

# Acupuncture for ischemic stroke: where are we now?

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## Abstract

Acupuncture is an effective treatment for ischemic stroke (IS) and plays a key role in neurological rehabilitation after IS. Acupuncture can improve the clinical symptoms of various complications after IS, including motor dysfunction, swallowing disorders, speech disorders, cognitive impairment, depression, insomnia, and fatigue. However, the mechanisms underlying the effects of acupuncture in IS remain unclear. Available evidence suggests that acupuncture may exert neuroprotective effects through neuroplasticity (neurogenesis and synaptogenesis), angiogenesis, cell proliferation and apoptosis, and regulation of oxidative stress, inflammation, and immunity. Further studies should be conducted to improve the high-quality evidence-based system of acupuncture intervention for IS, by focusing on the clinical and basic research design, increasing the sample size, standardizing and quantifying the standards of acupuncture operations, using multidisciplinary techniques and methods to systematically explore the key targets of acupuncture intervention for IS, and reveal the efficacy and mechanism of acupuncture in the treatment of IS.

**Keywords:** Acupuncture, Curative effect, Electroacupuncture, Ischemic stroke, Mechanism, Review

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## Introduction

Stroke is an acute focal injury of the central nervous system caused by vascular causes, including hemorrhagic and ischemic stroke (IS). The prevalence of stroke is approximately 2.5%, and age is the most important risk factor. IS is the most common cerebrovascular disease, accounting for approximately 70% of all strokes<sup>[1,2]</sup>. It is a serious threat to human health and is characterized by high morbidity, disability, and mortality. It ranks fifth among the causes of death after heart disease, cancer, chronic lower respiratory disease, and accidental injury<sup>[3]</sup>. IS is primarily caused by ischemic necrosis or softening of the restricted brain tissue due to impaired blood circulation to the brain, ischemia, and hypoxia. Beyond a specified time, the loss of neurons, supporting structures, and other irreversible damage to tissues can occur<sup>[4]</sup>. After ischemia occurs, a series of events such as loss of electrical function, membrane dysfunction, and inward calcium flow occur, ultimately leading to the disruption of brain cell membranes and cell lysis<sup>[1]</sup>. The major causes of IS include atherosclerosis of the

cerebral vasculature, cardiogenic embolism, and lacunar cerebral infarction; half of these are caused by atherosclerosis and the rupture of atherosclerotic plaques in the cerebral vasculature<sup>[5]</sup>. The primary event in 85% to 90% of acute strokes is impaired vascular supply to the brain, which is highly susceptible to ischemic injury because of its low respiratory reserve and dependence on aerobic metabolism<sup>[6]</sup>. The extent of the infarct site and the degree of neurological damage after the onset of IS often depend on the duration and location of the infarct site, severity of ischemia, and blood pressure<sup>[4]</sup>. After the occurrence of IS, different infarction sites have corresponding clinical symptoms and dysfunctions, including motor dysfunction<sup>[7,8]</sup>, dysphagia<sup>[9,10]</sup>, pain<sup>[11]</sup>, sleep disorders<sup>[12]</sup>, cognitive function defects<sup>[13–16]</sup>, such as language comprehension, attention, information processing, and memory ability, and other functional defects to varying degrees.

Currently, there are no clear and effective treatments or rehabilitation for IS. Complementary and alternative medicine are of increasing interest to hospitals

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and patients, and their use is ubiquitous in clinical practice<sup>[17,18]</sup>. Acupuncture, an important component of Chinese traditional medicine, has gained popularity worldwide. The World Health Organization recommends acupuncture as a complementary and alternative strategy for stroke treatment and improved post-stroke care<sup>[19]</sup>. A previous systematic review and meta-analysis of 56 publications that evaluated the effect of acupuncture on rehabilitation after IS in terms of exercise rehabilitation, analgesic effects, and perfusion volume around the infarct and ischemic penumbra, indicated a positive effect of acupuncture on rehabilitation<sup>[20]</sup>. A recent systematic review indicated that acupuncture is a safe and effective treatment for IS, improving neurological function, cognition, and activities of daily living in patients<sup>[21]</sup>. A randomized single-blind clinical study of 74 patients with IS also demonstrated significant improvements in neurological function, motor function, and activities of daily living<sup>[22]</sup>. A cohort study in Korea that included 2,299 patients with subacute and chronic IS showed that acupuncture may reduce mortality and prevent related complications<sup>[23]</sup>. Clinical trials and meta-analyses have shown that acupuncture effectively reduces mortality and prevents complications. The meta-analysis results suggest that acupuncture may play an active role in impairment and rehabilitation associated with the onset of IS, including dyskinesia<sup>[24]</sup>, dysphagia<sup>[25]</sup>, spasticity<sup>[26]</sup>, cognitive impairment<sup>[27]</sup>, aphasia<sup>[28]</sup>, insomnia<sup>[29]</sup>, dysarthria<sup>[30]</sup>, depression<sup>[31]</sup>, and fatigue<sup>[32]</sup>. In addition, acupuncture not only intervenes in IS as a therapeutic tool but can also be involved in the induction of ischemic tolerance as a preventive strategy<sup>[33]</sup>.

However, the exact mechanism of action of acupuncture in post-stroke dysfunction remains unclear. Acupuncture may enhance cerebral perfusion after IS, promote hemodynamic changes, release vasoactive substances, stimulate the production of new blood vessels, and improve microcirculation<sup>[34]</sup>. Another study indicated that interventions with appropriate electrodes for IS could exert neuroprotective and neuroregenerative effects<sup>[35]</sup>. The current study found that acupuncture may be involved in the treatment of IS in multiple ways, such as neuroplasticity regulation, neuroprotection, cell proliferation, inhibition of apoptosis, regulation of immunity and inflammation, regulation of oxidative stress, protection of the blood-brain barrier, and exosome regulation. Recently, brain imaging studies have been widely used to reveal the possible mechanisms of acupuncture interventions in terms of structure and function<sup>[36–38]</sup>. Acupuncture has generated a large body of clinical evidence for the treatment of stroke, which confirms the positive effects of acupuncture. However, no studies have systematically summarized the current state of acupuncture or explored the sources of its positive effects. Based on the mechanism of IS and a large body of clinical findings, we provide an overview of the clinical outcomes and a few acupuncture designs. In this study, we attempted to systematically demonstrate the role of acupuncture in injury repair. In addition, we provide a brief description of the mechanism of acupuncture in recent years and the proteins and genes involved.

## Methods

To summarize the literature on the application of acupuncture in IS, we performed advanced searches in Web of Science and PubMed databases. By using the terms “TS = (acupuncture) AND ((((((TS = (Ischemic Stroke)) OR TS = (Cryptogenic Ischemic Stroke)) OR TS = (Cryptogenic Stroke)) OR TS = (Cryptogenic Embolism Stroke)) OR TS = (Wake-up Stroke)) OR TS = (Acute Ischemic Stroke).” The search was conducted from January 1, 2013, to March 31, 2023. In total, 537 publications were retrieved. After the abstracts were read, 124 articles were selected and 413 articles were excluded. The reasons for this were as follows: (1) duplicate articles, (2) case reports, (3) non-IS, (4) summaries, and (5) non-acupuncture studies. After preliminary screening, we read 124 full-text articles that described acupuncture for the treatment of IS. All subjects included in the study had a single IS or multiple IS and were likely to have different post-stroke dysfunctions. After reading the full articles, we excluded six studies. The main exclusion criteria were as follows: (1) news coverage such as early access, (2) meeting summaries, (3) book chapters, and (4) edit materials. Of the 118 publications included, 56 involved clinical research and 62 involved animal experiments. We conducted a systematic review of these studies and presented the contents of some clinical and basic studies (Tables 1 and 2). By screening and summarizing the retrieved literature, we reviewed the clinical and basic research on acupuncture in the treatment of IS over the past 10 years, systematically summarized the clinical efficacy and outcomes of acupuncture in the treatment of dysfunction after IS, and reported the research progress of the internal mechanism of acupuncture in the multichannel intervention of IS. In clinical studies, acupuncture has shown certain advantages in terms of post-stroke dysfunctions, such as dyskinesia, cognitive impairment, aphasia, depression, insomnia, and fatigue. Simultaneously, clinical studies have explored the mechanisms of acupuncture sites through neuroimaging. Basic experimental studies have found that acupuncture may play a neuroprotective role in neuroplasticity (neurogenesis and synapse formation), angiogenesis, cell proliferation and apoptosis, and the regulation of oxidative stress, inflammation, and immunity. The content of the entire article is illustrated as a structural diagram in Figure 1.

