



# Chinese herbal medicine Dengzhan Shengmai capsule as adjunctive treatment for ischemic stroke: A systematic review and meta-analysis of randomized clinical trials



Xiao-Ying Yang<sup>a,1</sup>, Li-Qiong Wang<sup>a,1</sup>, Jin-Gen Li<sup>a</sup>, Ning Liang<sup>a</sup>, Ying Wang<sup>a</sup>, Jian-Ping Liu<sup>a,b,\*</sup>

<sup>a</sup> Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing 100029, China

<sup>b</sup> The National Research Center in Complementary and Alternative Medicine (NAFKAM), Department of Community Medicine, Faculty of Health Science, the Arctic University of Norway, 9037 Tromsø, Norway

## ARTICLE INFO

### Keywords:

Chinese patent medicine  
Dengzhan shengmai  
Ischemic stroke  
Randomized controlled trials  
Systematic review  
Meta-analysis

## ABSTRACT

**Objective:** The existing eligible randomized controlled trials (RCTs) were critically appraised for the effectiveness and safety of Chinese herbal medicine Dengzhan Shenmai for ischemic stroke.

**Design:** Systematic review and meta-analysis (CRD42016042914, <http://www.crd.york.ac.uk/PROSPERO>).

**Methods:** Six electronic databases were searched from inception to May 2016. Risk ratio (RR) and mean difference (MD) with a 95% confidence interval (CI) were used as effect estimates using RevMan 5.3. Meta-analysis was performed where data were available. A summary of finding table was generated by the GRADEpro (version 3.6).

**Results:** We identified 14 RCTs involving 5206 participants. Majority of the included trials were of high risk of bias in methodological quality. For acute ischemic stroke, adding DZSM capsule to conventional therapy achieved higher Barthel Index scores (MD 22.37, 95% CI 21.34–23.40), lower neurological function deficit scores (MD – 3.73, 95% CI – 5.27 to – 2.19) and lower recurrence rate (RR 0.22, 95% CI 0.10, 0.46). For patients in their convalescence (or sequelae) stage of ischemic stroke, DZSM capsule was superior in improving quality of life (MD 28.8, 95% CI 7.10–50.50) and recurrence rate (RR 0.71, 95% CI 0.51–0.99) compared to placebo. No trials reported serious adverse events.

**Conclusion:** DZSM capsule appears to improve neurological function, quality of life, and reduce recurrence rate based on conventional therapy for ischemic stroke. DZSM capsule seems generally safe for clinical application. However, the findings of benefit are inconclusive due to generally weak evidence, and further large, rigorous trials are still warranted.

## 1. Introduction

Strokes are caused by disruption of the blood supply to the brain.<sup>1</sup> It is now the second most common cause of death and a major cause of disability worldwide.<sup>2</sup> According to the World Health Organization, 15 million people suffer a stroke worldwide every year: 5 million people die and another five millions are left permanently disabled, placing a heavy burden on family and community.<sup>1</sup> Approximately 67% of all strokes are ischemic in Asian populations.<sup>3</sup> In China, the prevalence rate of stroke is 1.23% until 2013, the mortality is 1.88 million per year, cumulative recurrence rate during 5 years more than 30%, and stroke

survivors suffer serious neurological disorders (loss of vision, speech or both, paralysis, and confusion).<sup>4</sup>

According to its natural course, ischemic stroke can be divided into 3 stages: the acute stage (less than two weeks from symptom onset), convalescence stage (2 weeks to 6 months from symptom onset), and sequelae stage (6 months or longer from symptom onset).<sup>5</sup> At present, available therapies for acute ischemic stroke are reperfusion-based strategies, including intravenous fibrinolysis and endovascular intervention.<sup>5</sup> Because of their limitations of time or indications, they are only available for few patients and have a moderate effect.<sup>6,7</sup> In addition, the anti-platelet drugs were reported to have a high risk of

**Abbreviations:** DZSM, dengzhan shengmai; RCTs, randomized clinical trials; BI, Barthel Index; mRS, the modified Rankin Scale; NIHSS, national institutes of health stroke scale; NFDS, neurological function deficit score; SS, QOL Stroke Specific Quality of Life Scale

\* Corresponding author at: Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, 11 Bei, San Huan Dong Lu, Chaoyang District, Beijing 100029, China.

E-mail addresses: [yuki\\_ying24@163.com](mailto:yuki_ying24@163.com) (X.-Y. Yang), [912131198@qq.com](mailto:912131198@qq.com) (L.-Q. Wang), [lijingen198908@126.com](mailto:lijingen198908@126.com) (J.-G. Li), [liangning229@163.com](mailto:liangning229@163.com) (N. Liang), [huorentang@163.com](mailto:huorentang@163.com) (Y. Wang), [jianping\\_l@hotmail.com](mailto:jianping_l@hotmail.com), [Liujp@bucm.edu.cn](mailto:Liujp@bucm.edu.cn) (J.-P. Liu).

<sup>1</sup> Ms. Yang and Ms. Wang are co-first authors who contributed equally to this work.

<https://doi.org/10.1016/j.ctim.2017.12.004>

Received 10 July 2017; Received in revised form 18 October 2017; Accepted 4 December 2017

Available online 09 December 2017

0965-2299/© 2017 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

intracranial bleeding and the anticoagulants do not improve the long-term outcomes.<sup>8</sup> Despite aggressive control of known risk factors, the recurrence rate of stroke remains high.<sup>9</sup>

We searched PubMed and identified 2 systematic reviews.<sup>10,11</sup> of Chinese patent medicine for ischemic stroke. Both reviews included randomized controlled trials (RCTs) and showed that Chinese patent medicine Xingnaojing (13 RCTs, 1514 participants, searched up to Nov 2013) and Ligustrazine (3 RCTs, 643 participants, searched up to Dec 2012) might be beneficial for the treatment of stroke, but more high quality RCTs are needed to confirm the positive findings. In China, Dengzhan Shengmai (DZSM) capsule was commonly used for cardiovascular diseases, and it was approved for sequelae stage of stroke on market by the China Food and Drug Administration (CFDA) in 2002. As a Chinese patent herbal medicine, developed from the traditional classical prescription (Powder for Restoring Pulse Beat), it consists of ingredients from four herbs, including *Erigeron breviscapus*, *Panax ginseng*, *Ophiopogon japonicus* and *Schisandra chinensis*. It may augment the immunity through supplementing ‘Qi’, nourishing ‘Yin’, and promoting blood circulation based on traditional Chinese medicine theory.<sup>12</sup> *Erigeron breviscapus* has been shown to have an anti-oxidative and neuroprotective effect and reduce blood viscosity.<sup>13</sup> This review aimed to systematically collect all relevant randomized trials and critically appraise the effectiveness and safety of DZSM capsule for ischemic stroke.

