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Atractylodis macrocephalae rhizoma tianma soup mixed with peach kernel safflower fried in the treatment of acute cerebral infarction: A randomized controlled trial

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Abstract: We studied the effectiveness of Atractylodis Macrocephalae Rhizoma Tianma soup mixed with peach kernel safflower Fried in treating acute cerebral infarction. 96 patients were divided into two groups and received routine treatment as per hospital guidelines. 48 patients were given the herbal mixture while the rest were not. A comparison of inflammatory factors, coagulation, liver, and kidney function showed significant differences between the two groups on day 14. The observation group had higher APTT, PT, TT values and ALP levels, but lower BUN levels compared to the control group. The observation group had significantly higher ALP levels and GGT levels on day 14 compared to the control group, while Cr and BUN levels were lower. This difference was statistically significant ($P<0.05$). The peach kernel safflower fried and Attractylodis Macrocephalae Rhizoma Tianma soup combination reduces inflammation in acute cerebral infarction patients, improving clinical symptoms without any reported adverse reactions.

Keywords: Atractylodis macrocephalae rhizoma tianma soup, peach kernel safflower fried, plants, cerebral infarction, inflammatory factor.

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INTRODUCTION

Acute cerebral infarction is a prevalent clinical condition characterized by a high incidence rate, significant disability, and a substantial mortality rate (Zhou *et al*., 2019). Cerebral heart syndrome is among the most frequent complications following cerebral infarction. In less severe instances, it may manifest with no cardiac symptoms, manifesting only as abnormal electrocardiogram findings. However, in severe cases, it can precipitate acute heart failure or acute myocardial infarction, which may be life-threatening. Prompt diagnosis and intervention can ameliorate or resolve these cardiac complications (Xu *et al*., 2018). The globally recognized pathological mechanisms underlying cerebral infarction encompass a range of factors, including acidosis due to energy depletion, the toxic impact of excitatory amino acids, injurious effects of inflammatory cytokines, oxidative stress from nitric oxide free radicals, the polarization of the peri-infarct penumbra and cellular apoptosis (Xie *et al*., 2023). Consequently, contemporary medical understanding posits that disruption of cerebral blood supply is the fundamental cause of the cascade of physiological and pathological alterations induced by cerebral infarction (Wang *et al*., 2022).

Herbal remedies from traditional Chinese medicine and conventional pharmacological treatments have been validated for their clinical efficacy in the management of acute cerebral infarction (Ruqiao *et al*., 2020). This integrative therapeutic approach allows for a synergistic effect between Eastern and Western medical practices, addressing not only the disease process but also the holistic regulation of the patient's body (Xie *et al*., 2016). Accurate diagnosis facilitates the provision of targeted pharmacotherapy, enhancing the precision and effectiveness of treatment, which is pivotal for improving the patient's quality of life (Liu *et al*., 2021). Through extensive clinical experience, we have gained a profound understanding that the underlying pathogenesis of cerebral infarction is the obstruction of meridians by wind, phlegm and blood stasis, with blood stasis being the crux of the condition, and the combination of liver wind and phlegm turbidity representing its superficial manifestations (Luo *et al*., 2022). Therefore, in our treatment approach, we steadfastly adhere to the principle of prioritizing the alleviation of acute symptoms while addressing the root cause methodically. In acute settings, we focus on addressing external symptoms, such as liver wind and phlegm turbidity, to alleviate patient discomfort; during the convalescent phase, we concentrate on resolving the fundamental issue of blood stasis obstructing the meridians. The treatment of cerebral infarction primarily centers on promoting blood circulation and resolving phlegm. By invigorating blood circulation and clearing the meridians, we aim to ameliorate blood stasis, while dispelling phlegm and tranquilizing wind serves to eliminate phlegm turbidity and calm liver wind, thereby treating both symptoms and their root causes (Shi *et al*., 2019). This comprehensive treatment strategy not only significantly enhances therapeutic outcomes but also reduces the recurrence rate

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of the condition, which is of paramount importance for the rehabilitation of patients with acute cerebral infarction (Wang QY, *et al*., 2024). The integration of conventional medications with herbal therapies for the treatment of acute cerebral infarction is a modality that warrants broader application. Such an approach not only boosts the efficacy of treatment but also enhances the quality of life and improves the prospects for rehabilitation in patients with cerebral infarction.

