, macrophages, dendritic-like cells, and exuding neutrophils (45). This further promotes the chemotaxis of immune cells, activates and amplifies the innate immune response, accelerates vascular destruction and cell death, and ultimately forms a vicious cycle of vascular damage, inflammation, and neuronal death (46). The adaptive immune response is the second phase of the immune response after ischemic stroke, which arises from BBB disruption. Normally immune-isolated central nervous system antigens can contact antigen-presenting cells (APCs) in peripheral blood to induce autoimmune responses. DAMPs can promote the interaction between APCs and receptors to activate adaptive immune responses, which are mediated by effector T cells (47). Effector T cells play a role in the adaptive immune response by recruiting to ischemic areas, traversing the injured BBB, releasing inflammatory cytokines such as interferon gamma (IFN- $\gamma$ ) in the brain parenchyma, and ultimately leading to delayed neurotoxicity (39, 48). The immune response after IS is a self-limiting pathophysiological process that gradually subsides under the combined action of regulatory T cells and B cells, preparing for the structural and functional reconstruction of the later brain injury site. In the process of inflammation resolution, regulatory T cells play a role through IL-10 and transforming growth factor- $\beta$  (TGF- $\beta$ ) secreted by macrophages in the local tissues, inhibiting helper T cells to further induce inflammation, thereby promoting the repair of residual neurons (49, 50).

### 2.2.2 Immunosuppression after IS

After IS, while the immune system is activated, immunosuppression will occur at the same time. The systemic immune function is down-regulated within a few hours after

cerebral ischemia, the cellular immunity is suppressed, the number of various immune cells such as monocytes, T lymphocytes, B lymphocytes and natural killer cells is decreased, apoptosis is increased, or cell dysfunction occurs (51). Meanwhile, a variety of inflammatory factors, including IL-10, IL-1 $\beta$ , TNF- $\alpha$ , IL-6, etc. are inhibited. This immunosuppressive state is known as stroke-induced immunosuppressive syndrome (SIDS) (52). Its occurrence is related to the activation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system caused by stress, and the secretion of adrenocortical hormones and catecholamines increases and plays an immunosuppressive effect (53). Immune activation and immunosuppression after IS are a contradictory unity. The former removes necrotic tissue through inflammatory response to create conditions for nerve repair, and it can also cause secondary nerve damage due to an excessive inflammatory response. The latter can reduce the destruction of neurons by the immune system and play a neuroprotective role, but excessive immunosuppression inevitably increases the chance of infection and worsens clinical prognosis (54).

### 3 Mechanisms of microglia/macrophages in IS

#### 3.1 Physiological functions of microglia

Microglia account for approximately 10% of the CNS and are traditionally thought to function as immunocompetent cells of the brain and spinal cord, and undertake sensory functions of injury and infection in tissues (55). Microglia is derived from the primitive c-kit(+) erythroid precursor in the yolk sac, migrates into the brain during early embryonic development before the formation of the BBB, and remains there until the BBB is formed (56). Notably, this is a population of self-maintaining and renewing cells, and peripheral macrophages only contribute to this population in disease states, i.e. when the BBB is damaged (57). Initial studies generally believed that under normal physiological conditions, the microglia in the brain were branched with multiple slender protrusions and were in a resting state. However, recent studies have shown that the microglia never really rests, and the branched microglia constantly patrols the brain, using its motor branch as a sentinel to investigate and scan its nearby microenvironment to detect changes in brain homeostasis (58). Once a threat is identified, microglia rapidly activate to an amoeba-like phenotype with large cell bodies (59). Activated microglia can eliminate cellular debris through phagocytosis on the one hand, and produce a wide range of signaling molecules, including cytokines, neurotransmitters, and extracellular matrix proteins, to regulate neuronal and synaptic activity and their functional plasticity (58). Furthermore, when microglia are involved in the degradation of internalized targets in the phagosome, it may become a major

source of ROS. If these internalization targets are too large and not properly processed inside the phagosome, it will result in the release of toxic molecules, including ROS, from the surrounding microglia (60). The normal phagocytosis process is accompanied by the release of several anti-inflammatory cytokines, growth factors and neurotrophic factors, and reduced release of pro-inflammatory cytokines (61). As immune effector cells in the CNS, microglia are continuously active. They monitor the brain microenvironment in real time through the elongation and retraction of branches, modulate neural circuits through specific interactions with neuronal synapses (59, 62), participate in pruning synapses and clear apoptotic cells in time to maintain CNS homeostasis (63–65). They play an important role in most known CNS diseases. A study has monitored the interaction between neurons and fluorescently labeled microglia in transgenic mice by intravital two-photon microscopy imaging (66). They found that microglia made direct contact with neuronal synapses during imaging every 5 minutes for 1 hour. Microglia can rapidly change their phenotype in active response to perturbation of CNS homeostasis and are often activated based on changes in their morphology or cell surface antigen expression (67–69).

#### 3.2 Activation and differentiation of microglia/macrophages regulate immune inflammation

##### 3.2.1 Activation of microglia/macrophages after IS

M2-type microglia mainly regulate the repair of brain injury after IS. It mainly promotes the survival and recovery of injured neurons by secreting brain-derived neurotrophic factors, insulin secretion factors and transforming growth factors, and at the same time enhances the ability of neurons to withstand stimulation and damage (70, 71). It produces cytokines IL-10, TGF- $\beta$ , IL-4, IL-13, IGF-1, etc., which cooperate with the clearance of infiltrating neutrophils, thereby preventing neuronal damage caused by cytotoxic substances (72, 73). Unlike M2-type microglia, which inhibit inflammation, M1-type microglia will produce a large number of pro-inflammatory cytokines IFN- $\gamma$ , IL-1 $\beta$ , TNF- $\alpha$ , IL-6, etc. to activate the inflammatory cascade, and promote the activation of T and B lymphocytes to regulate immune responses. It can also increase the release of vasoactive factors, causing vasoconstriction and aggravating ischemic cerebral edema (74). M1 type acts on the extracellular matrix through the production of ROS and NO production as well as proteolytic enzymes (MMP9, MMP3), resulting in the decomposition of BBB (39, 75). M1 type also generates reactive oxygen species through nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which further aggravates the damage of cerebral ischemia (76, 77). Therefore,

regulating the homeostasis of M1/M2 type may become an important strategy for the treatment of IS.

### 3.2.2 Activation and differentiation of M1/M2 type microglia/macrophages

As the first line of defense of the immune system in the brain, microglia are rapidly activated within minutes of the acute phase of ischemic stroke, peak around day 2/3 of activation, and persist for several weeks after the onset of IS (78). At the core of ischemic injury, microglia activation is essentially triggered by excitotoxic signals generated during the ischemic cascade. In the peri-infarct region, the activation of microglia is associated with several innate immune receptors that can be activated by DAMP stimulation (79). For example, purinergic receptors, especially P2X7 and P2Y12, regulate microglial activation and mediate neurotoxicity, and similarly, pharmacological inhibition of P2X7 and P2Y12 reduces brain damage in experimental stroke models (80). Several other innate immune receptors involved in microglial activation include TLR, CD36 scavenger receptor, and receptor for advanced glycation end products (RAGE) (81). In addition to morphological changes, activated microglia also showed altered gene expression patterns, polarizing toward functionally distinct phenotypes: “classically activated” M1 and “alternatively activated” M2.

At present, the main signal pathways that contribute to the polarization of M1/M2 microglia are as follows: (1) IFN- $\gamma$  secreted by helper T cells 1 (Th1) induces the transformation of microglia into M1 phenotype by activating JAK1/JAK2 and STAT (82). (2) Another pathway to induce M1 activation is triggered by lipopolysaccharide (LPS) or DAMP stimulation of TLR4. Subsequently, an “activation complex” composed of myeloid differentiation factor 88 (Myd88), nuclear factor- $\kappa$ B (NF- $\kappa$ B), p65, p38 and interferon regulatory factor 3 (IRF3) is formed (83). This complex in turn regulates the expression of inflammatory mediators of M1-inducible nitric oxide synthase (iNOS), CD16, CD32, etc. and cell surface markers-histocompatibility complex (MHC-II), CD86, etc. Microglial polarization of the M1 phenotype is characterized by high expression of IL-12, high expression of IL-23 and low expression of IL-10 (84). M2-type microglial replacement activation is usually induced by IL4 or IL-10 and IL-13, and is usually characterized by high expression of IL-12, high expression of IL-23b, and low expression of IL-10. To activate M2-type microglia, IL4 or IL-13 binds to IL4R $\alpha$  or IL-13R $\alpha$ 1 to activate transcription factors, such as STAT6, peroxisome proliferator-activated receptor gamma (PPAR $\gamma$ ), Jumoni domain-containing protein 3 (Jmjd3), and IRF4, respectively. This subsequently causes M2-type microglia to release cytokines such as IL-10, transforming growth factor B (TGF $\beta$ ), IL-1 receptor agonists, CD302, CD163 and other inflammatory mediators such as platelet-derived growth factor (PDGF), fibronectin 1 and arginase 1 (Arg1), etc. (84).

### 3.2.3 Activation of microglia and activation, recruitment and polarization of blood-derived macrophages after IS

After IS, intracerebral microglia are rapidly activated within minutes of injury (85), while disruption of BBB integrity allows macrophages to infiltrate the injury site (86, 87). Cerebral ischemia results in dramatic changes in the morphology, density, and function of branched microglia, including processes such as cell body enlargement, debranching, and cell wall thickening. It eventually becomes “amebic”, produces inflammatory proteins, and undergoes changes in proliferation, migration, and phagocytosis (88). Because microglia and blood-migrating macrophages are morphologically indistinguishable and perform similar functions, they are represented as microglia/macrophages in many studies. The current single-cell transcriptomic sequencing also found that the two have similar phenotypes (89). Activated microglia/macrophages have been found to produce a variety of mediators, including iNOS (90), inflammatory cytokines (such as TNF- $\alpha$ , IL-1 $\beta$ , TGF- $\beta$ , IL-10) (86), nerve growth and trophic factors (such as IGF-1, bFGF, PDGF, BDNF) (91).

Many surface receptors involved in regulating the activation and function of microglia/macrophages have been found: (1) TLRs: TLRs represent a series of pattern-recognition transmembrane receptors that recognize relevant molecular patterns on the surface of pathogens. It is an essential component of the innate immune response of microglia and induces microglia to produce neurotoxic factors that contribute to the microglia response to neuronal damage (92, 93). Studies have found that stimulation of TLR2 and TLR4 activates microglia, produces pro-inflammatory cytokines, and exacerbates brain damage after focal cerebral ischemia (94–99). Knockdown of TLR2 or TLR4 reduces the production of TNF- $\alpha$ , iNOS and cyclooxygenase-2 (COX-2), contributing to smaller cerebral infarct volume (100, 101). (2) Purinergic receptors: Purinergic receptors consist of P1 adenosine receptors and P2ATP receptors (102). Among P1 adenosine receptors, A2A receptors are upregulated in microglia after focal cerebral ischemia and are involved in the control of microglial proliferation and BDNF release induced by LPS stimulation (103). The use of A2A receptor antagonists attenuates ischemia-induced brain damage (104). P2ATP receptors are composed of P2X and P2Y receptors, each containing distinct subunit subtypes (105, 106). Among them, the P2X7 receptor mediates microglia activation after ischemic stroke (107, 108). P2X7 receptor activation induces microglia to release proinflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$ , NO, CXCL2 and CCL (109, 110). In addition, P2Y12 is another purinoceptor expressed on microglia, and P2Y12 is down-regulated upon activation of microglia. The accumulation of microglia in the infarcted area was reduced after knockout of the

P2Y<sub>12</sub> receptor, while attenuating neuronal death following cerebral ischemia in mice (80). (3) CCR2: CCR2 is present in almost all immune cells and highly inflammatory mononuclear MPs (111). However, under normal conditions, CCR2 is poorly expressed in brain microglia (102, 112). CCR2 and its ligand monocyte chemoattractant protein-1 (MCP-1) are upregulated in microglia and migrating macrophages after ischemic stroke (113). Activation of CCR2 enhances cerebral inflammatory responses and significantly increases the volume of cerebral infarcts (114). Deletion of CCR2 in mice reduces blood immune cell recruitment, but does not affect microglia activation after transient MCAO (115). Thus, CCR2 appears to be critical for blood immune cell recruitment, but has little effect on microglia activation after focal cerebral ischemia. (4) Receptor for advanced glycation end products (RAGE): RAGE is another receptor that mediates the activation of microglia/macrophages and plays an important role in the inflammatory response of many diseases (116, 117). In IS patients, RAGE is upregulated in brain and plasma (117, 118). *In vitro* studies have shown that the interaction between RAGE and its ligand high mobility group box 1 (HMGB1) is critical for neuronal death induced by microglia activation (119).

