**Herbal medicines for Ischemic stroke: a systematic review of controlled clinical trials**

1. **INTRODUCTION**

Cerebrovascular disorders are reported as one of the three leading causes of death and also the first cause of disability across the globe (1). Stroke constitutes the third cause of death following myocardial infarction and cancer worldwide (2). According to the existing statistics, every three minutes one individual dies due to stroke in the USA. Recently, the number of people afflicted with stroke has been on the sharp rise in developing countries (3). The recent studies have highlighted the growing incidence and mortality rate of stroke among young adults, which, in turn, necessitates the significance of planning and management for the prevention and treatment (4). Brain ischemia is of the common causes related to disability in adulthood and is estimated to affect 23 million persons worldwide by 2030. This medical condition is associated with large expenses for patients as well as the country’s health system besides changes in the quality of life. It is also associated with different adverse effects, including motor paralysis, mental disorders, and even death. Despite the state-of-the-art advances in basic knowledge and therapeutic methods of stroke, its incidence is still growing (3, 5, and 6).

All of the aforementioned reasons highlight the importance and necessity for more effective treatments. This cerebrovascular disease develops as a result of insufficient blood flow in brain. Disturbances in blood flow may lead to reduced brain function, cells death and stroke (7, 8). This decline in the cerebral blood flow can arise from thrombosis, arterial emboli, or haemorrhage (8). Ischemic stroke, which is produced by the blocking of large cerebral artery, is the main pathological kind of stroke (9-11). In ischemic stroke, the cerebral blood flow is interrupted because of vascular obstruction, following a complex multistage pathophysiologic process known as an ischemic cascade at the cellular and tissue levels (2, 12). Moreover, some different damaging reactions occur in neurons containing inflammatory pathways, ionic imbalance, apoptosis, and so forth. These mechanisms induce the cellular and tissue impairments in two stages. The first stage is ischemia due to reduced blood flow at the target site. Thereafter, the second stage, known as reperfusion, commences due to the return of blood flow from the tissue (2, 13). Ischemic stroke and the subsequent reduction or blockage of local blood flow imposes damage and death upon those cells at the core area where blood flow is blocked. On the contrary, those cells at the penumbra also undergo damage and fail to function normally but are still alive. Therefore, they can be recovered by means of antioxidant drugs following tissue reperfusion (14).

Accordingly, (what matters first) for effective treatment of disability caused by ischemic stroke is early reperfusion to reduce infarction size after local blood flow blockage (15). Currently, common clinical training in considering patients with an acute ischemic stroke includes fibrinolytic therapy (administration of recombinant tissue-type plasminogen activator, rt-PA) and antiplatelet drugs (such as aspirin (11, 16, 17). However, rt-PA treatment is more effective only if given within approximately 3–4.5 hours of symptoms onset. Moreover, numerous revisions have stated that antiplatelet therapy did not expressively decrease the risk of repeated stroke as predictable, and additionally it increases the risk of haemorrhage and death (11, 16, 18, 19). The restrictions of these usages, likely reflecting the several processes involved in pathogenesis of ischemic strokes, so encouraged the wish to discover other treatment programs (16-18).

Currently, the most effective therapeutic method in these patients is intravenous tissue plasminogen activator (TPA) injection within 3 hours of symptom onset that is not possible for all patients (20). Furthermore, fibrinolytic agents, such as streptokinase and urokinase are not so effective and have some limitations along with adverse effects as well as mortality risk (7, 13, and 21).

Considering the complex pathophysiology and the several mechanisms behind stroke or a cerebrovascular accident (CVA), applying only one therapeutic strategy would not be so beneficial and thus combining thrombolytic therapy with protective treatments as other potential supplemental alternatives seems more adapted (13). Given the increasing incidence of stroke, adverse effects and high cost of physiotherapy and rehabilitation interventions, employing supplemental treatments, in association with modern medicine is recommended. Alternative therapy based on herbal medicine has shown promising results. Herbal compounds with relative safety can be used in addition to chemicals with adverse effects and incomplete effectiveness. They display not only synergistic effects with chemicals, but also negate their toxicity (21, 22).

