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Complementary Therapy with Traditional Chinese Medicine for Ischemic Stroke

Po-Yu Huang, Yu-Chiang Hung and Wen-Long Hu

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Abstract

Stroke has remained the leading cause of morbidity or mortality worldwide over the past decade. Stroke survivors suffer various degrees of disability and also contribute to the large socioeconomic disease burden. Traditional Chinese medicine (TCM) serves as an important alternative or complementary therapy in many countries. This chapter aims to explore the utility of TCM for ischemic stroke, including a review of recent literature on the mechanisms of herbal medicine and acupuncture therapy on ischemic stroke, a summary of clinical trial results for the safety and efficacy of acupuncture, and finally a discussion of acupuncture as a preventive therapy for ischemic stroke in clinical practice. On the basis of these reports, more and more scientific evidences suggest that TCM use was safe for ischemic stroke at acute and subacute stages. Moreover, TCM has benefit for stroke recovery as well as it reduces the likelihood of hospital readmission for cardiovascular or subsequent stroke events.

Keywords: ischemic stroke, traditional Chinese medicine, acupuncture

1. Introduction

Stroke has remained the leading cause of death worldwide over the past decade despite a gradual decline in stroke mortality in many industrialized countries. Stroke survivors suffer various degrees of disability, including urinary incontinence, dysarthria, limb deficits, swallowing deficits, dysphasia, and consciousness disorders. Stroke also contributes to the largest socioeconomic disease burden together with ischemic heart disease [1, 2]. Additional treatment strategies are needed to improve poststroke recovery. Traditional Chinese medicine (TCM) serves as an important alternative or complementary healthcare option in many

countries. The purpose of this review was to investigate and discuss the utility of TCM as a complementary therapy for ischemic stroke. English and Chinese articles on TCM and acupuncture for ischemic stroke published between 2006 and 2015 were sourced from the Cochrane Library, PubMed, and China National Knowledge Infrastructure databases. On the basis of these reports, this chapter presents a brief description of the pathophysiology of ischemic stroke, a review of recent literature on the mechanisms of herbal medicine and acupuncture therapy in ischemic stroke, a summary of clinical trial results for the safety and efficacy of acupuncture, and finally a discussion of acupuncture as a preventive therapy for ischemic stroke in clinical practice.

2. Ischemic stroke

2.1. Pathophysiology of ischemic stroke

Ischemic stroke accounts for approximately 80% of stroke events and is an acute neurological injury that occurs as a result of reduced cerebral blood flow [3]. Reductions in cerebral blood flow in ischemic stroke can be due to decreased systemic perfusion, severe stenosis, or blood vessel occlusion. Decreased systemic perfusion can be the result of low blood pressure, heart failure, or blood loss. An infarcted brain is initially pale due to a lack of perfusion. Within hours to days, the gray matter of an infarcted brain becomes congested with engorged, dilated blood vessels, and minute petechial hemorrhages. When an embolus blocking a major vessel migrates, lyses, or disperses, recirculation into the infarcted area can cause an additional hemorrhagic infarction and may aggravate edema formation due to disruption of the blood-brain barrier (BBB) [3]. Given the diversity of stroke characteristics, an accurate determination of the type of stroke can influence the treatment indicated.

2.2. Stroke subtypes

Acute ischemic stroke subtypes have been classified in clinical studies using a system developed by the Trial of Org 10172 in Acute Stroke Treatment (TOAST) trial [4]. The TOAST classification denotes five subtypes of ischemic stroke according to underlying cause: (1) large-artery atherosclerosis, (2) cardioembolism, (3) small-vessel occlusion, (4) stroke of other determined etiology, and (5) stroke of undetermined etiology.

2.3. Cerebral autoregulation during stroke

Cerebral autoregulation is the maintenance of cerebral blood flow at a relatively constant level despite moderate variations in perfusion pressure. Importantly, cerebral autoregulation is impaired during ischemic stroke. Normally, as cerebral perfusion pressure falls, cerebral blood vessels dilate to increase cerebral blood flow. However, a decrease in perfusion pressure beyond the compensatory ability of blood vessels results in an overall reduction in cerebral blood flow. In response to the impairment of cerebral autoregulation, the oxygen extraction fraction is initially increased in order to maintain necessary levels of oxygen delivery to the brain. With time, these mechanisms fail and a state of ischemia occurs [5–7].

2.4. Mechanisms of ischemic cell injury and death

The human brain is exquisitely sensitive and susceptible to even short durations of ischemia. Because the brain contains little or no energy stores of its own, it relies on blood flow for the delivery of important resources. Thus, even brief blood flow deprivation can lead to cellular death in affected brain tissue.

During ischemic stroke, reduced blood flow results in simultaneous glucose and oxygen deprivation [3]. Ischemic cell injury initiates a cascade of events that finally lead to cell death including adenosine triphosphate (ATP) depletion, changes in intracellular ionic concentrations of sodium, potassium, and calcium, increased lactate formation, acidosis, accumulated oxygen free radicals, intracellular accumulation of water, and the activating proteolytic processes [8, 9].

2.5. Loss of brain structural integrity

Cerebral ischemia and infarction lead to decreases in the structural integrity of the affected brain tissue and blood vessels [9]. This process of tissue damage and neurovascular disruption is mediated in part by the release of various proteases including matrix metalloproteases (MMPs) that degrade components of the basal lamina [8]. Loss of vascular integrity leads to breakdown of the blood-brain barrier and the development of cerebral edema.

2.6. Cerebral edema

Cerebral edema occurring as a complication of stroke can cause secondary damage via several mechanisms, including increased intracranial pressure. Intracranial pressure can lead to decreases in cerebral blood flow and the life-threatening displacement of brain tissue from one compartment to another (i.e., herniation).

Two types of cerebral edema can follow ischemic stroke [9]. Cytotoxic edema is caused by the failure of ATP-dependent sodium and calcium ion transport across the cell membrane. The result is cellular water accumulation and swelling of neurons, glia, and endothelial cells. Alternatively, vasogenic edema is caused by breakdown of the vascular endothelial cells and tight junctions that constitute the BBB [10]. Increases in the permeability of the BBB during vasogenic edema allow proteins and other macromolecules to enter the extracellular space, resulting in increased extracellular fluid volume.