### 3.2.4 Molecular mechanisms of signaling pathway transduction of M1 and M2 polarization under IS

Microglia/macrophages are activated and polarized upon an ischemic injury, and the degree of polarization changes with pathophysiological conditions (102, 120, 121). Different phenotypes of microglia/macrophages can differentially regulate dying cells after brain injury, possibly aggravating neuronal death or promoting damaged tissue repair (122, 123). Among them, iNOS, IL-1 $\beta$ , IL-6, TNF- $\alpha$ , etc. can be used as molecular markers of M1-type microglia/macrophages. IL-10, IL-4, TGF- $\beta$ , CD206, Ym1, etc. can be used as molecular markers of M2-type microglia/macrophages. Studies on the progression of IS over time found that on day 1, the M2 phenotype marker Ym1 was highly upregulated in border regions, which induces an M2-type response that provides a protective function for the damaged brain; on day 7, it performs a phagocytic function (124). Further studies showed that M1/M2 microglia participate in different stages of IS. Among them, M2 type mainly appeared in the early stage of cerebral ischemia, appeared 1 to 3 days after ischemia, rose to the highest peak in 3 to 5 days, and returned to the low level before injury on the 14th day. Then it gradually transformed into M1 type on the 3rd day, and maintained a high level for 14 days after ischemia (31). In addition, microglia/macrophages are susceptible to ischemia-induced injury, which may be related to the purinoceptors P2X<sub>4</sub> and P2X<sub>7</sub>, resulting in reduced numbers and suppressed activity of microglia/macrophages in the ischemic core (125, 126). Thus, low levels of microglia/macrophages in the ischemic core and high proportions of M1 and M2 phenotype cells in the peri-

infarct area may contribute to the pathological process of ischemic injury.

The signaling molecules associated with M1 phenotype polarization mainly include the following: (1) NF- $\kappa$ B: NF- $\kappa$ B is a traditional transcription factor that is activated by LPS and regulates the expression of most M1 phenotype marker genes. Substantial evidence suggests that the NF- $\kappa$ B signaling cascade adversely affects cerebral ischemia because of its role in regulating pro-inflammatory mediators, including IL-1, IL-2, IL-6, IL-12, TNF- $\alpha$ , iNOS and cyclooxygenase-2 (COX-2) (127, 128). In addition, NF- $\kappa$ B regulates the expression and activation of MMPs, leading to leakage of the BBB and exacerbating the inflammatory response (129, 130). (2) Notch signaling: Notch signaling in response to LPS activation enhances IFN- $\gamma$  production by co-recruiting p50 and c-Rel (131, 132). Notch signaling exacerbates ischemic brain injury by prolonging NF- $\kappa$ B activation with concomitant persistent inflammation and enhancing microglia/macrophage-induced neurotoxicity (131, 133). (3) Signal transducers and activators of transcription (STAT1 and STAT3): STAT1 and STAT3 can increase the expression of NF- $\kappa$ B/p65 (134). Inhibition of the activation of STAT1 and STAT3 attenuates the inflammatory response induced by cerebral ischemia while improving infarct volume (135, 136). (4) Glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ): Cerebral ischemia-induced dephosphorylation and activation of GSK-3 $\beta$  reduces cAMP response element-binding protein (CREB) activity while enhancing NF- $\kappa$ B signaling to initiate pro-inflammatory capacity (137, 138). (5) Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>): PGE<sub>2</sub> is the main product of cyclooxygenase and prostaglandin E synthase, and is considered to be a typical pro-inflammatory mediator in the brain. PGE<sub>2</sub> activates its downstream signaling pathways through the G protein-coupled E-prostaglandin (EP) receptors EP1-EP4 (139). The EP1 receptor is expressed in microglia, and EP1 deletion inhibits microglial activity and phagocytosis. Although EP2 is expressed in neurons and not in microglia, loss of EP2 results in increased activation of M1-type microglia, suggesting that EP2 mediates the interaction between neurons and microglia (140, 141). (6) mTORC1: mTORC1 is a protein complex downstream of the PI3K-Akt pathway, and is one of the participants in the dysregulation after ischemia and OGD. Maria J et al. (142) showed that blocking mTORC1 can reduce lesion size, improve motor function, significantly reduce the production of pro-inflammatory cytokines and chemokines, and reduce the number of M1-type microglia. Thus, mTORC1 blockade attenuates behavioral deficits and post-stroke inflammation after MCAO by preventing the polarization of microglia towards the M1 type. (7) Related microRNAs: Recent studies have also identified the role of microRNAs (miRNAs) in microglial polarization (143). Current studies have shown that miRNAs involved in the positive regulation of microglial activation and M1 transformation after IS include: miR-689, miR-124, miR-155, miRNAlet-7c-5p, miRNA-200b, MiR-377,

etc. These may be related to pro-inflammatory pathways and M1-type polarization (144, 145).

The signaling molecules associated with M2 phenotype polarization mainly include the following: (1) Peroxisome proliferator-activated receptor  $\gamma$  (PPAR $\gamma$ ): In the inflammatory response, PPAR $\gamma$  can inhibit the inflammatory response by competitively inhibiting the inflammatory signaling pathway and the generation of inflammatory mediators. Among them, the crosstalk between Notch and NF- $\kappa$ B signaling pathway can inhibit the expression of PPAR $\gamma$ , which will decrease the expression of PPAR $\gamma$  after stroke, thereby aggravating the inflammatory response (146, 147). (2) cAMP response element binding protein (CREB): CREB cooperates with C/EBP $\beta$  and amplifies the expression of M2 phenotype-specific genes such as IL-10 and Arg1, promoting tissue repair (148), while the expression of M1 phenotype genes encoding pro-inflammatory molecules is also regulated by C/EBP $\beta$  (149). The dual role of C/EBP $\beta$  in regulating gene expression of M1 and M2 phenotypes may result from the competition between CREB and NF- $\kappa$ B for binding to C/EBP (148, 150). (3) Interferon regulatory factor-3 (IRF-3): In response to TLR activation, PI3K/Akt signaling initiates phosphorylated IRF-3. Activated IRF-3 translocates into the nucleus and drives polarization of the M2 phenotype by interacting with CREB-binding protein (CBP) (151, 152). (4) Related microRNAs: Current studies have shown that miR-124, miR-711, miR-145, miRNA203 and miRNA27a, which are involved in the positive regulation of microglial activation and M2 transformation after ischemic stroke, may be involved in the regulation of anti-inflammatory pathways and M2-type polarization (144, 145). Among them, miR-146a can not only inhibit the LPS-induced M1-type polarization of microglia, but also promote the M2-type polarization of microglia (145).

### 3.3 Regulation of cellular interactions between microglia/macrophages, neurons, and other immune-inflammatory cells after IS

#### 3.3.1 The effect of the interactive regulation of microglia/macrophages and neurons on brain injury after IS

After IS, a large number of nerve cells die due to reduced blood flow and insufficient supply of glucose and oxygen. Dying neuronal cells release injury-associated ligands and excitotoxic glutamate to promote microglia/macrophage activation (153), thereby exacerbating neuronal damage (154). However, ischemia-induced neuronal injury can release IL-4, which can enhance the expression of IL-4 receptors in microglia/macrophages and promote microglia/macrophage polarization to the M2 phenotype. IL-4-activated PPAR $\gamma$  enhances the phagocytosis of apoptotic neurons by microglia/macrophages (155). The release of glutamate enables neurons to secrete

soluble fractalkine (sFKN), which enhances the ability of microglia/macrophages to clear neuronal debris (156). These studies suggest that damaged neurons can promote microglia/macrophage protection to help neurons survive ischemic conditions (154, 157–159). Microglia/macrophages play a beneficial role in tissue remodeling and regeneration after IS by eliminating dead or dying neurons (160). A study of the infiltration of microglia and macrophages in the brain of chimeric mice found that microglia in the brain could phagocytose neuronal debris as early as day 1, and reached a peak on day 2, while infiltrating macrophages began to clear neuronal debris on day 4 after MCAO. They found that microglia in the brain are more sensitive and important in defense against ischemia by eliminating dead neurons (115).

#### 3.3.2 The effect of interaction between microglia/macrophages and astrocytes on brain injury after IS

Microglia and astrocytes play important roles in the innate immune environment of the brain. In two-photon microscopy-based time-lapse imaging recordings, it was found that microglia directly contact astrocytes by extending their branches toward the astrocytes (161). When the brain microenvironment is disrupted, microglia/macrophages and astrocytes play important roles in various pathological states such as IS (162–164). Among them, modulators such as IL-1 $\beta$ , TNF- $\alpha$ , TGF- $\beta$ , adenosine, ATP and glutamate contribute to functional communication between microglia/macrophages and astrocytes (165–168), which is critical for immune responses in the brain (163). In the CNS, astrocytes mainly secrete cytokines such as IL-6, IL-1 $\beta$ , and IL-10. In addition, astrocytes secrete many chemokines, such as CCL2, CXCL1, CXCL10, and CXCL12, etc., and several chemokines have been found to be involved in microglial activation and polarization, as well as M1 and M2 phenotype switching. *In vitro* studies found that CCL2 released by primary astrocytes contributed to the polarization of M1-type microglia. The proinflammatory mediator lysophosphatidylcholine (LPC) produced by neurons and astrocytes after IS stimulates microglia/macrophages to upregulate the mRNA expression of Mcp-1 and Ccr2, which is involved in mediating the inflammatory response after cerebral ischemia (113). Therefore, there is a complex communication between microglia/macrophages and astrocytes.