During the ischemic process, the generation of free radical increases which ultimates in an elevated intermolecular oxidation, cellular impairment and cell death. The use of some herbal species with antioxidant properties could help to prevent oxidative damage triggered by free radicals (14).

Although many studies have demonstrated the beneficial effects of medicinal plants on stroke, this study was designed to classify the results of these studies.

1. **MATERIALS AND METHODS**

2-1 **Data sources**

The present research team designed a systematic search to calculate and judge only the randomized clinical trials (RCTs) that used herbal medicines to improve Ischemic stroke.

The keywords that were used on their own or in combination in this review are as follow: stroke, ischemic stroke, cerebral infarction, brain infarction, cerebral ischemia, brain ischemia, CVA, cerebrovascular accident, ischemic attack with keywords relating to complementary medicine including: herbal medicine, plant extracts, herb, botany, Phytotherapy, naturopathy, plants medicinal, 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, placebo.

Cochrane, ISI, PubMed, and Scopus were searched to 15 January 2018 for English language human studies.

2-2 **Inclusion criteria**

RCTs relating to the effects of medicinal plants on Ischemic stroke (both acute and chronic) up to Jan 2018 are included in this study.

1. Herbal species that have been documented in Persian medicine, Chinese medicine and other complementary medicines.
2. Human Adults with a clinical diagnosis for Ischemic stroke.
3. No restrictions in terms of administration, formulation or method of preparation of the plants such as capsules, granules, pills or injected agents, were taken into account.
4. Single extract, or combination of just 2 plants and no combined of more than 2 plant extracts
5. Herbs with therapeutic effect and not just preventive effect.
6. English language

Extracted data included the time and place of study, authors, methodology of research, plant species, number and method of administration, comparison between different regimens, duration of therapy and follow-up, number of participants and condition, number of excluded participants during follow-up, adverse effects, and primary and secondary outcomes.

2-3 **Bias assessment**

**Risk of bias within studies**

The quality and risk of bias in each trial were assessed using the Cochrane Collaboration’s tool (23). The results are summarized in table1. All of the in­cluded studies were described as randomized trials. Allocation concealment, proper blinding and double blinding were appropriately described in three out of four trials.

All main texts were retrieved and read by both reviewers (Delshad E and Ayati Z). All reviewers independently performed the screening of studies, selection, validation, data extraction, and the assessment of methodological quality. Disagreements in the calculation of data were determined by discussion and reviewed by other author (Naghedi H) and consensus was reached in all cases.

1. **RESULTS**

Two thousand Four hundred thirteen articles were recognized through the primary search. Following removal of 152 duplicates, 2261 articles were considered for evaluation. Reviewing the titles and abstracts of articles, leaded to the removal of 2191 and 71 articles, respectively among the remaining articles, upon a particular investigation, 36 were excluded because they were not written in English language and 20 were recognized against inclusion criteria. Finally, we review the full text of 15 remained articles specifically and carefully again. Nine articles were excluded due to using the more than 2 herbs or herb animal agents. And 2 of them were not specifically about Ischemic stroke.

Finally, 4 articles were excluded due to variances in population, intervention, and type of study, meaning that four articles were eligible for this study. Of the four included articles, three were done in China, and one in Iran. All studies were conducted between 2011 and 2017.

Summary details of these trials are described in [Table 1](http://www.sciencedirect.com/science/article/pii/S0965229914000041?via%3Dihub#tbl0005) and a flow chart viewing the process of study selection is presented in Figure 1.