3. Mechanisms of herbal medicines in ischemic stroke

3.1. Limiting postischemic inflammation as a mechanism of neuroprotection

Astrocytes, endothelial cells, and pericytes constitute a neurovascular network that attends the metabolic requirements of neurons. These cells contribute to postischemic inflammation during different stages of ischemia [11]. Upon ischemia onset, resident microglia and astrocytes as well as infiltrating immune cells become activated and release inflammatory factors

including cytokines, chemokines, enzymes, free radicals, and other small molecules. These inflammatory factors not only mediate further brain damage but also affect brain repair.

Recent research indicates that postischemic inflammation is an important therapeutic target for stroke [12–14]. In this context, TCM and related natural compounds are recognized as important resources for drug discovery. In the past decade, significant progress has been made in the identification of active compounds from herbal medicines useful for limiting postischemic inflammation [11]. In the subsequent sections, we discuss the different roles of inflammatory pathways in ischemic stroke, from initial arterial occlusion to brain repair, and review active ingredients observed to have antiinflammatory and neuroprotective properties relevant to ischemic stroke.

4. Chinese herbal formulas used in patients with ischemic stroke

4.1. Di Huang Yin Zi (DHYZ)

A double-blind randomized controlled trial (RCT) was conducted to investigate the safety and therapeutic efficacy of the Di Huang Yin Zi (DHYZ) herbal formula in patients affected by ischemic stroke [15]. In this study, 100 patients with an ischemic stroke event occurring in the previous 30 days were randomly assigned to receive either DHYZ treatment or placebo for 12 weeks. Both groups also received rehabilitation therapy during the study period. The results indicated that there were increases in both Fugl-Meyer Assessment (FMA) scores and Barthel index (BI) scores in both groups at 4, 8, and 12 weeks relative to baseline. However, FMA scores in the DHYZ group were statistically better than those in the placebo group at 8 and 12 weeks ($P < 0.05$), and BI scores were significantly higher in the DHYZ group at 12 weeks ($P < 0.05$). By the end of the study, DHYZ produced significantly greater improvements in FMA score than placebo (44.4% vs. 23.8%, respectively, $\chi^2 = 4.09$, $P < 0.05$). It was concluded that DHYZ showed good efficacy, safety, and tolerability in patients affected by ischemic stroke [15].

4.2. Bu-yang-huan-wu-tang (BYHWT) and Dan Shen

A study was conducted to investigate the prescription patterns and combinations of traditional Chinese herbal products (CHPs) for ischemic stroke in Taiwan. Every CHP prescription with a leading diagnosis of ischemic stroke between the years 2000 and 2010 (15,896 patients) was obtained from the National Health Insurance Research Database (NHIRD) of Taiwan and included for analysis. Bu-yang-huan-wu-tang (BYHWT) was by far the most frequently prescribed CHP formula for ischemic stroke (40.32%), while BYHWT with Shu-jin-huo-xue-tang (SJHXT) was the most commonly prescribed CHP formula combination (4.40%). Dan Shen was the most commonly prescribed single CHP for ischemic stroke (16.50%), and Shi Chang Pua with Yuan Zhi was the most commonly prescribed single-CHP combination (4.79%). These results provide information about individualized stroke therapy and propose specific CHP components and formulas for further pharmacological investigation and clinical evaluation [16].

4.3. Rhubarb root and rhizome (RRR)-based Chinese herbal prescriptions

Rhubarb root and rhizome (RRR)-based Chinese herbal prescription is one of the principal treatments for stroke. A systematic literature search of six databases was performed to identify RCTs comparing RRR-based prescriptions with Western conventional medicine (WCM) for the treatment of acute ischemic stroke [17]. A total of 968 participants were included from 12 eligible studies. The methodological quality of RCTs was assessed independently based on the 12 criteria recommended by the Cochrane Back Review Group. While all trials were deemed to have high a risk of bias, RRR-based prescriptions had a significantly better effect clinical efficacy rate ($n = 10$) and improved Barthel index scores ($n = 5$), National Institutes of Health Stroke Scale scores ($n = 2$), Glasgow Coma Scale scores ($n = 1$), and neurological deficit scores ($n = 5$) relative to WCM ($P < 0.05$ or $P < 0.01$) in the included studies. Six trials reported no adverse events for RRR-based prescriptions, while the remaining studies did not report adverse effect monitoring. Despite these positive findings, it is premature to recommend the routine use of RRR-based prescriptions for acute ischemic stroke due to methodological flaws in the aforementioned studies. However, RRR-based treatments merit further development and research. Larger sample sizes and more rigorously designed RCT paradigms are required in the future (Table 1).

Study	N	Design	Chinese herbal formulas	Outcomes
Yu et al. (2015) [15]	45:42	Double-blind RCT	DHYZ	DHYZ significantly improved FMA scores after 12 weeks of treatment relative to placebo control. DHYZ showed good efficacy, safety, and tolerability.
Hung et al. (2015) [16]	15,896	Observational study from NHIRD	BYHWT and Dan Shen	BYHWT and Dan Shen were the most frequently prescribed formula and single CHP, respectively, for ischemic stroke.
Lu et al. (2014) [17]	968	Systematic review of RCT	RRR-based prescriptions	RRR-based prescriptions had a significantly better effect clinical efficacy rate ($n = 10$) and improved BI scores ($n = 5$), NIHSS scores ($n = 2$), GCS scores ($n = 1$), and neurological deficit scores ($n = 5$) relative to WCM ($P < 0.05$ or $P < 0.01$).

NHIRD: National Health Insurance Research Database

Table 1. Chinese herbal formulas used in patients with ischemic stroke.

5. The mechanism of acupuncture therapy in ischemic stroke

5.1. Acupuncture promotes neurogenesis in experimental ischemic stroke

Previous studies have reported that acupuncture enhances stroke recovery by promoting neurogenesis. A systematic review and metaanalysis of preclinical studies assessing acupunc-

ture in ischemic stroke identified a total of 1617 animals in 34 eligible studies [18]. Neurogenesis markers including BrdU, Nestin, PSA-NCAM, NeuN, and GFAP were selected as major outcomes. The pooled results of 15 studies evaluating BrdU incorporation showed a significant positive effect of acupuncture on proliferation relative to control ($P < 0.01$); 13 studies evaluating Nestin labeling corroborated this finding ($P < 0.01$). Four studies examining PSA-NCAM identified a significant positive effect of acupuncture on cell migration ($P < 0.01$) while four studies examining NeuN labeling demonstrated a significant effect of acupuncture on neuronal differentiation ($P < 0.01$). These findings suggest that acupuncture is a prospective therapy for targeting neurogenesis in ischemic stroke.

