Drug Design, Development and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

Novel Insight into the Modulatory Effect of Traditional Chinese Medicine on Cerebral Ischemia-Reperfusion Injury by Targeting Gut Microbiota: A Review

Yisong Ren, Gang Chen, Ying Hong, Qianying Wang, Bo Lan, Zhaozhao Huang

Department of Critical Care Medicine, Chengdu Pidu District Hospital of Traditional Chinese Medicine, Chengdu, Sichuan Province, 611731, People's Republic of China

Correspondence: Zhaozhao Huang, Department of Critical Care Medicine, Chengdu Pidu District Hospital of Traditional Chinese Medicine, No. 169, Zhongxin Avenue, Pidu District, Chengdu, Sichuan Province, 611731, People's Republic of China, Email tcmhzz@126.com

Abstract: Cerebral ischemia-reperfusion injury (CIRI) is clinically characterized by high rates of morbidity, disability, mortality, and recurrence as well as high economic burden. The clinical manifestations of CIRI are often accompanied by gastrointestinal symptoms such as intestinal bacterial dysbiosis and gastrointestinal bleeding. Gut microbiota plays an important role in the pathogenesis of CIRI, and its potential biological effects have received extensive attention. The gut microbiota not only affects intestinal barrier function but also regulates gastrointestinal immunity and host homeostasis. Traditional Chinese medicine (TCM), a multi-component and multi-targeted drug, has shown remarkable effects and few adverse reactions in the prevention and treatment of CIRI. Notably, the effect of TCM on CIRI by regulating gut microbiota and maintaining gastrointestinal homeostasis has gradually become a hot topic. This review summarizes the functional role of the gut microbiota in the development and progression of CIRI and the therapeutic effects of TCM on CIRI by improving gut microbiota dysbiosis, affecting gut microbiota metabolism, and maintaining host immunity. The active ingredients of TCM used for the treatment of CIRI in relevant studies were saponins, triterpenoids, phenolics, and alkaloids. In addition, the clinical effects of TCM used to treat CIRI were briefly discussed. This review established the clinical significance and development prospects of TCM-based CIRI treatments and provided the necessary theoretical support for the further development of TCM resources for the treatment of CIRI.

Keywords: cerebral ischemia-reperfusion injury, ischemic stroke, gut-brain axis, gut microbiota, traditional Chinese medicine

Introduction

Ischemic stroke is a common cerebrovascular disease with high morbidity, lethality, and disability, and is becoming increasingly younger.[1,2] Globally, approximately 15 million patients suffer from ischemic stroke every year, resulting in more than half a million deaths and 5 million permanent disabilities.[3] The incidence of ischemic stroke has gradually increased owing to demographic changes and the prevalence of diabetes and obesity, which places a heavy economic burden on families and society.[4] Currently, treatment strategies for improving the clinical symptoms of ischemic stroke include thrombolysis, thrombectomy, and drugs.[5,6] Recombinant tissue plasminogen activator is the only drug approved by the US Food and Drug Administration for the treatment of ischemic stroke.[7] However, a few drawbacks of intravenous thrombolysis include partial recanalization, hemorrhagic transformation, delayed reperfusion, and secondary damage.[8] In addition, ischemic stroke is often accompanied by vascular recanalization and blood flow reperfusion, which further aggravates cellular metabolic disorders and organ damage, ultimately resulting in severe neurological function deficiencies known as cerebral ischemia-reperfusion injury (CIRI). Notably, CIRI can aggravate brain injury and lead to high rates of disability and death.[9] Unfortunately, the pathogenesis of CIRI remains unclear. Therefore, elucidating the

Received: 12 October 2024
Accepted: 21 December 2024
Published: 10 January 2025

pathogenesis of CIRI and developing safe and effective therapeutic agents are major research challenges in the field of ischemic stroke.

Increasing evidence has shown that the functional role of the intestinal microbiome in cerebrovascular diseases has recently attracted considerable attention from scholars at home and abroad.[10] The intestinal microbiome is a diverse community of microorganisms that lives in the gastrointestinal tract,[11] including bacteria, fungi, parasites, and viruses. The intestinal microbiome consists of six phyla: *Proteobacteria, Actinomycetes, Fusobacterium, Verrucomicrobia, Firmicutes*, and *Bacteroides*. Among them, *Firmicutes* and *Bacteroides* are the most abundant, accounting for 70–75% of healthy bacteria.[12] Of note, the intestinal microbiome is frequently referred to as a super "organ"[13] and is sometimes known as the "second brain"[14] because of its involvement in several immunological, neurological, and endocrine reactions. Moreover, the intestinal microbiome is of vital importance to the central and intestinal, this relationship is named as the "microbiome-gut-brain" axis.[15] Previous studies have found that gut microbiota dysbiosis is closely related to CIRI and is a key risk factor for cerebrovascular disease.[16] CIRI can alter in the composition of the gut microbiota and lead to change the secretion of gastrointestinal hormones, which are important factors with implications for the pathology and treatments of CIRI.[17,18] Numerous studies have demonstrated that gut microbiota disorders cause structural and functional abnormalities during the progression.[19] Wen et al[20] reported that 50% of patients with ischemic stroke developed gastrointestinal complications in the clinical setting, including dysphagia, gastrointestinal bleeding, constipation, and bowel incontinence. Notably, some studies have found that gut microbiota dysbiosis may serve as a new biomarker for the prevention and treatment of ischemic stroke.[21–23] Lou et al[24] proved that gut microbiota is closely related to the occurrence of high on-treatment platelet reactivity in patients with ischemic stroke. Meanwhile, *Bacteroidetes* have been shown to be highly correlated with infract size and neuroinflammation.[25,26] Through neuronal networks, the brain and gut communicate bidirectionally to form a complex "gut-brain" axis. On the one hand, the brain affects the function or permeability of the gut by transmitting nerve impulses to reduce intestinal motility and secretion.[27] On the other hand, the gut microbiota reversely makes an effect on the brain function by sending signals back into the brain through the neuro-immune and endocrine pathways.[28] Furthermore, other studies have shown that gut microbiota-derived metabolites such as phenylacetylglutamine and white matter hyperintensity.[29] Other gut microbiota metabolites may serve as therapeutic and prognostic biomarkers for CIRI, including trimethylamine-N-oxide (TMAO) and short-chain fatty acids (SCFAs).[30,31] Intriguingly, an inverse correlation emerges between SCFA levels and the prognosis of reperfused stroke, particularly in elderly patients contending with pronounced stroke events. Lee et al[32] reported that aged mice subjected to MCAO exhibited attenuated neuroinflammation and reduced neurological deficits when administered fecal transplants from young, SCFA-rich donors. Similarly, serum TMAO concentrations exhibit a positive correlation with the risk factors of stroke and the ensuing neurological deficits post-ischemic brain injuries.[33] Lipopolysaccharide (LPS), a key component of the outer membrane of Gram-negative bacteria, can enter the brain through compromised gut and BBB, and thereby accelerating CIRI progression.[34] Fecal microbiota transplantation from healthy donors exhibited a therapeutic effect on CIRI and other neurological disorders.[35,36] Therefore, the disordered "microbiome-gut-brain" axis plays an important regulatory role in the pathogenesis of cerebrovascular diseases, including CIRI.[37]

Recently, traditional Chinese medicine (TCM) has received increasing attention from international medical researchers because of its favorable therapeutic effects and low toxicity.[38] Preclinical experiments and clinical trials have demonstrated that TCM exerts therapeutic effects on CIRI owing to its antioxidant, gut microbiota modulation, free radical scavenging, antithrombotic, and neuroprotective properties.[39–41] Modern pharmacology has confirmed that TCM is a promising resource with great chemical diversity and multi-target and multi-pathway characteristics.[42] Increasing evidence has shown that TCM exerts an anti-CIRI effect by regulating the composition and metabolism of the gut microbiota.[43,44] Moreover, the theory of the "gut-brain" axis has been documented in Chinese medicine since ancient times, and TCM has improved gut microbiota dysbiosis and metabolic syndrome in the treatment of CIRI.[45] These findings suggest that gut microbiota may serve as a new therapeutic target for TCM in the prevention and treatment of CIRI.

This review summarizes the functional role of gut microbiota in the occurrence and progression of CIRI. In addition, the present review comprehensively summarizes the latest progress in TCM in curing CIRI through the "microbiome-gut-brain" axis, aiming to provide a theoretical basis for the development of new drugs against CIRI.

Functional Role of the "Microbiota-Gut-Brain" Axis in CIRI

Gut microbiota plays an important role in human health and diseases.[46] The "microbiota-gut-brain" axis is a bidirectional communication network between gut microbiota and their host.[47] Dysbiosis of the gut microbiota is related to the development of common stroke risk factors, such as obesity, diabetes, hypertension, and atherosclerosis, which increase the risk of CIRI.[48] Acute stress in ischemic stroke also changes the composition and abundance of the gut microbiota, which may affect the prognosis of CIRI.[49] Moreover, numerous studies have shown that the gut microbiota can improve ischemic stroke prognosis by regulating neuroactive molecules and immune cell functions, enhancing neural network plasticity, and reducing neuroinflammation.[18,50] These findings indicate that the pathogenesis of CIRI is closely related to an imbalance in gut microbiota. Herein, we summarize the functional role of the microbiota–gut–brain axis in the development and progression of CIRI (Figure 1) as well as the underlying mechanism.

Gut Microbiota Dysbiosis

Normal gut microbiota and the host are in a dynamic balance of mutual benefit and symbiosis. The "microbiome-gut-brain" axis consists of bidirectional communication between the brain and intestines, linking neural function, cognition, and emotion of the brain with peripheral intestinal functions.[51] Unfortunately, the "gut-brain" axis is disrupted in CIRI,[37] which contributes to alterations in the composition and abundance of gut microbiota. Wang et al[52] reported that the ratio of *Firmicutes* to *Bacteroidetes* in CIRI mice was lower than that in normal mice, which usually serves as a sign of gut disturbance. Recent studies have reported that *Enterobacteriaceae, Bifidobacterium, Lactobacillus, Desulfovibrio, Alloprevotella, Ruminococcus*, and *Escherichia* are enriched in high-risk ischemic stroke patients.[53,54] Another study found that patients with CIRI presented with an increased abundance of pathogenic bacteria in the intestinal tract, such as *Enterobacter* and *Megasphaera*, and a decreased abundance of commensal or beneficial genera, such as *Bacteroides* and

