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Clinical study of ligustrazine combined with radial extracorporeal shock wave therapy in stroke patients with upper limb spasticity

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Abstract: Upper limb spasticity is a common and serious sequelae in patients with hemiplegia after stroke. Radial extracorporeal shock wave therapy (rESWT) can improve upper limb dysfunction and relieve pain in patients, However, its efficacy as a single treatment is limited. In traditional Chinese medicine, Tetramethylpyrazine (TMP) is the main pharmacological component of *Ligusticum chuanxiong*. It exhibits significant effects on the prevention and treatment of ischemic cerebrovascular diseases, protecting against cascade reaction-induced damage. This study encompassed 120 stroke patients with upper limb spasticity and limited elbow mobility who were admitted to the Second Rehabilitation Hospital of Shanghai from March 2021 to March 2023. They were divided into 3 groups: A rESWT group received rESWT, a TMP group received TMP and a Coalition group received TMP combined with rESWT. Statistical analysis and evaluation were conducted using SPSS 29.0. The research findings revealed that compared with the rESWT group and TMP group, the Coalition group showed more significant improvements in FMA, MAS, VAS scores, spasticity of elbow flexors, NIHSS and BI scores after 4 weeks of treatment. The combination of rESWT and TMP can enhance spasticity in stroke patients with upper limb spasticity, alleviated pain, and improved motor function and neurological functions.

Keywords: Stroke, upper limb spasticity, ligustrazine, radial extracorporeal shock wave therapy, nerve function.

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INTRODUCTION

Stroke is a cerebrovascular disorder characterized by vascular obstruction. Annually, approximately 15 million individuals suffer from stroke (Feigin *et al*., 2023). Stroke constitutes a primary cause of death and dysfunction in Pakistan, and the incidence of stroke is higher in urban areas as compared to rural areas (Sana *et al*., 2023). Upper limb flexor spasm is a movement disorder that manifests as a speed-dependent hyperactive stretch reflex and commonly occurs as sequelae in hemiplegic stroke patients, with an incidence ranging from 17% to 66% (Tashiro *et al*., 2021, Du *et al*., 2022). Studies have demonstrated the close relationship between upper limb function and daily activities. Long-term upper limb muscle spasm can lead to joint stiffness and contracture deformity, etc. In severe cases, it may lead to spastic hemiplegia, thereby impacting patients' self-care abilities and overall quality of life (Alashram *et al*., 2019).

Extracorporeal shock wave therapy (ESWT) is a non-invasive physical therapy method characterized by the delivery of a series of single-velocity pulses with high peak pressure, short duration and rapid pressure rise through the skin to the affected area using an appropriate generator. It is widely utilized for treating various orthopedic and neurological diseases (Senarath *et al*., 2023, Wu *et al*., 2016). ESWT is available in both focused and divergent forms, with radial extracorporeal shock wave therapy (rESWT) becoming popular due to its applicability and lower cost. Recent studies have shown that ESWT represents a novel approach for managing spasticity, effectively reducing lower limb spasticity in stroke patients. However, it should be noted that the impact of a single treatment session is limited as patients may still experience residual neurological deficits post-treatment. Additionally, patients with cerebral thrombosis and cerebrovascular blockage are at risk of thrombus shedding which can lead to severe consequences (Mihai *et al*., 2021, Yang *et al*., 2021).

Drug treatment includes oral baclofen, tizanidine, eperisone, injection of botulinum toxin type A, edaravone, and xesetong, etc. Although these interventions can alleviate limb spasm and safeguard brain tissue, their efficacy varies in patients. Long-term use may lead to varying degrees of side effects such as fatigue, lethargy, and impairment of heart, brain, liver and kidney functions. Additionally, the cost associated with these treatments is relatively high, which further burdens families (Pinho *et al*., 2023, Vazquez *et al*., 2024). Therefore, there is an urgent need to explore more effective and safer therapeutic approaches.

In traditional Chinese medicine (TCM), upper limb spasm after stroke belongs to the category of 'tendon disease', 'spasm' and 'spasm syndrome'. The lesion is located in the tendons. TCM believes that this disease results from disharmony between yin and yang, the imbalance of cold

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and heat, qi-blood disharmony and inadequate nourishment of the tendons and veins. The treatment should focus on balancing yin and yang, reconciling qi and blood, dredging meridians and veins and warming tendons (Wu *et al*., 2024, Zhang *et al*., 2020).