5.2. Neuroprotective effects of electroacupuncture (EA) in experimental stroke

It is well established that EA has neuroprotective effects in animals [19]. A series of studies have proposed EA as a promising method for reducing brain damage after stroke and inducing brain ischemic tolerance prior to a stroke event. The mechanism of action for EA has been reported to involve the promotion of angiogenesis, alleviation of the inflammatory response, regulation of the BBB, and inhibition of apoptosis.

5.3. Acupuncture regulates cerebral glucose metabolism in functional regions

A previous study using (18)FDG PET-CT analyzed the relevance between acupuncture and cerebral glucose metabolism in functional regions of the brain in poststroke patients [20]. Forty-three patients with ischemic stroke were randomly assigned to five groups: a Waiguan (TE5) needling group, a TE5 sham needling group, a sham point needling group, a sham point and sham needling group, and a nonneedling group. Needling at TE5 resulted in the activation of Brodmann area (BA) 30. Sham needling at a sham point led to the deactivation of BA6, whereas needling or sham needling at TE5 or needling at the sham point did not deactivate any cerebral areas. Compared with sham needling at TE5, needling at TE5 activated BA13, BA19, and BA47, but did not deactivate any areas. Compared with needling at the sham point, needling at TE5 did not activate any areas but did deactivate BA9. This study concluded that needling at TE5 has a regulatory effect on cerebral glucose metabolism that potentially relates to its impact on poststroke recovery in patients [20].

5.4. Effects of acupuncture on motor function and white matter microstructure

Evidence shows that ischemic stroke can induce structural reorganization of the brain. One study used diffusion tensor imaging (DTI) to evaluate 14 ischemic stroke patients one month after either conventional treatment or acupuncture treatment [21]. While significant functional improvements as measured by FMA score were observed in the acupuncture group relative to the conventional treatment group, no significant differences in DTI indices were identified between the two groups. However, postpair *t*-tests in each group revealed that diffusion indices were significantly altered in the body of the corpus callosum, bilateral corticospinal tracts, inferior longitudinal fasciculus, inferior frontooccipital fasciculus, superior longitudinal fasciculus, forceps minor, cingulum gyrus, and thalamic radiation one month after treatment intervention. These data indicate that while successful treatment produced alterations in white

matter regions of the brain, the changes did not correlate with differences in functional improvement.

Study	N	Design	Possible mechanisms
Lu et al. (2016) [18]	1617	1. Systematic review and metaanalysis 2. Neurogenesis markers 3. Animals model	Neurogenesis markers including BrdU, Nestin, PSA-NCAM, NeuN, and GFAP are increased after acupuncture.
Feng et al. (2014) [19]		1. Review study 2. Animal model	EA reduces brain damage and induces brain ischemic tolerance by promoting angiogenesis, alleviating the inflammatory response, regulating the BBB, and inhibiting apoptosis.
Huang et al. (2012) [20]	43	1. Functional neuroimaging (F-18 FDG PET/CT) 2. Acupoint: Waiguan (TE5) 3. Five groups: TE5 needling group, the TE5 sham needling group, the sham point needling group, the sham point sham needling group and the nonneedling group.	Needling at TE5 regulates cerebral glucose metabolism functional areas of the brain.
Li et al. (2015) [21]	7:7	1. <i>Diffusion tensor imaging</i> studies 2. Acupoints: Baihui (GV20), Fengchi (GB20, bilateral), Xuanzhong (GB39, bilateral), Quchi (LI11 bilateral), Hegu (LI4, bilateral), Zusanli (ST36, bilateral), and Sanyinjiao (SP6, bilateral). 3. Conventional treatment group (CG) and acupuncture treatment group (AG).	Acupuncture had better functional benefits than conventional stroke therapy, but white matter microstructure changes were not significantly different from those elicited by conventional therapy.
Li et al. (2015) [22]	5:5	1. Functional magnetic resonance imaging study 2. Acupoint: Waiguan (SJ5) 3. Deqi group, non-Deqi group	Deqi can be observed as a change in brain activity during acupuncture. Cerebellar activation may be a central mechanism of the beneficial effect of acupuncture in stroke.

Table 2. The possible mechanisms of acupuncture therapy in ischemic stroke.

5.5. Brain activation in response to acupuncture and Deqi

The Deqi response in acupuncture (obtaining Qi, causing the acupuncture needle to elicit the patient's feeling of soreness, numbness, distension, heaviness, or even electric shock sensation around the acupuncture point together with the practitioner's feeling of tenseness around the needle) during acupuncture is a key factor that influences treatment outcome. Recent studies have mainly focused on the functional effects of Deqi in a physiological brain state. A functional magnetic resonance imaging (fMRI) study was conducted on 12 ischemic stroke patients receiving acupuncture at Waiguan (SJ5) and patients were group according to Deqi sensation [22]. In the Deqi group, the activated and deactivated areas were the left superior temporal gyrus (BA39) and the right anterior lobe of the cerebellum as well as left thalamus, respectively.

In the non-Deqi group, activated areas included the medial frontal gyrus of the right frontal lobe (BA11), right limbic lobe (BA30, 35), and left frontal lobe (BA47), while the right parietal lobe (BA40) was deactivated. Compared with the non-Deqi group, the Deqi group exhibited marked activation of the right anterior lobe of the cerebellum and right limbic lobe (BA30). These findings confirm that Deqi is a clinically measurable effect of acupuncture. Given the importance of Deqi for treatment outcome, cerebellar activation may be a central mechanism of the beneficial effect of acupuncture on ischemic stroke (**Table 2**).

6. Clinical studies of acupuncture therapy in ischemic stroke

6.1. A case match-controlled study of acupuncture in acute and subacute ischemic stroke

In order to reduce the healthcare burden of stroke, the Taiwan Department of Health initiated the Pilot Scheme of the Health Policy in Stroke Adjuvant Acupuncture Therapy (HPSAAT) in 2006. This study was conducted with cross-sectional, hospital-based, case match-controlled method retrospectively analyzed the clinical characteristics of acute and subacute ischemic stroke patients who electively joined the HPSAAT between 2006 and 2008 [23]. The study also evaluated the safety and clinical benefits of adjuvant acupuncture in acute and subacute ischemic stroke. Adjuvant acupuncture was concluded to be safe in the acute and subacute stages of ischemic stroke; however, due to uneven baseline severity between the 26 HPSAAT participants and 52 age- and sex-matched controls, the ability of acupuncture to reduce neurological deficits and improve functional recovery was not determined by this study [23].

