

## Original Research Article

# External application of Ruyi Jinhuang powder for phlebitis: A systematic review and meta-analysis

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### Abstract

**Purpose:** To systematically review the effectiveness of the external application, Ruyi Jinhuang powder, on phlebitis

**Methods:** Relevant literature was retrieved from Medline, Embase, China National Knowledge Infrastructure database (CNKI), Cochrane Central Register, Chongqing Vip, Wanfang Data and SinoMed using the search terms "Ruyi Jinhuang San", "Ruyi Jinhuang powder", "Ruyi Jinhuang cream", "Agreeable golden powder", "satisfactory golden powder", "Jinhuang cream", "phlebitis", "prevention and (or) treatment", "randomized controlled trials" and "RCRs". Two researchers independently arranged and analyzed the data.

**Results:** Significant differences were observed in the total effectiveness rate of Ruyi Jinhuang powder [relative risk (RR) = 1.27, 95% confidence interval (CI) = 1.19 to 1.36, and  $p < 0.0001$ ]. Ruyi Jinhuang powder can reduce the incidence of phlebitis versus conventional therapy in preventing phlebitis (RR = 0.32, 95% CI 0.24 to 0.42, and  $p < 0.0001$ ). Shorten the average healing time [mean difference (MD) = -32.17, 95% CI = -48.39 to -15.94, and  $p = 0.0001$ ]. Reduced pain relief time for phlebitis (MD = -3.29, 95% CI -5.42 to -1.16, and  $p = 0.002$ ). However, no statistical difference was observed with regard to the onset time of phlebitis (MD = -0.62, 95% CI -1.76 to 0.52, and  $p = 0.29$ ).

**Conclusion:** Clinicians consider Ruyi Jinhuang powder a viable complementary and alternative medicine for phlebitis following the stronger evidence being offered.

**Keywords:** Ruyi Jinhuang powder; Prevention and treatment; Phlebitis; Meta-analysis

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## INTRODUCTION

In clinical settings, over 80 % of hospitalized inpatients are given intravenous therapy upon admission [1]. A majority of drugs are administered via intravenous injection to maintain

highly efficient bioavailability. Approximately, 20 to 70 % of drugs may provoke infusion-induced phlebitis, which is a common and painful complication of peripheral intravenous cannulation. Such complication significantly reduces the drug compliance of patients.<sup>2</sup>

Patients with intravenous injection of antibiotics and antineoplastic drugs may develop a high risk of infusion - induced phlebitis. Peripherally inserted central catheters (PICC) - induced Mechanic phlebitis, indwelling needle-induced phlebitis; superficial thrombophlebitis, etc [2]. Phlebitis cause a cascade of unwelcome repercussions-significant swelling, erythema, pain, warmth, thickening and hardening of the injection site and fever [3,4]. Increased prevalence of thrombophlebitis may disrupt the follow-up and negatively impact the physical health of patients. More importantly, the incidence of bacterial phlebitis can compromise subsequent provoke the occurrence of blood infection [5].

Age, gender smoking habit, peripheral vascular diseases, repeated intravenous catheterization, location and duration of catheter indwelling, catheter length and materials, interval of replacement, infusion and filtration devices, type of infused medications that causes lack of sensation (peripheral neuropathy), high-pH drugs and solutions were potentially considered as the risk factors. Other medications and intravenous fluids (vancomycin and benzylpenicillin antibiotics, aminophylline, amiodarone hydrochloride and potassium chloride, aminophylline and amiodarone hydrochloride and 7.4% calcium glubionate, were identified with the strongest phlebitis potential [2-4].

Heparin is associated with the risk of bleeding from the operation site and thrombocytopenia. Corticosteroids are followed by an increased risk of infection through impaired defense system [9]. Local use of anti-inflammatory medications is employed to alleviate the pain of superficial thrombophlebitis, reduce the acute inflammation and discomforts. Nevertheless, whether these therapies can avoid relevant complications remains to be further validated. Thus, it is recommended to use simpler, more economical, and available methods. One of these methods appears to be the use of complementary and alternative medicine.

In China, TCM has been applied to treat human diseases for more than 2000 years. In the history of TCM, physicians have accumulated clinical experience in management of phlebitis [10]. As an integral part of TCM, external application of Ruyi Jinhuang Powder yields lower cost, less adverse events and higher efficacy compared with traditional treatment. Ruyi Jinhuang Powder could also be used on inflammatory external hemorrhoids, acute gouty arthritis and don't increase adverse reactions [11]. Considerable number of studies demonstrated that Ruyi

Jinhuang powder had various pharmacological effects including anti-inflammatory, anti-bacterial, and analgesic effects [12]. Moreover, Ruyi Jinhuang powder could promote granulation, adsorb wound secretion and keep the wound relatively moist [13]. However, the evidence of effectiveness and safety of phlebitis has not been assessed systematically. In addition, substantial numbers of studies could potentially be missed if literature searches are restricted to English-only sources [10].

In previous meta-analyses, the use of Ruyi Jinhuang powder has been applied to treat phlebitis [8,9]. They concentrated on the use of Ruyi Jinhuang powder compared with magnesium sulfate alone. The two meta-analyses were performed in 2010 and 2012, respectively.

