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Effect of SanQiTongShuan on Rats in Stroke Recovery Period

Chunhua Hao[1], Weiting Wang[1], Rui Zhang[1], Xianghua Zhang[2], Feng Guo[2], Zhuanyou Zhao[1] and Lida Tang[1*]

[1]State Key Laboratory of Pharmacokinetics and Pharmacodynamics, Tianjin Institute of Pharmaceutical Research, Tianjin 300193, PR China.
[2]Kunming Institute of Nephrology, Kunming 650000, PR China.

Authors' contributions

This work was carried out in collaboration between all authors. Authors CH, WW, RZ, ZZ and LT designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author WW contributed equally to this work and should be considered co-first authors. Authors XZ and FG managed the analyses of the study. Author RZ managed the literature searches. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Objective: This study aims to investigate the therapeutic effect and possible mechanisms of Chinese Medicine SanQiTongShuan(SQTS) on rats in stroke recovery period.
Methods: The cerebral ischemia stroke recovery period model was successfully induced by $FeCl_3$ after the fourth day and balance beam test≤4. A total of 70 rats were used in experiments. 60 model rats were divided into six groups (n=10). The model group was administered 0.5% carboxymethylcellulose sodium (CMC), the treated groups were administered SQTS (0.5, 1, 2 g /kg), and the positive control groups were administered Naodesheng (NDS, 1.24 g /kg) and Vinpocetine (VP, 1.55 mg/kg). In addition, the other 10 rats served as a sham group and were administered 0.5% CMC. Rats in the each group were treated each day last for 30 days orally with the volume of 10 ml/kg. The motor function of beam-walking test and forelimb muscle strength were

**Corresponding author: E-mail: tangld@tjipr.com;*
Email: 23006858@163.com;

performed before the occlusion and lasted for 10, 20 and 30 d after administration. The serum inflammatory factors IL-1β, IL-6, TNFα, ICAM-1 and VCAM were measured by assay kits. In addition, the optical microscopic examination of the serial sections of impact areas was performed.
Results: The ischemic rats displayed signs of brain damage on motor function, forelimb muscle strength and histopathology. SQTS (0.5, 1.0, 2.0 g /kg) restored the beam-walking scores by 14.8% (*P>0.05*), 22.2%(*P>0.05*), 37%(*P<0.05*) after 20 d treatment and 24.0%(*P>0.05*), 48.0%(*P<0.05*), 40.0%(*P<0.05*) after 30 d treatment; increased the strength by 39.0%(*P>0.05*), 45.6%(*P>0.05*), 54.0%(*P<0.05*) after 20 d treatment and 40.3%(*P>0.05*), 43.7%(*P<0.05*), 54.5%(*P<0.05*) after 30 d treatment. On the other hand, the histological changes were less severe and the inflammatory factors IL-6, TNFα, VCAM were decreased at the different degree, with respect to the model group.
Conclusion: We proposed that SQTS, a promising Traditional Chinese Medicine Patent Prescription, can be used as a therapeutic agent for stroke recovery period via alleviating inflammatory responses.

Keywords: SanQiTongShuan; stroke recovery period; rats; motor function; inflammatory factors.

1. INTRODUCTION

Ischemic stroke is a common disease with the characteristics of high incidence, high mortality, severe morbidity, high recurrence rate and serious complications, and it imposes a huge economic burden on the family and the society [1,2]. Stroke recovery period is generally from 2 weeks to 6 months after the onset of cerebral infarction, substantial functional recovery can take place in the first weeks [3], so early treatment is important for prognosis. Chinese Herbal Medicines, an essential part of Traditional Chinese Medicine, become more and more important in curing such chronic diseases [4]. SanQiTongShuan (SQTS) is a Traditional Chinese Medicine Patent Prescription including Panax pseudo-ginseng, *Carthamus tinctorius* and *Moschus berezovskii* Flerov, has been widely deemed to promot blood circulation for removing blood stasisused. In this study, we investigated the therapeutic effects of SQTS on rats in stroke recovery period, and the possible mechanism of these effects.

