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The effects of Chinese herbal medicines for treating diabetic foot ulcers: A systematic review of 49 randomized controlled trials

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ABSTRACT

Objective: To assess the effects and associated risks of Chinese herbal medicine (CHM) for diabetic foot ulcer (DFU).

Methods: We systematically searched seven electronic databases for randomized controlled trials (RCTs) about Chinese herbal medicines for treating diabetic foot ulcers. The methodological quality of RCTs was assessed by the Cochrane risk of bias tool. Data was synthesized using review manager (RevMan) 5.3. Meta-analysis was conducted if the data were available. A summary of finding table was generated by The GRADEpro Guideline Development Tool (GDT) online.

Results: Forty-nine RCTs, all conducted in China, involving 3646 participants were included. Most of the included trials had unclear or high risk of bias. Twenty-six trials could be pooled in five Meta-analyses, the remaining trials could not be pooled due to the obvious clinical heterogeneity. Only low evidence showed CHM therapy may have 42%–60.4% participants healed completely after treatment, approximately twice (RR 1.42–1.76) as much as the healed rates in conventional therapy (or plus hot water foot bath) group. Majority of the included trials reported benefit of CHM group on shortening healing time (4–23 days) and reducing ulcer wound size (at least 2 cm^2). No serious adverse events were reported related to the medication in all trials.

Conclusion: Weak evidence showed benefit of CHM as add-on treatment of conventional therapy on increasing number of ulcer heals in patients with DFU. That's about twice the healing rate of the conventional treatment (or plus hot water foot bath) group. With insufficient information, we could not draw confirmative conclusion on safety of CHM administration. These findings need to be tested in further large, rigorous trials.

1. Introduction

With 425 million people diagnosed with diabetes mellitus (DM) in 2017, the number is expected to reach to 629 million by 2045.[1] Foot ulceration is the most frequently recognized complication of Diabetes,[2] and 6% of people with diabetes have the tendency to multiple complications such as diabetic foot ulcer (DFU).[3] Patients who suffered from chronic wound of DFU may have a diminished quality of life, experience increased morbidity and mortality, causing great societal and economical costs. In developed countries, medical expenses for diabetic-related foot problems account for 15–25% of available resources for the treatment, but in some developing countries, the same cost may reach up to 40% of available resources for diabetic disease.[4]

There are several factors which contribute to DFU, including gender (male), duration of diabetes longer than 10 years, advanced age of patients, high Body Mass Index, diabetic peripheral neuropathy and vascular disease, HbA1C level, foot deformity, high foot pressure, infections, and inappropriate foot self-care habits.[5–9] Diagnosis and assessment of foot ulcers requires regular foot examinations, which usually include assessment of protective sensation, foot structure and

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biomechanics, vascular status, and skin integrity.[10] An International Working Group of the Diabetic Foot (IWGDF) developed a classification system for research purposes.[11] According to this system, diabetic foot ulcers are categorized by the extent of perfusion, size, depth/tissue loss, infection and sensation.[6]

Treatment strategies for diabetic foot ulcers include metabolic control of diabetes mellitus, eradication of infection, promotion of ulcer healing, and removal of pressure from the ulcers.[12–14] Approximately 20% of moderate or severe diabetic foot infections lead to some level of amputation.[15] Mortality after diabetes-related amputation exceeds 70% at 5 years for all patients with diabetes.[16]

Chinese herbal medicine (CHM) form the main part of Traditional Chinese Medicine, which is a 3000 year-old holistic system of medicine that combines medicinal herbs with acupuncture, food therapy, massage, and therapeutic exercise for both treatment and prevention of diseases.[17] CHM have been used for treating wounds, including DFU, and aim to eliminate toxins, improve circulation and dispel blood stasis, and promote wound healing. They can be used orally or topically, alone or in combination with conventional Western medicine.[18]

Since Chinese herbal medicine is widely used for chronic wound management in clinical practice, there is a need to critically appraise the clinical evidence based on evidence-based approach to inform current practice and guide future studies on Chinese herbs for DFU.

2. Methods

2.1. Eligibility criteria

The review protocol was registered at PROSPERO (NO: CRD42018110565), and the protocol is available at https://www.crd.york.ac.uk/PROSPERO/. The format of this review strictly follows the process of Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

2.1.1. Type of study

RCTs that evaluate the effects of CHM for treating foot ulcers in people with diabetes were included. Quasi-randomized trials were not included.

2.1.2. Type of participants

Adults (18 years or older) with clearly diagnosed Type 1 or Type 2 diabetes and a related foot ulcer, with or without infection were concerned as participants in this review. Other types of foot ulcers, such as ulcers caused by venous disease, vasculitis, or any conditions other than diabetes were excluded.

2.1.3. Type of interventions

Interventions of this review were grouped as follows: Single Chinese herb; Chinese proprietary herbal medicine, a kind of fixed formulation of herbs produced by a pharmaceutical company; Chinese Herbal mixture prescribed by herbalist (so called individualized treatment) and is usually tailored based on individual's pattern of symptoms.

The control intervention included placebo, non-medical treatment (such as dressings and hot water foot bath) or other interventions used with the intention of glycemic control, promotion of healing, or wound care. Studies with co-interventions were considered as long as all arms of the trial receive the same co-intervention(s).

2.1.4. Type of outcome

Trials that reported any one of the following outcomes were included.

2.1.4.1. Primary outcomes. Healing of ulceration (in terms of time to complete healing, proportion of ulcers completely, healed at a specified time point or change in total ulcer area); Quality of life.

2.1.4.2. Secondary outcomes. Number of amputations (diabetic foot ulcer related); Presence of symptoms (pain, sensory loss of lower extremity); Incidence of infection of the foot ulcer; Adverse events related to the intervention (for example liver toxicity, kidney damage); Cost of the medicine.

2.2. Search strategy

Published studies were comprehensively searched from seven major Chinese and English electronic databases from their inception to November 2018: PubMed, the Cochrane Library, EMBASE, Chinese National Knowledge Infrastructure Database (CNKI), VIP Chinese Science and Technique Journals Database, Wanfang Database and Sino-Med Database. Appendix-1 outlines the detailed search strategy of PubMed.

2.3. Study selection and data extraction

Four review authors (Y Wang, Cao HJ, Wang LQ, Zhang K) independently assessed the titles, abstracts and keywords of every record retrieved in terms of relevance and design according to the selection criteria, then full texts screening. Data concerning details of study population, intervention and outcomes were extracted. Disagreements were resolved by consensus, and through referring back to the original article. Authors of relevant studies identified were contacted to obtain additional references, unpublished trials, or data missing.

2.4. Quality assessment

Four review authors (Y Wang, HJ Cao, YQ Yan and CL Lu) independently assessed each included study using the Cochrane Collaboration tool for assessing risk of bias.[19] This tool addresses specific domains, namely sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting. Blinding and completeness of outcome data were assessed for each outcome separately. For the above items, the quality of each included trials was categorized to low/unclear/high risk of bias. If the evaluation items are correctly and completely reported, they are judged to low risk of bias. When the content of the item is misused and evaluated, it will be judged as a high risk of bias. If the information in the trial is incomplete and an accurate judgment cannot be made, the risk of bias is unclear. If all the evaluation items of the trial are low risk bias, it is judged as a high-quality study. When one or more items are evaluated as high-risk bias, the quality of the trial is judged as low. We presented assessment of risk of bias using a 'risk of bias summary figure', which presented all of the judgments in a cross-tabulation of study by entry and discussed any disagreement amongst all review authors to achieve a consensus.

2.5. Data analysis

Statistical analyses were carried by Review Manager 5.3 software (Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) from the Cochrane Collaboration. Dichotomous data were expressed as risk ratio (RR) with 95% confidence interval (CI). Continuous data were expressed as mean differences (MD) with 95% CI and an overall MD was calculated. Time serial data was expressed as hazard ratios where available.

