Preclinical Evidence and Potential Mechanisms of Electroacupuncture in Regulating Inflammatory Responses After Stroke: A Meta-analysis

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Abstract [**Objectives**] To investigate the evidence-based effect of electroacupuncture on the post stroke inflammatory response and elucidate its potential molecular mechanisms. [**Methods**] A systematic electronic search of the Medline, PubMed, and Web of Science databases was initially performed up to June 2024. The risk of bias of the included studies was evaluated using RevMan 5.4 software, in accordance with the guidelines set forth in the *Cochrane Handbook for Systematic Reviews*. The random-effects model or fixed-effects models was employed to estimate the standardized mean difference (*SMD*). [**Results**] A total of 15 studies, comprising a total of 182 rats or mice, were included in this review. The pooled analysis of these trials showed a statistically significant reduction in the level of TNF-α (12 studies, *SMD* = -2.38, [95% *CI*, -2.86 to -1.90], $P<0.000\ 01$, $I^2=49$), and IL-1β (11 studies, *SMD* = -2.41, [95% *CI*, -3.32 to -1.50], $P<0.000\ 01$, $I^2=57$). Additionally, the compiled data demonstrated a notable and statistically significant elevation in the IL-10 level (6 studies, *SMD* = 1.56, [95% *CI*, 0.42 to 2.70], $P=0.008$, $I^2=68$). [**Conclusions**] The findings of this systematic review and meta-analysis demonstrate that electroacupuncture stimulation has the potential to regulate the inflammatory responses after stroke.

Key words Electroacupuncture, Ischemic stroke, Inflammation, Meta-analysis, Mechanism

1 Introduction

Cerebral ischemic stroke, also referred to as cerebral infarction, is a syndrome characterized by the interruption of localized cerebral blood supply disorders, leading to the necrosis and softening of the brain tissue due to ischemia and hypoxia[1]. Clinically, the condition presents as sudden focal or diffuse neurological deficits. Ischemic stroke is the most prevalent form of cerebrovascular disease, accounting for approximately 70% of all acute cerebrovascular events[2]. The treatment of cerebral ischemic stroke is a multifaceted process that employs a combination of pharmacological and rehabilitative approaches, which are tailored to the patient's specific condition and stage of recovery. The inflammatory response plays a critical role in the pathogenesis and progression of ischemic stroke. Understanding this relationship and developing effective anti-inflammatory strategies hold promise for improving the treatment and prevention of this devastating disease[3].

Electroacupuncture (EA) is a therapeutic method involving the insertion of fine acupuncture needles into specific acupuncture points on the body, followed by the application of a minute electric current in close proximity to the body's bioelectricity through the needles. This technique employs the combined use of acupuncture needles and electrical stimulation to prevent and treat a range of medical conditions[4]. Extensive research has demonstrated that EA possesses the ability to modulate the inflammatory response in ischemic stroke, providing a promising avenue for therapeutic intervention in this debilitating condition[5]. Despite promising research, there is a scarcity of sufficient evidence-based literature to conclusively demonstrate that EA can regulate the inflammatory response following ischemic stroke. Although preliminary studies have shown the potential benefits of EA in modulating inflammatory markers and processes in animal models of ischemic stroke, there is a lack of systematic reviews in the literature examining the impact of EA on the inflammatory response in the rehabilitation of stroke.

2 Methods

2.1 Literature search We performed a systematic review consistent with the preferred reporting items for systematic reviews and meta-analyses (PRISMA)[6]. An electronic database search was initially performed in January 2024 and subsequently updated in June 2024 using the following databases: Medline, PubMed, and Web of Science. The electroacupuncture intervention search terms were: "electroacupuncture" OR ("electrical" And "acupuncture"). The selected terms for cerebral ischemia were: "Stroke [Mesh]" OR "cerebral ischemic" OR "ischemic stroke" OR "brain infarction" OR "brain ischemia". The search strategy for article types were: "animal study" OR "rat" OR "mice" OR "mechanism" OR "preclinical study". The three terms above were combined with the Boolean operator "AND" and then searched in "All Fields", with the English language as the limit. Additionally, the reference lists of the included studies and relevant reviews were examined to ensure that only eligible studies were considered, while irrelevant studies were excluded. At this stage, reviews, expert opinions, and case studies were excluded.