#### 3.3.3 The effect of the interaction between microglia/macrophages and T cells on brain injury after IS

After cerebral ischemia, T cells activate and infiltrate into brain tissue, release cytokines and ROS, and induce brain injury by inducing early inflammatory response (169). However, some T cell subtypes have protective effects on brain cells in the early stage of cerebral ischemia. Existing evidence shows that T cells also play an important role in the repair and regeneration of

brain tissue in the late stage of stroke (170). T cells include a variety of functional subsets, mainly pro-inflammatory Th1 and Th17 subsets and anti-inflammatory Th2 and Treg subsets. Different T cell subsets play different roles in ischemic brain injury (171). Among them, Th1 can secrete pro-inflammatory cytokines IL-2, IL-12, INF- $\gamma$  and TNF- $\alpha$ , and play an important role in IS; while Th2 can exert neuroprotective effects by secreting anti-inflammatory cytokines IL-4, IL-10, IL-5 and IL-13 (172). Th17 mainly secretes IL-17, which can promote the occurrence of inflammation (172). IL-10 secreted by Treg is also an important brain protective mediator, which exerts neuroprotective effects mainly by inhibiting the secretion of pro-inflammatory cytokines TNF- $\alpha$  and INF- $\gamma$ . Treg inhibits secondary infarct enlargement by inhibiting the production of pro-inflammatory cytokines, regulating lymphocyte activation and/or human invasion of ischemic brain tissue (172, 173). After IS, activated microglia and secreted cytokines promote the differentiation of T cells into different functional subsets (6). Among them, M1-type microglia promote the proliferation and differentiation of Th1, while M2-type microglia induce the production of Treg with strong inhibitory function. The interaction between them exerts pro-inflammatory and anti-inflammatory effects, respectively, after stroke, thereby inhibiting the occurrence of the disease or promoting the recovery of the disease (174). Immunofluorescence double-staining of IS brain tissue found that there was a certain interaction between microglia and T cells, indicating that T cells also had a certain regulatory effect on the mutual transformation of M1/M2 microglia (175, 176).

(1) Interaction between M1-type microglia and Th1/Th17: After ischemia, M1-type microglia can produce pro-inflammatory cytokines leading to BBB disruption (177). Both Th1 and M1 microglia can produce pro-inflammatory cytokines, and iNOS is closely related to inflammatory cells. Cerebral ischemia can induce the up-regulation of iNOS mRNA and protein expression in inflammatory cells, enhance iNOS activity, and promote the production of NO, which can further generate peroxynitrite, thereby aggravating brain damage (178, 179). Studies have shown that Th1 can produce IFN- $\gamma$  and promote the transformation of microglia into M1 type, thereby aggravating secondary ischemic injury (180). In addition, M1-type microglia can induce Th1 to secrete pro-inflammatory cytokines IL-12 and TNF- $\alpha$  (181–183), and the chemokines (CXCL9, CXCL10) they express can mobilize Th1 to participate in the inflammatory response. Therefore, Th1 and M1-type microglia interact after cerebral ischemia, and can simultaneously promote inflammatory response and aggravate brain injury. IL-17 secreted by Th17 is a powerful pro-inflammatory cytokine that induces the expression of other pro-inflammatory cytokines (such as IL-6 and TNF- $\alpha$ ), chemokines, and MMPs, causing inflammatory cell infiltration and tissue destruction. Meanwhile, M1-type microglia induce Th17 differentiation by secreting IL6 and IL-23, which together

promote immune response (181–183). Therefore, M1-type microglia and Th17 act as pro-inflammatory effects of brain injury after cerebral ischemia.

(2) Interaction between M2-type microglia and Th2/Treg: After cerebral ischemia, the expression of inflammatory mediators is up-regulated, which induces the accumulation of microglia to the injured area and breaks the dynamic balance between M1 and M2 types. The anti-inflammatory cytokines IL4 and IL-10 secreted by Th2 can further promote the polarization of microglia to M2 type (184, 185). This indicates that there is an interaction between M2-type microglia and Th2 cells, which together play an anti-inflammatory role after cerebral ischemia (186). After cerebral ischemia, Treg inhibits the activation of microglia and reduces the inflammatory response in the brain by secreting IL-10 and TGF- $\beta$  (187). In addition, Treg cell-derived osteopontin acts through integrin receptors on microglia to enhance the repair activity of microglia, thereby promoting oligodendrogliosis and white matter repair (188). Treg can induce the polarization of microglia to M2 type through the IL-10/GSK3  $\beta$ /PTEN signaling pathway, thereby reducing the inflammatory injury caused by cerebral hemorrhage (189–191). Treg regulates the expression of other cytokines and inhibits the activation of microglia by releasing IL-10 in the late stage of cerebral infarction. In addition, studies on amyotrophic lateral sclerosis show that Treg can promote the transformation of microglia to M2 type. This suggests that Treg can change its effect from neurotoxicity to neuroprotection without changing the number of microglia (189). After cerebral ischemia, Treg can reduce infarct volume and improve neurological function by reducing T cell infiltration, reducing microglia/monocyte activation, or promoting M2-type polarization of microglia (187). The key inflammatory responses after ischemic stroke are summarized in Figure 1.

## 4 Modulatory effects of natural botanical components on microglia-mediated immune inflammation in IS

### 4.1 Natural botanical component monomer

#### 4.1.1 Polyphenols and phenols

(1) Gastrodin: Gastrodin is an organic compound extracted from the dried roots of *Gastrodia elata* Bl (192). Gastrodin has a good sedative and sleeping effect on neurasthenia, insomnia, headache symptoms have eased. *Gastrodia elata* Bl. Is able to treat pain, dizziness, limb numbness, and convulsions. Clinically, *Gastrodia elata* Bl. is generally used to treat vertebrobasilar insufficiency, vestibular neuritis and vertigo (193). Gastrodin is one of the main effective monomer components of *Gastrodia elata* Bl. It is currently widely used in clinical applications, and can exert neuroprotective effects in neurological diseases through multiple

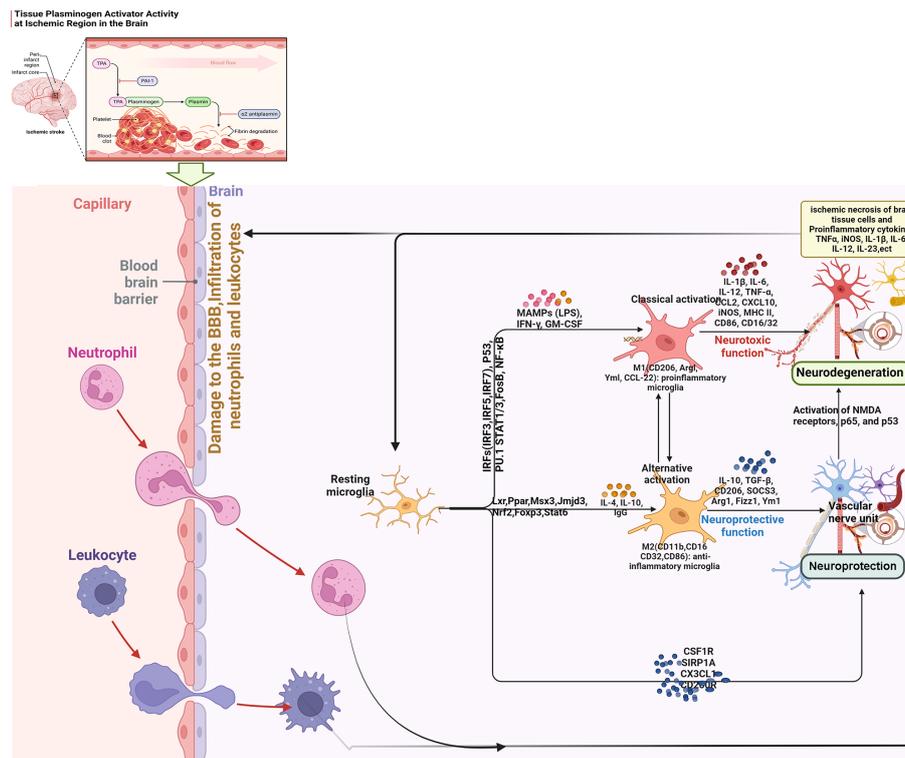


FIGURE 1

Summary of key inflammatory responses after ischemic stroke (BBB, blood brain barrier; IRF, interferon regulatory factor; STAT, signal transducer and activator of transcription; NF- $\kappa$ B, nuclear factor- $\kappa$ B; IFN, Interferon; NMDA, N-methyl-D-aspartate receptor; MAMPs, Metabolism-related molecular patterns; LPS, Lipopolysaccharide; GM-CSF, granulocyte-macrophage colony stimulating factor).

pathways such as anti-oxidative stress, anti-neuroinflammatory response, regulation of neurotransmitters, regulation of neural remodeling, anti-apoptosis and anti-autophagy. The study found that gastrodin pretreatment can significantly improve the neurological function of MCAO rats after 72h of reperfusion, and reduce the volume of cerebral infarction and BBB permeability. Gastrodin at 100 mg/kg *in vivo* and 40  $\mu$ mol/L *in vitro* can inhibit microglia MMP2, MMP9 and AQP4, and increase ZO-1 expression, thereby exerting its protective effect on ischemia-reperfusion injury in MCAO and OGD/R models. In addition, OGD/R and MCAO can significantly increase the expression of SOX4 in microglia *in vitro* and *in vivo*, and pretreatment with gastrodin can inhibit the trend of increasing SOX4. Overexpression of SOX4 could reverse the effects of gastrodin on MMP2, MMP9, AQP4, and ZO-1 in OGD/R microglia, suggesting that gastrodin could regulate MMP2, MMP9, AQP4, and ZO-1 through SOX4 to exert neuroprotective effects (194).

(2) Malibatol A: Malibatol A is a natural resveratrol oligomer purified from the leaves of serrata with antioxidant activity. Yang et al. (195) found that Malibatol A improved mitochondrial dysfunction induced by middle cerebral artery occlusion. Pan et al. (196) found that Malibatol A significantly reduced the

infarct size of mice with MCAO and improve neurological function. Weng et al. (197) found that Malibatol A can attenuate OGD/R-induced BV2 cell damage and promote M2 microglial polarization, which may be related to the inhibition of mammalian Ste20-like kinase 1 phosphorylation.

(3) Resveratrol: Resveratrol, a non-flavonoid polyphenolic organic compound, is an antitoxin produced by many plants when stimulated, with a chemical formula of C<sub>14</sub>H<sub>12</sub>O<sub>3</sub>. It can be synthesized in grape leaves and grape skins and is a bioactive component in wine and grape juice (198). *In vitro* and animal experiments have shown that resveratrol has anti-oxidation, anti-inflammatory, inhibition of platelet formation, blood clot adhesion to the vascular wall, anti-cancer and cardiovascular protection (199–201). Resveratrol reduces glial cell activation and prevents delayed neuronal cell death in MCAO rats (202). In addition, resveratrol may protect cranial nerves by reducing the production of inflammatory mediators such as IL-1 $\beta$ , TNF- $\alpha$  and ROS in the ischemic cortex, possibly mediated by attenuating the activation of microglia (203).

(4) 6-Shogaol: 6-shogaol, an active substance isolated from ginger, has a variety of biological activities, including anticancer, anti-inflammatory and antioxidant. For example, 6-shogaol reduced diethylnitrosamine (DEN)-mediated

elevation of serum aspartate aminotransferase and alanine aminotransferase and DEN-induced hepatic lipid peroxidation. The induction of Nrf2 and HO-1 by 6-shogaol was also confirmed in mice. 6-shogaol also restores the decreased activity of DEN and the protein expression of liver antioxidant enzymes such as superoxide dismutase, glutathione peroxidase and catalase in mice (204–206). 6-Shogaol also reduces inflammatory biomarkers levels in LPS-activated microglia and neuroinflammation in the brain. It also attenuates iNOS, NO, COX-2, PGE2, TNF- $\alpha$  and IL-1 $\beta$  production by downregulating MAPK (p38, JNK and ERK)/NF- $\kappa$ B signaling. The inhibition of microglial activation and inflammatory mediators by 6-Shogaol contributes to its neuroprotective effect (207).

(5) 6-Paradol: 6-Paradol reduces tMCAO-induced cerebral infarction, neurological deficit, and the inflammatory cascade in the ischemic brain, which is mainly mediated by inhibition of microglia/macrophage activation (208).