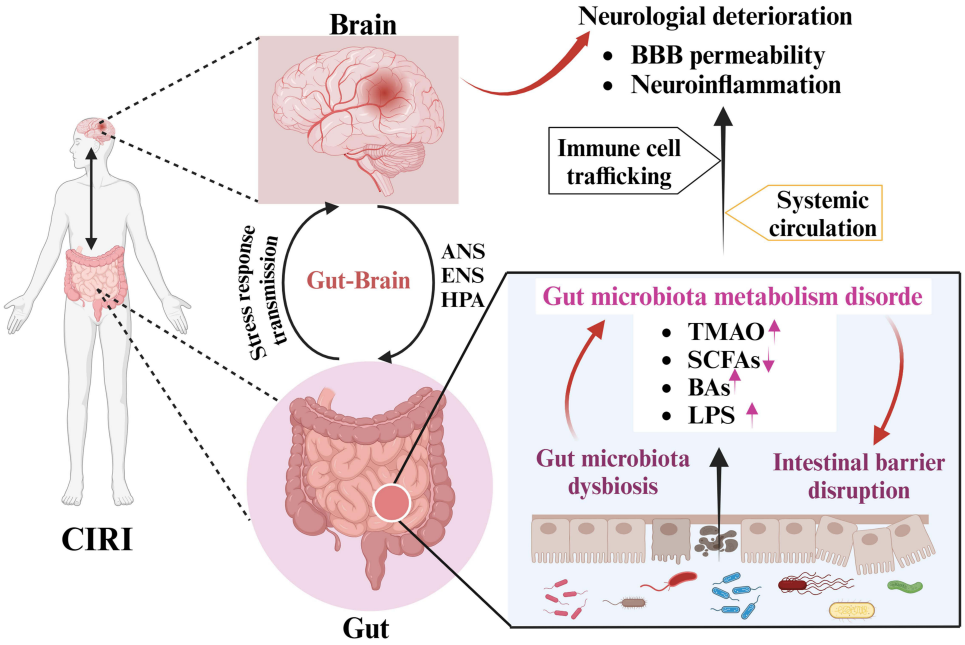

Figure 1 Schematic representation illustrating bidirectional interaction between CIRI and the gut microbiota via the gut-brain axis.
Note: Created in BioRender. Ren, (Y) (2024) https://BioRender.com/v74a311.
Abbreviations: CIRI, cerebral ischemia-reperfusion injury; ANS, autonomic nervous system; ENS, enteric nervous system; HPA, hypothalamic-pituitary-adrenal; BBB, blood-brain barrier; TMAO, trimethylamine N-oxide; SCFAs, short-chain fatty acids; BAs, bile acids; LPS, lipopolysaccharide.

https://doi.org/10.2147/DDDT.S500505

Prevotella, and these gut microbiota dysbiosis was positively associated with the pathological progression of CIRI.[55] Tan et al[56] reported that dysbiosis of the gut microbiota in patients with acute ischemic stroke enhances the subsequent risk of poor functional outcomes. Moreover, systemic exposure to *Porphyromonas gingivalis* may increase the risk of ischemic stroke.[57] Kawato et al[58] found that continual gram-negative bacteria induced accelerated stroke onset in stroke-prone spontaneously hypertensive rats. Other studies have reported that the compositional and functional imbalance of the gut microbiota is an independent predictor of poor prognosis in ischemic stroke.[18,59] A recent study has reported that *Enterobacteriaceae* may serve as a biomarker of cognitive impairment in CIRI.[21] Dysbiosis of the gut microbiota has a positive effect on neural function of the brain, which in turn exacerbates brain infarction.[50,60] Notably, prebiotic administration and fecal microbiota transplantation from healthy donors have been shown to inhibit CIRI progression and reduce brain infarct volume.[61,62] In summary, gut microbiota plays a vital role in the occurrence and development of CIRI.

Intestinal Mucosal Barrier

Integrity of the intestinal mucosal barrier is the foundation of multiple functions of the intestinal tract to keep normal.[63] Disruption of the intestinal mucosal barrier is an important pathophysiological process in ischemic stroke[64] and CIRI,[65] resulting in intestinal injury, secondary infection, and even death. A clinical study showed that dysbiosis of the gut microbiota is an independent risk factor for acute ischemic stroke-associated pneumonia.[66] Another study showed that stroke increased intestinal barrier permeability and dysfunction, which enhanced the translocation and dissemination of bacteria originating from the gut microbiota.[67] Chen et al[68] found that cerebral ischemic stroke not only caused intestinal barrier disruption but also aggravated gut microbiota translocation. Notably, probiotics have been found to modulate host intestinal barrier function through their surface components and metabolites. For example, S-layer protein 2 of vaginal *Lactobacillus crispatus* 2029 promoted the growth of immature Caco-2 cells, production of vascular endothelial growth factor, decreased paracellular permeability, and enhanced the intestinal barrier function of Caco-2 monolayer cells.[69] Hagihara et al[70] proved that *Clostridium butyricum* MIYAIRI588 increased the abundance of beneficial genera, protected intestinal barrier function, and enhanced anti-inflammatory lipid metabolites. Another study showed that administration of *Clostridium butyricum* ameliorated CIRI progression via antioxidant and anti-apoptotic mechanisms.[71] These results suggest that improving the function and integrity of the intestinal mucosal barrier is important in the treatment of CIRI.

Gut Microbiota Metabolism Disorder

Accumulating evidence has demonstrated that active metabolites produced by the gut microbiota play a crucial role in the maintenance of homeostasis, immune maturation, mucosal integrity, and energy metabolism.[72,73] Intestinal microbiota-derived metabolites, such as SCFAs, TMAO, LPS, and bile acids (BAs), can exert beneficial or deleterious effects on CIRI and various extraintestinal organs.[16] Among them, SCFAs are the main metabolites produced in the colon by bacterial fermentation of dietary fiber and resistant starch, including butyrate, acetate, and propionate,[74] which may affect cerebral ischemic stroke outcomes by modulation of the "gut-brain" axis.[75,76] For example, SCFAs produced by beneficial bacteria can promote motor function recovery after ischemic stroke by affecting the immune cells throughout the body.[77] Chen et al[62] reported that the intestinal levels of SCFAs in cerebral ischemic stroke model rats were lower than those in healthy rats, and that butyric acid showed the highest negative correlation with ischemic stroke. Lee et al[32] proved that fecal microbiota transplantation promotes post-stroke recovery by modulating the gut microbiota and reducing inflammation and neurological deficits. TMAO is a key indicator for evaluating the prognosis of patients with cerebral ischemic stroke.[78,79] A cross-sectional study showed that higher plasma TMAO level at admission was an independent predictor of stroke severity, infarct volume, and pro-inflammatory monocyte levels in patients with acute cerebral ischemia.[80,81] Liu et al[82] reported that trimethylamine produced by gut microbiota metabolism is converted to TMAO through hepatic endoflavin monooxygenase, which contributes to platelet hyperreactivity and thrombosis risk by augmenting Ca^{2+} release.[83] Other studies have reported that circulating LPS can worsen clinical outcomes after cerebral ischemic stroke by increasing brain inflammation and blood-brain barrier (BBB) permeability.[84–86] A recent study showed that elevated serum BAs levels contribute to improving poor functional outcomes after ischemic stroke.[87] Functionally, gut microbiota-derived metabolites are involved in the physiological regulation of CIRI by regulating

oxidative stress, inflammation, mitochondrial damage, apoptosis, ferroptosis, and neurological damage.[43,88,89] Taken together, gut microbiota and their metabolites may serve as promising therapeutic targets for the diagnosis and treatment of CIRI.

Gut Microbiota and Host Immunity

Based on current knowledge, the gut microbiota is not only essential for immune homeostasis but also influences the host's response to immune-mediated diseases and the function of the gastrointestinal immune system.[90] The gastrointestinal tract is considered to be the largest immune organ in the human body and contains more than 70% of the entire immune system in terms of the number of immune cells.[17] Previous studies have found that patients with cerebral ischemic stroke are susceptible to immunocompromised.[91,92] Notably, CIRI-induced gut microbiota dysbiosis can trigger immune responses via T cell activation.[93] Benakis et al[94] showed that dysbiosis of the gut microbiota weakened intestinal immune homeostasis and altered dendritic cell activity in a cerebral ischemic stroke mouse model, as evidenced by increased regulatory T cells and reduced interleukin (IL)-17-positive γδ T cells. Hu et al[89] summarized that gut microbiota dysbiosis activates the intestinal immune system and promoted pro-inflammatory cytokine levels, which in turn leads to CIRI. Other studies proved that CIRI causes persistent host gut microbiota dysbiosis and promoted pro-inflammatory cytokine secretion.[95,96] Moreover, intestinal dysbiosis facilitates ischemic stroke pathology and prognosis by regulating immunological pathways, such as the NF-κB pathway,[97] the type I interferon pathway,[98] and the inflammasome pathway.[99] Increasing evidence has demonstrated that gut dysbiosis reduces Treg cells and systemic anti-inflammatory cytokines[100,101] such as IL-10 and transforming growth factor-beta. Gut microbiota metabolites (such as SCFAs) promote Treg cell proliferation and serve as ligands for G-protein-coupled receptors.[102] SCFAs exhibit protective effects against CIRI progression by regulating host immune homeostasis and inhibiting inflammation.[103,104] Collectively, gut microbiota affects CIRI prognosis by regulating immune and inflammatory responses via the "gut-brain" axis.

Effect of TCM on Gut Microbiota in CIRI

CIRI belongs to the category of "stroke disease" in Chinese medicine, and its pathogenesis is rooted in the deficiency of the liver and kidney.[105] Currently, TCMs serves as a promising resource for the treatment of CIRI by activating blood circulation and removing blood stasis, modulating gut microbiota, clearing heat and removing toxins, benefiting qi and tonifying blood, nourishing yin, and activating blood.[40,106,107] Numerous studies have shown that TCM exerts anti-CIRI prevention and therapeutic effects by regulating the gut microbiota.[108,109] On the one hand, TCMs improved intestinal disorders caused by CIRI, as well as modulated the composition and abundance of gut microbiota.[110] In contrast, TCMs alleviate the organ dysfunction syndrome caused by pathogenic bacterial translocation and harmful gut microbiota metabolites in cerebral ischemic stroke.[111,112] In addition, TCM treatment improved the intestinal mucosal barrier and maintained intestinal homeostasis by regulating the composition of the intestinal microbiome.[113] The functional role of TCM in CIRI by regulating the gut microbiota is summarized in Figure 2 and Table 1.