2.2 Study inclusion/exclusion criteria Studies were included if they fulfilled the following criteria: (i) randomized controlled trials (RCTs); (ii) the treatment group received an electroacupuncture intervention, defined as a therapeutic method that involves the insertion of fine acupuncture needles into specific acupuncture points and the subsequent application of a minute electric current in proximity to the body's bioelectricity through the needles; (iii) only rats or mice with ischemic stroke were included in the study, and the animal models of stroke included permanent or

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temporary middle cerebral artery occlusion (MCAO); (iv) a detailed description of the electroacupuncture intervention, including waveform, amplitude, pulse width, frequency, and duration; (v) primary outcome included biomarkers that reflect the level of inflammation, such as TNF-α, IL-1β, IL-4, IL-6, IL-10, and so on. Studies that did not meet the inclusion criteria were excluded.

2.3 Study selection, extraction and data collection A data extraction sheet was extracted by the primary reviewer and subsequently verified by the secondary reviewer in accordance with the guidelines set forth in the *Cochrane Handbook for Systematic Reviews*. When the numerical values of the outcomes were not explicitly stated in the texts or tables of the published paper, a diligent effort was made to contact the corresponding author via email for clarification. Following two unsuccessful attempts at obtaining a response, two authors independently utilized the WebPlotDigitizer software to extract the data from the graphs presented in the paper[7]. The extracted data was deemed acceptable only if the discrepancy between the two authors' measurements did not exceed 20%. In cases where a study presented multiple follow-up endpoints, the endpoint exhibiting the most notable discrepancy was given precedence. Additionally, if the median, standard error, and interquartile range were provided, these values were carefully converted to the mean and standard deviation (SD) in order to ensure consistency and comparability. The following items were extracted: study ID, characteristics of the study design (such as experimental groups, number of animals), characteristics of the animal model (such as species, time of cerebral ischemia induction), characteristics of the intervention (such as waveform, amplitude, frequency, and duration), and the primary outcomes (such as levels of TNF-α, IL-1β, IL-4, IL-6, IL-10, and TGF-β).

2.4 Assessment risk of bias The risk of bias assessment table was generated using RevMan 5.4 software[8]. The selected literature was assessed for quality, with particular attention paid to the following aspects: correctness of random sequence generation, allocation concealment, implementation of blinding for the assessors and participants, blinding of outcome assessment, completeness of outcome data, selective reporting, and other biases.

2.5 Data analysis The analysis was performed using RevMan 5.4 software (the Cochrane Collaboration, Nordic Cochrane Center, Copenhagen, Denmark). In regard to continuous outcome variables, our practice was to express them as standard mean differences (SMD). Additionally, 95% confidence intervals (CIs) were employed as summary statistics, thereby ensuring a robust and comprehensive evaluation. Given the considerable heterogeneity of outcomes across various studies, we elected to employ a fixed-effects model, thereby ensuring consistency and reliability. In instances where the outcome measures were deemed comparable, the datasets were pooled in a meticulous meta-analysis. To evaluate the heterogeneity between studies, we employed the I^2 statistic, which is a robust indicator of variation. The I^2 test was utilized to scrutinize statistical heterogeneity, while the I^2 statistic itself was leveraged to assess the extent of inconsistency. Based on the I^2 results, both the fixed-effects model and the random-effects model were subjected to rigorous analysis. In cases where the I^2 value exceeded 50%, indicating significant heterogeneity, we employed the random-effects model to calculate the parameters. Conversely, in the absence of such heterogeneity, we assumed a fixed-effects model. Finally, to identify any potential publication bias, we employed the funnel plot, a tried-and-tested method, particularly when the datasets encompassed at least three studies. This methodology guaranteed that our analysis was not skewed by any undue biases, further strengthening the credibility of our findings. A two-tailed P-value of less than 0.05 was deemed to be statistically significant.

