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The Role of Gut Microbiota in Ischemic Stroke and Its Traditional Chinese Medicine Intervention

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Abstract: Ischemic stroke (IS) ranks among the leading causes of disability and mortality worldwide, imposing a significant burden upon society and families. Neuroprotection following ischemic stroke constitutes a vital therapeutic approach. In recent years, an increasing body of research has demonstrated that the gut microbiota and its regulation through traditional Chinese medicine may exert neuroprotective effects. This paper systematically reviews relevant studies, delving into the pathways and mechanisms by which traditional Chinese medicine counteracts cerebral ischaemic injury through modulating gut microbiota composition and metabolic functions. It aims to provide novel insights and theoretical foundations for the prevention and treatment of ischaemic stroke.

Keywords: IS; Gut Microbiota; Traditional Chinese Medicine

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1. Introduction

Ischemic stroke, as a prevalent cerebrovascular disorder, poses a significant global public health challenge due to its high incidence, disability rate, and mortality. This condition not only imposes a heavy burden on patients' families but also carries a substantial risk of recurrence. Its pathogenesis commences with intracranial arterial occlusion, subsequently triggering a complex cascade of pathophysiological responses. Core pathways encompass excitotoxicity, oxidative stress, neuroinflammation, and disruption of the blood-brain barrier. These interacting processes collectively culminate in parenchymal necrosis and neurological deficits. Research indicates that approximately half of stroke patients experience concomitant gastrointestinal symptoms, including constipation, gastrointestinal haemorrhage, and faecal incontinence[1].

Modern research defines the human gut microbiota as a vast, diverse, and highly dynamic ecosystem, comprising bacteria, archaea, fungi, viruses (including bacteriophages), and protozoa. Alterations in the composition and balance of this gut flora constitute a key factor in triggering intestinal dysfunction and, through the gut-brain axis, influencing brain function and emotional behaviour. It is also closely associated with the progression of diseases such as cerebral ischaemia. This aligns remarkably with the principles of traditional Chinese medicine[2].

Within the holistic framework of Traditional Chinese Medicine, the pivotal functions of the spleen and stomach are intrinsically linked to the generation and transformation of qi, blood, and body fluids. The proper functioning of

the spleen, stomach, and intestines in transporting and transforming the essence of food and drink forms the foundation for maintaining bodily health. Conversely, when this transport and transformation process is disrupted, it may lead to deficiencies in qi and blood or the accumulation of turbid toxins internally. Pathological by-products may then ascend to the cerebral vessels, resulting in stroke. Traditional Chinese medicine exerts its effects through multiple targets, pathways, and levels. An increasing body of research indicates that it can improve the prognosis of ischaemic stroke by regulating the gut microbiota. This paper reviews the relationship between the gut microbiota and ischaemic stroke, along with relevant aspects of its regulation by traditional Chinese medicine, with the aim of providing new insights and approaches for the prevention and treatment of ischaemic stroke using traditional Chinese medicine.

2. The Association Between Gut Microbiota and Ischemic Stroke

2.1. Gut Microbiota Dysbiosis and Ischemic Stroke

The normal gut microbiota maintains a dynamic equilibrium with its host through mutualistic symbiosis. This balance relies upon regulation via the bidirectional communication pathway known as the gut-brain axis, whilst the microbiota itself undergoes alterations in response to the host's disease state. Stroke disrupts the established equilibrium of the gut-brain axis. During the acute phase of cerebral ischaemia, the body's intense stress response activates the sympathetic nervous system and the hypothalamic-pituitary-adrenal axis, subsequently triggering reduced gastrointestinal blood flow, motility disorders, and increased permeability[3]with a highly dynamic pathological process. Post-stroke neuroinflammation, mediated by microglia, demonstrates a dual role in both injury and repair. The CX3CR1/CX3CL1 signaling axis, highly expressed in microglia, acts as a key regulator. This review examines the spatiotemporal dynamics of the axis across the stroke process and its involvement in neural repair. Crucially, this signaling pathway demonstrates stage-dependent functional duality: its cellular sources, receptor expression profiles, and functional consequences undergo temporally orchestrated shifts, manifesting coexisting or interconverting protective and damaging properties. Ignoring this dynamism compromises the therapeutic efficacy of targeted interventions. Thus, we propose a triple precision strategy of \"stroke phase-biomarker-targeted intervention\". It uses specific biomarkers for precise staging and designs interventions based on each phase's signaling characteristics. Despite challenges like biomarker validation, mechanistic exploration, and cross-species differences, integrating cutting-edge technologies such as spatial metabolomics and AI-driven dynamic modeling promises to shift stroke therapy toward personalized spatiotemporal programming. Temporally targeting CX3CR1 signaling may offer a key basis for developing next-generation precision neural repair strategies for stroke.","call-number":"3","container-title":"Brain Sciences","DOI":"10.3390/brainsci15070759","ISSN":"2076-3425","issue":"7","journalAbbreviation":"Brain Sci.","language":"en","note":"PMID: 40722349\nPMCID: PMC12293467","page":"759","source":"2.7","title":"Targeting CX3CR1 signaling dynamics: a critical determinant in the temporal regulation of post-stroke neurorepair","title-short":"Targeting CX3CR1 signaling dynamics", "volume":"15", "author":[{"family":"He", "given":"Quan"}, {"family":"Zhou", "given":"Tong"}, {"family":"He", "given":"Quanwei"}], "issued":{"date-parts":[["2025", 7, 17]]}}}], "schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} . This series of changes ultimately leads to dysbiosis of the gut microbiota, characterised by a marked reduction in diversity, decreased abundance of beneficial bacteria (such as Lactobacillus and Bifidobacterium), and an increased proportion of opportunistic pathogens (such as Enterobacteriaceae). This outcome has been corroborated in both clinical trials and animal models. Such microbial imbalance triggers gastrointestinal dysfunction, thereby accelerating systemic inflammatory responses. This adversely affects neurological recovery in stroke patients, ultimately impeding their rehabilitation process.