## 2. Methods

The review protocol was registered at PROSPERO (NO: CRD42016042914). The format of this review follows the checklist of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Additional file 1).

### 2.1. Eligibility criteria

#### 2.1.1. Type of study randomized controlled trials

2.1.1.1. *Type of participants.* People with ischemic stroke were included and should have been diagnosed by brain Computed Tomography or Magnetic Resonance Imaging to confirm infarction in brain and exclude hemorrhage regardless of their sex, age, and race or disease stage.

2.1.1.2. *Type of intervention.* DZSM capsule was tested as intervention regardless of its dosage or treatment duration. The control included placebo or conventional therapy. Co-interventions were allowed as long as all arms received the same co-intervention(s).

2.1.1.3. *Type of outcomes.* For acute stage, the primary outcomes were all-cause mortality, dependence defined as Barthel Index (BI) scores < 60 or the modified Rankin Scale (mRS) scores > 3<sup>14</sup> and serious adverse events including fatal, life threatening, requiring hospitalization or change of treatment regimen.<sup>15</sup> The secondary outcomes were changes of neurological function deficit assessed by validated scales such as the National Institute of Health Stroke Scale (NIHSS) or the nationally approved Neurological Function Deficit Score (NFDS), treatment failures defined according to the nationally approved criteria,<sup>16</sup> we regarded no change (function defect score decreased by 18%–45%), deterioration (function defect score decreased by about 17%) and death as treatment failures, quality of life, and non-serious adverse events. For convalescence (or sequelae) stage, the primary outcomes were dependence, recurrence rate of ischemic stroke, quality of life, and serious adverse events, and the secondary outcomes were all-cause mortality, neurological deficit, treatment failure, and non-serious adverse event.

### 2.2. Search strategy

We comprehensively searched the Cochrane Library, PubMed, Chinese Biomedical Database (SinoMed), China National Knowledge

Infrastructure (CNKI), Chinese Scientific Journal Database (VIP), Wanfang Database; from their inception to May 2016 (Additional file 2). References of all included trials were hand searched for additional eligible trials.

### 2.3. Study selection and data extraction

Two authors (XY Yang and JG Li) independently and in duplicate examined the titles and abstracts identified potentially eligible trials and then review the full text to identify the trials meeting eligibility criteria. And we extracted the data from included trials on the first authors and year of publication, detail of randomization, characteristics of participants (such as age, sex and clinical stage), sample size, descriptions of intervention/control and outcomes. The discrepancies were resolved through consensus and if necessary, arbitrated by the third author (Liu JP).

### 2.4. Quality assessment

Two authors (XY Yang and LQ Wang) independently assessed the methodological quality of RCTs using risk of bias tool provided by the Cochrane Hand-book for Systematic Reviews of Interventions.<sup>17</sup> Any disagreements were resolved by discussion with third author (JP Liu). We assessed the following quality items: random sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data, selective reporting, and other bias based on imbalance of the baseline information here. The quality of included trials was categorized to low/unclear/high risk of bias. Trials which met all criteria were categorized to low risk of bias, trials which met none of the criteria were categorized to high risk of bias, and other trials were categorized to unclear risk of bias if insufficient information acquired to make judgment.

### 2.5. Data analysis

The statistical analyses were carried out using Review Manager 5.3 software from the Cochrane Collaboration. Data were summarized using risk ratio (RR) with 95% confidence intervals (CI) for binary data or mean difference (MD) with 95% CI for continuous data. Meta-analysis was done if the trials had a good homogeneity on study design, participants, interventions, control, and outcome. Statistical heterogeneity was tested by examining both the Chi-squared test and the I-squared statistic ( $I^2$ )<sup>18</sup>, meaning that an  $I^2$  larger than 50% and  $P$  less than or equal to 0.1 indicated the possibility of statistical heterogeneity and random-effects model was adopted. We planned to perform a sensitivity analysis to test the robustness of the results by excluding study with unclear random sequence generation. We conducted intention to treat analysis for the missing data. Funnel plots were used to assess the publication bias if more than 10 RCTs tested the same outcome in one meta-analysis.

We would perform subgroup analyses by disease stage or by different neurological function deficit measurements if data were available. Quality of evidence was assessed across important outcomes using GRADE approach to support management recommendations by the GRADEpro software (version 3.6).

## 3. Results

### 3.1. Description of studies

The initial search yielded 253 records from the six databases, and an unpublished article was identified by contacting principal investigator. Full texts of 37 articles were read, and 18 trials were eligible. However, four trials,<sup>19–21</sup> did not report the disease stages, so we excluded them from this review. Therefore, fourteen trials<sup>22–35</sup> with a total 5206 participants were included in this review. Details of the study selection