Ligustrazine (Tetramethylpyrazine, TMP) is the main pharmacological component of alkaloids extracted from the root of *Ligusticum chuanxiong*. It exhibits significant effects on the prevention and treatment of ischemic cerebrovascular diseases, protecting against cascade reaction-induced damage. Its efficacy has been validated through clinical and experimental studies (Lin *et al*., 2022, Zhai *et al*., 2019, Wu *et al*., 2019). Neuroplasticity serves as the theoretical foundation for neurorehabilitation, with numerous studies focusing on neuroprotection in ischemic brain injury. TMP is used in clinical treatment for ischemic stroke, playing a role in restoring nerve function after cerebral ischemia through various mechanisms such as vasodilation, improves blood circulation, pain relief, inactivation of free radicals, calcium overload inhibition, suppression of apoptosis, and inflammatory response inhibition (Lin *et al*., 2021, Liu *et al*., 2022). Currently, there are limited clinical reports regarding the combination of TMP with rESWT for upper limb spasticity in stroke patients. Therefore, this study aims to verify the application value of TMP combined with rESWT in upper limb spasticity in patients with stroke through clinical trials.

MATERIALS AND METHODS

Research design

A total of 120 patients with cerebral apoplexy accompanied by upper limb spasm and limited elbow range of motion were selected from the rehabilitation ward of our hospital between March 2021 and March 2023. The inclusion criteria were: (1) Patients who met the diagnostic criteria of upper limb muscle spasm caused by stroke (Wang *et al*., 2023), confirmed by CT scan and presenting with limited elbow range of motion; (2) Age range of 35-65 years old, with first onset of disease and a disease duration between 3 to 12 months; (3) Upper limb dysfunction assessed using Fugl-Meyer Assessment (FMA); (4) Limited flexion and extension function of the elbow joint, with limited elongation >30° and flexion angle <120°; (5) table condition, capable of understanding and cooperating with treatment; (6) Patients signed informed consent. The exclusion criteria were: (1) Non-first onset or disease duration >12 months; (2) Upper limb spasm not caused by a stroke after examination; (3) Patients who cannot tolerate extracorporeal shock wave; (4) Patients with severe cognitive impairment; (5) Patients with serious organ diseases and contraindications; (6) Those who have received botulinum toxin injection or oral antispasmodic treatment. They were divided into 3 groups: A rESWT group received rESWT, a TMP group received TMP and a Coalition group received TMP combined with divergent extracorporeal shock wave therapy. Each group consisted of 40 patients. This study has been reviewed and approved by the ethics committee of our institution.

Treatment methods

For the rESWT group, The Dolor Clast® radical shock waves produced by EMS Dolor Clast company (Switzerland) were used, with patients positioned supine on the bed. The coupling agent was evenly applied to the abdominal skin overlying the biceps brachii and flexor carpi ulnalis muscles at their ventral aspect. The probe was firmly pressed against the abdominal muscle of the spastic flexor, applying a pressure of 2.0 bar and a frequency of 8 Hz; each session consisted of 4000-6000 pulses, followed by a 15-minute rest period after treatment. No significant discomfort was reported prior to discharge. rESWT were conducted once per week for a continuous duration of 4 weeks.

For the TMP group, the TMP hydrochloride injection (Sinopharmate code: H20055479, specification: 50 mg, Zhengzhou Zhuofeng Pharmaceutical Co., LTD., China) was diluted in 250-500mL of 5%-10% glucose injection. The infusion time was controlled at approximately 3 hours, with once-daily administration for a total of two courses lasting 14 days each (The intervention process is shown in fig. 1).

For the Coalition group, the administration of combined TMP hydrochloride injection and rESWT followed the same specific method as that of the rESWT group and TMP group, respectively.

Observation indexes

Motor function assessment: The FMA assessment was adopted (Hiengkaew *et al*., 2012), with upper limb function scoring 66 points and lower limb function scoring 34 points. A lower score indicates poorer motor function in the limbs.