(6) Honokiol: Honokiol is derived from the bark, root bark and branches of *Magnolia officinalis* Rehd. et Wils. or *M. officinalis* Rehd. et Wils. var. *biloba* Rehd. et Wils. (209). Honokiol has obvious and long-lasting central muscle relaxation, central nervous system inhibition, anti-inflammatory, antibacterial, anti-pathogenic microorganisms, anti-ulcer, antioxidant, anti-aging, anti-tumor, cholesterol-lowering and other pharmacological effects. It is used to treat acute enteritis, bacterial or amoebic dysentery, chronic gastritis, etc. (210, 211). Honokiol inhibits inflammatory biomarkers in the ischemic brain, including NF- $\kappa$ B transcriptional activation, NO, and TNF- $\alpha$  production (212), which are mainly produced by activated glial cells and infiltrating macrophages.

(7) Indole-3-propionic acid: Indole-3-propionic acid treatment not only inhibited glial (astrocyte and microglia) activation in the ischemic brain, but also reduced lipid peroxidation, neuronal DNA damage. Its neuroprotective efficacy is mainly related to the fight against glial cell activation (213).

(8) Paeonol: Paeonol is a monomer extracted from the dried roots of *Paeonia suffruticosa* Andr. or *Cynanchum paniculatum* (Bge.) Kitag., which has various pharmacological effects (214). Paeonol has the effect of treating cardiovascular and cerebrovascular diseases, such as lipid-lowering and anti-atherosclerosis, vasodilation and blood pressure lowering, anti-arrhythmia, anti-cerebral ischemia-reperfusion injury and neuroprotection. It also has anti-hepatic injury and liver fibrosis, anti-inflammatory, antibacterial activity, anti-inflammatory activity, antioxidant activity and anti-tumor activity (215–217). Paeonol also decreased IL-1 $\beta$  immunoreactive cell numbers and microglia/macrophage activation in the ischemic brain (218).

(9) Epigallocatechin gallate: Epigallocatechin gallate is a component extracted from green tea. It is the main active and water-soluble component of green tea and is a component of catechins (219). Catechins are mainly divided into four categories: epicatechin, epigallocatechin, epicatechin gallate, epigallocatechin gallate (220).

Epigallocatechin gallate has the activity of protecting dopaminergic neurons, inhibiting inflammation, inhibiting oxidative stress, anti-oxidation, protecting nervous system, anti-tumor and protecting cardiovascular and cerebrovascular (221, 222). Epigallocatechin gallate reduces infarct volume by reducing microglia/macrophage activation (223).

(10) Theaflavins: Theaflavins generally refers to tea yellow pigment, is a golden yellow pigment in black tea, is the product of tea fermentation. In biochemistry, tea yellow pigment is a class of polyphenols hydroxyl benzophenone structure of the material, with inhibition of inflammation, anti-oxidative stress and the neuroprotective effect (224–226). Theaflavins reduce infarct and edema volume by reducing microglial inflammatory mediators such as COX-2, iNOS, and ICAM-1 in the damaged brain (227).

(11) Propofol: Propofol reduces infarct volume and improves neurological function by reducing microglia/macrophage CD68 and Emr1 levels and inhibiting proinflammatory cytokines including TNF- $\alpha$ , IL-6, and IL-1 $\beta$ . Inhibition of microglial proinflammatory cytokine production during propofol-mediated MCAO contributes to neuroprotection against IS (228).

(12) Probulcol: The neuroprotective effect of probulcol is related to its anti-inflammatory effect in microglia. It downregulates NF- $\kappa$ B, MAPKs and AP-1 signaling pathways in LPS-activated microglia to reduce inflammatory mediators such as NO, PGE2, IL-1 $\beta$  and IL-6. It also reduces iNOS, COX-2, IL-1 and IL-6 in the brains of MCAO mice (229).

#### 4.1.2 Anthraquinones

(1) Emodin: Emodin, an active ingredient extracted from the *Rheum palmatum* L., has a wide range of pharmacological properties, including anticancer, hepatoprotective, anti-inflammatory, antioxidant and antibacterial activities (230). Previous studies have shown that (231, 232) emodin has neuroprotective effects, antagonizes CIRI, and prevents the formation of atherosclerotic plaques. However, its neuroprotective mechanism remains unclear. Cai et al. found that emodin may play a role in brain protection by inhibiting the activation of microglia and the release of inflammatory factors mediated by the TLR4/NF- $\kappa$ B pathway (233).

(2) Chrysophanol: Zhang et al. found that Iba-1 positive cells in the cerebral ischemic penumbra of MCAO model rats increased significantly, and were amoeba-shaped or round; the neurological deficit score, the percentage of cerebral infarction and the relative expression of Notch-1, TNF- $\alpha$  and ICAM-1 proteins in the ischemic penumbra were significantly increased (234). However, after chrysophanol intervention, Iba-1-positive cells in the cerebral ischemic penumbra were reduced; the neurological deficit score, the percentage of cerebral infarction and the relative expression of Notch-1, TNF- $\alpha$  and ICAM-1 proteins in the ischemic penumbra were significantly decreased (234). This suggests that chrysophanol has a certain cerebral

protective effect on cerebral ischemia injury model rats, and can reduce its nerve damage, and its mechanism may be related to the inhibition of Notch signaling pathway-mediated activation of microglia and the expression of inflammatory factors. In addition, some studies have used a neuroinflammation model of LPS-induced microglial activation, and found that chrysophanol can inhibit LPS-induced microglial inflammatory response and promote the transformation of microglial M1 type to M2 type. The mechanism may be related to down-regulation of TLR4/NF- $\kappa$ B signaling pathway (235).

#### 4.1.3 Terpenes and alkaloids

(1) Astragaloside IV: Astragaloside IV is an organic compound with a chemical formula of C<sub>41</sub>H<sub>68</sub>O<sub>14</sub>. It is a white crystalline powder and is extracted from the herbal medicine *Astragali radix*. The main active ingredients in *Astragali radix* are astragalus polysaccharides, astragalus saponins and isoflavones. Astragaloside IV is mainly used as a quality control standard to evaluate the quality of *Astragali radix* (236, 237). Studies have shown that astragaloside IV can reduce cerebral infarct volume, down-regulate the M1-type microglia/macrophage markers CD86, iNOS, TNF- $\alpha$ , IL-1 $\beta$  and IL-6 mRNA, and up-regulate the M2-type microglia/macrophage markers CD206, Arg-1, YM1/2, IL-10 and TGF- $\beta$  mRNAs. Astragaloside IV can also reduce the number of CD16/32+/Iba1+ cells and increase the number of CD206+/Iba1+ cells in the ischemic area of the brain. This suggests that astragaloside IV has a protective effect on cerebral ischemia injury in rats, which may be related to promoting the transformation of microglia/macrophages from M1 type to M2 type and inhibiting the inflammatory response (238). In addition, studies have shown that astragaloside IV can inhibit IFN- $\gamma$ -induced activation of microglia. This is related to inhibiting the activation of STAT1/I $\kappa$ B/NF- $\kappa$ B signaling pathway, reducing the gene expression of IL-1 $\beta$ , TNF- $\alpha$  and iNOS in microglia under inflammatory state, thereby reducing the production of NO and TNF- $\alpha$  (239).

(2) Cycloastragenol: Cycloastragenol is directly extracted from the dried roots of *Astragalus membranaceus* (Fisch.) Bge. var. *mongholicus* (Bge.) Hsiao or *Astragalus membranaceus* (Fisch.) Bge., or obtained by hydrolysis of Astragaloside IV (240, 241). It has oral safety, a wide range of pharmacological effects, anti-oxidation, anti-inflammatory, anti-aging, anti-apoptosis and cardiovascular protection (242, 243). Li et al. found that Cycloastragenol dose-dependently reduced cerebral infarct volume, significantly ameliorated functional deficits, and prevented neuronal cell loss in MCAO mice. Meanwhile, Cycloastragenol significantly reduced the activity of MMP9, prevented the degradation of tight junctions, and subsequently ameliorated the disruption of the BBB. Furthermore, Cycloastragenol significantly upregulated the expression of SIRT1 in the ischemic brain, but did not directly activate its enzymatic activity. Concomitant with SIRT1 upregulation, Cycloastragenol reduces p53 acetylation and Bax

to Bcl-2 ratio in the ischemic brain. Cycloastragenol also inhibits NF- $\kappa$ B p65 nuclear translocation. In summary, Cycloastragenol inhibits the expression of proinflammatory cytokines including TNF- $\alpha$  and IL-1 $\beta$  mRNA and inhibits the activation of microglia and astrocytes in the ischemic brain (243).

(3) Triptolide: Tripterygium is derived from the root bark of the traditional Chinese medicine *Tripterygium wilfordii*, which has anti-inflammatory, antioxidant and anti-cancer effects. Triptolide has been used in the treatment of various diseases, such as tumors [colorectal cancer (244), hepatocellular carcinoma (245)], autoimmune-related diseases [rheumatoid arthritis (246)], obesity (247), etc. Triptolide exerts anti-inflammatory and neuroprotective effects on cerebral ischemia rats through the nuclear factor- $\kappa$ B signaling pathway (248). Jiang et al. found that triptolide reduced neuronal apoptosis and inflammatory factor expression in rats with cerebral ischemia through IL-33/growth-stimulating expression gene 2 protein-mediated polarization of M2 microglia, thereby reducing cerebral infarct volume (249).

(4) Artesunate: Artesunate is a derivative of artemisinin with high water solubility and can pass through the BBB for the treatment of cerebral and other types of severe malaria (250). Artesunate can also maintain a high concentration in the nervous system, showing high efficiency and low toxicity (251–254). Studies have shown that artesunate may exert multiple functions, including anti-inflammatory, immunomodulatory, BBB protection, antibacterial and antitumor effects (253, 254). Studies have shown that the anti-inflammatory effects of artesunate are mediated by NF- $\kappa$ B and inflammatory cytokine inhibition. Lai et al. found that artesunate could alleviate liver fibrosis and inflammation by inhibiting the LPS/TLR4/NF- $\kappa$ B pathway (255). Okorji and Olajide found that artesunate reduced proinflammatory cytokine production by inhibiting the p38 MAPK-NF- $\kappa$ B signaling pathway in activated BV2 microglia (256). Artesunate also exerts a protective effect in CIRI and inhibits the expression of TNF- $\alpha$  and IL-1 $\beta$  (257). Liu et al. found that artesunate significantly improved neurological deficit score and infarct volume, and improved inflammation by reducing neutrophil infiltration, inhibiting microglial activation, and downregulating the expression of TNF- $\alpha$  and IL-1 $\beta$ . In addition, artesunate inhibits nuclear translocation of NF- $\kappa$ B and inhibits protein  $\alpha$  proteolysis. In summary, artesunate may protect against inflammatory injury by reducing neutrophil infiltration and microglial activation, inhibiting inflammatory cytokines and inhibiting NF- $\kappa$ B pathway. Therefore, artesunate is a potential IS treatment drug (258).

(5) Neo-Minophagen C: Glycyrrhizin is derived from the glycosides of *Glycyrrhizae radix et rhizoma*, among which Neo-Minophagen C has anti-inflammatory effect, immunomodulatory effect, inhibitory effect on experimental liver cell injury, inhibition of virus proliferation and inactivation of virus (259, 260). Neo-Minophagen C reduces

infarct volume and improves motor function and neurological deficits. The neuroprotective effect of Neo-Minophagen C is mediated by reducing neutrophil infiltration and microglial activation after ischemia. Neo-Minophagen C reduces inflammatory mediators and pro-inflammatory cytokines in LPS-activated microglia. Inhibition of microglial activation and inflammatory mediators contributes to the neuroprotective effect of neophagen C after cerebral ischemia (261).