3 Results and analysis

3.1 Eligible studies The preliminary search yielded a total of 932 articles, of which 817 were original articles. After a review of the abstracts, 600 were excluded. A total of 117 citations were examined in their entirety, and 15 relevant RCTs were identified that met the criteria for inclusion in the meta-analysis. Of these, 102 papers were excluded from further analysis. The majority of these were found to lack a relevant outcome measure of inflammation that could be incorporated into a meta-analysis. The process of selecting studies for inclusion is illustrated in Fig. 1.

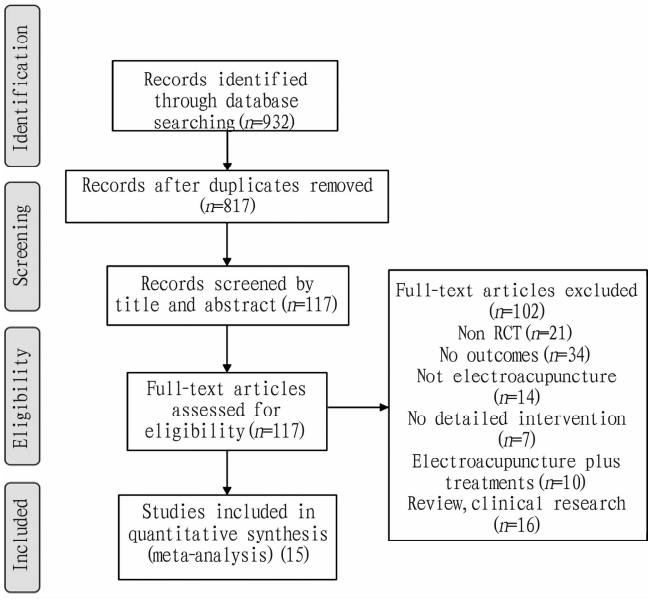


Fig. 1 Flow-chart illustrating the literature search strategy and the different phases of study eligibility assessment

3.2 Description of included studies A total of 15 studies, comprising a total of 182 rats or mice, published between 2014 and 2024, were included in the analysis. The studies included were written in English. The majority of the studies selected Sprague-Dawley rats as the primary animal model for prevention studies (13 studies). Electroacupuncture was performed subsequent to the surgical procedure in 11 studies, and only four studies reported follow-up results prior to the surgical intervention. With regard

to the frequency of acupoint utilization, a total of 12 acupoints were employed across the included studies. The four most commonly used acupoints were GV20 (11 occurrences), ST36 (4 occurrences), and GV24 (3 occurrences). A total of 12 studies employed disperse wave, with EA frequencies of 2/15, 2/20, and 4/20 Hz. The remaining studies employed continuous wave, with EA frequencies of 10, and 20 Hz. Regarding the course of treatment, all the included studies provided specific timeframes for each treatment, with typical durations ranging from 10 to 30 min (Table 1). The main outcomes for assessing inflammatory responses include the levels of proinflammatory factors TNF-α (11 occurrences) and IL-1β (11 occurrences), as well as the level of the anti-inflammatory factor IL-10 (6 occurrences).