2.2. The Intestinal Epithelial Barrier and Ischemic Stroke

An intact intestinal mucosal barrier serves as a crucial defence against pathogenic bacteria and harmful substances within the gut. However, dysbiosis induced by stroke exacerbates damage to this barrier, allowing intestinal endotoxins and

pathogens to enter the circulatory system. This subsequently triggers systemic secondary infections, ultimately becoming one of the significant contributing factors to mortality in stroke patients. To investigate the effects of stroke on the intestinal barrier, we established a rat model of middle cerebral artery occlusion (MCAO). Detection results revealed that the expression levels of key tight junction proteins—including occludin, claudin-5, and zonulin-1—were significantly downregulated in the colonic tissue of the model rats[4]. This finding reveals structural damage to the intestinal epithelial barrier and increased permeability following stroke. Concurrently, elevated plasma levels of diamine oxidase (DAO), lipopolysaccharide (LPS), and D-lactic acid indicate the occurrence of intestinal microbial translocation. Therefore, modulating gut probiotics to enhance the integrity and function of the intestinal epithelial barrier holds significant therapeutic potential for ischaemic stroke.

2.3. Gut Microbiota Dysbiosis and Ischemic Stroke

Gut microbiota metabolites play a pivotal role in regulating bodily equilibrium, with short-chain fatty acids (SCFAs) representing a quintessential beneficial product. Their function extends beyond maintaining intestinal homeostasis; by influencing immune cells, they also promote motor recovery following stroke, demonstrating significant therapeutic potential. Gut microbiota metabolites serve as crucial messengers in microbe-host interactions[5]. Furthermore, stroke-induced dysbiosis of the gut microbiota—particularly the proliferation of opportunistic pathogens—leads to elevated levels of harmful metabolites, thereby activating the body's immune inflammatory response. These inflammatory mediators subsequently migrate to the ischaemic brain region, further exacerbating cerebral injury.

3. Traditional Chinese Medicine improves ischaemic stroke outcomes by regulating the gut microbiota

Traditional Chinese Medicine exerts its effects through multi-targeted, multi-pathway, and multi-level mechanisms. By regulating the brain-gut axis through holistic intervention, it embodies the wisdom of treating different diseases with similar approaches and addressing upper-body ailments through lower-body interventions. An increasing body of research indicates that Traditional Chinese Medicine can improve outcomes in ischaemic stroke by modulating the gut microbiota. This section elaborates on the relevant findings.

3.1. Active constituents of traditional Chinese medicine

Astragalus is a traditional Chinese medicinal herb renowned for its properties of tonifying qi and fortifying the exterior, expelling toxins and draining pus, promoting diuresis and tissue regeneration. It is lauded in the Compendium of Materia Medica as the 'superior tonic herb'. Modern pharmacological research further reveals that its active constituents primarily comprise astragaloside IV and astragalus polysaccharides, each exerting therapeutic effects through distinct mechanisms. On the one hand, astragaloside IV regulates intestinal microbiota; on the other, astragalus polysaccharides inhibit NO protein expression that induces apoptosis following cerebral ischaemia-reperfusion, thereby mitigating brain tissue damage and enhancing therapeutic outcomes[6]. Ginseng possesses potent effects in replenishing vital energy, benefiting the lungs and strengthening the spleen, generating fluids and nourishing the blood, as well as calming the spirit and enhancing intelligence. It may be employed in the treatment of stroke. Its primary active component, ginsenosides, exhibits low direct absorption rates in the human body, undergoing metabolic conversion primarily within the intestinal tract by gut microbiota. Research confirms that although ginsenosides exhibit species-specific metabolic pathways in humans and rats, they ultimately convert into metabolites entering the bloodstream. Consequently, this intestinal metabolic process is recognised as the key mechanism through which ginseng exerts its broad pharmacological effects[7]. Research indicates that the kudzu root-chuanxiong combination exhibits protective effects against cerebral ischaemic injury. This action may be closely associated with its regulation of the gut-brain axis, specifically through promoting the growth of beneficial bacteria and correcting post-stroke gut dysbiosis[8]. Targeted metabolomics studies indicate that Gastrodia elata may mitigate

