Heliyon 10 (2024) e39162

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Pharmacological efficacy study of the cardio-cerebral stasis transforming medicines on cerebral ischemia and myocardial infarction in rats

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ARTICLE INFO

Keywords:
Ischemic stroke
Traditional Chinese medicine
Cardio-cerebral stasis transforming medicines
Malondialdehyde
Myeloperoxidase

ABSTRACT

The purpose of this study was to investigate the efficacy and mechanisms of cardio-cerebral stasis transforming medicines (CCSTM) against cerebral infarction (CI) and myocardial infarction (MI). CI modeling was conducted using the refined Longa suture-occluded technique, while MI modeling was accomplished through the occlusion of the anterior descending branch of the left coronary artery. We found that compared with the model groups, CCSTM decreased the infarct size in models of CI and MI in a dose-dependent manner. After brain ischemia, CCSTM decreased the level of myeloperoxidase (MPO) and malondialdehyde (MDA), and increased the level of superoxide dismutase (SOD). Besides, CCSTM reduced the concentrations of lactate dehydrogenase (LDH), malondialdehyde MDA, and endothelin (ET) in the plasma of rats injured with MI. Histological examination of brain sections revealed that CCSTM alleviated cerebral damage after ischemia compared with the model group. CCSTM can reduce myocardial and cerebral infarction injury, and the oxidation level after myocardial and cerebral infarction in rats.

1. Introduction

Vascular infarction, a prevalent ailment associated with aging, serves as a significant contributor to both disability and mortality [1,2]. For decades, cardiovascular diseases have been a leading cause of death worldwide. In 2021, approximately 20.5 million people died from cardiovascular diseases, accounting for about one-third of total global deaths [3]. Previous studies have elucidated its pathogenesis and explored potential drugs to treat infarction [4,5]. However, many of these drugs' specific targets and pharmacological actions remain unclear.

Both cerebral infarction (CI) and myocardial infarction (MI) are consequences of vascular occlusion. CI encompasses a series of

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https://doi.org/10.1016/j.heliyon.2024.e39162
Received 15 August 2024; Received in revised form 5 October 2024; Accepted 8 October 2024
Available online 11 October 2024

symptoms resulting from insufficient blood supply to the brain to meet the metabolic needs of brain tissue [6]. The clinical manifestations include dizziness, headache, numbness of limbs, or brief lapse of consciousness, which in severe cases can result in irreversible damage to brain function or even death [6]. The treatments of cerebral ischemia include pharmacotherapy, surgery, control of risk factors, and improving life habits [7,8]. In an acute attack of cerebral arterial thrombosis, intravenous thrombolytic therapy or interventional stent is required [9]. Nowadays, commonly used drugs include antiplatelet drugs (e.g., aspirin, clopidogrel, and dipyridamole), anticoagulant drugs (e.g., warfarin, rivaroxaban, and pradaxa), and statins [9,10]. However, these drugs need to be closely monitored because of bleeding tendencies. MI, characterized as a severe form of coronary artery disease, ensues from the untimely demise of cardiac cells triggered by ischemia-induced injury [11]. Notably, advanced age, male gender, smoking, obesity, familial history, atherosclerosis, and hyperlipidemia emerge as significant risk factors contributing to the onset of MI [12,13]. ST-elevation myocardial infarction (STEMI) patients suffer from a grievous cardiac arrest, catapulting the mortality rate to 53 % [14]. Percutaneous coronary intervention (PCI) is the primary strategy for MI therapy. Besides, anti-thrombus and anti-inflammation regimens are also important for MI therapy. However, the therapeutic effects of these two regimens are not better than PCI [15].

Emerging evidences reveal traditional Chinese medicine (TCM), such as *Salvia miltiorrhiza Bge.*, *Astragalus membranaceus (Fisch.) Bunge*, *Cyperus rotundus* L., and other TCMs, are good therapeutic drugs for MI treatment [16]. Many physicians use TCM in combination with Western drugs to potentiate the therapeutic effects [17]. In the TCM theory, Qi-deficiency and blood-stasis syndrome are the main pathogenesis of ischemia [18–20]. Researches in the anti-ischemia effect of TCM have led to the increased interest in the neuroprotective effects of TCMs [21,22]. TCMs that promote blood circulation and alleviate blood stasis can dredge blood vessels, which can improve the platelet function and hemodynamics of the patients to enhance blood supply [23–25]. Previous study has shown that the chance to develop hyperlipidemia in MI patients who treated with TCM is declined compared with that in the MI patients who didn't treat with TCM [26]. Still, the exact mechanisms of several TCMs remain to be fully understood. Hence, it's worth investigating the function of more TCMs in MI therapy.