Table 1 Electroacupuncture parameters of included studies

Study	Species	Ischemic time//min	Interventions (animal numbers)	Intervention start time	Acupoints	Frequency Hz	Intensity	Wave form	Time min	Outcomes
Cheng *et al.* [9]	SD	90	EA (3), Con (3)	After MCAO	LI11, ST36	4/20	1 mA	Disperse wave	30	TNF-α, IL-1β
Huang *et al.* [10]	SD	90	EA (6), Con (6)	After MCAO	GV20, GV24	2/20	0.2 mA	Disperse wave	30	IL-1β, IL-10
Jiang *et al.* [11]	SD	90	EA (8), Con (8)	Before MCAO	GV20	2/15	1 mA	Disperse wave	30	TNF-α, IL-10
Jin *et al.* [12]	SD	–	EA (8), Con (8)	After MCAO	ST36	10	1 mA	Continuous wave	20	TNF-α
Lan *et al.* [13]	SD	120	EA (8), Con (8)	After MCAO	LI11, ST36	1/20	–	Disperse wave	–	TNF-α, IL-1β
Lin *et al.* [14]	SD	120	EA (4), Con (4)	After MCAO	GV20, GV24	0.05	6 V	Disperse wave	30	TNF-α, IL-1β
Lin *et al.* [15]	SD	90	EA (4), Con (4)	After MCAO	GV20, GV24	2/20	0.2 mA	Disperse wave	30	IL-1β, IL-10
Liu *et al.* [16]	SD	–	EA (4), Con (4)	After MCAO	GV20, GV14	–	1–2 mA	Disperse wave	20	TNF-α, IL-1β
Long *et al.* [17]	SD	120	EA (8), Con (8)	Before MCAO	GV20, BL23, SP6	2/100	1 mA	Continuous wave	10	TNF-α, IL-1β
Ma *et al.* [18]	Wistar	120	EA (5), Con (5)	Before MCAO	GV20	2/15	1 mA	Disperse wave	30	TNF-α, IL-1β, IL-10
Ren *et al.* [19]	C57BL/6	40	EA (4), Con (4)	After MCAO	GV26, GV20	4/20	1–3 mA	Disperse wave	20	TNF-α, IL-1β, IL-10
Sha *et al.* [20]	SD	90	EA (5), Con (5)	After MCAO	TE5, ST36	20	1 mA	Continuous wave	30	IL-1β
Sun *et al.* [21]	SD	120	EA (12), Con (12)	Before MCAO	GV20, GB7	2/20	–	Disperse wave	30	TNF-α
Wen *et al.* [22]	SD	60	EA (6), Con (6)	After MCAO	GV20, PC6, KI1	1/20	2 mA	Disperse wave	30	TNF-α, IL-10
Xu *et al.* [23]	SD	120	EA (6), Con (6)	After MCAO	GV20, LR3	2/20	1 mA	Disperse wave	30	TNF-α, IL-1β

NOTE SD. Sprague-Dawley; EA. Electroacupuncture; TNF-α. Tumor necrosis factor-α; IL-1β. Interleukin-1β; IL-10. Interleukin-10.

3.3 Risk of bias Fig. 2 provides a clear illustration of the risk of bias in the efficacy analysis for each included RCT. Three studies were identified as having a high risk of bias, particularly with regard to their prospective matched control design and random sequence generation. A single study exhibited a low risk of bias with regard to allocation concealment, whereas six studies had outcome measures assessed by blinded evaluators. It is encouraging to note that all studies provided comprehensive reporting of the expected outcomes.