cerebral ischaemia-reperfusion injury in rats by modulating gut microbiota-associated amino acid metabolic pathways. Gastrodia regulates tryptophan metabolism, balances glutamate/glutamine levels, and reduces phenylalanine and arginine content. This subsequently influences the expression of inflammatory mediators such as IL-6 and TNF-α, ultimately mitigating inflammatory damage to brain tissue[9]the mechanism of G. elata Blume in improving CIRI by regulating the intestinal flora has not been reported until now. This research aimed to comprehensively evaluate the mechanism of G. elata Blume in CIRI based on fecal metabolomics and 16S rDNA sequencing. The rat model with CIRI was created based on the Zea Longa method. Enzyme-linked immunosorbent assay (ELISA).

3.2. Compound Chinese Medicinal Preparations

In MCAO model mice, Xingqichengqi Decoction significantly modulated gut microbiota composition, such as altering the abundance of Bacteroidetes and Firmicutes phyla, and elevated α-diversity indices including Chao1, Shannon, and Simpson indices, indicating its efficacy in enhancing gut microbial diversity. These beneficial microbial alterations were accompanied by improved neurological function in mice, suggesting its neuroprotective effects may be linked to regulation of the gut-brain axis[10]followed by behavioral evaluation, TTC and TUNEL staining. Additionally, to investigate the effects of gut microbiota on neurological function after stroke, C57BL/6 mice were treated with anti-biotic cocktails 14 days prior to ischemic stroke (IS. The Tongqiao Huoxue Decoction improves stroke outcomes by regulating post-stroke gut microbiota dysbiosis, repairing the intestinal barrier, and suppressing immune inflammatory responses. Experimental studies indicate that this formula increases bifidobacteria abundance in the intestines of MCAO model rats, promotes Treg cell expression, and inhibits the activation and migration of γδ T cells in the small intestine. Consequently, it reduces the secretion of the downstream pro-inflammatory factor IL-17 in the cerebral ischaemic area[11]the high throughput 16S ribosomal DNA (rDNA. Research indicates that An Gong Niu Huang Wan modulates multiple metabolic pathways in rats with middle cerebral artery occlusion (MCAO) and enhances uridine metabolism. Uridine is known to mitigate post-traumatic cerebral oedema and promote synaptic formation. Based on Spearman's correlation analysis, researchers hypothesise that uridine production may correlate with the formulation's regulation of gut microbiota, including genera such as Bacteroides and Ruminococcus[12]the mechanism of action of ANP in stroke treatment has rarely been reported. With increasing evidence for a mechanistic link between acute ischemic stroke and gut microbiota alterations, this study aimed to determine the mechanism of action of ANP in treating acute ischemic stroke from the perspective of the gut microbiota. A mouse model of acute ischemic stroke by middle cerebral artery occlusion (MCAO).

4. Conclusion and Outlook

Ischemic stroke is a prototypical network-based disorder, with pathological damage propagating along neural circuits to trigger complex secondary lesions, constituting the primary cause of poor prognosis. Consequently, neuroprotection targeting this process represents a key therapeutic strategy for improving stroke outcomes. The gut microbiota represents an emerging therapeutic avenue for ischaemic stroke, offering neuroprotective effects. However, its multi-targeted and complex mechanisms pose significant barriers to clinical translation. Traditional Chinese medicine, with its inherent advantages in stroke treatment through multi-targeted, multi-pathway, and multi-level effects, has been increasingly demonstrated to significantly correct post-stroke gut dysbiosis. This, in turn, regulates downstream metabolome and proteome expression, thereby improving outcomes for patients with ischaemic stroke.

Current research has primarily confirmed the phenomenon of traditional Chinese medicine regulating the microbiota and metabolites, yet the specific mechanisms underlying this remain a "black box", particularly lacking in-depth exploration and validation of the causal relationship between microbiota and metabolites. In future, it will be necessary to integrate techniques such as metabolomics and metagenomics to more precisely elucidate the specific bacterial strains influenced by traditional Chinese medicine, along with the precise action targets and signalling pathways of their key metabolites (such as secondary bile acids and indole derivatives). Through experimental methods such as faecal microbiota

transplantation and germ-free animal models, it has been further demonstrated that alterations in the gut microbiota constitute both a 'necessary condition' and a 'causal link' for the efficacy of traditional Chinese medicine. Moreover, multicentre clinical trials may be conducted to expand the sample size for traditional Chinese medicine treatment of ischaemic stroke, establish standardised herbal intervention protocols, and incorporate metagenomics for dynamic monitoring of patient microbiota changes. This approach will provide high-level evidence-based medical evidence for the clinical application of traditional Chinese medicine. In summary, the gut microbiota and its medicinal interventions hold immense potential as novel therapeutic targets for future stroke management.

Disclosure statement

The author declares no conflict of interest.

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