## METHODS

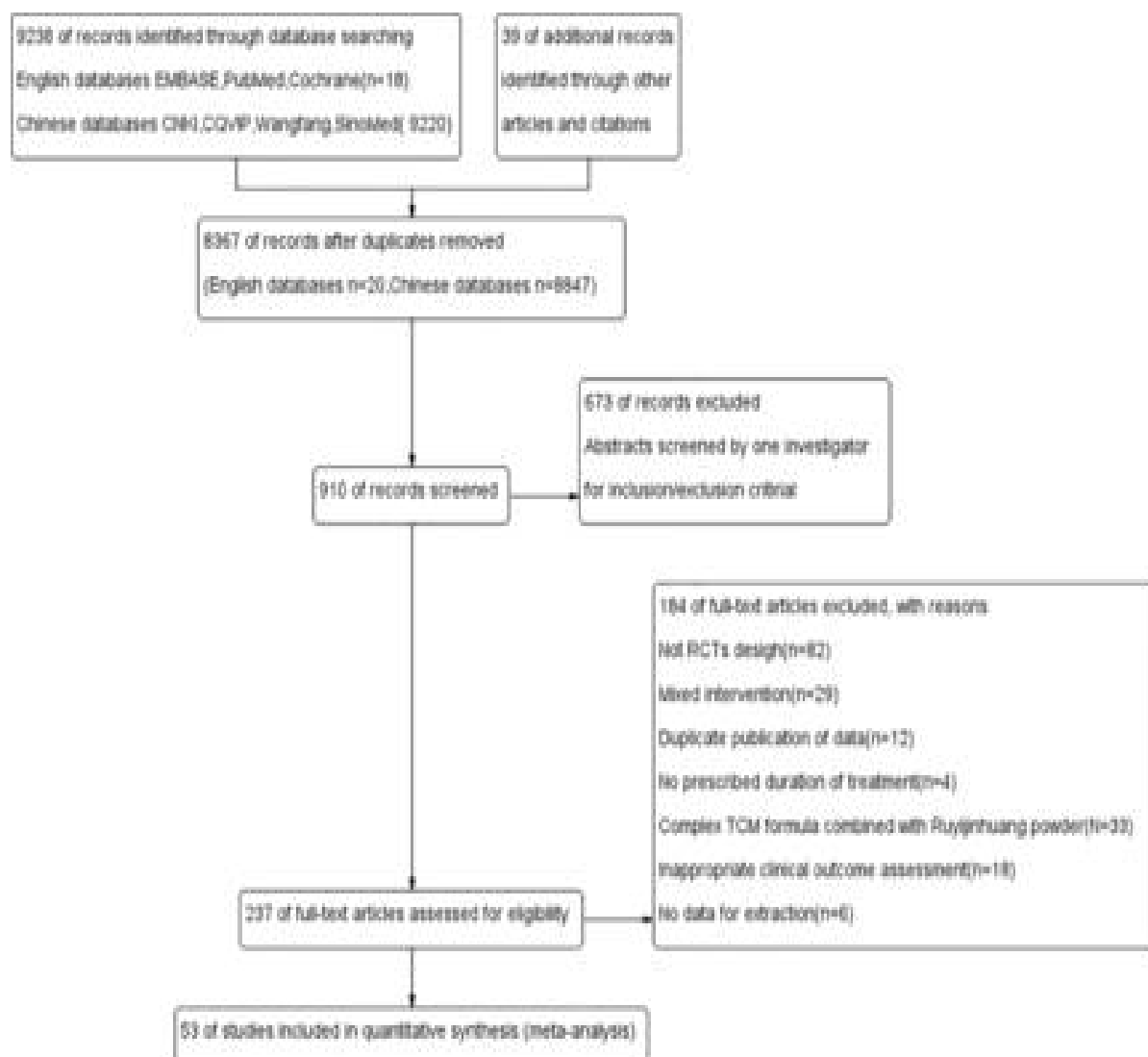
### Data source search

To identify relevant randomized clinical trials (RCTs), two reviewers (Qian Yang and Jian Zhang) performed systematical search from the Medline, Embase, China National Knowledge Infrastructure database (CNKI), Cochrane Central Register, Chongqing Vip, Wanfang Data and SinoMed using the search terms "Ruyi Jinhuang San", "Ruyi Jinhuang powder", "Ruyi Jinhuang cream", "Agreeable golden powder", "satisfactory golden powder", "Jinhuang cream", "phlebitis", "prevention and (or) treatment", "randomized controlled trials" and "RCTs." In this meta-analysis, the papers published until September 2016 were researched and included. The reference list of the chosen publications was searched to obtain more relevant articles. We did not limit the language and type of publications. Conference proceedings, abstract-only articles and graduation dissertation were all selected if they met our inclusion criteria (Figure 1).

### Study selection

#### Studies

Random control trials (RCTs) were included. Non-RCTs, Quasi-RCTs, or randomized trials with false randomization method design, mixed intervention, duplicate publication of data, no prescribed duration of treatment, complex TCM formula combined with Ruyi Jinhuang powder, inappropriate clinical outcome assessment and no data for extraction were excluded.



**Figure 1:** Summary of the literature identification and selection process. CNKI indicates the Chinese National Knowledge Infrastructure database; CQVIP, the Chinese Scientific Journals Full Text database; SinoMed, the Chinese Biomedical Literature Service System; RCT, randomized clinical trials.

### Participants

Patients diagnosed with phlebitis based on any set of explicit criteria were included. No restrictive limitations were set on age, gender, nationality, or basic diseases, intravenous injection drugs, phlebitis classification. Retrieval results included 17 chemotherapeutic phlebitis [11-27], 10 PICC-induced phlebitis [28-37], 19 infusion phlebitis [38-56], 7 intravenous indwelling needle-induced phlebitis [57-63] (Table 1 to Table 12). All phlebitis classifications were evaluated based on the Infusion Nursing Standards of Practice proposed by the American Infusion Nurses Society in 2006 [64].

### Interventions

The focused experimental groups received

external application of Ruyi Jinhuang Powder. We did not set limitations on dosages, intervals, times and mixtures of it, or types of conventional therapy used. Our comparison of Ruyi Jinhuang powder and conventional therapy included Ruyi Jinhuang powder alone [12,28,30,32,51] or Ruyi Jinhuang powder mixed with vinegar [11,14-17,38,48,52,54,59,60] mixed with honey [1,19-21,23,25,27,29,34,37,39,41,45,46,50,57,58,63] mixed with ethano [18,42,49,61] mixed with tea [22,33,35,43,44,47] mixed with sesameoil [24,31,40,62] mixed with water [26,36] or mixed with glycerin [53,55,56]. The wound sites were dabbed dry with sterile gauze, or the wounds were not debrided but cleaned with normal saline gauze. If they were soiled, then the combined mixtures would be smeared onto the wounds with a sterile gloved finger.

## Outcome measurement

To more accurately assess the efficacy of Ruyi jinhuang powder, the primary outcomes as total effectiveness rate (TER) in treating phlebitis, incidence of phlebitis (IP) for preventing phlebitis applied with Ruyi Jinhuang powder were evaluated. The secondary outcomes included average healing time (AHT), pain relief time (PRT) and incidence time of phlebitis (ITP).

## Data extraction

Two reviewers (Qian Yang and Jian Zhang) extracted data independently using a predetermined inclusion criteria. Disagreements were properly solved through mutual discussion or reaching a consensus by the third reviewer (Wen Xin Yang). The data extracted included the first author, year of publication, mean age, sample size, duration of trial period, basic diseases, intravenous infusion drugs, phlebitis classification, topical treatment of control group/experimental group. For studies lacking of sufficient information, the primary authors were contacted to obtain and validate the data. The use of modified JADAD scale evaluation, mainly includes 4 aspects as follow: (1) the generation of random sequence; (2) random hidden; (3) whether the use of blind method; (4) loss of access and withdrawal from the report. The highest score is 7 points, the lowest is divided into 0 points. At present, 1-3 is considered as a low quality, and 4-7 is considered as a high quality (Table 1). Data extraction and quality evaluation process, if there are different views, the use of collective discussion method solved it.

## Risk of bias assessment

The risk of bias in each study was assessed by two independent authors (Yong Qiong Deng and Xian Deng) using the Cochrane Risk of Bias tool [65] and disagreements were solved either by consensus or the third reviewer (Wen Xin Yang). Risk of bias and methodological quality of the selected papers are illustrated in Figure 2.

## RESULTS

### Study selection

The full texts of 237 relevant studies were reviewed from 9277 titles to validate the study eligibility.

Among 237 studies, 184 trials were excluded, including non-RCTs design (n=82), mixed intervention (n=29), duplicate publication of data (n=12), no prescribed duration of treatment

(n=4), complex TCM formula combined with Ruyi Jinhuang powder (n=33), inappropriate clinical outcome assessment (n=18), no data for extraction (n=6). Finally, 53 trials met the inclusion criteria and incorporated into the systematic review. All the selected studies were accomplished in China.

## Study characteristics

All included 53 trials were published in Chinese language. In total, 4119 participants were enrolled in these trials (n=2078 in the experimental group and n=2041 in the control group). The sample sizes of these trials ranged from 40 to 240 (Table 1). The dose and frequency of the Ruyi Jinhuang powder differed in each trial. External application of 50% magnem sulphate is the most frequently used in 34 trials. Further therapeutic and preventive measures used in clinical trials.

## Risk of bias assessment

The methodological quality of all selected trials was poor (Figure 2). All trials reported the randomization, but merely 12 explicitly described the randomization approach, 6 with random number table [14,17,25,32,36,46], 3 with random case sequence [28,39,65], one the envelope method [30], one based on the admission date [58] and one with convenience sampling method [60], detailed information regarding random sequence generation was absent in the other trials.

Moreover, allocation concealment or blinding of participants and study personnel were described in only one of the trials [36], all of the relevant trials adequately addressed incomplete outcome data, selective reporting could not be judged in all the studies because of the insufficient information provided. We found no other biases in the studies due to low methodological quality. An unclear risk of bias was delivered to all selected studies.

## Primary outcomes

### Incidence of phlebitis

Fourteen RCTs containing 1418 patients illustrated the results, the experimental group included 714 trials, while the control group included 704 trials, the experimental and control groups received Ruyi jinhuang powder and conventional therapy, respectively. All subjects received fundamental interventions, the 14 independent trials showed heterogeneity in the consistency ( $\chi^2 = 20.60$ ,  $p = 0.08$ ,  $I^2 = 37\%$ ).