Methodological heterogeneity was tested for using the Z score and the chi-squared test with significance being set at $P < 0.10$. In addition the amount of heterogeneity was assessed using the I^2 statistic. Values of I^2 over 50% indicate a substantial heterogeneity (over 75% represents a very high level of heterogeneity).[19]

Sensitivity analysis was used to test the robustness of the results by excluding study with unclear random sequence generation. Funnel plots were used to assess the publication bias if more than 10 RCTs tested the same outcome in one meta-analysis. Subgroup analysis was planned to explore the impact of the presence of ulcer infection at baseline and to separately analysis the effect of intervention with different formula or

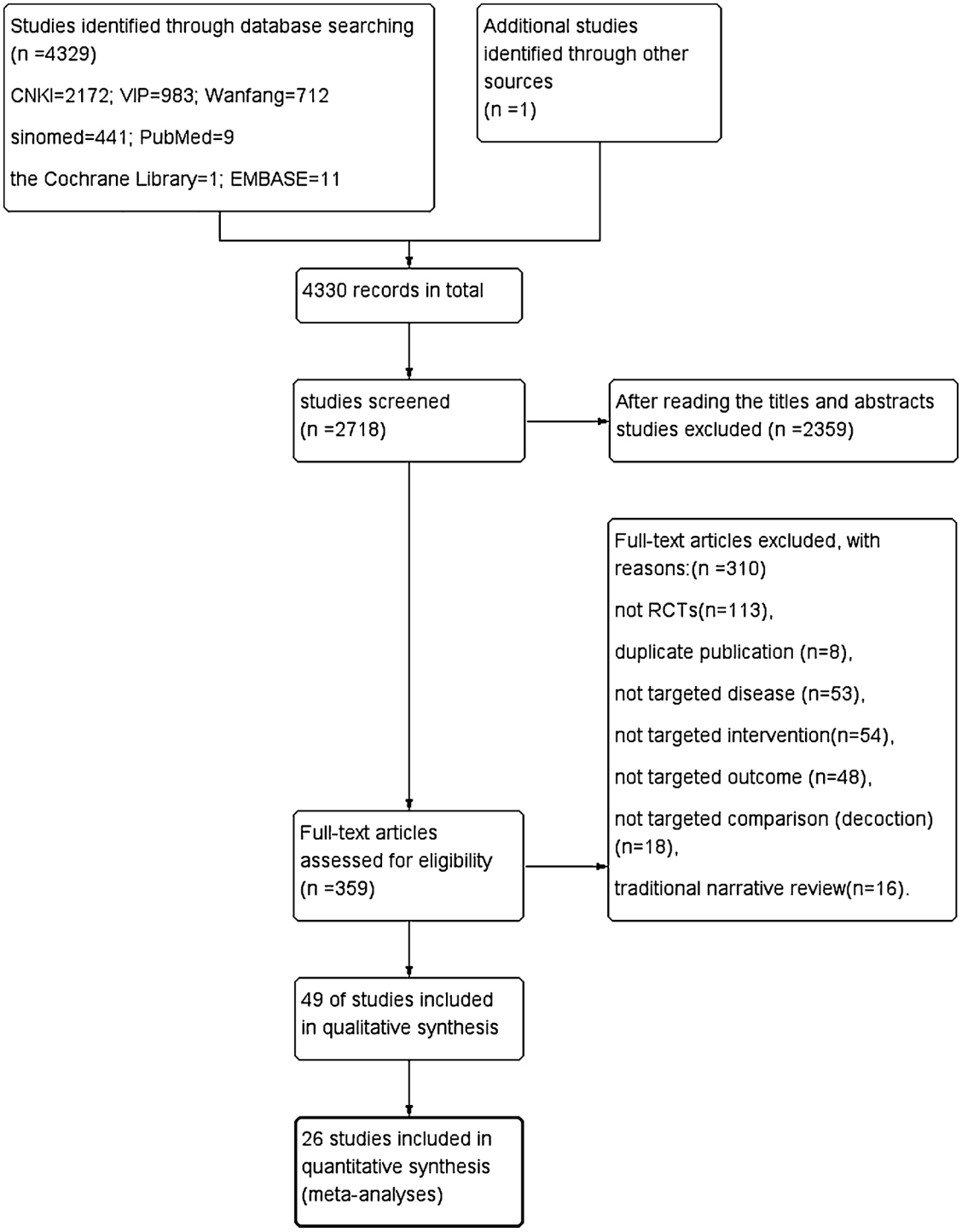

Fig. 1. Flow-chart of study selection.

treatment duration. Quality of evidence was assessed across important outcomes using GRADE approach to support management recommendations by The GRADEpro Guideline Development Tool (GDT) online.

3. Results

3.1. Description of studies

Totally 4330 records were retrieved after primary literature searching from pre-defined seven databases, 1612 duplicate articles were excluded, 2359 articles were excluded after reading titles and abstracts, and 310 articles were excluded after browsing the full text. Finally, only forty-nine studies met our inclusion criteria. Twenty-six trials could be pooled in five Meta-analyses, the remaining trials could not be pooled due to the obvious clinical heterogeneity. Study flow chart was shown in Fig. 1.

3.2. Study characteristics

The detailed characteristics are presented in Table 1. Forty-nine RCTs involving 3646 people with DFU were included in this review.

Table 1
Characteristics of included RCTs on Chinese herbal medicines for treating diabetic foot ulcers.