(6) Hyperforin: Hyperforin, as an active ingredient of *Hypericum perforatum* L, is used to alleviate mild to moderate depression and has a significant antidepressant effect (262). Further studies have shown that hyperforin has good anti-inflammatory, anti-tumor and neuroprotective effects (263, 264). Hyperforin reduces infarct size and improves nerve damage by inhibiting inflammatory microglial activation and promoting microglial polarization towards an anti-inflammatory M2 phenotype in the peri-infarct striatum (265).

(7) Ilexonin A: Ilexonin A is a water-soluble compound, 3-succinyl-18-dehydroursolic acid disodium salt, prepared by succinylation of 18-dehydroursolic acid isolated from the rhizome or root bark of *Ilex pubescens* Hook. et Arn (266). Ilexonin A is an antithrombotic drug whose chemical structure is different from the currently known antiplatelet aggregation drugs. Ilexonin A is effective in the treatment of ischemic cerebrovascular disease, coronary heart disease, central retinal choroiditis, peripheral vascular disease, etc., especially for the treatment of acute ischemic cerebrovascular disease (267, 268). Meanwhile, Ilexonin A reduces inflammatory microglial activation in the ischemic brain. Its neuroprotective effects may be related to neuronal regeneration, inhibition of microglial activation and increased angiogenesis (269).

(8) Huperzine A: Huperzine A is an alkaloid extracted from *Huperziaserrata* (Thunb.) Trev. It is a potent cholinesterase reversible inhibitor. Its characteristics are similar to neostigmine, but the duration of action is longer than the latter (270, 271). Huperzine A can effectively prevent brain neurasthenia in middle-aged and elderly people, restore brain nerve function, and activate brain nerve transmission substances (272). Huperzine A may inhibit NF- $\kappa$ B activity and pro-inflammatory mediator production in the cerebral cortex and striatum of MCAO rats. It reduces neurological deficits and glial cell activation after ischemic injury mainly through its anti-inflammatory effect in the post-ischemic brain (232). Huperzine A can also down-regulate MAPK signaling, especially JNK and p38, to reduce the level of the inflammatory factor TNF- $\alpha$ . Huperzine A exerts neuroprotection against 2-VO-induced cognitive impairment by promoting an anti-inflammatory response in the brain (273).

(9) Berberine: Berberine, a quaternary ammonium alkaloid isolated from COPTIDIS RHIZOMA, is the main active ingredient in COPTIDIS RHIZOMA for antimicrobial activity. Studies have shown that berberine regulates immune and inflammatory mechanisms (274, 275). Berberine also improves

ischemia-induced short-term memory impairment by reducing neuronal apoptosis, microglial activation and oxidative stress. Berberine exerts neuroprotective effects against ischemic injury by increasing the activation of the PI3K/Akt pathway through its phosphorylation in the hippocampus of ischemic gerbils (276). (10) Sinomenine: Sinomenine is the main active ingredient isolated from *Sinomenium acutum* (Thunb.) Rehd. et Wils (277), which is a kind of morpholine alkaloids, molecular formula is C<sub>19</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>. It has anti-inflammatory, antihypertensive, analgesic, anti-arrhythmic and other pharmacological activities, and also plays an important role in the treatment of chronic nephritis, anti-oxidation, anti-tumor, detoxification and so on (278, 279). Sinomenine also reduces glial cell activation by inhibiting the NLRP3-ASC-Caspase-1 inflammasome in mixed glial cultures exposed to OGD as well as in MCAO mice. Sinomenine also reduces OGD-induced K phosphorylation in A macrophages *in vitro*. The inhibition of NLRP3 and A-macrophage K activation in activated glial cells by sinomenine is a key cellular mechanism for its neuroprotective effect against stroke (280).

#### 4.1.4 Flavonoids

(1) Icariin: Icariin is the main active ingredient of *Epimedium folium*, which is an 8-prenyl flavonoid glycoside compound (281). Icariin can increase cardiovascular and cerebrovascular blood flow, inhibit inflammation, resist oxidative stress, regulate immunity, promote hematopoietic function, immune function and bone metabolism, and also has the effects of tonifying kidney and strengthening yang, anti-aging and so on (282–284). Tang et al. found that after icariin treatment, the neurological function score and cerebral infarction rate of MCAO model rats were improved, the activation of Iba1 and TLR4 in microglia decreased, the NF- $\kappa$ B p65 protein level decreased, and the content of inflammatory factors IL-1 $\alpha$  and TNF- $\alpha$  decreased significantly. This suggests that icariin may play a role in brain protection by regulating the activation of microglia, inhibiting the activation of TLR4 and its downstream NF- $\kappa$ B signaling pathway, and reducing the expression of related inflammatory factors IL-1 $\alpha$  and TNF- $\alpha$  (285).

(2) Eupatilin: Eupatilin, a lipophilic flavonoid isolated from ARTEMISIAE ARGYI FOLIUM, is a PPAR $\alpha$  agonist with anti-apoptotic, anti-oxidant and anti-inflammatory effects (286–288). Eupatilin may inhibit pro-inflammatory mediators including nitrite, PGE<sub>2</sub>, TNF- $\alpha$  and IL-6 in activated microglia *in vitro* and *in vivo* to combat focal cerebral ischemia. In the post-ischemic brain of mice challenged with tMCAO, eupatin significantly improved neurological function and reduced cerebral infarction. It also significantly reduced Iba1-immunopositive cells, microglia/macrophage proliferation, NF- $\kappa$ B signaling, IKK $\alpha$ / $\beta$  phosphorylation, I $\kappa$ B $\alpha$  phosphorylation, and I $\kappa$ B $\alpha$  degradation in the tMCAO-attacked brain. This suggests its powerful effect on counteracting the inflammatory response of microglia/macrophages in the ischemic brain (289).

(3) Heptamethoxyflavonoids: Heptamethoxyflavone protects neuronal cells from ischemia-induced injury by increasing BDNF production, CaMK II phosphorylation, and reducing microglia/macrophage activation (290).

(4) Wogonin: Wogonin is a flavonoid extracted from the root of *Scutellaria baicalensis* Georgi (291). Wogonin has attracted attention because of its various pharmacological activities, including antioxidant activity, anti-inflammatory, immune regulation, and cardiovascular protection. It also has neuroprotective effects during cerebral ischemia (292, 293). Wogonin reduces LPS-induced microglial activation by attenuating the production of inflammatory biomarkers, including iNOS, nitrite, IL-1 $\beta$ , TNF- $\alpha$  and NF- $\kappa$ B in microglia. Furthermore, wogonin treatment down-regulated hippocampal neuronal death by reducing inflammatory mediators such as iNOS and TNF- $\alpha$  after systemic ischemia. It also inhibited the level of microglia-specific isolectin B4 staining, suggesting its role in inhibiting microglial activation (294).

(5) Puerarin: Puerarin is the main active ingredient extracted from *Pueraria lobata* (Willd.) Ohwi (295). It has the effect of protecting cardiovascular and cerebrovascular and nerve cells, and can dilate blood vessels, lower blood pressure, lower blood sugar, anti-tumor, improve immunity, anti-oxidation, anti-inflammatory and regulate bone metabolism (296–298). Puerarin also reduces ischemia-induced COX-2 expression and reduces cerebral infarction in MCAO rats by inhibiting microglia and astrocyte activation (299).

(6) Quercetin: Quercetin is a naturally occurring phytochemical with good biological activity. It mainly exists in vegetables, fruits, tea and wine in the form of glycosides and has a healthy effect (300, 301). The anti-diabetic, anti-hypertensive, anti-Alzheimer's disease, anti-arthritis, anti-influenza virus, anti-microbial infection, anti-aging, autophagy and cardiovascular protective effects of quercetin have been extensively studied (302–304). Quercetin may reduce neuroinflammation and apoptosis by reducing the expression of iNOS and caspase-3, which is associated with hippocampal neuroprotection after systemic ischemia in rats (299).

(7) Fisetin: Fisetin is a compound extracted from natural plants with pharmacological effects against different pathological processes (305). The concentration of Fisetin in food is 2 ~ 160 $\mu$ g/g. The content of Fisetin in strawberry, apple and persimmon is high, and fisetin is also abundant in various legume trees and shrubs (306). Studies have shown that Fisetin has a certain therapeutic effect on neurological abnormalities, cardiovascular disease, diabetes, obesity, lung disease, immune disease, cancer and other inflammatory diseases (307, 308). Fisetin may reduce the infiltration of macrophages and dendritic cells into the ischemic hemisphere and reduces immune cell activation in the brain, as evidenced by decreased TNF- $\alpha$  levels. Fisetin significantly downregulates inflammation in LPS-activated microglia and macrophages by reducing NF- $\kappa$ B signaling and reducing TNF- $\alpha$  production. This anti-

inflammatory effect of Fisetin is associated with reduced neurotoxicity and neuroprotection by activated microglia and macrophages following ischemic injury (309).

(8) Breviscapine: Breviscapine is the extract of *Erigeron breviscapus* (Vant.) Hand.-Mazz. It is composed of flavonoids, lignans, coumarins, terpenoids, phytosterols and other chemical components (310). Modern pharmacological studies have shown that Breviscapine has a wide range of pharmacological effects, including anti-oxidation, anti-fibrosis, anti-inflammatory, anti-aging, anti-platelet aggregation, reducing blood lipids, increasing blood flow, improving microcirculation, preventing and treating tumors, and anti-brain injury. At present, Breviscapine has been widely used in the treatment of diabetes, cerebral insufficiency, sequelae caused by a cerebral hemorrhage, hyperviscosity, cerebral thrombosis, nephropathy, liver disease, Alzheimer's disease and other complex diseases (311–313). Breviscapine reduces microglial activation by inhibiting inflammatory biomarkers (such as ROS, NO, and iNOS) in LPS-activated microglia. It also inhibited pro-inflammatory cytokines, especially TNF- $\alpha$ , in the rat brain after ischemia (314). Breviscapine reduces levels of NF- $\kappa$ B, MCP-1 and Notch-1 signaling *in vitro* and *in vivo* in animal models of ischemia. It also reduced microglial migration and adhesion. Breviscapine also inhibits the inflammatory microglia/macrophage phenotype through the Notch pathway and contributes to neuroprotection against ischemia/stroke (315).

(9) Chrysin: Chrysin is a flavonoid found in plant species such as *Oroxylum indicum* (L.) Vent. It is mainly used for intervention in the treatment of hyperlipidemia, cardiovascular and cerebrovascular diseases, anxiety, inflammation, gout, cancer, muscle enhancement, etc. (316–318). Chrysin may reduce the number of activated glial cells, production of pro-inflammatory cytokines, iNOS, COX-2, and NF- $\kappa$ B signaling in the brain after ischemia. Through this anti-inflammatory mechanism, chrysin reduces infarct size and improves neurological deficits (319).

(10) Epicatechin: Epicatechin is a natural plant flavanol compound, chemical formula C<sub>15</sub>H<sub>14</sub>O<sub>6</sub>, with epigallocatechin, catechin gallate, epicatechin gallate, epigallocatechin gallate collectively referred to as catechin compounds (320, 321). Epicatechin and other flavonoids have the effects of anti-oxidation, scavenging free radicals, enhancing metabolism, regulating immunity and anti-tumor (322, 323). Epicatechin reduces oxidative stress by activating the antioxidant Nrf2 pathway, thereby increasing neuronal viability against OGD-mediated injury. In MCAO, epicatechin down-regulates motor dysfunction by down-regulating microglia/macrophage activation (324).