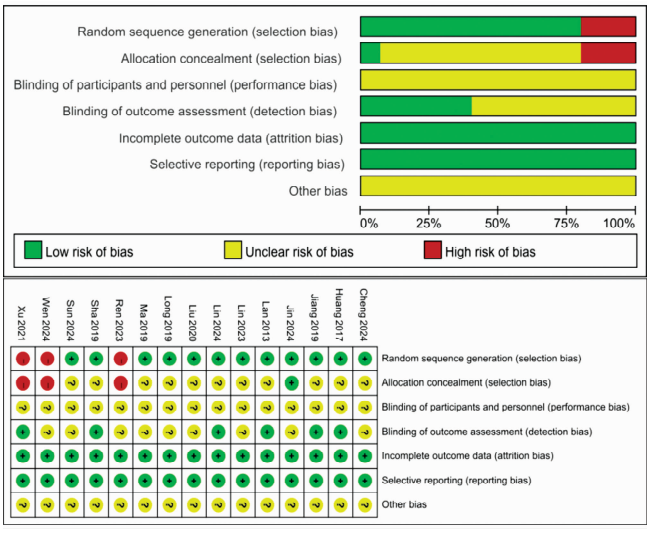
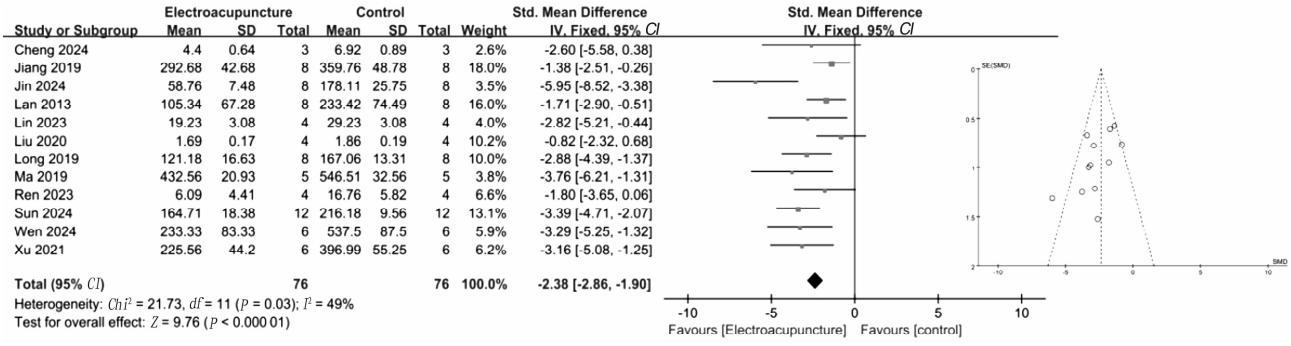


Fig. 2 Risk of bias in the included studies

3.4 Results from individual studies and synthesis of results

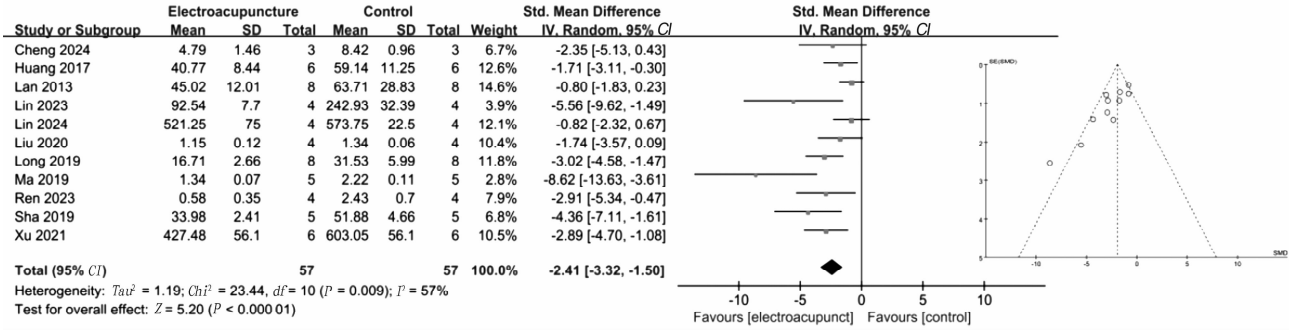
3.4.1 TNF-α. A comprehensive meta-analysis was conducted, employing a rigorous fixed-effects model. By pooling data from the 12 carefully selected studies, we observed a statistically significant reduction in the level of TNF-α, indicating a favorable outcome for the EA groups. Specifically, the SMD was calculated to be −2.38, with a 95% confidence interval ranging from −2.86 to −1.90 ($P<0.000\ 1$) (Fig. 3). Furthermore, our analysis underscored a substantial degree of heterogeneity among the studies included in the meta-analysis ($Chi^2=21.73$; $P=0.03$; $I^2=49$).

3.4.2 IL-1β. A meta-analysis was conducted using a random-effects model, which aggregated data from eleven carefully selected studies. The pooled analysis revealed a statistically significant decline in IL-1β levels, which favored the electroacupuncture groups. Specifically, the SMD was −2.41, with a 95% confidence interval of −3.32 to −1.50 ($P<0.000\ 01$), as illustrated in Fig. 4. This finding underscores the effectiveness of EA in reducing IL-1β levels. However, the meta-analysis also exposed a considerable degree of heterogeneity across the included studies, as indicated by the Chi^2 value of 23.44, the P-value of 0.009, and the I^2 statistic of 57. The observed heterogeneity suggests the need for future research to take into account potential variations in study designs, populations, or interventions.