Study ID	Sample size	Sex M/F	Age(years, average or range)	Diabetic foot (DF) Duration	Severity	Treatment group	Control group	Duration	Outcomes
Chen DQ 2015[20]	T:30 C:30	T:15/15 C:15/15	T: 57.5 ± 4.9 C: 57.2 ± 6.4	NR	Wagner/1-3	CHM (Mahuang Tincture) Eu, CT	CT	3m	UH-100%, AR, US-T
Chen HS 2013[21]	T:53 C:52	65/40	61.7 ± 6.4	18.6 ± 3.5 d	NR	CHM Fb, 30 min, 1/d, CT	CT	3m	UH-100%, US-T
Chen X 2013[22]	T:32 C:32	30/34	61.4 ± 2.8	1.1 ± 0.4 y	NR	CHM Fb, 20 min, 1/d, CT	CT	4w	UH-100%
Chen XM 2013[23]	T:30 C:34	T:10/20 C:6/24	T:45-72 C:40-69	T:7-11w C:5-11w	NR	CHM (Wenjing Sanhan Muzu formula) Fb, 25-35 min, 1/d, 2/w, CT	CT	5w	UH-100%
Chun HK 2013[24]	T:8 C:8	T:4/4 C:4/4	T: 74.0 ± 2.8 C: 72.1 ± 12.4	T: 36-147d C: 28-360d	NR	CHM (NF3: RR and AR) Ot, 5 g/sachet, 2/d, BT	placebo, BT	6m	T-CH
Cui QQ 2018[25]	T:35 C:35	T:20/15 C:21/14	T: 59.73 ± 9.76 C: 59.69 ± 9.34	NR	Wagner/1-4	CHM (Simiao Yongan Tang) Ot, 1dose /d, 2/d, CT	CT	4w	UH-100%, UH-50%
Dai XF 2012[26]	T:22 C:20	T:13/9 C:12/8	T: 65.3(54-81) C: 66.4(53-79)	NR	Wagner/1-3	CHM (Buyang Huanwu Tang) Ot, BT	BT	1.5m	UH-100%
Deng JH 2007[27]	T:33 C:30	T:17/16 C:15/15	T: 56.1 ± 11.3 C: 55.8 ± 12.1	T:52.5 ± 13.4 d C: 59.8 ± 14.2 d	Wagner/2-3	CHM(Raw Honey + Yunnan Baiyao) Eu, 1/d, CT	rivanol yarn + 654-2 Wc, 1/d, CT	4w	UH-100%, UH-50%
Du WS 2007[28]	T:20 C:20	T:12/8 C:13/7	T: 59 ± 7 C: 59 ± 8	T: 6.3 ± 3.6 m C: 6.7 ± 3.2 m	Wagner/1-2	CHM (Tangzu mixture) Ot, 1dose /d, 2/d, CT	CT	1m	UH-100%, UH-50%
Fan H 2011[29]	T:18 C:18	T:11/7 C:10/8	T: 45 - 80 C: 46 - 81	NR	Wagner/2-4	CHM(Tangju Ointment) Eu, BT	Vaseline + rivanol Eu, BT	6m	UH-100%, AR
Fan YY 2017[30]	T:53 C:52	T:30/23 C:31/21	T: 58.97 ± 5.42 C: 58.34 ± 5.31	T:18-94 d C:17-97 d	NR	CHM (Simiao Yongan Tang) Ot, 1dose /d, CT	CT	8w	UH-100%, UH-50%
Fu CH 2012[31]	T:36 C:35	T:21/15 C:21/14	T:51-70 C:51-75	T:1.61 ± 0.71 m C: 1.67 ± 0.76 m	NR	CHM Fb, 20-30 minutes, 2/d, CT	hot water Fb, 20-30 minutes, 2/d, CT	4w	UH-100%
Guo LQ 2009[32]	T:30 C:30	T:20/10 C:18/12	T: 61.2 ± 4.7 C: 60.7 ± 5.3	C: 41.2 ± 5.1d T:40.51 ± 4.9 d	Wagner/1-4	CHM Eu, 1/d, CT	654-2+ insulin Wc, CT	45d	UH-100%, US-T
Huang PM 2013[33]	T:24 C:24	T:15/9 C:14/10	T: 69(56-82) C: 70(57-83)	T: 40.51 ± 4.9 d C: 41.2 ± 5.1 d	Wagner/1-4	CHM (Simiao Yongan Tang) Ot, MEBO Eu, CT	sodium chloride + insulin + gentamycin Eu, CT	4w	UH-100%
Jiang H 2011[34]	T:17 C:17	T:10/7 C:9/8	52 ± 3.8	NR	Wagner/1-5	CHM Ointment Eu, CHM Ot, 1dose /d, CT	CT	6w	UH-100%
Jiang YF 2015[35]	T:67 C:64	NR	T: 61.6 ± 16.5 C: 63.3 ± 12.3	T: 45.7 ± 68.3 d C: 52.5 ± 79.6 d	NR	CHM (Jing Wanhong ointment) Eu, 1/2d	Sulfadiazine zinc gels Eu, 1/2d	2w	T-CH
Jiang Z 2016[36]	T:44 C:44	T:23/21 C:24/20	T: 52.4 ± 3.8 C: 52.1 ± 3.5	NR	NR	CHM Fb, 20 min, CT	hot water Fb,, 20 min, CT	1m	UH-100%, UH-50%
Leung PC 2008[37]	T:40 C:40	T:25/15 C:22/18	T: 66.3 ± 12.6 C: 68.5 ± 11.1	T: 7.8 ± 8.2 w C: 12.9 ± 24.6 w	NR	CHM Ot, 2/d, CT	Placebo, CT	24w	T-CH, AR
Liang GD 2012[38]	T:40 C:40	33/47	45-65	NR	NR	CHM Ot, 1dose /d ;CHM Fb, 30 min, 2/d,, CT	CT	8w	UH-100%
Li FL 2011[39]	T:31 C:31	T:18/13 C:16/15	T: 54.1 ± 14.8 C: 46.2 ± 13.9	NR	NR	CHM (Shengji ointment and Shengji powder) Eu, CT	mupirocin ointment + bFGF + Vaseline gauze Eu, CT	4w	UH-100%, T-CH
Li JH 2016[40]	T: 43 C:38	38/43	58.29 ± 11.97	NR	Wagner/2	CHM (MEBT/MEBO) Eu, 3 g/cm^2, 1/d, CT	rb-bFGF Eu, 3 g/cm^2, 1/d, CT	20d	UH-100%, UH-50%, US-T
Li SF 2011[41]	T: 28 C:28	T:18/28 C:13/28	T: 60 ± 13 C: 60 ± 11	T: 7m C: 7.5m	Wagner/1-3	CHM(Tangzu Yuyang Ointment) Eu, CT	CT	24w	UH-100%, AR
Li SY 2014[42]	T: 50 C:52	T: 26/24 C:28/24	T: 54.5 ± 3.9 C: 54.2 ± 4.1	T: 5.2 ± 2.4 m C: 5.3 ± 2.6 m	Wagner/1-5	CHM Ot, 1dose /d, 2/d, CHM Eu, CT	CT	6w	UH-100%
Liu L 2011[43]	T:50 C:47	T: 35/15 C:28/19	T: 31-70 C:40-71	NR	Wagner/1-3	CHM Fb, 40 min, 1dose /d, CT	hot water Fb, 40 min, 1dose /d, CT	4w	UH-100%, UH-50%
Liu L 2015[44]	T: 45 C:45	T: 26/19 C:25/20	T: 59.61 ± 1.85 C: 58.36 ± 1.57	T: 25.1 ± 3.6 y C: 23.9 ± 2.5 y	NR	CHM Ot, 1dose /d, 2/d, CHM powder Ot, 3/d, BT	BT	90d	UH-50%, US-T
Liu WQ 2016[45]	T: 30 C:30	56/4	55.9	NR	Wagner/2	CHM (Buyang Huanwu Tang) Ot, 1dose /d, 2/d, CT	CT	30d	UH-100%, UH-50%

(*continued on next page*)

Table 1 (*continued*)