Given that compromised cerebral blood supply is the underlying cause of a sequence of physiological and pathological alterations leading to cerebral infarction, we have explored the therapeutic efficacy of a combined herbal preparation consisting of Atractylodis Macrocephalae Rhizoma, Tianma soup and a mixture fried with Peach kernel and safflower for the treatment of acute cerebral infarction. The objective of this study is to provide a scientific foundation for the use of multifaceted herbal combinations in the management of cerebral infarction.

MATERIALS AND METHODS

Research object

We enrolled 96 patients with acute cerebral infarction between December 2021 and January 2024. Based on the treatment protocol, which included administration of Atractylodis Macrocephalae Rhizoma Tianma soup combined with a preparation fried with Peach kernel and safflower, the patients were randomly allocated into a control group and an observation group, each consisting of 48 individuals. The diagnostic criteria for acute cerebral infarction were derived from the Chinese Guidelines for the diagnosis and treatment of acute ischemic stroke, as established by the Neurology Branch of the Chinese Medical Association (Chinese, *et al*., 2018). The primary diagnostic criteria include acute onset; focal neurological deficits, occasionally with total neurological impairment; persistence of symptoms and signs for more than a few hours (with thrombolysis indications considered for patient selection) and the exclusion of cerebral hemorrhage and other lesions via cerebral CT or MRI, which should also reveal infarcted areas. This study was approved by the ethics committee of Linquan County People’s Hospital (Approval No. 20-LQ-EC-03). Signed written informed consents were obtained from the patients and/or guardians. This study was conducted in accordance with the Declaration of Helsinki.

Inclusion and exclusion criteria

Inclusion Criteria: Patients were in the acute phase of cerebral infarction. National Institutes of Health Stroke Scale (NIHSS) score was between 5 and less than 15 points. Age range was from 30 to 80 years.

Exclusion Criteria: Admission head CT scan revealed cerebral hemorrhage, space-occupying cerebral lesion, or was complicated by cerebral trauma. Presence of atrial fibrillation, malignancy, or autoimmune disease. Patients with acute ischemic stroke requiring thrombolytic therapy. Individuals with severe chronic kidney disease or hepatic and/or renal insufficiency. Patients with mental disorders, or those who were blind, deaf, mute, or had other disabilities. Pregnant or lactating females. Swallowing dysfunction, as indicated by a Toshio Koda water drinking test score of grade I or higher. Patients with acute infections of the respiratory, digestive, or urinary systems within 15 days prior to admission. Fibrinogen levels below 1.2g/L. Individuals with a bleeding tendency or severe coagulation disorders, those with peptic ulcer disease, or those in the active phase of tuberculosis. Patients with a symptom onset time greater than 3 days.

Treatment methods

The two groups received treatment in line with the clinical pathway for cerebral infarction developed by our hospital's Department of Encephalopathy. Patients were administered aspirin enteric-coated tablets, 100 mg, orally each night before bedtime. In cases of intolerance, patients were treated with Clopidogrel bisulfate tablets, 75 mg, orally every morning (manufactured by Shi Yao Group Euyi Pharmaceutical Co., Ltd., with the SinopOD Approval number H20193160). Additionally, Atorvastatin calcium tablets, 20 mg, were given orally each night before sleep (produced by Qilu Pharmaceutical Co., LTD., with the Sinopol Approval number H20193143). Tetramethylpyrazine hydrochloride injection, 120 mg, was administered once daily (manufactured by Harbin Sanlian Pharmaceutical Co., LTD., with the Sinopol Approval number H20030553). Concurrently, management of patients' other underlying conditions, such as hypertension and diabetes, was also addressed. Intravenous mannitol was administered as needed for patients with intracranial hypertension. In the event of concurrent infections or other complications, additional symptomatic treatments, including anti-infective therapies, were provided as necessary.

Our observation group received a combination therapy consisting of Atractylodis Macrocephalae Rhizoma Tianma soup and a preparation fried with Peach kernel and safflower. The botanical medicinal ingredients employed in this therapeutic regimen are varied and rich, with each herb possessing its distinctive therapeutic properties and functions. Through a carefully calibrated ratio, these components collectively exert their effects on patients to achieve the optimal therapeutic outcome. The botanical constituents included Gastrodia, Poria, Red Peony, and *Salvia miltiorrhiza,* each at 15 grams; Pinellia, Atractylodis Macrocephalae Rhizoma, Citrus Pericarpium, Peach Kernel, Safflower, Angelica, Rehmannia and Rhizoma Chuanxiong, each at 10 grams; and Licorice at 6 grams.