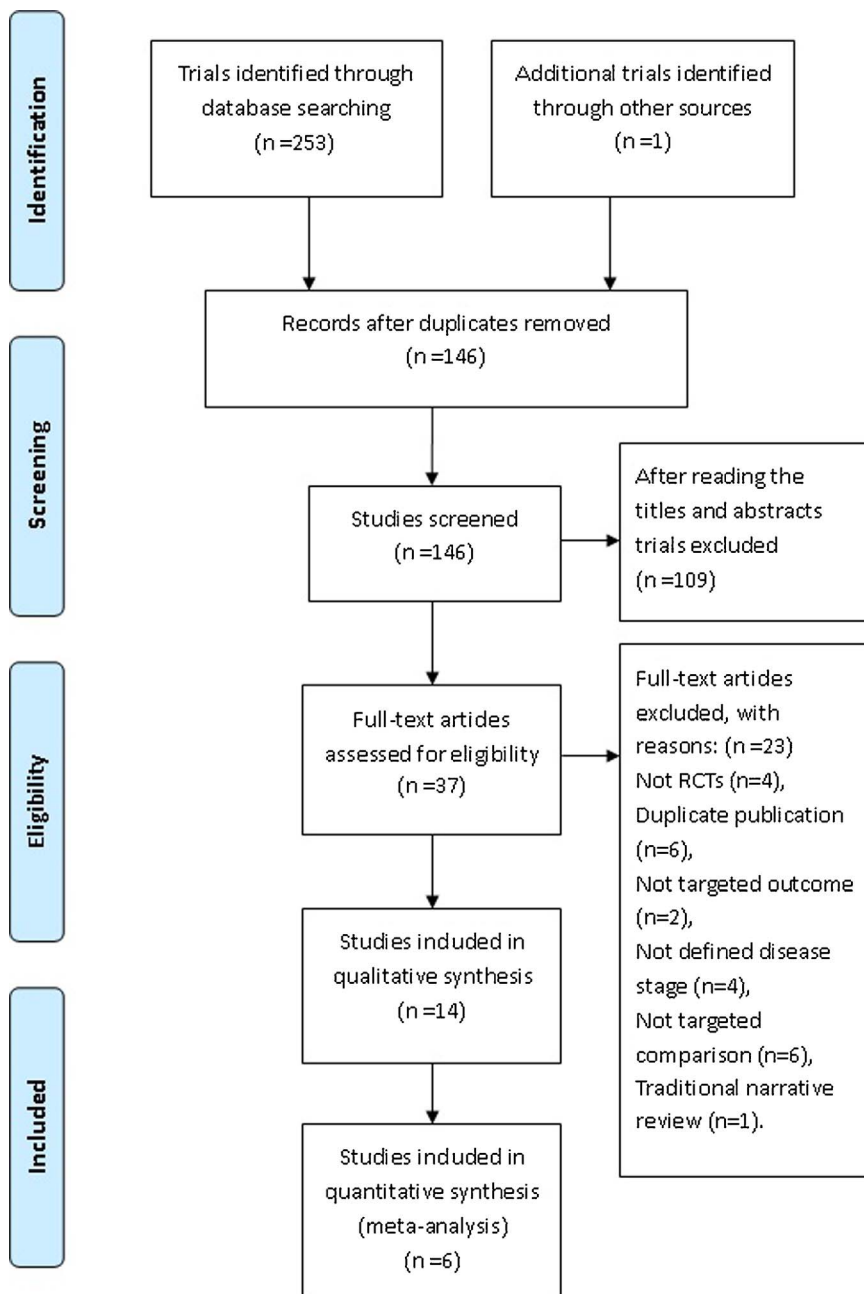


Fig. 1. This is the S1 Fig. Flow chart of study searching and selection.

are shown in Fig. 1. All included trials were two-armed trials, and were conducted in China.

### 3.2. Study characteristics

The detailed characteristics are presented in Table 1. The sample size ranged from 40 to 3032 participants (median 110 participants) per trial. The total sample size of males was more than females (3070/2052) except one trial ( $n = 96$ ) which did not reported gender. The mean age of participants is 65 years old (range 40–81.68). According to disease stages of ischemic stroke, four trials<sup>20–23</sup> enrolled participants in acute stage ( $n = 368$ ) and 10 trials<sup>24–33</sup> in convalescence (or sequelae) stage ( $n = 1838$ ).

There were two comparisons: DZSM capsule plus conventional therapy versus conventional therapy<sup>22–28,30,32–34</sup> DZSM capsule plus conventional therapy versus placebo plus conventional therapy.<sup>22,29,31,35</sup> The conventional therapy included antiplatelet,

anticoagulant, neuroprotective agents, nutritional support, controlling serum glucose and blood pressure, etc.

### 3.3. Risk of bias of included trials

According to the pre-defined criteria, all included trials were assessed as having high risk of bias (Figs. 2 and 3) except for one multi-center, double-blinded, randomized, placebo-controlled trial. The remaining 13 trials were single center with parallel group design. These trials provided very limited information about study designs and methodology such as unclear random method and allocation concealment. Although all the included trials reported ‘randomly allocating’ participants, only seven trials<sup>23,24,27,28,31,33,35</sup> reported generating random numbers by using the random number table or centralized randomization. Two trials<sup>28,31</sup> reported using central randomization to conceal the allocation, and the remaining trials reported no information about concealment. Four trials<sup>22,29,31,35</sup> were double-blind trials, and