6.2. Prospective RCTs of acupuncture in acute ischemic stroke

In a study of 290 first onset acute ischemic stroke patients aged 40–75 years old, patients initially (after 24 hours but within 14 days of the stroke event) received standard treatment and were then randomly allocated into an intervention group (treated with resuscitating acupuncture) or a control group (treated with sham acupuncture) [24]. Primary outcome measures included the Barthel index (BI), relapse, and mortality within a six-month period. There was one case of mortality in the intervention group and two cases in the control group ($P=0.558$). Six patients experienced relapse in the intervention group whereas 34 patients experienced relapse in the control group ($P<0.001$). The mean values for BI at six months were 70.25 ± 20.37 and 57.43 ± 19.61 for the intervention and control groups, respectively ($P<0.01$). The mean values for NIHSS score were also significantly different between groups at four weeks (4.15 ± 2.032 vs. 6.35 ± 3.131 , respectively, $P<0.01$) but not at two weeks. Acupuncture also produced greater improvements via the Chinese Stroke Scale (CSS) at four weeks (9.40 ± 4.51 vs. 13.09 ± 5.80 , respectively, $P<0.001$) and via the Stroke-Specific Quality-of-Life Scale (SS-QOL) at six months (166.63 ± 45.70 vs. 143.60 ± 50.24 , respectively, $P<0.01$). The results of this clinical trial therefore identified not only a clinically relevant decrease in relapse in patients treated with six months of resuscitating acupuncture, but also demonstrated improvements in self-care ability and quality of life as evaluated by the BI, NIHSS, CSS, Oxford Handicap Scale (OHS), and SS-QOL at various time points during and after treatment [24].

Another prospective RCT of acupuncture in 120 ischemic stroke inpatients and outpatients was conducted at Huashan Hospital and Fudan University in China [25]. Acupuncture, physiotherapy, and combined acupuncture with physiotherapy were utilized. Motor function of the limbs was measured using the FMA and the modified Barthel index (MBI) was used to rate activities of daily living. On the first day of therapy, FMA and MBI scores did not differ significantly among the treatment groups. By day 28 of therapy, the mean FMA scores for the physiotherapy, acupuncture, and combined treatment groups had increased relative to baseline by 65.6, 57.7, and 67.2%, respectively, and the mean MBI scores had increased by 85.2, 60.4, and 63.4%, respectively. FMA scores did not differ significantly among groups. By day 56, FMA scores had increased by 88.1, 64.5, and 88.6%, respectively ($P < 0.05$) and MBI scores had increased by 108.0, 71.2, and 86.2% at day 56, respectively ($P < 0.05$). FMA and MBI scores in the physiotherapy group were statistically higher than those in the acupuncture group ($P < 0.05$). No significant differences were identified between the combined treatment group and the other groups; in addition, FMA subscores for the upper extremities did not reflect any significant improvement in any group on day 56 of treatment [25]. The results of this study indicated that acupuncture is less effective than physiotherapy for rehabilitation. Moreover, the therapeutic effect of combined acupuncture and physiotherapy was not superior to that of physiotherapy alone. A larger-scale clinical trial is necessary to confirm these findings.

6.3. A pilot RCT of triple stimulation EA in ischemic stroke

A pilot study was conducted to objectively assess the effect of triple stimulation technique (TST) EA on motor functional recovery in patients with acute ischemic stroke [26]. Patients received either EA plus WCM ($n = 32$) or WCM alone ($n = 31$) for 14 days. EA plus WCM had a statistically higher total clinical effective rate than WCM alone ($P < 0.01$) and furthermore produced better improvements in FMA score, NIHSS score, and TST ratio ($P < 0.01$). Both before and after treatment, there was a positive correlation between the TST ratio and the NIHSS score ($P < 0.01$) and a negative correlation between the TST ratio and the FMA score ($P < 0.01$). Furthermore, there were no statistical differences in adverse events, electrocardiogram data, liver function, or kidney function between treatment groups. EA was concluded to be generally safe and beneficial for the motor functional recovery of patients with acute ischemic stroke. Moreover, TST was validated as a quantitative indicator of motor functional recovery that can objectively analyze the injury and recovery of corticospinal tract impairments.

6.4. A metaanalysis of EA RCTs in acute ischemic stroke

A systematic review was conducted to assess the effectiveness and safety of EA for acute ischemic stroke [27]. Eight databases were searched for relevant RCTs published prior to June 2013. Ultimately, 67 studies were identified and 1411 individuals from 18 studies were included in the analysis. According to the GRADE approach, the quality of evidence was mostly high or moderate. A significant difference in the total clinical efficacy rate was identified between EA and WCM, and significant effects of EA were observed on the BI score, FMA score, NIHSS score, and Revised Scandinavian Stroke Scale score relative to WCM. EA was well tolerated in

the six studies that monitored adverse events. Thus, this metaanalysis produced evidence supporting the use of EA acute ischemic stroke.

6.5. A multicentered RCT of EA in China

As aforementioned, acupuncture is frequently used as a complementary treatment for ischemic stroke in China; however, evidence available from previous RCTs was considered to be inconclusive. Thus, a more robustly designed, larger-scale trial was conducted. A multicentered, single-blinded RCT of 862 hospitalized patients with limb paralysis between 3 and 10 days after ischemic stroke onset was treated with either acupuncture plus routine care or routine care alone [28]. Acupuncture therapy was conducted five times per week for 3–4 weeks. The primary outcomes were defined as follows: (1) death/disability according to BI score and (2) death/institutional care at 6 months. Fewer patients were classified as having death/disability in the acupuncture group (20.7%) than in the control group (25.8%) at 6 months (odds ratio [OR], 0.75; 95% confidence interval [CI], 0.54–1.05). In a subgroup receiving ≥10 sessions of acupuncture (OR, 0.68; 95% CI, 0.47–0.98) was found therapeutic benefit. There was no significant difference in death/institutional care between two groups (OR, 1.06; 95% CI, 0.63–1.79). Severe adverse events occurred in 7.6 and 8.3% of patients in the acupuncture and control groups, respectively. The study concluded that acupuncture appeared to be safe in the subacute phase of ischemic stroke. However, confirmation of the observed therapeutic benefit is necessary in order to facilitate the widespread use of acupuncture in subacute ischemic stroke (Table 3).