Throughout the treatment period, patients were instructed to consume one dose of herbal decoction daily, with each dose consisting of 300 mL of herbal extract, divided into two equal administrations in the morning and evening. Following two weeks of treatment, the effects of the individual botanicals could be observed. Gastrodia was found to have a tranquilizing effect on liver wind, providing antispasmodic relief and addressing wind-phlegm symptoms in patients with cerebral infarction. Poria was used to strengthen the spleen and dispel dampness, thereby improving the spleen and stomach function of patients and enhancing the body's ability to transport nutrients. Red Peony root and Salvia miltiorrhiza were instrumental in ameliorating the pathological state of blood stasis obstructing the meridians. Pinellia was effective in drying dampness and resolving phlegm, significantly reducing phlegm turbidity within the body.

Atractylodis Macrocephalae Rhizoma was employed to reinforce spleen and qi, thereby enhancing the body's resilience. Citrus Pericarpium was used to regulate qi and eliminate phlegm, which helped to alleviate symptoms associated with qi dysfunction. Botanicals such as Peach Kernel, Safflower, Angelica, Rehmannia, and Rhizoma Chuanxiong all contributed to the circulation-activating and channel-clearing effects, working in concert to improve blood flow and alleviate blood stasis in the patient's meridians. Licorice served as an adjuvant to harmonize the other medicinal components, enhancing the efficacy of the herbal mixture and mitigating potential side effects. The combined therapy of Atractylodis Macrocephalae Rhizoma Tianma soup and the preparation fried with Peach kernel and safflower represents a principle approach in the treatment of cerebral infarction (fig. 1).

Observation Indicators

Coagulation Function Assessment: Blood samples were collected on admission and on the morning of the 14th day, following a 12-hour fast. A 2.5 ml sample of venous blood was drawn, to which 0.109 mol/L of steroconic acid was added at a ratio of 9:1 (blood to anticoagulant). The mixture was then centrifuged at 3000 rpm for 10 minutes to separate the plasma. (The anticoagulant reagent was supplied by Shanghai Sun Biotechnology Co., LTD.) Automated hemagglutination detection was performed using an ACLTOP 700 analyzer (USA). (Following plasma separation, APTT, TT and fibrinogen levels were measured using the ACLTOP 700, with matching reagents provided by the IL Company. Specimens were processed within 4 hours of collection.)

Inflammatory Markers and Liver and Kidney Function Evaluation: Venous blood samples were obtained after a 12-hour fast on admission and again on the morning of the 14th day. These samples were analyzed with an automated biochemical analyzer to evaluate the patient's inflammatory markers, as well as liver and kidney function. (The Shanghai Hitachi 7080 automated biochemical analyzer and associated reagent kits were used.) Data collection for these assessments was conducted by dedicated staff upon admission and on the 14th day.

STATISTICAL ANALYSIS

The data were analyzed and processed using IBM SPSS 26.0 statistical software (Armonk, NY, USA). The quantitative data conforming to normal distribution were measured by t test and expressed by standard deviation of mean soil (x±s). Quantitative data that did not conform to normality were tested by non-parametric test, expressed by median and quartile distance [M(P25-P75)]. All statistical tests were conducted with bilateral tests to obtain the exact probability P value. The chi-square test was used for counting data and the rank sum test for rank data. If $P<0.05$, the tested data was considered statistically significant.

ETHICAL APPROVAL

This study was approved by the ethics committee of Linquan County People’s Hospital (20-LQ-EC-03). Signed written informed consents were obtained from the patients and/or guardians.

RESULTS

Comparison of patients' baseline data

Our study found that both Observation group and Comparison group patients had similar average ages, sexes, body mass indexes (BMIs), blood pressures (SBPs, DBPs) and underlying diseases. P-value >0.05 indicates insignificant difference (table 1).

Comparison of inflammatory factors

The Observation group had lower CRP and IL-6 levels compared to the Comparison group, with significant differences on Day 14 (table 2).

Comparison of coagulation function

The Observation group had slightly higher APTT and PT values compared to the Comparison group. The Observation group had slightly higher thrombin time (TT) at 16.00±1.92 seconds compared to 15.95±1.90 seconds in the Comparison group. By Day 14, the Observation group consistently showed significantly higher values for APTT, PT and TT compared to the Comparison group ($P<0.05$).

Analysis of liver and kidney function

The observation group exhibited higher levels of GGT on Day 14 in comparison to the control group, while concurrently displaying lower levels of Cr and BUN.