**Table 1**  
Characteristics of included RCTs on DZSM for ischemic stroke.

Study ID	Sample size	Sex(M/F)	Age(years)	Course of disease	Interventions	duration	Outcomes	Follow up
Mao <sup>22</sup>	T:50 C:50	T:28/28 C:28/28	T:63 ± 4 C:65 ± 6	< 24 h	T:DZSMC(C) + CT C: Placebo + CT	30d	NFDS, AEs	NR
Zhen <sup>23</sup>	T:34 C:34	T:20/14 C:21/13	T:65.3 ± 6.8 C:63.5 ± 5.2	≤ 48 h	T:DZSMC(A, tid) + CT C:CT	14d	NIHSS	NR
Xia <sup>24</sup>	T:40 C:40	T:24/16 C:22/18	T:65.71 ± 10.96 C:64.48 ± 10.68	≤ 14d	T:DZSMC(A, bid) + CT C: CT	4w	Clinical effect <sup>a</sup> (NIHSS)	NR
Pan <sup>25</sup>	T:60 C:60	T:37/23 C:36/24	T:56.8 ± 7.9 C:58.2 ± 6.8	T:27 ± 8(h) C:2 ± 8(h)	T:DZSMC(A, tid) + CT C:CT	3 m	Recurrence rate, Clinical effect <sup>a</sup> , AEs	9m
Xue <sup>26</sup>	T:67 C:66	T:31/36 C:29/37	T:70.18 ± 11.50 C:69.33 ± 10.07	> 14d	T:DZSMC(A, tid) + CT C: CT	6 m	QOL(SF-36), mRS, BI	NR
Nan <sup>27</sup>	T:63 C:63	T:35/28 C:36/27	T:61.94 ± 10.46 C:62.42 ± 10.17	3w–4w	T:DZSMC(A, tid) + CT C:CT	6 m	QOL(SS-QOL), Recurrence rate, BI, mRS, death, NIHSS	NR
Cao <sup>28</sup>	T:33 C:31	T:16/17 C:21/10	T:64.18 ± 10.44 C:62.45 ± 11.62	21d–30d	T:DZSMC(2months A + 4month B, tid) + CT C:CT	6 m	BI, mRS, AEs QOL(SS-QOL), Recurrence rate, NIHSS, Death	6m
Li <sup>29</sup>	T:80 C:80	T:48/32 C:50/30	T:65.4 ± 6.7 C:66.1 ± 7.2	14d–180d	T:DZSMC(2months A + 4month B, tid) + CT C:Placebo + CT	6 m	Clinical effect <sup>a</sup> (NFDS), AEs, QOL(SS-QOL)	1y
Chen <sup>30</sup>	T:495 C:504	T:241/254 C:267/237	T:63.3 ± 9.1 C:66.3 ± 8.0	T:34.3 ± 9.3m C:30.1 ± 37.6m	T:DZSMC(A, tid) + CT C:CT	3 m	Recurrence rate, Death, AEs	1.5y
Cai <sup>31</sup>	T:1508 C:1524	T:989/519 C:966/558	T:61.3 C:61.2	14d–180d	T:DZSMCA, bid) + CT C:Placebo(A, bid) + CT	12 m	Recurrence rate, AEs	NR
Dong <sup>32</sup>	T:30 C:30	T:19/11 C:20/10	T:41–75 C:40–73	14d–180d	T:DZSMC(A, bid) + CT C:CT	3 m	Death, AEs	NR
Luo <sup>33</sup>	T:20 C:20	T:13/7 C:12/8	T:59.8 ± 7.1 C:61.2 ± 6.6	28d	T:DZSMC(A, tid) + CT C: CT	28d	Clinical effect <sup>a</sup> , NFDS	NR
Wu <sup>34</sup>	T:50 C:46	NR	T:65.21 ± 2.31 C:64.85 ± 2.42	14d–30d	T:DZSMC(A, tid) + CT C:CT	90d	NHSS, Clinical effect <sup>a</sup> , AEs	NR
Hu <sup>35</sup>	T:82 C:46	T:39/43 C:22/24	T:58.23 ± 0.21 C:57.32 ± 0.18	> 14d	T:DZSMC(A, tid) + CT C:Placebo + CT	2 m	Clinical effect <sup>a</sup> (NIHSS)	NR

A: 0.18 g per pill, each time 2 pills; B: 0.18 g per pill, each time 1 pills; C: 0.18 g per pill, 0.9 g/d.

<sup>a</sup> Clinical effect defined according to the nationally approved criteria, which divided clinical effect into ‘almost healed’, ‘markedly effective’, ‘effective’, ‘ineffective’, ‘exacerbation’ and ‘dead’. T: treatment group; C: control group; M: males; F: females; d: day; m: months; y: year; DZSMC: Dengzhan shengmai capsule; CT: conventional therapy; NR: not reported; NIHSS: National Institutes of Health Stroke Scale; NFDS: neurological function deficit score; AEs: adverse events; QOL: Quality of life; SS-QOL: Stroke Specific Quality of Life Scale.

the remaining 10 trials<sup>23–28,30,32–34</sup> appeared impossible to blind the participant and personnel as DZSM capsule only in experimental groups. Two trials<sup>22,31</sup> reported the blinding of outcome assessment, and one trial<sup>30</sup> was open and the remaining 11 trials<sup>23–29,32–35</sup> reported no information about it. Three trials<sup>26,30,31</sup> reported the dropout and only one trial<sup>24</sup> described the reasons for death; the remaining 11 trials<sup>16–19,22–25,27–35</sup> were unclear about it. One trial<sup>31</sup> provided information about trial registry; we assessed reporting bias by judging consistency between outcomes in the method section of the publication and or in the protocol. Because all remaining trials provided no

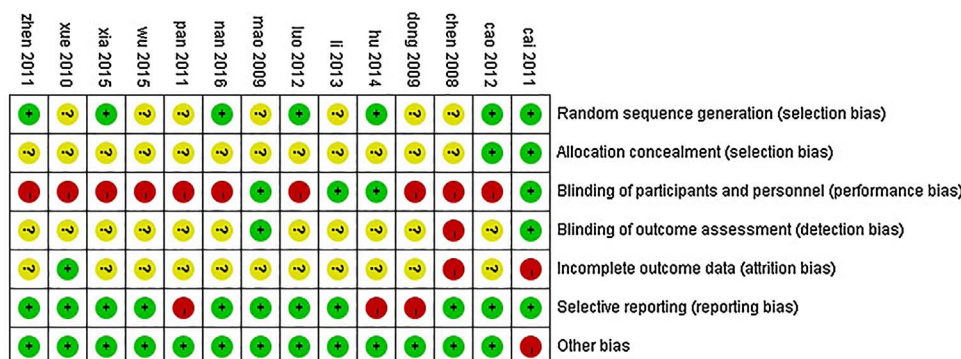
information about trial registry, we assessed trials which reported all outcomes mentioned in the “Methods” part as low risk of reporting bias, otherwise high risk of reporting bias would be rated. For other bias, 13 trials<sup>22–30,32–35</sup> were assessed as having low risk and one trial<sup>31</sup> was assessed as having high risk for baseline comparability.

### 3.4. Effects of interventions

#### 3.4.1. Acute stage of ischemic stroke

##### 3.4.1.1. Primary outcomes. No trial reported primary outcomes

Fig. 2. This is the S2 Fig. Risk of bias summary.