Effect of TCM on Gut Microbiota Dysbiosis

Currently, TCM is used both as the main therapeutic agent and an adjuvant therapy for the prevention and treatment of several neurological diseases, including CIRI.[139] Numerous studies using TCM have found that the gut microbiota serves as a key regulatory mechanism in the treatment of cerebrovascular diseases.[140,141] For example, Shengmai San,[142] NaoMaiTong,[143] Angong Niuhuang pill,[43] San Hua Tang,[120] Dan-deng-tong-nao capsule,[115] and other TCM formulas have been used to treat CIRI by modulating gut microbiota. Chen et al[68] reported that the Gegen and Chuanxiong combination treatment increased the abundance of beneficial bacteria and relieved the complications of CIRI, which was similar to the results of Wang et al.[44] Moreover, several Chinese herbs exhibited potent anti-CIRI therapeutic efficacy by modulating intestinal homeostasis, including *Gastrodia elata* Blume,[110] rhubarb,[144] and *Dioscorea polystachya*.[109] Furthermore, the active ingredients of TCM, including hydroxycinnamic acids,[145] rhubarb anthraquinone glycosides,[146] escin,[136] and notoginsenoside R1.[133] Xu et al[138] found that Astragaloside IV reduces autophagy and oxidative stress induced by gut microbiota dysbiosis in mouse models of acute ischemic stroke. Collectively, TCM can prevent the development and progression of CIRI by improving the dysbiosis of the gut microbiota.

 https://doi.org/10.2147/DDDT.S500505

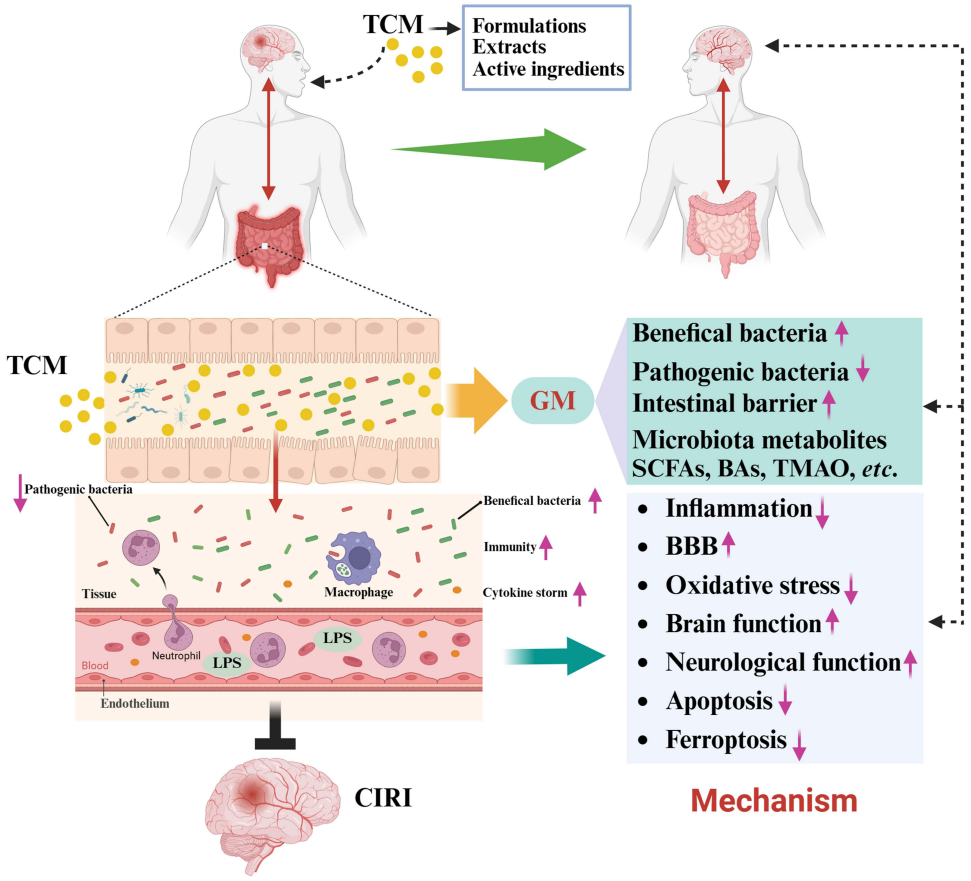

Figure 2 Traditional Chinese medicine in the treatment of CIRI via the "gut-brain" axis.
Note: Created in BioRender. Ren, (Y) (2024) https://BioRender.com/s71m955.
Abbreviations: TCM, traditional Chinese medicine; GM, gut microbiota.

Effect of TCM on Intestinal Mucosal Barrier and Host Immunity

TCMs have been reported to improve the integrity and permeability of the intestinal mucosal barrier by regulating the composition and abundance of gut microbiota and, in turn, reducing the immune-inflammatory response triggered by the migration of harmful bacteria and toxic metabolites of gut microbiota to other organs and the circulatory system.[45,147] For example, Qishiwei Zhenzhu pill treatment ameliorated CIRI progression by improving intestinal integrity and gut microbiota disorder and inhibiting inflammation.[129] Zhang et al[130] demonstrated that Tong-Qiao-Huo-Xue decoction had a protective effect

Table 1 Summary of Traditional Chinese Medicine in Treating CIRI by Regulating Gut Microbiota

Name	Microbiota Affected	Efficacy	Reference
Prescription			
Buqi-Huoxue-Tongnao decoction	The abundance of *Turicibacter* and *Faecalibaculum*↑	Infarct volume, neurological damage, and intestinal bacterial translocation↓ Intestinal barrier integrity and indole lactic acid levels↑	[114]
Dan-deng-tong-nao capsule	The abundance of *Firmicutes* and *Actinobacteria*↑ The abundance of *Proteobacteria* and *Verrucomicrobiales*↓	Infract volume and neurological deficit↓	[115]
Tao Hong Si Wu decoction	The abundance of *Firmicutes* and *Actinobacteria*↑ The abundance of *Proteobacteria*↓	Neurological damage, intestinal barrier destruction, and levels of IL-1β and TNF-α↓ Expression of LPS, DAO, and D-lactic acid↓ TLR-4/NF-κB pathway↓	[116]

(*Continued*)

Table 1 (Continued).

Name	Microbiota Affected	Efficacy	Reference
Sanhua decoction	The abundance of *Clostridia, Lachnospiraceae, Ruminococcaceae*, and *Coprococcus*↑ The abundance of *Enterobacteriaceae, Desulfovibrio*, and *Lactobacillus*↓	Infract volume and brain injury↓ Serum levels of butyric acid, isovaleric acid, valeric acid, and caproic acid↓ Fecal butyric acid↑	[117]
Naotaifang III	The abundance of *Firmicutes* and *Clostridium*↑ The abundance of *Bacteroides* and *prevotella_9*↓	Neurological deficit, brain damage, and infract volume↓ Levels of LPS and IL-1β↓ LPS/TLR-4/NF-κB pathway↓	[118]
Eleutherococcus senticosus	The abundance of *Lactobacillus reuteri* and *Clostridium butyricum*↑ The abundance of *Proteobacteria, Enterobacter, Oscillibacter*, and *Escherichia Shigella*↓	Oxidative stress and inflammation↓ Contents of 5-HT and GABA↑ Contents of ASP and Glu↓	[119]
San Hua Tang	The abundance of *Lactobacillales, Olsenella*, and *Bifidobacterium*↑ The abundance of *Bacteroidetes*↓	Neurological damage, infract volume, and inflammatory response↓ Intestinal mucosal barrier↑ Levels of acetic acid, butyric acid, and propionic acid↑	[120]
Shuanglu Tongnao	The abundance of *Paracoccus*↑ The abundance of *Bacteroidetes*↓	Neurological deficit and infract volume↓ Intestinal barrier function↑ TLR-4/NF-κB pathway↓	[121]
Puerariae lobatae Radix	The abundance of *Firmicutes, Bifidobacterium, Akkermansia, Romboutsia*, and *Butyricicoccus*↑ The abundance of *Bacteroidetes, Alistipes, Klebsiella, Fusobacterium*, and *Faecalibacterium*↓	Neurological impairment, infract size, dyslipidemia, and gut barrier disruption↓ Levels of glycine, L-phenylalanine, enkephalin L, and melatonin↑	[122]
Pushen capsule	The abundance of *Alistipes* and *Ruminiclostridium*↑ The abundance of *Lactobacillus, Bifidobacterium, Ruminococcus_2*, and *Pseudomonas*↓	Infarct volume↓ BBB, brain plasticity, and cognitive repair↑ Adora2a expression↓	[123]
Buzhong Yiqi decoction	The abundance of *Prevotellaceae_NK3B31_group* and *Akkermansia*↑ The abundance of *Bacteroidetes, Patescibateria, Tenericutes*, and *Cyanobacteria*↓	Neurological deficit and infract size↓ Cell apoptosis in the cortex↓	[124]
Zhilong Huoxue Tongyu capsule	The abundance of *Bacteroidetes, Actinobacteria*, and *Prevotella*↑ The abundance of *Firmicutes, Proteobacteria*, and *Tenericutes*↓	Infract size and intestinal barrier damage↓ Metabolic disturbances↓	[125]
Huangqi-Honghua	The abundance of *Blautia, Lachnospiraceae, Oscillibacter*, and *Bifidobacterium*↑ The abundance of *Ruminococcaceae, Bacteroides, Phascolarctobacterium*, and *Desulfovibrionaceae*↓	Neurological deficit, infarct volume, and rate of necrotic neurons↓ Intestinal barrier integrity and levels of allolithocholic acid, isolithocholic acid, and cholic acid↑	[44]
Angong Niuhuang pill	The abundance of *Lachnoclostridium, Enterorhabdus, Roseburia, Lachnospiraceae_UCG-006, and Colidextribacter*↑ The abundance of *Alloprevotella*↓	Infarct volume, neurological deficit, and neuronal death↓ Nissl bodies and levels of uridine, inosine, and guanosine↑	[43]
Xingnaojing injection	The abundance of *Akkermansia*↑ The abundance of *Flavobacteriaceae, Deferribacteraceae*, and *Deferribacteres*↓	Infract volume, brain tissue damage, and inflammation↓ Intestinal mucosal barrier and levels of short-chain fatty acids, propionate, valerate, isobutyrate, and isovalerate↑ TLR-4/NF-κB pathway↓	[126]

(*Continued*)

https://doi.org/10.2147/DDDT.S500505

Table 1 (Continued).