Muscle tone assessment: The modified ashworth scale (MAS) (Hiengkaew *et al*., 2012) was used to evaluate muscle tone, comprising 5 grades ranging from level 0 to 4 (0 to 4 points). A lower score indicates reduced muscle tension.

Intensity of pain: The visual analogue scale (VAS) (Reed and Van Nostran, 2014) was used to assess the intensity of pain, with a score ranging from 0 to 10. The VAS score demonstrated a direct correlation with the intensity of pain.

Degree of upper limb spasticity: A HUMAC NORM isokinetic machine (CSMI Company, USA) was used to evaluate the degree of spasm of the elbow flexor muscle in patients. Passive stretching of the elbow joint was performed at angular velocities of 5/s and 120/s, while measuring resistance in the absence and presence of

spasticity response, respectively. The evaluation parameter was peak torque (PT), representing the highest point on the torque curve (unit: N·M). A higher PT value indicates greater resistance and more severe spasms.

NIH Stroke Scale/Score (NIHSS) score and Barthel index (BI) score: The NIHSS (Kwah and Diong, 2014) was used to evaluate the neurological defects of the patients, with a total score of 42. A higher score indicates more severe neurological deficits. The BI (Huybrechts and Caro, 2007) was used to assess the patients' activities of daily living, with a total score of 100 which is directly proportional to their functional independence.

STATISTICAL ANALYSIS

Data analysis was performed using SPSS 29.0 software. Count data were presented as rates (%) and analyzed using the $\chi 2$ test, while continuous data were presented as mean ± standard deviation (SD) and analyzed using the t-tests. The statistical significance was defined as a level of $P < 0.05$.

Ethical approval

This study was approved by the Second Rehabilitation Hospital of Shanghai Ethics Committee (Grant No. 2023-04-01).

RESULTS

Baseline information

There was no significant difference in baseline information among the three groups ($P>0.05$) (table 1).

Comparison of motor function, muscle tone and Pain level in different groups

Before treatment, there was no significant difference in FMA, MAS, and VAS scores in the Coalition group, rESWT group, and TMP group ($P>0.05$). After 2 and 4 weeks of treatment, the FMA scores of upper limbs improved in the three groups, while the MAS and VAS scores significantly decreased. The Coalition group showed the most significant improvement in the FMA, MAS, and VAS scores of upper limbs at each time point after treatment compared to the other two groups (all $P< 0.05$) (fig. 2).

Comparison of degree of upper limb spasticity in different groups

Before treatment, there was no significant difference in PT values of elbow joint at angular velocities of 5/s and 120/s in Coalition group, rESWT group, and TMP group (all $P>0.05$). After 4 weeks of treatment, the PT values of elbow joint at angular velocities of 5/s and 120/s decreased in all 3 groups, and the above indexes were lower in Coalition group ($P<0.05$) (table 2).

Comparison of NIHSS scores and BI scores in different groups

Before treatment, no significant difference was observed in the NIHSS and BI scores of the three groups ($P>0.05$). After 2 and 4 weeks of treatment, the BI scores improved and NIHSS scores significantly decreased in all the 3 groups. Notably, the Coalition group exhibited the most significant improvement in the NIHSS and BI scores compared to the other two groups ($P<0.05$) (fig. 3).

DISCUSSION

Upper limb spasticity is a serious sequelae of stroke, characterized by increased muscle tension, hyperstretch reflex, increased extension resistance and flexor spasm. If left untreated, it can lead to muscle shortening, contractures and pressure sores, thereby impairing patients' activities and functions (Liao *et al*., 2022, Liu *et al*., 2020). It has been reported that the treatment costs for patients with spasms after stroke are 4 times higher compared to those without spasticity (Milte *et al*., 2020). Therefore, implementing effective intervention methods is crucial for enhancing the prognosis of individuals with cerebral apoplexy.