**Table 1:** Basic characteristics of the included studies

Study	Sample size E/C	Sex or Age E/C (Mean ± SD) years	Duration E/C(months)	Phlebitis E/C basic Diseases E/C Drugs E/C Phlebitis classification E/C	Topical treatment of control group	External application of experimental group	Main outcomes	JADAD
Zhang and Li 2016 [11]	80(40/40)	Sex:E:25/15 C:23/17 Age:E:m=58 C:M=53	2012.12-2013.12	Chemotherapy-induced phlebitis Chemotherapeutic drugs: vinorelbine, paclitaxel, fluorouracil, leurocristine, cisplatin, carboplatin, Cyclophosphamide, pharmorubicin)	Give 0.9% normal saline water or 5% glucose 10-20 mL fast rapid intravenous injection, and to dilute the residual chemical therapy drug content on blood vessel walls, and from the reducing of veins	External application of Ruyijinghuang Powder combined with winegar at 1 mm thickness for 12 hours, once a day for 5 days	IP	3
Yang et al 2013 [12]	60(30/30)	Sex:All women Age:E:28-53 M=45 C:27-55 M=46	2011.2-2012.9	Chemotherapy-induced phlebitis Chemotherapeutic drugs: Fluorouracil department of gynecology	external application of 50%maghem sulphate (MgSO <sub>4</sub> ) 8-10 ml ,20 min a time	external application of Ruyijinghuang Powder at 2mm thickness, once a day	IP	3
Jiang 2010 [13]	50(25/25)	Sex:All women Age:35-60 M=45	2008.1-2009.2	Chemotherapy-induced phlebitis Diseased:radical mastectomy Chemotherapeutic drugs Cyclophosphamide, pharmorubicin, 5 fluorouracil	Conventional care not take preventive measures	External application of Ruyijinhuang powder 15g mixed with honey at 2 mm thickness for 8 hours, twice a day	IP	3
Li 2012 [14]	(85/83)	Sex:55/45 Age:30-68	2010.3-2011.3	Chemotherapy-induced phlebitis non-small cell lung cancer, breast cancer, acute nonlymphocytic leukemia Blistering chemotherapy drugs (vinorelbine, Doxorubicin)	Dexamethasone sodium5 mg, sodium aescinate5 mg, add into 10ml sodium chloride solution, intravenous push for several times	external application of Ruyijinghuang Powder combined with winegar at 5mm thickniss for 24 hours	IP	4
Cheng 2012 [15]	120(60/60)	Sex:68/52 Age:28-76	2010.3-2011.3	Chemotherapy-induced phlebitis Diseases: esophageal carcinoma <sup>29</sup> , gastric cancer <sup>47</sup> , colon cancer <sup>20</sup> , pancreatic cancer <sup>7</sup> , breast cancer <sup>1</sup> , endometrial carcinoma <sup>3</sup> , gallbladder 2	infrared radiation for 0.5 hour once a day	external application of Ruyijinghuang Powder combined with winegar once a day	IP	3
Zhou 2013 [16]	48(24/24)	Sex:35/13 Age:38-75 M=64	2011.3-2012.12	Chemotherapy-induced phlebitis Disease: Gastric cancer <sup>17</sup> , colorectal cancer 17, breast cancer <sup>13</sup> , colon cancer Phlebitis :E: grade I 20, grade II 16, grade III 12	external application of 50%maghem sulphate (MgSO <sub>4</sub> ) for 30 minutes, 7 days as a course	Ruyijinhuang powdermixed with vinegar once a day, 7 days as a course	TER	3

Abbreviations: RCTs, Randomized Controlled Trials; E, Experimental group; C, Control group;NR, no report; IRP, Incidence Rate of phlebitis; TER, Total Effective Rate; AHT, The average healing time; PRT, pain relief time; IRP, ITP, Incidence time of phlebitis

**Table 1:** Basic characteristics of the included studies (*continued*)

Study	Sample size E/C	Sex or Age E/C (Mean ± SD) years	Duration E/C(months)	Phlebitis E/C basic Diseases E/C Drugs E/C Phlebitis classification E/C	Topical treatment of control group	External application of experimental group	Main outcomes	JADAD
Sun and Li 2015 [17]	50(25/25)	Sex: E: 17/8 C:11/14 Age:E:38-75 (57.3±7.4) C:36-77(57.8±7.6)	2010.2-2014.10	Chemotherapy-induced phlebitis E:grade I3, grade II 5, grade III 17 C:grade I 2, grade II 4, grade III 19	cold compress of 50% magnem sulphate (MgSO <sub>4</sub> ) for 24 hours, along with hot compress for the next 24 hours	external application of Ruyijinhuang powder 9g mixed with distilled vinegar 10 ml and honey 2 ml at 6 hourly intervals	TER	4
Yu et al 2010 [18]	88(44/44)	Sex:41/ 47 Age:22-74 M=54.2	2007.4-2008.4	Chemotherapeutic phlebitis-induced by indwelling needle Diseases: gastric cancer18, breast cancer12, endometrial cancer19, lung cancer9, liver cancer5, colon cancer12, pancreatic carcinoma8, lymphoma5 Chemotherapeutic drugs: Vinorelbine, pharmorubicin	External application of Hot towel (Temperature of 40 ~ 50 °C)	Wet compress of ruyi jinhuang powder 50 g dissolved in ethanol 50 ml for 2 h, once a day, 7 days as a course	TER	3
You et al 2010 [19]	60(30/30)	5/25 5/25 25-78	2007.9-2009.6	chemotherapy-induced phlebitis (Cyclophosphamide, cisplatin, PTX(paclitaxel) Thiotepa, ADM doxorubicin)	external application of hirudoid cream 2-3times a day	ruyijinhuang powder mixed with honey at 0.5 mm thickness 2-3cm for 12h,twice a day	TER	3
Wu 2008 [20]	86(43/43)	Sex:56/30 Age:31-76 M=51.3	2006.5-2007.10	Chemotherapy-induced phlebitis grade I25, grade II 41, grade III20 gastric cancer20, breast cancer15, endometrial carcinoma11, lung cancer9, liver cancer12, colon cancer14, lymphoma4	infrared radiation for 15 min, twice a day,7 days as a course	Wet compress of Ruyijinhuang powdermixed with honey for 24 h, once a day, 7 days as a course	TER	3
Liu 2011 [21]	40(20/20)	Sex:16/24 Age:33-75 M=55.2±8.3	2008.2-2009.10	Chemotherapy-induced phlebitis Leukemia, multiple myeloma, lymphoma E:grade I6, grade II 11, grade III3 C:grade I6, grade II 12, grade III2	external application of 50% magnem sulphate (MgSO <sub>4</sub> ) for 12h : Cooperate with external application of wet Towel (50 °C) 30 minutes a time, 2 times/d	external application of Ruyijinhuang powder 5g mixed with honey at 1 mm thickness for 10 minutes, twice a day	TER	3
Meng 2011 [22]	60(30/30)	Sex:7/53 Age:31-78 M=50.85	2010.1-2011.7	Chemotherapy-induced phlebitis chemotherapy drugs: Paclitaxel cyclophosphamide, Fluorouracil, Epirubicin. Phlebitis: grade I 37, grade II 19, grade III 4	external application of 50% magnem sulphate (MgSO <sub>4</sub> ) ,2-3 times a day	Ruyijinhuang powdermixed with dense tea at 3mm thickness.	TER	3

**Table 1:** Basic characteristics of the included studies (*continued*)

Study	Sample size E/C	Sex or Age E/C (Mean $\pm$ SD) years	Duration E/C(months)	Phlebitis E/C basic Diseases E/C Drugs E/C Phlebitis classification E/C	Topical treatment of control group	External application of experimental group	Main outcomes	JADAD
Liang 2012 [23]	68(34/34)	Sex:38/30 Age:28-73 M=51.2	2009.1-2011.6	Chemotherapeutic phlebitis disease: nasopharyngeal carcinoma (NPC)15, lung cancer24, esophageal cancer 14, malignant lymphoma5, rectal cancer3, breast cancer7,Phlebitis:E:grade I 15, grade II 12, gradeIII7 C:grade I 18, grade II 10, gradeIII6	hot-wet compression of 50% magnesium sulphuricum at 4 hours intervals ,3 days as a course	external application of RuyiJinhuang Powder mixed with honey at 3mm thickness at 12 hours intervals, 3 days as a course	TER	3
Kang et al 2013 [24]	59(30/29)	Sex:41/18 Age:32-69 M=52	2012.1-2012.10	Chemotherapy non exosmosis phlebitis Disease:Small cell lung cancer20, adenocarcinoma15, squamous carcinoma14, esophageal7, breast cancer3;Chemotherapeutic drugs: Carboplatin,cisplatin, docetaxel, paclitaxel, fluorouracil, etoposide, gemcitabine, doxorubicin	external application of 50%magnesium sulphate (MgSO <sub>4</sub> ) 2 times a day	external application of Ruyijinhuang powder mixed with sesame oil 50% magnesium sulfate once a day.	TER	3
Wang et al 2014 [25]	(60/60)	Sex: 62/58 Age: 36-72	2013.10-2014.4	Chemotherapy-induced phlebitis Diseases:lung cancer 36, gastric cancer 27, liver cancer 20 , breast cancer20, colon cancer17	External application of 50%magnum sulphate (MgSO <sub>4</sub> )	external application of Ruyijinhuang powder mixed with honey at 3mm thickness for 72 hours	IP	4
He 2012 [26]		Sex:E:28/12 C:25/15 Age:E:31-70,M=50.5 C:22-75,M=48.6	2010.8-2011.8	Chemotherapy-induced phlebitis Diseases:E:16 lung cancer, gastric cancer 8, 6 breast cancer, esophageal cancer3, colon cancer 7 C:lung cancer 15, 10 gastric cancer, colorectal cancer 8, esophageal cancer 2, breast cance5 Chemotherapeutic drugs:Gemcitabine, cisplatin, 5-fluorouracil, oxaliplatin, doxorubicin	Conventional care not take preventive measures	external application of Ruyijinghuang Powder mixed with distilled water, at 2mm thickness	IP	3
Wei 2009 [27]	86(43/43)	Age:17- 82	2006.9-2008.7	Chemotherapy-induced phlebitis Vinorelbine, pirarubicin, mitoxantrone, Docetaxel	external application of 50%magnum sulphate (MgSO <sub>4</sub> ) for 4 hours	external application of Ruyijinhuang powder mixed with honey at 0.5-1mm thickness for 4 hours, 2~ 3d	IP	3