Name	Microbiota Affected	Efficacy	Reference
NaoMaiTong	The abundance of *Coprococcus* and *Blautia*↑ The abundance of *Verrucomicrobiota* and *Escherichia Shigella*↓	Infract volume and neurological deficit↓ Oxidative stress and inflammation↓	[127]
Xinglou Chengqi decoction	The abundance of *Verrucomicrobia* and *Akkermansia*↑ The abundance of *Paraprevotella, Roseburia, Streptophyta*, and *Enterococcus*↓	Cerebral infarction, neuronal apoptosis, and inflammation↓ Neurological function and levels of levels of short chain fatty acids and butyric acid↑	[128]
Qishiwei Zhenzhu pill	The abundance of *Firmicutes*↑ The abundance of *Proteobacteria* and *Escherichia Shigella*↓	Infract volume and neurological deficit↓ Intestinal integrity↑ Inflammatory response↓	[129]
Dioscorea polystachya	The abundance of *Lactobacillus, Ruminococcus*, and *Clostridium*↑ The abundance of *Bacteroidetes*↓	Cognitive dysfunction and neurological deficit↓ LPS content, oxidative stress, and inflammation↓ The content of short-chain fatty acids, GABA, and 5-HT↑	[109]
Tong-Qiao-Huo-Xue decoction	The abundance of *Allobaculum, Lactobacillus*, and *Bifidobacterium*↑ The abundance of *Bacteroidetes*↓	Infract volume and neurological deficit↓ Intestinal epithelial barrier and FOXP3↑ γδT cell proportion and IL-17 expression↓	[130]
Puerariae lobatae Radix with Chuanxiong Rhizoma	The abundance of *Alloprevotella, Ruminococcaceae_UCG_005, Ruminococcaceae_NK4A214_group, Ruminococcaceae_UCG_004, Oscillospira, Lachnospiraceae_NK4B4_group, Akkermansia*, and *Megasphaera*↑ The abundance of *Escherichia Shigella*↓	Neurological deficit and infract size↓ Blood lipid levels and thrombotic risk↓ Intestinal permeability and gut microbiota translocation↓	[68]
Extract			
Water extract of *Rheum tanguticum*	The abundance of *Enterorhabdus, Defluviitaleaceae, Christensenellaceae*, and *Lachnospira*↑ The abundance of *Fournierella* and *Bilophila*↓	Infarct volume and neurological deficit↓ Levels of isoleucine, lactate, valine, N6-acetyllysine, methionine, choline, myo-inositol, lipid, and 3-aminoisobutyric acid↓ Levels of propylene glycol, N, N-dimethylglycine, trimethylamine N-oxide, glucose, and betaine↑	[131]
Acorus tatarinowii oil	The abundance of *Prevotella_copri*↑ The abundance of *Akkermansia* and *Verrucomicrobiales*↓	Infarct volume, neurological deficit, and inflammation↓ M2 phenotypic polarization of microglia↑	[132]
Rhubarb anthraquinone glycosides	/	Contents of 5-HT, 5-HIAA, and GABA↑ Contents of ASP and Glu↓	[19]
Active ingredient			
Notoginsenoside R1	The abundance of *Bacteroidota* and *Muribaculaceae*↑ The abundance of *Enterobacterales*↓	Infarct volume, neurological deficit, neuronal apoptosis, inflammation, and intestinal permeability↓ TLR4/MyD88/NF-κB pathway↓	[133]
Berberine	The abundance of *Akkermansia, Escherichia-Shigella, Bacteroides*, and *Parasutterella*↑ The abundance of *Odoribacter, Alistipes, Clostridium*_sensu_stricto_1, and *Helicobacter*↓	Brain infarct volume, the expressions of two synaptic-associated proteins (PSD95 and SYP), neurological deficit, and neuroinflammation↓ Glial cell activation and NLRP3 expression↓ The production of butyric acid↑	[134]

(*Continued*)

Table 1 (Continued).

Name	Microbiota Affected	Efficacy	Reference
Cornuside	The abundance of *Lachnospiraceae, Treponema, Prevotellaceae_NK3B31_group, Lactobacillus*, and *Ruminococcaceae*↑ The abundance of *Bacteroides*↓	Infarct volume and neurological deficit↓ Intestinal permeability, neuroinflammation, and intestinal inflammation↓ IL-17A/TRAF6/NF-κB pathway↓	[135]
Escin	/	Infarct volume, neuroinflammation, and intestinal dysfunction and permeability↓ Neurological function↑ LPS/TLR4/NF-κB pathway↓	[136]
Indole-3-propionic acid	The abundance of *Lactobacillus* and *Lachnospiraceae_NK4A136_group*↑ The abundance of *Akkermansia, Alistipes*, and *Mucispirillum*↓	Neurological deficit and infarct volume↓ Intestinal epithelial barrier and Th17 numbers↑ Tregs, neuroinflammation, and neuron apoptosis↓	[137]
Astragaloside IV	The abundance of *Holdemanella* and *Clostridium*↑The abundance of *Bifidobacterium* and *Escherichia-Shigella*↓	Levels of ROS and MDA↓ The T-AOC, SOD, and GSH↑ Autophagy↓	[138]

Abbreviations: ASP, aspartic acid; GABA, γ-aminobutyric acid; Glu, glutamic acid; GSH, glutathione; MDA, malondialdehyde; NLRP3, NLR family pyrin domain containing 3; ROS, reactive oxygen species; SOD, superoxide dismutase; T-AOC, total antioxidant capacity; 5-HT, 5-hydroxytryptamine; 5-HIAA, 5-hydroxy indole acetic acid.

against CIRI by improving intestinal mucosal barrier destruction and reducing the activation and migration of intestinal γδT cells. Treatment with Panax notoginsenoside extract exerts a neuroprotective effect on CIRI by upregulating brain-derived neurotrophic factor levels and inflammation by enhancing the abundance of beneficial bacteria (such as *Bifidobacterium longum*).[148] Moreover, Chinese herbal monomers exert a therapeutic effect on CIRI by improving the intestinal mucosal barrier and suppressing inflammation. For example, Dou et al[149] showed that resveratrol alleviates CIRI by inhibiting intestinal pro-inflammatory immunity, neuroinflammation, and inflammation-induced BBB disruption by modulating gut microbiota-mediated Th17/Tregs and Th1/Th2 polarity shifts. Similarly, cornuside restricts CIRI progression by inactivating the IL-17F/TRAF6/NF-κB pathway via maintaining intestinal barrier function, and reducing intestinal inflammation and neuroinflammation.[135] Collectively, TCM alleviated CIRI by inhibiting inflammation and promoting intestinal mucosal barrier repair induced by dysbiosis of the gut microbiota.

Effect of TCM on Intestinal Metabolism

Recent studies have found that the gut microbiota can participate in the progression of CIRI by releasing endotoxins and their harmful metabolites to mediate systemic and neuroinflammation.[86,150] Many gut microbiota metabolites have been identified,[151,152] such as SCFAs, BA, TMAO, LPS, indole-3-propionic acid, choline and its metabolites, ethanol, imidazole propionate, and endotoxins have been etc. TCM has been shown to alleviate CIRI progression by regulating the gut microbiota metabolites. For example, Tanhuo decoction mitigated acute ischemic stroke by reducing the levels of LPS and TMAO by modulating the "gut-brain" axis.[153] The Ang Niuhuang pill ameliorated CIRI by modulating microbial metabolites related to inflammation and neuroprotection,[43] such as uridine, guanosine, and inosine. Administration of San Hua Tang enhanced SCFA levels and inhibited inflammation in rats with CIRI.[120] Moreover, other TCMs ameliorated CIRI progression by regulating enteric metabolism. Huangqi-Honghua combination treatment reduced neurological deficits, cerebral infarct volume, and necrotic neuron rate in the CIRI rat model by maintaining gut homeostasis and affecting BA metabolism,[44] which is similar to the protective effect of rhubarb on CIRI.[154] NaoMaiTong treatment not only improved gut microbiota disturbances but also adjusted plasma metabolic disorders.[127] Liu et al[131] showed that Dahuang prevents CIRI progression by improving gut microbiota disorders and regulating amino acid and energy metabolism. Several studies have shown that gastrointestinal hormones play an important role in CIRI progression by maintaining intestinal and immune homeostasis,[155] which have become a therapeutic target for the treatment of CIRI with TCM.[156,157] Collectively, TCM treatment attenuated CIRI by regulating microbiota metabolites.

https://doi.org/10.2147/DDDT.S500505

Clinical Trials of TCM for CIRI Management

Preclinical studies have confirmed that TCM has a wide range of pharmacological effects on CIRI, and clinical trials are being conducted. For example, Guo et al[153] showed that acute ischemic stroke patients treated with Tanhuo decoction had increased abundance of beneficial bacteria (such as *Bifidobacteria, Streptococci*, and *Ruminococci*), decreased abundance of pathogenic bacteria (such as *Bacteroidetes, Anaerobacter*, and *Enterococci faecalis*), and reduced levels of aseptic inflammation and microbial metabolites (LPS and TMAO). Guo et al[140] showed that TCM treatment increased the microbial diversity and abundance of beneficial bacteria in patients with CIRI and the effect of approaching healthy people's gut microbiota. Other studies have shown that TCM therapy improves neurological function and limb motor impairment, and enhances the quality of life of patients with CIRI.[158,159] Moreover, ongoing clinical studies are exploring the safety and efficacy of TCM for the treatment of CIRI (Table 2). For example, a Singaporean substudy reported that Neuroaid (MLC601) was a safe TCM for ischemic stroke patients receiving a 3-month treatment.[160,161] Recently, a multicenter, randomized, and placebo-controlled trial found that Naoxintong capsule was a safe drug for treating cerebral ischemic stroke and reduced the 2-year stroke recurrence rate.[162] Another clinical study pointed out that the efficacy and safety of TCM for the treatment of CIRI are superior to those of Western medicine.[163] However, the specific active components of TCM against CIRI and their mechanisms remain unknown, and the combination of molecular docking studies, molecular dynamics simulations, network pharmacology, and genomics/transcriptomics analyses may deepen our understanding of the multi-targeted effects and potential efficacy of TCM in treating CIRI. Based on these findings, TCM is a promising alternative for clinical treatment of CIRI. Importantly, there is an urgent need to establish screening models of compatibility and screening targets for TCM in various diseases, including CIRI.

Discussion and Perspective

Gut microbiota has become a research hotspot and is emerging as an important new therapeutic target for the treatment of CIRI. The symptoms of CIRI are characterized by gut microbiota imbalance, intestinal and BBB dysfunction, and peripheral and central inflammations. Meanwhile, the imbalance in intestinal homeostasis facilitated the development and progression of CIRI, and probiotics or fecal microbial transplantation from healthy donors contributed to improving CIRI by modulating the composition and abundance of the gut microbiota. Moreover, gut microbiota dysbiosis may lead to the production of harmful metabolites and the disruption of gastrointestinal hormone secretion. Currently, both clinical and animal studies have shown that TCM has a corrective effect on disordered gut microbiota, such as increasing the abundance of beneficial bacteria, decreasing the abundance of pathogenic bacteria, and maintaining intestinal homeostasis. Increasing evidence has shown that TCM is effective in the prevention and treatment of CIRI by improving gut microbiota dysbiosis and intestinal barrier dysfunction, and altering gut microbiota metabolism. Therefore, elucidating

Table 2 Clinical Trials of Traditional Chinese Medicine in Cerebral Ischemic Stroke

Category	Year of Registration	Sponsor	Recruiting Status	Clinical Trial ID
Taohong Tongluo Xiaoban	2024	Beijing Electric Power Hospital, China	Not yet recruiting	NCT06549582
Suhexiang pill	2023	Dongzhimen Hospital, China	Recruiting	NCT05833932
DengzhanShengmai capsule	2007	Guangzhou University of Traditional Chinese Medicine, China	Completed	NCT00548223
Zhongfeng Huichun pill	2024	Dongzhimen Hospital Beijing University of Chinese medicine, China	Recruiting	ChiCTR2400083136
Naoshuantong capsule	2023	The First Affiliated Hospital of Henan University of Chinese medicine, China	Not yet recruiting	ChiCTR2300075877
Chuanzhitongluo pill	2023	The Second Affiliated Hospital of Chongqing Medical University, China	Recruiting	ChiCTR2300074147
Ruyi Zhenbao tablet	2023	The Second People's Hospital of Yuhuan, China	Not yet recruiting	ChiCTR2300073074
Breviscapine dripping pill	2023	The Third Affiliated Hospital of Beijing University of Chinese Medicine, China	Not yet recruiting	ChiCTR2300067750
Shenjingfuyuanfang granule	2020	Shanghai Municipal Hospital of Traditional Chinese Medicine, China	Not yet recruiting	ChiCTR2000040010
Ruyi Zhenbao tablet	2020	Xuanwu Hospital of Capital Medical University, China	Completed	ChiCTR2000036691
Sanchitongtshu capsule	2019	West China School of Medicine, Sichuan University, China	Not yet recruiting	ChiCTR1900022495
Xuesaitong soft capsule	2018	Xuanwu Hospital Capital Medical University, China	Completed	ChiCTR1800016363

the functional role and mechanisms of TCM in regulating gut microbiota by the "gut-brain" axis may provide a theoretical basis for new treatment strategy for CIRI.