Cardio-cerebral stasis transforming medicines (CCSTM), a famous Chinese herbal formulation, which are reported to have the ability to alleviate CI and MI [26–31]. However, the effect of CCSTM on CI and MI therapies are unclear. Therefore, this study was aimed to investigate the efficacy and mechanisms of CCSTM against CI and MI. After application of CCSTM on rats injured with CI or MI, the brains, hearts, and plasma were collected. The results of morphology and plasma indicators detection showed CCSTM could relieve the severities of CI and MI. Our study could help clarify the therapeutic efficacy of the CCSTM in treating acute ischemia and improve patient prognosis. In the study we compared the efficacy of CCSTM with the commercial products: Danshen dripping pill and Yi'an ning pill, which were reported to have the abilities of promoting blood circulation, removing blood stasis, treating heart disease, and calming nerves.

2. Materials and methods

2.1. Reagents

CCSTM were obtained from Beijing Jianhua Research Institute of Medice. Ingredients: 25 g *Salvia miltiorrhiza Bunge*, 15 g *Polygonatum odoratum (Mill.) Druce*, 5 g *Glycyrrhiza uralensis Fisch.*, 8 g *Atractylodes macrocephala Koidz.*, 5 g *Smilax glabra Roxb.*, 10 g *Rehmanniaglutinosa (Gaertn.) Libosch. ex Fisch. & C. A. Mey.*, 5 g *Ophiopogon japonicus (L. f.) Ker Gawl.*, 12 g *Astragalus membranaceus (Fisch.) Bunge*. The compound Danshen dripping pill obtained from Tasly Pharmaceutical Group Co., Ltd., Shanghai, China, Ingredients: *Salvia miltiorrhiza* Bunge, *Panax notoginseng* (Burkill) F. H. Chen ex C. H. Chow, *Dryobalanops aromatica* C.F.Gaertn. The Yi'an ning pill were obtained from Tongyitang Pharmaceutical Co., Ltd., Shanghai, China. Ingredients: *Panax quinquefolius* L., *Dendrobium nobile Lindl., Ophiocordyceps sinensis (Berk.) G.H. Sung, J.M.Sung, Hywel-Jones & Spatafora, Carapax Trionycis, cartialgenous, Schisandra chinensis (Turcz.) Baill., Galli Gigeriae Endothelium Corneum, Carapax Testudinis, Crocus sativus* L, *Panax notoginseng (Burkill) F. H. Chen ex C. H. Chow, Ganoderma lucidum (Curtis) P. Karst., Snake bile, Salvia miltiorrhiza Bunge, hippocampus.* Saline was purchased from Hunan Kelun Pharmaceutical Co., Ltd., Hunan, China. Lactate dehydrogenase (LDH, Cat. no.: JM-11249R1), malondialdehyde (MDA, Cat. no.: JM-061251O1), superoxide dismutase (SOD, Cat. no.: JM-02137R1), endothelin (ET, Cat. no.: JM-01774R1), and myeloperoxidase (MPO, Cat. no.: JM-01744R1) commercial kits were obtained from Jiangsu Jingmei Biotechnology Co., Ltd., Jiangsu, China.

2.2. Animals and treatments

Specific pathogen-free Sprague-Dawley rats (7–8 week, 200 in total, weighing 280–320 g) were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd. (Beijing, China) (license #SCXK2019-0004). The rats were housed in the animal room of the Experimental Animal Center of Hunan University of Chinese Medicine under a 12/12-h light/dark cycle at 60 % ± 10 % humidity and 22 ± 2 °C. The rats were fed in separate cages and received food and water, ad libitum. The study was performed according to all applicable laws, policies, and guidelines. The Animal Ethics Committee of the Hunan University of Chinese Medicine approved the study with the animal ethical approval No. LL2021030501.