Abbreviations: RCTs, Randomized Controlled Trials; E, Experimental group; C, Control group;NR, no report; IRP, Incidence Rate of phlebitis; TER, Total Effective Rate; AHT, The average healing time; PRT, pain relief time; IRP, ITP, Incidence time of phlebitis

**Table 1:** Basic characteristics of the included studies (*continued*)

Study	Sample size E/C	Sex or Age E/C (Mean $\pm$ SD) years	Duration E/C(months)	Phlebitis E/C basic Diseases E/C Drugs E/C Phlebitis classification E/C	Topical treatment of control group	External application of experimental group	Main outcomes	JADAD
Xiong and Yang 2013 [29]	74(38/36)	Sex:36/38 Age:18-65 M=42.0	2011.1-2.13.1	PICC-induced Mechanic Phlebitis breast cancer25, liver cancer15, cervical cancer13, lung cancer21	external application of 50%maghem sulphate (MgSO <sub>4</sub> )	external application of Ruyijinhuang powder mixed with honey at 1mm thickness at 24 hourly intervals	TER AHT	4
Gao and Li 2012 [30]	108(54/54)	Sex:67/41 Age:4-81 M=40.6 $\pm$ 7.1	2010.2-2011.1	PICC-induced Mechanic Phlebitis(Cisplatin (DDP) and fluorouracil) brain cancer22,nasopharyngeal carcinoma68, laryngeal cancer13, carcinoma of the parotid gland5	Infrared radiation twice a day for 3 days	external application of Ruyijinhuang Powder at 0.5-1.0 cm thickniss,twice a day for 3 days	IP	4
Liu Y and Yang LY 2009 [31]	74(40/34)	Sex:E:28/12 C:22/12 Age:M=35.2 C:33.8	2007.1-2009.3	PICC-induced Mechanic Phlebitis	external application of wet Towel (45-50 °C)for 30 min ,twice a day,7 days as a course	external application of Ruyijinhuang Powder combined with sesame oil once a day, 7 days as a course	IP	3
Duan PP et al.,2008 [32]	240(120/120)	Sex:E:78/42 C:78/42 E:21-89(58.45 $\pm$ 13.38) C:16-96(59.58 $\pm$ 14.85)	2005.10-2007.6	PICC-induced Mechanic Phlebitis	Conventional care not take preventive measures	external application of Ruyijinhuang Powder once a day for 3 days	IP ITP	4
Zhu et al 2008 [33]	42(21/21)	Sex:38/4 Age:E:2.6 $\pm$ 3.8 5 C:82.5 $\pm$ 3.7	2005.8-2007.7	Phebitis afterPICC catheterization in eldedypatients Non-Hodgkin lymphoma28, myelodysplastic syndrome9, acute myelogenous leukemia5 Phebitis :E:grade I5, grade II 14, gradeIII2 C:grade I7, grade II 12, gradeIII2	Ultrashort wave therapy for 20 minutes, twice a day	Rnyijinhuang powder 12 g mixed with Warm tea at 1mm thickness for40 minutes ,2-3times a day	TER	34

Abbreviations: RCTs, Randomized Controlled Trials; E, Experimental group; C, Control group;NR, no report; IRP, Incidence Rate of phlebitis; TER, Total Effective Rate; AHT, The average healing time; PRT, pain relief time; IRP, ITP, Incidence time of phlebitis



**Table 1:** Basic characteristics of the included studies (contd)

Study	Sample size E/C	Sex or Age E/C (Mean ± SD) years	Duration E/C (months)	Phlebitis E/C basic Diseases E/C Drugs E/C Phlebitis classification E/C	Topical treatment of control group	External application of experimental group	Main outcomes	JADAD
Li et al 2007 [34]	62(32/30)	Sex:26/36 Age:13-73 M=35±2.5	2004.6-2007.2	PICC-induced Mechanic Phlebitis department of hemopathology and oncology	external application of 50% magnem sulphate (MgSO <sub>4</sub> ) for 12h; Cooperate with infrared therapeutic apparatus irradiation, 30 rain each time, 2 times a day.	external application of Ruyijinhuang powder mixed with honey for 24 hours	TER ATP	3
Zhu et al 2009 [35]	70(36/340)	Age:20-70 M=42.13	2005.1-2008.1	PICC-induced Mechanic Phlebitis	external application of hirudoid cream ,4 times a day, for 2-4 days.	external application of Rnyjinhuang powder 5 g mixed with The filtered tea water 10ml 4 times a day, for 2-4 days	TER	3
Peng and Wang 2015 [36]		28/4,M=73	2008.1-2010.3	PICC-induced phlebitis Disease:colorectal cancer Chemotherapy drugs:Oxaliplatin, calcium, folinate fluorouracil	wet compression of 50% magnem sulphate (MgSO <sub>4</sub> ) infrared radiation for 20 minutes qn	external application of Ruyijinhuang powder 12g mixed with warm water 39-40°C for 30minutes,3 times a day, 5 days as a course	TER	5
Shi et al 2011 [37]	73(37/36)	Age:20-75 M=42± 2.5	2007.10-2010.10	PICC-induced Intermittent phlebitis	external application of Hirudoid ointment combined with infrared therapy for 30 minutes, twice a day,	external application of Ruyijinhuang powder mixed with honey at 24 hours intervals	TER ATP	3
Yao 2015 [38]	86(43/43)	Sex:All woman Age:30-62 M=41.6±10.1	2013.6-2014.10	Infusion phlebitis	external application of 50% magnesium sulphate (MgSO <sub>4</sub> ); once a day, 4 days as a period of treatment.	Ruyijinhuang powder mixed with vinegar once a day, 4 days as a period of treatment.	TER	3
Yu H2016[40]	80(40/40)	Sex:E:3/9 C:32/8 Age:E:8-80 M=44 C:6-78 M=47)	2013.1-2014.1	Infusion phlebitis(fat emulsion, Intravenous indwelling needle20, Mannitol20,other drugs26)	External application of 50% magnesium sulphate(MgSO <sub>4</sub> )3times a day,5 days as a course	Ruyijinhuang powder mixed with sesame oil twice a day, 5 days as a course	TER	3

Abbreviations: RCTs, Randomized Controlled Trials; E, Experimental group; C, Control group; NR, no report; IRP, Incidence Rate of phlebitis; TER, Total Effective Rate; AHT, The average healing time; PRT, pain relief time; IRP, ITP, Incidence time of phlebitis

