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Traditional Chinese Medicine Prevented Brain Injury *via* Regulating the Activation of Microglia After Ischemic Stroke*

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Abstract Inflammation plays a vital role in the pathophysiology of ischemic stroke. Resident microglia are the first to respond to inflammatory response in cerebral ischemia. Traditionally, Microglia are regard as an important contributor to inflammation to aggravate brain injury. However, Recent studies have found that activated microglia exert anti-inflammatory production against ischemic injury. Future therapies targeting microglia may not exclusively aim at suppressing microglia activation, but also at modulating microglia polarization at different stages of ischemic stroke. With lacking effective therapy strategies for stroke, considerable attention has been attracted by traditional Chinese Medicine (TCM). Many studies have reported that TCM protects ischemic injury by inhibiting activation of microglia and promote the different polarization of microglia phenotypes. The effects of TCM in mediating microglia activation and polarization during cerebral ischemia need to be further studied.

Key words stroke, microglia, inflammation, TCM
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Stroke is the leading cause of morbidity and mortality, which has become the most important heath issue worldwide[1]. About 6.7 million individuals were dead of stroke annually. Most alive stroke patients would suffer permanent disabilities, which increase economic burden of society[2]. The most common type of stroke are ischemic, accounting for 87% of all stroke[3]. Until now, tissue plasminogen activator (rtPA) is the only approved medical therapy of ischemic stroke by the Food and Drug Administration (FDA). The narrow therapy window and the risk of hemorrhagic transformation are the disadvantage of rtPA. Therefore, more than 95% of patients with ischemic stroke do not meet the criteria for thrombolysis. Even with rtPA thrombolysis, most stroke patients still have neurological deficits[4]. Therefore, developing new drugs for treating stroke is imminent.

After ischemia-reperfusion brain injury, microglia are rapidly recruited to the injured site and

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further activated to perform their function[5-6]. Activated microglia have dual functions at all stages of ischemic stroke[7]. On the one hand, microglia secrete pro-inflammatory and cytotoxic substance to exacerbate the damage[1,8]. On the other hand, microglia phagocytose cell debris and secrete anti-inflammatory to promote the recovery of the penumbra[9-10]. This dual action relates to the different phenotype of microglial under pathological stages after cerebral ischemia[11]. Reactive microglia are classified into M1 type producing deleterious effect and M2 type exerting neuroprotective function[12]. That developing new drug inhibits the activation of M1 microglia and promotes the polarization of microglia to M2 type might be an ideal therapeutic strategy for stroke[13].

The lack of effective treatment strategies for stroke has attracted the interests of researchers to traditional Chinese Medicine (TCM) [14-15]. Increasing evidence showed that TCM treats stroke *via* modulating the activation of microglia, indicating that TCM might be an ideal treatment strategy for CNS disease[16]. In this paper, we reviewed recent studies about using TCM to prevent ischemic damage *via* mediating microglia activation and polarization.

1 Microglia activation following stroke

Microglia exhibit ramified morphology branching under physiological conditions which is referred to as "resting microglia" state[17]. Microglia are resident macrophages which can be activated under pathological conditions[18]. Once activated, the microglia exhibit shortened processes with the increasing of cell volume and the disappearance of the cell surface, which is called as "amoeboid like"[19-21]. Multiple markers such as CD45, MHC II, CD86 are upregulated with activation of microglia[22]. In addition, Iba-1, F4/80 and CD69 were used to specifically identify activated microglia[23]. That patterns of markers of microglia are expressed in the peri-infarct region is different from that in infarct region after cerebral ischemic injury. The marker of microglia in the peri-infarct region is $Iba1^{+}CD68^{-}$, while the microglia in infarct region is $Iba\text{-}1^{+}CD68^{+}$[24-25]. Activated microglia in infarct region mainly express MHCI and act as scavenger cells[26]. While activated microglia away from the infarct region mainly express MHCII and participate in the process of Wallerian degeneration[27]. Therefore, microglia in different regions after cerebral ischemia perform different functions.

