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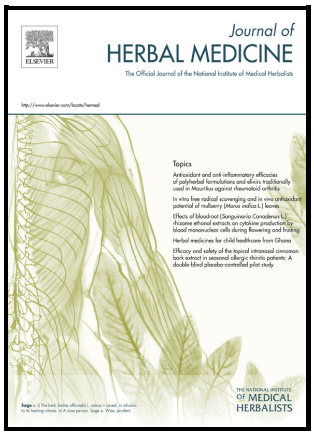

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PII: S2210-8033(22)00048-3

DOI: https://doi.org/10.1016/j.hermed.2022.100579

Reference: HERMED100579

To appear in: *Journal of Herbal Medicine*

Received date: 2 February 2021
Revised date: 1 March 2022
Accepted date: 7 June 2022

Please cite this article as: Wen-Hsin Tsou, Michael Heinrich and Anthony Booker, Chinese and Western Herbal Medicines for the Topical Treatment of Psoriasis-a critical review of Efficacy and Safety, *Journal of Herbal Medicine,* (2021) doi:https://doi.org/10.1016/j.hermed.2022.100579

Chinese and Western Herbal Medicines for the Topical Treatment of Psoriasis-a critical review of Efficacy and Safety

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Declarations of interest: none

Abstract

Introduction: This critical review of randomized controlled trials (RTCs) was conducted to evaluate the efficacy and safety of herbal products used in the topical treatment of psoriasis.

Method: Selected databases were systematically searched using keywords. RCTs focusing on mild to moderate psoriasis using herbal topical treatments in comparison either to standard medications or placebo were included. The methodological and reporting quality of included trials was assessed through Cochrane Risk of Bias 2.0 tool (ROB2) and Consolidated Standards of Reporting Trials (CONSORT) 2010 statement (with elaborations for herbal interventions), respectively. Meta-analysis was conducted via Review Manager (RevMan) 5.4 software. 14 RCTs published from 2010 to 2020 were included in this review.

Results: There is some evidence to suggest that topical herbal treatments are useful in the treatment of psoriasis. The meta-analysis favoured herbal treatment over conventional medicines and placebo and the herbal treatments caused fewer side effects. Indigo naturalis, *Hypericum perforatum* L. oil (Hypericaceae) and *Curcuma longa* L. Zingiberaceae (Turmeric) were particularly promising, due to their possible anti-inflammatory effects.

Conclusions: There is some evidence to suggest the use of topical herbal medicines in the treatment of psoriasis. However, the quality of included RCTs was poor and at a higher risk of bias in many domains. Therefore, larger, better designed and long-term RCTs should be conducted to enhance the quality of the evidence.

Keywords: Psoriasis, topical treatment, herbal medicines, Risk of Bias, CONSORT statement, RCT.

1. Introduction

Psoriasis is a common chronic inflammatory cutaneous disorder (Hawkes, Chan, and Krueger 2017), which affects the scalp, nails, joints or systemic areas (Menter et al. 2008), affecting around 2-3% of the world's population (Parisi et al. 2013). Five common types of psoriasis were documented by the World Health Organization (WHO)

in 2016, including psoriasis vulgaris, intertriginous psoriasis, guttate psoriasis, pustular psoriasis and erythrodermic psoriasis (World Health 2016). Around 90% of psoriasis patients are categorised as having psoriasis vulgaris (Raychaudhuri, Maverakis, and Raychaudhuri 2014) with the characteristics of redness (erythema), scaly plaques (scaling) and excessive proliferation of keratinocytes (thickness) (Enamandram and Kimball 2013).

Unclear trigger factors and delayed treatment can increase the severity of the disease, causing distressing symptoms and impacting on the patient's quality of life (Hong, Koo, and Koo 2008; Garg et al. 2001). Apart from the obvious psoriasis symptoms, including skin soreness, itching and swelling, there is a risk of associated diseases, such as psoriatic arthritis (Gladman et al. 2005; Ibrahim, Waxman, and Helliwell 2009) and cardiovascular-related diseases (El-Mongy et al. 2010; Fang, Jiang, and Fan 2016). These can lead to serious physical damage (Cantini et al. 2010). Additionally, uncomfortable feelings of embarrassment when the psoriasis is seen by others enhance the possibility of psychological symptoms (Russo, Ilchef, and Cooper 2004), including anxiety and depression (Gupta and Gupta 1998) and, in severe cases, may lead to suicidal thoughts (Gupta et al. 1993). These problems make psoriasis a disease of global concern (Hay et al. 2014).

Although a variety of treatments have been developed, the high cost and safety concerns hinder their widespread use. Conventional treatments for psoriasis can be divided into several categories, including oral systemic medications (methotrexate, retinoids, cyclosporine, 6-thioguanine, mycophenolate mofetil and troglitazone), topical agents (corticosteroids, vitamin D analogues, topical retinoids, psoralen, salicylates, dithranol and fumaric acid esters), UV phototherapies (psoralen plus UV-A and UV-B), currently growing biological therapies (etanercept, infliximab and adalimumab) and the combinations of these treatments (Rahman et al. 2012). According to statistical data

from the United States in 2008, the annual cost of psoriasis treatment was approximately $11.25 billion (Bhutani et al. 2013). Adverse effects, such as potential organ toxicity and the inefficacy of treatments (Christophers et al. 2006), can cause dissatisfaction and disappointment in 52.3% of psoriasis patients (Armstrong et al. 2013). These factors can lead patients to avoid conventional medications or turn towards to alternative therapies.

Medicines derived from plants, such as herbal medicines including Traditional Chinese Medicines (TCM), are commonly regarded as being efficacious for many diseases, due to their structural diversity and multi-mechanisms of action (Keseroglu and Gönül 2014). They are also generally believed to have fewer side effects. Taking Chinese Herbal Medicine (CHM) as an example, *Tripterygium wilfordii* Hook. F. (Celastraceae; TwHF) has been applied to the treatment of psoriasis because of its immunomodulatory mechanism (Lv et al. 2018), although there are some safety concerns with these species, due to its effects on leukocyte production.

Other medicinal plants have also been found to be potential anti-psoriasis agents, such as *Matricaria chamomilla* L. (Asteraceae; Chamomile) (Deng et al. 2013a) and *Hypericum perforatum* L. (Hypericaceae; St John's wort) (Najafizadeh et al. 2012b).

Among all the treatments, topical medicines for psoriasis are widely used because they are likely to be the first, relatively safe option for patients with mild to moderate psoriasis (Feldman et al. 2008). Many reviews that have integrated topical herbal treatments for psoriasis were completed before 2015 (Deng et al. 2013a, 2013b, 2014). However, the number of human trials relating to psoriasis has dramatically increased in the past decade, resulting in a better understanding of psoriasis by researchers and physicians (Hawkes, Chan, and Krueger 2017), and, therefore, an update is timely. Given a rigorous qualitative assessment of each trial and the fulfilment of the five-year

gaps, this review aimed to critically evaluate the efficacy and safety of current topical psoriasis treatments containing herbal medicines.