## Evidence from clinical studies

In the last decade, the number of clinical studies using acupuncture and acupuncture combined with other interventions as therapeutic tools for the treatment of IS has increased. In 2016, Cochrane reviewed 31 clinical studies of acupuncture for stroke involving 2,257 patients with subacute and chronic stroke and concluded that acupuncture was effective in improving the patient's ability to perform activities of daily living, overall neurological deficits, specific neurological impairment, cognitive ability, swallowing ability, and that the pain may be beneficial. Moreover, no significant adverse events have been associated with acupuncture in humans. Although the quality of most studies on this outcome was flawed, there is still a need for rigorously designed, randomized,



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**Table 1**  
**(Continued)**

Study	Types of research	Acupuncture intervention	Dysfunction	Duration	Needle type	Needle frequency	Needle response	Acupoint
Guo et al. 2022 <sup>[48]</sup>	Randomized controlled trial	MA	Motor	10 days	Xingnao Kaiqiao Acupuncture	Once a day	De qi	Neiguan (PC 6), Renzhong (GV 26), Sanyinjiao (SP 6), Jiquan (HT 1), Weizhong (BL 40), Chize (LU 5)
Zhan et al. 2022 <sup>[24]</sup>	Randomized controlled trial	MA	Motor	8 weeks	Scalp acupuncture	5 times per week	NR	MS-6
Wu et al. 2023 <sup>[9]</sup>	Retrospective study	MA	Motor	The days of hospitalization	Xingnao Kaiqiao Acupuncture	Once a day	De qi	Neiguan (PC 6), Renzhong (GV 26), Sanyinjiao (SP 6), Jiquan (HT 1), Weizhong (BL 40), Chize (LU 5)
Hung et al. 2019 <sup>[50]</sup>	Randomized controlled trial	MA	Cognize	12 weeks	Body acupuncture	Twice per week	De qi	Zusanli (ST 36), Xuehai (SP 10), Danzhong (RN 17), Zhongwan (RN 12), Qihai (RN 6), Baihui (GV 20), Fengtu (GV 16), Xinsu (BL 15), Yixi (BL 45), Tongli (HT 5), Zhaohai (KI 6), Taixi (K 13), Xuanzhong (GB 39), Fenglong (ST 40), Neiguan (PC 6), Gesu (BL 17)
Zhang et al. 2016 <sup>[25]</sup>	Prospective cohort study	MA	Dysphagia	4 weeks	Tongguan Liqiao acupuncture	Twice a day	De qi	Neiguan (PC 6), Renzhong (GV 26), Sanyinjiao (SP 6), Fengchi (GB 20), Wangu (GB 12), Yifeng (SJ 17)
Caot et al. 2022 <sup>[29]</sup>	Randomized controlled trial	MA	Insomnia	4 weeks	Body acupuncture	3 times per week	De qi	Baihui (GV 20), Shenting (GV 24), Shenmen (HT 7), Sanyinjiao (SP 6)

EA: Electroacupuncture; MA: Manual acupuncture; NR: Not reported.

multi-center, large-sample clinical studies<sup>[91]</sup>. Recovery from IS and long-term outcomes are critical for patients and directly affect their quality of life. A systematic evaluation and meta-analysis involving 931 patients with IS demonstrated mortality, recurrence, disability, and safety at the end of acupuncture treatment and three months of follow-up, suggesting an advantage of acupuncture in reducing disability and long-term outcomes compared to traditional means of rehabilitation or combined treatment<sup>[92]</sup>. Acupuncture is based on holistic regulation of functional reconstruction and it may be effective in improving balance, reducing spasticity, increasing muscle strength, and improving general health after IS<sup>[19]</sup>. In addition, it is worth mentioning the recent gradual development of brain imaging studies of acupuncture may aid the researchers to gain new insights into the changes in brain structure and function with acupuncture intervention. In the present review, we found that acupuncture improved the overall neurological function and health status of patients with IS. In addition, acupuncture has different treatment strategies for different functional disorders after IS, which are effective. These acupuncture points and their different dysfunctions are described in Figure 2.

*Acupuncture promotes the recovery of motor function*

Approximately 70% of stroke survivors exhibit functional impairments, with motor dysfunction being the most common and significant symptom<sup>[93]</sup>. Motor dysfunction severely affects the patient’s ability to perform activities of daily living, decreases social participation, and causes a significant financial and care burden on the patient’s family<sup>[94]</sup>. The Chinese guidelines for acute IS 2018 recommend acupuncture for motor dysfunction after IS (Class II, Level B). In the past decade, several clinical trials were conducted to assess the efficacy and safety of acupuncture in improving motor function recovery in patients with IS; however, the findings were not conclusive. The details of some of these clinical trials of acupuncture are presented in Table 1. Several randomized controlled trials (RCTs) have been conducted on electroacupuncture (EA) and manual acupuncture stimulation. Although the duration and frequency of interventions vary, these results support the clinical efficacy of acupuncture in improving motor dysfunction after IS<sup>[22,39-41,44-48]</sup>. In particular, acupuncture may improve patients’ National Institute of Health stroke scale (NIHSS) scores and the ability to perform activities of daily living. These studies included various types of acupuncture, such as body, scalp, neck, temporal triple, and Xingnao Kaiqiao acupuncture. Notably, Li et al.<sup>[46]</sup> compared acupuncture points for stroke in ancient texts and modern textbooks, especially for rehabilitation treatment alone, and found that acupuncture at two different points may have different efficacies. The points of ancient texts focus on improving neurological function, whereas the points of modern textbooks focus on improving the ability to perform activities of daily living. Sangtin et al.<sup>[42]</sup> measured the number of acupuncture interventions and the degree of recovery of patients’ activities of daily living using survival analysis techniques and found a significant improvement in the

**Table 2****Acupoints and manipulation parameters used in animal studies for IS**

Study	Mechanism	Acupoint	Pre/post-treatment	Method	Frequency	Intensity	Depth	Duration
Li et al. 2013 <sup>[51]</sup>	Neuroprotection	GV 26	Post	MA	180 per min	NR	5 mm	5 s
Kim et al. 2013 <sup>[52]</sup>	Neuroprotection	GV 20 and GV 14	Pre	EA	2 Hz	1 mA	3 mm	20 min
Xu et al. 2015 <sup>[53]</sup>	Neuroprotection	EX-B 2	Post	MA	NR	NR	2–3 mm	30 s
Liu et al. 2015 <sup>[54]</sup>	Neuroprotection	GV 20	Pre	EA	2/15 Hz	1 mA	NR	30 min
Dai et al. 2017 <sup>[55]</sup>	Neuroprotection	GV 20	Post	EA	2/15 Hz	1 mA	1 mm	30 min
Chi et al. 2018 <sup>[56]</sup>	Neuroprotection	GV 20 and GV 14	Post	MA/EA	2/15 Hz	1 mA	2 mm/5mm	30 min
Su et al. 2022 <sup>[57]</sup>	Neuroprotection	GV 20 and GV 24	Post	EA	1/20 Hz	1–3 mA	2 mm	30 min
Sun et al. 2019 <sup>[58]</sup>	Neuroprotection	GB 34	Post	MA	NR	NR	4–5 mm	30 min
Shi et al. 2017 <sup>[59]</sup>	Angiogenesis	GV 26	Post	EA	15 Hz	1 mA	2 mm	5 min
Yang et al. 2022 <sup>[60]</sup>	Angiogenesis	GV20 and ST36	Post	EA	2 Hz	1 mA	NR	20 min
Xu et al. 2022 <sup>[61]</sup>	Angiogenesis	GV 26 and GV 20	Post	EA	3.85/6.25 Hz	0.8–1.3 mA	1 mm	20 min
Shi et al. 2022 <sup>[62]</sup>	Angiogenesis	GV 20	Post	EA	3–15 Hz	2–4 mA	NR	30 min
Hong et al. 2013 <sup>[63]</sup>	Neuroplasticity	ST 36 and LI 11	Post	EA	5/20 Hz	2–4 mA	5 mm	20 min
Liao et al. 2017 <sup>[64]</sup>	Neuroplasticity	ST 36 and ST 37	Post	EA	2/15 Hz	NR	NR	NR
Young-Wook et al. 2019 <sup>[65]</sup>	Neuroplasticity	GV 20 and GV 14	Post	EA	2 Hz	2 mA	NR	20 min
Zhang et al. 2022 <sup>[66]</sup>	Neuroplasticity	ST 36 and PC 6	Post	EA	2 Hz	1 mA	2/1 mm	20 min
Luo et al. 2011 <sup>[67]</sup>	Neuroplasticity	GV 20 and GV 14	Post	EA	4/20 Hz	1–3 mA	15/7.5mm	30 min
Xie et al. 2019 <sup>[68]</sup>	Neuroplasticity	GV 20 and GV 24	Post	EA	1–20 Hz	0.2 mA	2–3 mm	30 min
Chen et al. 2012 <sup>[69]</sup>	Apoptosis	LI11 and ST36	Post	EA	1/20 Hz	NR	2–3 mm	30 min
Feng et al. 2013 <sup>[70]</sup>	Apoptosis	GV 20 and GV 24	Post	EA	1/20 Hz	NR	2–3 mm	30 min
Xie et al. 2013 <sup>[71]</sup>	Apoptosis	ST36 and LI11	Post	EA	1/20 Hz	NR	2–3 mm	30 min
Wu et al. 2015 <sup>[72]</sup>	Apoptosis	LU 5, LI 4, ST 36, and SP 6	Post	EA	2/15 Hz	2 mA	3/1/7/5 mm	20 min
Tao et al. 2016 <sup>[73]</sup>	Apoptosis	LI 11 and ST 36	Post	EA	1/20 Hz	NR	2–3 mm	30 min
Chen et al. 2015 <sup>[74]</sup>	Apoptosis	LI 11 and ST 36	Post	EA	1/20 Hz	NR	2–3 mm	30 min
Lin et al. 2016 <sup>[75]</sup>	Apoptosis	GV 20 and GV 24	Post	EA	1/20 Hz	1–3 mA	2–3 mm	30 min
Wang et al. 2016 <sup>[76]</sup>	Apoptosis	GV 26	Post	EA	2 Hz	1 mA	2 mm	10 min
Liu et al. 2018 <sup>[77]</sup>	Apoptosis	GV 24 and GV 20	Post	EA	1/20 Hz	1 mA	NR	30 min
Yang et al. 2019 <sup>[78]</sup>	Apoptosis	ST 36	Post	MA	NR	NR	3 mm	30 min
Xu et al. 2020 <sup>[79]</sup>	Apoptosis	GV 20 and BL 23	Post	EA	2 Hz	1–2 mA	NR	15 min
Zhang et al. 2020 <sup>[80]</sup>	Apoptosis	GV20, PC6, and SP6	Post	EA	2/15 Hz	1 mA	2 mm	20 min
Long et al. 2022 <sup>[81]</sup>	Apoptosis	GV20, BL23, and SP6	Pre	EA	2/100 Hz	1 mA	NR	1 h
Jin et al. 2013 <sup>[82]</sup>	Inflammation	GV 20	Pre	EA	2/15 Hz	1 mA	NR	30 min
Liu et al. 2016 <sup>[83]</sup>	Inflammation	ST 36 and LI 11	Post	EA	1/20 Hz	NR	2–3 mm	30 min
Shi et al. 2017 <sup>[84]</sup>	Inflammation	GV 20 and ST 36	Post	EA	2–100 Hz	2 mA	2 mm	20 min
Huang et al. 2017 <sup>[85]</sup>	Inflammation	GV 20 and GV 26	Post	MA	NR	NR	NR	30 min
Sha et al. 2019 <sup>[86]</sup>	Inflammation	TE 5 and ST 36	Post	EA	20 Hz	1 mA	3 mm	30 min
Jiang et al. 2019 <sup>[87]</sup>	Inflammation	GV 20	Post	EA	2/15 Hz	1 mA	NR	30 min
Li et al. 2020 <sup>[88]</sup>	Inflammation	GV 20	Post	MA	200 rpm/min	NR	NR	30 min
Liu et al. 2020 <sup>[89]</sup>	Inflammation	GV 20 and GV 14	Post	EA	20 times/min	1–2 mA	8/10 mm	30 min
Wang et al. 2023 <sup>[90]</sup>	Inflammation	GV20	Post	EA	2/15 Hz	1 mA	5 mm	20 min