2. MATERIALS AND METHODS

2.1 Animals

Adult male Sprague Dawley rats weighing 260 to 300 g [SCXK(JING)2012-0001] were obtained from Vital River Laboratory Animal Technology Co. Ltd. This study was carried out in strict accordance with the recommendations of AAALAC, and approved by IACUC of Tianjin Institute of Pharmaceutical Research.

2.2 Drugs, Reagents and Devices

Sanqitongshuan powder (SQTS, batch number 130712) was from Kunming Institute of Nephrology (Yunnan, China). Naodesheng (NDS, batch number 20130801) was from Harbin Huayu Pharmaceutical Group Co., Ltd. (Heilongjiang, China); Vinpocetine (VP, batch number 5131002) was from Northeast Pharmaceutical Group Shenyang No.1 pharmaceutical Co., Ltd. (Shenyang, China).

Reagents including ICAM-1 (batch number 201403), VCAM-1 (batch number 201403), IL-1β (batch number 201403), IL-6 (batch number 201403), TNFα (batch number 201403) ELISA assay kit were from Bio-Swamp Life Science Lab (Wuhan, China); Device including YLS-13A grasping tester was from Shandong Academy of Medical Sciences Ji'nan Yiyan Science and Technology Development Co., Ltd. (Shandong, China); Leika VT 1000S vibratome was from Leica, (Heiderberg, Germany).

2.3 Experimental Procedure

Sprague Dawley rats were anesthetized with an intraperitoneal injection of chloral hydrate 360 mg/kg, the cerebral ischemia model was made as same as Karatas HL reported [5]. The skin between right canthal and canal midpoint was dissected. After separation for the temporal muscle, the zygomatic arch was separated and cut off until the squamous part of the temporal bone was exposed. The trace of MCA was visualized after the squamous bone was removed using a high-speed drill, placed a piece of 50% $FeCl_3$-saturated filter paper (0.3×1 mm^2) over the middle cerebral artery for 30 min. After the filter paper was removed, the middle cerebral artery was washed with normal saline and the rats were applied penicillin 1.6 x 10^5/ U through intramuscular injection for three days.

The cerebral ischemia model was successfully established when balance beam test≤4 after the fourth day. The model rats were randomly divided into six groups: A, model (0.5% CMC); B, SQTS (0.5 g /kg); C, SQTS (1.0 g /kg); D, SQTS (2.0 g /kg); E, NDS (1.24 g /kg, clinical equivalent dose); F, VP (1.55 mg/kg, clinical equivalent dose). In addition, the rats in the sham group (without $FeCl_3$ incubation) were also given with 0.5% CMC. 10 rats in the each group were treated each day last for 30 days orally with the volume of 10 ml/kg.

2.4 Beam-walking Test [6,7,8]

The motor function was performed before the occlusion and lasted for 10, 20 and 30d of administration. The locomotion of rats was evaluated using a beam-walking test with an elevated narrow beam (122 cm long × 2.5 cm wide), one side of which using strength noise stimulation, the contralateral side was a black cage. The lowest score (a score of "1") was given if the animal was unable to traverse the beam and could not place the affected hind limb onto the horizontal surface. A score of "2" was given if the animal was unable to traverse the beam but placed the affected hind limb on the horizontal surface of the beam and maintained balance. A score of "3" was given if the animal traversed the beam while dragging the affected hind limb. A score of "4" was given if the animal traversed the beam and at least once placed the affected hind paw on the horizontal surface of the beam. A score of "5" was given if the animal used the affected limbs in fewer than half of its steps along the beam. The highest score (a score of "7") was given if the animal traversed the beam normally with no more than two feet slips.

2.5 Forelimb Strength Measurement [9]

The left forelimb muscle strength was measured by YLS-13A grasping tester before and 10, 20 and 30 d after treatment.

2.6 Histopathology

At the end of the experiment (at 30 d after treatment), rat brains were enucleated, fixed in 10% formaldehyde for 24 hours and then embedded in paraffin. Blocks were obtained from cutting through the whole globe coronally with Leika VT 1000S vibratome. Five-μm-thick sections were stained with Hematolxylin and Eosin (H&E) for light microscopic (LM) examination at ×20 magnification of the hippocampus CA1 and cortical region. The number of surviving neurons was counted.