**Table 7:** Basic characteristics of the included studies (*contd*)

Study	Sample size E/C	Sex or Age E/C (Mean $\pm$ SD) years	Duration E/C(months)	Phlebitis E/C basic Diseases E/C Drugs E/C Phlebitis classification E/C	Topical treatment of control group	External application of experimental group	Main outcomes	JADAD
Huang and Liu 2004[39]	62(31/31)	Sex:25/37 Age:27-80	1995.1-2002.3	Infusion phlebitis(Potassium chloride, nutrient solution and chemotherapy drugs) Disease:E:subtotal gastrectomy7, liver cancer2, colon cancer 3, acute pancreatitis4, Choledocholithotomy7 8 postoperative lung cancer 8/ C:subtotal gastrectomy 5 Choledocholithotomy 8, postoperative lung cancer 6, breast cancer 4, kidney carcinoma liver cance2, acute intestinal obstruction5 E:grade I6, grade II 24, gradeIII 1 C:grade I8, grade II 22, gradeIII 1	external application of 50%maghem sulphate (MgSO <sub>4</sub> )	external application of Ruyjinhuang powder mixed with honey at 3mm thickness for aborve 12 hours once a day	TER	4
Wu 2015 [41]	62(31/31)	Sex:48/ 14 Age: 42-89	2014.1-2015.7	Infusion phlebitis E:grade I16, grade II 14, gradeIII 1 C:grade I8, grade II 22, gradeIII 1	hot-wet compression of 50%maghem sulphate (MgSO <sub>4</sub> )	external application of Ruyjinhuang powder 12g mixed with honey at 1mm thickness for 3-5 days	TER	3

Abbreviations: RCTs, Randomized Controlled Trials; E, Experimental group; C, Control group;NR, no report; IRP, Incidence Rate of phlebitis; TER, Total Effective Rate; AHT, The average healing time; PRT, pain relief time; IRP, ITP, Incidence time of phlebitis

**Table 1:** Basic characteristics of the included studies (*continued*)

Study	Sample size E/C	Sex or Age (Mean $\pm$ SD) years	Duration E/C(months)	Phlebitis E/C basic Diseases E/C Drugs E/C Phlebitis classification E/C	Topical treatment of control group	External application of experimental group	Main outcomes	JADA D
Yan and Xu 2015 [42]	52(26/26)	Sex:24/28 Age:26-74 M=58.77 $\pm$ 13. 18	2012.9-2013.6	Infusion phlebitis transfusion drugs:Potassium chloride, dopamine, fat emulsion ,levofloxacin Phlebitis:E:grade I 4, grade II 20, gradeIII 2 C:grade I 6, grade II 18, gradeIII 2	external application of 50%maghem sulphate (MgSO <sub>4</sub> ) for 120minutes,twice a day	external application of Ruyijinhuang powder mixed with35%-40% ethanol at 1mm thickness, for 120minutes,twice a day	TER ATP	3
Liu et al 2014 [43]	56(28/28)	Sex:30/26	2011.10-2013.10	Infusion phlebitis Phlebitis:grade I 36, grade II 18, gradeIII 2	external application of 50%maghem sulphate (MgSO <sub>4</sub> ) 2-3times a day,5 days as a course	external application of RuyiJinhuang Powder 15g mixed with Green tea water at 2mm thickness for 24hours, at 8 hours intervals, 5 days as a course	TER	3
Zhang et al 2007 [44]	60(30/30)	Sex:36/24 Age:41-78	2003.8-2006.8	Infusion phlebitis (Potassium chloride injection, amiodarone, nitric acid glycerin, dopamine and levofloxacin)	external application of 50%maghem sulphate (MgSO <sub>4</sub> ) , Cooperate with external application of wet Towel (50 °C)for 30 min ,twice a day	Rnyijinhuang powder 5 g mixed with dense tea,at 3 mm thickness for 10min,twice a day	TER	3
Liu et 2012 [45]	100(50/50)	Sex:78/22 Age:35-71 M=51	2010.1-2012.1	Amiodarone induced phlebitis E:grade I34, grade II 15, gradeIII 3 C:grade I33, grade II 10, gradeIII 5	external application of 50%maghem sulphate (MgSO <sub>4</sub> )	external application of Ruyijinhuang powder 5g mixed with honey	TER	3
Zhang and Zhao 2015 [46]	60(30/30)	Sex:E:16/14 C:14/16 Age:E:62 $\pm$ 5.4 C:61 $\pm$ 4.8	2014.7-2017.12	Amiodarone-induced phelebitis Phlebitis:E:grade I 8, grade II 16, gradeIII 6 C:grade I 7, grade II 17, gradeIII 6	external application of 50%maghem sulphate (MgSO <sub>4</sub> ) at 6 hours interval	external application of Ruyijinhuang powder mixed with honey at 3mm thickness, at 6 hours interval	TER ATP PRT	4
Dai 2013 [47]	44(23/21)	Sex:29 /15 Age:40-83 M=66.25 $\pm$ 12.0 2	2011.1-2012.12	amiodarone-induced phlebitis	Conventional care not take preventive measures	Rnyijinhuang powder 5 g mixed with dense tea at 2mm thickness for 8 -10hours,twice a day	IP	3

Abbreviations: RCTs, Randomized Controlled Trials; E, Experimental group; C, Control group;NR, no report; IRP, Incidence Rate of phlebitis; TER, Total Effective Rate; AHT, The average healing time; PRT, pain relief time; IRP, ITP, Incidence time of phlebitis

**Table 9:** Basic characteristics of the included studies (contd)

Study	Sample size E/C	Sex or Age (Mean $\pm$ SD) E/C years	Duration E/C(months)	Phlebitis E/C basic Diseases E/C Drugs E/C Phlebitis classification E/C	Topical treatment of control group	External application of experimental group	Main outcomes	JADAD
Huo and Chang 2013 [48]	60(30/30)	Sex:33/27 Age:35-78M=54.23 $\pm$ 5.52	2008.10-2012.10	amiodarone-induced phlebitis	external application of 50% magnesium sulphate (MgSO <sub>4</sub> ); 30 minutes each time, 3 times a day, 3 days as a period of treatment.	Ruyi j inhuang Powder 15g mixed with vinegar at 0.5 mm thickness	TER	3
Chen et al 2013 [49]	60(30/30)	Sex:E:21/9 C:21/9 Age:E:36-78,M=67 C: 32-85,M=70	2011.1-2012.2	amiodarone-induced phlebitis in CCU department Phlebitis:E:grade I 17, grade II 9, grade III 4 C:grade I 13, grade II 11, grade III 6	external application of 50% magnem sulphate (MgSO <sub>4</sub> ) : twice a day	external application of Ruyijinhuang powder mixed with 75% ethanol at 3mm thickness for 8-12 hours twice a day	TER ATP PRT	3
Fu 2016 [50]	146(82/64)	Sex: E:34/30 C:43/39	2015.1-2015.12	sodium $\beta$ -seven-induced phlebitis E:grade I 36, grade II 27, grade III 19 C:grade I 28, grade II 22, grade III 14	wet compress of 50% magnesium sulphuricum for 1 hours, 3times a day, 5 days as a course	external application of RuyiJinhuang Powder tuned into a paste with honey at 2mm thickness for 22 hours, once a day, 5 days as a course	TER	3
Li et al 2013 [51]	80(40/40)	Sex:38/42 Age:M=52.3	2011.3-2012.9	fat emulsion-induced phlebitis diseases:severe acute pancreatitis62, tumor14, malnutrition4	external application of 50% magnesium sulphate (MgSO <sub>4</sub> ) 50g dissolved in 100mL warm water (40 -45°C) cooperate with microwave physiotherapy15-30 minutes,2-3 times a day 10-20 min each time	hydropathic compress of Ruyi Jinhuang powder 7 days for a course of treatment	TER ATP PRT	3
Yang 2012 [52]	75(37/38)	Sex:52/23 Age: 35-78	2010.1-2012.5	mannitol-induced phlebitis Phlebitis:E:grade I 27, grade II 10, grade III 0 C:grade I 30, grade II 8, grade III 0	external application of 25% magnem sulphate (MgSO <sub>4</sub> )	external application of Ruyijinhuang powder 2-3g mixed with vinegar at 2mm thickness	TER	3
Yang 2012 [52]	75(37/38)	Sex:52/23 Age: 35-78	2010.1-2012.5	mannitol-induced phlebitis Phlebitis:E:grade I 27, grade II 10, grade III 0 C:grade I 30, grade II 8, grade III 0	external application of 25% magnem sulphate (MgSO <sub>4</sub> )	external application of Ruyijinhuang powder 2-3g mixed with vinegar at 2mm thickness	TER	3

Abbreviations: RCTs, Randomized Controlled Trials; E, Experimental group; C, Control group; NR, no report; IRP, Incidence Rate of phlebitis; TER, Total Effective Rate; AHT, The average healing time; PRT, pain relief time; IRP, ITP, Incidence time of phlebitis