#### 4.1.5 Glycosides

(1) Salidroside: Salidroside is a phenylpropanol glycoside extracted from *Rhodiola rosea* L., which has good anti-inflammatory and antioxidant effects (325). Han et al. (326) found that salidroside can reduce the size of cerebral infarction

in IS rats and improve neurological function and histological changes in rats, which may involve the activation of Nrtf2 pathway and its endogenous antioxidant system. Liu et al. (327) found that in the IS mouse model, salidroside decreased the expression of M1-type markers, increased the expression of M2-type markers, and induced the transformation of microglia from M1 phenotype to M2 phenotype. Salidroside can also inhibit LPS-induced BV2 microglia inflammatory response, mainly by activating PI3K/Akt signaling pathway, promoting Akt phosphorylation, inhibiting NF- $\kappa$ B p50 nuclear transcription, and then inhibiting cytokines. In addition, in a model of neuroinflammation after spinal cord injury, Li et al. found that salidroside can restore motor function in rats, increase the M2/M1 polarization ratio in the spinal cord, reduce the expression of Bax, NF- $\kappa$ B, iNOS and COX-2 mRNA, increase the expression of Bcl-2, p-AMPK, and reduce the expression of p-mTOR.

(2) Forsythin: Forsythin is the dried fruit of *Forsythia suspensa* (Thunb.) Vahl (328, 329). Modern pharmacological studies have shown that *Forsythia suspensa* has antibacterial, anti-inflammatory, antiviral, hepatoprotective, anti-tumor, immune regulation and antioxidant effects (328). Studies have found that *Forsythia suspensa* (Thunb.) Vahl and its constituents have significant effects in improving neurodegenerative diseases and other neuroprotection in the elderly (330). Meanwhile, forsythin may protect neuronal cells in the CA1 region of the hippocampus after ischemia by attenuating glial activation. Forsythin also reduces the levels of pro-inflammatory cytokines such as IL-1 $\beta$  and TNF- $\alpha$  (331).

(3) Ginsenosides: Ginsenoside is a steroid compound, also known as triterpenoid saponins, which mainly exists in *Panax L* (332). The experimental results showed that Ginsenoside inhibited the formation of lipid peroxide in the brain and liver, reduced the content of lipofuscin in the cerebral cortex and liver, and also increased the content of superoxide dismutase and catalase in the blood (333, 334). In addition, some monomer saponins in Ginsenoside such as rb1, rb2, rd, rc, re, rg1, rg2, rh1, etc. can reduce the content of free radicals in the body to varying degrees. Ginsenoside can delay neuronal senescence and reduce memory impairment in the elderly, and has a stable membrane structure and increased protein synthesis, thereby improving the memory ability of the elderly (332, 335). The inhibitory effect of ginsenoside Rd on inflammation was demonstrated by reducing microglial activation and inflammatory biomarkers, including iNOS and COX-2, to exert neuroprotective effects against transient focal ischemia (336). Ginsenoside Rb1 improves neurological deficit and reduces infarct size by reducing microglia activation. Ginsenoside Rb1 treatment reduces the mRNA levels of proinflammatory cytokines such as IL-6, TNF- $\alpha$  by downregulating NF- $\kappa$ B-mediated transcription in the ischemic brain. This suggests that its neuroprotective efficacy is exerted by down-regulating the inflammatory response of activated glia (337).

(4) Kaempferol glycosides: Kaempferol is a flavonoid compound mainly derived from the rhizome of *Kaempferol galanga L*, which is widely found in various fruits, vegetables and beverages (338, 339). It has been widely concerned because of its anti-cancer, anti-inflammatory, antioxidant, antibacterial, antiviral and other effects (340–342). Kaempferol glycosides, kaempferol-3-O-rutinoside and kaempferol-3-O-glucoside significantly reduced infarct volume, neurological deficits, neuronal and axonal damage in the brains of tMCAO-injured rats. Furthermore, these glycosides inhibit inflammation by reducing transcription mediated by GFAP, OX-42, phosphorylated STAT3, and NF- $\kappa$ B. These glycosides also inhibit macrophage O, iNOS, TNF- $\alpha$ , IL-1 $\beta$ , ICAM-1 and MMP-9 production for neuroprotective effects (343).

(5) Paeoniflorin: Paeoniflorin is derived from the roots of *Paeonia albiflora* Pall, *P. suffersticosa* Andr and *P. delarayi* Franch, and its content is high in *P. lactiflora* (344). Its pharmacological effects of paeoniflorin has significant analgesic, sedative, anticonvulsant effect, antithrombotic effect, anti-platelet aggregation, anti-hyperlipidemia effect, etc. (345, 346). Paeoniflorin ameliorates learning and memory impairment by reducing morphological and structural changes in the CA1 region of brain injury in rats with cerebral hypoperfusion. This neuroprotective efficacy was associated with reductions in inflammatory mediators (eg, NO) and proinflammatory cytokines (eg, IL-1 $\beta$ , TNF- $\alpha$ , and IL-6), and increases in anti-inflammatory cytokines (IL-10 and TGF- $\beta$ 1). Thus, down-regulation of the pro-inflammatory phenotype and increased anti-inflammatory phenotype of activated microglia/macrophages are associated with the neuroprotective efficacy of paeoniflorin (347).

#### 4.1.6 Others

(1) Fingolimod (FTY720): FTY720 is a high affinity agonist for sphingosine 1-phosphate (S1P) receptors and was developed from a sphingosine analogue extracted from *Ophiocordyceps sinensis* (Berk.) G.H. Sung, J.M.Sung, Hywel-Jones & Spatafora as a lead compound; it is approved by the US Food and Drug Administration for the treatment of relapsing-remitting multiple sclerosis (348). Among the four S1P receptor subtypes targeted by FTY720, the current study found that S1P1 and S1P3 are associated with cerebral ischemia (349). The therapeutic mechanism of FTY720 for ischemic stroke is not fully understood. Li et al. (350) found that FTY720 can activate the mammalian target of rapamycin/p70S6 signaling pathway and inhibit neuronal autophagy activity. Many scholars believe that (351, 352), the beneficial effect of FTY720 on IS has nothing to do with direct neuronal protection, but is anti-inflammatory and vascular protection by reducing the invasion of brain lymphocytes. Gaire et al. (349) found that FTY720 inhibits S1P3, thereby inhibiting the transformation of microglia to M1 type. Qin et al. (352) found that FTY720 activates signal

transducer and activator of transcription 3 and promotes the polarization of microglia from M1 to M2.

(2) 3-N-butylphthalide (NBP): NBP is a compound isolated from celery seeds, and there are three types of derivatives: L-NBP, D-NBP and DL-NBP (353). L-NBP has been approved for use in China. Among the three derivatives, L-NBP has the strongest biological effect and the best safety (353). NBP has neuroprotective effects on ischemic stroke animal models by inhibiting oxidative damage, neuronal apoptosis and glial cell activation, increasing the level of circulating endothelial progenitor cells (354, 355). Li et al. (356) observed that L-NBP could enhance the M2 polarization of microglia in animal models of cerebral ischemia and inhibit the M1 polarization.

(3) Danshenol bornanyl ester: Danshenol bornanyl ester is a new compound with anti-cerebral ischemia effect, which is designed and synthesized based on the active ingredient of *Salvia miltiorrhiza* Bge. and the effective structural fragment of borneol by using the principle of modern drug design (357, 358). Danshenol bornanyl ester significantly inhibits NF- $\kappa$ B activity, inhibits the production of pro-inflammatory mediators, and simultaneously promotes the expression of M2 mediators in LPS-stimulated BV2 cells and mouse primary microglia. Danshenol bornanyl ester also exhibits antioxidant activity by enhancing Nrf2 nuclear accumulation and transcriptional activity, increasing HO-1 and NQO1 expression, and inhibiting LPS-induced ROS production in BV2 cells. The aforementioned anti-neuroinflammatory and antioxidant effects could be reversed by Nrf2 knockdown. In addition, Danshenol bornanyl ester improves disease behavior in mice with neuroinflammation induced by systemic LPS administration, significantly reduces infarct volume in rats with transient MCAO (tMCAO), and improves sensorimotor and cognitive function. Danshenol bornanyl ester also restores microglia morphological changes and alters M1/M2 polarization (359).

(4) Arctigenin: Arctigenin is a lignan compound from *Arctium lappa* L., which can effectively inhibit the release of inflammatory factors. It inhibits the proliferation, migration and angiogenesis of human umbilical vein endothelial cells (HUVECs) induced by high glucose, and plays a protective and anti-oxidative stress role in HUVECs injury (360–362). Arctigenin reduces the activation of microglia by reducing the release of TNF- $\alpha$  and IL-1 $\beta$  in rats with ischemic injury. This anti-inflammatory effect of arctigenin contributes to its neuroprotective effect (363).

(5) Sesamin: Sesamin mainly comes from the roots of *Acanthopanax sessiliflorus* (Rupr. et Maxim.) Seem., the seeds or seed oil of *Sesamum indicum* DC., and the wood of *Paulownia tomentosa* (Thunb.) Steud. Its main pharmacological effects are inhibition of inflammation and anti-oxidative stress (364, 365). Current research found that sesamin may inhibit oxidative stress and reduces cleaved-caspase-3 activation, lipid peroxidation and increases GSH activity. It also inhibited inflammatory mediators such as peroxynitrite, iNOS, COX-2, Iba1, Nox-2 in the brains of

MCAO-challenged mice to exert their neuroprotective effects (366).

(6) Edaravone: Edaravone ameliorates cognitive decline and delays neuronal death after focal cerebral ischemia by inhibiting inflammatory biomarkers including iNOS, NO, ROS, IL-1 $\beta$  and TNF- $\alpha$  production. In addition, inhibition of inflammation, oxidative stress, and astrocyte activation are thought to be relevant mechanisms for the neuroprotective effect of edaravone against ischemic injury (314, 367).

(7) Tetramethylpyrazine (Ligustrazine): Ligustrazine is an alkyl pyrazine extracted from *Ligusticum wallichii* (368). It has potential anti-neural and anti-inflammatory activity in rats, can protect vascular endothelial cells, reduce capillary permeability, reduce vascular resistance in anesthetized dogs, and increase blood flow in brain, cerebral arteries and lower limbs (369, 370). Ligustrazine can also reduce the damage of neurons and microvascular endothelial cells and improve neurological signs. It has a short-term improvement effect on complete cerebral ischemia, and has a certain degree of promoting cerebral resuscitation, antagonizing systemic circulation and pulmonary blood pressure after cerebral ischemia (371). Ligustrazine has a strong inhibitory effect on rabbit platelet aggregation induced by ADP, collagen and thrombin *in vitro*, and inhibits the production of platelet malondialdehyde. Its mechanism is to inhibit the phosphorylation of phosphatidylinositol 4-phosphate (PIP) kinase and 20K protein in platelets (87). Ligustrazine can also reduce whole blood viscosity, red blood cell and platelet electrophoresis speed up, reduce fibrinogen, inhibit thrombosis (372). In regulating microglia, ligustrazine can reduce the activation of microglia/macrophages, lymphocyte infiltration and the production of inflammatory mediators in the brain after ischemia. It also reduces inflammatory responses and increases antioxidant/anti-inflammatory responses in microglia/macrophages and post-ischemic neurons *via* Nrf2/HO-1 (373).

(8) Cannabidiol: Cannabidiol is an ingredient extracted from *Cannabis sativa* L (374, 375). At present, its main pharmacological effects are analgesic and anti-inflammatory, inhibition of nerve growth factor-induced mast cell degranulation and neutrophil aggregation to inhibit allergic inflammation, and thus mediate immunosuppression (376, 377). Cannabidiol inhibits hippocampal neurodegeneration, cognitive and memory impairment, glial responses, and white matter damage against BCCAO. It also induces BDNF production in the hippocampus, promoting neurogenesis and dendritic reorganization in BCCAO mice (378).