However, the treatment of CIRI using TCM still faces challenges that must be addressed. (1) The metabolism, toxicity, and pharmacokinetic profile of TCM in clinical trials of CIRI should be further explored. (2) Research on the active ingredients of TCM is limited by its unstable chemical structure, low bioavailability, and susceptibility to oxidation. The quality, safety and effectiveness of TCM can be controlled by the use of well-defined compounds. (3) The greatest challenge in TCM drug delivery into the brain is bypassing the BBB, which prevents the entry of many potential therapeutic agents. Currently, there exist primarily three approaches for achieving drug delivery to the brain through BBB targeting, such as receptor-mediated transcytosis, carrier-mediated transcytosis, and absorptive-mediated transcytosis.[164] (4) Nearly 25,000 Chinese herbals will become extinct, severely limiting the clinical use of TCM for the treatment of CIRI. (5) There is a lack of sufficient clinical data on the efficacy of TCM against CIRI. (6) The detailed molecular mechanisms of TCM anti-CIRI by regulating the "gut-brain" axis are not clear.

Conclusion

TCMs have excellent anti-CIRI effects and are important agents for the treatment of cerebrovascular diseases. This review analyzed the functional role of gut microbiota in the pathogenesis of CIRI and systematically summarized recent advancements in research on TCM for the prevention and treatment of CIRI, along with clinical evidence, which provides a scientific and comprehensive reference for the use of TCM in the treatment of CIRI and promotes the utilization and development of TCM resources.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors declare no conflicts of interest in this work.

References

1. Nakamura A, Otani K, Shichita T. Lipid mediators and sterile inflammation in ischemic stroke. *Int Immunol*. 2020;32(11):719–725. doi:10.1093/intimm/dxaa027
2. Putaala J. Ischemic stroke in young adults. *Continuum*. 2020;26(2):386–414. doi:10.1212/con.0000000000000833
3. Feigin VL, Brainin M, Norrving B, et al. World Stroke Organization (WSO): global stroke fact sheet 2022. *Int J Stroke*. 2022;17(1):18–29. doi:10.1177/17474930211065917
4. Feigin VL, Stark BA, Johnson CO; Global, regional, and national burden of stroke and its risk factors, 1990-2019. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the global burden of disease study 2019. *Lancet Neurol*. 2021;20(10):795–820. doi:10.1016/s1474-4422(21)00252-0
5. Feske SK. Ischemic stroke. *Am J Med*. 2021;134(12):1457–1464. doi:10.1016/j.amjmed.2021.07.027
6. Naik Bukke SP, Gopalakrishnaiah T, Onohuean H, et al. Drug utilization analysis of analgesics and adjuvants used in pain management. *Arch Pharm Prac*. 2024;15(2):4. doi:10.51847/wHhW6w9i1C
7. Chapman SN, Mehndiratta P, Johansen MC, et al. Current perspectives on the use of intravenous recombinant tissue plasminogen activator (tPA) for treatment of acute ischemic stroke. *Vasc Health Risk Manag*. 2014;10:75–87. doi:10.2147/vhrm.S39213
8. Khandelwal P, Yavagal DR, Sacco RL. Acute ischemic stroke intervention. *J Am Coll Cardiol*. 2016;67(22):2631–2644. doi:10.1016/j.jacc.2016.03.555
9. Yang K, Zeng L, Ge A, et al. A systematic review of the research progress of non-coding RNA in neuroinflammation and immune regulation in cerebral infarction/ischemia-reperfusion injury. *Front Immunol*. 2022;13:930171. doi:10.3389/fimmu.2022.930171
10. Zou X, Wang L, Xiao L, et al. Gut microbes in cerebrovascular diseases: gut flora imbalance, potential impact mechanisms and promising treatment strategies. *Front Immunol*. 2022;13:975921. doi:10.3389/fimmu.2022.975921

11. Aya V, Flórez A, Perez L, et al. Association between physical activity and changes in intestinal microbiota composition: a systematic review. *PLoS One*. 2021;16(2):e0247039. doi:10.1371/journal.pone.0247039
12. Qin J, Li R, Raes J, et al. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature*. 2010;464(7285):59–65. doi:10.1038/nature08821
13. Kuziel GA, Rakoff-Nahoum S. The gut microbiome. *Curr Biol*. 2022;32(6):R257–r264. doi:10.1016/j.cub.2022.02.023
14. Ochoa-Repáraz J, Kasper LH. The second brain: is the gut microbiota a link between obesity and central nervous system disorders? *Curr Obes Rep*. 2016;5(1):51–64. doi:10.1007/s13679-016-0191-1
15. Liang X, Fu Y, Cao WT, et al. Gut microbiome, cognitive function and brain structure: a multi-omics integration analysis. *Transl Neurodegener*. 2022;11(1):49. doi:10.1186/s40035-022-00323-z
16. Zhang W, Dong XY, Huang R. Gut microbiota in ischemic stroke: role of gut bacteria-derived metabolites. *Transl Stroke Res*. 2023;14(6):811–828. doi:10.1007/s12975-022-01096-3
17. Li N, Wang X, Sun C, et al. Change of intestinal microbiota in cerebral ischemic stroke patients. *BMC Microbiol*. 2019;19(1):191. doi:10.1186/s12866-019-1552-1
18. Pluta R, Januszewski S, Czuczwar SJ. The role of gut microbiota in an ischemic stroke. *Int J Mol Sci*. 2021;22(2):915. doi:10.3390/ijms22020915
19. Guo Y, Li Q, Yu X, et al. Rhubarb anthraquinone glycosides protect against cerebral ischemia-reperfusion injury in rats by regulating brain-gut neurotransmitters. *Biomed Chromatogr*. 2021;35(5):e5058. doi:10.1002/bmc.5058
20. Wen SW, Wong CHY. An unexplored brain-gut microbiota axis in stroke. *Gut Microbes*. 2017;8(6):601–606. doi:10.1080/19490976.2017.1344809
21. Ling Y, Gong T, Zhang J, et al. Gut microbiome signatures are biomarkers for cognitive impairment in patients with ischemic stroke. *Front Aging Neurosci*. 2020;12:511562. doi:10.3389/fnagi.2020.511562
22. Xiang L, Lou Y, Liu L, et al. Gut microbiotic features aiding the diagnosis of acute ischemic stroke. *Front Cell Infect Microbiol*. 2020;10:587284. doi:10.3389/fcimb.2020.587284
23. Park SY, Lee SP, Kim D, et al. Gut dysbiosis: a new avenue for stroke prevention and therapeutics. *Biomedicines*. 2023;11(9):2352. doi:10.3390/biomedicines11092352
24. Lou Z, Ouyang H, Chen G, et al. Gut microbiota as predictors of the occurrence of high on-treatment platelet reactivity in acute ischemic stroke patients. *Front Cell Infect Microbiol*. 2023;13:1257317. doi:10.3389/fcimb.2023.1257317
25. Benakis C, Poon C, Lane D, et al. Distinct commensal bacterial signature in the gut is associated with acute and long-term protection from ischemic stroke. *Stroke*. 2020;51(6):1844–1854. doi:10.1161/strokeaha.120.029262
26. Liu N, Liu C, Yang Y, et al. Xiao-Xu-Ming decoction prevented hemorrhagic transformation induced by acute hyperglycemia through inhibiting AGE-RAGE-mediated neuroinflammation. *Pharmacol Res*. 2021;169:105650. doi:10.1016/j.phrs.2021.105650
27. Cervi AL, Lukewich MK, Lomax AE. Neural regulation of gastrointestinal inflammation: role of the sympathetic nervous system. *Auton Neurosci*. 2014;182:83–88. doi:10.1016/j.autneu.2013.12.003
28. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat Rev Neurosci*. 2012;13(10):701–712. doi:10.1038/nrn3346
29. Yu F, Feng X, Li X, et al. Gut-derived metabolite phenylacetylglutamine and White matter hyperintensities in patients with acute ischemic stroke. *Front Aging Neurosci*. 2021;13:675158. doi:10.3389/fnagi.2021.675158
30. Liu Y, Qu J, Xu J, et al. Trimethylamine-N-oxide: a potential biomarker and therapeutic target in ischemic stroke. *Front Neurol*. 2023;14:1156879. doi:10.3389/fneur.2023.1156879
31. Chou PS, Yang IH, Kuo CM, et al. The prognostic biomarkers of plasma trimethylamine N-oxide and short-chain fatty acids for recanalization therapy in acute ischemic stroke. *Int J Mol Sci*. 2023;24(13):10796. doi:10.3390/ijms241310796
32. Lee J, d'Aigle J, Atadja L, et al. Gut microbiota-derived short-chain fatty acids promote poststroke recovery in aged mice. *Circ Res*. 2020;127(4):453–465. doi:10.1161/circresaha.119.316448
33. Rexidamu M, Li H, Jin H, et al. Serum levels of Trimethylamine-N-oxide in patients with ischemic stroke. *Biosci Rep*. 2019;39(6):BSR20190515. doi:10.1042/bsr20190515
34. Darbandi ZK, Amirahmadi S, Goudarzi I, et al. Folic acid improved memory and learning function in a rat model of neuroinflammation induced by lipopolysaccharide. *Inflammopharmacology*. 2024;32(2):1401–1411. doi:10.1007/s10787-023-01314-w
35. Wei J, Wang G, Lai M, et al. Faecal microbiota transplantation alleviates ferroptosis after ischaemic stroke. *Neuroscience*. 2024;541:91–100. doi:10.1016/j.neuroscience.2024.01.021
36. Hediyal TA, Vichitra C, Anand N, et al. Protective effects of fecal microbiota transplantation against ischemic stroke and other neurological disorders: an update. *Front Immunol*. 2024;15:1324018. doi:10.3389/fimmu.2024.1324018
37. Zhang Y, Yang H, Hou S, et al. Influence of the brain-gut axis on neuroinflammation in cerebral ischemia-reperfusion injury (Review). *Int J Mol Med*. 2024;53(3):30. doi:10.3892/ijmm.2024.5354
38. Hu Q, Calduch RM. On traditional Chinese medicine regulation in China: how quality and safety of use are insured. *Pharmacol Res*. 2017;119:371–372. doi:10.1016/j.phrs.2017.02.025
39. Sun K, Fan J, Han J. Ameliorating effects of traditional Chinese medicine preparation, Chinese materia medica and active compounds on ischemia/reperfusion-induced cerebral microcirculatory disturbances and neuron damage. *Acta Pharm Sin B*. 2015;5(1):8–24. doi:10.1016/j.apsb.2014.11.002
40. Cheng X, Hu J, Liu X, et al. Therapeutic targets by traditional Chinese medicine for ischemia-reperfusion injury induced apoptosis on cardiovascular and cerebrovascular diseases. *Front Pharmacol*. 2022;13:934256. doi:10.3389/fphar.2022.934256
41. Zhou J, Sun F, Zhang W, et al. Novel insight into the therapeutical potential of flavonoids from traditional Chinese medicine against cerebral ischemia/reperfusion injury. *Front Pharmacol*. 2024;15:1352760. doi:10.3389/fphar.2024.1352760
42. Li X, Liu Z, Liao J, et al. Network pharmacology approaches for research of traditional Chinese medicines. *Chin J Nat Med*. 2023;21(5):323–332. doi:10.1016/s1875-5364(23)60429-7
43. Zhang H, Hui X, Wang Y, et al. Angong niuhuang pill ameliorates cerebral ischemia/reperfusion injury in mice partly by restoring gut microbiota dysbiosis. *Front Pharmacol*. 2022;13:1001422. doi:10.3389/fphar.2022.1001422