Baihui: GV 20; Chize: LU 5; Dazhui: GV 14; EA: Electroacupuncture; Hegu: LI 4; Jiayi: EX-B 2; MA: Manual acupuncture; Neiguan: PC 6; NR: Not report; Quchi: LI 11; Shangjuxu: ST 37; Shenshu: BL 23; Shenting: GV 24; Shuigou: GV 26; Waiguan: TE 5; Yanglingquan: GB 34; Yinlingquan: SP 6; Zusanli: ST 36.

Barthel Index at the 16<sup>th</sup> acupuncture session. After this session, the degree of improvement in activities of daily living by acupuncture decreased significantly. Xu et al.<sup>[43]</sup> used a retrospective cohort study to explore the duration of acupuncture treatment for motor dysfunction and

found that early initiation of acupuncture treatment with a one-year follow-up may be beneficial to the recovery of motor function. In addition, they noted that acupuncture treatment within 48 h after IS may be beneficial to the early recovery of motor function. A recent meta-analysis

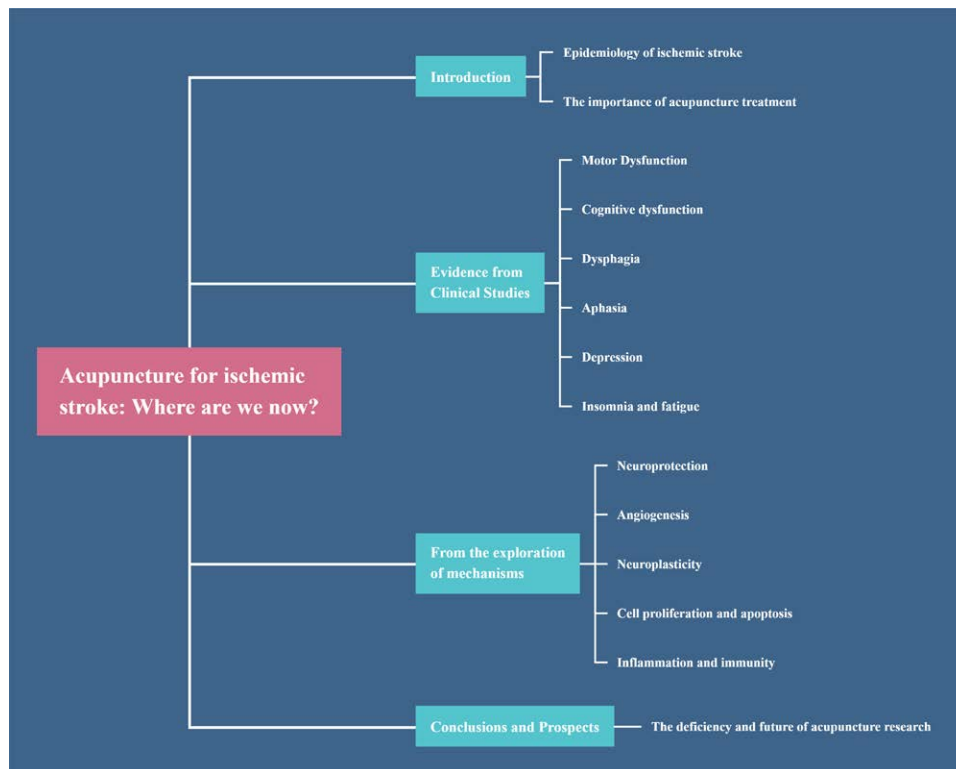
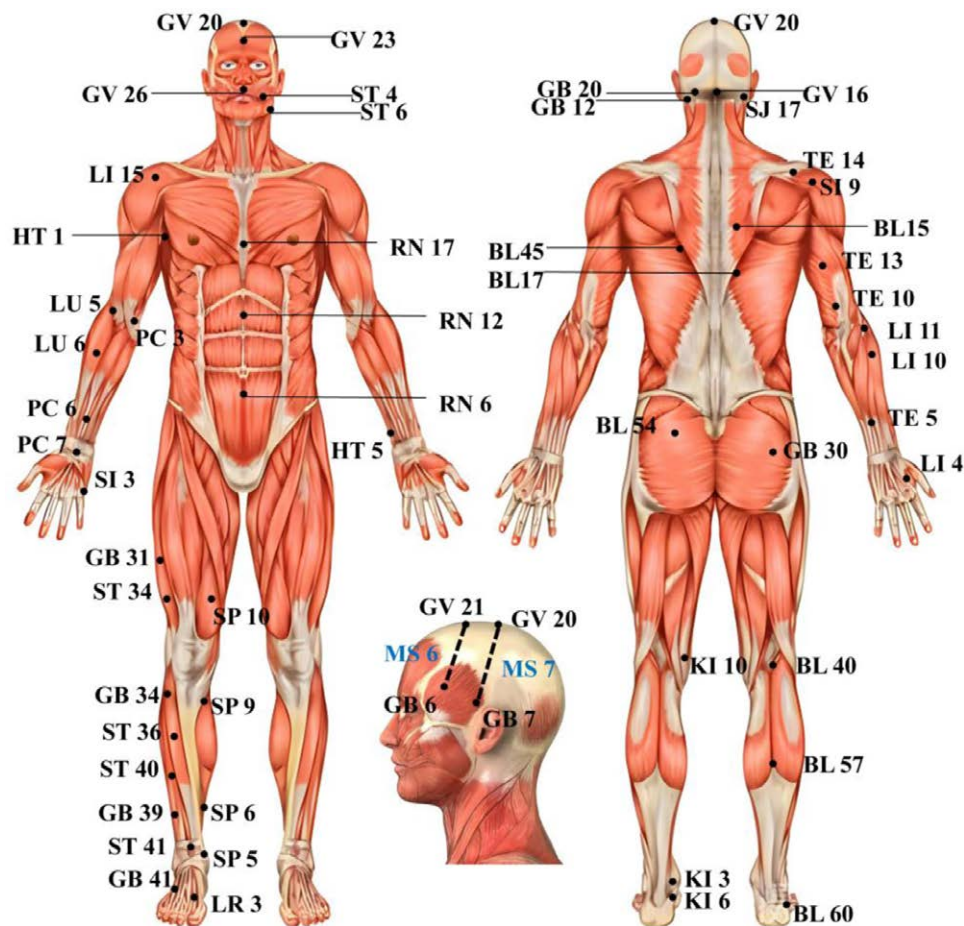


Figure 1. Structure and flowchart of the manuscript.

that included 38 trials involving 3,836 subjects also evaluated patients for motor function and activities of daily living impairment and found that the optimal time point for acupuncture intervention for stroke was within 48 hours after stroke, which was significantly valid until 15 days after onset<sup>[95]</sup>. Another retrospective study of 5,046 patients also found similar results, that early initiation and increased frequency of acupuncture may facilitate the recovery of limb motor function after IS<sup>[49]</sup>. All these clinical studies confirmed the safety of acupuncture and the absence of adverse events. Therefore, we believe that acupuncture is beneficial to improving the neurological function and activities of daily living. Acupuncture should be performed as early as possible to treat dyskinesia after stroke. This may lead to greater clinical benefits. However, the optimal timing of acupuncture initiation after stroke requires further clinical investigation. This is because the amount of stimulation and the effect of acupuncture are complex.

The objective measurement of acupuncture stimulation includes the objective measurement of the acupuncture operation (movement form and strength of the acupuncture needle) and the objective measurement of the body (acupoint) response to acupuncture stimulation, which is a key link in evidence-based acupuncture. The objective measurement of acupuncture manipulation has always been a challenge in acupuncture research. With the development of magnetic resonance imaging technology in recent years, methods such as functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) have been used to explain the effects of acupuncture. This method can explain the mechanisms of changes in the central structure and function of the body induced by acupuncture at a single point, group point, immediate

effect, or cumulative effect. First, several studies have observed functional connectivity changes in different brain regions and networks in patients with ischemia treated with single-point acupuncture intervention. For example, acupuncture at Waiguan (TE 5) can alter different brain functions, such as motor, sensory, and visual functions, activate synchronization and coordination in different regions, and activate brain regions on the contralateral side<sup>[96,97]</sup>. This finding suggests that acupuncture has a compensatory mechanism. Similar findings were reported in a resting-state fMRI study on acupuncture at Yanglingquan (GB 34). However, they found that acupuncture enhanced the resting-state functional connectivity of the anterior cingulate cortex to the posterior cingulate cortex before and after acupuncture treatment<sup>[98]</sup>. Additionally, the task and resting states of the acupuncture GB 34 were significantly different. The matrix of the former was weaker than that of the latter. This suggests that the task was relatively weak in improving connectivity in brain regions related to motor function in patients with IS<sup>[99]</sup>. In addition, scalp acupuncture improved the functional connectivity of the dominant hemisphere before and after treatment in patients with IS, specifically strengthening the connectivity between brain regions related to motor function, cognition, language, vision, sleep control, and planning. This mechanism may be related to motor recovery<sup>[100,101]</sup>. Currently, the addition of neuroimaging has provided a good boost to acupuncture research. However, these studies have mainly focused on cortical and subcortical aspects of acupuncture interventions. In the future, multimodal magnetic resonance imaging should be combined to further study the neuroplasticity produced by acupuncture in different parts or acupoints.



