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Current evidence on the effectiveness of systemic herbal medicine for psoriasis: A systematic review with meta-analysis

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Abstract

Herbal medicines have been used to treat psoriasis for many years with anecdotal reports of efficacy which have attracted public attention. We seek to assess the effects of systemic herbal medicine in the treatment of psoriasis. Medical database PubMed/MEDLINE, AMED, CINAHL, and CENTRAL were searched. Randomised controlled trials of systemic herbal medicine used in the treatment of psoriasis included in the meta-analysis. Two reviewers independently applied eligibility criteria, assessed the quality of the trials and extracted data. Any discrepancies were discussed with additional reviewer to achieve consensus. Nine randomised controlled trials met the inclusion criteria. The trials randomised 785 participants. Three RCTs revealed that herbal medicine performed better than placebo control (RR=3.98, 1.36-11.62, 95%CI, I2=68%, p=0.01), four RCTs demonstrated that the western drug competitor is superior to herbal medicine(RR=0.73, 0.53-0.97, 95%CI, I2=52%, p=0.03), two RCTs suggested that herbal medicine combined with other medication, (i.e. Auricular Acupuncture or Acitretin (a systemic retinoid), is more effective than herbal medicine alone (RR=1.92, 1.28-2.88, 95%CI, I2=0%, p=0.002). The results of one RCT indicated that herbal medicine reduced the occurrence of adverse reactions of Acitretin, when it was used in combination with herbal medicine. The findings are not conclusive due to the high risk of bias of the included trials and the limited number of trials testing individual herbal medicines. Further well-designed larger scale trials are required to determine the safety and efficacy of oral herbal interventions in the treatment of psoriasis.

Introduction

Psoriasis is a common, chronic, and recurrent inflammatory disease of the skin [1-3]. Worldwide psoriasis prevalence rates range from 0.6 percent to 4.8 percent [4]. Prevalence is higher in European 1.5%-3.5% [5,6] compared with 0.1%-0.3% in the Far East and China [6,7]. Psoriasis impacts on daily living activities and may cause a financial burden on affected individuals [8-12]. A population-based survey conducted by Stern *et al.* [13] showed that 60% (n=4.5million) of patients report the disease affects their everyday life and 26% (n=4.5 million) report a change or discontinuation of their daily activities. In the United States, total direct and indirect cost of psoriasis is estimated at 11.25 billion dollars annually, national direct medical costs increased from 650 million to 4.3 billion dollars over 6 years time period [8,11]. The cause of psoriasis is genetic with multiple inherited and acquired factors interacting [14].

Conventional treatment options focus on symptomatic management and may be associated with unwanted side effects and the development of drug tolerance [15-17]. Herbal medicine has been used as medicine for thousands of years [18], for example, saw palmetto was used for urinary symptoms in ancient Egypt [19], and a Chinese classic book named Inner Classic of the Yellow Emperor describes traditional Chinese herbs on skin diseases [20]. Herbal medicines are popular in America: in the 19th century, around two-thirds of medicine listed in the first edition of the United States Pharmacopoeia USP published in 1820 was botanical substances [21-23]. Fermentation products and highly purified or chemically modified botanical substances are not considered as botanical drug by FDA.

It is reported that in the China and USA around 43%-69% of patients inquire about traditional medicine (Herbal medicine, Traditional Chinese Medicine TCM, complementary alternative medicine CAM) to seek long-term psoriasis remission without side effects [24-29]. Studies have shown that some herbal medicines may be effective for psoriasis [30-33]. There were some alternative and complementary medicine CAM for psoriasis treatment reviews published previously [6,32,34-36], but literature reviews based on evidence from randomised control trials on systemic herbal intervention are rare.

Due to lack of standard clinical practice on systemic herbal medication and a knowledge gap in regards of evidence-based medicinal use of systemic herbal medicine in psoriasis patients, the following two research questions were constructed:

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Key words: *psoriasis, herbal medicine, Chinese medicine, plant medicine, oriental medicine, kampo medicine, complementary medicine, alternative medicine, botanical drug*

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The primary aims:

1. What, if any, evidence from randomized controlled trials (RCTs) exists for treatment of psoriasis with systemic herbal medicine?
2. What is the quality of the evidence for published systemic herbal medicine RCTs on psoriasis?

In order to answer these clinical questions, a systematic literature review was undertaken to evaluate the published RCTs on the safety and efficacy of treatment of psoriasis with systemic herbal medicine compared with placebo or comparator or herbal medicine +/- western medicine. The objectives of this review are to:

1. Identify and examine the safety and efficacy of herbal systemic intervention in the treatment of psoriasis
2. Critically appraise and summarise the available literature relating to systemic herbal therapy in psoriasis patients
3. Provide physicians and patients with up-to-date evidence-based recommendations of systemic herbal medicine for psoriasis.

The findings of the examined randomized controlled trials will be analysed.

Methods

We conducted a systematic review on the efficacy and safety of systemic herbal treatments for psoriasis.

Database and search strategies

The query search using patient characteristics, type of intervention, control, and outcome PICO format [35] was used to facilitate the literature searching process. MEDLINE/PubMed via PICO (http://pubmedhh.nlm.nih.gov/nlmd/pico/piconew.php)search provided by National Library of Medicine is applied as a primary search strategy in this paper. In PICO (patient, intervention, control, and outcome) category searching, "psoriasis" is used in patient category, keywords and synonyms "herbal medicine", "Chinese medicine", "plant medicine", "oriental medicine", "kampo medicine", "complementary medicine", "alternative medicine" and "botanical drug" are used in intervention category, control and outcome category leave in blank. Publication type is selected as "clinical trial" and "review". The relevant reference of review articles generated by PICO searching and reference of the references in the related literatures are also searched and retrieved.