Study ID	Sample size	Sex M/F	Age(years, average or range)	Diabetic foot (DF) Duration	Severity	Treatment group	Control group	Duration	Outcomes
Liu X 2018[46]	T: 40 C:40	T: 26/14 C: 24/16	T: 58.75 ± 7.09 C:59.05 ± 6.83	T: 4.62 ± 0.52 m C: 4.83 ± 0.54 m	Wagner/1-2	CHM Fb, 30 min, 2 /d, CT	CT	4w	UH-100%, UH-50%, T-CH
Li XX 2012[47]	T: 46 C:43	T: 21/25 C:21/22	T: 61.80 ± 7.54 C: 66.20 ± 9.91	T: 1.65 ± 0.81 m C: 1.68 ± 0.79 m	Wagner/1-3	CHM Fb, 20 min, CT, nursing care	hot water Fb, CT, nursing care	4w	UH-100%, CT
Li ZH 2017[48]	T: 45 C:45	48/42	50-78	NR	NR	AP:CHM (Simiao Yongan Tang) Ot; RP:CHM (Buyang Huanwu + Buzhong Yiqi Tang) Ot, CHM (Shengji Yuhong) Eu, CT	CT	4w	UH-100%, UH-50%
Lv XQ 2013[49]	T: 31 C:31	T: 18/13 C:16/15	T:60.3 ± 12.4 C: 60.3 ± 11.8	NR	Wagner/1-4	CHM(Simiao Yongan Tang) Ot, 200 ml, 1dose /d, CT	CT	4w	UH-100%, US-T
Lv YD 2010[50]	T: 45 C:45	T: 28/17 C:27/18	T: 62.5 ± 8.17 C: 64.5 ± 9.17	T: 1.74 ± 0.89 m C: 1.68 ± 0.75 m	Wagner/1-3	CHM Fb, 20 min, 1/d, CT, nursing care	hot water Fb, 20 min, 1/d, CT, nursing care	4w	UH-100%, T-CH
Ni HG 2011[51]	T: 24 C:24	T: 15/9 C:14/10	T: 59 ± 5 C: 48 ± 6	T: 14 ± 5 d C: 12 ± 6 d	NR	CHM (Bingmi Ointment) Eu, CHM (Buyang Huanwu Tang) Ot, CT	CT	2w	UH-50%, CT
Ni HG 2011[51]	T: 24 C:24	T: 15/9 C:13/11	T: 59 ± 5 C: 52 ± 5	T: 14 ± 5 d C: 12 ± 5 d	NR	CHM (Bingmi Ointment) Eu, CHM (Buyang Huanwu Tang) Ot, CT	Alprostadil (10ug/d), mecobalamine (0.5 mg/d), 1/d,CT	2w	UH-50%, CT
Pei WW 2018[52]	T: 30 C:30	T: 18/12 C:16/14	T:57.59 ± 13.34 C:60.32 ± 11.56	NR	Wagner/1-3	CHM Fb, 1dose /d, 2/d, CT	CT	16w	UH-100%, UH-50%, T-CH, CT
Peng WJ 2015[53]	T: 15 C:15	13/17	T: 60.23 ± 8.54 C: 59.79 ± 9.01	NR	NR	CHM Fb, 30 min, 1/d, CT	CT	2w	UH-100%
Su WJ 2012[54]	T: 30 C:30	38/22	58-89	NR	NR	CHM (Buyang Huanwu Tang) Ot, gentamicin 160000U + anisodamine 32U + insulin 20 mg Eu; CT	gentamicin 160000U + anisodamine 32U + insulin 20 mg Eu; CT	6w	UH-100%
Wang L 2013[55]	T: 49 C:47	T: 35/14 C:28/19	T: 66.8 ± 11.1 C: 65.4 ± 11.7	NR	Wagner/1-4	CHM (Yinlian Tang) Ot, CHM Fb; CT	CT	3m	UH-100%
Wu X 2010[56]	T: 35 C:33	NR	61.3	NR	Wagner/1-4	CHM (San huang Tang) Fb, 0.5-1 h, 1-2/d, BT	saline20ml + gentamycin 8 × 104U + anisodamine 10 mg,+insulin 12U Wc, 30-40 min, 1-2/d, BT	20d	UH-100%, UH-50%
Xie JN 2018[57]	T:41 C:41	T:21/20 C:22/19	T:45-69 C:48-73	NR	Wagner/2-4	CHM (Xiangpi Shengji ointment) Eu, 1/d, CT	CT	4w	US-T
Xu Y 2015[58]	T: 84 C:84	T: 45/39 C:44/40	T: 60.4 ± 4.6 C: 58.5 ± 6.5	T: 6.3 ± 3.6 m C: 6.7 ± 3.2 m	NR	CHM (Jingjie Lianqiao Tang) Fb, 45 min, 1/d, CHM Eu, BT	BT	4w	US-T
Yang SB 2008[59]	T: 30 C:30	T: 18/12 C:17/13	T: 52.23 ± 3.37 C: 51.97 ± 3.65	T: 1w-10m C:1w-12m	Wagner/1-4	CHM (Shengji Powder) Eu, 1/d, CT	Gentamycin Wc, 1/d, CT	20d	UH-100%, US-T
Yuan XM 2009[60]	T: 30 C:28	T: 19/11 C:18/10	T: 60.3 ± 9.1 C: 61.2 ± 8.8	T: 2.5 ± 1.2 m C: 2.6 ± 1.3 m	Wagner/2-4	CHM ointment Eu, 1/d, CT	CT	30d	UH-100%, US-T
Xu HT 2018[61]	T:65 C:61	T:44/21 C:43/18	T: 62.37 ± 8.89 C: 62.29 ± 8.99	T: 3.90 ± 1.02 w C: 3.75 ± 0.99 w	TEXAS/2-A	CHM (Shenxiao Shengji Powder) Eu, 1/2d, CT	rb-bFGF Eu, 1/2d, CT	56d	UH-100%, UH-50%, US-T, T-CH
Yu Y 2016[62]	T: 32 C:28	T: 18/14 C:15/13	T: 57.28 ± 8.09 C: 57.18 ± 7.72	T: 2.00 ± 0.61 m C:1.86 ± 0.87 m	Wagner/1-3	CHM(Yiqi Jiedu Quyu Tang) Ot, 300 ml, 1dose /d, CT	CT	1m	UH-100%, UH-50%
Zhang HJ 2015[63]	T: 57 C:59	T: 30/27 C:33/26	T: 55.7 ± 11.5 C: 56.4 ± 10.3	T: 3.1 ± 1.4 m C: 3.3 ± 1.6 m	Wagner/2-3	CHM Ot, 1dose /d, CHM Fw 30 min, CHM Eu 30 min, 1dose /d, 2/d, CHM (Ruyi Jinhuang Powder) Eu, CT	CT	8w	UH-100%, US-T
Zhang XZ 2012[64]	T: 33 C:31	T: 21/12 C:21/10	T: 59.2 C:60.5	T: 3.1 ± 1.4 m C: 3.3 ± 1.6 m	Wagner/1-5	CHM Fb, 20-30 min, CT	CT	40d	UH-100%
Zhao ZF 2015[65]	T:40 C:40	37/43	77.98 ± 11.19	NR	Wagner/2-4	CHM(Liqi ointment) Eu, 2-3/d, CT	CT	12w	UH-100%, US-T
Zhao ZX 2012[66]	T: 42 C:40	44/38	T: 57.68 ± 9.86 C: 58.74 ± 9.58	T: 30.96 ± 24.48y C: 32.20 ± 22.12y	NR	CHM(Mai Fu Sheng Mixture) Ot, 50 ml, 2/d, CT	CT	30d	US-T
Zhou GY 2015[67]	T: 36 C:36	43/29	61.30 ± 12.33	15.00 ± 4.50 d	NR	CHM Eu, 500 ml, 1-1.5 h, 2-3/d, CHM Fb 20 min, CHM Ot, 1dose /d, BT	654-2+ insulin + gentamycin, BT	4w	UH-100%, T-CH

(*continued on next page*)

Table 1 (*continued*)

Study ID	Sample size	Sex M/F	Age(years, average or range)	Diabetic foot (DF) Duration	Severity	Treatment group	Control group	Duration	Outcomes
Zhou W 2009[68]	T: 25 C:23	T: 17/8 C:15/8	T: 59.2 C:60.5	NR	NR	CHM Fb, 20 min, 1/d, CT	hot water Fb, 20 min, 1/d, CT	4w	UH-100%

T: treatment group; C: control group; M: males; F: females; d: day; m: months; y: year; NR: not reported; CHM: Chinese herbal medicine; Fb: foot bath; Ot: oral taking; Eu: external use; Fw: fumigate-wash; CT (appearing in treatment group and control group): conventional therapy; BT: basic therapy; min:minutes; RR: Radix Rehmanniae; AR (appearing in treatment group): Astragali Radix; AP: Acute attack period; RP: Remission period; UH-100%: Ulcer healing achieved 100%; UH-50%: Ulcer healing achieved 50%; AR (appearing in outcomes): Amputation rate; US-T: Ulcer size after treatment (cm2); T-CH: Time to complete healing (days); CT (appearing in outcomes): Cost of the treatment (1000 yuan).

Forty-five of them were published in Chinese, and the remaining four trials[24,37,39,41] conducted in China but published in English. Except one three-arm trial,[51] all the remaining forty-eight trials were parallel two arms randomized controlled trials. The average size of the trial was 75 participants, ranging from 16 to 168 per trial. Ratio of male to female was approximately 1.4:1. Average age of the 3646 participants was 64.28 years. The mean duration of DF ranged from 6 days to 54 years. All the studies had specific diagnostic criteria for diabetes or DFU. However, twenty-one of the included trials did not report the Wagner classification of the participants. Treatment duration varied from two weeks to six months, with an average of 1.8 months.

In summary, there are three big types of comparisons among the 49 included trials. Thirty trials[20–23,25,26,28,30,34,38,41,42,44,45,46,48,49,51–55,57,58,60,62–66] compared CHM plus basic/conventional therapy with basic/conventional therapy alone. Eighteen trials[24,27,29,31–33,36,37,40,43,47,50,51,56,59,61,67,68] compared CHM plus basic/conventional therapy with other treatments plus basic/conventional therapy. Basic therapy was defined as blood glucose control and anti-inflammatory therapies, insulin and some classic antibiotics. Conventional therapy included basic therapy and further treatments, such as vascular management, infection management and prevention, trophic nerve and pressure relief. The remaining two trials[35,39] compared CHM ointment with western medicine.

Quality of life was not reported in any of the included trials.

3.3. Risk of bias of included trials

A majority of trials provided limited information about design and methodology. Insufficient information made it difficult to determine a "low" or "high" risk of those trials for selection bias, detection bias and attrition bias. The summary of the methodological quality is shown in Fig. 2.