**Figure 2.** Acupoints from clinical operation for IS. In clinical studies, the acupoints of acupuncture for IS are mainly concentrated in the limbs and head, and a few are distributed in the trunk. In order to make it easier for readers to see the acupoints that play a role more intuitively, we have shown these acupoints in the figure. Anterior oblique parietal-temporal line: MS-6; Baihui: GV 20; Chengshan: BL 57; Chize: LU 5; Daling: PC 7; Danzhong: RN 17; Dicang: ST 4; Fengchi: GB 20; Fengfu: GV 16; Fenglong: ST 40; Fengshi: GB 31; Geshu: BL 17; Hegu: LI 4; Houxi: SI 3; Huantiao: GB 30; IS: Ischemic stroke; Jiache: ST 6; Jianliao: TE 14; Jianyu: LI 15; Jianzhen: SI 9; Jiexi: ST 41; Jiquan: HT 1; Kongzui: LU 6; Kunlun: BL 60; Liangqiu: ST 34; Naohui: TE 13; Neiguan: PC 6; Posterior oblique parietal-temporal line: MS-7; Qihai: RN 6; Quchi: LI 11; Quze: PC 3; Sanyinjiao: SP 6; Shangqiu: SP 5; Shangxing: GV 23; Shenmen: HT 7; Shousanli: LI 10; Shuiguo: GV26; Taichong: LR 3; Taixi: K I3; Tianjing: TE 10; Tongli: HT 5; Waiguan: TE 5; Wangu: GB 12; Weizhong: BL 40; Xinshu: BL 15; Xuanzhong: GB 39; Xuehai: SP 10; Yanglingquan: GB 34; Yifeng: SJ 17; Yingu: K I10; Yinlingquan: SP 9; Yixi: BL 45; Zhaohai: KI 6; Zhibian: BL 54; Zhongchong: PC 9; Zhongwan: RN 12; Zulingqi: GB 41; Zusanli: ST 36.

**The positive effect of acupuncture on cognitive function**

Early studies suggested that IS may increase the risk of cognitive impairment or dementia, especially in the elderly<sup>[102]</sup>. The results of a 2015 community-based epidemiological survey showed that the overall prevalence of post-stroke cognitive impairment (PSCI) was 80.97%<sup>[103]</sup>. PSCI has an insidious onset and a slow progression. As the disease progresses, patients may exhibit varying degrees of memory loss, language impairment, thought disorders, and cognitive dysfunction. In recent years, acupuncture has played an important role in improving cognitive function and clinical manifestations. Several systematic evaluations and meta-analyses have confirmed the positive effects of acupuncture on cognitive function after stroke with no significant adverse events<sup>[50,104-106]</sup>. It is consistent with the results of a recent multi-center RCT conducted in China, comparing up to 12 weeks of acupuncture intervention with oral citicoline in 216 patients with PSCI with a 6-month follow-up. The results showed comparable or even superior long-term efficacy of acupuncture in improving cognition and daily life performance<sup>[107]</sup>. The details of this study are presented in Table 1. Second, the use

of acupuncture at more than two acupoints in human or animal brain structures or functions has gradually increased in recent years. For example, in middle cerebral artery occlusion (MCAO) rats, acupuncture of Zusanli (ST 36) and Quchi (LI 11) activated the motor cortex, dorsal thalamus, striatum, and other regions of motor function<sup>[108]</sup>, and the connectivity between different regions was enhanced<sup>[109]</sup>. However, acupuncture at Baihui (GV 20) and Shenting (GV 24) activated the sensory cortex, hippocampus, retrosplenic cortex, cingulate gyrus, and other areas that are mainly related to sensation and cognition<sup>[110]</sup>. In addition, a retrospective cohort study of 9,547 patients with stroke over a 3-year follow-up period, after adjusting for selective confounders, found that patients who received acupuncture had a significantly lower risk of developing PSCI<sup>[111]</sup>. Conversely, earlier clinical studies have reported that acupuncture had no effect on PSCI<sup>[112]</sup>. Two meta-analyses of acupuncture interventions for PSCI also provided insufficient evidence to recommend acupuncture<sup>[50,104]</sup>. This could be because of the relatively few high-quality clinical studies and the variability in the inclusion of outcome indicators, these studies had small sample sizes

and poor methodological quality. These inherent flaws have led to heterogeneity in the reported studies, thus making the results subject to cautious interpretation. The advantages of acupuncture in the treatment of PSCI are gradually being demonstrated. Therefore, it needs to be complemented by large samples, multi-center studies, and high-quality clinical evidence.

#### *Acupuncture promotes the recovery of dysphagia and reduces the risk*

Dysphagia is a common post-stroke complication with an incidence of 37% to 78%, leading to malnutrition, weight loss, dehydration, and aspiration pneumonia, which can be life-threatening in severe cases<sup>[113]</sup>. Additionally, prolonged dysphagia may lead to low mood and even depression<sup>[114]</sup>. Therefore, rehabilitation of dysphagia after IS is extremely important for patients. Swallowing rehabilitation includes oral sensory training (cold stimulation training and gustatory training), compensatory strategies (postural training and dietary modification), biofeedback, neuromuscular electrical stimulation, and balloon dilation techniques. However, the effectiveness of these treatments is limited to some extent<sup>[115,116]</sup>. A recent meta-analysis of 29 studies involving 2,190 patients and new evidence reported that the efficacy and safety of acupuncture for short-term dysphagia after stroke were improved compared with those of conventional rehabilitation or pharmacological treatment<sup>[117]</sup>. However, the quality of this evidence needs to be improved and supported by additional high-quality clinical studies. A previous prospective cohort study of 64 patients with dysphagia treated with Tongguan-Liqiao acupuncture showed that acupuncture was more than 90% effective, especially in patients with medullary infarctions. This suggests that acupuncture may repair the connections between the upper motor neurons and motor nuclei of the medulla oblongata<sup>[25]</sup>. Another propensity score-matched cohort study matched 3,618 patients with IS between 2010 and 2020 using acupuncture and non-acupuncture and showed that acupuncture treatment reduced the risk of dysphagia in stroke patients<sup>[109,118]</sup>. Unfortunately, this was a single-center study, and follow-up is pending. A multi-center approach is required to further expand this study. A recent study reported the long-term efficacy of acupuncture in patients with post-stroke dysphagia. They conducted a retrospective observational study of 1,127 patients with IS, ultimately including 375 patients (152 in the acupuncture group and 223 in the control group), and carried out a 6-month follow-up. The results showed that acupuncture shortened the time to clinical improvement and promoted recovery in patients with dysphagia<sup>[119]</sup>. In conclusion, the methodologies and reports of RCTs published internationally on the treatment of dysphagia after IS with acupuncture are not of high quality. Future studies should be conducted with more scientifically rigorous protocol designs to improve clinical evidence for treatment.

#### *Acupuncture improves communication function and speech disorder*

Aphasia is a specific cognitive disorder that is a common manifestation of neurological impairment in IS. It is a disorder of language comprehension and

expression caused by functional impairment in specific brain regions<sup>[120]</sup>. Epidemiological data from the American Stroke Association show that aphasia is present in approximately 30% of patients with a first cerebral infarction<sup>[121]</sup>. Impaired language function severely damages the ability of patients with aphasia to participate in society, and greatly reduces their quality of life<sup>[122]</sup>. In addition, patients with aphasia after a stroke spend 1.3 times more on rehabilitation than patients without aphasia, increasing the difficulty of clinical rehabilitation and the economic burden on health care. Acupuncture is inexpensive and effective for the treatment of post-stroke aphasia (PSA), as recommended by international evidence-based medicine<sup>[123]</sup>. In 2019 and 2020, two systematic reviews and meta-analyses explored acupuncture interventions for PSA. A meta-analysis first assessed that acupuncture was effective in treating PSA, and a second affirmed the impact of acupuncture on patients' communication function<sup>[124]</sup>. In addition, traditional, scalp, and combined acupuncture did not significantly improve functional communication or the severity of speech disorders; however, the results were limited owing to methodological defects. However, another meta-analysis showed that scalp and tongue acupuncture improved overall effectiveness compared with traditional acupuncture<sup>[125]</sup>. In 2022, a meta-analysis reported that head acupuncture could improve the Aphasia quotient (AQ) and Boston Diagnostic Aphasia Exam (BDAE) scores of patients with PSA, but with high heterogeneity<sup>[126]</sup>. Simultaneously, they pointed out that head acupuncture should be avoided in the treatment of aphasia to prevent local hematoma of the eye socket, damage to the eyeball, medulla bulbar, and other serious adverse events. However, these three studies did not significantly assess the safety of acupuncture. In the same year, a meta-analysis suggested that acupuncture might have a beneficial effect on aphasia after IS, particularly during the subacute phase<sup>[28]</sup>. However, the sample sizes of these meta-analyses were insufficient, thereby limiting the results. At the same time, there are many types of aphasia, and a subgroup analysis of acupuncture for different types was not carried out in these evaluations, perhaps because aphasia was not classified in the original RCTs, and further systematic evaluation is required.