2.7 Measurement of Inflammatory Factors

Samples of the serum supernatants from the rats were obtained at 30 d after treatment, and the inflammatory factors TNF-α, IL-1β, IL-6, ICAM-1, VCAM-1 were quantified with an ELISA kit according to the manufacturer's protocol.

2.8 Statistical Analysis

All results were expressed as mean±SD. Comparison between multiple groups was performed with one-way analysis of variance (ANOVA) followed by multiple comparison post hoc tests (LSD). P≤0.05 was considered statistically significant.

3. RESULTS

3.1 Effect of SQTS on Motor Function

Compared with the sham group, the motor function decreased significantly after 10, 20 and 30 d (*P<0.001*) in the model group. SQTS (0.5, 1.0, 2.0 g /kg) restored the scores by 14.8% (*P>0.05*), 22.2% (*P>0.05*), 37% (*P<0.05*) after 20 d treatment; 24.0% (*P>0.05*), 48.0% (*P<0.05*), 40.0% (*P<0.05*) after 30 d treatment. The positive control of NDS (1.25 g /kg) decreased by 25.9% (*P<0.05*), 20% (*P<0.05*) administered 20 d, 30 d treatment; VP(1.55 mg/kg) decreased by (*P<0.05*), 44.4% (*P<0.01*), 56% (*P<0.01*) in the treatment of 10, 20 and 30 d respectively. SQTS (1.0 g /kg) was stronger than NDS (48% vs 20%), weaker than VP(48% vs 56%). As shown in Table 1.

3.2 Effect of SQTS on Forelimb Muscle Strength

Compared with the sham group, the forelimb muscle strength of model group decreased significantly after 10, 20 and 30 d (*P<0.01～0.001*). SQTS (0.5, 1.0, 2.0 g/kg) increased the strength by 39.0% (*P>0.05*), 45.6% (*P>0.05*), 54.0% (*P<0.05*) after 20 d treatment; 40.3% (*P>0.05*), 43.7% (*P<0.05*), 54.5% (*P<0.05*) after 30 d treatment. The positive control of NDS (1.25 g/kg) increased by 41.3% (*P<0.05*), 45.0% (*P<0.05*) administered 20 d, 30 d treatment; VP (1.55 mg/kg) increased by 61.5% (*P<0.05*), 62.7% (*P<0.05*) in the treatment of

20 and 30 d respectively. SQTS (1.0 g /kg) was the same as Naodesheng (43.7% vs 45.0%), weaker than VP (43.7% vs 62.7%). As shown in Table 2.

3.3 Effect of SQTS on Pathohistology Changes and Numbers of Neurons

The optical microscopic examination of serial sections of impact areas demonstrated that there were no morphology changes in the sham group, cell nuclear membrane and clear nucleolus were integrated. In the model group, there was significant neuronal damage in the pyramidal cell layer of the hippocampal CA1 region, including the loose neurons arrangement, smaller number and volume, cytoplasm deepened dyeing and nuclear pyknosis. Cortical region cells arranged in irregular and were sparse, the nuclear shriveled and deeply dyed, the cytoplasm was eosinophilic. In each treatment group, these histological changes were less severe, differing in extent according to the dose of SQTS administrated. As shown in Figs. 1, 2.

Table 1. Effect of SQTS on motor function of rats in stroke recovery period ($\bar{x}\pm$s, n=10)

Group	Dose (g /kg)	Before treatment (scores)	After treatment (scores)		
			10 d	20 d	30 d
Sham	-	6.6±0.7	6.8±0.4 (0.2±0.4)	6.8±0.4 (0.2±0.4)	6.9±0.3 (0.3±0.7)
Model	-	3.2±1.5$^{\Delta\Delta\Delta}$	3.5±1.4$^{\Delta\Delta\Delta}$ (0.3±1.3)	4.1±1.3$^{\Delta\Delta\Delta}$ (0.9±1.0)	4.4±1.3$^{\Delta\Delta\Delta}$ (1.2±1.1)
SQTS	0.5	3.4±1.0	3.6±1.6 (0.2±1.6)	4.5±1.5 (1.0±1.6)	5.0±1.1 (1.5±1.4)
SQTS	1.0	3.3±1.3	3.4±1.3 (0.1±1.8)	4.7±1.5 (1.4±1.4)	5.6±0.5 (2.3±1.1*)
SQTS	2.0	2.8±1.3	3.9±2.0 (1.1±2.2)	5.1±1.0 (2.3±1.3*)	5.4±0.7 (2.6±1.3*)
NDS	1.24	2.4±1.2	3.7±1.5 (1.3±1.2)	4.8±1.3 (2.4±1.4*)	4.9±1.3 (2.5±1.3*)
VP	1.55 mg/kg	3.0±1.3	4.5±1.2 (1.5±1.2*)	5.3±0.8 (2.3±1.2**)	5.8±0.6 (2.8±1.2**)

