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Review Article

Are Herbal Medicines Effective in the Treatment of Ischemic Stroke? A Systematic Review of Human-Controlled Clinical Trials

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Abstract

Cerebrovascular diseases are common, and stroke constitutes the third cause of death as well as the first cause of disability all over the world. Many studies have demonstrated the beneficial effects of herbal preparations on stroke. This research was designed to categorize the results of these studies. The materials presented in the databases of Cochrane, ISI, PubMed and Scopus until January 30, 2019, were searched to examine human studies written in English. Only randomized controlled trials (CRTs) were included. Four randomized controlled trials were selected to be examined in this systematic review. Six medicinal herbs were assessed in every article. Not only inclusion and exclusion criteria but also outcome measures differed between the articles. The results of these studies indicated that these medicinal plants might contribute to the management of stroke. No severe reactions had been described during the administration of herbal medicines in these six studies. Further investigations are required to examine the efficacy of herbal medicines on ischemic stroke.

Keywords: Complementary medicines, Herbal medicines, Stroke

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Introduction

Cerebrovascular diseases have been reported as one of the first three leading causes of death following myocardial infarction and cancer, and the first cause of disability all over the world (1, 2). According to the available evidence, one individual dies due to stroke in the USA every three minutes. Moreover, the number of people suffering stroke has dramatically increased in developing countries (1). Brain ischemia is of the common causes related to disability in adulthood, and is estimated to affect 23 million people all over the world by 2030. Hence, the proper planning and management for its prevention and treatment are

necessary. This medical condition is associated with large costs and burden and various adverse effects such as motor paralysis and mental disorders that affect the quality of life and creativity (1-3).

Disturbances in blood flow may lead to reduced brain function, death of some cells, and even stroke (4, 5). Ischemic stroke, which is induced by large cerebral artery blocking, is considered the main pathological kind of stroke (6-8). In ischemic stroke, the cerebral blood flow is interrupted because of vascular obstruction, having led to a complex multistage pathophysiologic process known as an ischemic cascade at the cellular and tissue levels (9, 10). Moreover, a complex of different reactions occurs in neurons containing inflammatory pathways, ionic imbalance, apoptosis, and so forth. Ischemic stroke and the subsequent reduction or blockage of local blood flow impose damages and death upon the cells at the core area where blood flow is blocked. On the contrary, the cells at the penumbra also undergo damages, and they have not normal function, but are still alive. Therefore, they can be recovered by means of antioxidant drugs following tissue reperfusion (11).

As a result, early reperfusion has the greatest effect on disability following ischemic stroke through reducing infarction size after local blood flow blockage (12). Currently, common medications in the management of acute ischemic stroke include fibrinolytic therapy and antiplatelet drugs (such as aspirin, rt-PA and tissue plasminogen activator (8, 13, 14). However, these medications are effective, particularly within early hours after the onset the symptoms of ischemic stroke but they are associated with adverse effects such as increased risk of hemorrhage and mortality, and therefore they would not be used for all patients (7, 13, 18-21).

Considering the complicated pathophysiology and several mechanisms involved in stroke, applying only one therapeutic strategy is not effective. Hence, combining thrombolytic therapy with protective treatments such as potential supplemental alternatives seems more beneficial (15). Given the increasing incidence of stroke, its adverse consequences and high costs of physiotherapy and rehabilitation interventions, employing supplemental treatments, in association with modern medicine is recommended. Alternative therapy based on herbal medicines gives rise to promising results. Herbal agents with relative safety could be used in addition to chemical medicines to cope with complicated conditions such as stroke. Not only do they display synergistic effects with chemicals, but also they negate their toxicity consequences (16, 17). Moreover, these herbal medicines improve brain microcirculation and protect cells against damages and apoptosis (23).

Many studies have revealed the beneficial effects of medicinal plants on stroke (24). This research was designed to classify the results of these studies.

Materials and Methods

The research team working on the present study designed a systematic search to review only the randomized clinical trials (RCTs) that are used herbal drugs in ischemic stroke.

The keywords that were used on their own or in combination in this review included stroke, ischemic stroke, cerebral infarction, brain infarction, cerebral ischemia, brain ischemia, CVA, cerebrovascular accident, ischemic attack, herbal medicine, plant extracts, herb, botany, phytotherapy, naturopathy, herbal drugs, pharmacognosy, herbal remedy, herbal preparations, herbal product, medicinal plants, herbal supplement, traditional medicine, Unani medicine, complementary medicine, Chinese medicine, alternative medicine, Persian medicine, randomized clinical trial, randomized controlled trial, randomized clinical trial allocating, single blind method, RCT, double blind method, random allocation, and placebo. Searches were carried out in Cochrane, ISI, PubMed and Scopus until 30 January, 2019 for English language human studies.