In addition to the different pattern recognition molecules on the cell surface, multiplicity of morphological types of microglia can be seen in post-ischemia[11]. At the 1−3 days of ischemic injury, "stellate" microglia with intense and shortened processes were discovered in the cortex. While in the 6 days after ischemia, "amoeboid" microglia with large and round cell body were found in the infarct zone[28-29]. The morphological diversity of microglia is related to the different functions of microglia, which can reflect the severity of ischemic injury[30-31].

2 Dual functions of Microglia during ischemic stroke

As the first line of defense in the brain, microglia can be activated and recruited to the lesion area in a few minutes to several hours after ischemia[32]. Despite being the first to respond to brain injury, the activation of microglia would last for 2 weeks[33]. During the pathological of cerebral ischemia, microglia have functionally distinct phenotypes. M1 type microglia is characterized by molecular histocompatibility complex (MHCI), differentiation group CD16, CD32 and inducible nitric oxide synthase (iNOS) [34-35]. M1 type microglia perform detrimental function through producing proinflammation cytokine, such as IL-1β, TNF- α, MMP9, and cytotoxic substance to promote the destruction of pathogens, the damage of neurons and the destruction of blood-brain barrier[36-38]. Microglia can either exacerbate damage or promote repair, relying on the activation signals they receive. *In vitro* stimulated "resting microglia" with IL-4 to induce the differentiation of M2 type microglia[39]. The surface maker of M2 microglia include CD206, CD301 and Arginase-1[39-40]. Conversely, M2 microglia secrete anti-inflammatory factors such as IL-4, IL-13, IL-10 and transforming factor β (TGF- β) to protect tissue from the damage of inflammation[41-42]. In addition, M2 microglia can also participate in the tissue repair by altering gene expression to promote the expression of neuroprotective factors such as brain-derived neurotrophic factor (BDNF), glial cell line-derived

neurotrophic factor (GDNF) and insulin-like growth factor (IGF)[43-44].

The microglia phenotype in the peripheral zone of the infarct showed dynamic changes. The main microglia type is M2 with high expression of CD206 during the first 24 hours of stroke. Temporal analyses of microglial phenotypes demonstrated that M2-like microglia were detectable from 12 hours, peaked at 24 hours in ischemic animals[45]. M1 microglia with high expression of CD16 was not expressed in a large amount on the first day after cerebral ischemia, but the total amount exceeded M2 type microglia at 48 hours. M1 type microglia can be persistently expressed in the whole subacute phase of cerebral ischemia[41-45].

3 Traditional Chinese medicine mediate microglia after stroke

In the above, we discussed the different functions of microglia after ischemic stroke. In summary, microglia have an M2 type that is activated at an early stage and have an anti-inflammatory effect. The amount of M1 type microglia are robustly increased follow neuron damaging. Under proper stimulations, M1 type microglia then converts to an M2 type that promotes repair during the recovery period. Given the lack of neuroprotective agent development for ischemic stroke, treatment strategies targeting microglial cells seem to be feasible. For the treatment of ischemic stroke by regulating microglia, the first is to suppress the inflammatory effect after stroke by inhibiting the generation of M1 type, and the second is to activate the M2 type to play a protective role to promote tissue repair[46]. However, the development of drugs to regulate the phenotypic transition of microglia requires clearing the specific role of drugs on microglia to select the appropriate time window.

It has been several centuries that traditional Chinese Medicines (TCM) were widely used in cardiovascular diseases[47]. Recent studies have shown that TCMs are effective for the treatment of stroke. TCMs include TCM preparation, Chinese herb medicine, and TCM-derived active compounds[48]. We summarized TCM used for treating stroke by regulating microglia (Figure 1 and Table 1).