44. Wang K, Chen Y, Cao J, et al. Mechanism of Huangqi-Honghua combination regulating the gut microbiota to affect bile acid metabolism towards preventing cerebral ischaemia-reperfusion injury in rats. *Pharm Biol*. 2022;60(1):2189–2199. doi:10.1080/13880209.2022.2136209
45. Gao L, Xia X, Shuai Y, et al. Gut microbiota, a hidden protagonist of traditional Chinese medicine for acute ischemic stroke. *Front Pharmacol*. 2023;14:1164150. doi:10.3389/fphar.2023.1164150
46. Gomaa EZ. Human gut microbiota/microbiome in health and diseases: a review. *Antonie Van Leeuwenhoek*. 2020;113(12):2019–2040. doi:10.1007/s10482-020-01474-7
47. Quigley EMM. Microbiota-brain-gut axis and neurodegenerative diseases. *Curr Neurol Neurosci Rep*. 2017;17(12):94. doi:10.1007/s11910-017-0802-6
48. Lai Y, Dhingra R, Zhang Z, et al. Toward elucidating the human gut microbiota-brain axis: molecules, biochemistry, and implications for health and diseases. *Biochemistry*. 2022;61(24):2806–2821. doi:10.1021/acs.biochem.1c00656
49. Zhuo Z, Wang H, Zhang S, et al. Selenium supplementation provides potent neuroprotection following cerebral ischemia in mice. *J Cereb Blood Flow Metab*. 2023;43(7):1060–1076. doi:10.1177/0271678x231156981
50. Xu K, Gao X, Xia G, et al. Rapid gut dysbiosis induced by stroke exacerbates brain infarction in turn. *Gut*. 2021;8:gutjnl–2020–323263. doi:10.1136/gutjnl-2020-323263
51. Mayer EA, Nance K, Chen S. The gut-brain axis. *Annu Rev Med*. 2022;73(1):439–453. doi:10.1146/annurev-med-042320-014032
52. Wang H, Ren S, Lv H, et al. Gut microbiota from mice with cerebral ischemia-reperfusion injury affects the brain in healthy mice. *Aging*. 2021;13(7):10058–10074. doi:10.18632/aging.202763
53. Zeng X, Gao X, Peng Y, et al. Higher risk of stroke is correlated with increased opportunistic pathogen load and reduced levels of butyrate-producing bacteria in the gut. *Front Cell Infect Microbiol*. 2019;9:4. doi:10.3389/fcimb.2019.00004
54. Chen YZ, Huang ZY, Zhou WW, et al. Uncovering the characteristics of the gut microbiota in patients with ischemic stroke and hemorrhagic stroke. *Sci Rep*. 2024;14(1):11776. doi:10.1038/s41598-024-62606-x
55. Yin J, Liao SX, He Y, et al. Dysbiosis of gut microbiota with reduced trimethylamine-N-oxide level in patients with large-artery Atherosclerotic stroke or transient ischemic attack. *J Am Heart Assoc*. 2015;4(11):e002699. doi:10.1161/jaha.115.002699
56. Tan C, Wu Q, Wang H, et al. Dysbiosis of gut microbiota and short-chain fatty acids in acute ischemic stroke and the subsequent risk for poor functional outcomes. *JPEN J Parenter Enteral Nutr*. 2021;45(3):518–529. doi:10.1002/jpen.1861
57. Pussinen PJ, Alfthan G, Jousilahti P, et al. Systemic exposure to Porphyromonas gingivalis predicts incident stroke. *Atherosclerosis*. 2007;193(1):222–228. doi:10.1016/j.atherosclerosis.2006.06.027
58. Kawato T, Tanaka H, Tabuchi M, et al. Continual Gram-negative bacterial challenge accelerates stroke onset in stroke-prone spontaneously hypertensive rats. *Clin Exp Hypertens*. 2013;35(1):28–34. doi:10.3109/10641963.2012.689042
59. Xia GH, You C, Gao XX, et al. Stroke dysbiosis index (SDI) in gut microbiome are associated with brain injury and prognosis of stroke. *Front Neurol*. 2019;10:397. doi:10.3389/fneur.2019.00397
60. Singh V, Roth S, Llovera G, et al. Microbiota dysbiosis controls the neuroinflammatory response after stroke. *J Neurosci*. 2016;36(28):7428–7440. doi:10.1523/jneurosci.1114-16.2016
61. Akhoundzadeh K, Vakili A, Shadnoush M, et al. Effects of the oral ingestion of probiotics on brain damage in a transient model of focal cerebral ischemia in mice. *Iran J Med Sci*. 2018;43(1):32–40. doi:10.4161/gmic.29232
62. Chen R, Xu Y, Wu P, et al. Transplantation of fecal microbiota rich in short chain fatty acids and butyric acid treat cerebral ischemic stroke by regulating gut microbiota. *Pharmacol Res*. 2019;148:104403. doi:10.1016/j.phrs.2019.104403
63. Camilleri M, Madsen K, Spiller R, et al. Intestinal barrier function in health and gastrointestinal disease. *Neurogastroenterol Motil*. 2012;24(6):503–512. doi:10.1111/j.1365-2982.2012.01921.x
64. Prame Kumar K, McKay LD, Nguyen H, et al. Sympathetic-mediated intestinal cell death contributes to gut barrier impairment after stroke. *Transl Stroke Res*. 2023. doi:10.1007/s12975-023-01211-y
65. Pan P, Song Y, Du X, et al. Intestinal barrier dysfunction following traumatic brain injury. *Neurol Sci*. 2019;40(6):1105–1110. doi:10.1007/s10072-019-03739-0
66. Xia GH, Zhang MS, Wu QH, et al. Dysbiosis of gut microbiota is an independent risk factor of stroke-associated pneumonia: a Chinese pilot study. *Front Cell Infect Microbiol*. 2021;11:715475. doi:10.3389/fcimb.2021.715475
67. Stanley D, Mason LJ, Mackin KE, et al. Translocation and dissemination of commensal bacteria in post-stroke infection. *Nat Med*. 2016;22(11):1277–1284. doi:10.1038/nm.4194
68. Chen R, Wu P, Cai Z, et al. Puerariae lobatae radix with chuanxiong rhizoma for treatment of cerebral ischemic stroke by remodeling gut microbiota to regulate the brain-gut barriers. *J Nutr Biochem*. 2019;65:101–114. doi:10.1016/j.jnutbio.2018.12.004
69. Abramov VM, Kosarev IV, Priputnevich TV, et al. S-layer protein 2 of vaginal Lactobacillus crispatus 2029 enhances growth, differentiation, VEGF production and barrier functions in intestinal epithelial cell line Caco-2. *Int J Biol Macromol*. 2021;189:410–419. doi:10.1016/j.ijbiomac.2021.08.150
70. Hagihara M, Kuroki Y, Ariyoshi T, et al. Clostridium butyricum modulates the microbiome to protect intestinal barrier function in mice with antibiotic-induced dysbiosis. *iScience*. 2020;23(1):100772. doi:10.1016/j.isci.2019.100772
71. Sun J, Ling Z, Wang F, et al. Clostridium butyricum pretreatment attenuates cerebral ischemia/reperfusion injury in mice via anti-oxidation and anti-apoptosis. *Neurosci Lett*. 2016;613:30–35. doi:10.1016/j.neulet.2015.12.047
72. Debnath N, Kumar R, Kumar A, et al. Gut-microbiota derived bioactive metabolites and their functions in host physiology. *Biotechnol Genet Eng Rev*. 2021;37(2):105–153. doi:10.1080/02648725.2021.1989847
73. Wang J, Zhu N, Su X, et al. Gut-microbiota-derived metabolites maintain gut and systemic immune homeostasis. *Cells*. 2023;12(5):793. doi:10.3390/cells12050793
74. Silva YP, Bernardi A, Frozza RL. The role of short-chain fatty acids from gut microbiota in gut-brain communication. *Front Endocrinol*. 2020;11:25. doi:10.3389/fendo.2020.00025
75. Henry N, Frank J, McLouth C, et al. Short chain fatty acids taken at time of thrombectomy in acute ischemic stroke patients are independent of stroke severity but associated with inflammatory markers and worse symptoms at discharge. *Front Immunol*. 2021;12:797302. doi:10.3389/fimmu.2021.797302