Inclusion criteria

RCTs associated with the effects of medicinal plants on ischemic stroke (both acute and chronic phases) up to January 30, 2019 were included in this study.

Inclusion criteria were the following:

1-Herbal species that have been documented in Persian medicine, Chinese medicine and other complementary medicines.

2- Adults with a clinical diagnosis for ischemic stroke.

3-All the restrictions concerning administration, formulation or method of preparation of the plants such as capsules, granules, pills or injected agents,

were excluded.

4-Single extract or combination of maximum 2 herbal extracts

5- Herbs with therapeutic effect and not preventive effect.

6- Studies written in English.

Extracted data included several items such as the time and location of research, authors, the methodology used to conduct research, plant species, the number and method of administration, comparison between different regimens, the duration of therapy and follow-up, the number of participants and conditions, the number of participants that were excluded during follow-up, harmful effects, and primary as well as secondary outcomes.

Bias Assessment

Risk of Bias within Studies

This study used Cochrane Collaboration's tool (Higgins and Green 2011) to evaluate the quality and risk of bias of every trial. The results have been indicated in Table 1. All of the studies included in this research were randomized clinical trials. Allocation concealment, proper blinding, and double blinding were appropriately described in four out of the six trials.

All of the major texts were retrieved and studied by both reviewers (Delshad E and Ayati Z). The reviewers independently carried out the screening of studies, selection, validation, data extraction, and the assessment of methodological quality. Disagreements in data evaluation were determined by discussion and reviewed by the other author (Naghedi H), and finally consensus was reached in all cases.

Results and Discussion

Two thousand four hundred and seventy-two articles were recognized through the primary search. Following the exclusion of 162 duplicates, 2310 articles persisted for evaluation. Reviewing the titles and abstracts of articles led to the exclusion of 2235 articles. Among the remaining articles (75), following a particular investigation, 36 articles were excluded because they were not written in English, and 21 articles did not meet the inclusion criteria. Finally, we reviewed the full text of 18 articles in detail. Ten articles were excluded because they had used more than 2 herbs or herb animal agents, and 2 of them were not specifically about ischemic stroke.

Finally, 6 articles were evaluated exactly through variances in population, intervention, and type of the study, meaning that six articles were eligible for this study. Of the six articles included, five were carried out in China, and one in Iran. All of the studies were conducted between 2011 and 2018. Summaries of these trials have been described in Table 1, and a flowchart indicating the process of study selection have been presented in Figure 1.

In total, five hundred fourteen patients were included in the six clinical trials, aged 18 and 80 years. Inclusion criteria were not completely similar in the 6 trials. Two studies conducted by He and Oskouei were enforced on an ischemic stroke in the anterior cerebral circulation. The studies by Wei in 2017, Peng in 2018 involved acute ischemic attack. Another study by Wei in 2015 focused on ischemic stroke according to clinical standards in China that were in the rehabilitation period according to TCM criteria (between 15 days and 6 months after the onset of symptoms.)

Exclusion criteria were the same in some aspects and were different in other aspects as follows:

The first four of them exclude patients with chronic and severe diseases such as heart, liver and kidney disorders, and also profound loss of consciousness such as coma, stupor, severe dementia and psychiatric disorders. Wei, 2017, and He excluded cerebral hemorrhage or tumor, and He and Oskouei excluded pregnancy and lactation. Furthermore, in the study carried out by Peng, patients who had cerebral hemorrhage, resuscitated encephalopathy and a GCS score of 4 or less were excluded.

Moreover, Wei, 2017, and Peng, 2018, excluded patients with diseases in hematopoietic system, endocrine system, bones and joints, cardiovascular system, and patients who had any surgery or intervention in cardiovascular system which cannot be performed with MRI. The other exclusion criteria of the study by Li were ischemic stroke caused by inflammation, and the interval between the former attack of stroke and current episode less than 3 months, and having allergy to some drugs and meanwhile participating in other pharmaceutical studies. Moreover, Wei, 2015, excluded TIA (transient ischemic attacks), major cognitive impairment,