*$^{\Delta\Delta\Delta}$P<0.001 compared with the corresponding data of sham group.*P<0.05, **P<0.01, compared with the corresponding data of model group. *P>0.05, compared SQTS (1.0 g/kg) with the corresponding data of NDS and VP. The difference before and after administration are available in brackets*

Table 2. Effect of SQTS on forelimb muscle strength of rats in stroke recovery period ($\bar{x}$ ±s, n=10)

Group	Dose (g /kg)	Before treatment (g force)	After treatment (g force)		
			10 d	20 d	30 d
Sham	-	1009.9±203.0	1016.2±179.6 (6.2±82.9)	1035.3±174.7 (25.3±97.1)	1059.7±232.2 (49.7±76.1)
Model	-	723.4±134.0$^{\Delta\Delta}$	750.3±107.5$^{\Delta\Delta\Delta}$ (27.0±123.9)	769.9±125.9$^{\Delta\Delta}$ (46.6±133.5)	775.3±122.9$^{\Delta\Delta}$ (51.9±168.2)
SQTS	0.5	752.7±125.6	810.9±157.7 (58.2±168.0)	873.3±133.4 (120.6±189.3)	889.8±116.8 (137.1±159.7)
SQTS	1.0	717.2±140.9	849.5±195.0 (132.3±134.6)	891.0±171.2 (173.8±151)	899.7±167.2 (182.6±99.9*)
SQTS	2.0	735.2±140.4	854.1±164.5 (118.9±172)	913.1±132.0 (177.9±137.6*)	930.4±167.9 (195.2±124.6*)
NDS	1.24	710.4±146.6	831.9±109.3 (121.5±135.3)	879.5±80.1 (169.0±109.0*)	903.4±81.6 (193.0±121.6*)
VP	1.55 mg/kg	745.8±110.2	883.1±79.5 (137.4±119.7)	933.2±115.8 (187.5±164.6*)	953.6±133.7 (207.8±154*)

$^{\Delta\Delta}$P<0.01, $^{\Delta\Delta\Delta}$P<0.001 compared with the corresponding data of sham group. *P<0.05, compared with the corresponding data of model group. *P>0.05, compared SQTS (1.0 g/kg) with the corresponding data of NDS and VP. The difference before and after administration are available in brackets

The number of neurons in hippocampal CA1 and cortical region of model group decreased significantly compared with sham group($P < 0.001$). SQTS (0.5, 1.0, 2.0 g/kg) increased neurons in hippocampal CA1 region by 13.5%(*P>0.05*), 28.6%(*P>0.05*), 35.5%(*P<0.05*); increased neurons in cortical motor region by 12.1%(*P>0.05*), 26.1%(*P<0.05*), 37.5%(*P<0.05*). The positive control of NDS and VP also increased neurons. As shown in Table 3, Fig.1, 2.

3.4 Effect of SQTS on Inflammatory Factors

Serum levels for IL-1β, IL-6, TNFα, ICAM-1 and VCAM-1 increased in the model groups (*P<0.05～0.01*). Treatment with SQTS (0.5, 1.0, 2.0 g/kg) dose-dependent decreased IL-6, TNFα, VCAM-1 respectively. IL-6 decreased by 22.1%(*P>0.05*), 63.2%(*P<0.05*), 69.3%(*P<0.05*); TNFα decreased by 19.0%(*P>0.05*), 64.1%(*P<0.05*), 75.3%(*P<0.05*); VCAM-1 decreased by 42.5%(*P>0.05*), 61.6%(*P>0.05*), 82.2%(*P<0.05*). So there might be a certain relationship between the protctive role of SQTS and IL-6, TNFα, VCAM-1. The positive control of NDS and VP also reduced IL-6, TNFα, VCAM-1. As shown in Table 4.