Table 1: Comparison of baseline data of patients

	Observation group (48)	Comparison group (48)	t/x^2	*P-value*
Average age (years)	58.6±6.8	58.8±6.1	0.151	0.439
Gender (Male/female)	25/23	22/26	0.375	0.540
BMI (kg/m^2)	23.84±1.26	23.88±1.23	0.157	0.437
SBP(mmHg)	143.07±12.49	142.63±10.79	0.184	0.426
DBP(mmHg)	92.93±6.57	94.20±6.46	0.533	0.297
Underlying disease			0.829	0.842
Hypertension	16	12		
Diabetes	11	13		
Hyperlipidemia	10	11		
Coronary heart disease	11	12		

Table 2: Comparison of inflammatory factors between the two groups ($\bar{x}$ ±sd)

	CRP(mg/L)		IL-6(pg/ml)	
	Day 1	Day 14	Day 1	Day 14
Observation group (48)	8.21±2.39	5.50±1.26	5.84±1.38	3.09±0.16
Comparison group (48)	8.57±2.34	7.56±1.18	5.99±1.11	3.72±0.13
t	0.745	8.267	0.586	4.368
P-value	0.228	0.001	0.279	0.003

Table 3: Comparison of coagulation function between the two groups ($\bar{x}$ ±sd)

	APTT		PT		TT	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
Observation group (48)	41.91±7.26	36.54±4.62	13.99±3.02	13.36±2.00	15.86±1.69	16.00±1.92
Comparison group (48)	41.49±6.7	35.71±4.52	14.05±3.43	13.45±2.43	15.82±1.71	15.95±1.90
t	0.294	3.672	1.772	2.331	1.413	2.254
P-value	0.384	0.021	0.079	0.022	0.268	0.026

Table 4: Analysis of liver and kidney function in two groups ($\bar{x}$ ±sd)

	ALT (IU/L)		AST (IU/L)		ALP (IU/L)	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
Observation group (48)	18.6 (12.7-24.6)	18.6 (13.4-24.6)	18.7 (15.4-31.1)	18.5 (14.7-32.0)	79.4 (68.8-92.1)	75.7 (64.2-87.1)
Comparison group (48)	18.5 (12.2-24.1)	18.1 (12.2-24.1)	19.0 (15.6-28.8)	18.4 (15.6-27.3)	79.2 (69.1-92.0)	75.5 (64.3-87.0)
t	0.072	0.006	0.101	5.371	1.094	11.593
P-value	0.924	0.894	0.919	0.020	0.277	0.0001
	GGT (IU/L)		Cr (umol/L)		BUN (mmol/L)	
	Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
Observation group (48)	29.6 (19.1-33.4)	29.3 (18.6-34.1)	79.53±13.70	76.59±13.42	5.76±3.47	5.32±2.04
Comparison group (48)	29.8 (19.3-33.2)	28.4 (19.3-33.2)	79.42±13.70	76.83±14.25	5.66±3.37	5.90±3.34
t	0.750	7.136	0.458	3.062	0.071	3.519
P-value	0.456	0.004	0.648	0.037	0.829	0.021

Additionally, ALP levels were elevated in the observation group on Day 14. No significant differences in liver and kidney function tests were observed between the groups on both Day 1 and Day 14, with the exception of GGT, Cr, and BUN levels on Day 14, which demonstrated significant disparities (P-value<0.05). Please refer to table 4 for detailed data.

DISCUSSION

Traditional Chinese Medicine (TCM) addresses acute cerebral infarction by enhancing blood circulation, mitigating cerebral edema, preventing thrombosis, reducing inflammation and promoting overall circulatory health (Shen *et al*., 2023). These mechanisms and principles underscore the distinctive benefits and potential

of TCM in the management of acute cerebral infarction. TCM ingredients exert a multifaceted impact on the treatment of this condition (Guo *et al*., 2023). Danshen injection, for instance, contains danshousu, which inhibits platelet aggregation, improves systemic circulation, particularly cerebrovascular hemodynamics and thus prevents thrombosis (Wang *et al*., 2023). Salvia miltiorrhiza is employed to promote blood circulation and resolve stasis, while vinpocetine is used to enhance blood supply to ischemic areas. TCM can alleviate the damage caused by cerebral ischemia by improving a variety of physiological factors (Huang, 2024).