#### *Acupuncture reduces depression*

Post-stroke depression (PSD) is a common condition. Depression occurs in more than one third of stroke patients and the mortality rate is as high as 8.7%<sup>[127]</sup>. Post-stroke depression not only causes significant psychological disorders in patients but also aggravates cognitive dysfunction, delays the recovery process after stroke, and significantly increases the disability, mortality, and recurrence rates of patients<sup>[128]</sup>. Currently, PSD treatment in Western medicine is mainly based on the use of oral antidepressants. Although these drugs can effectively relieve the symptoms of PSD, most need to be taken for a long time and are prone to adverse reactions, making it difficult for patients to adhere to treatment. As an economical, safe, and effective "green therapy," acupuncture has achieved a positive effect in the treatment of PSD, and has been widely used and recognized in

clinical practice. In 2015, an RCT of acupuncture intervention in stroke patients, including ischemic and hemorrhagic stroke patients, confirmed that body acupuncture could effectively reduce depression in stroke patients<sup>[129]</sup>. The advantage of acupuncture over Western medication is mainly reflected at the time point after 2 weeks of treatment, and the advantage is not obvious after 6 weeks and 3 months of treatment. Li et al.<sup>[31]</sup> had similar findings, showing that the efficacy of acupuncture was almost equivalent to that of drugs; however, the onset of action was earlier for drugs. Moreover, the acupuncture group showed better Asberg antidepressant side effect scale (SERS) scores than the medication group. In a large cohort of 13,823 patients with depression after hemorrhage and IS, patients who received acupuncture had significantly lower incidence and hazard ratios than those who did not receive acupuncture<sup>[130]</sup>. At 5 years of follow-up, 7.22% of the patients who received acupuncture had a stroke compared with 14% of those who did not receive acupuncture. Since 2017, five systematic reviews have evaluated the effects of acupuncture, EA, and other acupuncture methods on PSD. Firstly, 18 meta-analyses of EA in the treatment of PSD included in 2018 showed that the efficacy of EA was similar to that of antidepressant drugs at 4 and 8 weeks, but the incidence of adverse events was lower than that of antidepressant drugs<sup>[131]</sup>. However, two meta-analyses conducted in 2021 and 2023 showed positive results, suggesting that acupuncture or other treatments such as combined therapy, are superior to other treatments<sup>[132,133]</sup>. In addition, a meta-analysis of 10 studies involving 708 patients showed that abdominal acupuncture had overall efficacy in the treatment of PSD, but the evidence for improvement in neurological function was insufficient<sup>[134]</sup>. In the same year, another network meta-analysis compared 51 studies using 12 methods, including scalp a plus conventional acupunctures, auricular acupuncture, eye acupuncture, conventional acupuncture, and medication, and found that scalp plus conventional acupuncture was the most effective treatment<sup>[135]</sup>.

#### *Acupuncture improves insomnia and fatigue*

Insomnia after IS is an easily overlooked risk factor. However, the incidence among patients after IS is 56% to 58%, which is much higher than that among healthy individuals<sup>[136]</sup>. If not treated promptly and effectively, it may lead to mood changes, fatigue, and cognitive impairment, which seriously affect recovery from stroke and alter its outcome<sup>[137]</sup>. Antidepressants, such as diazepam, zolam, and benzodiazepines, are commonly used to treat insomnia after IS. These drugs can temporarily relieve symptoms but cannot solve fundamental problems, and adverse reactions, such as headache, drowsiness, addiction, and dependence limit their long-term application. In comparison, acupuncture has the advantages of obvious curative effects and no side effects, and can better promote the recovery of patients<sup>[138]</sup>. A cohort study involving 1,680 patients with stroke in Guangdong, China, showed that acupuncture reduced the risk of insomnia after stroke, which was higher in men than in women. A 144-patient RCT conducted by Cao et al.<sup>[29]</sup> demonstrated that acupuncture is effective in improving insomnia, quality of

life, and affective symptoms in patients with IS. And with the extension of time, this effect gradually expanded. This effect was also observed with the use of a wireless ambulatory sleep monitor by Song et al.<sup>[139]</sup> However, the evidence was based on a single-center design, which makes the results insufficiently convincing. The clinical design should be improved in future studies.

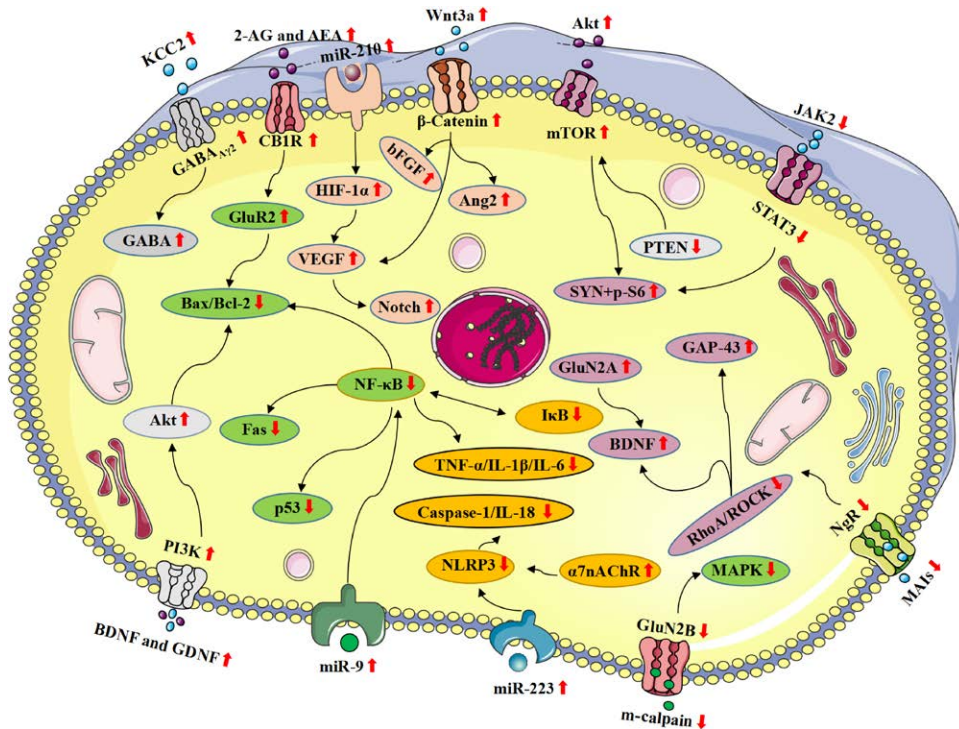
In conclusion, acupuncture is beneficial with recovery from post-stroke dysfunction. Currently, in the treatment of IS, acupuncture mainly involves multiple acupoints, including the limbs and head. A very small proportion of acupuncture prescriptions used single-point treatment. This acupuncture prescription also reflects the complexity of stroke relative to other diseases. In addition, for the treatment of limb dysfunction, the prescription of acupuncture mainly consists of body acupuncture. In patients with cognitive and emotional disorders, acupuncture acupoints are mainly concentrated on the head and face. This is in line with the view of local treatment in the traditional Chinese medical theory. However, this phenomenon must be explored using a higher level of evidence in modern medicine.

#### **From the exploration of mechanisms**

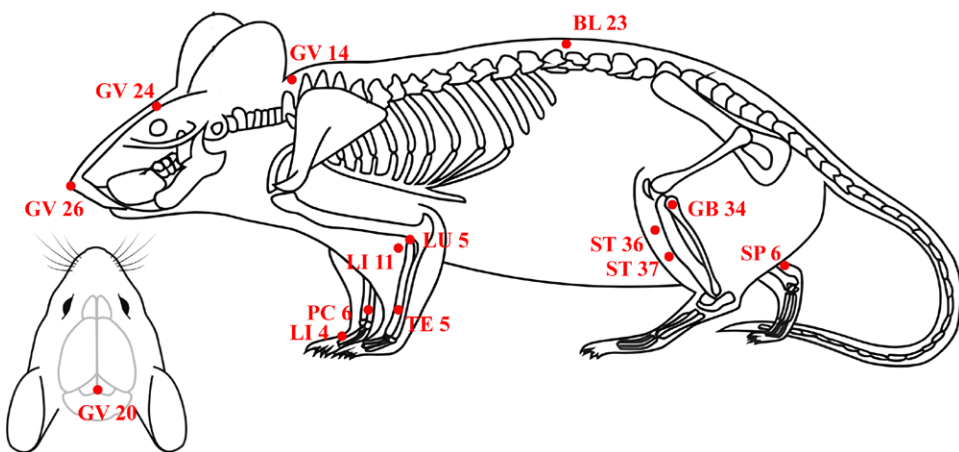
Rehabilitation of IS is a complex process. Acupuncture and its effects on the treatment of IS have been discussed previously. Acupuncture stimulates acupoints and plays a bidirectional regulatory role in the body. However, its mechanism of action remains unclear. Previously, we discussed a large amount of clinical evidence for acupuncture treatment of post-stroke motor dysfunction, dysphagia, cognitive impairment, and other aspects. In recent years, considerable research has been conducted on this topic. After analyzing these studies, we found that the possible mechanisms underlying the protective effects of acupuncture include neuroprotection, nerve function regulation, neuroplasticity (neurogenesis and synaptic formation), angiogenesis, cell proliferation and apoptosis, regulation of oxidative stress, inflammation, and immunity. In general, acupuncture activates different reaction cascades of specific tissues through the multi-target and multi-pathway intervention of these links, to restore homeostasis under different physiological and pathological conditions. We discussed these possible links separately, explored the synergistic effect of acupuncture on these links, and demonstrated the pathways involved (Figure 3). The acupuncture protocols of these studies are recorded in Table 2, and the acupoints used are demonstrated (Figure 4), to provide a basis for exploring the multi-link mechanism of acupuncture in the treatment of IS.