2. Methods

2.1 Search strategy

This review complies with the statement of preferred reporting items for systematic reviews and meta-analyses (PRISMA) by using five electronic databases, namely PubMed, EMBASE, MEDLINE (via Ovid SP), CINAHL Plus, CENTRAL and Allied and Complementary Medicine (AMED). The retrieval time ranges from January 2010 to July 2020. Three categories of search terms were used as follows: condition (psoriasis vulgaris); intervention type (Traditional Chinese Medicine); and study type (Randomised controlled trial (RCT)). These terms were used individually and were combined together to reinforce the results. Full lists of search terms are shown in Supplementary material 1. Citations listed in relevant review articles were screened for additional studies. All references were exported to management software (EndNote) for further title and abstract screening.

2.2 Inclusion and exclusion criteria

RCT articles that compared TCM or herbal topical products with either placebo or active medicines, which were published in journals and written in English, were included. Participants included were diagnosed with psoriasis with no restriction on their age, sex, stage, area, duration or severity. Adverse events (AEs) and toxicology studies were considered as additional sources when evaluating the safety of products. *In vitro* studies, animal studies and studies not in the English language were excluded. Repeated publications or those with incomplete data were not considered. Publications not relevant to psoriasis treatment or not using either TCM or herbal medicine were

also excluded. Moreover, other treatments, such as injection therapy and acupuncture, were excluded.

2.3 Study Selection.

The selected papers were filtered through the PRISMA flowchart (Figure 1). Firstly, the title and the abstract of the articles were screened based on inclusion and exclusion criteria to remove irrelevant studies. Secondly, preliminary trials and studies without a full text were also discarded. Finally, the full texts of papers were screened to ensure that the studies matched the standard.

2.4 Data Extraction

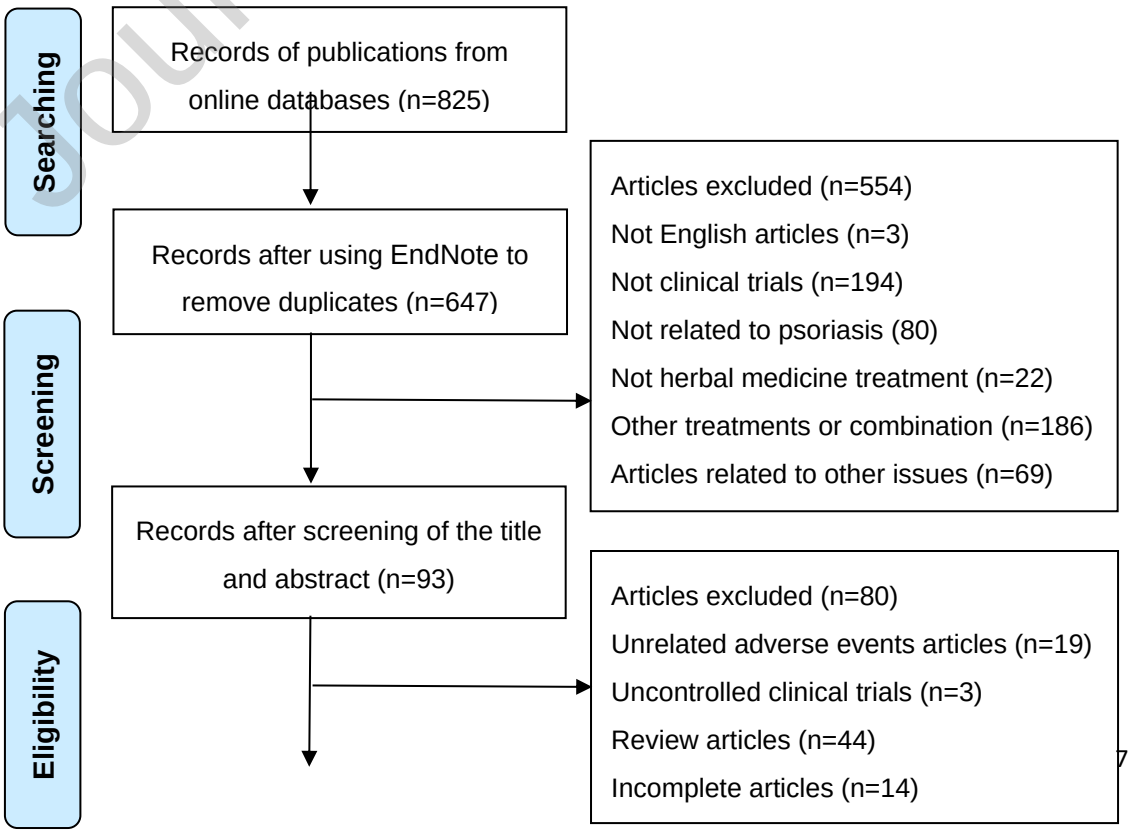
A data extraction form was developed based on previous similar articles (Deng et al. 2013b, 2014). The following information was collected: the name of the first author, year published, country, sample size, participant gender and age, diagnosis including area and duration of psoriasis, intervention, comparison, treatment duration and outcome. The number and the ratio of AEs were also recorded.

2.5 Quality assessment

The methodological quality of the eligible RCTs was assessed based on Cochrane Risk of Bias 2.0 tool (ROB2) (Sterne et al. 2019) criteria including: randomisation process, deviations from intended interventions, missing outcome data, measurement of the outcome, selection of the reported result and overall bias. The risk of bias of included studies was determined as either "low risk", "some concern" or "high risk" according to the judging criteria. Moreover, the Consolidated Standards of Reporting Trials (CONSORT) 2010 checklist (Schulz et al. 2010) and the elaborated CONSORT statements for trials with herbal medicines (Gagnier et al. 2006) were used to assess the reporting quality of included studies.

2.6 Data Analysis

The meta-analysis was performed using Review Manager (RevMan) 5.4 software. Only studies with similar design and outcome measurement were selected to accomplish the meta-analysis. Dichotomous data was expressed as odds ratio (OR) whereas continuous outcomes as mean difference (MD), with a 95 % confidence interval (95 % CI). If the statistical heterogeneity (I^2) was less than 50%, a fixed-effect model was used to calculate the estimated effect of intervention across trials, whereas a random effect model was applied when included studies were in a higher heterogeneity (I^2>50%).