rESWT is a high-energy mechanical wave composed of a series of single pulses, which can reach the peak voltage rapidly and has the characteristics of a short period and wide spectrum. It was first used in the lithotripsy treatment of kidney stones. With a deeper understanding of its mechanism, rESWT has been successfully applied in the treatment of various musculoskeletal diseases. In recent years, it has shown satisfactory efficacy in improving limb spasms after stroke and has become an emerging rehabilitation technology that attracts much attention due to its safety, non-invasiveness, painlessness, and long-lasting effects (Senarath *et al*., 2023, Lee *et al*., 2024). As rESWT enters the body radially, it is suitable for treating soft tissue diseases with fewer adverse reactions than focused shock wave therapy. Therefore, it is more commonly used to treat muscle spasms after stroke. Sohn *et al*. (Sohn *et al*., 2011) and Yang *et al*. (Yang *et al*, 2023) have explored the mechanisms of ESWT to relieve spasticity from the perspectives of electrophysiological and mechanical vibration stimulation respectively. However, expected results have not yet been obtained. Currently, one of the more recognized mechanism is that shock wave therapy can reduce the acetylcholine receptors in neuromuscular junctions. ESWT regulates the central nervous system by inducing nitric oxide synthesis, thereby alleviating spasms (Kenmoku *et al*., 2012). Relevant studies have also shown that ESWT effectively ameliorates limb muscle spasms and mitigates muscle strength decline, leading to improved motor function and reduced pain in patients. However, this treatment method also has some shortcomings. For instance, patients may still exhibit neurological deficits. Additionally, if ischemic stroke occurs in patients undergoing ESWT treatment, it can potentially trigger thrombosis and subsequently accelerate brain edema and ischemia-reperfusion injury.

Table 1: Baseline information

Group	Gender		Age (years)	Educational level			Course of disease (month)	Disease type	
	Male	Female		Junior high school and below	High school or technical secondary school	College or above		Hemorrhagic	Ischemic
Coalition group (n=40)	24(60.00)	16(40.00)	53.85±9.56	11(27.50)	17 (42.50)	12(30.00)	7.60±2.05	13(32.50)	27(67.50)
TMP group (n=40))	25(62.50)	15(37.50)	54.05±9.37	8(20.00)	17(42.50)	15(37.50)	7.51±1.95	17(42.50)	23(57.50)
rESWT group (n=60)	21(52.50)	19(47.50)	53.67±9.67	13(32.50)	18(45.50)	9(2250)	7.71±2.10	14(35.00)	26(65.00)
χ^2/F	0.891		0.081		2.726		0.098	0.933	
P	0.640		0.982		0.605		0.907	0.627	

Table 2: Degree of upper limb spasticity in different groups

Group	5 /s constant velocity passive drafting test PT value		120 /s constant velocity passive drafting test PT value	
	Pre-treatment	After 4 weeks of treatment	Pre-treatment	After 4 weeks of treatment
Coalition group (n=40)	5.23±1.30	3.54±0.70[a]	9.61 ± 2.15	6.17 ± 1.40[a]
TMP group (n=40)	5.28±1.28	4.83±1.04[a]	9.55 ± 2.05	8.56 ± 1.86[a]
rESWT group (n=40)	5.31±1.33	4.25±0.90[a]	9.50 ± 2.02	7.67 ± 1.77[a]
F	0.038	20.947	0.028	20.518
P	0.963	<0.001	0.972	<0.001

Note. a, <0.05.