NOTE To assess publication bias and heterogeneity, a funnel plot was utilized. The *P*-value, derived from the *z*-test, provided statistical significance, while I^2 indicated the degree of heterogeneity among the studies within each group.

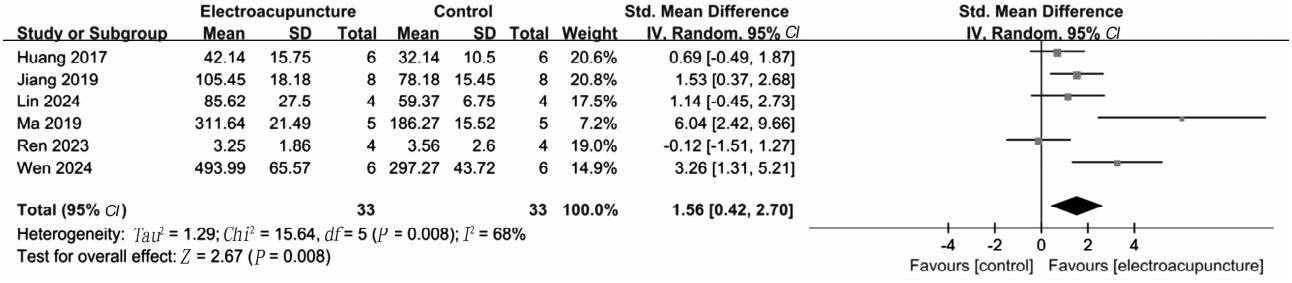
Fig. 3 Forest plot illustrating the overall impact of EA on TNF-α levels in animal models of cerebral ischemic stroke



NOTE To assess publication bias and heterogeneity, a funnel plot was utilized. The *P*-value, derived from the *z*-test, provided statistical significance, while I^2 indicated the degree of heterogeneity among the studies within each group.

Fig. 4 Forest plot illustrating the overall impact of EA on IL-1β levels in animal models of cerebral ischemic stroke

3.4.3 IL-10. A meta-analysis was carried out, employing a random-effects model and incorporating data from six rigorously selected studies. The compiled data showed a notable and statistically significant elevation in IL-10 levels, suggesting a positive effect for the EA groups, with a SMD of 1.56 (95% confidence interval ranging from 0.42 to 2.70) and a *P*-value of 0.008. This significant finding is vividly exhibited in Fig. 5, highlighting EA's effectiveness in boosting IL-10 levels. Nevertheless, the meta-analysis uncovered a considerable amount of heterogeneity across the included studies. This diversity was quantitatively assessed using statistical metrics, resulting in a Chi^2 value of 15.64, a *P*-value of 0.008, and an I^2 statistic of 68.



NOTE The *P*-value, derived from the *z*-test, provided statistical significance, while I^2 indicated the degree of heterogeneity among the studies within each group.

Fig. 5 Forest plot illustrating the overall impact of EA on IL-10 levels in animal models of cerebral ischemic stroke

4 Discussion

A comprehensive systematic review and meticulous meta-analysis were undertaken to assess the effects of electroacupuncture on the inflammatory response within the cerebral ischemic stroke model. The primary findings of this rigorous meta-analysis indicate that electroacupuncture stimulation is remarkably effective in reducing proinflammatory cytokines such as TNF-α and IL-1β, while simultaneously enhancing the production of the anti-inflammatory cytokine IL-10.