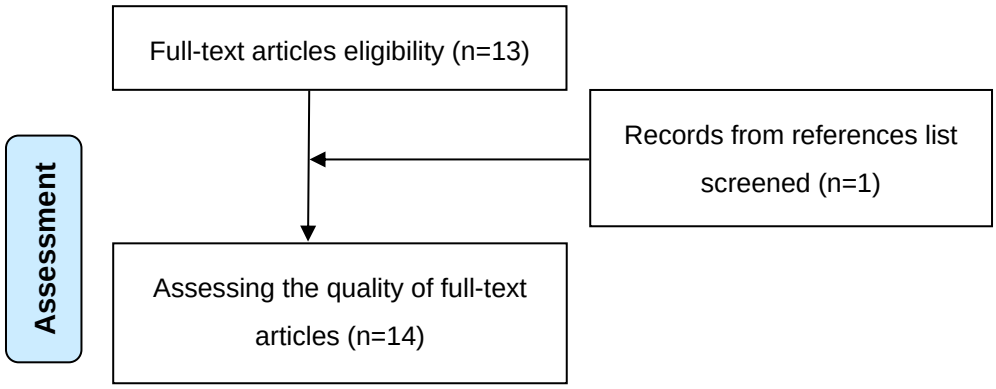


Figure 1. PRISMA flowchart of study selection process.

3. Results

3.1 Study Selection Process

825 potentially relevant studies were retrieved from electronic databases with 647 records left after removing duplicates. Another 554 articles were discarded in either the title or the abstract screening process because they did not meet the criteria for language, study design, patient conditions, studies interventions or treatment method. When considering the clinical trial conditions, study types and contents, 80 of 93 full-text articles were also excluded. 13 RCTs remained in this review, and one additional trial was collected from another review. A PRISMA flowchart describes the full study selection process (Figure 1).

3.2 Description of Studies.

The selected RCTs involved a total of 795 patients with the recruitment size ranging from 10 to 294. Participants were aged from 12 to 75 years. Most of the trials recruited a higher proportion of males than females, having three individuals not disclosing their gender.

There were two studies on nail psoriasis, and two trials reported the affected areas (trunk, arms or legs). Various descriptions of psoriasis were reported, such as mild to

moderate psoriasis, chronic plaque psoriasis or psoriasis vulgaris. Of all articles found, six trials compared the efficacy between intervention and control group on patients with bilateral symmetric lesions. In most of the trials, participants received treatment twice daily, but for different durations. Most trials were performed over 4 or 8 weeks, with the exception of one lasting 11 weeks and two trials lasting 24 weeks. The study with bath immersion treatment was only conducted over ten days. A summary of all included studies is shown in Table 1.

3.3 Intervention and comparator

Indigo naturalis, *H. perforatum*, curcumin, Pulian ointment, *M. chamomilla*, sea buckthorn, *Aloe vera, Gynura pseudochina* DC. var. *hispida* Thv. (Asteraceae) and herbal anti-inflammatory treatment (HAT1) were used in intervention groups in selected RCTs. Among them, Indigo naturalis was used in four trials with three being placebo controlled (Lin et al. 2014; Cheng, Wu, Wang, et al. 2017; Yan et al. 2015) and another with calcipotriol (Lin et al. 2015). Two studies used *H. perforatum* and two trials applied treatments containing curcumin as the intervention in all cases compared with placebo (Najafizadeh et al. 2012a; Mansouri et al. 2017; Sarafian et al. 2015; Shathirapathiy, Nair, and Hyndavi 2015). Similar study design could be seen in the other three trials with the Pulian ointment (Li et al. 2017), *M. chamomilla* preparation (Kolahdooz et al. 2018) and sea buckthorn (*Hippophae rhamnoides* L.) extract (Boca et al. 2019) as the herbal intervention. The use of conventional drugs as the control group was found in the remaining three RCTs. Two of the above three studies demonstrated the efficacy of 0.1% triamcinolone acetonide (TA) and herbal medicines, which were *Aloe vera* (L.) Burm.f. (Choonhakarn et al. 2010) and *Gynura pseudochina* DC. var. *hispida* Thv. (Asteraceae) (Rerknimitr et al. 2016), respectively. Another article implemented HAT1, which is an over-the-counter product approved by the US Food and Drug Administration (FDA) and compared with calcipotriol (Alex et al. 2020).

3.4 Outcome measurement

Outcome measures of all 14 RCTs are presented in Table 2. Psoriasis area severity index (PASI)-75, a reduction of 75% of the PASI score, was used for the end point of outcome in three selected studies (Choonhakarn et al. 2010; Cheng, Wu, Wang, et al. 2017; Alex et al. 2020), and two out of these three (Choonhakarn et al. 2010; Cheng, Wu, Wang, et al. 2017), as well as another article (Shathirapathiy, Nair, and Hyndavi 2015), which also provided the specific mean PASI scores before and after the treatment. Boca et al. (Boca et al. 2019), on the other hand, presented the individual PASI score at the baseline and endpoint. The changes in erythema, thickness, and scaling scores as a primary outcome measurement were reported in the other seven trials (Kolahdooz et al. 2018; Najafizadeh et al. 2012a; Rerknimitr et al. 2016; Sarafian et al. 2015; Mansouri et al. 2017; Li et al. 2017; Yan et al. 2015). The remaining two trials involving nail psoriasis reported single hand Nail Psoriasis Severity Index (shNAPSI) and modified target NAPSI (mtNAPSI) as their primary outcome (Lin et al. 2014; Lin et al. 2015). Quality of life (QoL) was only assessed in three trials while the Physician's Global Assessment (PGA) was evaluated in four studies to enhance the credibility of the results.

3.5 Patients lost to follow-up and adverse events (AEs)

Table 3 shows the number of patients lost to follow-up and suffering from AEs during the trials reported in the included RCTs. Nine studies (Lin et al. 2014; Lin et al. 2015; Kolahdooz et al. 2018; Choonhakarn et al. 2010; Cheng, Wu, Wang, et al. 2017; Alex et al. 2020; Yan et al. 2015; Li et al. 2017; Sarafian et al. 2015) reported the missing follow-up visits, with five of them (Lin et al. 2014; Lin et al. 2015; Cheng, Wu, Wang, et al. 2017; Li et al. 2017; Kolahdooz et al. 2018) clarifying reasons such as conflicts with work schedules for dropping out. In all 14 RCTs, no AEs were reported in three trials

(Lin et al. 2014; Najafizadeh et al. 2012a; Mansouri et al. 2017) while another two studies did not mention this information (Shathirapathiy, Nair, and Hyndavi 2015; Boca et al. 2019). Either an equal or a higher rate of AEs was reported in the control group when compared with the intervention group in the remaining trials (Yan et al. 2015; Li et al. 2017; Rerknimitr et al. 2016; Sarafian et al. 2015; Kolahdooz et al. 2018; Lin et al. 2015; Alex et al. 2020; Cheng, Wu, Wang, et al. 2017) with the exception of the trial completed by Choonhakarn et al. (Choonhakarn et al. 2010).