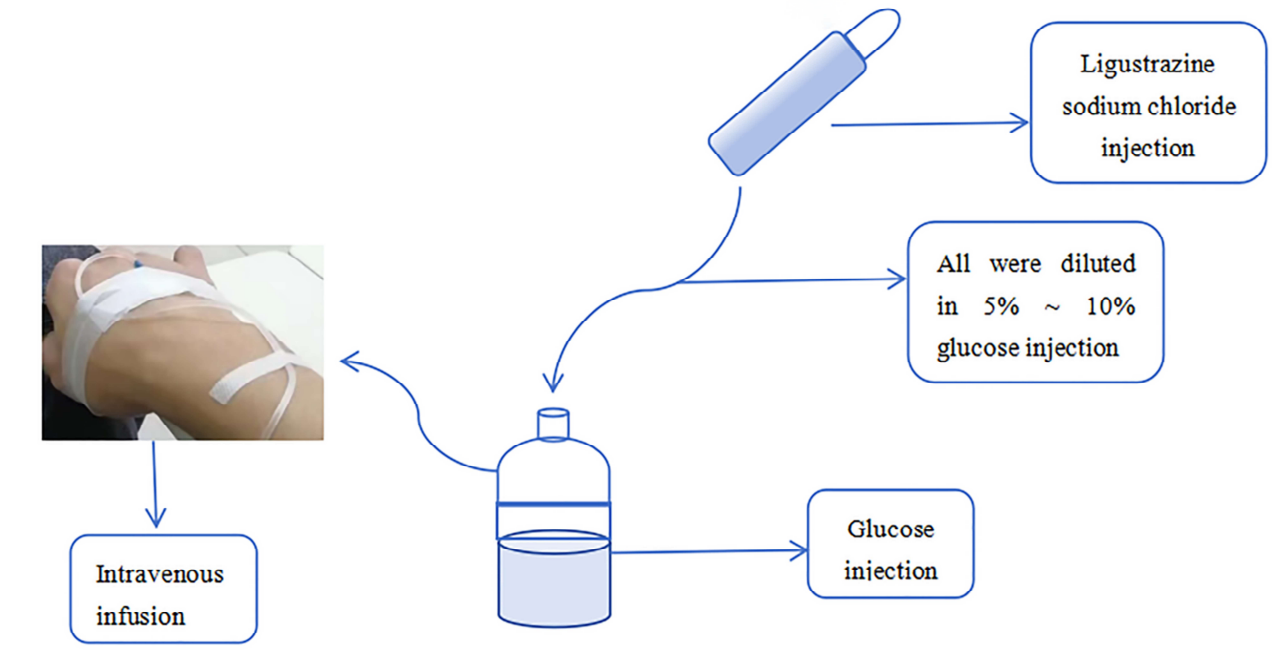

Fig. 1: Intervention flow chart.

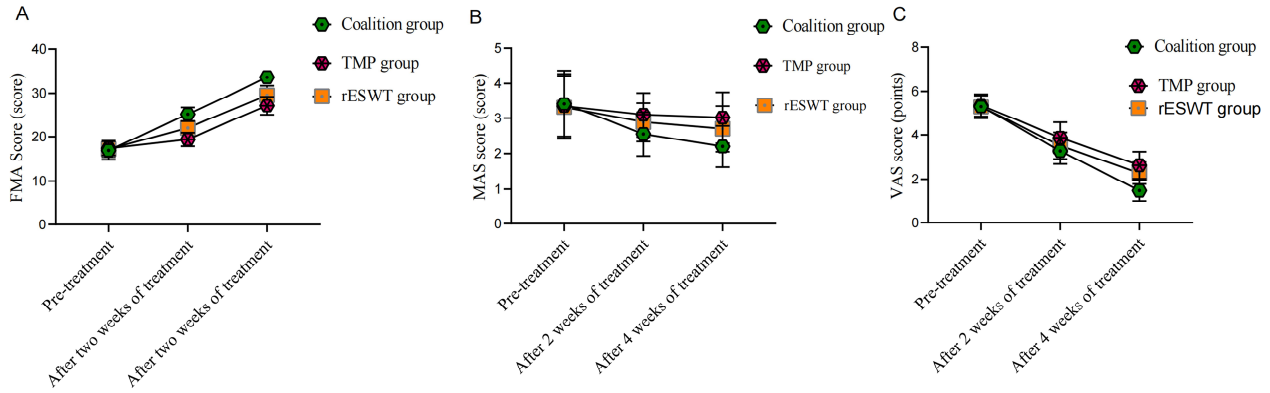

Fig. 2: Motor function assessment, muscle tone assessment, pain degree of patients before treatment, 2, 4 weeks after treatment; (A) FMA score, (B) MAS score, (C) VAS score.

Moreover, cerebral edema serves as a primary factor to cytotoxicity in patients with ischemic stroke. The occurrence of cerebral edema shortly after an ischemic event may promote the formation of cerebral ischemic penumbra, which further compromises cerebral nerve function (Dymarek *et al*., 2020).

The drug treatment of upper limb spasticity focuses on alleviating limb spasms, thrombolysis, anticoagulation, and vascular clearance. However, its efficacy remains limited. Long-term drug treatment may lead to varying degrees of side effects. Some patients are unable to fully care for themselves due to the complications of the disease.