3.4. Effects of interventions

3.4.1. Comparison 1: Chinese herbal medicine plus other therapy versus other therapy alone

Thirty trials involved in this comparison, ten[25,26,28,30,44,45,49,54,62,66] of them used oral herbal decoction as intervention, eight[21–23,46,52,53,58,64] of them used herbal foot bath, five[20,41,57,60,65] of them employed herbal ointment, the remaining seven trials observed the effect of combination of herbal medicine oral administration and external use (foot bath[38,55] or ointment [34,42,48,51,63]). Subgroup analysis was conducted according to the different type of intervention.

The results for the primary outcome showed CHM oral administration,[25,26,28,30,45,49,54,62] foot bath[21–23,46,52,53,64] or combination of CHM oral administration and external ointment[34,42,48] may had superior add-on effect on increasing the number of patients whose ulcer healing achieved 100% (RR 1.52, 95%CI 1.21–1.90, 499 participants, 8 trials; RR 1.58, 95%CI 1.25–2.00, 463 participants, 7 trials; RR 1.60, 95%CI 1.22–2.10, 226 participants, 3 trials, respectively), no difference [38,55] was found between combination of CHM oral decoction and foot bath as add-on treatment of other therapy and other therapy alone on this outcome (RR 1.76, 95%CI 0.87–3.55, 176 participants, 2 trials), one trial [65] found better effect compared herbal ointment external used plus others with others (RR 2.42, 95%CI 1.45–4.03, 80 participants). Inconsistent results were found for herbal ointment alone use or combined with other therapies compared to other therapies on this outcomes, due to the obvious statistical heterogeneity among trials, meta-analyses was not conducted, details of the results were showed in Table 2.

Oral administration herbal decoction[25,28,30,45,62] (RR 1.36, 95%CI 0.73–2.54, 70 participants; RR 1.19, 95%CI 0.93–1.51, 40 participants; RR 1.28, 95%CI 0.91–1.80, 105 participants; RR 0.80, 95%CI 0.24–2.69, 60 participants; RR 2.10, 95%CI 0.84–5.23, 60 participants, respectively), herbal ointment external used[48,51] (RR 0.89, 95%CI

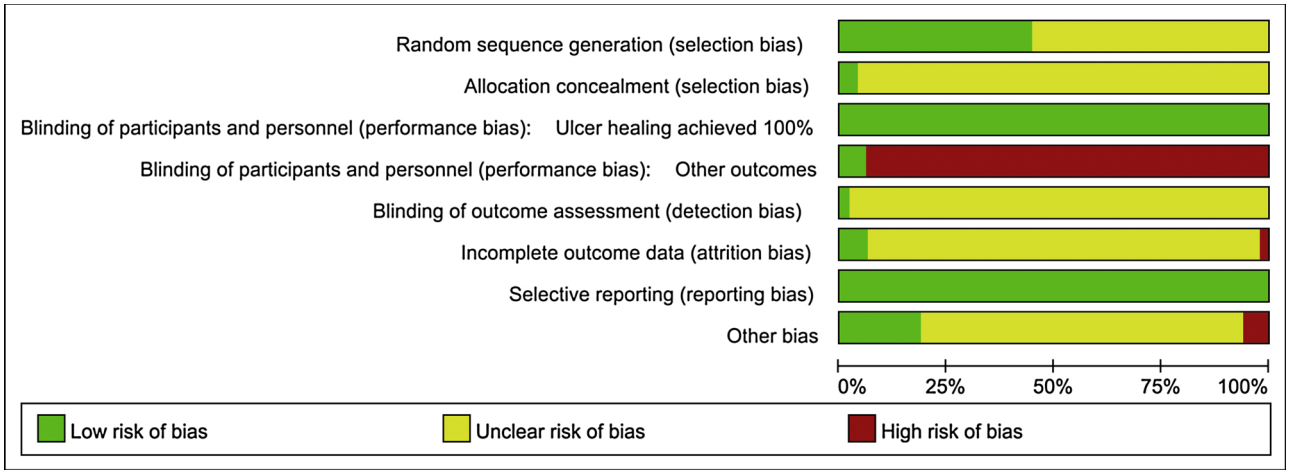

Fig. 2. Risk of bias graph.

0.38–2.10, 90 participants; RR 1.14, 95%CI 0.96–1.35, 48 participants) or herbal foot bath[46,52] (RR 1.62, 95%CI 0.61–4.25, 80 participants; RR 2.29, 95%CI 0.80–6.50, 60 participants)combined with other therapies all showed no better effect than other therapies alone on increasing the number of patients whose ulcer healing achieved more than 50%. Only one trial[44] reported the opposite results on this outcome (RR 1.58, 95%CI 1.17–2.14, 90 participants) when compared herbal decoction plus other treatment to other treatment alone.

Ten trials[20,21,44,49,57,58,60,63,65,66] showed reduced ulcer size in CHM group than control group, meta-analyses could not be conducted due to obvious clinical heterogeneity among those trials. Details of the results were showed in Table 2.

For the secondary outcome, two trials[51,52] reported that each patient in CHM group may save at least 2000 Chinese Yuan (MD -2500 Yuan, 95%CI -2740 Yuan to -2260 Yuan, 48 participants; MD -2090 Yuan, 95%CI -2150 Yuan to -2030 Yuan, 60 participants) than those in basic therapy group. Two trials[46,52] showed CHM foot bath group needed shorter time than control group (MD -4.94 days, 95% CI -6.86 days to -3.02 days, 80 participants; MD -5.75 days, 95% CI -7.70 days to -3.80 days, 60 participants) to healing completely. One case of amputations was reported in control group after three months' treatment,[20] and eight amputations with four in each group was showed in another trial[41] after six months.

3.4.2. Comparison 2: Chinese herbal medicine plus other treatment versus placebo plus other treatment

Two trials[24,37] involved in this comparison. One trial[24] found no difference between CHM oral administration and placebo based on basic therapy when reported the time (days) which ulcer to healing completely in each group (MD -12.00 days, 95% CI -69.61 days to 45.61 days, 16 participants), but another trial[37] got opposite result on this outcome (MD -23.10 days, 95%CI -28.22 days to -17.98 days, 80 participants). Details of the intervention and control therapies were varied between these two trials, thus meta-analyses was not conducted.

For the secondary outcome, amputations in the CHM group (3/40) compared with the placebo group (9/40) was showed only in one trial[37] (RR = 0.33, 95%CI 0.1–1.14, 80 participants). Another trial[24] reported that there were fewer adverse effects in CHM group (1/8, constipation) than placebo group (3/8, 1 constipation, 1 coagulopathy, 1 swollen leg).

3.4.3. Comparison 3: Chinese herbal medicine foot bath plus conventional therapy versus hot water foot bath plus conventional therapy

Six trials[31,36,43,47,50,68] used this comparison. Two[47,50] of them added nursing care in both groups and they got inconsistent results (RR 1.25, 95%CI 0.98–1.58, 179 participants, 2 trials) on increasing the number of patients whose ulcer healing achieved 100%, however, the total meta-analyses showed CHM foot bath may have better effect (RR 1.42, 95% CI 1.19–1.70, p < 0.0001, I^2 = 0%, fixed-effect model, 483 participants, 6 trials, Table 2) than hot water foot bath based on conventional therapy (or nursing care).

Two trials[36,43] showed opposite results on increasing the number of patients whose ulcer healing achieved 50%, one trial[43] found significant difference between CHM foot bath and hot water foot bath based on conventional therapy (RR 1.69, 95% CI 1.27–2.25, 97 participants), but another trial[36] reported opposite result on this outcome (RR 1.25, 95% CI 0.54–2.87, 88 participants). One trial [50] reported the CHM foot bath group needed shorter time than hot water foot bath group (MD -5.70 days, 95% CI -8.60 days to -2.80 days, 90 participants) to healing completely.

For the secondary outcome, no difference was found between CHM foot bath group and hot water foot bath group on the cost of the medicine[47] (MD -340 Yuan, 95%CI -770 Yuan to 90 Yuan, 89 participants). There was no adverse event occurred during the treatment duration were reported in three trials.[31,50,68]

3.4.4. Comparison 4: Chinese herbal medicine plus other therapy versus western medicine plus other therapy

Ten trials involved in this comparison, six[27,29,32,40,59,61] of them used herbal ointment as intervention, one[56] of them used herbal foot bath, the remaining three trials[33,51,67] observed the effect of combination of herbal medicine oral administration and herbal ointment. Due to the obvious statistical heterogeneity among trials, meta-analyses was not conducted.