3-1 **Sub-types of studies**

All four involved studies were placebo-controlled RCTs in ischemic stroke patients. Three studies ([He](https://www.sciencedirect.com/science/article/pii/S0944711310003211%22%20%5Cl%20%22%21)[, Chen](https://www.sciencedirect.com/science/article/pii/S0944711310003211%22%20%5Cl%20%22%21)[, Zhou](https://www.sciencedirect.com/science/article/pii/S0944711310003211%22%20%5Cl%20%22%21)[, Zhang](https://www.sciencedirect.com/science/article/pii/S0944711310003211%22%20%5Cl%20%22%21)[, Yang](https://www.sciencedirect.com/science/article/pii/S0944711310003211%22%20%5Cl%20%22%21) [and Yang](https://www.sciencedirect.com/science/article/pii/S0944711310003211%22%20%5Cl%20%22%21), 2011)(1) , (Savadi Oskouei, Rikhtegar, Hashemilar, Sadeghi-Bazargani, Sharifi-Bonab, Sadeghi-Hokmabadi, Zarrintan and Sharifipour, 2013)(24), ( [Wei](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wei%20D%5BAuthor%5D&cauthor=true&cauthor_uid=26221294), [Lv](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lv%20C%5BAuthor%5D&cauthor=true&cauthor_uid=26221294), [Zhang](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhang%20J%5BAuthor%5D&cauthor=true&cauthor_uid=26221294), [Peng](https://www.ncbi.nlm.nih.gov/pubmed/?term=Peng%20D%5BAuthor%5D&cauthor=true&cauthor_uid=26221294),  [Hu](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hu%20L%5BAuthor%5D&cauthor=true&cauthor_uid=26221294), [Zhang](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhang%20Z%5BAuthor%5D&cauthor=true&cauthor_uid=26221294), and  [Wang](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wang%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=26221294), 2015)(25) were double blinded, and one study was single-blinded (Wei, Xie, Li, Chen, Qi, Wang, Zhang, Chen, Li and Zhang, 2017)(11). In addition the study by Wei etal, 2015 was a pilot study, ( [Wei](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wei%20D%5BAuthor%5D&cauthor=true&cauthor_uid=26221294), [Lv](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lv%20C%5BAuthor%5D&cauthor=true&cauthor_uid=26221294), [Zhang](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhang%20J%5BAuthor%5D&cauthor=true&cauthor_uid=26221294), [Peng](https://www.ncbi.nlm.nih.gov/pubmed/?term=Peng%20D%5BAuthor%5D&cauthor=true&cauthor_uid=26221294),  [Hu](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hu%20L%5BAuthor%5D&cauthor=true&cauthor_uid=26221294), [Zhang](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhang%20Z%5BAuthor%5D&cauthor=true&cauthor_uid=26221294), and  [Wang](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wang%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=26221294), 2015)(25).

**3-2 Participants**

Three hundred sixteen patients were included in the four clinical trials, with ages ranging between 18 and 80 years.

Inclusion criteria were not completely the same in the 4 trials. Two studies, by He ([He, Chen, Zhou, Zhang, Yang and Yang](https://www.sciencedirect.com/science/article/pii/S0944711310003211#!), 2011) and Oskouei ( Oskouei, Rikhtegar, Hashemilar, Sadeghi-Bazargani, Sharifi-Bonab, Sadeghi-Hokmabadi, Zarrintan and Sharifipour, 2013) were enforced on an ischemic stroke in the anterior cerebral circulation. The study by Wei (Wei, Xie, Li, Chen, Qi, Wang, Zhang, Chen, Li and Zhang, 2017) was involved acute ischemic attack with NIHSS score between 3 and 10. Another study ( [Wei](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wei%20D%5BAuthor%5D&cauthor=true&cauthor_uid=26221294), [Lv](https://www.ncbi.nlm.nih.gov/pubmed/?term=Lv%20C%5BAuthor%5D&cauthor=true&cauthor_uid=26221294), [Zhang](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhang%20J%5BAuthor%5D&cauthor=true&cauthor_uid=26221294), [Peng](https://www.ncbi.nlm.nih.gov/pubmed/?term=Peng%20D%5BAuthor%5D&cauthor=true&cauthor_uid=26221294),  [Hu](https://www.ncbi.nlm.nih.gov/pubmed/?term=Hu%20L%5BAuthor%5D&cauthor=true&cauthor_uid=26221294), [Zhang](https://www.ncbi.nlm.nih.gov/pubmed/?term=Zhang%20Z%5BAuthor%5D&cauthor=true&cauthor_uid=26221294), and  [Wang](https://www.ncbi.nlm.nih.gov/pubmed/?term=Wang%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=26221294), 2015) was 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 features as follows:

All of them excluded the chronic and severe diseases such as disorders of heart, liver, kidney, and profound loss of consciousness such as coma, stupor, severe dementia and psychiatric disorders. Wei, 2017 and He excluded cerebral haemorrhage or tumour, and He and Oskouei excluded pregnancy and lactation.