#### *Acupuncture promotes the release of neurotransmitters*

The therapeutic role of acupuncture in protecting against ischemic brain injury remains unclear. A 2013 study found that acupoint acupuncture (Shenshu (GV 26)) improved nerve function deficits and cerebral blood flow in MCAO rats compared with non-acupoint acupuncture. This study illustrates the neuroprotective effects of acupuncture and demonstrates the specificity of acupoints<sup>[51]</sup>. In the same year, a study indicated that EA pretreatment at



**Figure 3.** Neurons death and survival pathways that involve in the protective effect of acupuncture in experimental IS models. We demonstrate the complex process of acupuncture intervention in IS, including neurotransmitters, vascular regeneration, neuroplasticity, proliferation and apoptosis, inflammation, and oxidative stress. Among them, KCC2/GABA signaling pathway, PI3K/Akt signaling pathway, and Notch signaling pathway, etc. are mainly related to the release of neurotransmitters associated with nerve regeneration (shown in gray). HIF-1 $\alpha$ /VEGF/Notch 1 signaling pathway, and Wnt/ $\beta$ -catenin signaling pathway, etc. are mainly related to vascular regeneration (shown in pink). RhoA/ROCK signaling pathway, mTOR signaling pathway, JAK2/STAT3 signaling pathway, etc. are mainly associated with neuroplasticity (shown in purple). PI3K/Akt signaling pathway, NF- $\kappa$ B signaling pathway, ERK signaling pathway, and Wnt/ $\beta$ -catenin signaling pathway, etc. are mainly associated with cell proliferation and apoptosis (shown in green). NF- $\kappa$ B signaling pathway and miR-223/NLRP3 signaling pathway, etc. are mainly associated with inflammation (shown in yellow). We showed the upstream and downstream cytokines of these signaling pathways. As the process of acupuncture is very complex, we show only a part of the whole process. 2-AG and AEA: Endocannabinoid ligands; Akt: Protein kinase B; BDNF: Brain-derived neurotrophic factor; CB1R: Cannabinoid CB1 receptors; GABA:  $\gamma$ -Aminobutyric acid; GAP-43: Growth-associated protein-43; GDNF: Glial cell line-derived neurotrophic factor; GluN2B: Glutamate proapoptotic receptor GluN2B; GluR2: Glutamate receptor subunit 2; HIF-1 $\alpha$ : Hypoxia-inducible factor-1 $\alpha$ ; IS: Ischemic stroke; JAK2: Janus-activated kinase 2; JNKs: Jun N-terminal kinases; KCC2: K-Cl cotransporter; MAIs: Myelin-associated inhibitors; MAPKs: Mitogen-activated protein kinases; mTOR: Mammalian target of rapamycin; MYPT1: Myosin phosphatase target subunit-1; NF- $\kappa$ B: Nuclear factor- $\kappa$ B; PI3K: Phosphatidylinositol 3-kinase; STAT3: Signal transducer and activator of transcription 3; SYN: Synaptophysin; VEGF: Vascular endothelial growth factor.



**Figure 4.** Acupoints in MCAO rats from basic experimental manipulation. In animal experiments, acupoints implicated in ischemic stroke-related mechanisms are relatively single. These acupoints were mainly concentrated in the extremities of the rats. Chize: LU 5; Baihui: GV 20; Dazhui: GV 14; Hegu: LI 4; MCAO: Middle cerebral artery occlusion; Neiguan: PC 6; Quchi: LI 11; Shangjuxu: ST 37; Shenshu: BL 23; Shenting: GV 24; Shuigou: GV 26; Waiguan: TE 5; Yanglingquan: GB 34; Yinlingquan: SP 6; Zusanli: ST 36.

GV 20 and Dazhui (GV 14) could improve tissue and functional outcomes in MCAO rats, and regulate the expression of brain-derived neurotrophic factor (BDNF)

and stromal cell-derived factor-1 $\alpha$  (SDF-1 $\alpha$ ). It has been suggested that acupuncture has neuroprotective effects and increases tolerance to cerebral ischemia<sup>[52]</sup>. An intact



infarction, and the recovery of nerve function requires neurogenesis and synaptogenesis to activate neuroplasticity in the injured brain region<sup>[145]</sup>. Neuroplasticity occurs at multiple levels, from synaptic transmission efficacy, neurogenesis, and synaptic regeneration to the adjustment of global neural circuits, brain network structure, and function. Acupuncture plays a role at multiple levels. Retinoic acid (RA) is involved in the normal development of the central nervous system. RA expression and signaling are sustained in the postnatal and adult brain, stimulating the neonatal subventricular zone and adult hippocampal neurogenesis<sup>[146]</sup>. A 2013 study noted that EA intervention upregulated RA expression and improved neurological function in ischemia-reperfusion rats<sup>[63]</sup>. Notably, at an early stage, Yang et al.<sup>[147]</sup> found that EA not only promoted the regeneration of neurons and migration of newborn neurons in the striatum of MCAO rats but also promoted the maturation of newborn neurons. Zhang et al.<sup>[66]</sup> used EA at ST 36 and PC6 to treat MCAO rats and observed changes in the corticospinal tract. Comparing with the model group, they observed a more compact arrangement and an increased number of neurons, GAP-43, and SYN in the contralateral cerebral cortex. The authors found that this expression was mediated through the mammalian target of rapamycin (mTOR) pathway. It was also found that EA altered the negative regulatory effect of PTEN on the mTOR pathway and further activated the mTOR pathway by inhibiting PTEN. Liao et al.<sup>[64]</sup> used 2 and 15 Hz EA of ST 36 and Shangjuxu (ST 37), respectively, to treat ischemia-reperfusion rats. Studies have found that although both frequencies of EA can improve nerve function, 2 Hz EA has more advantages in neurogenesis, reducing the number of Ki67- and nestin-immunoreactive cells and increasing the number of glial fibrillary acidic protein (GFAP) immunoreactive cells. It has also been suggested that EA can improve the regional cerebral blood flow and play a neuroprotective role by regulating astrocytes. Another study used EA at GV 20 and GV 14 to intervene in rats with subacute cerebral infarction and found that EA increased the density of GFAP-positive astrocytes in the junction of the number of neurons in the ischemic area<sup>[65]</sup>. These results suggest that EA therapy regulates post-stroke remodeling by promoting neurogenesis and astrocyte proliferation around ischemic tissues. Notably, a 2018 meta-analysis of animal experiments involving 44 studies including 2,411 subjects reported that the quality of current studies on acupuncture on neurogenesis in animal models of stroke is generally poor<sup>[148]</sup>. Future researchers should rigorously adopt and adhere to well-developed reporting guidelines and modified STRITA statements.

The synapse is the contact site between neurons and the main structure of chemical neurotransmission in the nervous system. Synaptic plasticity is a basic neuronal function that involves structural changes and functional modifications. It is physiologically related to brain development, learning, and memory; participates in neural circuit reconstruction; and promotes nerve recovery and regeneration under pathological conditions<sup>[149]</sup>. The loss of synaptic activity is a consequence of the early stages of IS<sup>[150]</sup>. Previous studies in China have shown that acupuncture improves synaptic plasticity in the hippocampus

of rats after IS. A 2011 study reported that acupuncture studies on synaptic structural plasticity mainly focused on the peri-infarct area. They observed changes in the synaptic structure following EA stimulation of GV 20 and GV 14 in cerebral infarction. It was found that the postsynaptic density, thickness, width of the synaptic cleft, and curvature of the synaptic interface around the infarct zone were significantly reduced after EA treatment in rats<sup>[67]</sup>. Chen et al.<sup>[151]</sup> further explored the molecular mechanism by which EA alters synaptic structures. They suggested that EA downregulated hippocampal myelin-associated inhibitors (MAIs), including myelin-associated glycoprotein (MAG), in MCAO rats. Neurite outgrowth inhibitor A (NogoA) and oligodendrocyte-myelin glycoprotein (OMgp) inhibit the RhoA/ROCK signaling pathway, upregulating the expression of growth-associated protein-43 (GAP-43) and BDNF. This may explain the molecular mechanisms by which EA promotes axonal regeneration and structural changes. Another study reported similar results. They suggested that EA stimulation of GV 20 and GV 24 in MCAO rats resulted in an increase in the number of synapses in the hippocampal CA1 region with a compact and abundant vesicle distribution. However, they suggested that the EA upregulates Jakus-activated kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling pathway to improve synaptic plasticity<sup>[68]</sup>.

In conclusion, acupuncture may improve neuroplasticity following IS, including changes in neural function, neurogenesis, and synaptic structure. However, this study has some limitations. First, the points were mainly selected from the head, and there are few studies on other points. This disconnects the results of clinical treatment. Secondly, in terms of the plasticity of neural structure, the studies mainly focus on the ultrastructural changes of synapses, while the research on the structure of other parts is less: in terms of the plasticity of neural function, there are few researches on electrophysiology, and the researches mainly focus on factors, such as nerve growth factors, apoptosis genes, and nerve-related proteins. Therefore, we suggest that future studies should be more comprehensive, systematic, and in-depth regarding the improvement of structural and functional plasticity by acupuncture.

#### *Acupuncture regulated cell proliferation and apoptosis*

In the early stages of cerebral ischemia, the death of nerve cells in the ischemic center is mainly necrosis, whereas cells in the ischemic penumbra are still metabolically active, and their subsequent death is mainly apoptosis<sup>[152]</sup>. Restoring the blood supply to the ischemic focus after acute cerebral infarction is critical for reducing damage to nerve tissue and restoring the function of residual nerve cells. Although the reperfusion process of ischemic brain tissue increases the local blood supply, brain cells are inevitably stimulated by the corresponding inflammatory cytokines induced by reperfusion, which leads to a series of complex pathophysiological changes. It causes nerve cell apoptosis, infarct formation, and nerve function defects. Neuronal apoptosis is an important mechanism of nervous system injury after acute cerebral infarction<sup>[153]</sup>. In the early stages,