Electronic searches were conducted on the following databases: PubMed/MEDLINE, AMED (Allied and Complimentary Medicine), CINAHL, and Cochrane Central Register of Controlled Trials (CENTRAL). The search terms were a combination of Medical Subject Heading MeSh terms and their synonyms.A combination of MeSH terms and synonyms in PubMed/Medline, is listed in Table 1.

Table 1. Literature search in PubMed/Medline.

No.	Search term	Search syntax	Hits on 11 July 2013
1	Randomized controlled trial	Publication type	435,264
2	Randomized controlled trial as topic	MeSH	116,520
3	Psoriasis	MeSH	34,292
4	Chinese medicine	MeSH	70,661
5	Herbal medicine	MeSH	21,078
6	Traditional medicine	MeSH	68,902
7	Phytotherapy	MeSH	28,072
8	Botanical drug	MeSH	1,575
9	Oriental medicine	MeSH	16,104
10	Alternative medicine	MeSH	218,695
11	Complementary medicine	MeSH	192,255
12	Kampo medicine	MeSH	878
13	Term 1 or 2		435,264
14	Term 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12		323,908
15	Term 3 and 13 and 14		42

Inclusion/exclusion criteria

Inclusion criteria

- The research participants to be included in this review are patients who are clinically diagnosed with psoriasis or psoriatic arthritis.
- Placebo, no treatment or competitor medicine treatment as control interventions.
- No age limit was set.
- Only randomized controlled trials articles will be included in the analysis.
- Intervention was any herbal medicine or combination of herbal medicines administered for systemic effect for psoriasis where herbal medicine(s) could be described as vegetable materials, which may include plant materials, algae, macroscopic fungi, combinations thereof, or may derived from plants or parts of plants i.e. leaves, stems, buds, flowers, roots or tubers.
- Limits were set for publication within 11 years (Jan 2002 to Jan 2013). The Consolidated Standards of Reporting Trials (CONSORT) Statement was first published in 1996 [39] as a clinical trial reporting guideline. The revised CONSORT Statement was published in 2001 and endorsed by three prestigious international medical journals, The Journal of the American Medical Association, Lancet and Annals of Internal Medicine. Therefore reviewers choose the clinical studies on psoriasis published since 2002.

Exclusion criteria

Articles excluded if:

- It is not published in the English language due to time constraints;
- It does not use "randomization";
- It does not have the primary end point as a clinical assessment;
- It contained interventions that used non-herbal therapies (vitamin, mineral supplements, fish oils, spa therapy, psychotherapy, acupuncture etc.);
- It used topical herbal therapies (ointment, cream, lotion etc.);
- It used therapies using plant-derived chemicals or synthetic chemicals that contain constituents of plants.

Analytic framework

Once the literature search was complete, two reviewers (T.Y.T and F.L) independently conducted the selection and data extraction. Any discrepancies were resolved by additional reviewer (J.D).

From the list of included studies, the identified literature were appraised and assessed for methodological quality by using CONSORT Statement for Herbal Interventions [40] and for the risk of bias by using Cochrane Collaboration's tool [41] for assessing risk of bias.

Data analysis

Data were analysed and the meta-analysis were conducted in statistical software RevMan5 that was provided by The Cochrane Collaboration IMS. Dichotomous data were presented as risk ratio RR Mantel-Haenszel method with a 95% confidence interval 95%CI. Meta-analysis was performed if the intervention, control and outcome were all the similar. The statistical heterogeneity was presented as significant when I^2>50% or P<0.1.

Findings

Study selection

Literature search in PubMed/Medline (Table 1) yielded a total of 42 articles, in Cochrane/CENTRAL yielded a total of 49 articles, in CINAHLE/EBSCO host yielded a total of 124 articles, in AMED/EBSCO host yielded a total of 75 articles respectively. PICO search via PubMed/Medline yield a total of 24 review articles. After screening the reference of review articles, total 8 clinical trials paper were identified. PICO search via PubMed/Medline yield a total of 25 clinical trials papers. After screening titles and abstracts, duplicates, non-herbal studies, non-English articles, non-controlled trials were excluded. A total 63 articles were screened out from electronic database searches. The selection of randomised controlled trials RCTs of herbal medicines for psoriasis is described in Figure 1, a flow diagram using the PRISMA template described in the PRISMA statement [42]. A total 13 full text articles were retrieved for further evaluation, 2 were not a randomised controlled trial, 1 was not a herbal intervention. Data were extracted from the remaining 10 [43-52], Hegazi *et al.* (2013) [52] study was excluded from the meta-analysis because it contains 4 intervention groups and therefore did not meet the inclusion criteria for this review.