4. DISCUSSION

Ischemic stroke occurs because of a loss of blood supply to part of the brain, initiating the ischemic cascade. Brain tissue ceases to function if deprived of oxygen for more than a few minutes, and after approximately three hours

Table 3. Effect of SQTS on neurons numbers of rats in stroke recovery period ($\bar{x}$ ±s, n=10)

Group	Dose(g /kg)	hippocampal CA1 region(numbers)	Cortical region (numbers)
Sham	-	129.1±20.4	119.1±9.6
Model	-	84.0±19.3△△△	76.2±12.6△△△
SQTS	0.5	90.1±14.5	81.4±13.4
SQTS	1.0	96.9±11.7	87.4±10.4*
SQTS	2.0	100.0±11.9*	92.3±14.3*
NDS	1.24	97.1±15.2	93.9±15.1*
VP	1.55 mg/kg	108.7±16.4**	96.6±17.9*

*△△△P<0.001, compared with the corresponding data of sham group; *P<0.05, **P<0.01, compared with the corresponding data of model group; #P>0.05, compared SQTS (1.0 g/kg) with the corresponding data of NDS and VP*

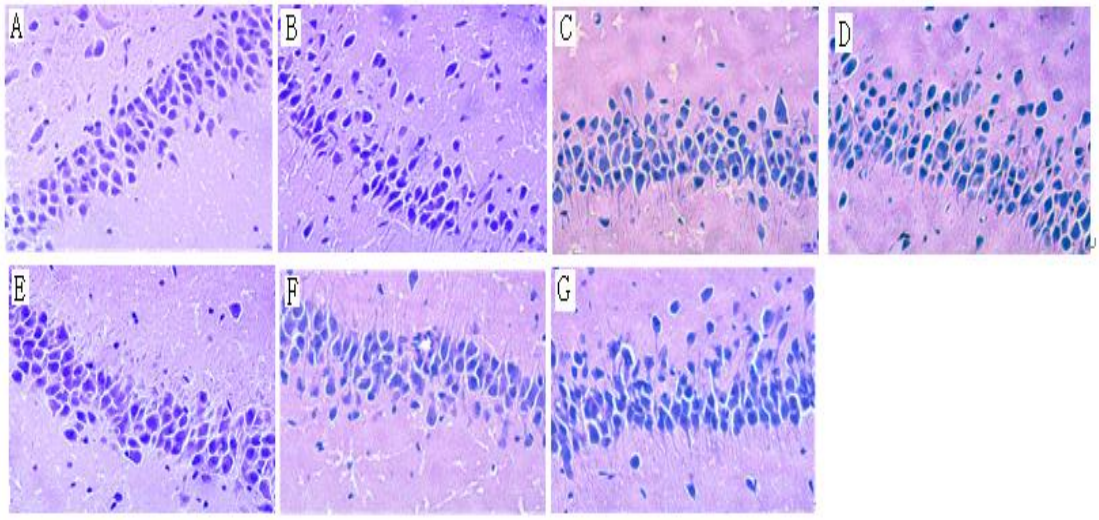

Fig. 1. Effect of SQTS on neurons numbers in hippocampal CA1 region (HE×200)
A: Sham; B: Model; C: NDS 1.24 g/kg; D: VP 1.55 mg/kg
E: SQTS 0.5 g/kg; F: SQTS 1.0 g/kg; G: SQTS 2.0 g/kg