The results for the primary outcome showed herbal external ointment[29,40] (RR 3.75, 95% CI 1.54–9.12, 36 participants; RR 1.99, 95% CI 1.18–1.35, 81 participants) or the combination of herbal medicine oral administration and external ointment[67] (RR 2.07, 95%CI 1.33–3.22, 72 participants) may had superior add-on effect compared to western drugs on increasing the number of patients whose ulcer healing achieved 100%. Other trials in this comparison, whether herbal foot bath, herbal ointment external used or combination of herbal medicine oral administration and external ointment all found inconsistent results compared to western drugs on this outcome. Details of the results were showed in Table 2.

Neither herbal ointment external used[27,40,61] (RR 1.19, 95% CI 0.95–1.48, 63 participants; RR 0.66, 95% CI 0.40–1.10, 81 participants; RR 1.10, 95% CI 0.83–1.46, 126 participants, respectively) nor the combination of herbal medicine oral administration and external ointment[51] (RR 1.00, 95% CI 0.92–1.08, 48 participants) combined with other therapies showed no better effect than western drugs plus other therapies on increasing the number of patients whose ulcer healing

Table 2
Summary of main effect estimates of Chinese herbal medicines for treating diabetic foot ulcers.

Study ID	Sample size	Estimate effect [95% CI]	Outcome	P
CHM oral decoction + conventional therapy VS conventional therapy				
Cui QQ 2018[25]	T:35 C:35	RR 1.71 [0.77, 3.84]	Ulcer healing achieved 100%	0.1899
		RR 1.36 [0.73, 2.54]	Ulcer healing achieved 50%	0.3277
Dai XF 2012 [26]	T:22 C:20	RR 2.91 [1.31, 6.48]	Ulcer healing achieved 100%	0.0090
Du WS 2007 [28]	T:20 C:20	RR 1.27 [0.78, 2.08]	Ulcer healing achieved 100%	0.3341
		RR 1.19 [0.93, 1.51]	Ulcer healing achieved 50%	0.1624
Fan YY 2017[30]	T:53 C:52	RR 1.23 [0.53, 2.86]	Ulcer healing achieved 100%	0.6369
		RR 1.28 [0.91, 1.80]	Ulcer healing achieved 50%	0.1487
Liu L 2015[44]	T:45 C:45	RR 1.58 [1.17, 2.14]	Ulcer healing achieved 50%	0.0027
		MD -2.87 [-2.99, -2.75]	Ulcer size after treatment	0.0000
Liu WQ 2016[45]	T:30 C:30	RR 1.13 [0.89, 1.44]	Ulcer healing achieved 100%	0.3212
		RR 0.80 [0.24, 2.69]	Ulcer healing achieved 50%	0.7185
Lv XQ 2013[49]	T:31 C:31	RR 2.00 [0.77, 5.18]	Ulcer healing achieved 100%	0.1532
		MD -2.83 [-5.13, -0.53]	Ulcer size after treatment	0.0188
Su WJ 2012[54]	T:30 C:30	RR 1.71 [0.78, 3.75]	Ulcer healing achieved 100%	0.1772
Yu Y 2016[62]	T:32 C:28	RR 2.19 [0.46, 10.40]	Ulcer healing achieved 100%	0.3252
		RR 2.10 [0.84, 5.23]	Ulcer healing achieved 50%	0.1107
Zhao ZX 2012[66]	T:40 C:42	MD -0.82 [-1.56, -0.08]	Ulcer size after treatment	0.0306
CHM foot bath + conventional therapy VS conventional therapy				
Chen HS 2013[21]	T:53 C:52	RR 1.31 [0.81, 2.11]	Ulcer healing achieved 100%	0.2692
		MD -2.64 [-2.81, -2.47]	Ulcer size after treatment	0.0000
Chen X 2013[22]	T:32 C:32	RR 1.56 [1.06, 2.31]	Ulcer healing achieved 100%	0.0257
Chen XM 2013[23]	T:30 C:30	RR 1.50 [0.81, 2.79]	Ulcer healing achieved 100%	0.1998
Liu X 2018[46]	T:40 C:40	RR 2.00 [0.54, 7.45]	Ulcer healing achieved 100%	0.3015
		RR 1.62 [0.61, 4.25]	Ulcer healing achieved 50%	0.3343
		MD -4.94 [-6.86, -3.02]	Time to complete healing (days)	0.0000
Pei WW 2018[52]	T:30 C:30	RR 2.57 [1.26, 5.24]	Ulcer healing achieved 100%	0.0093
		RR 2.29 [0.80, 6.50]	Ulcer healing achieved 50%	0.1290
		MD -5.75 [-7.70, -3.80]	Time to complete healing (days)	0.0000
		MD -2.09 [-2.15, -2.03]	Cost of the treatment (1000 yuan)	0.0000
Peng WJ 2015[53]	T:15 C:15	RR 4.00 [0.50, 31.74]	Ulcer healing achieved 100%	0.1896
Xu Y 2015[58]	T:84 C:84	MD -16.32 [-16.84, -15.80]	Ulcer size after treatment	0.0000
Zhang XZ 2012[64]	T:33 C:31	RR 1.20 [0.64, 2.22]	Ulcer healing achieved 100%	0.5717
CHM ointment external application + conventional therapy VS conventional therapy				
Chen DQ 2015[20]	T: 30 C:30	RR 1.64 [0.94, 2.85]	Ulcer healing achieved 100%	0.0813
		MD -4.51 [-5.69, -3.33]	Ulcer size after treatment	0.0000
		RR 0.33 [0.01, 7.87]	Amputation rate	0.4958
Li SF 2011[41]	T:28 C:28	RR 1.36 [0.87, 2.13]	Ulcer healing achieved 100%	0.1831
		RR 1.00 [0.28, 3.61]	Amputation rate	1.0000
Xie JN 2018[57]	T:41 C:41	MD -1.35 [-2.44, -0.26]	Ulcer size after treatment	0.0178
Yuan XM 2009[60]	T:30 C:28	RR 1.44 [0.83, 2.52]	Ulcer healing achieved 100%	0.1972
		MD -15.40 [-17.36, -13.44]	Ulcer size after treatment	0.0000
Zhao ZF 2015[65]	T:40 C:40	RR 2.42 [1.45, 4.03]	Ulcer healing achieved 100%	0.0007
		MD -12.93 [-22.31, -3.55]	Ulcer size after treatment	0.0085
CHM oral decoction + CHM external ointment + others VS others				
Jiang H 2011[34]	T:17 C:17	RR 2.75 [1.09, 6.94]	Ulcer healing achieved 100%	0.0323
Li SY 2014[42]	T:50 C:52	RR 1.78 [1.05, 3.04]	Ulcer healing achieved 100%	0.0334
Li ZH 2017[48]	T:45 C:45	RR 1.32 [0.96, 1.81]	Ulcer healing achieved 100%	0.0843
		RR 0.89 [0.38, 2.10]	Ulcer healing achieved 50%	0.7879
Ni HG 2011[51]	T:24 C:24	RR 1.14 [0.96, 1.35]	Ulcer healing achieved 50%	0.1270
		MD -2.50 [-2.74, -2.26]	Cost of the treatment (1000 yuan)	0.0000
Zhang HJ 2015[63]	T:59 C:57	RR 1.38 [0.77, 2.46]	Ulcer healing achieved 100%	0.2745
		MD -0.71 [-0.91, -0.51]	Ulcer size after treatment	0.0000
CHM oral decoction + CHM foot bath + conventional therapy VS conventional therapy				
Liang GD 2012[38]	T:40 C:40	RR 1.32 [0.88, 1.97]	Ulcer healing achieved 100%	0.1838
Wang L 2013[55]	T:49 C:47	RR 2.64 [1.31, 5.33]	Ulcer healing achieved 100%	0.0069
CHM + others VS placebo + others				
Chun HK 2013[24]	T:8 C:8	MD -12.00 [-69.61, 45.61]	Time to complete healing (days)	0.6893
Leung PC 2008[37]	T:40 C:40	MD -23.10 [-28.22, -17.98]	Time to complete healing (days)	0.0000
		RR 0.33 [0.10, 1.14]	Amputation rate	0.0802
CHM foot bath + conventional therapy VS hot water foot bath + conventional therapy				
Fu CH 2012[31]	T:36 C:35	RR 1.54 [1.05, 2.28]	Ulcer healing achieved 100%	0.0288
Jiang Z 2016[36]	T:44 C:44	RR 1.31 [0.80, 2.16]	Ulcer healing achieved 100%	0.2849
		RR 1.25 [0.54, 2.87]	Ulcer healing achieved 50%	0.5985
Liu L 2011[43]	T:50 C:47	RR 2.09 [1.06, 4.12]	Ulcer healing achieved 100%	0.0333
		RR 1.69 [1.27, 2.25]	Ulcer healing achieved 50%	0.0003
Li XX 2012[47]	T:46 C:43	RR 1.32 [0.96, 1.82]	Ulcer healing achieved 100%	0.0820
		MD -0.34 [-0.77, 0.09]	Cost of the treatment (1000 yuan)	0.1188
Lv YD 2010[50]	T:45 C:45	RR 1.17 [0.82, 1.67]	Ulcer healing achieved 100%	0.3957
		MD -5.70 [-8.60, -2.80]	Time to complete healing (days)	0.0002
Zhou W 2009[68]	T:25 C:23	RR 1.61 [0.83, 3.11]	Ulcer healing achieved 100%	0.1565
CHM ointment external application + others VS WM external application + others				
Deng JH 2007[27]	T:33 C:30	RR 1.21 [0.60, 2.46]	Ulcer healing achieved 100%	0.5948
		RR 1.19 [0.95, 1.48]	Ulcer healing achieved 50%	0.1377