4.1 Cytokines/chemokines The inflammatory response that occurs following an ischemic stroke is characterized by the activation of leukocytes within the cerebral vasculature, a surge in in-

flammatory mediators, and abnormal vascular reactions[24]. Through the administration of acupuncture at the Quchi and Zusanli points, a significant reduction in the levels of pro-inflammatory cytokines, including interleukin-1beta (IL-1β), IL-6, and tumor necrosis factor alpha (TNF-α), has been observed in ischemic stroke rat models[9]. The acupuncture treatment has been demonstrated to mitigate ischemic brain injury, inhibit cytokine-driven inflammatory responses, and suppress leukocyte infiltration. It accomplishes this by hindering white blood cell infiltration, fostering nerve function recovery, downregulating the expression of IL-1β and TNF-α, and upregulating the expression of IL-10. Furthermore, acupuncture has been demonstrated to reduce the expression of IL-6, IL-1β, and TNF-α, thereby inhibiting the activation of microglial cells in ischemic brain tissue. This suggests that the activation of microglial cells may be closely linked to acupuncture's anti-inflammatory effects. The acupuncture treatment targeting the Baihui and Shenting points has been demonstrated to effectively reduce the overexpression of purinergic ion channel type 7 (P2X7R)-mediated inflammatory cytokine IL-1β in spinal cord microglial cells, thus alleviating pain hypersensitivity[15].

4.2 Nuclear transcription factor (NF-kappaB) signaling pathway NF-kappaB, a pivotal transcriptional regulator within cells, typically exists in a quiescent state as a heterodimer of p50-p65, complexed with its inhibitory protein IKB. Upon activation by various stimuli, including viruses, TNF, B cell activation factor, and lymphotoxin, NF-kappaB triggers the expression of numerous genes, thereby regulating the production of cytokines that are essential for inflammatory responses[25]. Among these cytokines, those induced by NF-kappaB and linked to chronic inflammatory reactions encompass a range of proteins, including cytokines, chemokines, adhesion molecules, and enzymes that generate secondary inflammatory mediators such as COX-2 and inducible nitric oxide synthase (iNOS)[26]. Interestingly, electrostimulation of specific acupoints, including Baihui, Hegu, and Taichong has been shown to hinder the expression of the neuronal chemokine CX3CL1, restrain NF-kappaB's nuclear translocation, and consequently suppress the activation of proinflammatory cytokines and microglial cells in the vicinity of infarction[27]. The anti-inflammatory effect of electroacupuncture is achieved by the inhibition of the neuronal NF-kappaB pathway, which is associated with the elevated expression of zinc finger protein A20 in rat ischemic brain neurons[28]. Furthermore, the anti-inflammatory effect observed with acupuncture at Quchi and Zusanli points may be attributed to the activation of the miRNA-9/NF-kappaB signaling pathway[29].

4.3 Signal transducer and activator of transcription (STAT) STAT, a nuclear transcription factor, typically responds to a diverse array of extracellular signals, including cytokine and growth factor signals. It belongs to a class of SH2 signal molecules that harbor tyrosine phosphorylation binding sites[30]. Recent research indicates that the down-regulation of STAT expression, which is triggered by electroacupuncture, shows considerable promise as a treatment for both chronic and acute ischemic stroke in rats[31]. Notably, targeted single electroacupuncture stimulation at the Baihui and Shuigou acupoints has been demonstrated to significantly enhance the levels of STAT5a, Stat5b, and Stat6, whereas multiple sessions of electroacupuncture have been shown to result in a remarkable decrease in the expression of STAT1 and Stat2[31]. Furthermore, electroacupuncture has been demonstrated to effectively diminish the peak expression of heat shock protein 70 (Hsp70) and adrenocorticotropic hormone (ACTH), thereby fostering neuronal repair, mitigating inflammatory reactions, and suppressing excessive stress responses[32].

5 Conclusions

A thorough systematic review and meticulous meta-analysis have been conducted to evaluate the impact of electroacupuncture on inflammatory responses within a cerebral ischemic stroke model. The key findings of this rigorous analysis reveal that electroacupuncture stimulation is exceptionally efficacious in diminishing proinflammatory cytokines, including TNF-α and IL-1β, while concomitantly augmenting the production of the anti-inflammatory cytokine IL-10. Further research is required in the form of large, high-quality RCTs to explore the optimal protocol of electroacupuncture at different stages of stroke recovery.

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