2.3. Cerebral ischemia

The modified Longa suture-occluded method was used to make a rat transient medium cerebral artery occlusion model [32]. The surgical suture (Beijing Cinontech Co., Ltd., Beijing, China) was fixed, and 1–2 cm of the surgical suture was carefully pulled out and

cut off after 1.5 h to achieve reperfusion. The awakened rats were evaluated using the Longa 5-point scale [32], and only those with scores of 1–3 were used in the subsequent experiments. In the sham-operated group, after anesthesia, the corresponding vessels were isolated, the external carotid artery was ligated, and the common carotid artery and internal carotid artery were transiently clamped without inserting a suture. The intraoperative and postoperative room temperature was strictly controlled at 24–25 °C, and the anal temperature of the rats was maintained at about 37 °C during the experiment until they resumed activities.

2.4. Myocardial infarction

The rats in the control group were kept, and the remaining rats were anesthetized using 10 % chloral hydrate with the criterion of 0.3 mL/100 g via intraperitoneal injection [33,34], followed by being intubated endotracheally and breathing with ventilator. Then the heart was exposed and the left anterior descending coronary artery was ligated. When the color of left ventricular wall turned pale, the thoracic wall was sutured. And the intubation tube was removed when spontaneous respiration occurred. An elevation of more than 0.1 mV of ST segment compared with that before operation meant the successful establishment of myocardial infarction. For the rats in the sham-operated group, all of the operations were the same as those in the myocardial infarction group except for ligation of the left anterior descending coronary artery.

2.5. Preparation of CCSTM solution

To prepare the drug solution, weigh 200 g of CCSTM. Finely grind these materials and transfer them into a round-bottom flask. Add 2000 mL distilled water soak for 2 h, and perform reflux for 1 h, followed by filtration. Repeat this reflux process for an additional hour with fresh distilled water, then filter again. Combine the filtrates from both reflux sessions and concentrate them under vacuum at 48–52 °C to obtain extract, calculated based on the weight of the raw herbs. Store the resulting solution in a refrigerated environment for future use.

2.6. Drug treatment

The rats with successful modeling were randomly divided into the model group, the compound danshen dripping pill (0.0109 g/mL) group, the Yi'an ning pill (0.0837 g/mL) group, and the low-, medium-, and high-dose CCSTM group (0.6075, 1.12150, and 2.4300 g/mL). Each group was given the corresponding medication in a volume of 10 mL/kg [35]. The rats injured with cerebral ischemia were administered with the drug once every 12 h for four days [35], for a total of seven times. And the rats injured with myocardial infarction were administered with the drug once a day for seven days. The blank control and model groups were given an equivalent volume of saline.

2.7. Triphenyl tetrazolium chloride (TTC) staining

Rats underwent a 7-day treatment as described previously. At the endpoint, the rats were intraperitoneally anesthetized using chloral hydrate (Hefei Bomei Biotechnology Co., Ltd., Hefei, China) 1 h after the final administration. Blood samples were obtained from the aorta abdominalis. Brain and cardiac tissues were quickly dissected within 10 min after euthanizing the rats through decapitation and then frozen at −20 °C for 30 min. These brain and cardiac tissues were sectioned at a thickness of 2 mm and immersed in a 1 % TTC solution (Sigma-Aldrich, St, Louis, MO, USA). They were shielded from light and incubated for 30 min in a water bath at 37 °C, with shaking the container slightly every 5 min and turning it over every 10 min. After that, the brain and cardiac sections were washed with phosphate-buffered saline (Procell Life Science & Technology, Co., Ltd., Wuhan, China) for 3–5 min. Pictures were captured immediately. The sections were fixed with 10 % neutral formaldehyde (Biosharp, Shanghai, China) for 12 h. The images were analyzed using the Image J software (National Institutes of Health, Bethesda, MD, USA).

2.8. Biochemistry

Plasma LDH, MDA, SOD, ET, MPO, levels were measured with commercial kits according to the manufacturer's instructions.

2.9. Histological examinations

Hematoxylin & eosin staining and Nissl staining (Wuhan Biofavor Biotechnology Service Co., Ltd., Wuhan, China) were performed routinely. Hematoxylin & eosin staining: carefully remove tissue, then the samples were fixed in 4 % paraformaldehyde, then dehydrated with a gradient of 70 %, 80 %, 95 %, and 100 % alcohol for 30 min each, cleared with xylene twice for 20 min each, infiltrated with paraffin in two baths for 12 min each, embed in paraffin and cut into 4 μm sections along the coronal plane, then the slides were baked. For staining, slides were immersed in three xylene baths for 8 min each, followed by two 100 % alcohol baths for 8 min each, and then 90 %, 80 %, and 60 % alcohol for 8 min each to hydrate. The samples were stained with hematoxylin for 4 min, rinsed, differentiated with hydrochloric acid alcohol for 2–3 s, then rinsed again, treated with 0.5 % ammonia for 20 s, rinsed, and stained with 0.5 % eosin for 1 min. The samples were differentiated in 80 % and 90 % alcohol for 3–5 s each, then placed in 95 % alcohol for 5 min, cleared in three 100 % alcohol baths for 5 min each and in two xylene baths for 5 min each. Sealed with neutral resin and observed under a light microscope. For Nissl staining, the sections were dewaxed and rehydrated, then toluidine blue was added