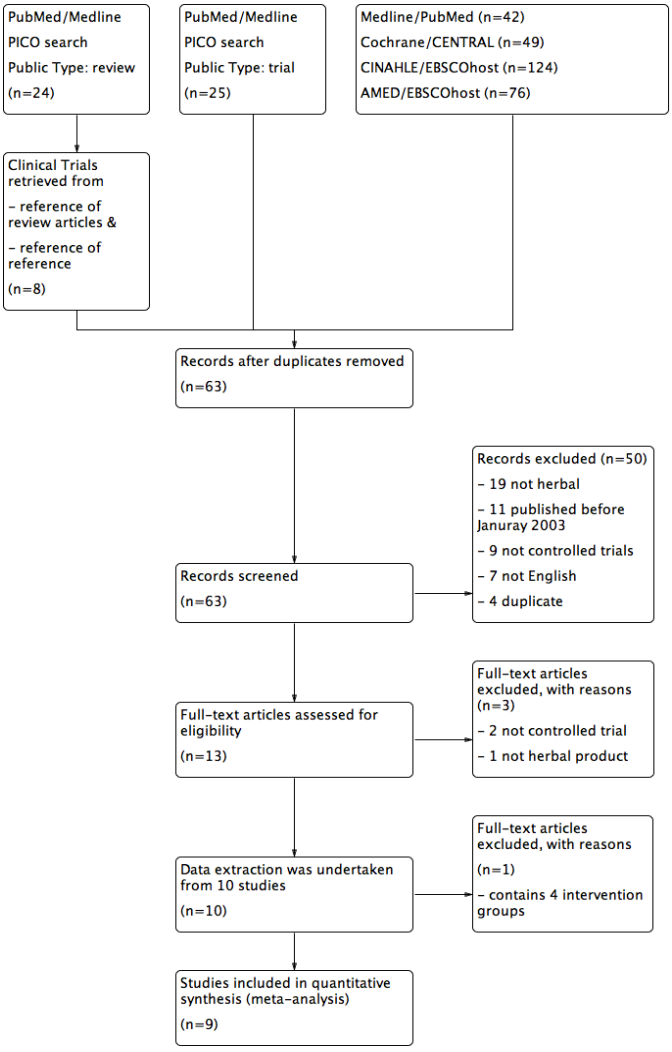

Figure 1. Flow chart of selection of randomised controlled trials (RCTs) of systemic herbal medicines for psoriasis.

Characteristics of included studies

The 9 studies from which data were extracted included a total of 785 participants with psoriasis. The studies' characteristics, methods, participants, interventions and outcome are summarized on Table 2.

Clinical efficacy of herbal medicine

The 9 RCTs [43-51] involved 785 participants are conducted in meta-analysis by using the Cochrane Collaboration's tool Review Manager (RevMan) [Computer program Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012]. These 9 RCTs were divided into 3 sub-groups according to the measures of intervention used: Group A: 3 RCTs [43,46,48] used herbal as intervention and were controlled using placebo as illustrated in Figure 2. Group B: 4 RCTs [44-47] used herbal as intervention and were controlled using competitor (herbal or western drug) as illustrated in Figure 3. Group C: 2 RCTs [49,51] used herbal medicine in combination with other medicine as intervention and were controlled using herbal product alone as illustrated in Figure 4.

Three studies, Ahmadi *et al.* [43], Ho *et al.* [46], Lone *et al.* [48], included in the subgroup A meta-analysis (Figure 2) and listed in the first column "study or subgroup". The individual study findings are displayed in this subgroup meta-analysis with binary outcomes (herbal intervention/placebo control). For example, in Figure 2, there are 9 out of 14 participants of herbal invention group show treatment efficacy, and there are 0 out of 14 participants of placebo control group show treatment efficacy in Ahmadi *et al.* [43] study. The influence of each individual study on overall meta-analysis are weighted at 11.5%, 73.3% and 15.1% by Ahmadi *et al.* [43], Ho *et al.* [46] and Lone *et al.* [48] respectively. The Risk Ratio (RR) effect measure, Mantel-Haenszel (M-H) statistical method and the Fixed Effect analysis model with 95% Confidence Interval used to perform the meta-analysis. Each study is represented by a horizontal line on the forest plot. There is a blue square box in the line for each study. The width of the line shows the confidence intervals of the effect estimate of individual studies. The mid-point of the box represents the point effect estimate, that is, the mean effect estimate for each study. The area of the box represents the weight given to the study. The black diamond shape below the 3 studies represents the overall effect. The width of the diamond shows the confidence intervals for the overall effect estimate. The middle of the diamond sits on the value for the overall effect estimate of the Risk Ratio (RR). There is a vertical line that corresponds to the value 1 in the forest plot. This is the line of no treatment effect. Note also that it says "Favours Placebo" to the left of the vertical line and "Favours Herbal" to the right of the vertical line. On the forest plot shown on Figure 2, the 95% confidence intervals of the two studies (Ho *et al.* [46],

Table 2. Characteristics of included studies.

Ahmadi *et al.* 2008	
Methods	Design: randomised, double-blind, placebo-controlled Duration: 6 months trial and 6 months follow-up Interval of assessment: every 4 weeks
Participants	Number randomised: 28 (14 in each group) Sex (M/F): 5/9 in treatment group and 6/8 in placebo groups Age of participants: Not specified Country and setting: Iran, single university centre Inclusion criteria of the study • Diagnostic criteria: clinical diagnosis of psoriasis vulgaris Exclusion criteria of the study • Erythrodermic • Exfoliative • Pustular psoriasis • Skin infections, • Systemic and/or topical antipsoriatic treatment in the 8-week prior to the study, • PUVA, UVB • pregnancy or breastfeeding
Interventions	• Treatment group: HESA-A tablet 25 mg/Kg BD orally • Placebo group: Not specified
Outcomes	6-point scale: absent (no evidence of psoriasis), very mild (controlled, but not entirely cleared), mild (lesions of slight redness, thickness and scaliness), moderate (red lesions with moderate thickness and scaliness), severe (very red lesions with severe thickness and scaliness), and very severe (extremely red lesions with very severe thickness and scaliness).
Notes	
Chang *et al*. 2006	
Methods	Design: randomised, active comparator-controlled Duration: 8 weeks Interval of assessment: start and end of study
Participants	Number randomised: 120 (60 in each group) Sex (M/F): 34/26 in treatment group and 31/29 in placebo group Age of participants (mean): 35.47 ± 12.5 in treatment group and 36.40 ± 11.32 in placebo group Country and setting: China, single centre Inclusion criteria of the study • Diagnostic criteria: Principle for Directing Clinical Studies on New Drugs of Chinese Materia Medica for Treating Psoriasis, MOH, China • Blood-heat syndrome in traditional Chinese medicine Exclusion criteria of the study • Severe cardiovascular • Cerebrovascular • Pustular psoriasis • Hepatic diseases • Renal diseases • Mental disorders • Women in pregnancy or breastfeeding
Interventions	• Treatment group: Yin Xie Ping Granules, 4.5 g each time, 2 times daily • Control group: Xiao Yin Pian Tablets, 7 tablet each time, 3 times daily
Outcomes	1. Degree of silvery scales 2. Red patches 3. Pruritus 4. Area of papules
Notes	Ingredients used in control group Xiao Yin Pian Tablets was not stated
Deng *et al*. 2010	
Methods	Design: randomised, active comparator-controlled Duration: 4 weeks and 3 months follow-up Interval of assessment: at 4 weeks, 3 months.
Participants	Number randomised: 64 (32 in each group) Sex (M/F): 19/13 in treatment group and 22/10 in placebo group Age of participants (mean, rang): 48.7 (28-62) in treatment group and 45.6 (24-68) in placebo group Country and setting: China, single centre Inclusion criteria of the study • Diagnostic criteria: clinical diagnosis of psoriasis vulgaris • Blood-heat syndrome in traditional Chinese medicine Exclusion criteria of the study • Severe cardiovascular • Cerebrovascular • Prior Acitretin treatment within 1 months • Hepatic diseases • Renal diseases • Mental disorders • Women in pregnancy or breastfeeding
Interventions	• Treatment group: Xuebijing injection, 30 ml daily • Control group: Acitretin Tablets, 30 mg/d
Outcomes	PASI score