(9) Ligustolide: Ligustolide is the main active ingredient in the volatile oil of *Angelica sinensis* (379). The current pharmacological Ligustolide can inhibit the proliferation of vascular smooth muscle cells and cell cycle progression, and inhibit vasoconstriction (380). It also increases vasodilation, antithrombotic and serotonergic activity, and reduces

platelet aggregation (381, 382). Currently, Ligustolide is widely used in the research and treatment of cardiovascular and cerebrovascular diseases and ischemic brain injury (383). Ligustolide can inhibit neuroinflammation and oxidative stress on CIRI damage (384) and reduces cerebral infarct volume and improves neurological function. Ligustolide-induced neuroprotection was accompanied by amelioration of neuropathological changes, decreased activation of microglia and macrophages, infiltration of neutrophils and lymphocytes, and downregulation of inflammatory mediators. This anti-inflammatory effect is controlled by the ERK/NF- $\kappa$ B signaling axis in the ischemic brain. Ligustolide-mediated inhibition of TLR4/Prx6 signaling induces neuroprotection against ischemic stroke (384).

## 4.2 Herb Extracts

### 4.2.1 Salvia Polyphenolic Acid

Salvia Polyphenolic Acid is an active ingredient extracted from *Salvia miltiorrhiza* Bge. Its main function is to improve the viscous state of blood, with blood circulation, blood stasis, and good clinical tolerance (385, 386). Current studies have shown that its mechanism of action is to inhibit the inflammatory response of endothelial cells, improve energy metabolism, promote vascular endothelial cell migration, and improve ischemia-reperfusion injury (380, 387, 388). Studies have shown that salvianolic acid can reduce the inflammatory factors (such as ICAM-1, IL-1 $\beta$ , IL-18 and TNF- $\alpha$ ) in the cerebral cortex of the rat brain MCAO/R model, and reduce the apoptosis of cortical neurons. Salvianolic acid can alleviate the cell damage of oxygen glucose deprivation/reoxygenation (OGD/R)-treated neurons alone and co-cultured with microglia, improve cell viability, and reduce the rate of apoptosis, suggesting that salvianolic acid may reduce the cytotoxicity of microglia to neurons. Salvianolic acid can reduce the expression of NLRP3 in microglia after cerebral ischemia-reperfusion injury (CIRI) in rats, and inhibit the expression of pro-inflammatory factors such as IL-1 $\beta$  and IL-18 in the brain. It can also inhibit the cleavage of the pyroptosis-related protein GSDMD in microglia after CIRI, and reduce the expression of NLRP3, ASC, caspase1, and IL-1 $\beta$  mRNA in microglia. Salvianolic acid can also reduce the number of Iba1 and P2X7 double-labeled microglia in the MCAO/R model rat cerebral cortex, and can reduce the expression of P2X7 protein and mRNA in microglia (194).

### 4.2.2 Panax notoginseng saponins

Panax notoginseng saponins are the main active ingredients of *Panax notoginseng* (Burkill) F. H. Chen ex C. H., mainly containing ginsenoside Rb1, ginsenoside Rg1, notoginsenoside R1 and other components (389). It can inhibit platelet aggregation in rabbits caused by ADP, and can also dilate cerebral vessels and increase cerebral blood flow (390, 391).

Current studies have shown that Panax notoginseng saponins have a wide range of functions in the central nervous system, cardiovascular system, blood system, immune system, anti-fibrosis, anti-aging, anti-tumor, etc. (392–394). Jia et al. found that Panax notoginseng saponins can improve cerebral blood flow, neurological deficits, tissue morphology, and neuronal damage. It can also promote the expression of CD206/Iba-1 in M2-type microglia, and up-regulate the expression of CD206, TGF- $\beta$  and IL-10 protein; inhibit the expression of CD16/Iba-1 in M1 type microglia cells and down-regulate the expressions of IL-1 $\beta$ , IL-6, TNF- $\alpha$  and iNOS protein. This suggests that Panax notoginseng saponins may promote the transition from M1-type polarization to M2-type in microglia (395).

### 4.2.3 Omega-3 polyunsaturated fatty acids (n-3 PUFA)

n-3 PUFA is one of the members of the PUFA family, mainly derived from deep-sea fish and some plants, among which eicosapentaenoic acid and docosahexaenoic acid are most involved in the regulation of human physiology. n-3 PUFAs play a role in the prevention and treatment of ischemic stroke (396, 397) can promote neurogenesis, increase peri-infarct vascular formation, improve glial scarring after cerebral ischemia, reduce mitochondrial dysfunction, reduce neuroinflammation, etc. (398, 399). Jiang et al. (400) found that n-3 PUFAs can switch the phenotype of microglia from M1 to M2 in mice with cerebral ischemia, which helps to improve white matter integrity and sensorimotor recovery.

### 4.2.4 Notoginseng leaf triterpenes

Notoginseng leaf triterpenes, as a valuable drug, have been found to have neuroprotective effects. It can reduce the expression of HMGB1, inhibit the inflammation caused by HMGB1, and inhibit the activation of microglia (IBA1) in hippocampus and cortex, thereby reducing the concentration of inflammatory cytokines including VCAM-1, MMP-9 and MMP-2 and ICAM-1 of IS in a dose-dependent manner. In addition, it can inhibit the activation of MAPKs and NF- $\kappa$ B, thereby ameliorating the neuropathological changes induced by CIRI (401).

### 4.2.5 Fructus Gardenia Extracts

Fructus Gardenia is a TCM with various pharmacological effects, such as anti-inflammatory, antidepressant, improving cognition and ischemic brain injury. GJ-4 is a natural extract from Fructus Gardenia, GJ-4 can significantly improve memory impairment, cerebral infarction and neurological deficit in MCAO/R-induced vascular dementia (VD) rats. Further studies showed that GJ-4 attenuated VD-induced neuronal damage. In addition, GJ-4 can protect the synapses of VD rats by up-regulating the expression of synaptophysin, postsynaptic density 95 protein (PSD95) and down-regulating the expression of N-methyl-D-aspartate receptor 1 (NMDAR1). Subsequent

investigations into the underlying mechanism found that GJ-4 could inhibit neuroinflammatory responses, supported by inhibiting microglia activation and reducing the expression of inflammatory proteins, ultimately exerting neuroprotective effects on VD (402).

The structures of those components are shown in Figure 2. The effects of natural botanical components on microglia/macrophages after cerebral ischemia are summarized in Table 1 and Figure 3.

## 5 Prospect

Microglia play a biphasic regulatory role in ischemic stroke. After IS, microglia were activated, migrated, and exerted pro-inflammatory and anti-inflammatory effects through M1/M2 phenotype polarization, respectively, and at the same time played a protective role by inhibiting M1 phenotype polarization or promoting M2 phenotype polarization. However, the research on induced cell polarization is limited to animal experiments and *in vitro* experiments, and the potential mechanism still needs further research. Apoptosis after IS involves many complex signaling pathways. Regulating the programmed death of neurons in the ischemic penumbra can save dying neurons to the greatest extent and promote the recovery of neural function. In addition, activation of SIPRs, TLRs, NLRPs, PPARs, and P2X7R may be the potential mechanisms for regulating

microglia after IS, however, the mechanisms need to be further studied.

Natural plant compounds may have great potential as therapeutic agents to reduce pro-inflammatory responses after cerebral ischemia. As can be seen from the foregoing, most of the current studies describe M1/M2 polarization, but most studies show a mixed signature of M1 or M2 microglial/macrophage phenotypes after cerebral ischemia. An urgent need to address is the need to define the M1 or M2 microglia/macrophage phenotype in experiments with these natural compounds. Furthermore, the markers currently used to differentiate M1 and M2 phenotypes are not microglia or macrophage specific. Therefore, technologies that can separate M1 from M2 microglia/macrophages (such as microfluidics and single-cell transcriptomics to identify novel microglia-specific biomarkers) are needed in the future.

The limitation of this review is that this review focuses on the detailed mechanisms of microglia/macrophages in IS and the mechanisms of natural compound intervention, but lacks a summary of other immune cells such as T cells, B cells, and neutrophils in IS. Since immune cells such as T cells and B cells also play an important role in the pathophysiological process of IS, it is recommended to review the mechanism of these immune cells in IS in the future (39, 169, 172).

In summary, it can be seen that not only single-component natural botanical components can exert a therapeutic effect on IS by regulating microglia, but multi-component natural botanical components also show potential synergistic effects in regulating

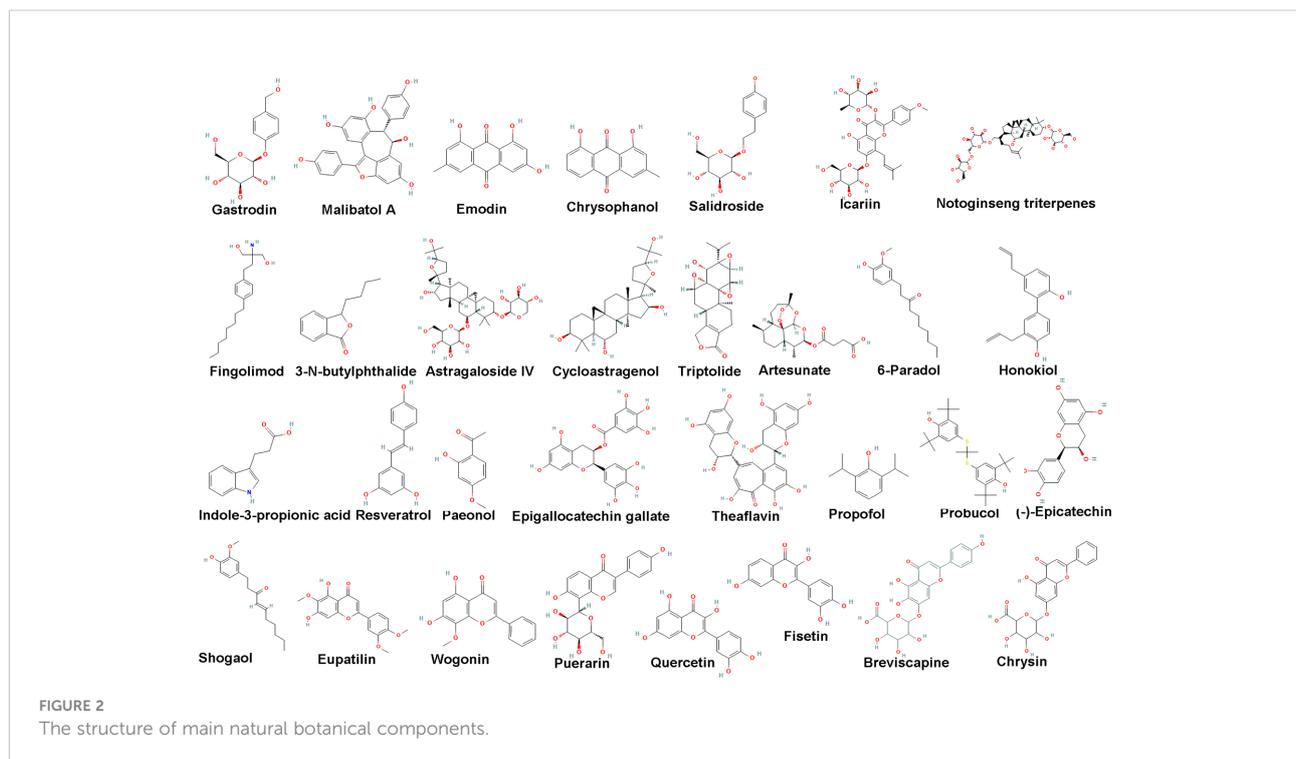


TABLE 1 Summary of the role of natural botanical components on IS.