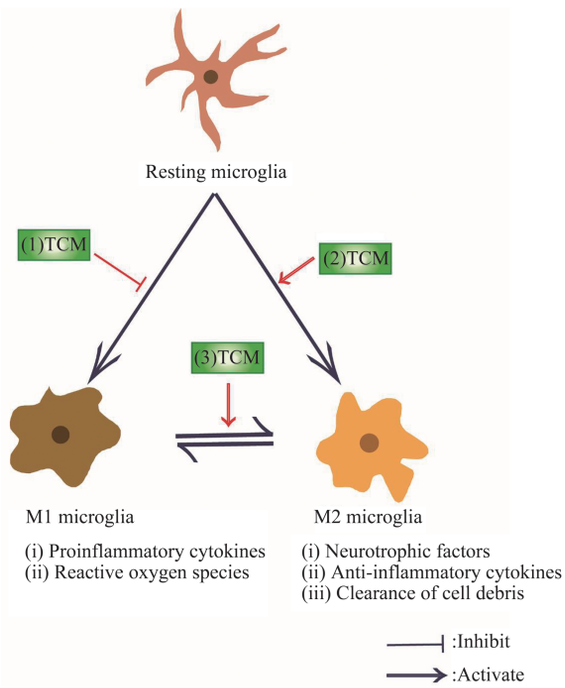

Fig. 1　Traditional Chinese medicine (TCM) CH exert neuroprotective effect against ischemic injury by modulating microglia after stroke: (1) TCM inhibit activation of microglia; (2) CTM promote "resting microglia" differentiating to M2 type microglia; (3) TCM modulate M1 microglia transform to M2 microglia

4 TCM preparation

4.1 Gualou Guizhi decoction

Gualou Guizhi decoction (GLGZD), a wellestablished traditional Chinese Medicinal formulation, is composed of six herbs, including *Ramulus cinnamomi* , *Trichosanthis radix, Glycyrrhiza, Paeonia lactiflora, Zingiber officinale Ros*coe and *Fructus jujubae*, based on traditional Chinese medical theories "yin yang". It was widely used for the treatment of neurological disease, such as stroke, epilepsy and spinal cord injury. In the rat model of focal cerebral ischemia-reperfusion, admonition of 14.4 g/kg GLGZD improve neurological defects through neurological score. Brain cerebral infarct size was also significantly decreased at day 7 following cerebral ischemia after treated with GLGZD[49]. GLGZD inhibited M1 type microglial

cells induced by LPS *in vitro*. LPS induced BV2 cells also released less proinflammatory cytokine including IL-6, TNF-α, IL-1β and iNOS after treated by GLGZD[50]. Those proinflammatory mediator were also decreased *in vivo*[49]. Of note, the motility of BV2 induced by LPS was significantly inhibited by GLGZD[51]. In the MCAO model, treatment with GLGZD significantly reduced NF-κB translocating to nucleus which means that GLGZD affecting microglia mainly dependend on the NF-κB pathway microglia[52-53]. Another study found that the MAPK signaling pathway also involved in GLGZD improving ischemic brain injury.

4.2 Shaoyao−gan cao decoction

Shaoyao-gan cao decoction (SGD) is composed of 2 herbs, *Pasenia lactiflora* and *Glycyrrhiza uralensis*. Paeoniflorin, the main active compound of SGD, has been shown the ability to protect against neuronal loss *in vitro*[54]. SDG can ameliorate brain infarct volume after ischemic stroke. Administration of SGD can significantly reduce the accumulation of microglia in the cortex at 96 hours following cerebral ischemia-reperfusion. At the same time, the M1 type microglia pro-inflammatory factor TNF-α was significantly decreased, while the M2 type microglial cytokine TGF and VEGF were robustly increased[55]. SGD is the only TCM preparation reported to inhibit M1 type microglia and promote M2 type microglia, which imply SGD can be not only used to promote injury reaction but also facilitate repair.