Moreover Wei, 2017 excluded hematopoietic system, endocrine system, bone and joint diseases and heart system diseases and any surgery or intervention in heart system which cannot be performed with MRI too. Another exclusion criterion of Li study 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 study. Moreover Wei, 2015 excluded TIA (transient ischemic attacks), major cognitive impairment, intracranial tumour and a history of psychoactive medication use or drug addiction, and Oskouei excluded having the indication of anticoagulant therapy too.

**3-3 Interventions**

Four herbal agents were tested in the 4 RCTs. One study evaluated the effects of Radix/Rhizoma Notoginseng extract (Sanchitongtshu) on ischemic stroke. Another study valued the effect of *Ginkgo biloba* on functional outcome of patients with acute ischemic stroke, and the two last studies assessed the positive effects of Xueshuan Xinmai tablets on ischemic stroke. Xueshuan Xinmai (XXMT) is composed of two herbs including *Ligusticum wallichii* (chuanxiong in Chinese) and *Salvia miltiorrhiza* (danshen in Chinese). Treatment durations were different in studies. In He study was about 1 month, in Oskouei 2013 Study, 3 months, inWei, 2017 study 2 weeks and in Wei, 2015, was 3 months.

**3-4 outcomes**

Outcome events were not the same in the different articles, but the primary outcome of all articles was an examination of the subjective signs of patients, whereas secondary outcomes were more focused on Para clinical findings.

As an example, the primary outcomes in the study by Wei 2017 were assessment of the neurologic deficits (NIHSS) and the quality of life (SSQOL) but in the study by Wei 2015 were neuropsychological tests for evaluating general cognitive status and other domains, such as memory(AVLT, ROCF), attention(SCWT, SDMT); spatial processing (ROCF,CDT) ,executive function and language ability(SCWT, SCWT,BNT,CVFT). The primary outcomes in the study by He 2011 was evaluation of neurological deficit which was measured by European Stroke Scale (ESS) and improvement in activities of daily living, measured with Barthel index (BI), both after 28 days of treatment; while the primary outcomes of the study by Oskouei 2013 was just assessment of the neurologic deficits by NIHSS score

Secondary outcomes in the studies by Wei 2015, And Wei 2017, were assessed according to brain activity (rfMRA), also the other secondary outcome in the study by Wei 2017, was blood viscosity.

Moreover, the secondary outcome in the He 2013 study was haemorrhagic transformation administration; and the study by Oskouei 2013 has not any secondary outcome. (Table 2)

3-5 **Mode of administration**

In the studies by Wei 2015, Wei 2017 and Savadi Oskouei, the herbal preparations were used in tablet form, whereas in the He 2011 study, capsule form was administrated. In the studies by Wei 2015, Wei 2017, compound preparations were used while in the studies by Oskouei and He preparations were simple.

**3-6 Therapeutic results**

According to the stated consequences, there was a clinical improvement in patient signs in all four studies. This was evaluated by the NIHSS and SSQOL questionnaire in Wei 2017 study, whereas the other study by Wei 2015 stated improvement of symptoms and brain function that was assessed by neuropsychological tests and fMRI.

NIHSS was also used in the study by Oskouei, 2013 and evaluated more stage improvement and more patients with 50% reduction in NIHSS score in intervention group comparing to placebo group. The study by He 2011, was reported significant improvement in neurological deficit and activities of daily living, using ESS and BI scales.

**3-9 adverse effects**

No severe side effects were described during the administration of herbal preparations in the four studies. But in study by He 2011 [gastro-intestinal](https://www.sciencedirect.com/topics/medicine-and-dentistry/gastrointestinal) adverse reactions was reported that occurred equally in both groups.

1. **DISCUSSION**

The present systematic review involved four articles recording clinical trials of medicinal preparations in patients with ischemic stroke. The probability of bias and quality of eligible RCTs was assessed using the Cochrane Collaboration tool for the risk of bias (Table [3](http://onlinelibrary.wiley.com/doi/10.1002/ptr.5968/full#ptr5968-tbl-0003))

Through the four studies, four medicinal plants were used. One of the major challenges in other similar systematic review articles is comparing the effectiveness of interventions because of the variety of plants used in their studies. For this reason, we excluded the studies with more than 2 herbs in their preparations to evaluate the effectiveness of herbs exactly.