(*continued on next page*)

Table 2 (*continued*)

Study ID	Sample size	Estimate effect [95% CI]	Outcome	P
Fan H 2011[29]	T:18 C:18	RR 3.75 [1.54, 9.12]	Ulcer healing achieved 100%	0.0036
		RR 0.20 [0.01, 3.89]	Amputation rate	0.2880
Guo LQ 2009[32]	T:30 C:30	RR 1.88 [0.94, 3.75]	Ulcer healing achieved 100%	0.0754
		MD -2.86 [-3.10, -2.62]	Ulcer size after treatment	0.0000
Li JH 2016[40]	T:43 C:38	RR 1.99 [1.18, 3.35]	Ulcer healing achieved 100%	0.0098
		RR 0.66 [0.40, 1.10]	Ulcer size after treatment	0.1123
		MD -5.55 [-11.51, 0.41]	Ulcer healing achieved 50%	0.0609
Yang SB 2008[59]	T:30 C:30	RR 1.42 [0.83, 2.43]	Ulcer healing achieved 100%	0.2049
		MD -17.10 [-19.47, -14.73]	Ulcer size after treatment	0.0000
Xu HT 2018[61]	T:65 C:61	RR 2.19 [0.90, 5.33]	Ulcer healing achieved 100%	0.0844
		RR 1.10 [0.83, 1.46]	Ulcer healing achieved 50%	0.5152
		MD -4.07 [-8.35, 0.21]	Time to complete healing (days)	0.0591
		MD -0.08 [-0.27, 0.11]	Ulcer size after treatment	0.4005
CHM foot bath + basic therapy VS WM + basic therapy				
Wu X 2010[56]	T:35 C:33	RR 1.49 [0.87, 2.57]	Ulcer healing achieved 100%	0.1490
		RR 1.30 [1.04, 1.62]	Ulcer healing achieved 50%	0.0233
CHM oral decoction + CHM external ointment + others VS WM + others				
Huang PM 2013[33]	T:24 C:24	RR 1.36 [0.91, 2.02]	Ulcer healing achieved 100%	0.1302
Ni HG 201151	T:24 C:24	RR 1.00 [0.92, 1.08]	Ulcer healing achieved 50%	1.0000
		MD -2.50 [-2.71, -2.29]	Cost of the treatment (1000 yuan)	0.0000
Zhou GY 2015[67]	T:36 C:36	RR 2.07 [1.33, 3.22]	Ulcer healing achieved 100%	0.0012
		MD -3.50 [-5.03, -1.97]	Time to complete healing (days)	0.0000
CHM external ointment application VS Western medicine external ointment application				
Jiang YF 2015[35]	T:67 C:64	MD -21.40 [-27.16, -15.64]	Time to complete healing (days)	0.0000
Li FL 2011[39]	T:27 C:26	RR 1.24 [0.54, 2.83]	Ulcer healing achieved 100%	0.6132
		MD -3.85 [-7.41, -0.29]	Time to complete healing (days)	0.0379

achieved more than 50%. Only one trial[56] reported the opposite results on this outcome (RR 1.30, 95% CI 1.04–1.62, 68 participants) when compared herbal foot bath plus other treatment with western drugs plus other treatment.

Two trials[32,36] found a significant decrease of ulcer size when used CHM external ointment than western drugs based on other therapies (MD -2.86 cm^2, 95%CI -3.10 cm^2 to -2.62 cm^2, 60 participants; MD -17.10 cm^2, 95% CI -19.47 cm^2 to -14.73 cm^2, 60 participants, respectively), however, another two trials[40,61] reported no difference between CHM external ointment group and western drugs group on this outcome (MD -5.55 cm^2, 95% CI -11.51 cm^2 to 0.41 cm^2, 81 participants; MD -0.08 cm^2, 95% CI -0.27 cm^2 to 0.11 cm^2, 126 participants). One trial [67] showed the combination of CHM oral decoction and herbal external ointment group needed shorter time than western medicine group (MD -3.50 days, 95% CI -5.03 days to -1.97 days, 72 participants) to healing completely, but another trial[61] reported opposite result when used CHM external ointment than western drugs based on other therapies (MD -4.07 days, 95% CI -8.35 days to 0.21 days, 126 participants).

For the secondary outcome, no significant difference was found between CHM ointment group (0/18) and western drugs group (2/18) on the outcome of amputation rate[29] (RR 0.20 and 95% CI 0.01–3.89, 36 participant). One trial[51] showed each patient in combination of herbal medicine oral administration and herbal ointment group may save at least 2000 Chinese Yuan than control group (MD -2500 Yuan, 95%CI -2740 Yuan to -2260 Yuan, 48 participants).There was no adverse event occurred during the treatment duration were reported in three trials.[27,33,59]

3.4.5. Comparison 5: CHM ointment external application versus western medicine external application

Two trials[35,39] involved in this comparison, they all showed patients in CHM external ointment group earlier got completely healing than control group (MD -21.40 days, 95%CI -27.16 days to -15.64 days, 131 participants; MD -3.85 days, 95%CI -7.41 days to -0.25 days, 53 participants, respectively). Only one trial[39] reported acceptable pain (1 case) after CHM external ointment treatment, but it found CHM group was no better than western group on increasing the number of patients whose ulcer healing achieved 100% (RR 1.24, 95%CI 0.54–2.83, 53 participants).

3.4.6. Overall quality of evidence by GRADE

Grading of Recommendations Assessment Development and Evaluation (GRADE) criteria was used to assess the quality of the evidence, factors that may downgrade the quality level include imprecision, inconsistency, indirectness, limitations, and bias of the evidence.

Five meta-analyses were conducted in this review, all these related to the primary outcome - ulcer healing achieved 100%. Thus, we listed all of them in one summary of finding table and the results from each type of comparisons were assessed separately in this review (details in Table 3). We downgraded the evidence's level because of the potential selection, detection and the inconsistency of the results between the included studies. Thus, we could find only low quality evidence for CHM therapy in increasing the number of patients whose ulcer healed completely.