and incubated at room temperature for 5 min. Then the samples were rinsed twice with distilled water, dehydrated with gradient ethanol, cleared with xylene, and mounted for photography.

2.10. Statistical analysis

The data were presented as means ± standard error of the mean (SEM) and analyzed through ANOVA and Tukey's post hoc test. Two-sided *P*-values <0.05 were considered statistically significant. The data were entered and compiled using Excel 2016 (Microsoft, Redmond, WA, USA). Data analysis was performed using GraphPad Prism 8 (GraphPad Software Inc., San Diego, CA, USA) and SPSS 25.0 (IBM, Armonk, NY, USA).

3. Results

3.1. CCSTM alleviates cerebral ischemia in rats

To visually explore the effects of CCSTM in cerebral ischemia, we performed the HE and Nissl stainings in brain tissues. According to the results of HE staining, in the blank and sham groups, the cell morphology, cells were normal, and the cell arrangement was orderly. When the rats underwent cerebral ischemia (model group), lots of cells became degenerated and necrotic, the nucleus of cerebral cortex was shrunk, and the cell body became smaller. In addition, the cells were disorderly arranged. While CCSTM treatment alleviated the cell degeneration and necrosis in a dose-dependent manner (Fig. 1), the cell size and morphological structure tended to Sham group, and the Dandi and Yi'an ning treatment groups also showed these effects.

Nissl staining revealed that the Nissl bodies in the control and sham groups were normal and the Nissl bodies' distributions were regular in blank and sham group, the cortical neurons were arranged in a complete structure, the cytoplasm was dyed dark blue, and the number of Niches was abundant, and the dendrite structure was not abnormal. However, the number of Nissl bodies were reduced in the brain tissues of rats underwent cerebral ischemia (model group). More importantly, CCSTM treatment could increase the number of Nissl-positive neurons in a dose-dependent manner, which was also observed in the Dandi and Yi'an ning treatment groups (Fig. 2). These results indicated CCSTM could ameliorate the cerebral ischemia.

3.2. CCSTM decreases the infarct area after brain and cardiac ischemia

To evaluate the cerebral and myocardial infarction status, we conducted TTC staining for brain and heart tissues of each group, and calculated the cerebral and myocardial infarction area (white part), respectively. As shown in Fig. 3A and B, the control group and the sham-operated group did not show cerebral infarction, while the model group displayed obvious cerebral infarction, with the brain tissues fragile and brittle. In contrast with the model group, the positive drug groups showed a significant decrease in the infarction area. Specifically, the treatment effect of the Yi'an ning group was better. In the CCSTM groups, there were dose-dependent therapeutic effects, and the infarction area decreased with the increasing CCSTM doses.

In the myocardial infarction model, the difference of the heart infarction was also compared by measuring the TTC staining area. As shown in Fig. 4A and B, in contrast with the control group, there was no difference in the sham-operated group, while the model group displayed a significant increase of the infarction area (19.61 % vs. 0.38 %, $P < 0.01$). All the positive drug groups exhibited significant infarction area decrease when compared with the model group, demonstrating the positive therapeutic efficacy of these drugs. It is noteworthy that CCSTM treatment showed a dose-dependent alleviation of infarction, and both the medium-dose and high-dose of CCSTM groups showed obviously lower myocardial infarction area than Yi'an ning group and Dandi group, indicating that appropriate dose of CCSTM would have potential better therapeutic effect than Yi'an ning and Dandi. Taken together, CCSTM and positive drugs had noticeable therapeutic effects, and CCSTM demonstrated remarkable superior ability in alleviating the cerebral and myocardial infarction.