4.3 Xueshuantong

Sanqi, the root of *Panax notoginseng*, is widely used in vascular disease. Xueshuantong (XST) for injection (lyophilized) is a standardized product extracted from *Sanqi*. In the rat MCAO model, oral administration of 50 mg/kg XST significantly reduced infarction area[56]. Other research found that the counted number of microglia that positively reacted to Iba-1 were significantly reduced after treating with XST. Although the study of XST did not directly describe the role of regulating the phenotype of microglia, we can find that administration of XST can inhibit M1 type microglia production (IL-1β, iNOS) in the early stage of cerebral ischemia from related investigations[56]. In addition, XST can exhibit an antioxidant effects through ROS signaling pathway to protect vascular wall cells[57]. In conclusion, XST may be an effective M1-type microglia inhibitor that can be used as neuroprotective agent in the early stage of stroke.

5 Herb

5.1 Ligusticum chuanxiong

Ligusticum chuanxiong (LCX) is a commonly TCM applied in the empiric treatment of cerebrovascular disease[58]. It has been verified that both herbs and extracts of LCX can be used to protect neuron from oxidative stress *in vivo* models[59-60]. Recent studies reveal that LCX has anti-inflammatory effect. Senkyunolide A and Z-ligustililde were extracted from LCX remarkably down-regulate the expression of TNF-α in LPS induced BV2 cells with no influence on the viability of BV2 cells[61]. So far, only a few studies have showed that LCX inhibits LPS-induced M1 microglia. Whether LCX has promotive effect to M2 type has not been reported. In addition, the mechanism by which LCX modulate over-activation of microglia need to be further invested.

5.2 Cuscuta chinensis

The semen of Cuscuta chinensis (CS) was known to process various biological activities, such as antioxidant, neuroprotective and to improve liver conditions. CS inhibits M1 type microglia induced by LPS *via* blocking the NF-κB pathway. Unlike other M1 type microglia inhibitors, CS suppresses M1 type microglia COX-2 and PGE_2 production[62]. Oxidative stress is one of the main factors causing hemorrhagic transformation[63-64]. The application of CST in preventing hemorrhagic transformation after rtPA treatment to ischemic stroke is worthy to further studying.

5.3 Magnolia officinalis

Magnolia officinalis is a traditional Chinese medicine has various bioactivities, including anti-apoptosis[65], anti-oxidation[66] and anti-inflammation[67]. Studies have shown that more than one components of Magnolia can improve ischemic injury. Honokiol and Magnolol which are active ingredients of Magnolia officinalis treat cerebral ischemic damage by inhibiting the activation of microglia to reduce the production of inflammatory

factors[68-69]. At present, only few studies on Magnolia officinalis mentioned that Magnolia officinalis can inhibit the activation of microglia and inhibit the production of M1 type microglia. Therefore, the specific mechanism of Magnolia officinalis regulating microglia require further research to fully understand the therapeutic effect of Magnolia officinalis on ischemic stroke and the appropriate administration time.

6 Active compounds

6.1 Schisandrin B

Schisandirin B (Sch B) is an active compound of *Schisandra* fruit which is known to process pharmacological effects on multiple pathological phenomena. There are more than 30 ligands isolated from Schisandra fruit to the date. Pretreatment with Sch B infused could suppress the brain lesion, improve the neurological deficits and decrease the level of proinflammatory cytokine IL-1β, TNF-α[61]. In addition, the activation of microglia was inhibited after administration of Sch B in the rat MCAO model. Other studies found that Sch B was capable to reduce neuronal death in LPS-treated cocultures of neuron-microglia *via* inhibiting production of ROS, NO and IL-1β[70]. Further experiments were carried out to explore the specific mechanism of Sch B inhibiting the activation of microglia. The study found that Sch B not only inhibits the NF-κB signaling pathway, but also activates PPARγ signaling pathway[70-71]. The protective effect of Sch B on cerebral ischemia may be due to the regulation of microglia polarization to M2 type.

6.2 Asiaticoside

Asiaticoside (AS) is an active compound isolated from *Centella asiatica (L.)*. In the mice model of transient bilateral common carotid artery occlusion, memory impairment of mice was attenuated with the reduction of the activation of microglia after treated with AS[72]. More experiments should be performed to figure out the specific role of AS in regulating microglia.