Notes	Ingredients used in control group Xiao Yin Pian Tablets was not stated. Concomittent treatment: permitted emollients.
Ho *et al.* 2009	
Methods	Design: randomised, placebo-controlled Duration: 6 months Interval of assessment: every 2 months Number randomised: 61
Participants	Sex (M/F): 26/22 total (18/2 in MTX group, 14/7 in TCM group, 18/2 in placebo group) Age of participants (mean, range): 38.45 (21-68) in MTX, 43.45 (25-80) in TCM, 43.45 (27-61) in placebo Country and setting: China, single centre Inclusion criteria of the study • Diagnostic criteria: not state • Psoriatic plaque affect more than 20% of body surface area • aged more than 18-year-old • Written informed consent Exclusion criteria of the study • Renal or liver impairment • Active infection • Immunosuppression or other serious concomitant • Women in pregnancy or breastfeeding • MTX group: Methotrexate (2.5 mg/week to 30 mg/week), Folic acid 5 mg daily
Interventions	• TCM group: Wen-tong-hua-yu capsule, dose not stated • Placebo group: ingredients and dose not stated
Outcomes	1. PASI score 2. PGA and PDI
Li *et al.* 2008	
Methods	Design: randomised, active comparator-controlled Duration: 4 weeks Interval of assessment: every 2 weeks
Participants	Number randomised: 58 Sex (M/F): 37/21 total (19/11 in TCM group, 18/10 in placebo group) Age of participants (mean, range): 42.16 ± 11.26 in TCM, 38.08 ± 9.64 in placebo Country and setting: China, single centre Inclusion criteria of the study • Diagnostic criteria: Practice guidelines for diagnosis and therapeutic effect evaluation of disease. Peoples's Military Medical Press. 1998. Beijing. China • Blood-heat syndrome in Traditional Chinese Medicine. Diagnostic and therapeutic effect evaluation criteria for diseases and syndromes of traditional Chinese medicine. Nanjing University Press. 1994. China • Aged from 18 to 60 years old • Psoriasis history from 3 months to 20 years Exclusion criteria of the study • Unknown high fever in previous two months • Prior systemic immunosuppressants therapy used within three months • Prior high potent corticosteroid application within three months • Psoriatic type rather than Psoriasis vulgaris • Women in pregnancy or breastfeeding
Interventions	• Treatment group: Qinzhu Liangxue Decoction, 30 ml two times daily. • Controlled group: Compound Amino-polypeptide Tablets, 5 tables, three times daily.
Outcomes	1. PASI score (Psoriasis Area and Severity Index) 2. DLQI score (Dermatology Life Quality Index) 3. VEGF level (Vascular Endothelial Growth Factor)
Notes	
Lone *et al*. 2011	
Methods	Design: randomised, single-blind, placebo-controlled study Duration: 8 weeks Interval of assessment: fortnightly
Participants	Number randomised: 30 Sex (M/F): 21/9 total (20 in herbal group, 10 in placebo group) Age of participants 11-60 years Country and setting: India, Bangalore, single centre Inclusion criteria of the study • Illness history • Dermatological examination • Aged from 11 to 60 years old • Biopsy of the affected area Exclusion criteria of the study • Aged blow 11 years and above 60 years • Prior systemic immunosuppressants therapy used within three months • Unable to give consent • Psoriasis concomitant with diabetes, vitiligo, dermatophytosis, pityriasis, eczema • Women in pregnancy or breastfeeding or mentally retarded persons • Priorlocal or systemic antipsoriatic therapy used within two months