**Table 1:** Basic characteristics of the included studies (*continued*)

Study	Sample size E/C	Sex or Age (Mean $\pm$ SD) years	Duration E/C(months)	Phlebitis E/C basic Diseases E/C Drugs E/C Phlebitis classification E/C	Topical treatment of control group	External application of experimental group	Main outcomes	JADAD
Tang G and Meng JH 2012[53]	60(30/30)	Sex:36/24 Age:37-72 M=68 $\pm$ 9	2007.3-2010.9	Gadopentetate dimeglumine - induced phlebitis grade I40, grade II 18, grade III 2	external application of 50% magnem sulphate (MgSO <sub>4</sub> ) twice a day	external application of Ruyijinghuang Powder combined with glycerinum, twice a day	TER	3
Li et al 2010 [55]	100(50/50)	E:75-82M=78.5 $\pm$ 3.2) C:75-84M=(79.9 $\pm$ 2.9)	2008.10-2009.6	Alprostadil-induced superficial phlebitis	external application of Dermlin dressing, once a day	external application of Ruyijinghuang Powder 12g combined with glycerinum 20ml for 30 minutes, 2-3 times a day 3 days as a course	TER	3
Mei 2010 [56]	100(50/50)	Sex:48/52 Age:63-84	2009.3-2009.12	superficial phlebitis E:grade I, grade II 17, grade III 6 C:grade I 30, grade II 17例, grade III 3	external application of Dermlin dressing, once a day	external application of Ruyijinghuang Powder 12g combined with glycerinum 20 mL, at 0.3 cm thickniss, 2-3times a day, 7 days as a course	TER	4
Zhang and Wang 2013 [57]	50(25/25)	Sex: 28/22 Age:50-90 M=70	2012.8-2012.12	indwelling needle- induced phlebitis	Conventional care not take preventive measures	external application of Ruyijinhuang powder mixed with honey for 12 hours, twice a day	IP	3
Zhou et al 2012 [58]	128(64/64)	Age:E:28-70(52.22 $\pm$ 12.98) C:26-72(52.47 $\pm$ 13.32)	2009.1-2010.10	indwelling needle- induced phlebitis desease:cervical carcinom Chemotherapeutic drugs: Fluorouracil	Conventional care not take preventive measures	external application of RuyiJinhuang Powder 15g mixed with honey for 24hours, 5 days as a course	IP ITP	4
Yu et al 2010 [59]		Sex:30/18 Age: 25-83	2008.1-2009.12	indwelling needle-induced phlebitis phlebitis:grade I 35, grade II 13	external application of 50% magnem sulphate (MgSO <sub>4</sub> ) : Cooperate with external application of hot-water bag ,at 4 hours intervels,5 day as a course	external application of Ruyijinhuang powder mixed with vinegar at 0.2-0.4cm thickness, once a day ,5 day as a course	TER	3
Xin 2012 [60]	60(30/30)	Sex:32/28 Age:26-82 M=54 $\pm$ 12.5	2010.1-2011.1	indwelling needle- induced phlebitis cardiothoracic surgery department	external application of 50% magnem sulphate (MgSO <sub>4</sub> ) , Cooperate with external application of hot-water bag (50 °C) ,4 times a day,7 days as a course	Ruyijinhuang powder 9g mixed with distilled vinegar 20 ml at 12 hourly intervals, 7 days as a course	TER	4

**Table 1:** Basic characteristics of the included studies (*continued*)

Study	Sample size E/C	Sex or Age E/C (Mean $\pm$ SD) years	Duration E/C(months)	Phlebitis E/C basic Diseases E/C Drugs E/C Phlebitis classification E/C	Topical treatment of control group	External application of experimental group	Main outcomes	JADAD
Xu et al 2011 [61]	120(60/60)	40/20(2-84M=43) 38/22 (4-80M=42)	2008.6-2010.6	indwelling needle- induced phlebitis E:Swelling type 37, vascular sclerosis type 21, necrosis Type 2 C:Swelling type 36, vascular sclerosis type 22, necrosis type2	0.5% povidone iodine solution cotton swab sterile needle, anisodamine10mg plus NS soaked 10 ml sterile gauze to cover, cover with plastic wrap. 30 minutes each time, 2 times a day, 5 days as a period of treatment.	Ruyi jinhuang Powder mixedwith ethyl alcohol (applied the Ruyi jinhuang Powder which had been put on the gauze evenly to the damaged skin according to its Size)as well as TDP based on sys temic, twice per day , 30 minutes each time, 5 days as a course.	TER	3
Song et al 2014 [62]	32(16/16)	Sex:E:20/17 C:21/15 Age:E:60-72.5 C:60.5-71.9	2012.5-2014.1	indwelling needle- induced phlebitis	external application of 50%magnesium sulphate (MgSO <sub>4</sub> ) 50g dissolved in 100mL warm water (40 -45°C) 3 times a day 10-20 min each time,4-6 days as a course	Ruyijinhuang powder mixed with sesame oil twice a day, 4-6 days as a course	TER	3
Liu and Zhou 2012 [63]	46(23/23)	Sex:30/16 Age:22-85	2010.1-2011.8	indwelling needle- induced phlebitis (breast cancer 6, lung cancer 18, colorectal cancer 10/ cervical cancer 8, brain tumor 2, non-Hodgkin's lymphoma 2)	external application of 50%magnem sulphate (MgSO <sub>4</sub> ) for 2h,3times a day,3days as a course	Ruyijinhuang powdermixed with honey for 12h, once a day, 3days as a course	TER	3

Abbreviations: RCTs, Randomized Controlled Trials; E, Experimental group; C, Control group;NR, no report; IRP, Incidence Rate of phlebitis; TER, Total Effective Rate; AHT, The average healing time; PRT, pain relief time; IRP, ITP, Incidence time of phlebitis

Thus, randomized-effect model should be used for statistical analysis. The combined effects showed that there was some beneficial evidence regarding the effect on reducing incidence of phlebitis after external application of Ruyi jinhuang powder versus conventional therapy (RR = 0.32, 95 % CI = 0.24 and 0.42, and  $p < 0.0001$ ) (Figure 3).



**Figure 3:** Meta-analysis of the incidence rate of phlebitis Ruyi jinhuang powder versus conventional therapy based on the same intervention strategies in preventing phlebitis. CI indicates confidence interval

### Total effectiveness rate of Ruyi Jinhuang powder versus conventional therapy in treating phlebitis

39 RCTs contained 2701 patients illustrated the results. The experimental group (1364 trials) and control groups (1337 trials) received Ruyi Jinhuang powder and conventional therapy, respectively. The 39 trials yielded significant heterogeneity ( $\chi^2 = 171.17$ ,  $P < 0.0001$ ,  $I^2 = 78\%$ ). Thus, random-effect model should be used for statistical analysis.

The aggregated results indicated that comparison revealed significant differences in total effectiveness rate of Ruyi Jinhuang powder versus conventional therapy groups (RR = 1.27, 95% CI = 1.19, 1.36, and  $P < 0.0001$ ).

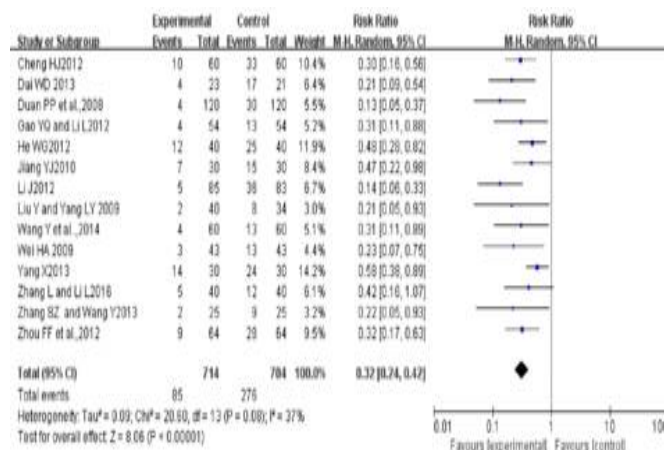
Significant differences were also found between subgroups of chemotherapy-induced phlebitis (RR = 1.19, 95% CI = 1.10, 1.27, and  $p < 0.0001$ ). PICC-induced phlebitis (RR = 1.65, 95 % CI = 1.39, 1.96, and  $p < 0.00001$ ). infusion phlebitis (RR = 1.21, 95 % CI = 1.10, 1.33, and  $p = 0.0001$ ) and indwelling needle-induced phlebitis (RR = 1.28, 95 % CI = 1.08, 1.52, and  $p = 0.007$ ; Figure 4 to Figure 6).