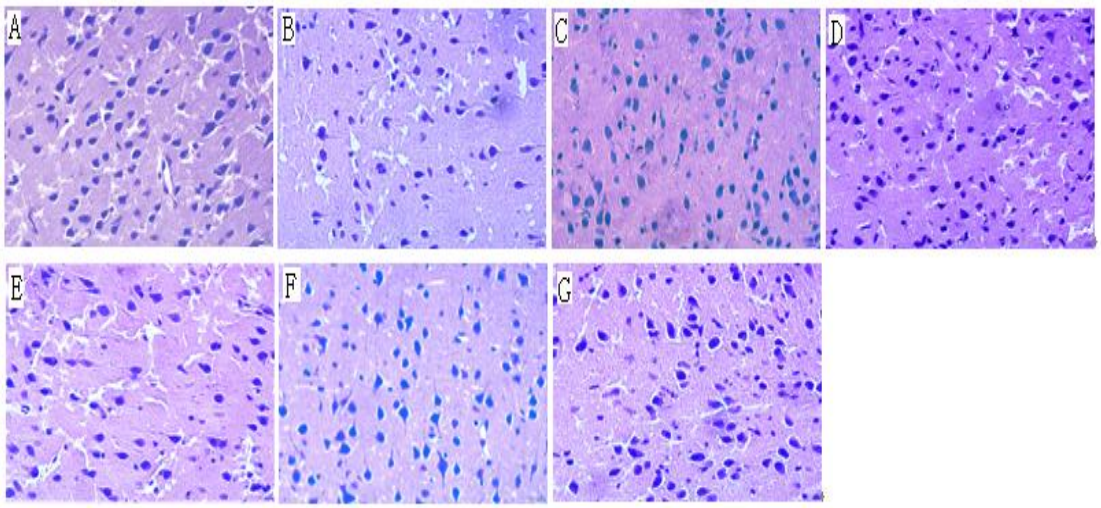

Fig. 2. Effect of SQTS on neurons numbers in cortical region (HE×200)
A: Sham; B: Model; C: NDS 1.24 g/kg; D: VP 1.55 mg/kg
E: SQTS 0.5 g/kg; F: SQTS 1.0 g/kg; G: SQTS 2.0 g/kg

Table 4. Effect of SQTS on Inflammatory Factors of rats in stroke recovery period ($\bar{x}\pm s$，n=10)

Group	Dose (g /kg)	IL-1β (pg/ml)	IL-6 (pg/ml)	TNF-α (pg/ml)	ICAM-1 (pg/ml)	VCAM-1 (pg/ml)
Sham	-	8.08±2.03	31.13±3.49	46.28±5.63	12.06±1.95	282.52±69.93
Model	-	10.36±1.51$^{\triangle}$	36.92±3.82$^{\triangle\triangle}$	56.23±7.33$^{\triangle\triangle}$	14.83±2.52$^{\triangle}$	364.18±67.4$^{\triangle}$
SQTS	0.5	9.73±1.16	35.64±3.88	54.34±4.45	14.42±2.09	329.44±86.59
SQTS	1.0	9.74±0.75	33.26±3.66*	49.85±5.50*	14.07±1.57	313.90±43.58
SQTS	2.0	9.31±1.05	32.91±3.85*	48.74±3.98*	13.56±2.38	297.04±43.27*
NDS	1.24	9.65±1.09	32.63±4.09*	49.76±2.58*	13.82±1.88	302.69±68.37
VP	1.55 mg/kg	9.31±1.27	31.33±3.44**	48.95±3.49*	13.18±2.78	300.40±58.72*

$^{\triangle}P<0.05$, $^{\triangle\triangle}P<0.01$, compared with the corresponding data of sham group. $^{*}P<0.05$, $^{**}P<0.01$, compared with the corresponding data of model group. $^{*}P>0.05$, compared SQTS (1.0 g/kg) with the corresponding data of NDS and VP

will suffer irreversible injury possibly leading to the death of the tissue, i.e., infarction. This is why fibrinolytics such as alteplase are given only until three hours since the onset of the stroke [10]. Due to very short of the treatment time window (3h), options for acute interventions (e.g., thrombolytic therapy for ischemic stroke) are limited to the minority of patients.The remaining patients are frequently left with profound neurological disabilities that substantially impact quality of life, economic productivity, and increase caregiver burden [11]. Recovery from stroke is a multifaceted process depending on different mechanisms that become operational at different phases after the acute insult ranging from hours to many months [12], and most recovery at both the impairment and functional level occurs in the first 3 months [13], so treatment at this stage is very important. Traditional Chinese medicine, with advantages of no drug resistance, lasting efficacy, safety for long-term use, is suitable for such chronic disease. SQTS composed with three medicinal plants including Panax pseudo-ginseng, *Carthamus tinctorius* and *Moschus berezovskii* Flerov. Panax notoginseng saponins are one of the most important compounds derived from roots of the herb Panax notoginseng which are traditionally used as a hemostatic medicine to control internal and external bleeding in China for thousands of years [14]. The present study verified the effect of 50 mg/L of Panax notoginseng saponin exposure following hypoxia-reoxygenation injury in fetal rat cortical neurons [15]. *Carthamus tinctorius* L., commonly known as Safflower, are widely used in traditional Chinese medicine in treating cerebrovascular and cardiovascular disease [16]. In addition, in