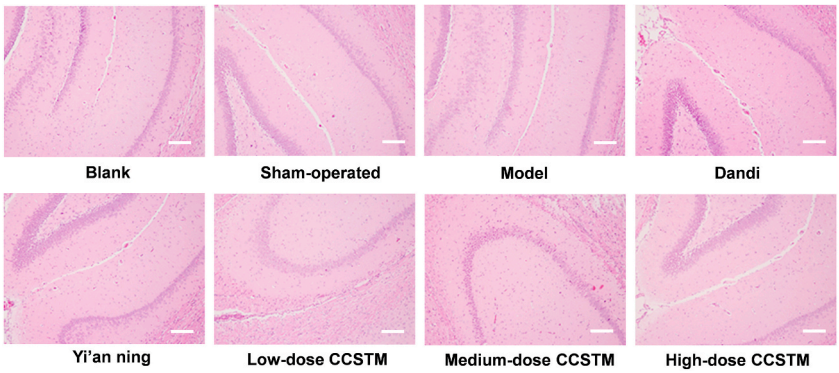

Fig. 1. Hematoxylin & eosin staining in the brain infarction areas of the rats in each group. Scale bar: 100 μm.

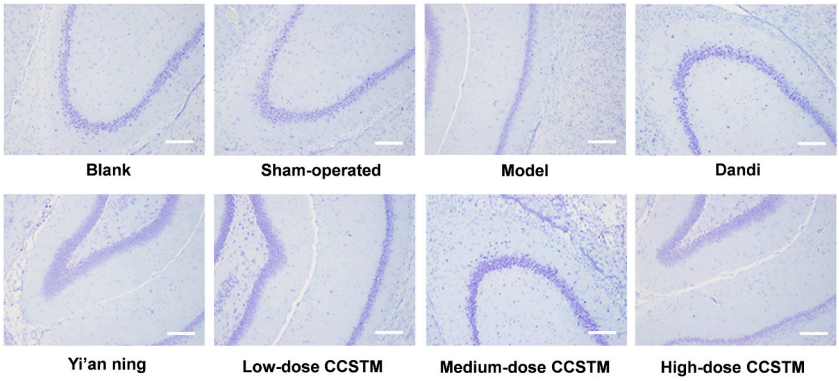

Fig. 2. Nissl staining in the brain infarction areas of the rats in each group. Scale bar: 100 μm.

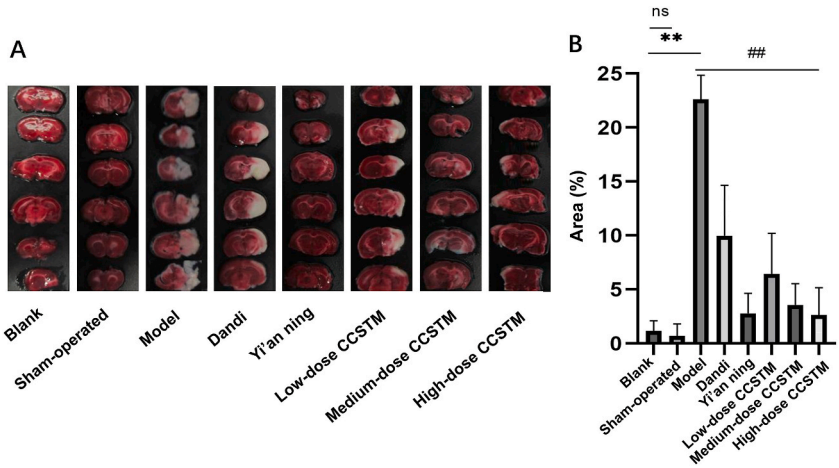

Fig. 3. Brain infarction of rats in each group by TTC staining. (A) TTC staining images of brain tissues. (B) Quantification of the infarct areas. $^{**}P < 0.01$ vs. the sham-operated group. $^{\#\#}P < 0.05$ vs. the model group. Ns, no significant difference. The brain is about 1 cm in height and 1.6–2 cm in width.