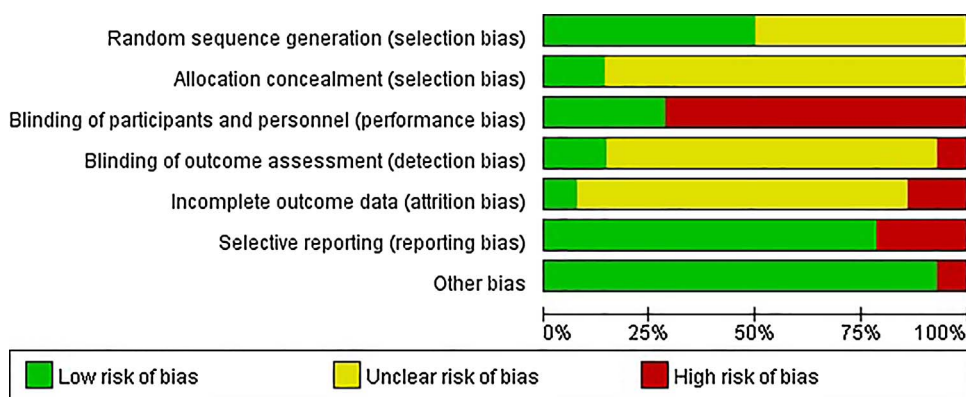


Fig. 3. This is the S3 Fig. Risk of bias graph.

including all-cause mortality, dependence or serious adverse events.

### 3.4.1.2. Secondary outcomes

**3.4.1.2.1. Changes of neurological function deficit.** One trial<sup>22</sup> measured this outcome by NFDS, and the result showed that DZSM group achieved lower neurological function deficit score at 14 days and 30 days after treatment (Both: MD  $-3.00$ , 95% CI  $-5.16$ ,  $-0.84$ ,  $P = 0.007$ , 100 participants) compared to placebo based on conventional therapy. One trial<sup>23</sup> measured this outcome by NIHSS, and the result showed that adding DZSM can significantly decrease neurological function deficit score compared to conventional therapy (MD  $-3.73$ , 95% CI  $-5.27$ ,  $-2.79$ ,  $P < 0.001$ , 68 participants).

**3.4.1.2.2. Treatment failure.** Two trials<sup>24,25</sup> reported treatment failure and the pooled result showed no significant difference between DZSM capsule plus conventional therapy and conventional therapy alone (RR 0.17, 95% CI 0.03, 1.17,  $P = 0.07$ ,  $I^2 = 64\%$ , 200 participants, random effect models).

**3.4.1.2.3. Recurrence rate.** Only one trial<sup>25</sup> reported recurrence rate, the result showed adding DZSM capsule to conventional therapy achieved lower recurrence rate (RR 0.22, 95% CI 0.10, 0.46,  $P < 0.0001$ , 120 participants).

**3.4.1.2.4. Non-serious adverse events.** Two trials<sup>22,25</sup> observed 220 participants with one reporting no adverse events. One trial<sup>22</sup> observed 100 participants and reported adverse events included dizziness ( $n = 2$ ), headache ( $n = 1$ ), insomnia ( $n = 1$ ), nausea ( $n = 1$ ), sleepiness ( $n = 1$ ), elevation of blood pressure ( $n = 1$ ) in DZSM group, this trial reported no information about adverse event from control group. These adverse events disappeared after symptomatic treatment, and one patient dropped out because of adverse event.

### 3.4.2. Convalescence (or sequelae) stage of ischemic stroke

**3.4.2.1. Primary outcomes.** No trial reported serious adverse events.

**3.4.2.2. Dependence.** Three trials<sup>26–28</sup> assessed dependence by BI score and mRS score in 323 participants, and no significant difference was found when DZSM capsule plus conventional therapy compared with conventional therapy (BI: MD 9.5, 95% CI  $-0.12$ , 19.13,  $P = 0.05$ ,  $I^2 = 86\%$ ; mRS: MD  $-0.42$ , 95% CI  $-1.26$ , 0.42,  $P = 0.33$ ,  $I^2 = 88\%$ ).

**3.4.2.3. Quality of life.** Three trials compared DZSM capsule as add-on treatment on conventional therapy for quality of life. Of these, one trial<sup>26</sup> assessed quality of life by SF-36 in 133 participants, and found no significant difference between two groups on items of role physical, social function, mental health and role emotional. On items of physical function (MD 9.64, 95% CI 6.99, 12.29), limb pain (MD 11.31, 95% CI 7.86, 14.76), general health (MD 5.65, 95% CI 3.54, 7.76) and vitality (MD 6.96, 95% CI 3.81, 10.11), adding DZSM capsule did significantly differ from conventional therapy.

Two trials<sup>27,28</sup> assessed quality of life by Stroke Specific Quality of Life Scale (SS-QOL), and found no significant difference between two

groups (MD 15.26, 95% CI  $-5.33$ , 35.85,  $P = 0.15$ ,  $I^2 = 0\%$ , 190 participants).

One trial<sup>29</sup> compared DZSM capsule with placebo based on conventional therapy, and assessed quality of life by SS-QOL in 160 participants, showing no significant difference between two groups at the end of six months' treatment (MD 14.90, 95% CI  $-9.28$ , 39.08,  $P = 0.23$ ), while DZSM capsule achieved higher score after one year follow-up (MD 28.8, 95% CI 7.10, 50.50,  $P = 0.009$ ).

**3.4.2.4. Recurrence rate.** Three trials<sup>27,28,30</sup> compared DZSM capsule as add-on treatment on conventional therapy for recurrence rate. One trial<sup>30</sup> reported recurrence rate in 1481 person-years, and there was no significant difference between two groups at the end of six months' follow-up (RR 0.65, 95% CI 0.33, 1.26,  $P = 0.20$ ). Another two trials<sup>27,28</sup> reported recurrence rate in 190 participants, and the pooled result showed no significant difference between two groups (RR 0.39, 95% CI 0.08, 1.96,  $P = 0.25$ ,  $I^2 = 0\%$ ).

One large trial with 3032 participants<sup>31</sup> compared DZSM capsule with placebo based on conventional therapy, the result showed no significant difference between two groups (Per-protocol: RR 0.76, 95% CI 0.56, 1.05,  $P = 0.10$ ; Full analysis set: RR 0.78, 95% CI 0.57, 1.07,  $P = 0.12$ ) at the end of 12 months' treatment. In this trial, 201 participants were lost to follow up in DZSM group and 228 participants in placebo group. According to worst-case scenario principle, we regarded all the participants lost to follow up in two groups as recurrence, and thus, the result showed no significant difference between two groups (RR 0.89, 95% CI 0.77, 1.03,  $P = 0.12$ ).