Trial	N	Design	Test group	Control group	Acupoints	Outcomes/conclusion
Wei et al. (2011) [23]	26:52	Case controlled study	Acupuncture plus WCM	WCM	NA	Acupuncture was concluded to be safe for use in the acute and subacute stages of ischemic stroke. The clinical benefits in reducing neurological deficits and functional recovery were not concluded.
Shen et al. (2012) [24]	145:145 RCT		Acupuncture	Sham-acupoints	PC6, DU26, SP6, HT1, BL40, LU5. auxiliary acupoints: GB20, TE17, GB12, LI4, CV23, EX-HN 12, EX-HN 13; cross-foot, puncture-GB40 toward KI 6.	(1) BI at six months ($P < 0.01$). (2) NIHSS at four weeks ($P < 0.01$). (3) CSS at four weeks ($P < 0.001$). (4) SS-QOL at six months ($P < 0.01$).
Bai et al. (2013) [25]	39:40:41 RCT		(1) Acupuncture group (2) Combined therapy group	Physiotherapy only	GV20, LI15, SI9, LI11, TE5, LI4, GB34, BL60, GB39, GB30, GB31, PC6, SP5,	FMA and MBI scores did not significantly differ between the physiotherapy and the combined therapy groups. The therapeutic effect of combined acupuncture

Trial	N	Design	Test group	Control group	Acupoints	Outcomes/conclusion
Tan et al. (2013) [26]	32:31	Pilot RCT	EA plus WCM	WCM	LR3, SP9, SP6, KI10, PC7, LI4, SI3, HT1, LU5, PC3. LI15 and TE14, LI11 and LI4, LU5 and PC6 ST36 and GB34, ST40 and GB39, SP6 and LR3 (at hemiparetic limb).	and physiotherapy was not superior to that of physiotherapy alone. (1) FMA score ($P < 0.01$). (2) NIHSS ($P < 0.01$). (3) TST _{ratio} ($P < 0.01$). EA was concluded to be safe and beneficial for motor functional recovery.
Liu et al. (2015) [27]	1411	Systematic review and metaanalysis of RCT	EA	WCM	NA	(1)BI ($P < 0.00001$). (2)FMA score ($P < 0.00001$). (3)NIHSS ($P < 0.00001$). (4) RSSS ($P < 0.00001$). This metaanalysis produced evidence supporting the use of EA for acute ischemic stroke.
Zhang et al. (2015) [28]	427: 435	Multicentered, RCT	Acupuncture plus WCM	WCM	DU26, PC6, SP6, DU20, ST36, ST40, LK3, LL5, GB20, RN6	Acupuncture appeared to be safe in the subacute phase of ischemic stroke. Subgroup analysis showed that only when patients who received ≥ 10 sessions of acupuncture had a significant difference in death or dependency at 6 months (OR, 0.68; 95% CI, 0.47–0.98; NNT 15).

CSS, Chinese Stroke Scale; EA, electroacupuncture; FMA, Fugl-Meyer assessment; MBI, modified Barthel index; NNT, number needed to treat; RSSS, Revised Scandinavian Stroke Scale; SS-QOL, Stroke-Specific Quality-of Life-Scale; WCM, Western *conventional* medicine.

Table 3. Clinical trials of acupuncture therapy in ischemic stroke.

7. Scalp acupuncture (SA)

Scalp acupuncture (SA) is one of the several specialized acupuncture techniques. Although SA has been practiced for thousands of years, SA was only developed for clinical use in recent decades. In 1984 and 1989, a standard nomenclature for acupuncture points was developed and redesigned to combine the teachings of different schools of SA, and resulted in the proposal of 14 therapeutic lines or zones [29]. Subsequently, “*A Proposed Standard International Acupuncture Nomenclature: 3.6 Scalp acupuncture lines*” was formally published by the World Health Organization in 1991 [30]. SA therapy for both ischemic stroke and hemorrhagic stroke has been empirically established and is now widely used in clinics around the world [31, 32].

7.1. A metaanalysis of SA RCTs in acute ischemic stroke

A metaanalysis of RCTs of SA in acute ischemic stroke was conducted [33]; a total of 538 acute ischemic stroke patients from eight eligible studies were included [34–41]. The main findings were that SA therapy improved neurological deficits and had a better clinical effective rate relative to WCM. However, this evidence was insufficient to warrant a clinical recommendation due to the generally low methodological quality of included studies.

7.2. Baihui (GV20)-based SA in experimental ischemic stroke

A systematic review and metaanalysis was conducted to assess current evidence for a beneficial effect of Baihui (GV20)-based SA in animal models of focal cerebral ischemia [42]. Six databases were searched for relevant studies published prior to June 2013. Primary outcomes were infarct size and neurobehavioral outcome. Ultimately, a total of 1816 animals from 54 eligible studies were included in the analysis. Twelve studies reported significant effects of Baihui (GV20)-based SA on infarct volume in middle cerebral artery occlusion ($P < 0.01$), and 32 studies reported significant beneficial effects of Baihui (GV20)-based SA on neurological function relative to control ($P < 0.01$). Therefore, in conclusion, Baihui (GV20)-based SA may specifically improve infarct volume and neurological function in experimental ischemic stroke (Table 4).

Study	N	Study design	Test group	Control group	Outcomes/conclusion
Wang et al. (2012) [33]	538	Metaanalysis of SA RCTs	SA	WCM	6 RCTs improving neurological deficit scores ($P < 0.01$); 4 RCTs favoring the clinical effective rate ($P < 0.01$).
Wang et al. (2014) [42]	1816	1. Systematic review and metaanalysis 2. Animal model	GV20-based SA	MCAo group	12 studies improving infarct volume ($P < 0.01$) 32 studies improving the neurological function score ($P < 0.01$). Baihui (GV20)-based SA improves infarct volume and neurological function in experimental ischemic stroke.

MCAo, middle cerebral artery occlusion.

Table 4. Scalp acupuncture in ischemic stroke.