vivo and in vitro neuroprotective effects of *Carthamus tinctorius* extract on cerebral ischemic injury were reported that reduced neurological deficit scores in a rat infarction model [17,18]. Moschus is a dried secretion from the ripe, male musk cyst of *Moschus berezovskii* Flerov, M. sifanicus Przewalski, or M. moschiferus Linnaeus [19]. Moschus has been shown to contribute to bidirectional central nervous system modulation: low dose moschus excites the center, and high doses inhibit the center [20], and resuscitation have been reflected in aspects of sedative and hypnosis, anti-convulsion, anti-epilepsy, cerebral protection, anti-hypoxia [21]. All of these pharmaceutical composition were made and observed therapeutic effect on rats in stroke recovery period. In our experiments, the motor function and forelimb strength was decreased followed with neuronal damage in the pyramidal cell layer of the hippocampal CA1 region and cortical region at the recovery stage of ischemic stroke. It was confirmed that SanQiTongShuan significantly upgraded the scores and strength, suggested the restoring of the nervous system including movement, sensation and other neurological signs. On the other hand, the histological changes were less severe, differing in extent according to the dose of SQTS administrated.

Chinese herbal medicine NDS and VP were used as the positive control. NDS (including Radix Notoginseng, Hizoma Chuanxiong, Flos Carthami, Pueraria lobata, and Fructus Crataegi) ameliorates cerebral arterioclerosis, ischemic stroke, sequela of ischemic cerebrovascular disease. VP is a cerebral vasodilator that improves brain blood flow, and a cerebral metabolic enhancer by enhancing oxygen and glucose uptake and increasing neuronal ATP production, which has been widely used in many countries for the prevention of cerebrovascular disorders and cognitive impairment, including stroke, senile dementia, and memory disturbances [22]. Our experiment confirmed that SQTS (1.0 g/kg) could be capable of restoring neurons as the same as NDS (1.24 g /kg), weaker than VP (1.55 mg/kg).

Of the mechanisms responsible for brain damage pathogenesis after cerebral infarction, oxidative stress and inflammation may be the most crucial involved in ischemic stroke [23,24]. The global ischemia neurons in the CA1 and CA2 regions of the hippocampus, which are selectively vulnerable, undergo inflammatory and apoptosis after 3 to 7 days [25]. Pro-inflammatory cytokines such as IL-1β, TNFα, IL-6, VCAM-1, ICAM-1 are the principal mediators of the inflammatory reaction they are produced mainly by immune cells. Our experiments revealed that SQTS can decrease IL-6, TNFα, VCAM-1 levels in serum. These results indicated that SQTS might improved nerve reconditioning by anti-inflammatory. However, our results just only provide a basis for an investigation into the role of SQTS on rats in stroke recovery period. Further more studies should be done by other models, and other therapeutic mechanisms such as anti-oxadation and anti-apoptosis should be studied.

5. CONCLUSION

In summary, a rat model of $FeCl_3$ induced ischemic stroke recovery period was successfully established, and decrease of motor function and forelimb muscle strength accompany with histological changes was observed. SQTS can be used as a therapeutic agent for stroke recovery period via alleviating inflammatory responses.

CONSENT

It is not applicable.

ETHICAL STATEMENT

This study was carried out in strict accordance with the recommendations in the guidance on the treatment of experimental animals of China Ministry of Science and Technology and AAALAC animal ethics. The protocol was approved by the IACUC of Tianjin Institute of Pharmaceutical Research.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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