76. Wang T, Pan C, Xie C, et al. Microbiota metabolites and immune regulation affect ischemic stroke occurrence, development, and prognosis. *Mol Neurobiol*. 2023;60(11):6176–6187. doi:10.1007/s12035-023-03473-x
77. Sadler R, Cramer JV, Heindl S, et al. Short-chain fatty acids improve poststroke recovery via immunological mechanisms. *J Neurosci*. 2020;40(5):1162–1173. doi:10.1523/jneurosci.1359-19.2019
78. Liu D, Gu S, Zhou Z, et al. Associations of plasma TMAO and its precursors with stroke risk in the general population: a nested case-control study. *J Intern Med*. 2023;293(1):110–120. doi:10.1111/joim.13572
79. Zhang P, Wang R, Qu Y, et al. Gut microbiota-derived metabolite trimethylamine-N-oxide and stroke outcome: a systematic review. *Front Mol Neurosci*. 2023;16:1165398. doi:10.3389/fnmol.2023.1165398
80. Wu C, Xue F, Lian Y, et al. Relationship between elevated plasma trimethylamine N-oxide levels and increased stroke injury. *Neurology*. 2020;94(7):e667–e677. doi:10.1212/wnl.0000000000008862
81. Haghikia A, Li XS, Liman TG, et al. Gut microbiota-dependent trimethylamine N-oxide predicts risk of cardiovascular events in patients with stroke and is related to proinflammatory monocytes. *Arterioscler Thromb Vasc Biol*. 2018;38(9):2225–2235. doi:10.1161/atvbaha.118.311023
82. Liu C, Li Z, Song Z, et al. Choline and butyrate beneficially modulate the gut microbiome without affecting atherosclerosis in APOE*3-Leiden. CETP mice. *Atherosclerosis*. 2022;362:47–55. doi:10.1016/j.atherosclerosis.2022.10.009
83. Zhu W, Gregory JC, Org E, et al. Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk. *Cell*. 2016;165(1):111–124. doi:10.1016/j.cell.2016.02.011
84. Daulatzai MA. Fundamental role of pan-inflammation and oxidative-nitrosative pathways in neuropathogenesis of Alzheimer's disease in focal cerebral ischemic rats. *Am J Neurodegener Dis*. 2016;5(2):102–130.
85. Catorce MN, Gevorkian G. Evaluation of anti-inflammatory nutraceuticals in LPS-induced mouse neuroinflammation model: an update. *Curr Neuropharmacol*. 2020;18(7):636–654. doi:10.2174/1570159x18666200114125628
86. Jiang Z, Li L, Liu L, et al. Ischemic stroke and dysbiosis of gut microbiota: changes to LPS levels and effects on functional outcomes. *Altern Ther Health Med*. 2023;29(5):284–292.
87. Wang Z, Li J, Xu Y, et al. Elevated gut microbiota metabolite bile acids confer protective effects on clinical prognosis in ischemic stroke patients. *Front Neurosci*. 2024;18:1388748. doi:10.3389/fnins.2024.1388748
88. Zhang Y, Geng J, Hong Y, et al. Orally Administered crocin protects against cerebral ischemia/reperfusion injury through the metabolic transformation of crocetin by gut microbiota. *Front Pharmacol*. 2019;10:440. doi:10.3389/fphar.2019.00440
89. Hu W, Kong X, Wang H, et al. Ischemic stroke and intestinal flora: an insight into brain-gut axis. *Eur J Med Res*. 2022;27(1):73. doi:10.1186/s40001-022-00691-2
90. Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. *Nat Rev Immunol*. 2016;16(6):341–352. doi:10.1038/nri.2016.42
91. Koch HJ, Uyanik G, Bogdahn U, et al. Relation between laterality and immune response after acute cerebral ischemia. *Neuroimmunomodulation*. 2006;13(1):8–12. doi:10.1159/000092108
92. Ellis JP, Kalata N, Joekes EC, et al. Ischemic stroke as a complication of cryptococcal meningitis and immune reconstitution inflammatory syndrome: a case report. *BMC Infect Dis*. 2018;18(1):520. doi:10.1186/s12879-018-3386-0
93. Choi J, Kim BR, Akuzum B, et al. T(REG)king from gut to brain: the control of regulatory T cells along the gut-brain axis. *Front Immunol*. 2022;13:916066. doi:10.3389/fimmu.2022.916066
94. Benakis C, Brea D, Caballero S, et al. Commensal microbiota affects ischemic stroke outcome by regulating intestinal γδ T cells. *Nat Med*. 2016;22(5):516–523. doi:10.1038/nm.4068
95. Chen Y, Liang J, Ouyang F, et al. Persistence of gut microbiota dysbiosis and chronic systemic inflammation after cerebral infarction in cynomolgus monkeys. *Front Neurol*. 2019;10:661. doi:10.3389/fneur.2019.00661
96. Zhang Q, Deng P, Chen S, et al. Electroacupuncture and human iPSC-derived small extracellular vesicles regulate the gut microbiota in ischemic stroke via the brain-gut axis. *Front Immunol*. 2023;14:1107559. doi:10.3389/fimmu.2023.1107559
97. Egashira Y, Suzuki Y, Azuma Y, et al. The growth factor progranulin attenuates neuronal injury induced by cerebral ischemia-reperfusion through the suppression of neutrophil recruitment. *J Neuroinflammation*. 2013;10(1):105. doi:10.1186/1742-2094-10-105
98. Giles EM, Stagg AJ. Type 1 Interferon in the human intestine-a co-ordinator of the immune response to the microbiota. *Inflamm Bowel Dis*. 2017;23(4):524–533. doi:10.1097/mib.0000000000001078
99. Macia L, Tan J, Vieira AT, et al. Metabolite-sensing receptors GPR43 and GPR109A facilitate dietary fibre-induced gut homeostasis through regulation of the inflammasome. *Nat Commun*. 2015;6(1):6734. doi:10.1038/ncomms7734
100. Yan J, Greer JM, Etherington K, et al. Immune activation in the peripheral blood of patients with acute ischemic stroke. *J Neuroimmunol*. 2009;206(1–2):112–117. doi:10.1016/j.jneuroim.2008.11.001
101. Liesz A, Hu X, Kleinschnitz C, et al. Functional role of regulatory lymphocytes in stroke: facts and controversies. *Stroke*. 2015;46(5):1422–1430. doi:10.1161/strokeaha.114.008608
102. Park J, Kim M, Kang SG, et al. Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR-S6K pathway. *Mucosal Immunol*. 2015;8(1):80–93. doi:10.1038/mi.2014.44
103. Gonçalves P, Araújo JR, Di Santo JP. A cross-talk between microbiota-derived short-chain fatty acids and the host mucosal immune system regulates intestinal homeostasis and inflammatory bowel disease. *Inflamm Bowel Dis*. 2018;24(3):558–572. doi:10.1093/ibd/izx029
104. Smith PM, Howitt MR, Panikov N, et al. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science*. 2013;341(6145):569–573. doi:10.1126/science.1241165
105. Zhang Y, Fang XM. The pan-liver network theory: from traditional Chinese medicine to western medicine. *Chin J Physiol*. 2023;66(6):401–436. doi:10.4103/cjop.CJOP-D-22-00131
106. Hou Y, Qieni X, Li N, et al. Longzhibu disease and its therapeutic effects by traditional Tibetan medicine: ershi-wei Chenxiang pills. *J Ethnopharmacol*. 2020;249:112426. doi:10.1016/j.jep.2019.112426
107. Wang Y, Liu X, Zhang W, et al. Synergy of "Yiqi" and "Huoxue" components of QishenYiqi formula in ischemic stroke protection via lysosomal/inflammatory mechanisms. *J Ethnopharmacol*. 2022;293:115301. doi:10.1016/j.jep.2022.115301
108. Sun J, Wang F, Ling Z, et al. Clostridium butyricum attenuates cerebral ischemia/reperfusion injury in diabetic mice via modulation of gut microbiota. *Brain Res*. 2016;1642:180–188. doi:10.1016/j.brainres.2016.03.042

109. Pang SQ, Luo ZT, Wang CC, et al. Effects of Dioscorea polystachya 'yam gruel' on the cognitive function of diabetic rats with focal cerebral ischemia-reperfusion injury via the gut-brain axis. *J Integr Neurosci*. 2020;19(2):273–283. doi:10.31083/j.jin.2020.02.69
110. Ding X, Liu Z, Liu Y, et al. Comprehensive evaluation of the mechanism of gastrodia elata Blume in ameliorating cerebral ischemia-reperfusion injury based on integrating fecal metabonomics and 16S rDNA sequencing. *Front Cell Infect Microbiol*. 2022;12:1026627. doi:10.3389/fcimb.2022.1026627
111. Dong Q, Lin X, Shen L, et al. The protective effect of herbal polysaccharides on ischemia-reperfusion injury. *Int J Biol Macromol*. 2016;92:431–440. doi:10.1016/j.ijbiomac.2016.07.052
112. Yang B, Zhang LY, Chen Y, et al. Melatonin alleviates intestinal injury, neuroinflammation and cognitive dysfunction caused by intestinal ischemia/reperfusion. *Int Immunopharmacol*. 2020;85:106596. doi:10.1016/j.intimp.2020.106596
113. Su LJ, Ren YC, Chen Z, et al. Ginsenoside Rb1 improves brain, lung, and intestinal barrier damage in middle cerebral artery occlusion/reperfusion (MCAO/R) micevia the PPARγ signaling pathway. *Chin J Nat Med*. 2022;20(8):561–571. doi:10.1016/s1875-5364(22)60204-8
114. Liu Y, Zhao P, Cai Z, et al. Buqi-Huoxue-Tongnao decoction drives gut microbiota-derived indole lactic acid to attenuate ischemic stroke via the gut-brain axis. *Chin Med*. 2024;19(1):126. doi:10.1186/s13020-024-00991-1
115. Shi Y, Du Q, Li Z, et al. Multiomics profiling of the therapeutic effect of Dan-deng-tong-nao capsule on cerebral ischemia-reperfusion injury. *Phytomedicine*. 2024;128:155335. doi:10.1016/j.phymed.2023.155335
116. Zhang L, Xue S, Fei C, et al. Protective effect of Tao Hong Si Wu Decoction against inflammatory injury caused by intestinal flora disorders in an ischemic stroke mouse model. *BMC Complement Med Ther*. 2024;24(1):124. doi:10.1186/s12906-024-04417-1
117. Ni Y, Cai L, Gou X, et al. Therapeutic effect of Sanhua decoction on rats with middle cerebral artery occlusion and the associated changes in gut microbiota and short-chain fatty acids. *PLoS One*. 2024;19(2):e0298148. doi:10.1371/journal.pone.0298148
118. Nie H, Ge J, Yang K, et al. Naotaifang III protects against cerebral ischemia injury through LPS/TLR4 signaling pathway in the microbiota-gut-brain axis. *Drug Des Devel Ther*. 2023;17:3571–3588. doi:10.2147/dddt.S421658
119. Wang R, Sun Y, Wang M, et al. Therapeutic effect of Eleutherococcus senticosus (Rupr. & Maxim.) Maxim. leaves on ischemic stroke via the microbiota–gut–brain axis. *Phytother Res*. 2023;37(10):4801–4818. doi:10.1002/ptr.7947
120. Luo S, Chen Y, Zhao R, et al. Application of omics technology to investigate the mechanism underlying the role of San Hua Tang in regulating microglia polarization and blood-brain barrier protection following ischemic stroke. *J Ethnopharmacol*. 2023;314:116640. doi:10.1016/j.jep.2023.116640
121. Zhai Y, Luo Y, Mo X, et al. Zhuang medicine Shuanglu Tongnao compound recipe treats stroke by affecting the intestinal flora regulated by the TLR4/NF-κB signaling pathway. *Ann Transl Med*. 2023;11(4):174. doi:10.21037/atm-23-253
122. Lian Z, Xu Y, Wang C, et al. Gut microbiota-derived melatonin from puerariae lobatae radix-resistant starch supplementation attenuates ischemic stroke injury via a positive microbial co-occurrence pattern. *Pharmacol Res*. 2023;190:106714. doi:10.1016/j.phrs.2023.106714
123. Zhang Y, Shen L, Xie J, et al. Pushen capsule treatment promotes functional recovery after ischemic stroke. *Phytomedicine*. 2023;111:154664. doi:10.1016/j.phymed.2023.154664
124. Li Q, Cao M, Wei Z, et al. The protective effect of Buzhong Yiqi decoction on ischemic stroke mice and the mechanism of gut microbiota. *Front Neurosci*. 2022;16:956620. doi:10.3389/fnins.2022.956620
125. Wang R, Liu M, Ren G, et al. Zhilong Huoxue Tongyu Capsules' effects on ischemic stroke: an assessment using fecal 16S rRNA gene sequencing and untargeted serum metabolomics. *Front Pharmacol*. 2022;13:1052110. doi:10.3389/fphar.2022.1052110
126. Liu G, Lin J, Zhang L, et al. Uncovering the mechanism of the xingnaojing injection against ischemic stroke using a combined network pharmacology approach and gut microbiota analysis. *Evid Based Complement Alternat Med*. 2022;2022:5886698. doi:10.1155/2022/5886698
127. Xian M, Shen L, Zhan S, et al. Integrated 16S rRNA gene sequencing and LC/MS-based metabolomics ascertained synergistic influences of the combination of acupuncture and NaoMaiTong on ischemic stroke. *J Ethnopharmacol*. 2022;293:115281. doi:10.1016/j.jep.2022.115281
128. Gao Q, Han ZY, Tian DF, et al. Xinglou Chengqi Decoction improves neurological function in experimental stroke mice as evidenced by gut microbiota analysis and network pharmacology. *Chin J Nat Med*. 2021;19(12):881–899. doi:10.1016/s1875-5364(21)60079-1
129. Fu K, Zhang D, Song Y, et al. Tibetan medicine Qishiwei Zhenzhu Pills can reduce cerebral ischemia-reperfusion injury by regulating gut microbiota and inhibiting inflammation. *Evid Based Complement Alternat Med*. 2021;2021:2251679. doi:10.1155/2021/2251679
130. Zhang F, Zhai M, Wu Q, et al. Protective effect of Tong-Qiao-Huo-Xue decoction on inflammatory injury caused by intestinal microbial disorders in stroke rats. *Biol Pharm Bull*. 2020;43(5):788–800. doi:10.1248/bpb.b19-00847
131. Liu X, Wang Y, Tian Y, et al. The water extract of rhubarb prevents ischemic stroke by regulating gut bacteria and metabolic pathways. *Metabolites*. 2024;14(4):216. doi:10.3390/metabo14040216
132. Huang Y, Li Y, Guan D, et al. Acorus tatarinowii oils exert protective effects on microglia-mediated inflammatory injury via restoring gut microbiota composition in experimental stroke rats. *Brain Res Bull*. 2024;213:110990. doi:10.1016/j.brainresbull.2024.110990
133. Zhang S, Chen Q, Jin M, et al. Notoginsenoside R1 alleviates cerebral ischemia/reperfusion injury by inhibiting the TLR4/MyD88/NF-κB signaling pathway through microbiota-gut-brain axis. *Phytomedicine*. 2024;128:155530. doi:10.1016/j.phymed.2024.155530
134. Duan H, Hu J, Deng Y, et al. Berberine mediates the production of butyrate to ameliorate cerebral ischemia via the gut microbiota in mice. *Nutrients*. 2023;16(1):9. doi:10.3390/nu16010009
135. Yan C, Liu Z, Xie W, et al. Cornuside protects against ischemic stroke in rats by suppressing the IL-17F/TRAF6/NF-κB pathway via the brain-gut axis. *Exp Neurol*. 2024;373:114672. doi:10.1016/j.expneurol.2023.114672
136. Li M, Wang S, Zhang C, et al. Escin alleviates stress-induced intestinal dysfunction to protect brain injury by regulating the gut-brain axis in ischemic stroke rats. *Int Immunopharmacol*. 2023;115:109659. doi:10.1016/j.intimp.2022.109659
137. Xie Y, Zou X, Han J, et al. Indole-3-propionic acid alleviates ischemic brain injury in a mouse middle cerebral artery occlusion model. *Exp Neurol*. 2022;353:114081. doi:10.1016/j.expneurol.2022.114081
138. Xu N, Kan P, Yao X, et al. Astragaloside IV reversed the autophagy and oxidative stress induced by the intestinal microbiota of AIS in mice. *J Microbiol*. 2018;56(11):838–846. doi:10.1007/s12275-018-8327-5
139. Zhao N, Gao Y, Jia H, et al. Anti-apoptosis effect of traditional Chinese medicine in the treatment of cerebral ischemia-reperfusion injury. *Apoptosis*. 2023;28(5–6):702–729. doi:10.1007/s10495-023-01824-6
140. Guo Q, Ni C, Li L, et al. Integrated traditional Chinese medicine improves functional outcome in acute ischemic stroke: from clinic to mechanism exploration with gut microbiota. *Front Cell Infect Microbiol*. 2022;12:827129. doi:10.3389/fcimb.2022.827129