Based on the understanding of the etiology and pathogenesis of apoplexy, it is believed that the etiology of apoplexy mainly involves wind-fire-phlegm-stasis deficiency in the brain. TCM has made significant progress in treating upper limb spasticity after apoplexy. The current treatment methods mainly include activating blood stasis, supplementing qi and blood, eliminating phlegm, regulating liver function, clearing heat and removing toxins, dispelling wind and activating collaterals, as well as improving brain functions. These approaches have proven to be highly effective in clinical practice.

Ligustrazine injection is commonly used for the treatment of ischemic cerebrovascular diseases. Its active component TMP is an alkaloid monomer and the main active component of *Ligustrum chuanxiong*. TMP exerts neuroprotective effects by inhibiting neuronal apoptosis (Ye *et al*., 2023). Relevant studies have confirmed that TMP has a good effect in inhibiting calcium overload and inducing vasodilation. Moreover, it has the effects of scavenging free radicals and inhibiting apoptosis and reducing inflammatory response. The application of TMP in the treatment of ischemic stroke contributes to enhancing neurological function recovery in patients (Qi *et al*., 2024, Feng *et al*., 2023). In addition, TMP exhibits potent inhibition of arachidonic acid synthesis, platelet activating factor, platelet aggregation induced by adenosine diphosphate, while also inducing platelet depolymerization.

In this study, by comparing the three treatment regiments, we found that the FMA, MAS and VAS scores of the upper limbs in the Coalition group, rESWT group and TMP group were similar before treatment. After 2 and 4 weeks of treatment, the FMA scores of upper limbs in all the 3 groups improved, while the MAS and VAS scores significantly decreased. Notably, the rESWT group demonstrated higher improvements compared to the TMP group.

The Coalition group showed the most significant improvement in the FMA, MAS and VAS scores at each time point after treatment (P<0.05). After 4 weeks of treatment, the PT values of elbow joint at angular velocities of 5/s and 120/s decreased in all 3 groups, with the Coalition group showing significantly lower values compared to the other two groups (P<0.05). The study demonstrated that combining ligustrazine injection with rESWT effectively alleviated limb spasm and improved upper limb function in stroke patients. Furthermore, compared to pre-treatment levels, both the BI scores increased and NIHSS scores decreased significantly after 2 weeks and 4 weeks of treatment in all three groups. However, these improvements were more pronounced in the Coalition group (all P<0.05). These findings suggest that ligustrazine injection combined with rESWT can effectively enhance neurological impairment recovery in patients, potentially exerting a neuroprotective effect (fig. 4).

CONCLUSION

In this study, we found that the combined treatment of rESWT and TMP effectively ameliorated upper limb spasticity, alleviated pain and improved motor function and nerve function in stroke patients.

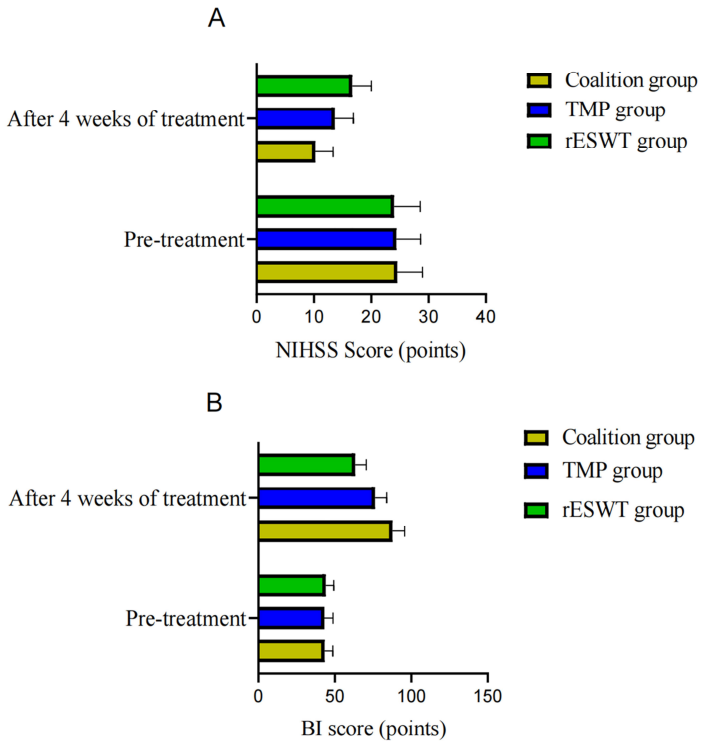

Fig. 3: NIHSS score and BI score, (A) NIHSS score, (B) BI index.