8. Specific acupuncture points studied in the context of ischemic stroke

8.1. Waiguan (SJ5)

Sixteen patients with ischemic stroke were randomly assigned to receive either true point acupuncture at right SJ5 or sham point acupuncture during fMRI. SJ5 acupuncture produced

activation in the right parietal lobe (BA7 and BA19), right temporal lobe (BA39), right limbic lobe (BA23), and bilateral occipital lobes (BA18) as well as deactivation of the bilateral frontal lobes (BA4, BA6, and BA45), right parietal lobe (BA1 and BA5), and left temporal lobe (BA21). Sham point acupuncture produced activation in the precuneus of the right parietal lobe (BA7) and deactivation of the left superior frontal gyrus (BA10). Compared with sham point acupuncture, SJ5 acupuncture inhibited the contralateral BA5 in stroke patients. These results suggested that altered specificity of the sensation-associated cortex (BA5) is a possible mechanism of the beneficial effect of SJ5 acupuncture in stroke patients [43].

8.2. Hegu (LI4)

A 14-day treatment study was conducted to determine the clinical efficacy of acupuncture at LI4 in central facial nerve paralysis after ischemic stroke and to explore the dose-response effect of different stimulation intensities [44]. Patients received either different stimulation intensities of acupuncture at LI4 combined with facial paralysis acupoints including Yingxiang (LI20), Dicang (ST4), Jiache (ST6), and Quanliao (SI18), acupuncture at facial paralysis acupoints alone, acupuncture at stroke acupoints including Neiguan (PC6), Shuigou (GV26), and Sanyinjiao (SP6), or medication treatment. The House-Brackmann Facial Nerve Grading System (H-B), Toronto Facial Grading System (TFGS), Degrees of Facial Nerve Paralysis (DFNP), Facial Disability Index (FDI), and clinical efficacy were used as outcome measures. Various intensities of LI4 stimulation improved H-B score, TFGS score, DFNP score, and FDI physical function score ($P < 0.05$), but LI4 stimulation had no effect on FDI social function score. No changes were observed in the control group. The study concluded that LI 4 acupuncture had clinical efficacy in central facial nerve paralysis after ischemic stroke and that oblique needle insertion along the opposite direction of the meridian with five seconds of twirling manipulation had the best clinical effect (Table 5).

Study	N	Study design	Test group	Control group	Acupoint	Outcomes/conclusion
Qi et al. (2014) [43]	7:7	fMRI	SJ5 acupuncture	Sham acupoint	Waiguan (SJ5)	SJ5 acupuncture altered specificity of the sensation-associated cortex (BA5) is a possible mechanism of the beneficial effect in stroke patients.
Li et al. (2014) [44]	50	Case controlled study	Hegu 1 Hegu 2 Hegu 3 Hegu 4	WCM	Hegu (LI4) combined with facial paralysis acupoints	H-B in the Hegu 1 to 4 groups ($P < 0.05$). TFGS in the Hegu 2 group ($P < 0.05$). DFNP in the Hegu 1 and Hegu 2 groups ($P < 0.05$). LI4 acupuncture had clinical efficacy in central facial nerve paralysis after ischemic stroke.

H-B, The House-Brackmann facial never grading systems; TFGS, Toronto facial grading system; DFNP, degrees of facial never paralysis; FDI, facial disability index.

Table 5. Specific acupuncture point study.

9. The role of acupuncture therapy in preventive medicine

On average, the annual risk of ischemic stroke after an initial ischemic stroke event or transient ischemic attack is 3–4% [45, 46]. Antiplatelet therapy is a preventive medical option that has utility for the prevention of hypertension, atrial fibrillation, arterial obstruction, and hyperlipidemia [1]. However, preventive options for ischemic stroke are limited. Therefore, the role of acupuncture therapy in preventive medicine was explored in a preliminary study.

9.1. The effect of acupuncture on stroke recurrence

A retrospective study evaluated 30,058 cases of first onset ischemic stroke between the years 2000 and 2004 based on claims history from the Taiwan National Health Insurance Research Database [47]. Uses of acupuncture treatment and stroke recurrences were identified in a follow-up period between 2000 and 2009. Use of acupuncture treatment was associated with a decrease in the rate of stroke recurrence from 71.4 to 69.9 cases per 1000 person-years ($P < 0.001$). Acupuncture treatment was also associated with a reduced risk of stroke recurrence (hazard ratio [HR], 0.88; 95% CI, 0.84–0.91). The effect of acupuncture on stroke recurrence was noted in patients independent of medical treatment for stroke prevention: the HRs of stroke recurrence for those had medical treatment, acupuncture, and both were 0.42 (95% CI, 0.38–0.46), 0.50 (95% CI, 0.43–0.57), and 0.39 (95% CI, 0.35–0.43), respectively. However, the effect of acupuncture on stroke recurrence decreased with patient age. This study raises the possibility that acupuncture may have utility for preventing stroke recurrence after an initial event, even in patients already taking medications for stroke prevention. Confirmation in the form of a prospective RCT is required to establish the efficacy of acupuncture as a preventive practice in ischemic stroke [47].

9.2. The effect of acupuncture on acute myocardial infarction (AMI) risk after stroke

A retrospective study evaluated 23,475 stroke patients aged 40–79 years who received acupuncture treatment and 46,950 propensity score-matched control stroke patients who did not receive acupuncture treatment between the years 2000 and 2004 based on claims history from the Taiwan National Health Insurance Research Database [48]. Both stroke cohorts were followed until the end of 2009. Stroke patients who received acupuncture therapy (9.2 per 1000 person-years) had a lower incidence of AMI compared with those who did not receive acupuncture therapy (10.8 per 1000 person-years), with an HR of 0.86 (95% CI, 0.80–0.93) after adjustment for age, sex, low income, coexisting medical conditions, and medications. These results reveal that acupuncture therapy may be useful for the prevention of AMI in stroke patients aged 50–69. However, the study was limited by lack of information relating to stroke severity and acupuncture points. Further prospective randomized trials are required to establish the efficacy of acupuncture for preventing AMI after stroke.

9.3. The effect of acupuncture on stroke risk after traumatic brain injury (TBI)

Patients with TBI are subject to an increased risk of stroke. A retrospective study evaluated 7409 TBI patients who received acupuncture treatment and 29,636 propensity score-matched

control TBI patients who did not receive acupuncture treatment between the years 2000–2008 based on claims history from the Taiwan National Health Insurance Research Database. Both TBI cohorts were followed until the end of 2010. TBI patients who received acupuncture treatment (4.9 per 1000 person-years) had a lower incidence of stroke compared with those who did not receive acupuncture treatment (7.5 per 1000 person-years), with an HR of 0.59 (95% CI, 0.50–0.69) after adjusting for sociodemographic information, coexisting medical conditions, and medication use. Moreover, TBI patients who received acupuncture treatment during the follow-up period had a lower probability of stroke than those who did not receive acupuncture treatment ($P < 0.0001$). However, this study was limited by lack of information regarding lifestyle, biochemistry results, TBI severity, and acupuncture points [45].