141. Yu T, Xing Y, Gao Q, et al. Ginkgo biloba extract drives gut flora and microbial metabolism variation in a mouse model of Alzheimer's disease. *Pharmaceutics*. 2023;15(12):2746. doi:10.3390/pharmaceutics15122746
142. Xuejiang W, Magara T, Konishi T. Prevention and repair of cerebral ischemia-reperfusion injury by Chinese herbal medicine, shengmai san, in rats. *Free Radic Res*. 1999;31(5):449–455. doi:10.1080/10715769900301011
143. Lin H, Chen S, Shen L, et al. Integrated analysis of the cecal microbiome and plasma metabolomics to explore NaoMaiTong and its potential role in changing the intestinal flora and their metabolites in ischemic stroke. *Front Pharmacol*. 2021;12:773722. doi:10.3389/fphar.2021.773722
144. Mao M, Cao X, Liang Y, et al. Neuroprotection of rhubarb extract against cerebral ischaemia-reperfusion injury via the gut-brain axis pathway. *Phytomedicine*. 2024;126:155254. doi:10.1016/j.phymed.2023.155254
145. Shen H, Tong X, Yang J, et al. Biotransformation of natural hydroxycinnamic acids by gut microbiota from normal and cerebral ischemia-reperfusion injured rats: a comparative study. *Food Funct*. 2020;11(6):5389–5395. doi:10.1039/d0fo00775g
146. Li Q, Guo Y, Yu X, et al. Protective mechanism of rhubarb anthraquinone glycosides in rats with cerebral ischaemia-reperfusion injury: interactions between medicine and intestinal flora. *Chin Med*. 2020;15(1):60. doi:10.1186/s13020-020-00341-x
147. Wang M, Fu R, Xu D, et al. Traditional Chinese Medicine: a promising strategy to regulate the imbalance of bacterial flora, impaired intestinal barrier and immune function attributed to ulcerative colitis through intestinal microecology. *J Ethnopharmacol*. 2024;318(Pt A):116879. doi:10.1016/j.jep.2023.116879
148. Li H, Xiao J, Li X, et al. Low cerebral exposure cannot hinder the neuroprotective effects of Panax notoginsenosides. *Drug Metab Dispos*. 2018;46(1):53–65. doi:10.1124/dmd.117.078436
149. Dou Z, Rong X, Zhao E, et al. Neuroprotection of resveratrol against focal cerebral ischemia/reperfusion injury in mice through a mechanism targeting gut-brain axis. *Cell Mol Neurobiol*. 2019;39(6):883–898. doi:10.1007/s10571-019-00687-3
150. Kurita N, Yamashiro K, Kuroki T, et al. Metabolic endotoxemia promotes neuroinflammation after focal cerebral ischemia. *J Cereb Blood Flow Metab*. 2020;40(12):2505–2520. doi:10.1177/0271678x19899577
151. Ahmed H, Leyrolle Q, Koistinen V, et al. Microbiota-derived metabolites as drivers of gut-brain communication. *Gut Microbes*. 2022;14 (1):2102878. doi:10.1080/19490976.2022.2102878
152. Li S, Zhao X, Lin F, et al. Gut flora mediates the rapid tolerance of electroacupuncture on ischemic stroke by activating melatonin receptor through regulating indole-3-propionic acid. *Am J Chin Med*. 2022;50(4):979–1006. doi:10.1142/s0192415x22500409
153. Guo Q, Jiang X, Ni C, et al. Gut microbiota-related effects of Tanhuo decoction in acute ischemic stroke. *Oxid Med Cell Longev*. 2021;2021 (1):5596924. doi:10.1155/2021/5596924
154. Xian M, Ma Z, Zhan S, et al. Network analysis of microbiome and metabolome to explore the mechanism of raw rhubarb in the protection against ischemic stroke via microbiota-gut-brain axis. *Fitoterapia*. 2024;175:105969. doi:10.1016/j.fitote.2024.105969
155. Ghosh S, Pramanik S. Structural diversity, functional aspects and future therapeutic applications of human gut microbiome. *Arch Microbiol*. 2021;203(9):5281–5308. doi:10.1007/s00203-021-02516-y
156. He X, Cai Q, Li J, et al. Involvement of brain-gut axis in treatment of cerebral infarction by β-asaron and paeonol. *Neurosci Lett*. 2018;666:78–84. doi:10.1016/j.neulet.2017.12.036
157. Xia ZY, Luo C, Liu BW, et al. Shengui Sansheng Pulvis maintains blood-brain barrier integrity by vasoactive intestinal peptide after ischemic stroke. *Phytomedicine*. 2020;67:153158. doi:10.1016/j.phymed.2019.153158
158. Zhao QY, Tang RH, Lu GX, et al. Efficacy of Getong Tongluo capsule for convalescent-phase of ischemic stroke and primary hypertension: a multicenter, randomized, double-blind, controlled trial. *Chin J Integr Med*. 2021;27(4):252–258. doi:10.1007/s11655-020-3320-3
159. Yu Y, Tang L, Cui F, et al. Effect of Qizhitongluo capsule on lower limb rehabilitation after stroke: a randomized clinical trial. *Pharmacol Res*. 2021;165:105464. doi:10.1016/j.phrs.2021.105464
160. Venketasubramanian N, Chen CL, Gan RN, et al. A double-blind, placebo-controlled, randomized, multicenter study to investigate Chinese medicine neuroaid efficacy on stroke recovery (CHIMES Study). *Int J Stroke*. 2009;4(1):54–60. doi:10.1111/j.1747-4949.2009.00237.x
161. Young SH, Zhao Y, Koh A, et al. Safety profile of MLC601 (Neuroaid) in acute ischemic stroke patients: a Singaporean substudy of the Chinese medicine neuroaid efficacy on stroke recovery study. *Cerebrovasc Dis*. 2010;30(1):1–6. doi:10.1159/000313398
162. Yu XF, Zhu XY, Yuan CX, et al. Naoxintong capsule for secondary prevention of ischemic stroke: a multicenter, randomized, and placebo-controlled trial. *Chin J Integr Med*. 2022;28(12):1063–1071. doi:10.1007/s11655-022-3586-8
163. Xie RM, Chen HX, Xie YM. Effects of integrative medicine protocols on the improvement of neural function deficit and disability outcomes in patients with acute ischemic cerebral stroke. *Zhongguo Zhong Xi Yi Jie He Za Zhi*. 2011;31(9):1175–1180.
164. Sarma KN, Thalluri C, Mandhadi JR. Nanofibers in drug delivery systems: a comprehensive scientific review of recent approaches. *Int J Pharm Investig*. 2024;14(3):633. doi:10.5530/ijpi.14.3.75