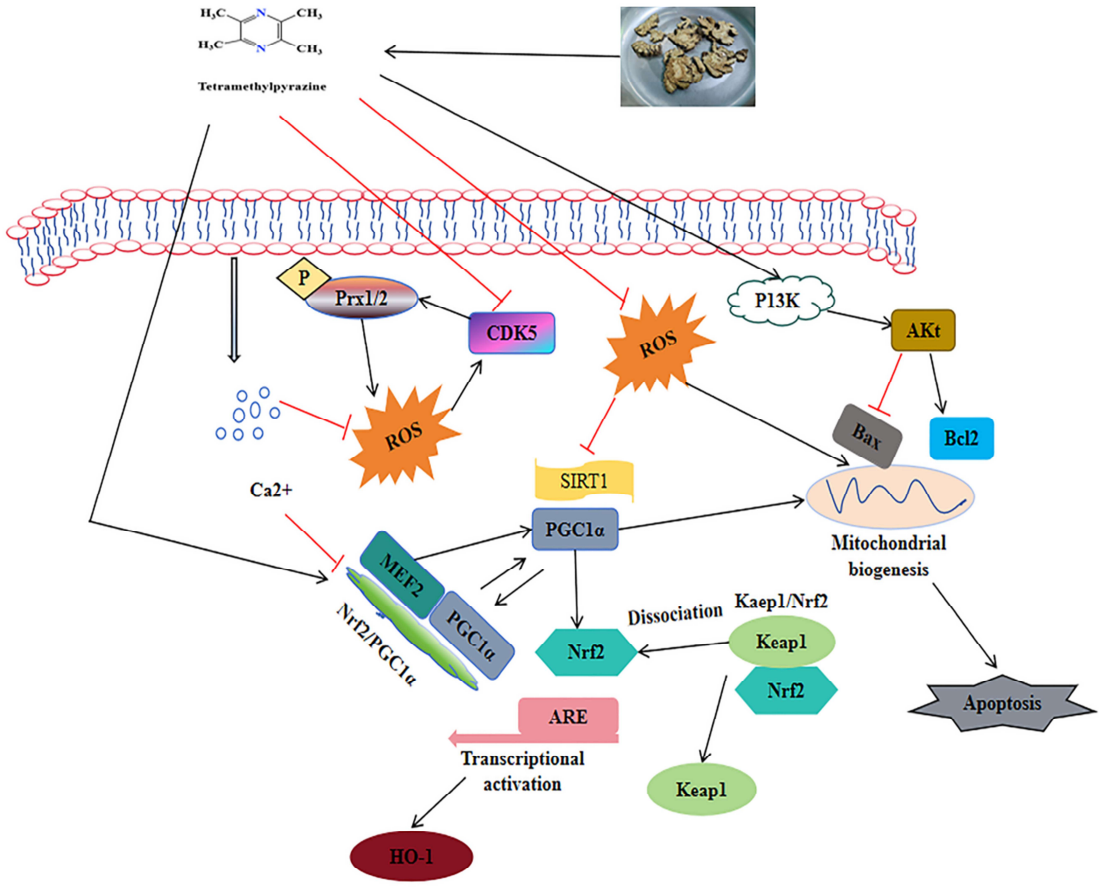

Fig. 4: Possible mechanisms of action of TMP.

Furthermore, this study elucidated the potential mechanism by which TMP enhances neurological impairment in these patients, providing valuable insights for the clinical application of TMP in treating post-stroke upper limb flexor spasm and laying a foundation for future research on the synergistic effects of TCM preparations and physical therapy.

Conflict of interest

The authors have no conflicts of interest to declare.

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