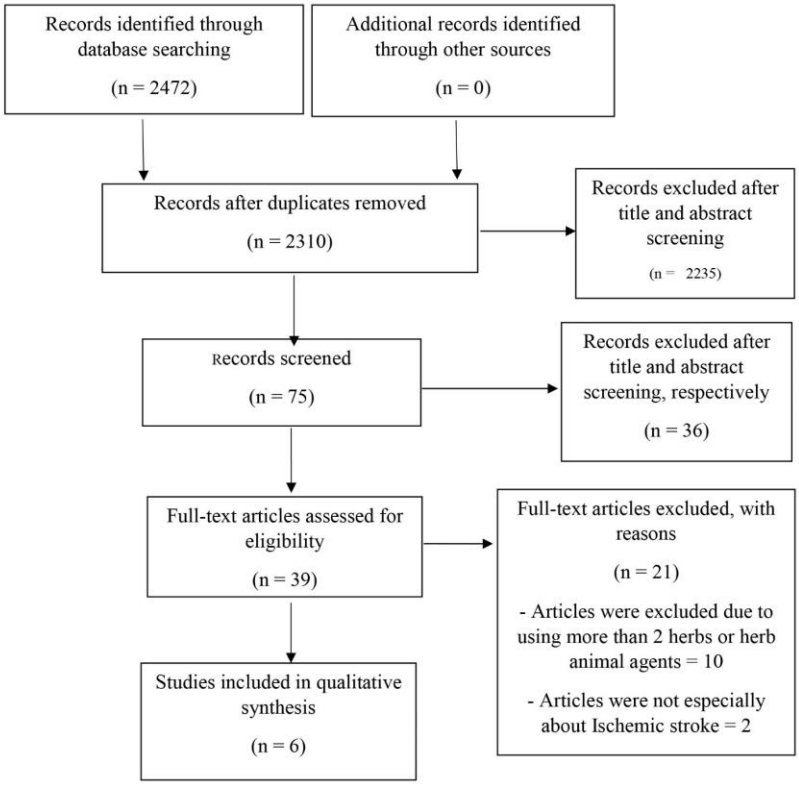

Figure 1. Flowchart indicating the process of study selection

intracranial tumor and a history of psychoactive medication use or drug addiction, and Oskouei excluded having the indication of anticoagulant therapy. Exclusion criteria of the study by Liu concluded all of the above-mentioned criteria in addition to abnormal levels of creatinine and alanine transaminase and chronic pulmonary disease.

The present systematic review involved six articles recording clinical trials of medicinal preparations in patients with ischemic stroke. The probability of bias and quality of eligible RCTs were assessed using the Cochrane Collaboration tool for the risk of bias (Table 3)

Through the six studies, five medicinal plants were utilized. One of the main challenges in other same systematic review articles is comparing the efficacy of interventions because of the variety of plants used in their researches. For this reason, we excluded the studies with more than 2 herbs in their preparations for the exact evaluation of the effectiveness of herbs.

Regarding the various herbal extracts, different measured variables, and research instrument in the reviewed studies, the exact comparison between the results is not possible although we can compare the overall effect of the herbal medicines consumed by patients with ischemic stroke.

He *et al.* demonstrated that the main component of Sanchitongshu capsule is Panaxatriol saponins (PTS), and it has been considered as an antiplatelet agent (18). The results of this study indicated that the combination of Aspirin (50 mg/d) and Sanchitongshu is associated with significant effects in daily activities and neurological deficits after 28 days of treatment without increasing risk of hemorrhage compared to the control group. The synergistic action was widely known for its capacity to ameliorate the movement of the limbs (1).

Based on the results of the study conducted by Oskouei *et al*., the administration of *Ginko biloba* led to the amelioration of functional recovery and improvement neurological deficits in patients with acute ischemic stroke. Furthermore, in this study (n=102), 20 patients in the G biloba group and 18 patients in the placebo group were lost and also 19 patients in the G biloba group and 18 patients in the placebo group could not continue the trial (25). Hence, the generalizability of the finding is decreased.

A review study demonstrated that Ginkgo extracts,

such as EGb761, powerfully decrease cellular edema and neurodegeneration in ischemic condition in vivo and in vitro separately. This process seems to be related to a

Table 1: Characteristics of the included studies.