4. Discussion

4.1. Summary of main results

Totally 49 trials were included in this review, and effect of Chinese herbal medicine as add-on treatment of basic/conventional therapy were assessed. Due to potential risk of bias among trials and the small sample size of the studies, only low evidence showed CHM foot bath or CHM combination therapy may have 42% to 60.4% participants healed completely after treatment, which was approximately twice (RR 1.42 to 1.76) as much as the healed rates in conventional therapy (or plus hot water foot bath) group. Even though majority of the included trials reported benefit of CHM plus conventional therapy on shortening healing time (4 to 23 days) and reducing ulcer wound size (at least 2 cm^2) compared to conventional therapy alone. However, no confirm conclusion could be draw for other CHM therapies or other type of comparisons on wound healing relevant outcomes or cost-effect measurements, since data were extracted from small and poor quality trials without pooling.

4.2. Comparison with previous studies

During the literature searching, we found a published review[18] which systematic assessed the effect of CHM for diabetic foot. This

Table 3
Summary of main findings of Chinese herbal medicines for treating diabetic foot ulcers.

Chinese herbal medicine for diabetic foot ulcer					
Patient or population: patients with diabetic foot ulcer					
Settings: In-patient or Out-patient Department of traditional Chinese medicine hospitals					
Intervention: Chinese herbal medicine					
Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Control	Corresponding risk CHM group			
Ulcer healing achieved 100% - CHM oral administration + other treatment vs. other treatment	276 per 1000	420 per 1000 (334 to 525)	RR 1.52 [1.21 to 1.90]	499 (8 studies)	⊕⊖⊖⊖ **very low**[1,2,3]
Ulcer healing achieved 100% - CHM foot bath + conventional therapy vs. conventional therapy	287 per 1000	453 per 1000 (359 to 574)	RR 1.58 [1.25 to 2.00]	463 (7 studies)	⊕⊕⊖⊖ **low**[1,2],
Ulcer healing achieved 100% - CHM decoction + ointment + conventional therapy vs. conventional therapy	377 per 1000	604 per 1000 (460 to 792)	RR 1. 60 [1.22 to 2.10]	226 (3 studies)	⊕⊕⊖⊖ **low**[1,2],
Ulcer healing achieved 100% - CHM oral administration + CHM foot bath + conventional therapy vs. conventional therapy	310 per 1000	546 per 1000 (270 to 1000)	RR 1. 76 [0.87 to 3.55]	176 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,3]
Ulcer healing achieved 100% - CHM foot bath + conventional therapy vs. hot water foot bath + conventional therapy	414 per 1000	587 per 1000 (492 to 703)	RR 1. 42 [1.19 to 1.70]	483 (6 studies)	⊕⊖⊖⊖ **very low**[1,2,3]

GRADE Working Group grades of evidence.
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.
Footnotes.
[1] Majority trials had unclear risk of selection bias (unknown methods of random number generation and allocation concealment), detection bias (unknown methods of blinding to statisticians), attrition bias (unknown about the complete of the sample and missing data) and other bias.
[2] Only few trials published in Chinese were included.
[3] 95% confidence intervals were partially overlapped, I-square test showed potential statistical heterogeneity among trials.
* 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). **CI:** Confidence interval; **RR:** Risk ratio.

review included randomized trials, and the searching process was ended on August 2015. With sixteen included studies, only 1412 participants involved. The author demonstrate that TCM can improve the total effective rate and the healing rate, promote the healing of ulcers, reduce the amputation rate, shorten the healing time, and the security when compared with modern medical treatment alone. However, many different factors may have affected the results in that review, including differences in the various studies, the language limitation of the included studies, the variety of CHM and clinical heterogeneity.

Our review only focused on DFU, 49 RCTs with 3646 participants involved. Risk of bias assessment was employed for critical appraisal. Though the main treatment principles of CHM in our review were similar to the previous study, different forms of CHM were assessed (including herbal decoction, CHM foot bath, CHM external ointment, and combination of CHM therapies). GRADE was used to evaluate the quality of the evidence. Other outcome measurements included ulcer healing relevant outcomes, cost for medications and adverse events.

4.3. Strengths and limitations

We did a comprehensive search of major database and manually searched the titles and abstracts of major conferences to avoid the selection bias, but a major limitation of this review is the low quality of the original trials and insufficient details to report for characteristics of included trials affected the reliability of the results. Though funnel plot was not conducted due to insufficient number of trials included in the meta-analyses, it may have publication bias of this review.

4.4. Implications for research

For future clinical trials, adequate sample sizes should be recruited. Researchers should use appropriate randomization, blinding and statistical methods. Herbal intervention should be described according to the CONSORT Statement for herbal medicine; the components of complex interventions should be clearly reported. The control interventions should be designed as either placebo, or standard treatment or usual care as applied in western medicine, and the use of western medicine should be based on current evidence for their practice for diabetic foot ulcers. Reporting of the trials should follow the Consolidated Standards of Reporting Trials (CONSORT), and trials should be registered prospectively.

5. Conclusion

Weak evidence showed benefit of CHM as add-on treatment of conventional therapy on increasing number of ulcer heals in patients with DFU. That's about twice the healing rate of the conventional treatment (or plus hot water foot bath) group. With insufficient information, we could not draw confirmative conclusion on safety of CHM administration. These findings need to be tested in further large, rigorous trials.

Authors' contributions

JP Liu conceived and designed the review. Y Wang, HJ Cao, HM Zhang, LQ Wang, K Zhang, YQ Yan and CL Lu were responsible for the searching, screening and selecting studies. Y Wang and HJ Cao contributed to performing data analyses and drafting the manuscript. Liu JP, Y Wang, HJ Cao, CL Lu, LQ Wang, YQ Yan, K Zhang, Hao Lu and HM Zhang were all involved in critically revising the manuscript. All authors have read and approved the final manuscript.

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Conflicts of interest

There is no conflict of interest in our article.

Statement

All data included in this review are supported by seven open Chinese and English electronic databases for published studies, details of the electronic databases were showed in Search strategy.

Appendix 1 Searching strategy for electronic databases

databases	date
PubMed	30/11/2018
#1. DRUGS CHINESE HERBAL [Title/Abstract] OR Chinese medicine[Title/Abstract] OR herbal medicine[Title/Abstract] OR Chinese drugs [Title/Abstract] OR traditional Chinese medicine [Title/Abstract]	
#2. diabetic foot [Title/Abstract] OR diabetic foot ulcer [Title/Abstract] OR diabetic foot leg [Title/Abstract]	
#3. randomized controlled trial[Title/Abstract] OR clinical trial[Title/Abstract] OR random[Title/Abstract] OR randomized [Title/Abstract]	
#4. English[Language]	
#5. #1 AND #2 AND # 3 AND #4	
The Cochrane library	30/11/2018
#1. DRUGS CHINESE HERBAL [Title/Abstract/Keywords] OR Chinese medicine[Title/Abstract/Keywords] OR herbal medicine[Title/Abstract/Keywords] OR Chinese drugs[Title/Abstract/Keywords] OR traditional Chinese medicine [Title/Abstract/Keywords]	
#2. diabetic foot[Title/Abstract/Keywords] OR diabetic foot ulcer [Title/Abstract/Keywords] OR diabetic foot leg [Title/Abstract/Keywords]	
#3. randomized controlled trial[Title/Abstract/Keywords] OR clinical trial[Title/Abstract/Keywords] OR random[Title/Abstract/Keywords] OR randomized [Title/Abstract/Keywords]	
#4. #1 AND #2 AND # 3	
China National Knowledge Infrastructure (CNKI), and modified for the other three Chinese databases	30/11/2018
#1. zhongyi (traditional Chinese medicine) OR zhongyao (traditional herbs) OR zhongyiyao (traditional Chinese medicine) OR zhongchengyao (Chinese patent medicine) OR caoyao (herb)	
#2. tangniaobingzu(diabetic foot) OR tangniaobingzukuiyang (diabetic foot ulcer)	
#3. Suiji(random) OR duizhao (Control)	
#4. dongwu (animal) OR shu (mouse) OR quan (dog) OR tu (rabbit) OR xitongzongshu (systematic review) OR xitongpingjia (systematic review) OR meta	
#5. #1 AND #2 AND # 3 NOT #4	

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