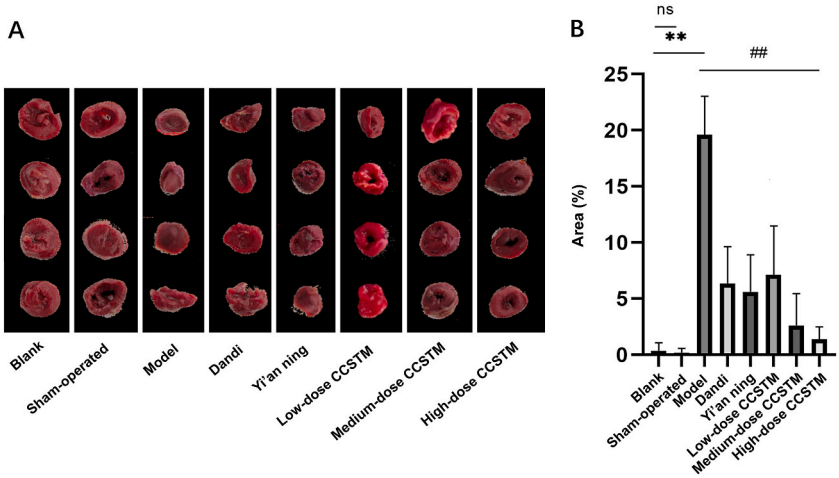

Fig. 4. Myocardial infarction of rats in each group by TTC staining. **(**A) TTC staining images of brain tissues. (B) Quantification of the myocardial in farction of rats in each group. $^{**}P < 0.01$ vs. the sham-operated group. $^{\#\#}P < 0.01$ vs. the model group.

3.3. CCSTM decreases the oxidation levels after cerebral ischemia

To explore the pharmacological mechanisms of CCSTM on cerebral infarction, we detected the MDA (an important index associated to the oxidative stress), SOD (a key free radical scavenger), and MPO (a pro-inflammatory factor) levels in each group [36,37]. Fig. 5A–C shows that there were no significant differences between the control and sham-operated groups. Compared with the control group, there was a remarkable increase of MDA (Fig. 5A) and MPO (Fig. 5C) levels and decrease of SOD (Fig. 5B) level in the model group, suggesting that the rats were at high oxidation levels after brain ischemia. Furthermore, the Dandi, Yi'an ning groups, and CCSTM exhibited a significant decrease of MDA, while all these groups except the low-dose CCSTM group displayed a remarkable decrease of MPO level and increase of SOD level. Collectively, CCSTM significantly alleviated the oxidative stress in cerebral infarcted rats and showed considerable effects in inhibiting the cerebral infarction progression.

3.4. CCSTM decreases the oxidation levels after myocardial infarction

Next, we detected the levels of LDH, SOD, MDA, and ET in the plasma of each group, which would increase in the plasma after MI. As shown in Fig. 6A–D, low concentrations of ET (Fig. 6A), LDH (Fig. 6B), MDA (Fig. 6C), and SOD (Fig. 6D) were found in the plasma of rats in the control and sham groups. However, when the rats were injured with MI, the levels of ET, LDH, MDA, and SOD were obviously elevated compared to those in the control and sham groups. Surprisingly, CCSTM treatment greatly reduced the concentrations of ET, LDH, MDA, and SOD in the plasma of rats injured with MI in a dose-dependent manner. And the effects of high-dose CCSTM on reduction of ET, LDH, and MDA in the plasma of rats injured with MI were similar to those in the Dandi and Yi'an ning groups. These data revealed CCSTM could protect heart from myocardial infarction via decreasing the levels of ET, LDH, and MDA in the plasma.

4. Discussion

This study aimed to investigate the efficacy and mechanisms of CCSTM against cerebral and myocardial infarction. The results suggested that CCSTM decreased the infarct size and related damage in rat cerebral ischemia and myocardial infarction models.

Ischemia/reperfusion injury involves increased oxidative stress in tissues, contributing to the injury's extent [38]. Therefore, targeting oxidative stress is considered as a potential approach to prevent tissue damage after acute ischemia and reperfusion, although the exact methods remain controversial [39,40]. Recently, several TCMs have been reported effective against ischemia damage [16]. In the present study, the significantly elevated MDA and MPO and decreased SOD levels reflected an increased oxidative stress after brain and heart ischemia and reperfusion [36–40]. The Dandi and Yi'an ning are well-known drugs decreasing oxidative stress after hypoxia or ischemia [41–43]. By significantly reducing the MDA and MPO levels and increasing SOD levels, CCSTM demonstrated its antioxidative properties. This reduction in oxidative stress is crucial as excessive free radicals and oxidative damage can lead to exacerbated tissue injury. The ability of CCSTM to mitigate this stress suggests that it can prevent the progression of damage following infarction, and this could be an essential factor in its therapeutic effect. The present study also showed that CCSTM could reduce oxidative stress after brain ischemia, although its efficacy was not greater than that of the two positive drugs. The study further indicated that CCSTM's effects on oxidative stress were dose-dependent, with higher doses providing more pronounced benefits. This dose-dependence reflects a possible correlation between CCSTM concentration and its capacity to scavenge free radicals, thus preventing tissue damage. This finding emphasizes the potential for using CCSTM in clinical settings, particularly when considering that the higher doses achieved better therapeutic results without observed toxicity. Nevertheless, the long-term safety of even higher doses needs further investigation.