### 3.4.2.5. Secondary outcomes

**3.4.2.5.1. All-cause mortality.** Five trials with 1405 participants compared DZSM capsule as add-on treatment on conventional therapy for all-cause mortality. Among them, pooled result of three trials<sup>26,27,32</sup> showed no significant difference at the end of treatment between two groups (RR 0.85, 95% CI 0.41, 1.77,  $P = 0.67$ ,  $I^2 = 0\%$ , 342 participants). Other trial<sup>28</sup> assessed mortality during six months follow-up, and the result showed no significant difference between two groups (RR 0.47, 95% CI 0.04, 4.92,  $P = 0.53$ , 64 participants). Another trial<sup>30</sup> assessed mortality during 1.5 years follow-up, which showed significantly lower mortality from the DZSM group (RR 0.27, 95% CI 0.10, 0.71,  $P = 0.008$ , 999 participants); during treatment and follow-up period, 11 participants were lost to follow up (relocation) in DZSM group and one (relocation) in control group. According to worst-case scenario principle, we regarded all the participants lost to follow up in two groups as death, and thus, the result showed no significant difference between two groups (RR 0.81, 95% CI 0.43, 1.56,  $P = 0.53$ ).

One trial<sup>31</sup> compared DZSM capsule with placebo based on conventional therapy, and reported no significant difference on mortality between two groups (Full analysis set: RR 1.01, 95% CI 0.47, 2.19,  $P = 0.98$ , 3032 participants).

**3.4.2.5.2. Changes of neurological function deficit.** Two trials with

166 participants compared DZSM capsule as add-on treatment on conventional therapy. One trial<sup>33</sup> measured changes of neurological function deficit by NFDS, and found DZSM group did significantly differ in improving neurological function deficit score (MD  $-5.10$ , 95% CI  $-6.46$ ,  $-3.74$ ,  $P < 0.001$ , 40 participants). One trial<sup>27</sup> measured changes of neurological function deficit by NIHSS, and showed no significant difference between two groups (MD  $-0.76$ , 95% CI  $-2.29$ ,  $-0.77$ ,  $P = 0.33$ , 126 participants).

**3.4.2.5.3. Treatment failure.** Two trials with 136 participants compared DZSM capsule as add-on treatment on conventional therapy. One trial<sup>33</sup> reported treatment failure by measuring NFDS, and the result showed no significant difference between two groups (RR 0.43, 95% CI 0.13, 1.43,  $P = 0.17$ , 40 participants). One trial<sup>34</sup> reported treatment failure by measuring NIHSS, and found that DZSM group achieved lower rate of treatment failure (RR 0.17, 95% CI 0.04, 0.71,  $P = 0.02$ , 96 participants).

Two trials<sup>29,35</sup> comparing DZSM capsule with placebo based on conventional therapy in 288 participants showed no significant difference between two groups. Of these, one trial<sup>35</sup> assessed treatment failure by NIHSS and DZSM group can significantly decrease treatment failure (RR 0.37, 95% CI 0.14, 0.98,  $P = 0.05$ , 128 participants). One trial<sup>29</sup> showed no significant difference on treatment failure by NFDS between two groups (RR 0.77, 95% CI 0.57, 1.04,  $P = 0.09$ , 160 participants).

**3.4.2.5.4. Non-serious adverse events.** Five trials<sup>28–32,34</sup> tested 4411 participants and reported no non-serious adverse events in two groups. One trial<sup>30</sup> observed 999 participants for 3 months treatment and reported non-serious adverse events including anaphylaxis ( $n = 2$ ), insomnia ( $n = 2$ ), dizziness ( $n = 2$ ), headache ( $n = 1$ ), drowsiness ( $n = 1$ ), elevation of blood pressure with oppression in chest ( $n = 1$ ), loss of appetite and abdominal pain ( $n = 1$ ) in DZSM group, but reported no information about adverse event in control group. These symptoms disappeared after 1–48 h or after symptomatic treatment.

### 3.4.3. Additional analysis

Due to insufficient number of trials, we could not perform a meaningful sensitivity analysis and funnel plot analysis.

### 3.4.4. Overall quality of evidence by GRADE

We graded the overall quality of available evidence by GRADE approach. The quality of evidence for all-cause mortality was moderate because of its particularity. The quality of evidence for other outcomes was downgraded to “low” or “very low” mainly due to high risk of performance bias, and imprecision (small number of total events or small sample size) (Table 2).

## 4. Discussion

### 4.1. Summary of findings

In this systematic review, for acute stage of ischemic stroke, we found that the addition of DZSM capsule to conventional therapy may have an effect on decreasing recurrence rate. Based on conventional therapy, DZSM capsule may have an effect on decreasing neurological function deficit score by NFDS comparing placebo. In convalescence (or sequelae) stage, the addition of DZSM capsule may have an effect on decreasing all-cause mortality, treatment failure by NIHSS, neurological function deficit score by NFDS and improving quality of life by SF-36. Compared with placebo, DZSM capsule may have an effect on improving quality of life by SS-QOL (at one year follow-up).

In order to better guide clinical practice, we assessed the achieved evidence by GRADE approach. Due to the low quality of included trials and the above outcomes from individual trials, we could not draw firm conclusions from current evidence.

Eight of the 14 trials described the non-serious adverse events, with two reporting non-serious adverse events in DZSM group. These

symptoms disappeared after symptomatic treatment or improved without treatment. No trials reported serious adverse events in the included 14 trials, which suggested that DZSM capsule maybe safe for ischemic stroke.

### 4.2. Comparison with previous studies

We can't find similar systematic review or meta-analysis about DZSM capsule for ischemic stroke. Our primary findings need be confirmed in future clinical trials.

### 4.3. Strengths and limitations

In our review, we did a comprehensive search of major databases and try to identify all available randomized trials on DZSM capsule for ischemic stroke. We limited the control intervention as placebo or conventional therapy and evaluated clinical relevant outcomes. However, the promising findings are not conclusive due to the lower quality of included studies. A major limitation of this review is that the lower quality of the original trials and insufficient information reported in the included trials, which may weaken the implication of the findings. Poor quality trials may have high risk of performance bias and detection bias. In addition, we believed that drop out or withdrawal was inevitable during the period of treatment and follow up, but only three trials reported drop-out or withdrawal. Second, for acute stage of ischemic stroke, none of trials reported on all-cause mortality. Only four trials evaluated quality of life, which is meaningful for ischemic stroke patients at convalescence (or sequelae) stage. Finally, we could not assess the long-term effects of DZSM capsule for ischemic stroke due to the lack of long-term follow up in majority of the trials.