10. Conclusions

The use of complementary therapies in stroke is increasing due to a rising demand for better poststroke rehabilitation and management. TCM is a popular complementary therapy in East Asia and throughout the world. Increasing scientific evidence suggests that TCM can significantly improve stroke recovery as well as reduce the likelihood of hospital readmission for cardiovascular or subsequent stroke events. Therefore, patients can benefit from comprehensive treatment plans that combine standard and complementary therapies to address immediate medical concerns, minimize the occurrence of future complications, and ultimately decrease medical costs. Further studies on the therapeutic targets mediating the beneficial actions of TCM may additionally lead to the development of novel therapeutic strategies.

Abbreviations

ATP	adenosine triphosphate
BA	Brodmann Area
BBB	blood brain barrier
BI	Barthel index
BYHWT	Bu-yang-huan-wu-tang
CHPs	Chinese herbal products
DHYZ	Di Huang Yin Zi
DTI	Diffusion Tensor Imaging
EA	electro-acupuncture
FMA	Fugl-Meyer Assessment
FDG PET-CT	Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography and Computed

ATP	adenosine triphosphate
	Tomography
fMRI	Functional magnetic resonance imaging
MMP	matrix metalloproteases
OGD	oxygen-glucose deprivation
SA	Scalp acupuncture
SJHXT	Shu-jin-huo-xue-tang
TCM	Traditional Chinese medicine
TOAST	the Trial of Org 10172 in Acute Stroke Treatment
TST	triple-stimulation technique

Author details

Po-Yu Huang¹, Yu-Chiang Hung^{1,2} and Wen-Long Hu^{1,3,4*}

*Address all correspondence to: oolonghu@gmail.com

1 Department of Chinese Medicine, Kaohsiung Chang Gung Memorial Hospital and School of Traditional Chinese Medicine, Chang Gung University College of Medicine, Kaohsiung, Taiwan

2 School of Chinese Medicine for Post Baccalaureate, I-Shou University, Kaohsiung, Taiwan

3 Kaohsiung Medical University College of Medicine, School of Medicine, Kaohsiung, Taiwan

4 Fooyin University College of Nursing, School of Nursing, Kaohsiung, Taiwan

References

[1] Kernan, W.N., et al., Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*, 2014. 45(7): 2160–2236.

[2] Mozaffarian, D., et al., Heart disease and stroke statistics-2016 update: a report from the American Heart Association. *Circulation*, 2016. 133(4): e38–e360.

- [3] LR., C., Basic pathology, anatomy, and pathophysiology of stroke. In: Caplan's Stroke: A Clinical Approach, 4th ed., Saunders Elsevier, Philadelphia, 2009: p. 22.
- [4] Adams, H.P., Jr., et al., Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST Trial of Org 10172 in Acute Stroke Treatment. *Stroke*, 1993. 24(1): 35–41.
- [5] Eames, P.J., et al., Dynamic cerebral autoregulation and beat to beat blood pressure control are impaired in acute ischaemic stroke. *J Neurol Neurosurg Psychiatry*, 2002. 72(4): 467–472.
- [6] Atkins, E.R., et al., Dynamic cerebral autoregulation is compromised acutely following mild ischaemic stroke but not transient ischaemic attack. *Cerebrovasc Dis*, 2010. 29(3): 228–235.
- [7] Aries, M.J., et al., Cerebral autoregulation in stroke: a review of transcranial Doppler studies. *Stroke*, 2010. 41(11): 2697–2704.
- [8] Doyle, K.P., R.P. Simon, and M.P. Stenzel-Poore, Mechanisms of ischemic brain damage. *Neuropharmacology*, 2008. 55(3): 310–318.
- [9] Deb, P., S. Sharma, and K.M. Hassan, Pathophysiologic mechanisms of acute ischemic stroke: an overview with emphasis on therapeutic significance beyond thrombolysis. *Pathophysiology*, 2010. 17(3): 197–218.
- [10] Yang, Y. and G.A. Rosenberg, Blood-brain barrier breakdown in acute and chronic cerebrovascular disease. *Stroke*, 2011. 42(11): 3323–3328.
- [11] Gu, Y., J. Chen, and J. Shen, Herbal medicines for ischemic stroke: combating inflammation as therapeutic targets. *J Neuroimmune Pharmacol*, 2014. 9(3): 313–339.
- [12] Carden, D.L. and D.N. Granger, Pathophysiology of ischaemia-reperfusion injury. *J Pathol*, 2000. 190(3): 255–266.
- [13] Barone, F.C., et al., Tumor necrosis factor-alpha. A mediator of focal ischemic brain injury. *Stroke*, 1997. 28(6): 1233–1244.
- [14] Abulafia, D.P., et al., Inhibition of the inflammasome complex reduces the inflammatory response after thromboembolic stroke in mice. *J Cereb Blood Flow Metab*, 2009. 29(3): 534–544.
- [15] Yu, M., et al., The beneficial effects of the herbal medicine Di-Huang-Yin-Zi (DHYZ) on patients with ischemic stroke: a randomized placebo controlled clinical study. *Complement Ther Med*, 2015. 23(4): 591–597.
- [16] Hung, I.L., et al., Chinese herbal products for ischemic stroke. *Am J Chin Med*, 2015. 43(7): 1365–1379.