### Secondary outcomes

#### Average healing time

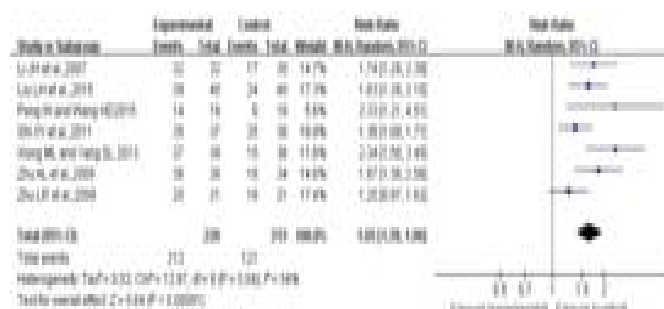
Seven RCTs consisting of 461 patients illustrated the results. The experimental group included 233 trials, and the control groups included 228 trials. The 7 trials shown significant heterogeneity ( $\chi^2$

=303.59,  $p < 0.00001$ ,  $I^2 = 98\%$ ) compared to conventional therapy. External application of Ruyi jinhuang powder exerted a superior effect on the average healing time using the random-effect model (MD = -32.17, 95 % CI = [-48.39, -15.94], and  $P = 0.0001$ ) (Figure 7).

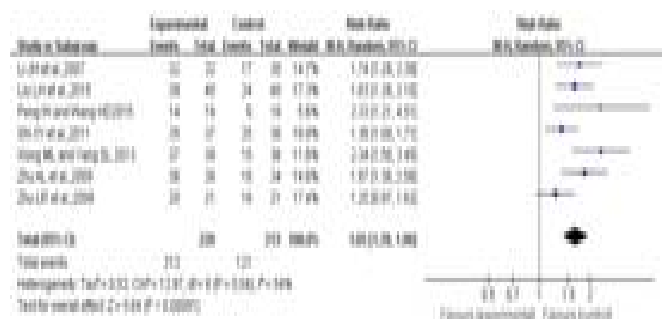


**Figure 4:** Meta-analysis of the total effectiveness rate of external application of Ruyi jinhuang powder versus conventional therapy based on the same intervention strategies. CI indicates confidence interval.

#### A: Chemotherapy-induced phlebitis

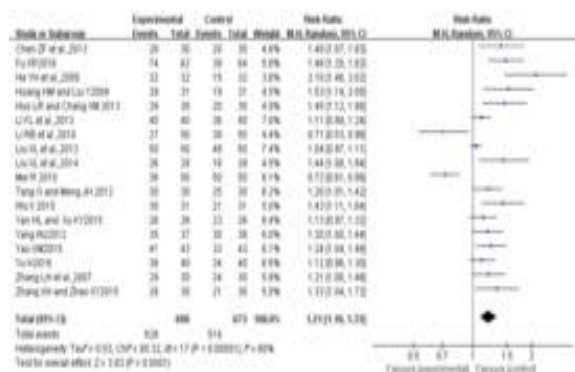


#### B: PICC-induced phlebitis



**Figure 5:** Meta-analysis of the total effectiveness rate of external application of Ruyi jinhuang powder versus conventional therapy based on the same intervention strategies. CI indicates confidence interval.

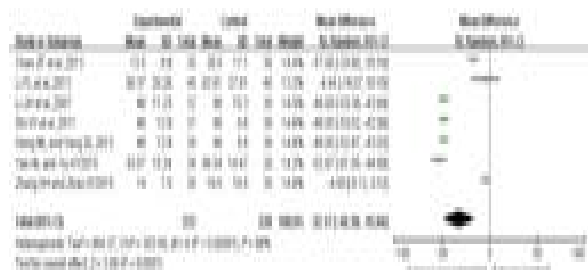
**C: Infusion phlebitis**



**D: Indwelling needle-induced phlebitis**

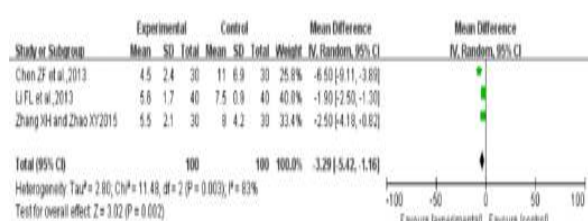


**Figure 6:** Meta-analysis of the total effectiveness rate of external application of Ruyi jinghuang powder versus conventional therapy based on the same intervention strategies. CI indicates confidence interval.



**Figure 7:** Meta-analysis of the average healing time of external application of Ruyi jinghuang powder versus conventional therapy

**Pain relief time**



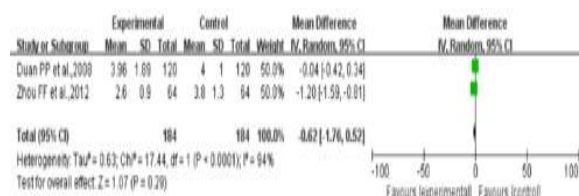
Three studies contained 200 patients reported pain relief time, the experimental group included 100 trials and the control group included 100 trials. The 3 trials yielded significant heterogeneity ( $\chi^2 = 11.48, P = 0.003, I^2 = 83\%$ ), the

results of meta-analysis using the randomized-effect model indicated significant difference on pain relief time of phlebitis (MD= -3.29, 95% CI =[-5.42, -1.16],  $P = 0.002$ ), as illustrated in Figure 8.

**Figure 8:** Meta-analysis of the average healing time of external application of Ruyi jinghuang powder versus conventional therapy

**Incidence time of phlebitis**

Two RCTs consisting of 368 patients illustrated the results. The experimental group included 184 trials and control group included 184 trials. These 2 trials yielded significant heterogeneity ( $\chi^2 = 17.44, p < 0.0001, I^2 = 94\%$ ), but result of meta-analysis indicated there was no statistical significance in incidence time of phlebitis (MD = -0.62, 95 % CI = [-1.76, 0.52],  $p = 0.29$ ), as demonstrated in Figure 9.



**Figure 9:** Meta-analysis of the incidence time of phlebitis of external application of Ruyi jinghuang powder versus conventional therapy

**Adverse events**

Only one patient reported adverse event as rash reaction with topical application of Ruyi jinghuang powder mixed with distilled water, manifested as local skin irritation, itching, neck visible red rash, after removing the topical drug immediately and intramuscular injection of diphenhydramine 20 mg was given at the same time, rash symptoms relieved within 30 min [26]. No other study has reported adverse events induced by Ruyi jinghuang powder. However, the effect of Ruyi jinghuang powder expression still need to further standardize and clear, usage of unknown “for external use” has become the underlying causes for the incidence of adverse reactions [27,28].

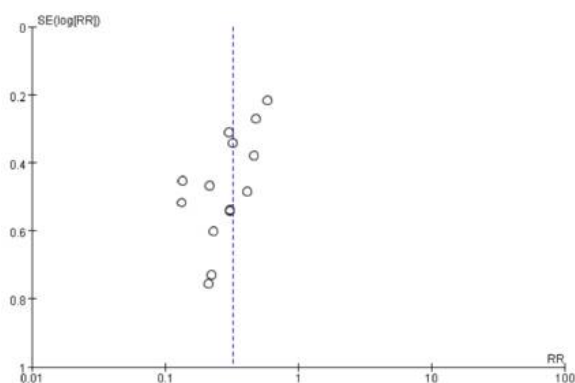
**Sensitivity analysis**

Using the leave-one-out approach, sensitivity analysis demonstrated the finding was reliable and independent, no significant change was noted in the direction of the combined estimates after the study removal, suggesting that the meta-analysis was robust and the data was accurate.