6.3 Astragaloside IV

Astragaloside IV (AS-IV) is the major components in extracts of Chinese medicine herb *Astragalus membranaceus*[73]. AS-IV was found to improve cognitive impairments caused by cerebral ischemia. Studies indicated that AS-IV significantly decreased the levels of M1 type microglia proinflammatory cytokine such as TNF-α, IL-1β and iNOS through inhibiting the activation of microglia in the mice model of cerebral ischemia and reperfusion (CIR) [74]. Judging from the current research, it is likely to be exerted by suppressing the polarization of M1 type microglia.

6.4 MLC901

MLC901 (NeuroAiD II), a product of combing herbal extracts, has been shown to have neuroprotection *in vivo* and *in vitro*[75]. In animal ischemic models, administration of MLC901 significantly reduced inflammatory cytokine TNF-α, IL-1β and remarkably increased the anti-inflammatory cytokine IL-10 with reduction of NF-κB subunit while inhibiting microglia activation[76].

6.5 Icariin

Icariin is a flavonoid component isolated from *Herba Epimedii*[77]. Icariin improve neurological deficit and reduce brain infarct volume *via* inhibiting the NF-κB pathway and activating PPARγ signaling pathways[78]. Icariside II, a metabolite of icariin, can also protect against cerebral ischemia-reperfusion injury inhibition of inflammatory response mediated by NF-κB and PPARγ in rats[79]. NF-κB signaling and PPARγ are the key mechanisms of microglia polarization regulation[80-81]. That Icariin can inhibit NFκB and promote PPARγ suggests that Icariin may not only inhibit M1 type polarization, but also can inhibit M2 type polarization. Therefore, the next study can focus on considering extending the administration time of Icariin to observe whether Icariin has a long-term effect.

6.6 Scutellarin

Scutellarin is the main active component isolated from *Erigeron breviscapus*[82]. It has been reported that Scutellarin plays a neuroprotective role in the animal ischemic model[83]. Antioxidant and anti-apoptotic properties of Scutellarin may contribute to neuroprotective function of Scutellarin[84-86]. NO production is decreased at the early stages of neuron damage induced by hydrogen peroxide after treating with Scutellarin[85]. In addition, Scutellarin exhibits anti-inflammatory functions through reducing

inflammatory mediators, inhibiting activation of microglia and resecting mobility of microglia[87]. Further studies found that the expression of NF-κB and Notch-1 was significantly attenuated by admiration of Scutellarin in activated. Notably, the phenotype of microglia can be altered by Scutellarin[83].

6.7 Senkyunolide I

Senkyunolide I(SEI) is a natural product extracted from *Ligusticum chuanxiong* Hort[88]. In the oxygen-glucose deprivation (OGD) model of BV2 cells, SEI show the ability of exerting anti-inflammation. The release of pro-inflammatory mediator, including TNF-α, IL-6 and iNOS, were significantly inhibited by SEI exposure to OGD for 3 hours. This study also found that SEI suppressed the activation. After treatment with SEI, the level of inducible Hsp70 is dramatic increased depending on TLR4/MyD88 pathway, which is also confirmed in rat primary microglia[89].

6.8 Andrographolide

Andrographolide is a bioactive compound derivatized from *Andrographis panlculata*[90]. In the rat permanent MCAO model, reduction in neurological deficits and brain infarct volume can be observed after treatment with Andrographolide. Consistent with previous research, the number of microglia in both the infarct core and the peri-infarct region was dramatic decreased with inhibiting activity of microglia[91]. In microglia cultures, the level of M1 type microglia proinflammatory mediators including NO, ROS and TNF-α can be suppressed by administration of Andrographolide[92]. Researcher found that NF-κB pathway is involved in the anti-inflammatory effect of Andrographolide[91]. From the above conclusions, we can find that Andrographolide exerts anti-inflammatory effects to treat ischemic stroke by inhibiting M1-type polarization.