Natural botanical component	Effects	Ischemia type	Category	Reference
Gastrodin	The volume of cerebral infarction and BBB permeability ↓; MMP2, MMP9, AQP4, IL-1β, COX-2 and iNOS↓; ZO-1↑	MCAO/R and OGD/R	Polyphenols and Phenols	(194)
Malibatol A	Promoting M2 microglial polarization	OGD/R	Polyphenols and Phenols	(195–197)
Emodin	MMP-9, TLR4, NF-κB, TNF-α, ICAM-1 ↓	MCAO	Anthraquinones	(230–233)
Chrysophanol	Notch-1, TNF-α and ICAM-1 protein ↓; Iba-1 positive cells↓; promoting the transformation of microglial M1 type to M2 type	MCAO	Anthraquinones	(234, 235)
Salidroside	CD16, CD32, CD11b, iNOS↓; CD206, Arg-1, TGF-β, Ym-1/2 ↑	MCAO	Glycosides	(326, 327)
Icariin	the activation of Iba1 and TLR4 in microglia ↓NF-κB p65 protein ↓; IL-1α and TNF-α ↓	MCAO	Flavonoids	(285)
Salvia Polyphenolic Acid	ICAM-1, IL-1β, IL-18, TNF-α, NLRP3, GSDMD, ASC, CASP1↓; Iba1/P2X7 double-labeled microglia↓	MCAO/R and OGD/R	Polyphenols and Phenols	(194)
Panax notoginseng saponins	CD206, TGF-β and IL-10↑;IL-1β, IL-6, TNF-α and iNOS↓;Promoting the expression of CD206/Iba-1 in M2-type microglia; Inhibiting the expression of CD16/Iba-1 in M1 type microglia cells	MCAO/R	Glycosides	(395)
Notoginseng leaf triterpenes	ICAM-1, VCAM-1, MMP-9, MMP-2, HMGB1 ↓	MCAO/R	Terpenes and Alkaloids	(401)
Omega-3 polyunsaturated fatty acid	Promoting the phenotype of microglia from M1 to M2.	MCAO	Lipids	(398–400)
Fingolimod	promoting the polarization of microglia from M1 to M2	Bilateral carotid artery stenosis	Other	(349–352, 403)
3-N-butylphthalide	Inhibiting oxidative damage, neuronal apoptosis and glial cell activation, increasing the level of circulating endothelial progenitor cells; promoting the M2-type polarization of microglia, inhibiting the M1-type polarization	IS patients; MCAO animal	Other	(356)
Danshenol bornanyl ester	HO-1 and NQO1↑; NF-κB ↓ Altering M1/M2 polarization	MCAO/R	Other	(359)
Astragaloside IV	M1-type microglia/macrophage markers CD86, iNOS, TNF-α, IL-1β and IL-6 mRNA ↓; M2-type microglia/macrophage markers CD206, Arg-1, YM1/2, IL-10 and TGF-β mRNAs ↑; the number of CD16/32+/Iba1+ cells↓; the number of CD206+/Iba1+ cells ↑; IL-1β, TNF-α and iNOS↓	MCAO	Terpenes and Alkaloids	(238, 239)
Cycloastragenol	SIRT1↑; p53, Bax/Bax ratio ↓;TNF-α and IL-1β mRNA↓; Inhibiting NF-κB p65 nuclear translocation; Inhibiting the activation of microglia and astrocytes	MCAO	Terpenes and Alkaloids	(243)
Triptolide	IL-1β, IL-6, TNF-α, IL-33, IL-10 ↓; promoting the M2-type polarization	IS patients; MCAO/R and OGD/R animal	Terpenes and Alkaloids	(248, 249)
Artesunate	TNF-α and IL-1β ↓; Inhibiting microglial activation	MCAO	Terpenes and Alkaloids	(255–258)
6-Paradol	Iba1 ↓; TNF-α and iNOS↓; Inhibiting microglia/macrophages	MCAO/R	Polyphenols and Phenols	(208)
Honokiol	NF-κB, NO, and TNF-α↓; Inhibiting the M1 phenotypes	2 vessel occlusion/ reperfusion	Polyphenols and Phenols	(212)
Indole-3-propionic acid	Iba1 ↓; Inhibiting microglia; Inhibiting the M1 phenotypes	2 vessel occlusion/ reperfusion	Polyphenols and Phenols	(213)

(Continued)

TABLE 1 Continued

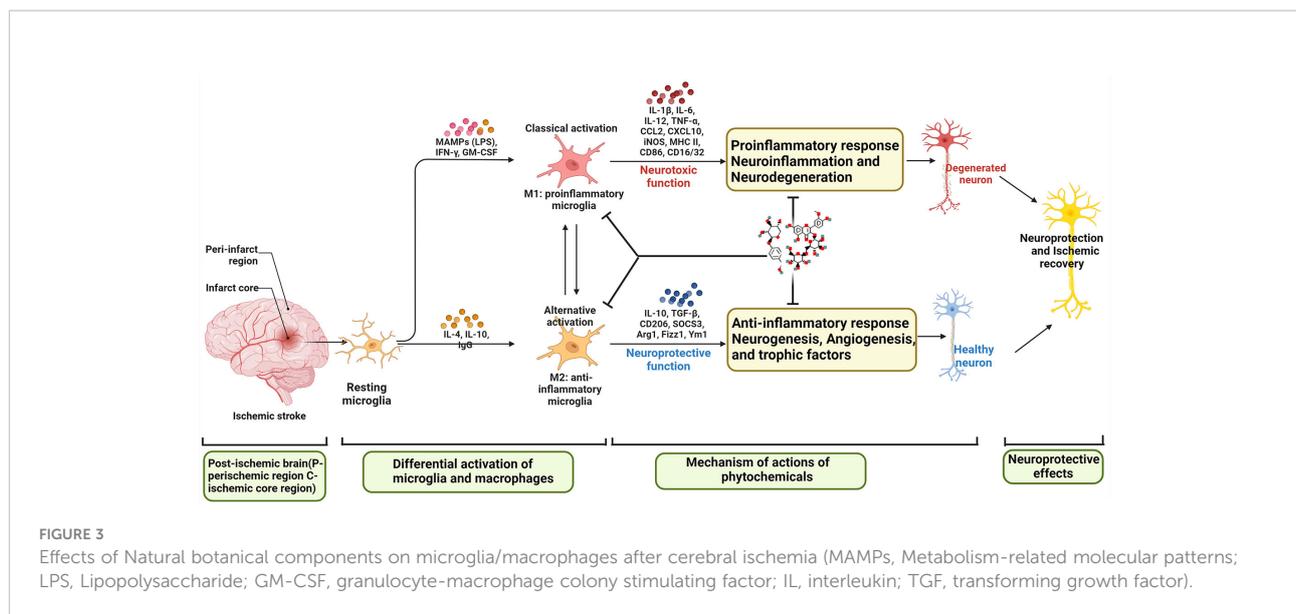
Natural botanical component	Effects	Ischemia type	Category	Reference
Resveratrol	Iba1 ↓; IL-1β and TNF-α↓; Inhibiting microglia; Inhibiting the M1 phenotypes	MCAO/R; Bilateral common carotid artery occlusion	Polyphenols and Phenols	(202, 203)
Paeonol	IL-1β↓; Inhibiting microglia; Inhibiting the M1 phenotypes	MCAO/R	Polyphenols and Phenols	(218)
Epigallocatechin gallate	iNOS↓; Inhibiting the M1 phenotypes	MCAO/R	Polyphenols and Phenols	(223)
Theaflavin	COX-2, iNOS↓; Inhibiting the M1 phenotypes	MCAO/R	Polyphenols and Phenols	(227)
Propofol	IL-1β, IL-6, TNF-α↓; Inhibiting microglia; Inhibiting the M1 phenotypes	MCAO/R	Polyphenols and Phenols	(314)
Probuco	COX-2, IL-1β, IL-7, iNOS↓; Inhibiting the M1 phenotypes	MCAO/R	Polyphenols and Phenols	(229)
6-Shogaol	Iba1 ↓; Inhibiting microglia	2 vessel occlusion/ reperfusing	Polyphenols and Phenols	(207)
Eupatilin	Iba1 ↓; Inhibiting microglia; Inhibiting the M1 phenotypes	MCAO/R	Flavonoids	(289)
Heptamethoxyflavonoids	BDNF↑; Iba1 ↓; Inhibiting microglia; Promoting the M2 phenotypes	2 vessel occlusion	Flavonoids	(290)
Wogonin	TNF-α, iNOS↓; Inhibiting microglia; Inhibiting the M1 phenotypes	MCAO	Flavonoids	(294)
Puerarin	COX-2↓; Inhibiting microglia; Inhibiting the M1 phenotypes	4 vessel occlusion	Flavonoids	(299)
Quercetin	iNOS↓; Inhibiting the M1 phenotypes	Bilateral common carotid artery occlusion	Flavonoids	(299)
Fisetin	TNF-α↓; Inhibiting the M1 phenotypes	MCAO/R	Flavonoids	(309)
Breviscapine	TNF-α, NF-κB, Notch-1, MCP-1, Hes-1 and iNOS↓; Inhibiting microglia; Inhibiting the M1 phenotypes	MCAO	Flavonoids	(314, 315)
Chrysin	Iba1, iNOS, COX-2, CD68, IL-1β, IL-6, IL-12, IL-1α, IL-17a, IFN-γ, and TNF-α ↓; Ym-1↑; Inhibiting microglia; Inhibiting the M1 phenotypes	MCAO/R	Flavonoids	(319)
Epicatechin	Iba1 ↓; Inhibiting the M1 phenotypes	MCAO	Flavonoids	(324)

microglia. This suggests that the combination of natural botanical components to treat multiple inflammatory models (including macrophages and microglia) is a promising direction, and we can see that the combination of natural botanical components will be more effective to achieve the desired therapeutic effect.

## 6 Conclusion

Intervention of natural botanical components and their derivatives in microglia-mediated neuroinflammation in IS is a promising research direction. In the absence of effective

neuroprotective drugs, we should pay more attention to the mechanisms of natural botanical components in regulating microglia-mediated neuroinflammatory diseases such as IS. Future research directions are suggested as follows: (1) Differentiate between microglia and macrophages through new techniques (such as single-cell transcriptomics and its derivatives) to more accurately determine the regulatory effects of natural compounds. (2) A more standardized and stable IS model is needed to determine the effects of drugs. (3) Using spatiotemporal omics to map the dynamic continuity state of microglia in natural botanical components intervening in IS. (4) Validate the long-term brain-protective effects of natural botanical components and the mechanisms regulating microglia in rodent and mammalian IS



models. (5) Pay attention to the pharmacokinetics, pharmacodynamics, and toxicological properties of natural botanical components. (6) Explore the synergistic effect of natural botanical components in inhibiting neuroinflammation. (7) If all results are favorable, the next step is to conduct clinical trials of potential phytochemicals to investigate their neuroprotective effects on cerebral ischemia/stroke (For example, the team is currently conducting a clinical trial of Naotai Fang in the treatment of cerebral small vessel disease: ChiCTR1900024524).

## Author contributions

TB, and JZ are responsible for the study concept and design. TB, JZ, KY, SW, WX, XZ, AG, LZ, JG are responsible for the data collection, data analysis and interpretation; JZ and KY drafted the paper; JG supervised the study; all authors participated in the analysis and interpretation of data and approved the final paper.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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