Interventions	• Treatment group: Majoon Ushba 5 g two times daily, Rogbane Hindi 5-10 ml topical apply two times daily. • Controlled group: Wheat flour 5 g two times daily, Coconut oil topical apply two times daily.
Outcomes	1. Itching severity, scaling severity, erythema severity. 2. PASI score (Psoriasis Area and Severity Index)
Notes	
Lu *et al.* 2012	
Methods	Design: randomised, active comparator-controlled Duration: 8 weeks Interval of assessment: every 2 weeks
Participants	Number randomised: 84 Sex (M/F): 61/23 total (28/15 in TCM + Auricular therapy group, 33/8 in TCM group) Age of participants (mean, range): 38.58 ± 13.13 in TCM + Auricular, 38.98 ± 13.80 in TCM Country and setting: China, single centre Inclusion criteria of the study • Diagnostic criteria: Clinical guidelines of Psoriasis 2008 by Chinese Medical Association China • Aged from 18 to 65 years old • Sign informed consent. Exclusion criteria of the study • Allergic to Yinxieling Formula or the composition of it • Women in pregnancy or breastfeeding • Prior oral steroid therapy used within two weeks • Prior oral retinoid or topical steroid treatment within one week • Arhropathic, pustular, or erythrodermic psoriasis • Severe heart, cerebrovascular, live, kidney, hematopoietic system, cancer, psychosis diseases.
Interventions	• Treatment group: Auricular + Yinxieling Decoction, 10 ml two times daily. • Controlled group: Yinxieling Decoction, 10 ml two times daily.
Outcomes	1. PASI score (Psoriasis Area and Severity Index) 2. DLQI score (Dermatology Life Quality Index) 3. VAS (Visual Analogue Scale) 4. SDS (Self-rating Depression Scale) 5. SAS (Self-rating Anxiety Scale)
Notes	
Yang *et al.* 2002	
Methods	Design: randomised, active comparator-controlled Duration: 8 weeks Interval of assessment: before and end of study
Participants	Number randomised: 260 Sex (M/F): 144/116 total (88/72 in treatment group, 56/44 in comparator controlled group) Age of participants (mean, range): 30.0 ± 2.8 in treatment group, 30.0 ± 20 in TCM Country and setting: China, single centre Inclusion criteria of the study • Not stated Exclusion criteria of the study • Not stated • Treatment group: LeYin Decoction, 50ml two times daily, and Vitamin E moisturizer application.
Interventions	• Controlled group: Yinxieling Granule, 10 g two times daily and Vitamin E moisturizer application.
Outcomes	1. Therapeutic effect evaluation 2. Changes of T-cell subsets 3. Adverse reactions
Notes	
Zhang *et al.* 2009	
Methods	Design: randomised, active comparator-controlled Duration: 8 weeks Interval of assessment: before and at end of week 8
Participants	Number randomised: 80 Sex (M/F): 74/6 total (37/2 in TCM+Acitretin, 37/4 in TCM group) Age of participants (mean, range): 42.6 in TCM + Auricular, 43.1 in TCM Country and setting: China, single centre Inclusion criteria of the study • Blood-heat syndrome in Traditional Chinese Medicine Duiding Principles of Clinical Research on New Drugs of Traditional Chinese Medicine. China • Diagonosed with psorasis Exclusion criteria of the study • Severe photosensitivity • Women in pregnancy or breastfeeding or planing for pregnancy • Sensitive to acitretin • Prior oral acitretin or immunosuppressive therapy within two months • Complicated with other skin diseases • Severe heart, cerebrovascular, live, kidney, hematopoietic system, cancer, psychosis diseases.
Interventions	• Treatment group: TCM decoction + Qingkailing Injection 40ml daily + Acitretin 20-30 mg daily • Controlled group: TCM decoction + Qingkailing Injection 40 ml daily
Outcomes	1. PASI score (Psoriasis Area and Severity Index)

Lone *et al.* [48]) overlap 1, the 95% confidence intervals of the study (Ahmadi *et al.* [43]) do not overlap 1. There is statistical significance at the meta-analysis level. The herbal intervention is better than control as the overall effect estimate and its 95% confidence intervals are to the right of the line of no treatment effect. The total number of participants in the herbal intervention groups is 48 and the control group is 41.

The heterogeneity test is shown at the bottom of the Figure 2 on the left hand side, the number of interest is the I^2 value. I^2 was developed and introduced as the preferable and more reliable test for heterogeneity (Higgins *et al.* [52]). I^2 ranges between 0 and 100%, the values of I^2 equal to 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively. Heterogeneity measures the variability between studies, in other words it gives an indication how comparable studies in the meta-analysis are. A useful visual guide to assess heterogeneity is to check the overlap of the CIs, i.e. the horizontal lines in the meta-analysis graph. Studies are regarded as homogeneous if CIs of all studies overlap. The heterogeneity of this subgroup studies are moderate (I^2=68).The test for overall effect is statistical significance with the probability value (p=0.01).

Four studies, Chang *et al.* [44], Deng *et al.* [45], Ho *et al.* [46] Li *et al.* [47], included in the subgroup B meta-analysis (Figure 3). The total number of participants in the herbal intervention groups is 136 and the competitor group is 139. The mean effect estimate for 3 studies Deng *et al.* [45], Ho *et al.* [46], Li *et al.* [47] which using herbal intervention compare with western drug treatment favours western drug treatment. The 95% confidence intervals of Ho *et al.* [46] study are to the left of the line of no treatment effect that show the MTX is superior than the herbal intervention. Chang *et al.* [44] used competitive herbal medicine to compare with investigative herbal medicine, the mean effect estimate favours herbal intervention, but the 95% confidence intervals overlap 1. On the forest plot shown on Figure 3, the competitor is better than herbal intervention as the overall effect estimate and its 95% confidence intervals are to the left of the line of no treatment effect. The heterogeneity of this subgroup studies are moderate (I^2=52). The test for overall effect is statistical significance with the probability value (p=0.03).There is statistical significance at the meta-analysis level.