As expected, CI model group showed significantly larger infarct size and histological damage than the blank and sham groups,

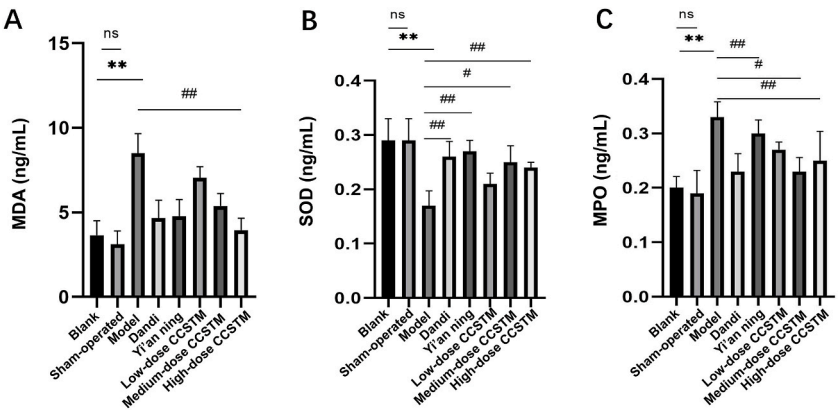

Fig. 5. (A) MDA, (B) SOD, and (C) MPO levels in the plasma of rats injured with brain infarct in each group. $^{**}P < 0.01$ vs. the sham-operated group. $^{\#}P < 0.05$ vs. the model group. $^{\#\#}P < 0.01$ vs. the model group. ns, no significant difference.

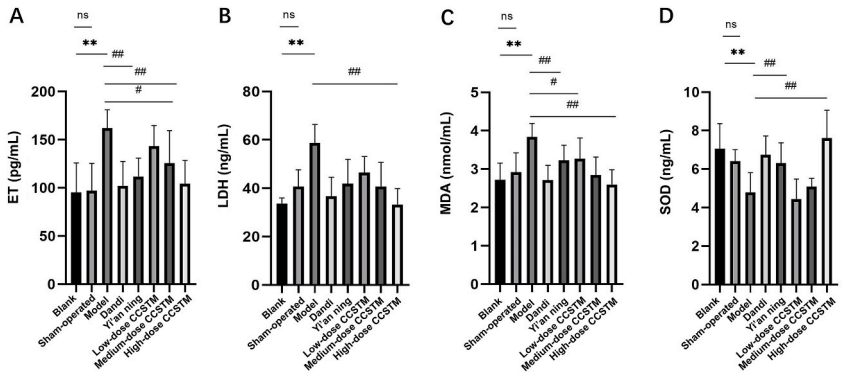

Fig. 6. CCSTM reduces the concentrations of ET, LDH, MDA, and SOD after myocardial infarction. ELISA analysis of (A) ET, (B) LDH, (C) MDA, and (D) SOD in the plasma of rats injured with MI. $^{**}P < 0.01$ vs. the sham-operated group. $^{\#}P < 0.05$ vs. the model group. $^{\#\#}P < 0.01$ vs. the model group. ns, no significant difference.

confirming the rat model of CI was established successfully. The two positive drugs (Dandi and Yi'an ning) are often used to manage stroke [44,45]. Not surprisingly, both of the positive drugs could alleviate the infarct size of CI, together with decreasing the oxidative stress response. CCSTM was mainly consisted of Dan-shen and Huang-qi. Actually, Dan-shen and Huang-qi were reported to inhibit CI development [29,30]. However, the effect of CCSTM on CI was unknown. In line with the previous study, we found CCSTM decreased the infarct size compared with the model group, and the effect was similar to the two positive drugs. The significant reduction in infarct size, especially in the high-dose CCSTM group, suggests that CCSTM could be a more effective treatment for infarction. This superior effect could be attributed to the combined actions of its components, which not only act on oxidative stress but may also influence inflammation and vascular function. Nevertheless, the results suggest that CCSTM can potentially manage CI.