In the formulation of Dagentian Decoction, ingredients such as rhizomachiuanxiong, Duhuo, Angelica, Paeoniae, and others are administered as a water decoction. This approach achieves the effects of clearing wind and heat, nourishing blood, and promoting circulation, while also reducing the expression level of serum inflammatory factors, improving microcirculation, and enhancing therapeutic efficacy (Liu *et al*., 2022). In TCM, phlegm stasis is considered a pivotal factor in the pathogenesis of cerebral infarction. Treatment involves the use of specific herbs to balance the body's energy flow (Chen, *et al*., 2020). Herbs such as Bupleurum can disperse phlegm and expel pathogenic factors, Atractylodis Macrocephalae Rhizoma can strengthen the spleen and reduce phlegm, peony can nourish blood and Yin and licorice and ginseng can reinforce the spleen and qi. Additionally, Chinese herbs are used to invigorate and replenish blood (Zhang *et al*., 2022). These herbs, when boiled to create a decoction, can significantly enhance the therapeutic effect.

On day 14, the observation group exhibited lower blood urea nitrogen (BUN) levels and higher alkaline phosphatase (ALP) levels compared to the control group. However, other measures of liver and kidney function did not exhibit significant differences between the groups on days 1 and 14. Several studies have demonstrated that C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) and other inflammatory factors are involved in the inflammatory response following cerebral infarction, exacerbating brain tissue injury, enlarging the infarct size and worsening the extent of cerebral neurofunctional deficit (Yan *et al*., 2023). Modern pharmacological research has indicated that substances such as gastrodia and licorice can attenuate the inflammatory response and reduce the over expression of inflammatory factors in cerebral infarction and have demonstrated neuroprotective effects (Ruqiao *et al*., 2020). Furthermore, modern pharmacological studies have revealed that pinellia possesses lipid-lowering properties. Tuckahoe is beneficial for water metabolism and resolving retention, as well as for regulating immune function. Gastrodia can effectively prevent thrombosis and mitigate cerebral ischemia-reperfusion injury. Red peony root can effectively increase coronary blood flow and has the effect of preventing thrombosis and promoting hemostasis (Huang *et al*., 2022). *Salvia miltiorrhiza* can eliminate free radicals, reduce hyperlipidemia and exhibits vasodilating effects. Atractylodis Macrocephalae Rhizoma protects the liver and gallbladder and enhances immune function. Citrus Pericarpium corrects lipid metabolism disorders, improves microcirculation, inhibits platelet aggregation, and reduces blood viscosity. Rehmannia glutinosa has significant effects on blood pressure regulation, hypoglycemia, and immune modulation (Tai *et al*., 2020). Peach kernel has vasodilating, anticoagulant and thrombosis-preventing properties, which can improve hemorheological indices and reduce red blood cell aggregation. Safflower inhibits platelet aggregation, increases cerebral blood flow, eliminates free radicals and promotes thrombolysis. Rhizoma Chuanxiong increases coronary flow, improves microcirculation and prevents thrombosis (Li *et al*., 2023). Angelica sinensis exhibits certain free radical scavenging and antioxidant effects, effectively inhibiting cerebral hypoxia.

On day 14, the observation group displayed significantly higher levels of APTT, PT and TT compared to the control group. Additionally, GGT levels were elevated in the observation group, while Cr and BUN levels were reduced. These discrepancies were statistically significant. The rationale for these findings is multifaceted. Atractylodis Macrocephalae Rhizoma Tianma soup is a prevalent herbal formula used as an expectorant, known for its effects in calming liver wind, eliminating phlegm, drying dampness, promoting diuresis and strengthening the spleen. It can augment blood flow and reduce vascular resistance (Li *et al*., 2024). This formula effectively disperses pathogenic factors and enhances blood circulation to address the precursor syndrome of ischemic stroke (Yang *et al*., 2023). Modern medical research has established that ischemic stroke aura is associated with hemodynamic disturbances due to atherosclerosis, and abnormal blood viscosity is a risk factor for stroke aura.