Table 1. Characteristics of included RCTs.

First author, Year; Location	Patients (R/A); Gender (M/F); Age (years): mean ± SD (range)	Diagnosis; Area	Intervention	Control	Duration
Alex, 2020 USA (Alex et al. 2020)	I:14/14, C:14/14; NS; I:41.1 ± 8.8, C:39.4 ± 6.3 (12-60)	Mild to moderate chronic psoriasis; Body	HAT1 spray[a]	Calcipotriol (0.005%)	Twice daily 11 weeks
Boca, 2019 Romania (Boca et al. 2019)	10/10; NS; > 18years old	Psoriasis with bilateral symmetric plaques; Body	Oily sea buckthorn extract	Placebo	Twice daily 8 weeks
Choonhakarn, 2010 Thailand (Choonhakarn et al. 2010)	I:40/37, C:40/38; I:17/21, C:19/19; I: 43.4 ± 11.2 (27-65), C: 44.2 ± 13.0 (23-71)	Chronic plaque psoriasis; Body	Aloe mucilage (70%) cream	Triamcinolone acetonide (TA) (0.1%)	Twice daily 8 weeks
Cheng, 2017 Taiwan (Cheng, Wu, Wang, et al. 2017)	I:16/16, C: 8/7; I:10/6, C: 7/1; I: 39.3 ± 10.1, C: 40.1 ± 10.9 (20-65)	Moderate psoriasis; Body	Indigo naturalis	Placebo	Twice daily 8 weeks
Kolahdooz, 2018 Iran (Kolahdooz et al. 2018)	40/37; 17/20; 36.8 ± 13.3 (20-60)	Mild to moderate plaque-type psoriasis with bilateral symmetric plaques; Upper and lower extremities.	ChP oleogel[b]	Placebo	Twice daily 4 weeks
Lin, 2014 Taiwan (Lin et al. 2014)	31/31; 24/7; 40.7 ± 12.6 (20-65)	Symmetrically comparable psoriatic nails; Nail	Indigo naturalis	Placebo	Twice daily 12 weeks,
Lin, 2015 Taiwan (Lin et al. 2015)	33/28; 22/11; 41.9 ± 9.4 (20-65)	Symmetrically comparable psoriatic nails; Nail	Indigo naturalis	Calcipotriol	Twice daily 24 weeks,
Lin, 2017 China (Li et al. 2017)	I:149/143, C:145/135; I:78/65, C:74/61; I: 40 ± 13, C: 36 ± 12 (18-65)	Psoriasis vulgaris of blood-heat syndrome; Body	Pulian ointment[c]	Placebo	Twice daily 4 weeks

First author, Year; Location	Patients (R/A); Gender (M/F); Age (years): mean ± SD (range)	Diagnosis; Area	Intervention	Control	Duration
Mansouri, 2017 Iran (Mansouri et al. 2017)	20/11; 3/8; 41.25 ± 14.24 (18-55)	Mild to moderate plaque-type psoriasis with bilateral symmetric plaques; Body	*Hypericum perforatum* L.	Placebo	Twice daily 4 weeks
Najafizadeh, 2012 Taiwan (Najafizadeh et al. 2012a)	10/10; 5/4; (20-55)	Mild plaque psoriasis with bilateral symmetric lesions; Body	*Hypericum perforatum* L.	Placebo	Twice daily 4 weeks
Rerknimitr, 2016 Thailand (Rerknimitr et al. 2016)	25/25; 13/12; 48.6 (19–80)	Chronic plaque psoriasis with bilateral symmetric lesions; Trunk, arms and legs	*Gynura pseudochina* DC. var. *hispida* Thv.	Triamcinolone acetonide (TA) (0.1%)	Twice daily 4 weeks
Sarafian, 2015 Iran (Sarafian et al. 2015)	40/34; 20/14; 31.7(18-60)	Mild to moderate psoriasis with bilateral symmetrical lesions; Legs and arms	Microemulsion: 0.5% curcumin	Placebo	Twice daily 3 weeks
Shathirapathiy, 2015 India (Shathirapathiy, Nair, and Hyndavi 2015)	I:30/30, C:30/30; I:21/9, C:19/11; I:40.81 ± 13.39, C: 32.33 ± 8.70 (20-60)	Psoriasis; Body	Starch fortified turmeric bath	Naturopathy	10 days
Yan, 2015 China (Yan et al. 2015)	I:50/45, C:50/48; I:34/16, C:30/20; I:46.9 ± 11.3 (21-64), C: 44.7 ± 12.2 (22-64)	Chronic plaque-type psoriasis; Body	SDRG ointment[d]	Placebo	Twice daily 8 weeks

Abbreviations: R/A, registration/analysis; M/F, male/female; NS, not stated; I, intervention group; C, control group.

[a]HAT1 spray: 20% of extract containing *Achillea millefolium, Aesculus hippocastanum, Althaea officinalis, Avena sativa, Berberis vulgaris, Cochlearia officinalis, Conium maculatum, Ervumlens, Hamamelis virginiana, Hydrastis canadensis, Malva sylvestris, Matricaria chamomilla, Nasturtium officinale, Phytolacca decandra, Pimpinella saxifraga, Populus alba, Populus tremuloides, Rhus toxicodendron, Sambucus nigra, Sanguinaria canadensis, Scrophularia nodosa, Smilax medica, Tussilago farfara, Veronica officinalis and Vincetoxicum officinale* in a 5% ethanol solution.

[b]ChP oleogel: *Matricaria chamomilla* oil (direct heat method), *Cucurbita pepo* seed oil, and colloidal silicon dioxide (47.5%: 47.5%: 5%).

[c]Pulian ointment: *Phellodendron amurense* Rupr. (Huang Bai), *Scutellaria baicalensis* Georgi (Huang Qin), and white petroleum jelly

[d]SDRG ointment: Indigo naturalis (Qing Dai), Cortex Phellodendri (Huang Bai), Gypsum (Duan Shi Gao), Smithsonite (Lu Gan Shi), and Gallae Rhois Chinensis (Wu Bei Zi).

Table 2. Outcome measures of included RCTs.