ID	Study(Author, Year, Country)	Study design	Sample size	Population	Type of plant	Intervention	Duration of treatment
1	He 2011 China (1)	Multi centered, Randomized, placebo controlled, double blind	140	Ischemic stroke in anterior cerebral circulation (commenced within one month)	Sanchitongtshu (panaxatriol saponins extracted from *Radix not ginseng* root)	Group A: Aspirin (50 mg/d) + Sanchitongshu (1 capsule TID) Group B: Aspirin (50 mg/d) + placebo (1 capsule TID)	4 weeks
2	Oskouei 2013 Iran (25)	Randomized, placebo controlled, double blind	102	Acute Ischemic stroke	*Ginkgo biloba*	Group A: *G biloba* tablet(40 mg TID) Group B: placebo (40 mg TID)	4 month
3	Wei 2017 China (11)	Single blind, placebo controlled, Randomized clinical trial	44	Patients with acute ischemic stroke	. *Ligusticum wallichii* (chuanxiong in Chinese) and *Salvia miltiorrhiza* (Danshen in Chinese) are two major components of XXMT.		2 week
4	Wei 2015 China (26)	a pilot, randomized, double-blind controlled placebo study	28	Patients in the rehabilitation period of ischemic stroke	. *Ligusticum wallichii* (chuanxiong in Chinese) and *Salvia miltiorrhiza* (Danshen in Chinese) are two major components of XXMT.	Group A: XXMT tablet oral 0.8 g/ TID Group B: Placebo tablet 0.8 g/TID	3 Month
5	Peng et al 2018 China (27)	a randomized controlled blinded +placebo study	159	Patients with diagnosis of acute ischemic stroke	Salvianolic acid (SA) is an extract of *Salvia miltiorrhiza Bunge* (Danshen)	Control group: aspirin enteric-coated tablets 100 mg/day and atorvastain tablets 20 mg/day + 250 ml normal saline IV (as placebo) experimental group: SA (0.13 g/day) in 250 ml	14 days

						normal saline+ standard therapy. rtPA in patients vulnerable to thrombolysis in control or SA group.	
6	Liu et al 2018 China (28)	Randomized controlled study	67	Patients with acute cerebral infarction	Kudiezi (KDZ) is made of *Ixeris sonchifolia* (Bge.)	antiplatelet, anticoagulant, fibrinolysis, and dilation and neuroprotective therapy in the control group KDZ group received basic treatments + infusion of Kudiezi injection (40 ml in 250 ml of 0.9% sodium chloride) was intravenously injected once daily at 40 drops/min	14 days

Table 2: Characteristics of the included studies.

ID	Study (author, year, country)	Primary outcome	Secondary outcome	Adverse events	Result
1	He 2011 China **(1)**	improvement in neurological deficit, after 28 days measured with European Stroke Scale **(ESS**) improvement in activities of daily living after 28 days, measured with Barthel index (**BI**)	effect of Sanchitongshu capsule on hemorrhagic transformation administration (by analysis of blood and urine routine tests, biochemistry tests and electrocardiogram examinations)	no severe adverse events or deaths; slight to moderate gastro-intestinal adverse reaction in some of the patients in both groups which lasted for 2-7 days	1) Significantly better effects of sanchitongshu than aspirin alone in improving activities of daily living and neurological deficit after 28 days of treatment (increased score of ESS: t=-5.02, p<0.0001) 2) synergistic action of sanchitongshu with aspirin in ameliorating the movement of limbs (activities of daily living (increased score of BI: t=-2.4, p=0.0178) 3) No hemorrhagic

					transformation of the infarct by using sanchitongshu combined with aspirin.
2	Oskouei 2013 Iran **(25)**	reduction of NIHSS score		Not reported	- More stage improvement in *G. biloba* group. - No significant differences in regression analysis of the trend of NIHSS scores changes between 2 groups. - more 50% reduction in NIHSS score in *G. biloba* group than placebo group**.** In addition, multivariate regression adjusted for age and sex showed a significant NIHSS reduction in the G biloba group compared to the control (P<0.05).
3	Wei 2017 China (11)	neurologic deficits (NIHSS) quality of life (SSQOL)	brain functional connectivity (rs-fMRI) blood viscosity (htc)	no severe adverse events or deaths	Significant improvement of neurological deficit, quality of life and blood viscosity and not infarct volume. In addition, experimental group showed significant enhancement in functional connectivity within the default mode, frontalparietal, and motor control networks. Also, the changed connectivity in the left precuneus is correlated to