### 4.4. Implications for research

Future researches by adopting a multi-center, large sample size and double-blind placebo controlled design are encouraged and to report trial according to the CONSORT (Consolidated Standards for Reporting Trials) Statement. In addition, trials should be registered prospectively, and get accessed. Lastly, in order to address clinical relevance, future trials should focus on clinically important and patient-centered outcomes, such as all-cause mortality, dependence, quality of life, as well as serious adverse events. A follow-up of at least six months for acute ischemic stroke and a follow-up of at least 12 months for convalescence (or sequelae) are needed to demonstrate evidence of its long-term benefit.

## 5. Conclusion

This review of 14 randomized trials shows that DZSM capsule appears to improve neurological function, quality of life and reduce recurrence rate based on conventional therapy for ischemic stroke. DZSM capsule seems generally safe for clinical application. However, the beneficial findings are inconclusive due to generally weak evidence, and further large, rigorous trials are still warranted.

### Authors' contributions

XY Yang and JP Liu conceived and designed the review. XY Yang and LQ Wang were responsible for the searching, screening, selecting studies and assessing the methodological quality. Data extraction and of the studies were also performed by XY Yang and JG Li. XY Yang contributed to performing data analyses and drafting the manuscript. JP Liu, XY Yang, LQ Wang, JG Li, N Liang and Y Wang were all involved in critically revising the manuscript. All authors have read and approved the final manuscript.

**Table 2**  
Summary of main findings.

Dengzhan Shengmai + conventional therapy compared to Conventional therapy for ischemic stroke in convalescence (or sequelae) stage					
<b>Patient or population:</b> patients with ischemic stroke in convalescence (or sequelae) stage					
<b>Settings:</b> Inpatients					
<b>Intervention:</b> Dengzhan Shengmai + conventional therapy					
<b>Comparison:</b> Conventional therapy					
Outcomes	Illustrative comparative risks <sup>b</sup> (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Conventional therapy	Corresponding risk Dengzhan Shengmai + conventional therapy			
BI scores		The mean BI in the intervention groups was 9.5 higher (0.12 lower to 19.13 higher)		323 (3 studies)	⊕ ⊕ ⊕ ⊕ very low <sup>a,c,d,e</sup>
mRS scores		The mean mRS in the intervention groups was 0.42 lower (1.26 lower to 0.42 higher)		323 (3 studies)	⊕ ⊕ ⊕ ⊕ very low <sup>a,c,d,e</sup>
SS-QOL scores		The mean SS-QOL in the intervention groups was 15.26 higher (5.33–35.85 higher)		190 (2 studies)	⊕ ⊕ ⊕ ⊕ low <sup>a,c</sup>
All-cause mortality	48 per 1000	25 per 1000 (31–135)	RR 0.51 (0.29–1.77)	1405 (5 studies)	⊕ ⊕ ⊕ ⊕ moderate <sup>b</sup>
Recurrence rate	53 per 1000	21 per 1000 (4–104)	RR 0.39 (0.08–1.96)	190 (2 studies)	⊕ ⊕ ⊕ ⊕ low <sup>a,b</sup>

Dengzhan Shengmai + conventional therapy compared to placebo + Conventional therapy for ischemic stroke in convalescence (or sequelae) stage					
<b>Patient or population:</b> patients with ischemic stroke in convalescence (or sequelae) stage					
<b>Settings:</b> Inpatients					
<b>Intervention:</b> Dengzhan Shengmai + conventional therapy					
<b>Comparison:</b> Placebo + conventional therapy					
Outcomes	Illustrative comparative risks <sup>b</sup> (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Placebo + conventional therapy	Corresponding risk Dengzhan Shengmai + conventional therapy			
Reurrence rate	54 per 1000	38 per 1000 (384–752)	RR 0.71 (0.51–0.99)	3032 (1 study)	⊕ ⊕ ⊕ ⊕ low <sup>d,f</sup>
SS-QOL scores		The mean SS-QOL in the intervention groups was 14.9 higher (9.28 lower to 39.08 higher)		160 (1 study)	⊕ ⊕ ⊕ ⊕ low <sup>c,g</sup>
All-cause mortality	8 per 1000	8 per 1000 (4–18)	RR 1.01 (0.46–2.24)	3032 (1 study)	⊕ ⊕ ⊕ ⊕ low <sup>d,f</sup>

CI: Confidence interval; RR: Risk ratio; BI: Barthel index; mRS: modified Ranking scale; SS-QOL: Stroke Specific Quality of Life Scale.

<sup>a</sup> All the trials had high risk of performance bias for not blinding the participants.

<sup>b</sup> Total numbers of events is less than 300.

<sup>c</sup> Total sample size is less than 400.

<sup>d</sup> Pooled results included no effects.

<sup>e</sup> The significant heterogeneity with a large  $I^2$  value.

<sup>f</sup> The baseline between two groups is inconsistent.

<sup>g</sup> The trial had high risk of performance bias for not blinding the outcome assessor.

<sup>h</sup> The basis for the assumed risk (e.g. the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

## Funding

This work is supported by a research capacity establishment grant from the State Administration of Chinese Medicine (201207007), and supported by research fund from Yunnan Biovalley Pharmaceuticals.

## Conflicts of interest

The authors have declared no conflicts of interest.

## Acknowledgements

We thank Prof. Yefeng Cai from Guangdong Provincial Hospital of Chinese Medicine for providing us their unpublished data for our analysis, and thank Associate Prof. Yu-tong Fei and Dr. Jin Sun from Beijing University of Chinese Medicine for their advice of methodology.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.ctim.2017.12.004>.

## References

- World Health Organization. *The Atlas of Heart Disease and Stroke*. 2017; 2017 [http://

[www.who.int/ardiovascular diseases/resources/atlas/en/](http://www.who.int/ardiovascular diseases/resources/atlas/en/) (accessed November 2016)].