Publication	**PASI score; Changes**	**Psoriasis lesions**			**Other measures**
		Erythema	**Scaling**	**induration**	
Alex, 2020 (Alex et al. 2020)	PASI 75: I = 85.7%, C = 21.4% (p < 0.01)	-	-	-	PGA reduction >1: I= 78.57%; C= 21.43%
*Boca, 2019 (Boca et al. 2019)	I > C	-	-	-	DLQI: (P=0.002)
Choonhakarn, 2010 (Choonhakarn et al. 2010)	PASI 75: I = 16.2%, C = 10.5%; I = from 11.6 to 3.9, C = from 10.9 to 4.3 (p = 0.0237)	-	-	-	DLQI: I = from 8.6 to 2.5, C = from 8.1 to 2.3 (p = 0.5497)
Cheng, 2017 (Cheng, Wu, Wang, et al. 2017)	PASI 75: I = 56.3%, C = 0%; I = from 10.1 ± 4.3 to 2.64 ± 1.5, C = from 11.1 ± 3.7 to 8.30 ± 4.0 (p = 0.01)	-	-	-	PGA (0-6) I = from 3.0 ± 0.5 to 1.31 ± 0.9, C = from 3.3 ± 0.5 to 2.86 ± 1.5 (p = 0.03)

Publication	PASI score; Changes	Psoriasis lesions			Other measures
		Erythema	Scaling	induration	
*Kolahdooz, 2018 (Kolahdooz et al. 2018)	-	Scale (0-8) I = from 3.44 ± 1.36 to 2.44 ± 1.21, C = from 3.34 ± 1.25 to 3.21 ± 1.22; Decline: I = 1 ± 1, C = 0.13 ± 0.48	Scale (0-8) I = from 4.09 ± 1.38 to 2.28 ± 1.55, C = from 3.80 ± 1.30 to 3.63 ± 1.34; Decline: I = 1.80 ± 1.1, C = 0.17 ± 0.87	Scale (0-8) I = from 3.46 ± 0.93 to 2.17 ± 0.96, C = from 3.27 ± 0.95 to 3.09 ± 0.99; Decline: I = 1.28 ± 1.03, C= 0.17 ± 0.58	-
		Sum (0-24): I = from 11 ± 2.64 to 6.90 ± 3.04, C = from 10.42 ± 2.71 to 9.94 ± 2.56 Decline: I = 4.09 ± 2.24, C = 0.48 ± 1.39			
Lin, 2014 (Lin et al. 2014)	shNAPSI: I = 10.7 ± 6.2, C = 15.5 ± 6.2 (p < 0.0001); mtNAPSI: I = 5.5 ± 3.4, C = 10.3±5.0 (p < 0.0001)	-	-	-	PGA (0-6): I = 2.8 ± 1.2, C = 1.2 ± 1.1 (p < .001); SGA score: I = 2.4 ± 1.1, C = 1.2 ± 1.2 (p < .001)
Lin, 2015 (Lin et al. 2015)	shNAPSI: I = 14.4 ± 8.9, C = 20.4 ± 8.5 (p < 0.001); mtNAPSI: I = 5.9 ± 4.1, C = 9.5 ± 5.2 (p < 0.001)	-	-	-	-
Lin, 2017 (Li et al. 2017)	Decline: I = 2.49, C = 1.78 (p = 0.043)	Decline: I = 0.44, C = 0.35 (p = 0.12)	Decline: I = 0.4, C = 0.32 (p = 0.15)	Decline: I = 0.42, C = 0.36 (p = 0.29)	SF-36 and HAMA;
*Mansouri, 2017 (Mansouri et al. 2017)	-	Scale (0-3) Decline: I > C (p = 0.014)	Scale (0-3) Decline: I > C (p =0.003)	Scale (0-3) Decline: I > C (p = 0.002)	Pruritus: I > C (p = 0.008)

Publication	PASI score; Changes	Psoriasis lesions			Other measures
		Erythema	Scaling	induration	
*Najafizadeh, 2012 (Najafizadeh et al. 2012a)	-	Scale (0-3) I = from 2.6 ± 0.5 to 1.1 ± 0.74, C = from 2.6 ± 0.7 to 1.9 ± 0.74 (p = 0.01)	Scale (0-3) I = from 2.5 ± 0.85 to 0.7 ± 0.48, C = from 2.4 ± 0.52 to 2.1 ± 0.57 (p = 0.004)	Scale (0-3) I = from 2.4 ± 0.52 to 1.1 ± 0.74, C = from 2.1 ± 7.4 to 1.8 ± 0.42 (p = 0.04)	-
*Rerknimitr, 2016 (Rerknimitr et al. 2016)	-	Scale (0-4) I = from 1.96 ± 0.45 to 1.08 ± 0.57, C = from 1.96 ± 0.45 to 1.12 ± 0.44	Scale (0-4) I = from 1.64 ± 0.70 to 0.44 ± 0.58, C = from 1.64 ± 0.70 to 0.80 ± 0.71 (p = 0.03)	Scale (0-4) I = from 1.68 ± 0.48 to 0.68 ± 0.48, C = from 1.68 ± 0.48 to 0.76 ± 0.52	PGA: (p = 0.375); SAS: I > C (p = 0.034)
		Sum (0-12): I = From 5.28 ± 1.10 to 2.2 ± 1.08, C = From 5.28 ± 1.06 to 2.68 ± 1.44			
*Sarafian, 2015 (Sarafian et al. 2015)	Improvement: I > C (p < 0.05)	Improvement: I > C (p < 0.05)			-
Shathirapathiy, 2015 (Shathirapathiy, Nair, and Hyndavi 2015)	I = from 23.2 ± 8.7551 to 9.273 ± 5.4745, C = From 22.983 ± 9.4150 to 22.830 ± 8.7768	-	-	-	-
Yan, 2015 (Yan et al. 2015)	-	Scale (0-4) week 8: I = 1.2 ± 0.7, C = 1.9 ± 0.8	Scale (0-4) week 8: I = 0.8 ± 0.9, C = 1.7 ± 0.8	Scale (0-4) week 8: I = 0.8 ± 0.9, C = 1.5 ± 0.9	-
		Sum (0-12): I = from 6.4 ± 1.3 to 2.7± 2.2, C = from 6.4 ± 1.6 to 5.1 ± 2.1; decline: I = 3.8 ± 1.9, C = 1.3 ± 1.4 (p < 0.0001)			

*indicates that the intra-patient with the intervention and control treatment was applied bilaterally on symmetrical lesions (the intra-patient application).

Abbreviations: I, intervention group; C, control group; PASI, Psoriasis Area Severity Index; PGA, Physician's Global Assessment; DLQI, Dermatology Life Quality Index; shNAPSI, single hand Nail Psoriasis Severity Index; mtNAPSI, modified target NAPSI; SGA, subject global assessment; HAMA, Hamilton Anxiety Rating Scale; SF-36, 36-Item Short Form Health Survey; SAS, Self-Assessment Score.

Table 3. Adverse events reported in the included RCTs.