					the improvement of NIHSS and SSQOL scores positively.
4	Wei 2015 China (26)	neuropsychological tests: general cognitive status and other domains, such as memory(AVLT, ROCF),attention(SCWT, SDMT);, spatial processing (ROCF,CDT) executive function and language ability (SCWT,BNT,CVFT).	brain activation (rsfMRI)	no severe adverse events or deaths	In the experimental group, the patients' episodic memory showed significant improvement. The resting-state fMRI analysis showed that a remarkable reduction in the fractional amplitude of low-frequency fluctuation value in the bilateral middle cingulate gyrus. Also, Cognitive improvement over 3 month of rehabilitation
5	Peng et al 2018 China (27)	Based on the changes in PWI (perfusion-weighted magnetic resonance imaging) parameters, there was no significant differences between SA and control groups in Rcbv (relative cerebral blood volume), rCBF (relative cerebral blood flow), rMTT (regional mean transit time), and rTTP (regional time to peak) in the DWI (diffusion-weighted magnetic resonance imaging) lesion or its surroundings. Although compared with the different responsible vessel, there was a significant difference between the two groups in ICA (internal carotid artery) in rCBV, rCBF, and rMTT; but there was no significant difference in VBA. Comparing the perfusion states showed that there was no significant difference in normal perfusion. However, a significant	neurological function measurment through National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) at admission and 3 month-follow up indicated that there was no significant difference in NIHSS between the two groups at admission (8.43±6.05 in the SA group vs. 9.12±5.98 in the control group P=0.47). While at the 3-month follow-up, NIHSS in the SA group was significantly reduced compared to control group (3.25±4.67 vs. 5.76±3.82; P=0.001), and mRS was significantly decreased in the SA group (1.26±1.58 vs. 2.01±1.58, P=0.005)	The adverse events or death is not reported in the study	The findings indicate that patients with hypoperfusion may benefit from SA more than patients with normal perfusion. Also, the neurological evaluation showed that the SA has a neurological protective effect on ischemic brain tissue. Overally, more patients in the SA group has good condition at the 3-month follow-up significantly compared with the control group.

		difference indicated in the hypoperfusion between the two groups in rCBV, rCBF, rMTT, and rTTP, either in the DWI lesion or in its surrounding.		
6	Liu et al 2018 China (28)	In both groups, NIHSS score was improved. There were no significant difference in NIHSS scores between the two groups on days 1, 3, and 14 but on days 5 and 7, NIHSS scores in the KDZ group were lower than in the control group (day 5: P=0.030; day 7: P=0.042)	NSE (Serum neuronspecific enolase) and S100B (S100 calcium-binding protein B) levels reduced in both groups significantly. There were no differences in NSE and S100B between the two groups on days 1 and 3. From day 5, the KDZ group showed lower NSE and S100B compared with control (NSE: P=0.001 and P=0.0006; S100B: P<0.0001 and P<0.0001) From day 1 to day 14, the levels of IL-6, Il-18, and MMP-9 (matrix metalloproteinase-9) decreased in both groups, while IL-10 levels increased (P <0.05). Compared with the control group, IL-6 levels were lower in the KDZ group on days 3, 5, and 14 (P <0.0001, P<0.0001, and P=0.0006); IL-18 levels were lower in the KDZ group on days 5 and 14 (P<0.0001 and P= 0.0005); IL-10 levels were higher in the KDZ group on day 3 (P=0.0003); and finally, MMP-9 levels were lower on days 3 and 14 (P=0.02 and P= 0.0009)	On day 5, the NIHSS scores were positively correlated with IL-18 and S100B On day 14, the NIHSS scores were negatively correlated with IL-10. No other correlations were showed between NIHSS scores at different time points and biomarkers. Kudiezi injection Could significantly decrease serum IL-6, IL-18, MMP-9, NSE, and S100B levels and increase IL-10 levels in patients with acute stroke earlier than conventional stroke treatment.

Note. TID = Three times in a day; htc= hematocrit; rsfMRI= Resting-state functional magnetic resonance imaging; NIHSS = National Institutes of Health Stroke Scale; SSQOL= Stroke-Specific Quality of Life Scale; ESS = European Stroke Scale; BI= Barthel Index; ROCF= Rey-Osterrieth Complex Figure Test; SCWT= Stroop Color and Word Test; SDMT= Symbol Digit Modalities Test; ROCF= Rey-Osterrieth Complex Figure Test; CDT= Clock Drawing Test; SCWT= Stroop Color and Word Test; BNT= Boston Naming Test; CVFT= Category Verbal Fluency Test, PWI=perfusion-weighted magnetic resonance imaging;
Rcbv=relative cerebral blood volume; rCBF=relative cerebral blood flow; rMTT =regional mean transit time; rTTP =regional time to peak; DWI =diffusion-weighted magnetic resonance imaging; ICA: internal carotid artery; NSE =Serum neuronspecific Enolase; S100B =S100 calcium-binding protein B; MMP-9 =matrix metalloproteinase-9