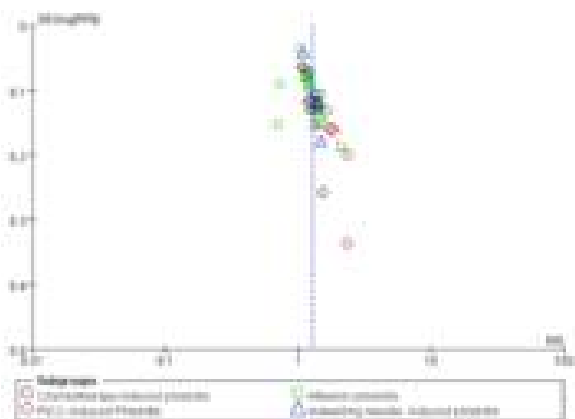


### Publication bias assessment

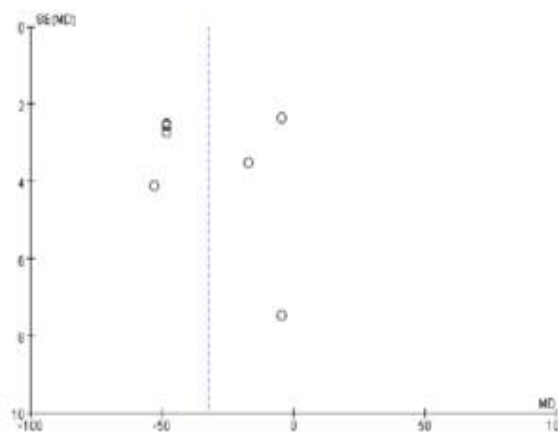
In this review, although all of included literatures were the comparisons of the Chinese literature, the funnel plots of incidence of phlebitis, total effectiveness rate in treating phlebitis, average healing time, pain relief time, incidence time of phlebitis performed included 14 RCTs, 39 RCTs, 7 RCTs, 3 RCTs and 2 RCTs, respectively (Figure 8-10). The use of funnel plots of pain relief time and incidence time of phlebitis was limited because of the sample size. Regarding these studies of Ruyi Jinhuang powder for phlebitis, the publication bias was small because the spots were substantially symmetric, and none of the studies lies outside the limits of the 95%CI. However, caution is advised in interpreting the results of publication bias of average hospitalization time after operation because of a small subset of studies. Consequently, the publication bias probably occurs in this meta-analysis.



**Figure 10:** Funnel plot of the incidence rate of phlebitis with Ruyijinhuang Powder versus conventional therapy based on the same intervention strategies in preventing phlebitis



**Figure 11:** Funnel plot of the total effectiveness rate of phlebitis with external application of Ruyijinhuang Powder versus conventional therapy based on the same intervention strategies



**Figure 12:** Funnel plot of the average healing time of phlebitis with external application of Ruyi Jinhuang powder versus conventional therapy based on the same intervention strategies

## DISCUSSION

### Summary of evidence

This systematic review searched a wide variety of electronic databases for relevant articles. A total of 53 RCTs were identified, a detailed subgroup analysis based on different comparisons revealed the clinical outcome of phlebitis. Despite the fact that most of the trials had small sample sizes and poor methodological quality, analysis of the pooled data showed a consistently superior effect of Ruyi Jinhuang powder in terms of increasing the total effectiveness rate, which is in accordance with the prior two meta-analyses [8,9]. Whereas, reducing the incidence of phlebitis, which was not consistent with previous study [9], one important probable cause was the expanded sample size. Furthermore, our study showed that Ruyi jinhuang powder could even lead to a shorter postoperative recovery time by decreasing average healing time and pain relief time of phlebitis compared to the control groups, which were not mentioned in the two prior studies. However, result of meta-analysis indicated there was no statistically significant difference in incidence time of phlebitis. Moreover, no patients dropped out of their trials due to adverse effects, suggesting that Ruyi Jinhuang powder was relatively safe for clinical use.

### Strengths of this review

The prior two meta-analyses of Ruyi Jinhuang powder demonstrated significant benefits compared with 50% magnesium sulfate and no adverse drug reaction has been reported [8,9]. Six trials were included in one study,

the obvious effective rate was statistically different [OR = 11.07, 95%CI 4.39-27.91, Z= 5.10,  $P < 0.001$ ] [8], whereas ten RCTs were included in another study, the total efficiencies of the two drugs had statistical significance [RR=12.96, 95 % CI ( 5.81, 28.89),  $p < 0.00001$ ], obviously effective rates were statistically different [RR = 9.11, 95 % CI (3.98, 20.88),  $p < 0.00001$ , but there was no statistical difference between Ruyi Jinhuang powder and magnesium sulfate in the incidence of phlebitis and grade I skin injury in the 72 h of treatment [RR = 7.76 and 0.13, 95 % CI: (0.94, 64.19) and (0.02, 1.07),  $p > 0.05$ ] [9].

### Limitations of this review

Even with these promising results, there are some limitations of the present study. First, although we were confident that our search strategy located all relevant studies, there remained a certain degree of uncertainty. Our study based on the findings of others about the heterogeneous quality of randomized trials from China. In our own experience in China, we have doubted that many methodological features attributed to randomized trials, were in fact conducted, while several explanations for this phenomenon existed, a likely explanation was the slow uptake of evidence-based medicine and clinical trials methodology in academic research centers. Second, the quality scores of the included RCTs were generally poor. Risk bias study showed that many of the studies are unclear with high risks in allocation concealment, blinding of participants and personnel, as well as outcome assessments. The unclear and high risk of bias in the included studies weakens the conclusion and well-designed randomized clinical trials are warranted to confirm the efficacy of Ruyi Jinhuang powder. While Cochrane's  $P_2$  and  $P_2$  tests revealed no statistical heterogeneity among these studies.

### Possible rationale for use of Ruyi jinhuang powder for phlebitis

According to the TCM theory, first, the primary pathogenesis of phlebitis stagnated blood obstructing meridians and collaterals, resulting in such symptoms and signs as ischemia, thrombosis, ecchymosis and localized pain. Second, animal experiments carried out in recent years have demonstrated that phlegm-dampness firstly formed in these patients and then developed into stasis, resulting in combination of phlegm and stasis. Third, spasm and obstruction of the blood vessels will induce circulatory impairment of the affected limb, manifested by pallor, aversion to cold, distension pain, severe

pain and muscle twitch. Last, damp-heat of phlebitis is manifested by redness, edema and slightly infected gangrene. Therefore, treating basic principles is to invigorate blood circulation and remove blood stasis, resolving phlegm and dredging meridians and collaterals, warming Yang and relieving spasm and cleaning up toxic heat. In conclusion, external application of Ruyi Jinhuang powder using on treating and preventing phlebitis as an important complementary therapy is based on these definite principles [26-44].

This powder can shorten the time of licking, which shown that this powder has analgesic effect ( $P < 0.05$ ) [36,42]. Another clinical observation of golden powder combined with external application of antibiotics on epididymitis and orchitis shown that in the clinical efficacy significantly differed ( $P < 0.05$ ) and the scrotum in the treatment group in the signal measurement of blood levels, TCM syndrome, body temperature returned to nominal time, and the disappearance time of scrotal swelling and the disappearance time of clinical symptoms. The incidence of complications in these two groups was significantly lower than that in the control group ( $P < 0.05$ ) and yielded no adverse reactions [56]. What's more, Jinhuang powder-polyurethane dressing, a suitable material for temporary wound coverage of traditional Chinese orthopedics, was based on the famous prescription Ruyi Jinhuang powder. Polyurethane can absorb liquid higher than nearly 15-20 times of its own weight due to excellent suction performance. Using immersion method to make the Jinhuang powder-polyurethane dressing can have high drug-loading capacity, which can be applied to the acute wound of Guinea pig and plays a role in mitigating inflammatory responses and eliminating necrotic tissues without irritation to the skin [48].

### Implications for research

As an important complementary therapy, although a substantial amount of research has investigated the chemical constituents of Ruyi jinhuang powder. However, more trials with rigorous methods of design, measurement and evaluation (DME) following the Cochrane Handbook should be applied to enhance the representativeness of the sample. Clinical trial registries should be specifically encouraged to provide details of the protocols for treating phlebitis, placebo-controlled clinical trials are essential. Randomized controlled trials, for instance, should be strictly required in study design and reported based on the Consolidated Standards of Reporting Trials (CONSORT).

## CONCLUSION

This systematic review demonstrates positive evidence for the effectiveness of Ruyi jinhuang powder in the management of phlebitis. Nevertheless, extreme heterogeneity in the analyses remains unexplained, and the number of high-quality studies was not large enough in this systematic review; thus, the outcome of the review is not conclusive. Therefore, more high-quality RCTs, with low risk of bias and adequate sample sizes, are required to demonstrate its true effects.

## DECLARATIONS

### Conflict of Interest

No conflict of interest associated with this work.

### Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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