Publication	Lost follow-up	Adverse events (AEs) (number of patients)		AE rate (%)	
	Numbers	Intervention group (I)	Control group (C)	I	C
Alex, 2020	I:1, C:2	0	Burning and irritation (3)	0%	25%
Boca, 2019	0	Not mentioned	Not mentioned	-	-
Choonhakarn, 2010	I:3, C:2	Stinging and itching (6)	0	16.2%	0%
Cheng, 2017	1	Pruritus (4), Rash (2), Nasopharyngitis (2), Abdominal distension (1), Constipation (1), Cough (1), Dizziness (1), Oropharyngeal pain (1).	Pruritus (1), Gout (1), Allergies (1), Pyrexia (1)	44%	50%
Kolahdooz, 2018	3	Itching and Irritation (3) I>C		7.5%	7.5%
Lin, 2014	1	0	0	0%	0%
Lin, 2015	5	Irritation (2)	Irritation (10)	6.1%	30.3%
Lin, 2017	I:17, C:17	0	Itch (1)	0%	0.78%
Mansouri, 2017	0	0	0	0%	0%
Najafizadeh, 2012	0	0	0	0%	0%
Rerknimitr, 2016	0	Stinging (3), Itch (7)	Itch (7), Hypopigmentation (3)	40%	40%
Sarafian, 2015	6	Dryness (~2), Burning (~2), Irritation (~1)		15%	15%
Shathirapathiy, 2015	0	Not mentioned	Not mentioned	-	-
Yan, 2015	I:5, C:2	0	Mild worsening of psoriasis (2)	0%	4.17%

3.6 Methodological quality

Nine RCTs provided the details of random sequence generation either in their protocol or final report (Choonhakarn et al. 2010; Lin et al. 2014; Lin et al. 2015; Rerknimitr et al. 2016; Mansouri et al. 2017; Kolahdooz et al. 2018; Shathirapathiy, Nair, and Hyndavi 2015; Li et al. 2017; Alex et al. 2020). However, only four of these nine studies reported the allocation concealment and had a similar baseline between the treatment and the control group (Kolahdooz et al. 2018; Choonhakarn et al. 2010; Mansouri et al. 2017; Li et al. 2017). Six trials used insufficient blinding either in participants or personnel (Lin et al. 2014; Lin et al. 2015; Yan et al. 2015; Alex et al. 2020; Rerknimitr et al. 2016; Shathirapathiy, Nair, and Hyndavi 2015). However, two of these trials (Alex et al. 2020; Shathirapathiy, Nair, and Hyndavi 2015) claimed that there were no changes between intervention groups, and an intention-to-treat (ITT) analysis was used to estimate the treatment effects. Therefore, the assessment of this domain remained as "low risk". Conversely, another double-blinded study was assessed as "high risk" because the method of analysing the treatment efficacy was unknown (Cheng, Wu, Wang, et al. 2017).

Five trials employed the intra-individual, right-left comparative study designs, suggesting that the result may not be influenced by whether follow up data is missing or not (Choonhakarn et al. 2010; Yan et al. 2015; Lin et al. 2015; Mansouri et al. 2017; Kolahdooz et al. 2018), whereas one study was found to have an apparent difference between ITT and per-protocol set (PPS) and was therefore assessed as "high risk" in this domain (Li et al. 2017). Four of 14 RCTs were insufficiently blinded for the evaluators, which gave a high risk in the field of outcome measurement (Alex et al. 2020; Boca et al. 2019; Najafizadeh et al. 2012a; Rerknimitr et al. 2016). Six out of all studies were classified into "low risk" for the selection of the reported result sector owing to the consistency of outcomes with pre-specified methods (Alex et al. 2020; Cheng, Wu, Wang, et al. 2017; Li et al. 2017; Kolahdooz et al. 2018; Sarafian et al.

2015; Lin et al. 2015). Overall, there were five "high risk" studies, and others were assessed as "some concerns."

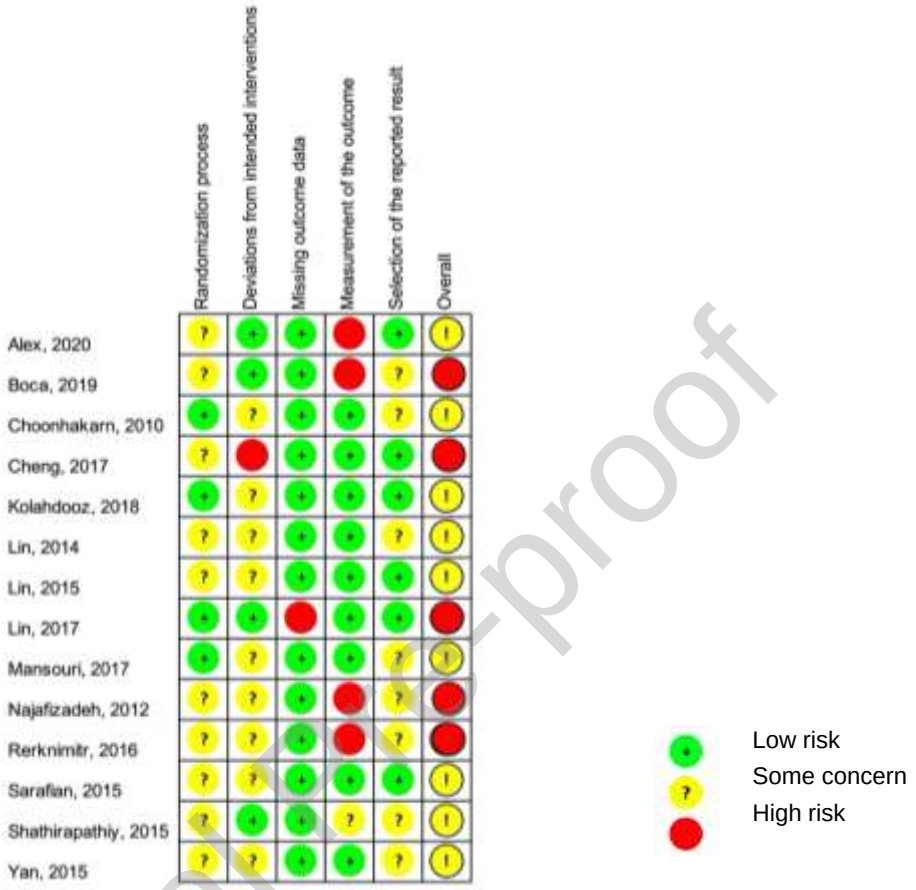


Figure 2: Risk of bias assessment.