Two studies, Lu *et al.* [49] and Zhang *et al.* [51] included in the subgroup C meta-analysis (Figure 4). The total number of participants in the herbal intervention groups is 82 and the herbal combine other medication group is 81. The mean effect estimates for these two studies favours herbal medicine in combination with Auricular acupuncture or western medicine Acitretin group. The 95% confidence intervals of Lu *et al.* [49] study are to the right of the line of no treatment effect that show the herbal combing with Auricular therapy is superior than the herbal intervention alone. Zhang *et al.* [51] used herbal medicine combine with Acitretin to compare with herbal medicine alone, the mean effect estimate favours herbal combination therapy, but the 95% confidence intervals overlap 1. On the forest plot shown on Figure 4, the competitor is better than herbal intervention as the overall effect estimate and its 95% confidence intervals are to the right of the line of no treatment effect. The heterogeneity of this subgroup studies are

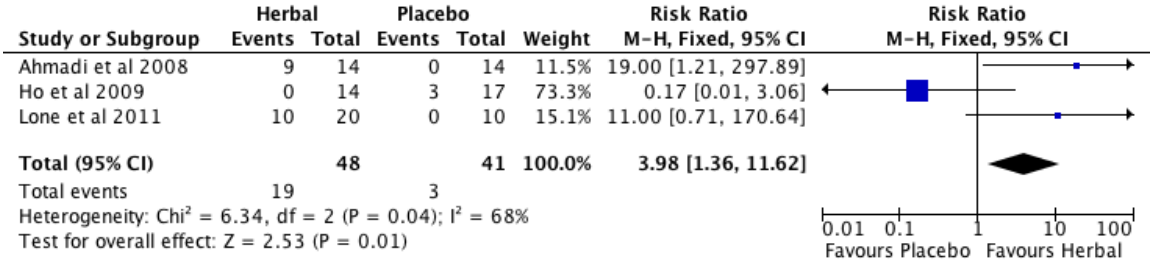

Figure 2. Subgroup A. Meta-analysis of Effective Rate of Herbal vs. Placebo (*CI:* confidence interval, *M-H*: Mantel-Haenszel).

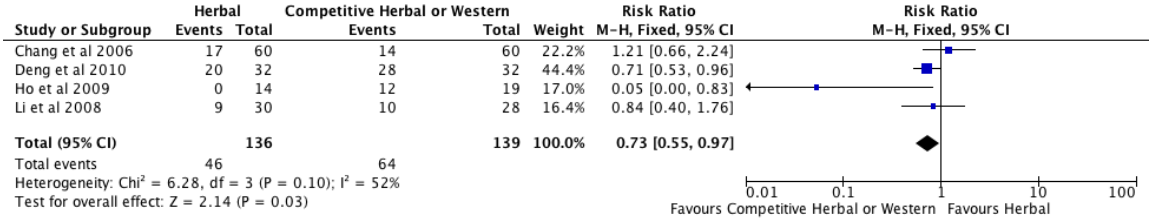

Figure 3. Subgroup B. Meta-analysis of Effective Rate of Herbal vs. Competitor (herbal or western drug) (*CI:* confidence interval, *M-H*: Mantel-Haenszel).

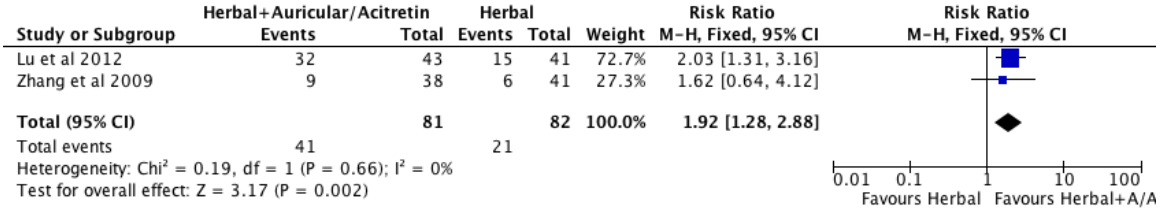

Figure 4. Subgroup C. Meta-analysis of Effective Rate of Herbal + other medication vs. Herbal Alone (*CI:* confidence interval, *M-H*: Mantel-Haenszel).

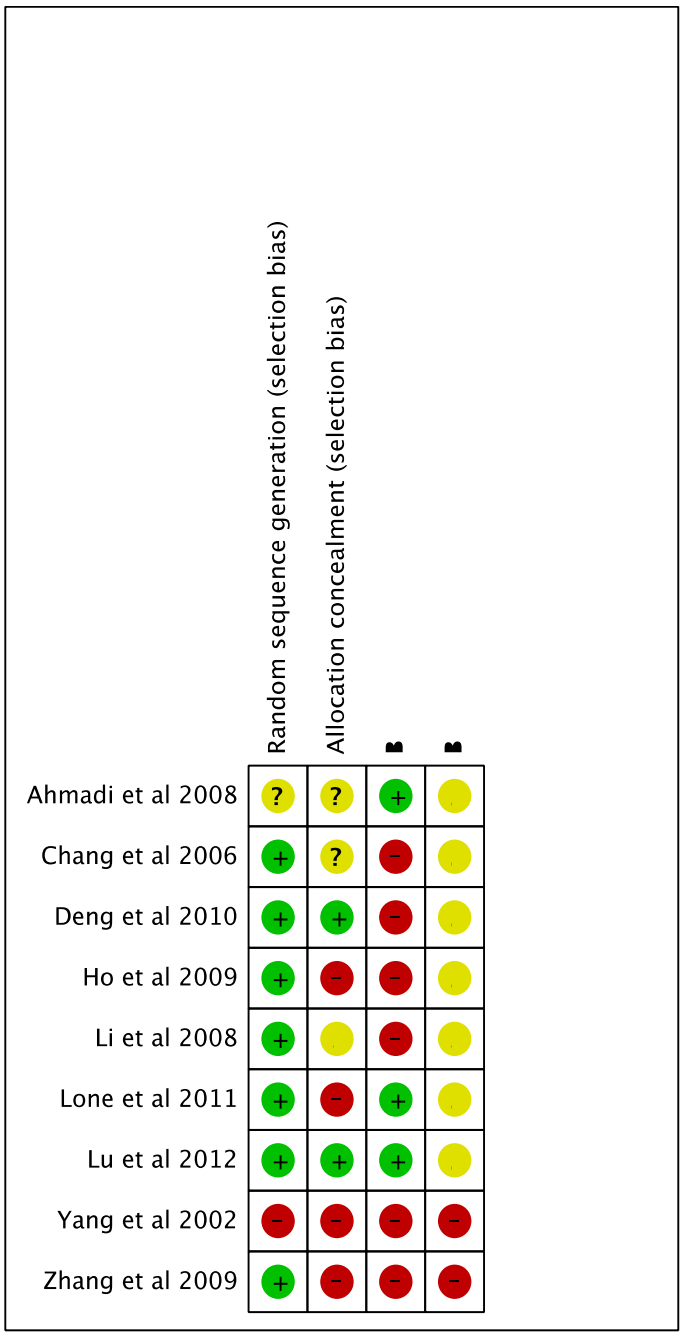

Figure 5. Summary of risk of bias assessment.
(+: Low Risk, -: High Risk, ?:Unclear)

low (I^2=0). The test for overall effect is statistical significance with the probability value (p=0.002). There is statistical significance at the meta-analysis level.