- World Health Organization. *The Top 10 Causes of Death*. 2017; 2017 [http://www.who.int/mediacentre/factsheets/fs310/en/ (accessed November 2016)].
- Peter AGS, Carl C, Mei-Chiun T, Emanuela C. Oral antiplatelet therapy for acute ischaemic stroke attack. *Cochrane Database of Syst Rev*. 2014;3:CD000029.
- Wang LD, Wang JH, Peng B, et al. Reports of prevention and treatment of stroke in China 2016. *Chin J Cerebrovasc Dis*. 2017;14:217–224.
- Neurological Branch of Chinese Medical Association, Cerebrovascular Group Of Neurological Branch Of Chinese Medical Association. Chinese guideline for diagnosis and treatment of acute ischemic stroke 2014. *Chin J Neurol*. 2015(48):246–257.
- Adeoyo O, Hornung R, Khatri P, Kleindorfer D. Recombinant tissue-type plasminogen activator use for ischemic stroke in the united states: a doubling of treatment rates over the course of 5 years. *Stroke*. 2011;42:1952–1955.
- Saver JL. Improving reperfusion therapy for acute ischaemic stroke. *J Thromb Haemost*. 2011;9:333–343.
- Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet*. 2015;375:1695–1703.
- He J, Gu D, Wu X, et al. Major causes of death among men and women in Chi-na. *N Engl J Med*. 2005;353:1124–1134.
- Peng W, Yang J, Wang Y, et al. Systematic review and meta-analysis of randomized controlled trials of xingnaojing treatment for stroke. *Evid Based Complement Alternat Med*. 2014;2014:210851.
- Ni X, Ni X, Liu S, et al. Medium- and long-term efficacy of ligustrazine plus conventional medication on ischemic stroke: a systematic review and meta-analysis. *J Tradit Chin Med*. 2013;33:715–720.
- Li D-Q, Li Z-C, Dai Z-Y. Selective serotonin reuptake inhibitor combined with dengzhanhengmai capsule improves the fatigue symptoms: a 12-week open-label pilot study. *Int J Clin Exp Med*. 2015;8:11811–11817.
- Lin X, Wang M, Liu Q. Effects of Dengzhan Xixin injection on hemorheology of cerebral infarction patients. *J Clin Neurol*. 2003;16:375.
- Sulter G, Steen C, De Keyser J. Use of the barthel index and modified rankin scale in

- acute stroke trials. *Stroke*. 1999;30:1538–1541.
15. Ziganshina LE, Abakumova T. Cerebrolysin for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2015;6:CD007026.
  16. The Fourth National Cerebrovascular Conference. Cerebral apoplexy patients clinical nerve function deficit score criteria. *Chin J Neurol*. 1996;29:381–383.
  17. Higgins J, Green S. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0*. 2017; 2017 [updated March 2011].
  18. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statist Med*. 2002;21:1539–1558.
  19. Ma L, Chu Z, Zhao S. Effect of DengzhanShengmai capsules on the secondary prevention of atherosclerotic cerebral infarction. *Chin J Clin Pharmacol*. 2014;19:442–445.
  20. Fang L. The effect observation of DengzhanShengmai capsules on cerebral infarction. *J Med Forum*. 2015;36:148–149.
  21. Lin X, Yu H, Yang L, Ye Y, Weng K. The effects of DengzhanShengmai capsules on cerebral infarction. *Guangdong Med J*. 2013;34:1925–1927.
  22. Mao D, Tang Y, Guo R, Zang Y, Hou R. Changes of sCD40L and expressive rate of NF- $\kappa$ B for patients with acute progressive cerebral infarction and the intervenient role of deng zhan sheng mai. *Chin J Stroke*. 2009;4:656–660.
  23. Zhen J, Zhang L, Kou L, Kong M, Liu H, Li Z. Clinical observation of Dengzhan Shengmai Capsule affecting the level of serum neuron specific enolization enzyme on patients with acute cerebral infarction. *J Chin Med Mater*. 2011;34:655–657.
  24. Xia L, Li X, Xie Y. The effects of Deng Zhan Sheng Mai capsule on serum leptin in patients of acute cerebral infarction. *Herald Med*. 2015;34:1050–1052.
  25. Pan Y. Analysis of Dengzhan Shengmai in the treatment and prevention of cerebral infarction. *Chin J Pract Nerv Dis*. 2011;14:11–13.
  26. Xue H, Guo Z, Liu X. Effects of deng zhan sheng mai capsules on quality of life and neurologic function of cerebral infarction patients. *Guangdong Med J*. 2010;31:1734–1735.
  27. Nan M, Li D. The effects of Dengzhan Shengmai capsule on secondary prevention of ischemic stroke. *China Foreign Med Treat*. 2016;09:146–148.
  28. Cao X, Zhou X, Zhuang H, Wang X. Clinical investigation of Dengzhan Shengmai capsule on ischemia stroke convalescence. *Global Tradit Chin Med*. 2012;5:56–57.
  29. Li J. Clinical investigation of Dengzhan Shengmai capsule on ischemic stroke. *Chin Foreign Med Res*. 2013;11:142–143.
  30. Chen B, Fang X, Wu Y, Jin S, Liu H, Li S. The effects of Dengzhan Shengmai capsule on secondary and tertiary prevention of ischemic stroke. *Chin J Neurol*. 2008;41:195–200.
  31. Cai Y, Zhang X, Huang Y, Wang L. *Dengzhan Shengmai Capsule Reduces the Recurrence Rate of Stroke: The Secondary Prevention Trial for Ischemic Stroke with Dengzhan Shengmai Capsule (SPIRIT-DZSM-1)*. 2011; 2011.
  32. Dong X, Wang Z. Effects of deng zhan sheng mai capsules on FIB and LDL-C of cerebral infarction patients. *Yunnan J Trad Chin Med Materia Med*. 2009;30:8–9.
  33. Luo Y. Dengzhan Shengmai capsule combine with conventional western medicine therapy treat 20 patients with middle cerebral artery infarction convalescence. *Guiding J Tradit Chin Med Pharm*. 2012;18:46–48.
  34. Wu H, Wang K. Clinical investigation of Dengzhan Shengmai Capsule on ischemia stroke convalescence. *J Qiqihar Univ Med*. 2015;36:534–535.
  35. Hu P, Li C. The clinical effect of DengzhanShengmai capsules on cerebral infarction. *China J Pharm Econ*. 2014;8:209–210.