3.7 Reporting quality

Full assessments of reporting quality are shown in Supplementary material 2. The percentages of studies failing to conform with the CONSORT checklist are presented in Table 4. Most of the RCTs (93) gave adequate information about background, objectives and hypotheses in the introduction. More than half of the RCTs (ranging from 50 to 71%) poorly reported the description of randomisation, including sequence generation, allocation concealment, implemented person and blinding. Nearly half of the trials failed to show a flow diagram and baseline score as recommended in the CONSORT statement in the results sections. 50% of RCTs did not indicate their limitations while 29% of the included studies missed or unclearly described the

interpretation of findings and generalisability in the discussion sections. Only one study had a protocol that could be found online and just over half of the trials (57%) were registered.

Table 4. Rates of non-adherence to reporting standards provided in the (CONSORT) 2010 statement and Elaborated statement for Herbal intervention for the RCTs (n=14) included.

Section/Topic	**Item No**	No. (%)	
Title and abstract	1	14	(100)
Introduction	2	1	(7)
Methods			
Trial design	3	0	(0)
Participants	4	8	(57)
Interventions	5	12	(86)
	5A (Herbal medicinal product name)	14	(100)
	5B (Characteristics of the herbal product)	14	(100)
	5C (Quantitative description)	11	(79)
	5D (Qualitative testing)	13	(93)
	5E (Placebo/Control group)	8	(57)
	5F (Description of the practitioners)	14	(100)
Outcomes	6	6	(43)
Sample size	7	10	(71)
Randomization			
Sequence generation	8	8	(57)
Allocation concealment	9	9	(64)
Implementation	10	10	(71)
Blinding	11	10	(71)
Statistical methods	12	0	(0)
Results			
Participant flow	13	6	(43)
Recruitment	14	10	(71)
Baseline data	15	5	(36)
Numbers analysed	16	1	(7)
Outcomes	17	0	(0)
Ancillary analyses	18	0	(0)
Harms	19	2	(14)
Discussion			
Limitations	20	5	(36)
Generalisability	21	4	(29)
Interpretation	22	4	(29)
Other information			
Registration	23	6	(43)
Protocol	24	13	(93)
Funding	25	3	(21)

3.8 Effects of Interventions

Due to the variety of study designs and results reported in all 14 RCTs, only seven studies were selected to compare the effects of interventions. These seven trials were separated into three categories according to the control groups used and the standard used for measuring the results. The first two groups, evaluating the effectiveness of herbal medicines for psoriasis, were further divided into the first and second group, because of the differences in control groups, with the former using conventional drugs and latter using placebo. The last category included studies mainly assessing the effects of Lindioil in nail psoriasis.

3.8.1 Effects of herbal medicine on psoriasis

Calcipotriol and TA are two common conventional topical medicines used to treat psoriasis. When the above two drugs were compared with herbal medicines, namely HAT1 spray (Alex et al. 2020) and Aloe cream (Choonhakarn et al. 2010), respectively, in group 1 of the meta-analysis (Figure 3), there was a higher heterogeneity in statistical analysis (P = 0.07, I^2 = 70%). Therefore, a random-effect model was reported. The pooled result of PASI-75 was statistically significant based on the meta-analysis, showing that these two herbals tend to be more effective than current conventional drugs in treating psoriasis (OR: 4.31 [95%CI: 0.55, 33.51]).

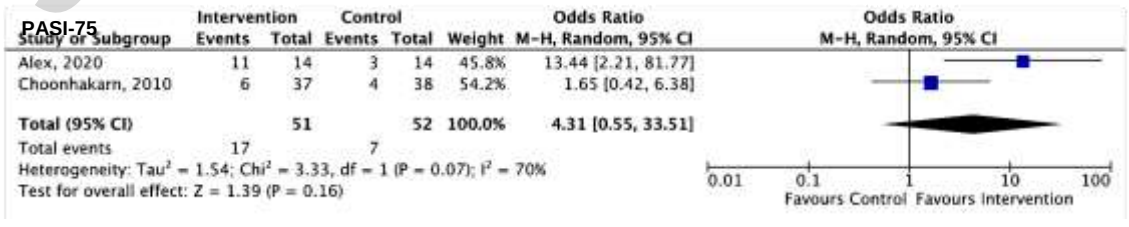


Figure 3. Effects of herbal medicines for psoriasis compared with active interventions.

Compared to placebo, the intervention group treatment was more likely to reduce the severity of erythema, scaling and induration in three studies (Figure 4). A significant difference was found in terms of erythema (MD: -0.73 [95%CI: -0.98, -0.48], I^2 =0%)

and induration (MD: -0.86 [95%CI: -1.11, -0.62], I^2 =0%) scores with no heterogeneity between these three trials, whereas a higher heterogeneity was reported when evaluating the scaling scores (MD: -1.11 [95%CI: -1.68, -0.61], I^2 =69%).

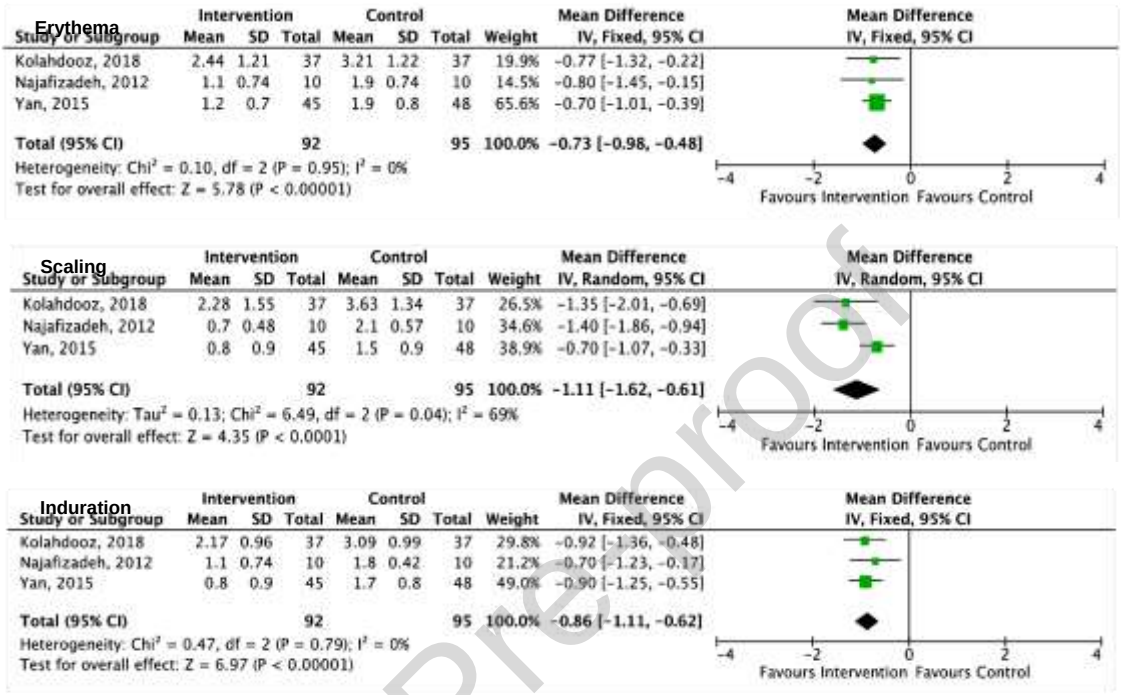
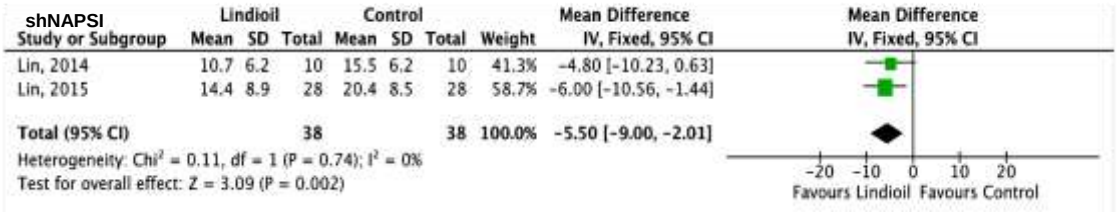