Synthesis and interpretation

In total, 9 RCTs [43-52] were included in the qualitative synthesis (Table 2) and 9 RCTs [43-52] were included in the meta-analysis (Figures 2-4). Regarding the effectiveness of herbal medication for psoriasis, 3 RCTs revealed that herbal medicine performed better than placebo control, 3 RCTs showed that the western drug competitor is superior than herbal intervention, 1 RCT showed the herbal medicine performed better than competitive herbal medicine, 2 RCTs suggested that herbal combined with other medication (Auricular or Acitretin) is better than herbal medicine alone. Regarding adverse reactions, the abnormal liver function were reported in 8 participants in Acitretin (western drug) group (Deng *et al.*) [45], the results of Zhang *et al.* [51] indicated that herbal medicine reduce the occurrence of adverse reaction of western medicine Acitretin when it is used combine with herbal medicine. The adverse events were reported by 65% in the MTX (western drug) group, 48% in the herbal intervention group and 30% in the placebo group (Ho *et al.*) [46].

This review showed no significant safety concerns regarding systemic herbal medication for psoriasis. But in these 9 studies, herbal medicine was only administered for 4 weeks to 6 months under controlled conditions. The included studies used different methods of medication delivery: 4 studies [47,49-51] used decoctions,1 used powder (Lone *et al.*[48]), 1 used tablet (Ahmadi *et al.* [43]), 2 used capsule (Hagazi *et al.* [52], Ho *et al.* [46]), 1 used granules (Chang *et al.* [44]) and 1 used injection (Deng *et al.* [45]). It remains unclear if the different methods of herbal medicine delivery influence their treatment effects [53,54].

Quality evaluation on the evidence

The risk of bias assessment is conducted by using the Cochrane Collaboration's tool for assessing risk of bias [41]. The overall risk of assessment found that the quality of studies was poor (Figure 5), therefore the results from the meta-analysis have to be translated with caution. None of 9 RCTs was judged with "Low Risk" in all domains for bias assessment. All 9studies had "High Risk" or "Unclear" judgements in ≥2 domains (Figure 5).

7 RCTs (Ahmadi *et al.* [43], Chang *et al.* [44], Ho *et al.* [46], Li *et al.* [47], Lone *et al.* [48], Yang *et al.* [50], Zhang *et al.* [51]) did not state the method used to conceal the allocation sequence, hence selection bias may occurred due to inadequate concealment of allocations prior to assignment.

6 RCTs (Chang *et al.* [44], Deng *et al.* [45], Ho *et al.* [46], Li *et al.* [47], Yang *et al.* [50], Zhang *et al.* [51]) failed to blind study participants and personnel from knowledge of which intervention a participant received. The granules were used as intervention and tablets were used as control (Chang *et al.* [44]). The herbal injection was used as intervention and tablets used as control (Deng *et al.* [45]). Capsules were used as intervention, tablets were used as competitor, placebos were used as control, but investigators did notdescribe the details on the chemical properties of the herbal placebo (Ho *et al.* [46]). The decoctions were used as intervention and tablet were used as control (Li *et al.* [47]). The decoctions were used as intervention and granule were used as control (Yang *et al.* [50]). The decoction combined with injection and tablet used as intervention and decoction plus injection used as control (Zhang *et al.* [51]). Therefore the performance bias may incur due to knowledge of the allocated interventions by participants and personnel during these studies.

The detection bias is high risk in all 9 RCTs because none of these studies describe measures used to blind outcome assessors from knowledge of which intervention a participant received and provide any information relating to whether the intended blinding was effective.

The quality of reporting is evaluated by using the CONSORT framework [40] to check if the adequate important aspects of research information are included in reports of controlled clinical trials of

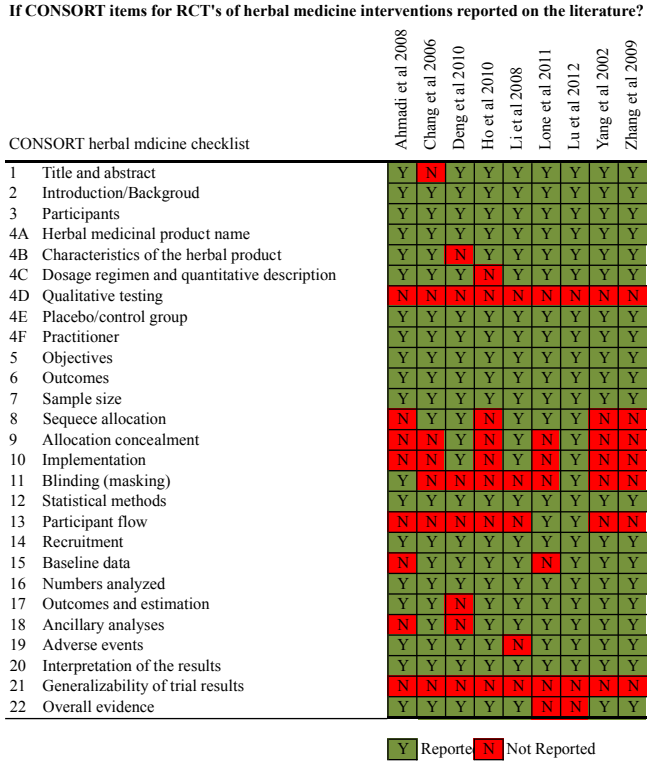

Figure 6. Summary of CONSORT 22 items for RCTs of herbal medicine.

herbal interventions. The 22-item checklist of the CONSORT for herbal intervention is compiled on Figure 6.