reduction of excitotoxicity through the inhibition of ischemia-induced discharge of glutamate. Ginkgo extracts, such as EGb761, might be beneficial to stop the damages caused by ischemia in stroke-prone patients (19). Another study by Lie *et al*, 2010, indicated that Ginkgolide B reduced infarct size, improved the neurological insufficiency and the permeability of brain blood barrier (BBB). Ginkgolide B has protective effects on cerebral damages through stopping the inflammation induced by ischemia/reperfusion injuries (20). Two studies conducted by Wei in 2015 and 2017 evaluated the effect of XXMT in stroke patients (11, 26). XXMT has been extensively consumed in traditional Chinese medicine for treating ischemic stroke, cerebral thrombosis and coronary heart disease (21).

Wei *et al.* assessed, in a study carried out in 2015, the effect of XXMT on general cognitive status. The patients who had received XXMT had better condition compared to the control group. This treatment alleviates cognitive impairment, and enhances brain activation in the three-month period of post-stroke rehabilitation (26). Another study focused on neurological deficits through NIHHS score, functional

Table 3: Risk of bias.

Trials	Random sequence generation	Allocation concealment	Blinding (Study patient)	Blinding (treating physician)	Blinding of clinical outcomes	Incomplete outcome data addressed	Free of selective reporting	Free of other bias
He 2011 China	+	+	+	+	_	+	+	+
Oskouei 2013	+	+	+	+	_	+	+	_
Wei 2017, China	+	_	?	_	_	+	+	+
Wei 2015, China	+	+	+	+	_	+	+	+
Peng 2018, China	+	+	+	?	?	?	+	+
Liu 2018, China	+	+	-	-	?	?	+	+

MRI, blood viscosity and quality of life. Changes in NIHSS and quality of life are related to changed connectivity in brain that was indicated through functional MRI (11). Similar findings were observed in a study conducted by Peng *et al.* through PWI (perfusion-weighted magnetic resonance imaging). In this study, significant improvements were observed in NIHSS score and modified Rankin scale in a three-month follow-up in patients treated by salvianolic acid. Patients with hypoperfusion at admission time benefit more than patients with normal brain perfusion based on the PWI parameters. These findings indicated the effect of herbal medicines in brain perfusion and consequently in NIHSS score (11, 26, 27).

According to the aforementioned results, Zhang *et al.*, demonstrated that XXMT had a beneficial effect on blood stasis by decreasing the whole blood viscosity (WBV). XXMT improved blood stasis by regulating the expressions of F13a1, Car1, and Tbxa2r (32). Other studies have established that tetramethylpyrazine (TMP), the main extract of *Ligusticum Wallichii*, is a naturally active alkaloid that stimulates vasodilatation and prevents platelet mass in addition to antioxidant effects (33-36).

In accordance with the research carried out by Peng, the studies conducted on *salvia miltiorrhiza* demonstrated that tanshinone IIA (Tan IIA), the major extract of *salvia miltiorrhiza*, is a lipid-soluble active compound capable of having several properties, including anti-inflammatory, anti-oxidant, anti-apoptotic and neuroprotective properties (22)

The last reviewed study, Liu *et al.*, 2018, assessed the effect of Kudiezi on serum inflammatory biomarkers in patients with acute cerebral infarction. The findings suggested that patients who had received this herbal extract had lower scores in NIHSS and lower levels of inflammatory cytokines (S100 calcium binding protein B as a high sensitive biomarker for brain damage which lead to release of pro-inflammatory cytokines, neuron-specific enolase, interleukin-6, interleukin-18, and matrix metaloproteinase-9; by enzyme-linked immunosorbent assay compared to control group, while IL-10 as anti-inflammatory cytokine was higher in the KDZ group. The higher level of proinflammatory cytokines is positively related to higher scores of NIHSS in patients with acute ischemic stroke (28).

Conclusion

Overall, all of the selected articles indicated the efficacy of medicinal herbs in the treatment of ischemic stroke. The aforementioned studies assessed the positive effects of herbal medicines in reducing brain damage through different aspects such as anti-platelet and anti-inflammatory effects, and improving brain perfusion. However, the absence of the same

protocol for the evaluation of these studies was the major challenge in comparing the effectiveness of herbal medicines. Other limitations included the small number of populations, and short-term follow-up after treatment. Finally, due to these limitations along with the risk of bias in some studies, the efficacy of herbal medicines on ischemic stroke needs to be further proven through future studies.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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