6.9 Celastrol

Celastrol is a quinone compound isolated from *Tripterygium wilfordii* and *Celastrus regelii*[93-94]. Recent studies found that brain infarct volume was reduced after treatment with celastrol. Furthermore, the expression of inflammatory mediators induced by OGD was inhibited through IL-33/ST2 axis-mediated M2 microglia polarization after treatment with Celastrol[95].

6.10 Ilexonin A

Ilexonin A is an active compound isolated from traditional Chinese medicine *Ilex pubescens* Hook. Recent studies found that the number of Iba-1 positive cells were significantly decreased with the treatment of Ilexonin A in the animal ischemic model, which suggest that Ilexonin A inhibit activation of microglia induced by stroke. Additionally, it is found that number of amoebalike cells significantly decreased, whereas the number of rodlike cells increased after treatment with Ilexonin A. The neuroprotective function of microglia is based on release of anti-inflammatory mediator of M2 type microglia. VEGF and Flk1 were progressively increased following CIR and administration of Ilexonin A[96]. Therefore, the next study may consider long-term administration of Ilexonin to observe the effect on M2 microglia.

6.11 Esculentoside A

Esculentoside A (EsA) is a saponin compound isolated form *phytolacca esculenta*. It has been reported that EsA pretreatment significantly decreased production of proinflammatory mediators including iNOS, COX-2, IL-1β and TNF-α induced by LPS in both BV2 microglia and primary cultured microglia[97]. The inhibitory effect of EsA on M1 microglia *in vitro* has been verified, so the therapeutic effect of EsA on ischemic animal models is imminent.

6.12 Trans−Cinnamaldehyde

Trans-Cinnamaldehyde (TCA) is an active compound isolated from *Cinnamomum cassia*. TCA protects neuronal PC12 cells from viability loss and apoptosis insulted by OGD/R, which is associated with reduction of production of NO. The neuroprotection of TCA can be abolished by administration of the inhibitor of phosphoinositide 3-kinase (PI3K), suggesting that TCA exert neuroprotective against ischemic injury by provoking PI3K pathway[98]. In the mice MCAO model, brain infarct volume and neurological deficit can be significantly reduced after treatment with TCA. Additionally, the activation of BV2 microglia cell induced by LPS can be suppressed by TCA. Further study found that TCA protect neuron from cerebral ischemia by blocking NF-κB pathway[99].

Table 1 Effect of TCM on microglia after ischemic stroke

Type	TCMs	Influence on microglia	Mechanism
TCM preparation	*Gualou Guizhi decoction*	Inhibiting the polarization of M1 type[48] Suppressing M1 type proinflammatory cytokine IL-6, TNF-α IL-1β and iNOS[48] Inhibiting the motility of BV2[49]	Inhibiting NF-κB signaling pathway and MAPK signaling pathway[50-51]
	Shaoyao-gan cao decoction	Inhibiting the polarization of M1 type and promoting polarization of M2 type[53]	Unknown
Herb	*Xueshuantong*	Reducing M1 type microglia production IL-1β,iNOS[55]	Inhibiting Nrf2 signaling pathway[55]
	Ligusticum chuanxiong	Inhibiting M1 type microglia production IL-1β, TNF-α[59]	Unknown
	Cuscuta chinensis	Inhibiting M1-type microglia products COX-2 and PGE_2 production[60]	Inhibiting NF-κB pathway[60]
	Magnolia officinalis	Inhibiting the activation of microglia Reducing the release of M1 type production IL-1β, TNF-α[66-67]	Unknown
Active compounds	*Schisandrin B*	Inhibiting the release of M1 type production IL-1β, TNF-α, ROS and NO[68]	Inhibiting the NF-κB signaling pathway[72] promoting PPARγ signaling pathway[73]
	Asiaticoside	Inhibiting the release of M1 type production[70]	Unknown
	Astragaloside IV	Decreaseing the levels of M1 type production TNF-α, IL-1β and iNOS[72]	Unknown
	MLC901	Reducing the M1 inflammatory cytokine TNF-α, IL-1β[74]	Inhibiting the NF-κB signaling[74]
	Icariin.	Inhibiting the polarization of M1 type and promoting polarization of M2 type[76]	Inhibiting the NF-κB signaling pathway promoting PPARγ signaling pathway[77]
	Scutellarin.	Reducing the M1 production NO[83] Inhibiting activation of microglia and resecting mobility of microglia[85]	Inhibiting NF-κB and Notch-1[81]
	Senkyunolide I.	Reducing the M1 inflammatory cytokine TNF-α, IL-6 and Inos[87]	TLR4/MyD88 pathway with increasing the level of inducible Hsp70[87]
	Andrographolide.	Inhibiting M1type production NO, ROS and TNF-α[90]	Inhibiting NF-κB pathway[89]
	Celastrol	Inhibiting M1type production and promoting the polarization of M2 type[92]	IL-33/ST2 axis[92]
	Ilexonin A	Inhibiting M1type production and increasing M2 type production VEGF and Flk1[93]	Unknown
	Esculentoside A.	Inhibiting M1 type production iNOS, COX-2, IL-1b and TNF-α[94]	Unknown
	Trans-Cinnamaldehyde	Inhibiting the polarization of M1 type[96]	Provoking PI3K pathway[95] Blocking NF-κB pathway[96]