In this study, we also found the therapeutic effect of CCSTM in myocardial infarction. The dose-dependent therapeutic effects of CCSTM observed in this study suggest that its active components, particularly danshen and astragalus, may work synergistically to enhance its efficacy. The treatment of CCSTM demonstrated dose-dependent reduction of myocardial infarction area and showed superior efficacy compared to the positive drugs, namely, danshen dripping pill and Yi'an ning pill. In addition to the cerebrovascular protective effect, Danshen, the prominent bioactive component in both danshen dripping pill and Yi'an ning pill, has also been broadly documented for its cardiovascular protective actions [46,47]. Importantly, Danshen is also a principal active component of CCSTM. As a fact of that, it is conceivable that CCSTM might confer therapeutic benefits in the context of myocardial infarction. Furthermore, CCSTM contains astragalus as another principal component. Astragalus polysaccharide, a bioactive component of astragalus, is well-recognized for its application in management of cardiovascular diseases for its anti-oxidative effects [48,49]. The current study unveiled the anti-oxidative properties of CCSTM, thus providing evidence that the Danshen and Astragalus might have synergistic effects in alleviating myocardial infarction progression. Consequently, CCSTM emerges as a prospective candidate for the treatment of myocardial infarction.

The results of this experiment show that the therapeutic effects of CCSTM are primarily attributed to its antioxidative and anti-inflammatory properties, distinguishing it from the current standard treatments for cerebral and myocardial infarction. While anti-platelet and anticoagulant therapies, such as aspirin and warfarin, aim to prevent thrombus formation, they are associated with a considerable risk of bleeding [50,51]. In contrast, CCSTM operates by alleviating oxidative stress and inflammation, potentially providing a safer complementary approach to conventional antithrombotic treatments without exacerbating bleeding risks. The oxidative stress reduction is speculated to be the may molecular pathways involved. Moreover, percutaneous coronary intervention (PCI), the current standard of care for myocardial infarction, is effective in restoring blood flow but does not address ischemia-reperfusion injury [52], in which oxidative stress plays a pivotal role. CCSTM could potentially reduce oxidative damage following PCI, indicating its possible role as an adjunctive therapy. Although statins, commonly used for long-term cardiovascular risk management, primarily focus on lipid reduction [53], CCSTM's ability to rapidly address oxidative and inflammatory damage positions it as a valuable treatment option during the acute phase of ischemic injury. Whether it can be safely combined with Western drugs remains to be determined.

5. Conclusion

CCSTM can decrease oxidative stress and infarct area in rat cerebral ischemia and myocardial infarction models. Hence, CCSTM could be used in the management of ischemic injuries.

CRediT authorship contribution statement

Ruilian Liu: Writing – original draft, Investigation, Data curation, Funding acquisition, Conceptualization, Formal analysis. **Yangchu Chen:** Investigation, Funding acquisition, Conceptualization. **Xili Zhang:** Investigation. **Yuhan Cai:** Software. **Shuang Xu:**

Methodology. **Qian Xu:** Methodology. **Xin Li:** Methodology. **Wenjiao Li:** Methodology. **Pingan Liu:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization. **Wenlong Liu:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization.

Ethics statement

The animal experiment was approved by the Animal Ethics Committee of the Hunan University of Chinese Medicine (LL2021030501).

Data availability statement

Some or all data that support the findings of this study are available from the corresponding author upon reasonable request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We gratefully acknowledge the CCSTM sample provided by Yangchu Chen in Beijing Jianhua Research Institute of Medicine, and the financial support from Research and Development Program in Key Fields of Hunan Province (2023SK2046), Natural Science Foundation of Hunan Province (2023JJ60460, 2023JJ60474), Innovative Province Construction of Hunan Province (2023NK4110), Scientific and Technological Innovation Program of Hunan Province (2023NK4144), Key Items of Scientific Research Program of Traditional Chinese Medicine in Hunan Province (A2022005, 2021028), The Natural Science Foundation of Changsha (KQ2208191), the Key Program of Joint Fund of the Hunan Provincial Natural Science Foundation and the Hunan Medical Products Administration (2024JJ8112) and The Hunan University of Traditional Chinese Medicine Graduate Student Innovation Project (2023CX145).

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