None of 9 RCTs report the item 4D (Qualitative Testing) (Figure 6) investigational product's chemical fingerprint and methods used and which laboratory performed them. Herbal medicines are often contaminated [55], thus a complete description of any special testing or purity testing (e.g. heavy metal test) and the removal of unwanted components should be included in reports.

Only two RTCs (Ahmadi *et al.* [43], Lone *et al.* [48]) reported blinding item 11 (Blinding) (Figure 6). Ahmadi *et al.* [43] state the trials as "double-blind", but did not give the details on the properties of the herbal placebo. Lone *et al.* [48] state the trails as "single blind" and specified wheat flour serviced as control to compare with investigational herbal "Majoon Ushba". However these 2 RCTs did not state whether those investigators administering the intervention and those assessing the outcomes were blinded, how the success of blinding of participant was evaluated.

None of 9 RCTs report the external validity of trial result item 12 (Generalizability) (Figure 6). Generalizability is the extent to which the results of a study hold true in other individuals or groups, other similar interventions, dosages, timing, administration routes and other settings [40]. The herbal medicinal products are available widely on the market with variable quality and ingredients, how the products used in the RCTs relate to what is available and used by consumers and health care practitioners is quite valuable information which enable reader to understand products that may act similarly to the one used in the trial.

The 9 included RCTs reported adequate information on Title and Abstract section (item 1) and Introduction section (item 2), showed the minor issue on reporting Result section (item 13-19) and Discussion section (item 20-22) as item 13 (Participant Flow) and item 21 (Generalizability) are uncompleted reported, and showed the non-adequate reporting in Methods section (item 3-12) because the item 4D (Qualitative Testing), item 8 (Sequence Allocation), item 9 (Allocation Concealment), item 10 (Implementation) and item 11 (Blinding) are poorly reported lacked with details. Such findings on checklist of the CONSORT for herbal intervention (Figure 6) are also corresponded with the risk of bias assessment (Figure 5).

Discussion

This review did not include unpublished studies, case reports, case-series, or retrospective studies, non-English studies. The reviewers are aware of the high possibility of publication bias due to exclusion of non-English language publication in this review. The exclusion of Chinese language articles may result in partial estimate of intervention effect for herbal interventions [56].

Only 9 small inadequate reported RCTs with short study duration were available for assessment. None was effectively blinded. Although blinding presents practical difficulties when herbal decoctions are used, without blinding it is impossible to conclude that the benefit observed was due to herbal medicine alone. The evidence is inconclusive due to the high risk of bias of the included trials and the limited number of trials with each of herbal medication formulas, as well as the limited number of included participants and patient relevant outcomes. Hence the author cannot be certain of the effectiveness and safety of the studies in this review of herbal medicines for the treatment of psoriasis.

To obtain a high level of evidence on herbal medicines on psoriasis treatment and to give guidance on clinical practice, more international, multicentre, rigorously designed, high-quality trials with large sample sizes are required. Attention should be paid to the sample size estimation, the definition of outcomes, duration of treatment and follow-up, and the reporting of adverse events. In addition, the following methodological issues should be addressed: the trial design should be according to the SPIRIT Statement (www.spirit-statement.org), including the methods of randomisation and blinding with the use of placebo with the same appearance, taste, and smell, and reporting trials according to the CONSORT statement for herbal intervention (www.consort-statement.org). To improve the quality of future trials, the author suggest that all researchers receive the necessary training on clinical trial methodology before designing a trial and register the trial on an internationally recognised public trial registry. From the results of this review, the detailed description of the pharmacology of the interventions and clinical outcomes should be emphasised for herbal medicines. Information about species, geographical origin of herbs, season for collecting the herbs, and quality of the preparations should be provided [40].

3 RCTs (Figure 2) revealed that herbal medicine performed better than placebo control (RR=3.98, 1.36-11.62, 95%CI, I^2=68%, p=0.01), but results were heterogeneous (I^2 >50%). 4 RCTs (Figure 3) showed that the western drug competitor is superior than herbal intervention (RR=0.73, 0.53-0.97, 95%CI, I^2=52%, p=0.03), but results were heterogeneous (I^2 >50%). 2 RCTs (Figure 4) suggested that herbal medicine combined with other medication (Auricular or Acitretin) is more effective than herbal medicine alone (RR=1.92, 1.28-2.88, 95%CI, I^2=0%, p=0.002), but these results need to be interpreted with caution due to methodological weaknesses and the lack of replicated studies. The results of 1 RCT (Zhang *et al.* [51]) indicated that herbal medicine reduce the occurrence of adverse reaction of western medicine Acitretin when it is used combine with herbal medicine. We found no significant

difference on adverse effects between herbal medicine and placebo control groups. However, the findings are not conclusive due to the high risk of bias of the included trials and the limited number of trials testing individual herbal medicines. All the studies had small sample size that can decrease the chances of finding a positive effect if one truly exists, moreover most of the studies had short study duration from 4 weeks to 8 weeks which can hide potential undetectable long-term side effect of investigational herbal medicine if one truly exists. In reviewers' opinion, it is premature to recommend any of these herbal medicines to psoriasis patients. Therefore there is clearly a need for well-designed and larger scalerigorous randomized controlled trials with CONSORT reporting format to determine the safety and efficacy of these herbal interventions.

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