- [17] Lu, L., et al., Rhubarb root and rhizome-based Chinese herbal prescriptions for acute ischemic stroke: a systematic review and meta-analysis. *Complement Ther Med*, 2014. 22(6): 1060–1070.
- [18] Lu, L., et al., Acupuncture for neurogenesis in experimental ischemic stroke: a systematic review and meta-analysis. *Sci Rep*, 2016. 6: 19521.
- [19] Feng, R. and F. Zhang, The neuroprotective effect of electro-acupuncture against ischemic stroke in animal model: a review. *Afr J Tradit Complement Altern Med*, 2014. 11(3): 25–29.
- [20] Huang, Y., et al., Acupuncture regulates the glucose metabolism in cerebral functional regions in chronic stage ischemic stroke patients—a PET-CT cerebral functional imaging study. *BMC Neurosci*, 2012. 13: 75.
- [21] Li, Y., et al., The Effect of acupuncture on the motor function and white matter microstructure in ischemic stroke patients. *Evid Based Complement Altern Med*, 2015. 2015: 164792.
- [22] Li, M.K., et al., Acupuncture for ischemic stroke: cerebellar activation may be a central mechanism following Deqi. *Neural Regen Res*, 2015. 10(12): 1997–2003.
- [23] Wei, Y.C., et al., Pilot scheme of health policy in stroke adjuvant acupuncture therapy for acute and subacute ischemic stroke in taiwan. *Evid Based Complement Altern Med*, 2011. 2011: 689813.
- [24] Shen, P.F., et al., Acupuncture intervention in ischemic stroke: a randomized controlled prospective study. *Am J Chin Med*, 2012. 40(4): 685–693.
- [25] Bai, Y.L., et al., Prospective randomized controlled trial of physiotherapy and acupuncture on motor function and daily activities in patients with ischemic stroke. *J Altern Complement Med*, 2013. 19(8): 684–689.
- [26] Tan, F., et al., A randomized controlled pilot study of the triple stimulation technique in the assessment of electroacupuncture for motor function recovery in patients with acute ischemic stroke. *Evid Based Complement Altern Med*, 2013. 2013: 431986.
- [27] Liu, A.J., et al., Electroacupuncture for acute ischemic stroke: a meta-analysis of randomized controlled trials. *Am J Chin Med*, 2015. 43(8): 1541–1566.
- [28] Zhang, S., et al., Acupuncture efficacy on ischemic stroke recovery: multicenter randomized controlled trial in China. *Stroke*, 2015. 46(5): 1301–1306.
- [29] Liu, Z., et al., History and mechanism for treatment of intracerebral hemorrhage with scalp acupuncture. *Evid Based Complement Altern Med*, 2012. 2012: 895032.
- [30] WHO Scientific Group on International Acupuncture Nomenclature. A Proposed Standard International Acupuncture Nomenclature. Report of a WHO Scientific Group, World Health Organization, Geneva, Switzerland, 1991.

- [31] Zheng, G.Q., et al., Meta-analysis of scalp acupuncture for acute hypertensive intracerebral hemorrhage. *J Altern Complement Med*, 2011. 17(4): 293–299.
- [32] Hsing, W.T., et al., Clinical effects of scalp electrical acupuncture in stroke: a sham-controlled randomized clinical trial. *J Altern Complement Med*, 2012. 18(4): 341–346.
- [33] Wang, Y., et al., Scalp acupuncture for acute ischemic stroke: a meta-analysis of randomized controlled trials. *Evid Based Complement Altern Med*, 2012. 2012: 480950.
- [34] Tang QS, S.S., Clinical and experimental research on acute cerebral infarction treated by needling Shu Xue on head. *J Beij Coll Trad Chin Med*, 1996. 19(4): 37–39.
- [35] Yu CD, W.B., Hong AH, Bei JY, Yu Z., Changes of serum MDA content and neurological rehabilitation in cerebral infarction patients treated with scalp acupuncture plus medication. *Acupuncture Res*, 2004. 29(3): 222–226.
- [36] Wei TH, X.T., Tang Q., The evaluation of scalp acupuncture combined with recovery techniques on the movement dysfunction after cerebral infarction. *Chin J Rehabil Theor Pract*, 2005. 11(7): 522–523.
- [37] Xu HB, Z.G., Li NP, et al., Treatment of acute cerebral infarction with scalp acupuncture combined with Yinxingdamo injection. *J Clin Exp Med*, 2007. 6(8): 140–141.
- [38] Chen J, J.L., Clinical application of cluster needling of scalp point therapy combined with swallowing functional training in treatment of dysphagia after acute cerebral infarction. *Chin J Trau Dis Med*, 2008. 16(5): 70–71.
- [39] Yu CD, W.G., Wu BH, Li ZW, Song HM, Yu Ze., Effects of cranial sutures acupuncture plus drugson recovery of neural function and serum SOD and MDA in acute cerebral infarction patients with phlegm syndrome. *J Fuj Univ TCM*, 2010. 20(2): 7–9.
- [40] Zhang LR, S.B., Luo HL, Dong GR, Bao CL, Guo YQ., Effect of bilateral scalp-acupoint penetrating acupuncture on serum levels of VEGF. *Chin J Rehabilita*, 2011. 26(3): 214–215.
- [41] Zhu GQ, H.S., Effect of Xingnaoyinyang penetration needling method on the level of Ca^{2+} in serum of patients with acute cerebral infarction. *J Emerg Trad Chin Med*, 2011. 20(1): 9–11.
- [42] Wang, W.W., et al., A systematic review and meta-analysis of Baihui (GV20)-based scalp acupuncture in experimental ischemic stroke. *Sci Rep*, 2014. 4: 3981.
- [43] Qi, J., et al., Acupuncture at Waiguan (SJ5) and sham points influences activation of functional brain areas of ischemic stroke patients: a functional magnetic resonance imaging study. *Neural Regen Res*, 2014. 9(3): 293–300.
- [44] Li, L.X., et al., Different stimulation intensities of acupuncture at Hegu (LI 4) for central facial nerve paralysis after ischemic stroke: a randomized controlled trial. *Zhongguo Zhen Jiu*, 2014. 34(7): 669–674.

- [45] Dhamoon, M.S., et al., Recurrent stroke and cardiac risks after first ischemic stroke: the northern manhattan study. *Neurology*, 2006. 66(5): 641–646.
- [46] Hong, K.S., et al., Declining stroke and vascular event recurrence rates in secondary prevention trials over the past 50 years and consequences for current trial design. *Circulation*, 2011. 123(19): 2111–2119.
- [47] 47. Shih, C.C., et al., A retrospective cohort study comparing stroke recurrence rate in ischemic stroke patients with and without acupuncture treatment. *Med (Baltimore)*, 2015. 94(39): e1572.
- [48] Chuang, S.F., et al., Decreased risk of acute myocardial infarction in stroke patients receiving acupuncture treatment: a nationwide matched retrospective cohort study. *BMC Complement Altern Med*, 2015. 15: 318.