7 Conclusion

Inflammation plays an important role in ischemic stroke. As the first line of defense in the brain, Microglia participate in the pathological process of inflammatory response to stroke[6]. After the onset of cerebral ischemic, microglia respond to ischemic rapidly and are activated. As we knew, inflammation can be divided into 3 phases[18]. TCM involves changes in the alteration and phagocytosis in the second phase of exudation by altering microglia. Microglia play dual role following stroke with different phenotype. In the ischemic injury, regulating the transformation of microglia M1 to M2 is beneficial to the recovery of ischemic injury. TCMs protect neurons against the initial ischemic injury by regulating activation of microglia, but whether those TCMs can modulate the polarization of microglia is not invested. That Many TCMs inhibit the proinflammatory effect of microglia referred to inhibit polarization of microglia to M1 phenotype, which means that those TCMs are capable to regulate the polarization of microglia to M2 phenotype. Only a

few of TCMs have been studied whether they can regulate M2 polarization. Those TCMs are worth to be further invested, which can help those TCMs be used more widely. TCMs are inexpensive, easily accessible, and safe, so they attract considerable attention as pharmacological intervention against stroke. If these active herbal compounds are found in laboratory research to help treating stroke, then large and well-designed study to confirm whether they are effective in humans. Further study on TCMs to regulate the polarization of microglia after stroke can benefit discover of component for stroke, but also help scientist to learn more about the pathological role of microglia after stroke.

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中药通过调节小胶质细胞激活改善缺血性脑卒中*

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摘要　炎症反应是造成脑卒中继发性脑损伤的关键因素之一. 小胶质细胞作为脑内免疫细胞，在脑卒中的炎症反应具有重要作用. 传统观念认为小胶质细胞促进炎症反应加重脑损伤. 近年来的研究发现，激活的小胶质细胞还能产生抗炎作用来加速脑损伤修复. 因此，目前的研究将小胶质细胞分为促炎的M1型和抗炎的M2型. 结合目前缺血性脑卒中的神经保护剂相对较少，靶向调控小胶质细胞的极化可能成为脑卒中新的治疗策略. 研究发现中药能够通过抑制M1型小胶质细胞，并促进M2型的小胶质细胞来改善缺血性脑损伤，从而展现出对缺血性脑卒中的治疗潜力. 本文综述中药通过调节小胶质细胞极化表型来治疗脑卒中的相关研究，以期为缺血性脑卒中药物开发提供新的思路.

关键词　脑卒中，小胶质细胞，炎症，中药

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