acupuncture was found to inhibit neuronal apoptosis, induce neural stem cell regeneration, and promote neural functional remodeling. Baba et al.<sup>[154]</sup> found that acupuncture at ST 36 and LI 11 could regulate the PI3K/Akt signaling pathway, downregulate the Bax/Bcl-2 ratio, and inhibit apoptosis<sup>[69]</sup>. The activation of this pathway may be related to neurotrophic factors, such as BDNF and glial cell line-derived neurotrophic factor (GDNF). Simultaneously, some studies have found that, while inhibiting Bax, EA upregulates the expression of the circadian rhythm proteins clock and Bmal1, which are related to anti-neuronal apoptosis<sup>[79,155]</sup>. Tao et al.<sup>[156]</sup> proposed that EA upregulates Notch signaling and the secretion of neurotrophic factors, which may lead to the proliferation of hippocampal neural stem cells and have therapeutic effects on IS. Another study found that EA improved cognition in rats with cerebral infarction by regulating the nuclear factor (NF)- $\kappa$ B signaling pathway. EA can neutralize the upregulation of Nf- $\kappa$ B p65 and I $\kappa$ B, upregulation of apoptosis-related factors Fas and Bax<sup>[70]</sup> and downregulation of p53<sup>[78]</sup> caused by the activation of NF- $\kappa$ B signaling pathway after ischemia. A recent study found that EA preconditioning induces downregulation of neuronal transient receptor potential vanilloid 1 (TRPV1) expression and protects against cerebral ischemia-reperfusion injury in MCAO rats by inhibiting the NF- $\kappa$ B signaling pathway to exert an anti-apoptotic effect<sup>[81]</sup>. Extracellular signal-regulated kinase (ERK) signaling is a major pathway involved in cell survival and proliferation. EA inhibits the expression of c-Jun N-terminal kinases (JNK) and p38<sup>[77]</sup>, enhances the phosphorylation of ERK, and upregulates Ras protein expression after IS. Activation of downstream cyclin D1 and cyclin-dependent kinase4 (CDK4) protein expression promotes cell proliferation in the cerebral cortex and striatum<sup>[71]</sup>, and retards apoptosis in the hippocampal CA1 region<sup>[72]</sup>. A recent study found that EA at GV 20, Yinlingquan (SP 6), and Neiguan (PC 6) downregulated the NR2B-containing NMDA receptor (GluN2B) and inhibited the expression of m-calpain and p38 MAPK<sup>[80]</sup>. However, GluN2A also activates the ERK pathway downstream<sup>[157]</sup>. However, the synergistic effects of acupuncture remain to be elucidated. Another study showed that EA at LI 11 and ST 36 promoted the proliferation of GFAP/vimentin/nestin-positive reactive astrocytes in the cortex and striatum of ischemia-reperfusion rats and may upregulate BDNF. It also exerts neuroprotective effects<sup>[73]</sup>. The Wnt/ $\beta$ -catenin pathway is an important marker of neural progenitor cell proliferation and self-renewal. Wnt/ $\beta$ -catenin signaling is reduced after the onset of cerebral ischemia<sup>[158]</sup>. EA at LI 11 and ST 36 can also promote the expression of Wnt1 and  $\beta$ -catenin in the cortical infarct area while down-regulating the transcription of glycogen synthase kinase-3 (GSK3) and activating the Wnt/ $\beta$ -catenin pathway<sup>[74]</sup>. MMP-2 and MMP-9 are closely related to vascular and neuronal injury after ischemia and participate in myelin formation and neuronal apoptosis during neuroplasticity<sup>[159]</sup>. EA at GV 20 and 24 inhibited the expression of matrix metalloproteinase (MMP) -2 and MMP-9 in the hippocampus after ischemic brain injury, thereby inhibiting neuronal apoptosis and improving cognitive status<sup>[75]</sup>. In addition, from an electrophysiological perspective, depolarization

around ischemic foci occurs within 2 to 24 hours after cerebral infarction, leading to calcium overload and neuronal death. During this period, excessive activation of large-conductance Ca<sup>2+</sup>-activated K<sup>+</sup> channels (BKCa channels) may lead to large amounts of potassium efflux and membrane hyperpolarization, reduce neuronal excitability, and lead to neuronal apoptosis or death. EA has been shown to reduce the protein and mRNA levels of BKCa channels and improve ischemia-reperfusion injury<sup>[76]</sup>.

In summary, EA is currently used as the main intervention in the study of the anti-apoptotic and pro-proliferative effects of acupuncture, which involve a variety of classical pathways. Most studies have confirmed that acupuncture plays an anti-apoptotic role and promotes the proliferation of nerve cells. However, mechanisms underlying the effects of acupuncture on neuronal proliferation remain unclear, although the aforementioned studies have explored it to varying degrees. However, this process may be accomplished through the participation of multiple regulatory factors and signaling pathways. Alternatively, acupuncture indirectly stimulates certain adjustment factors through related signaling pathways of apoptosis or proliferation. Therefore, the internal mechanism underlying this process requires further investigation.

#### *Acupuncture relieves inflammation and regulates immunity*

In the process of IS injury, in addition to the relevant mechanisms discussed previously, neuroinflammation and immune response play a particularly key role in the pathogenesis of IS<sup>[160]</sup>. The inflammatory response in the brain after IS is characterized by the rapid activation of microglia, followed by the initiation of inflammatory cell infiltration into central inflammatory areas, including neutrophils, T cells, monocytes/macrophages, and other cells<sup>[161]</sup>. In the acute phase of cerebral ischemia, inflammatory cytokines, chemokines, neurotransmitters, and oxygen-free radicals are rapidly released from damaged tissues. Among these, regulators induce the expression of adhesion molecules on brain endothelial cells and leukocytes, thereby promoting the adhesion of circulating leukocytes to the vascular endothelium, leading to vascular endothelial damage. In the subacute phase, infiltrating leukocytes release cytokines and chemokines, especially the excessive production of reactive oxygen species (ROS) and the activation of matrix metalloproteinases. This leads to the release of more inflammatory factors, expands the inflammatory response, and eventually leads to the destruction of the blood-brain barrier, causing brain edema and neuronal necrosis. At present, it is believed that the neuroprotective effect of acupuncture or the inhibition of ischemic damage may be related to inflammation; however, the relevant mechanism remains unclear. Several studies have been conducted on these mechanisms from different perspectives. Monocyte chemoattractant protein-induced protein 1 (MCP-1) is a negative regulator of macrophage activation. Jin et al.<sup>[82]</sup> pretreated rats with GV20 EA before inducing MCAO. They found that MCP-1 expression was evident in neurons, but not in astrocytes, after EA pretreatment. Compared with the non-acupuncture group, EA

pretreatment downregulated the expression of proinflammatory cytokines including tumor necrosis factor (TNF)- $\alpha$ , interleukin (IL)-1 $\beta$ , IL-6, and monocyte chemoattractant protein (MCP)-1<sup>[82]</sup>. We mentioned above that NF- $\kappa$ B signaling pathway is involved in the process of apoptosis. In addition, miR-9 is involved in the NF- $\kappa$ B signaling pathway, in which microglia are activated by lipopolysaccharide (LPS) stimulation, and the lack of miR-9 leads to the upregulation of TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and MCP-1<sup>[162]</sup>. Liu et al.<sup>[83]</sup> found that EA can activate miR-9 and participate in the inhibition of the NF- $\kappa$ B signaling pathway, thereby reducing the expression of TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and MCP-1. NF- $\kappa$ B signaling pathway is essential for the process of inflammation. EA can also directly downregulate NF- $\kappa$ B p65, and IL-1 $\beta$ , and inhibit the transformation of microglia to M1<sup>[89]</sup>. In addition, NF- $\kappa$ B and B-cell inhibitor  $\alpha$  (I $\kappa$ B- $\alpha$ ) can regulate each other. Manual acupuncture may play the same role as EA in this regulatory process. It has been found that manual acupuncture stimulation at GV20 and GV26 in MCAO rats can directly reduce the expression of NF- $\kappa$ B and I $\kappa$ B- $\alpha$  in hippocampal neurons<sup>[85]</sup>. Li et al.<sup>[88]</sup> found that hand acupuncture downregulated the expression of TNF- $\alpha$  and IL-1 $\beta$  and upregulated BDNF expression in the hippocampus of MCAO rats at GV20. In addition to the key NF- $\kappa$ B signaling pathway. Recently, it has been found that EA can regulate the inflammatory response of MCAO rats by regulating the miR-223/nucleotide-binding domain-like receptor family (NLRP3) signaling pathway<sup>[86]</sup>. In this study, EA stimulation at TE5 and ST36 in rats could activate miR-223 and downregulate the expression of NLRP3 in neurons, thereby downregulating the expression of caspase-1, IL-18 and IL-1 $\beta$  in the infarcted cortex. Jiang et al.<sup>[87]</sup> found another upstream molecule of NLRP3,  $\alpha$ 7 nicotinic acetylcholine receptor ( $\alpha$ 7nAChR), and suggested that EA could intervene in the inflammatory process after stroke through this pathway. They found that EA upregulated the expression of  $\alpha$ 7nAChR in neurons and inhibited the expression of NLRP3 and procaspase-1 while down-regulating the expression of IL-18 and TNF- $\alpha$  in the infarct tissue.

The body responds to stress when inflammation occurs. Acupuncture may also neutralize or even inhibit the stress response caused by inflammation after the inflammatory processes occur. The release of the adrenocorticotrophic hormone (ACTH) from the pituitary gland is a key signal that occurs before the body responds to stress. Heat shock protein 70 (Hsp70) is a hallmark of the body's stress response. Some studies have shown that EA interferes with this process and reduces the expression of ACTH and Hsp70<sup>[84]</sup>. In addition to this, recent studies have found that gut-derived immune cells preferentially migrate to the CNS, especially gut T cells, after IS<sup>[163]</sup>. EA can intervene in this process and regulate Tregs and  $\gamma$  $\delta$ T cells in the ischemic brain and small intestine, thus playing a role in regulating inflammation<sup>[90,164]</sup>.

In conclusion, the inflammatory response is an important cause of post-ischemic injury and may induce secondary injury to brain tissue after ischemia. The activation and aggregation of various immune cells play key roles in the reception and transmission of inflammatory signals. We also confirmed the inhibitory effect of acupuncture on inflammatory injury after IS in both the laboratory and

the clinic. However, acupuncture is currently believed to regulate the body through the neuroendocrine-immune network, which is a complex process. Various signaling chains can influence each other, and the specific role of acupuncture intervention in these processes requires further evidence. This helped us observe acupuncture intervention under the overall inflammation of the dynamic response.