He 2011 study, demonstrated that Sanchitongshu [capsule](https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/capsule) has been considered as [antiplatelet agents](https://www.sciencedirect.com/topics/medicine-and-dentistry/antiplatelet-drug) which the main component is panaxatriol [saponins](https://www.sciencedirect.com/topics/medicine-and-dentistry/saponin) (PTS)(1). The synergistic action of Sanchitongshu capsule combined with aspirin, used to treat patients of [ischemic stroke](https://www.sciencedirect.com/topics/medicine-and-dentistry/ischemic-stroke) within 30 days of onset, showed significantly better effects than aspirin alone in improving activities of daily living and [neurological deficit](https://www.sciencedirect.com/topics/medicine-and-dentistry/functional-neurological-deficit) after 28 days of treatment. In special, the synergistic action was prominent in ameliorating movement of the limbs.

This study showed that Sanchitongshu capsule combined with smaller dosage of aspirin (50 mg/d) had synergistic action for ischemic stroke without increasing risk of haemorrhage, indicating that Sanchitongshu can be safely used as a complementary anti-platelet remedy.

The Oskouei, 2013 study found that administration of *G biloba* could ameliorate functional recovery in patients with AIS (24). Although ,20 patients in G biloba group and 18 patients in placebo group were lost and also 19 patients in G biloba group and 18 patients in placebo group could not continue the trial,

This review study demonstrated that Ginkgo extracts such as EGb761 powerfully decreases cellular oedema formation and neurodegeneration under conditions of ischemia in vivo and in vitro separately. The process of action seems to be related to a reduction of excitotoxicity, because ischemia-induced discharge of glutamate was strongly inhibited. Ginkgo extracts such as EGb761 may be valuable to stop ischemia-induced damage in stroke-prone patients.(26)

A different study by Lie et al, 2010 expressed that Ginkgolide B reduced infarct size, improved the neurological insufficiency and the permeability of BBB. Ginkgolide B has protective effects on cerebral damage by stopping the inflammation induced by ischemia/reperfusion injury (27).

Wei 2015 and Wei 2017 studies explained the mechanism of XXMT action.

XXMT has been extensively consumed in the TCM clinical practice for treating ischemic stroke, cerebral thrombosis and coronary heart disease(28).

[Zhang](https://www.hindawi.com/38690891/) et al, 2015 demonstrated XXMT had a good healing effect on blood stasis by decreasing the whole blood viscosity (WBV), plasma viscosity (PV), increasing PT, APTT and TT, and by preventing platelet accumulation. XXMT improved blood stasis by regulating the expressions of F13a1, Car1, and Tbxa2r.

The other studies have established that tetramethylpyrazine (TMP), the main extract of *ligusticum wallichii*, is a naturally active alkaloid that stimulates vasodilatation, prevents platelet mass and exhibits significant antioxidant effects (29-32).

In the same way, tanshinone IIA (Tan IIA), the main extract of *salvia miltiorrhiza*, is a lipid-soluble active compound that owns potential anti-inflammatory, anti-oxidant, anti-apoptotic and neuroprotective properties (33).

XXMT is able to suppress clot formation, expand blood vessels, improve the tolerance of ischemic brain tissue to hypoxia and defend against ischemic reperfusion damage in ischemic stroke patients. All these together improve the episodic memory and brain activation in ischemic post-stroke patients (33, 34).

In conclusion, all involved articles resulted in the efficacy of medicinal herbs used in treatment of ischemic stroke. However, the absence of a same protocol for evaluation of these studies was the major challenge in comparing the effectiveness of herbal medicines. Small number of populations involved in the studies, as well as short term follow-up in continuation of treatment was other limitations. Although several research studies have been implemented on phytopharmacology of these herbs, new trials are needed to prove the efficacy of medicinal herbs on Ischemic stroke.

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**CONFLICT OF INTEREST**

The authors have no conflicts of interest to declare.

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