The constituents of the formula, such as Pinellia, aid in reducing dampness and phlegm, reversing vomiting; Gastrodia calms the liver to extinguish wind and suppress Yang; Atractylodis Macrocephalae Rhizoma and Poria strengthen the spleen, remove dampness and address the root cause of phlegm; Citrus Pericarpium regulates qi and eliminates phlegm; Peach kernel and Safflower promote blood circulation and dissipate stasis; Angelica tonifies blood and promotes circulation (Wu and Hu, 2020). Rhizoma Chuanxiong promotes blood circulation and qi, while adding Salvia miltiorrhiza to the formula aids in removing blood stasis and enhancing the flow of channels and collaterals. Collectively, the formula supports qi, resolves phlegm, promotes blood circulation and dissipates blood stasis. Pinellia exhibits antioxidant effects, while Peach kernel dilates blood vessels, increases

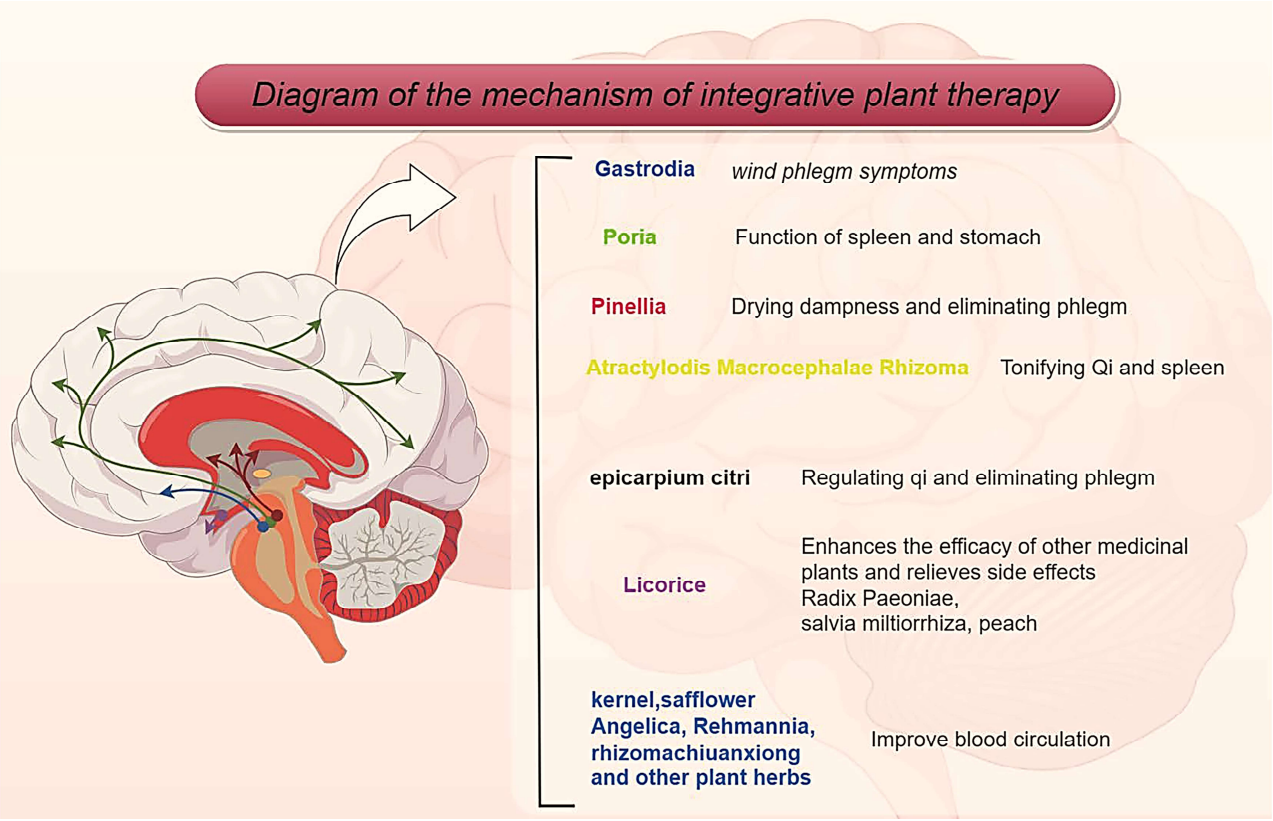

Fig. 1: Principle of treating cerebral infarction with combination of traditional Chinese medicine and plants (By Figdraw)

organ blood flow and possesses antithrombotic properties (Zhan *et al*., 2022). Safflower possesses anticoagulant effects and improves circulation, while Salvia miltiorrhiza enhances blood flow and reduces cerebral ischemia-reperfusion injury.

CONCLUSION

Tianma soup with Peach kernel safflower Fried is effective in treating acute cerebral infarction by reducing inflammation and improving clinical symptoms. This therapy has shown positive results in patient rehabilitation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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