In addition to the above-mentioned mechanisms of acupuncture in IS, it plays a therapeutic role through a variety of pathways, such as protecting the blood-brain barrier, regulating oxidative stress responses, and improving the metabolic and microbial environments. However, few of these studies have been published in the past ten years, and they cannot be systematically elaborated upon. Therefore, we briefly discuss these studies. Jung et al.<sup>[165]</sup> found that EA preconditioning improved neurological function in MCAO rats by reducing blood-brain barrier disruption and brain edema, as well as reducing ROS production, and NADPH oxidase 4(NOX4) expression. Guo et al.<sup>[166]</sup> also found similar changes in diabetic mice with cerebral ischemia. In addition, Jittiwat<sup>[167]</sup> highlighted the antioxidant and anti-inflammatory effects of acupuncture in MCAO rats. They found that GV 20 treatment with acupuncture significantly increased memory and neuronal density in the CA1 and CA3 regions, improved neurological function scores in the hippocampus, increased glutathione peroxidase and superoxide dismutase activities, and decreased IL-6 levels. However, the description of the effect of acupuncture on IS only through a certain pathway or mechanism of action is limited. Acupuncture treatment involves the overall regulation of the human body. Therefore, researchers have attempted to comprehensively explain the effects of acupuncture using omics and microbiological methods. For example, Xian et al.<sup>[168]</sup> found that acupuncture not only adjusted gut microbiota disorders by enriching species diversity, reducing the abundance of pathogenic bacteria, and increasing the abundance of beneficial bacteria but also improved metabolic disorders by restoring metabolite plasma levels to normal levels. Moreover, he demonstrated a significant correlation between the gut microbiota and plasma metabolic profiles and attempted to explore potential targets for the acupuncture treatment of IS. Pan et al.<sup>[169]</sup> used proteomics to detect changes in serum protein levels in 18 patients with IS after EA treatment. He found a down-regulation of SerpinG1 protein expression and an up-regulation of gelsolin, complement component I, C3, C4b, and  $\beta$ 2 glycoprotein I protein expression in the serum of patients. Based on the above studies, we found that the mechanism of action of acupuncture in the treatment of IS is a complex, multi-pathway, and multi-target process. It is difficult to fully demonstrate this process using only one or several signaling pathways. However, we believe that with new research methods (such as proteomic technology), this problem can be resolved in the future.

## Conclusions and prospects

We reviewed the literature on acupuncture treatment for IS over the last 10 years. Acupuncture has been in practice for over two millennia. Currently, it has received

international attention for the treatment of IS. It is widely used in the rehabilitation of patients with stroke to improve motor and cognitive abilities, reduce muscle spasms, and improve balance, and post-stroke status. We performed a comprehensive examination that encompassed clinical trials and animal experiments and included clinical manifestations and pathophysiological mechanisms. Numerous international publications have reported the clinical efficacy and mechanism of acupuncture. However, the majority of these studies have limitations. First, from a clinical perspective, the technique of acupuncture needs to be improved. Regarding dysfunction after IS, the clinical design of the acupuncture intervention lacks multi-center and large-sample study protocols, as well as long-term follow-up and evaluation. The design of acupuncture treatments in China was primarily based on expert consensus and experience. We have illustrated the acupuncture points commonly used for the treatment of IS (Figure 2). Second, it was difficult to control patient and acupuncturist expectations of efficacy, which may have affected the results of blind evaluations and the effectiveness of acupuncture. Future clinical trials should compare standard care. There are numerous combinations of acupuncture stimulation frequencies, intensities, sites, and evaluation methods. Different studies adopted different scoring criteria, and the clinical experimental methods and patient characteristics are diverse. Therefore, the optimal stimulation scheme and parameters for rTMS remain unclear. In the future, rigorous and more standardized clinical design should be adopted to optimize the acupuncture treatment plan and improve the evaluation mechanism. This should be the focus of future clinical trials.

Despite the lack of strong evidence in clinical trials, international clinicians still recognize the efficacy of acupuncture in IS treatment. However, the mechanisms underlying the therapeutic effects of acupuncture remain unclear. It is worth mentioning that in recent years, many emerging techniques have been employed to understand the mechanism of acupuncture effect. The imaging aforementioned can reveal the changes in brain function and structure caused by acupuncture in various dysfunctions after IS. It has been demonstrated that acupuncture can strengthen the functional connectivity between brain regions and improve white matter fiber structure. However, there are numerous limitations to the current exploration of the clinical mechanisms of acupuncture. Moreover, the multimodal imaging technology is relatively mature. It can be used as an effective tool in the study of acupuncture for the treatment of IS. However, most current designs focus on a single functional or structural analysis or explain the injury and recovery of the IS. Furthermore, these studies did not provide a complete chain of evidence. At present, research on acupuncture overemphasizes changes in cortical areas and overlooks the damage and repair of subcortical structures. We believe that the prospects of radiomics are promising. With the help of neuroimaging, acupuncture requires a more rigorous design and a larger sample size. In this manner, relevant brain-computer interface or machine learning research can be conducted to further explain the current local-central effect of acupuncture in the treatment of IS. Multi-omics technology is widely used in clinical practice. Based on the holistic

concept of traditional Chinese medicine, the cumulative effect of acupuncture may be explained using multi-omics techniques. Currently, there are a few multi-omics studies on acupuncture in patients with stroke. First, the study design was simple. Whether multi-omics technology can be used to explore the clinical effects of acupuncture in the treatment of IS requires further study. In the future, we hope to clarify the differences between distinct acupuncture intervention designs using multi-omics techniques. By improving the high-quality evidence-based system of acupuncture intervention for IS and applying neuroimaging and biological multi-omics technology to analyze the neuroimaging effect loop of acupuncture intervention under physiological and pathological conditions in patients after IS, an omics mechanism database of acupuncture intervention for stroke was constructed, and the neuroimaging markers and biomarkers of acupuncture intervention for IS were systematically explored. To provide digital intelligent technical support for the establishment of an intelligent prediction-assistant decision model and the development of intelligent rehabilitation equipment in follow-up research, strengthen the voice of acupuncture in the international field of stroke treatment, and formulate a comprehensive evidence system for acupuncture intervention in IS require sustained effort.

In this study, we summarize the results of key fundamental research that have been actively explored by recent researchers over the past decade. Acupuncture plays a neuroprotective role by regulating the survival and death of neurons. This occurs mainly through the following mechanisms: promoting angiogenesis and improving cerebral blood flow, regulating neural plasticity, promoting neurogenesis and synaptogenesis, improving neuronal structure and function, regulating immune function and reducing the inflammatory response, improving cell apoptosis, and promoting neuronal proliferation. We found that the effects of acupuncture are diverse, but the underlying mechanisms remain unclear. The acupoints used in MCAO rats also exhibited diversity. In contrast to clinical research, most acupoints used in basic research are single, and few studies have used acupoint protocols consistent with clinical research standards. These studies confirmed that acupuncture could upregulate BDNFs, such as NGF and BDNF. In addition, acupuncture activated certain nerve and vascular protective pathways, such as PI3K/Akt, HIF-1 $\alpha$ /VEGF/Notch, JAK2/STAT3, Notch/GAP-43/BDNF, etc. Simultaneously, acupuncture plays an important role in inhibiting inflammation and regulating immune-related pathways, such as the classical NF- $\kappa$ B signaling pathway. Among the aforementioned targets and pathways, acupuncture interventions embody the characteristics of bidirectional regulation. It exerts beneficial effects on IS by modulating different mechanisms originating in the central nervous system. However, the results of the current study still have certain limitations. There is a lack of unified standards for acupoint selection in animal models of IS, and it is necessary to further compare the effectiveness and safety of acupoints from different meridians. The construction of animal models lacks stability, and some dysfunctions are not consistent with those in humans. Due to the specificity of acupuncture, no cell experiments related to acupuncture for IS have been conducted. Many signaling

pathways are based on correlations in the regulation of upstream and downstream pathway indicators and lack further validation.

In conclusion, acupuncture is effective in the treatment of IS and plays a key role in the process of neurological rehabilitation after IS. It can improve the clinical symptoms of motor dysfunction, dysphagia, language disorders, cognitive impairment, depression, insomnia, fatigue, and other IS complications. However, the underlying mechanism of action of acupuncture in IS treatment remains unclear. Existing evidence suggests that acupuncture plays a neuroprotective role in neuroplasticity (neurogenesis and synapse formation), angiogenesis, cell proliferation, apoptosis, oxidative stress regulation, inflammation, and immunity. Currently, with the advances in detection methods, imaging, transcriptomics, exosomes, and other emerging methods, the mechanism of acupuncture in the treatment of IS is gradually being revealed. This review systematically describes the mechanisms of action of acupuncture in the treatment and rehabilitation of patients with IS. Although the complete effect of this process has not yet been elucidated, we have attempted to provide ideas and insights into the studies of acupuncture treatment for IS. This review attempts to explain the current progress and shortcomings of acupuncture research on IS, combined with its different research directions. In addition, this review may guide future clinical and basic research on acupuncture in the treatment of IS from the perspectives of clinical efficacy, point selection, and molecular pathways. In the future, researchers should continue to improve the clinical trial design, increase the sample size, standardize and quantify acupuncture operations, and use multidisciplinary techniques and methods to provide more powerful evidence.

### Conflict of interest statement

The authors declare no conflict of interest.

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### Author contributions

Weiming Zhu conceived and wrote the manuscript. Qingqing Jia and Alberto Cantidio Ferreira helped with

the figure and drafted the manuscript. Hailun Jiang, Jieying Zhang, Boxuan Li, Menglong Zhang, Bifang Zhuo, Yuanhao Lyu, Junjie Chen, Li Li, Guang Tian, and Shizhe Deng revised the manuscript. The study design/planning and collection of funding were all conducted by Zhihong Meng and Xuemin Shi. All authors have read and approved the final manuscript.

### Ethical approval of studies and informed consent

Not applicable.

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### Data availability

All data generated or analyzed during this study are included in this published article.

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