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,12=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,12=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,12-09, 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 large 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://pubmedh.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 searching, “psoriasis” is used in patient category.

The relevant reference of review articles generated by PICO searching and reference of the references in the related literature 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 Headings MeSH terms and their synonyms. A combination of MeSH terms and synonyms in PubMed/Medline, is listed in Table 1.

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.

Table 1. Literature search in PubMed/Medline.

<table>
<thead>
<tr>
<th>No.</th>
<th>Search term</th>
<th>Search syntax</th>
<th>Hits on 11 July 2013</th>
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<td>2</td>
<td>Randomized controlled trial as topic</td>
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<td>Chinese medicine</td>
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<td>5</td>
<td>Herbal medicine</td>
<td>MeSH</td>
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<tr>
<td>6</td>
<td>Traditional medicine</td>
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<td>7</td>
<td>Phytotherapy</td>
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<tr>
<td>8</td>
<td>Botanical drug</td>
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<td>Complementary medicine</td>
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<td>12</td>
<td>Kampo medicine</td>
<td>MeSH</td>
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<tr>
<td>15</td>
<td>Term 3 and 13 and 14</td>
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<td>42</td>
</tr>
</tbody>
</table>

- 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 I² >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 CINAHL/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.

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], 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 intervention 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],
Ahmadi et al. 2008

<table>
<thead>
<tr>
<th>Methods</th>
<th>Design: randomised, double-blind, placebo-controlled</th>
<th>Duration: 6 months trial and 6 months follow-up</th>
<th>Interval of assessment: every 4 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Number randomised: 28 (14 in each group)</td>
<td>Sex (M/F): 5/9 in treatment group and 6/8 in placebo groups</td>
<td>Age of participants: Not specified</td>
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<tr>
<td>Interventions</td>
<td>Treatment group: HESA-A tablet 25 mg/Kg BD orally</td>
<td>Placebo group: Not specified</td>
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<tr>
<td>Outcomes</td>
<td>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).</td>
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</table>

Chang et al. 2006

<table>
<thead>
<tr>
<th>Methods</th>
<th>Design: randomised, active comparator-controlled</th>
<th>Duration: 8 weeks</th>
<th>Interval of assessment: start and end of study</th>
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<tbody>
<tr>
<td>Participants</td>
<td>Number randomised: 120 (60 in each group)</td>
<td>Sex (M/F): 34/26 in treatment group and 31/29 in placebo group</td>
<td>Age of participants (mean): 35.47 ± 12.5 in treatment group and 36.40 ± 11.32 in placebo group</td>
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<td>Interventions</td>
<td>Treatment group: Yin Xie Ping Granules, 4.5 g each time, 2 times daily</td>
<td>Control group: Xiao Yin Pian Tablets, 7 tablet each time, 3 times daily</td>
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<tr>
<td>Notes</td>
<td>Ingredients used in control group Xiao Yin Pian Tablets was not stated</td>
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</table>

Deng et al. 2010

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<thead>
<tr>
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<th>Duration: 4 weeks and 3 months follow-up</th>
<th>Interval of assessment: at 4 weeks, 3 months.</th>
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<tbody>
<tr>
<td>Participants</td>
<td>Number randomised: 64 (32 in each group)</td>
<td>Sex (M/F): 19/13 in treatment group and 22/10 in placebo group</td>
<td>Age of participants (mean, range): 48.7 (28-62) in treatment group and 45.6 (24-68) in placebo group</td>
</tr>
<tr>
<td>Interventions</td>
<td>Treatment group: Xuebijing injection, 30 ml daily</td>
<td>Control group: Acitretin Tablets, 30 mg/d</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>PASI score</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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
Number randomised: 58

Participants
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
• Aged from 18 to 60 years old
• Psoriasis history from 3 months to 20 years
• Unknown high fever in previous two months
• Prior systemic immunosuppressants therapy used 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
Number randomised: 30

Participants
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 below 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
• Prior local 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
  - Athrophagic, purulal, 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
  - Diagnosed with psoriasis
- 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 I² value. I² was developed and introduced as the preferable and more reliable test for heterogeneity (Higgins et al. [52]). I² ranges between 0 and 100%, the values of I² 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 (I²=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 comparator 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 compared 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 (I²=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 combined other medication group is 81. The mean effect estimates for these two studies favours herbal medicine in comparison 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 combing with Acitretin to compare with herbal medicine alone, the mean effect estimate favours 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 moderate (I²=44). The test for overall effect is statistical significance with the probability value (p=0.03).
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 not describe 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
If CONSORT items for RCT’s of herbal medicine interventions reported on the literature?

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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, I²=68%, p=0.01), but results were heterogeneous (I²=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, I²=52%, p=0.03), but results were heterogeneous (I²=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, I²=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.

References


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