Figure 4. Effects of herbal medicines for psoriasis compared with placebo.

3.8.2 Lindioil (Indigo naturalis oil) for nail psoriasis

Group 3 showed that regardless of whether the control group was placebo (Lin et al. 2014) or calcipotriol (Lin et al. 2015), the shNAPSI (MD: -5.50 [95%CI: -9.00, -2.01], I^2 =0%) and mtNAPSI (MD: -3.96 [95%CI: -6.01, -1.91], I^2 =0%) scores were lower in those who received Lindioil therapy. These results indicate that the efficacy was higher in the treatment of Lindioil when compared with either placebo or Calcipotriol. The statistical heterogeneity between these two trials was low.



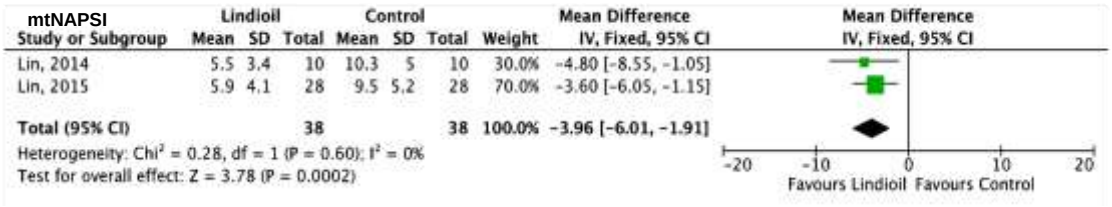


Figure 5. Effects of Lindioil for nail psoriasis.

4. Discussion

The present review may be the first study that critically evaluates the methodological and reporting quality of RCTs regarding the clinical efficacy and safety of topical herbal medicines in the treatment of psoriasis. These results show that overall, herbal preparations seem to be more efficacious than placebo and even standard drugs. However, because of the generally low or substandard quality of these RCTs the validity of evidence is limited. This meta-analysis points to the urgent need for high quality, carefully designed primary clinical trials.

4.1 Efficacy and safety of herbal products

Most of the studies stated that topical herbal formulations resulted in a significant improvement in psoriasis in comparison with either placebo or conventional therapy. However, only trials with similar outcome assessment were included in the clinical efficacy meta-analysis. In a small number of included studies, the differences between intervention and control group and the study design diversity make the results of group 1 and group 2 questionable. Two similar RCTs in group 3 were probably performed by the same team, giving doubts over the repeatability of the study.

Herbal medicines generally perform well regarding safety and clinical superiority compared with standard treatments. However, it is surprising that Choonhakarn et al. (Choonhakarn et al. 2010) reported a higher AEs rate in the application of Aloe cream, (mainly mild itching). Three trials recorded the same proportion of AEs between the two

groups. Considering that their study designs mainly compared the treatment for bilateral symmetric plaques, the fact that the percutaneous treatment mechanism is unknown suggests that it is unclear whether AEs were caused by herbals, placebo vehicles or control interventions. Therefore, it is assumed that herbal medicines are generally safe in topical use. However, the history of allergenic ingredients in formulations remains a concern to prevent AEs. RCTs with a longer treatment time are also required to better ensure the safety of the long-term use of topical herbal medicines.

4.2 Potential therapeutic actions

Many plants were administered in the included RCTs as they have suggested activities relevant to treatment of psoriasis e.g., anti-inflammatory. The most commonly used herbals in these trials were Indigo naturalis, *H. perforatum* and *C. longa* (Turmeric). A better understanding of the mechanisms of action of these medicinal plants would aid in the development of more rigorously evaluated topical psoriasis medicines.

Indigo naturalis is a TCM known as Qing Dai, derived from several indigo plants, including *Baphicacanthus cusia* (Nees) Bremek. (Acanthaceae) (Koo and Arain 1998). Recent relevant studies demonstrated biological activities, including antipyretic, anti-inflammatory (Lin et al. 2009), antitumor and antiviral effects (Zhang et al. 2019). Two active constituents of Indigo naturalis, indirubin and tryptanthrin, have demonstrated anti-inflammatory and immune regulatory activities *in vitro*. The former has been reported to inhibit cyclin-dependent kinase (Hoessel et al. 1999; Leclerc et al. 2001) and the activities of the signal transducer and activator of transcription-3 (STAT3) (Nam et al. 2005; Schwaiberger et al. 2010), a transcription factor helping in the differentiation of the T-helper cell 17 (Th17). The latter has been shown to suppress

many immune system modulators, such as interferon-γ (Takei et al. 2003), NO and prostaglandin E2 (Ishihara et al. 2000).

Moreover, one of the included studies has showed that tryptanthrin can inhibit the activity of interleukin-17 (IL-17) secreted by TH17 (Cheng, Wu, Wang, et al. 2017). Unsurprisingly, the extract of whole Indigo naturalis also has been proven to exhibit certain anti-inflammatory effects, especially inhibition of the O^{2-} generation and the release of elastase in neutrophils (Lin et al. 2009). However, individual metabolites, such as indirubin and tryptanthrin, did not show the same activity when compared to extracts. Therefore, although their potential synergistic effects and interactions are still unclear, the relationship between these two compounds and their linked influence on Th17 via STAT3 and IL-17 are probably useful directions for further study.

H. perforatum is a traditional herbal used in wound healing (Fahimi et al. 2015) (Yadollah-Damavandi et al. 2015), due to its anti-inflammatory, anti-bacterial activities (Akhbari, Batooli, and Mozdianfard 2012) and the ability of activating fibroblast and epithelial cell proliferation (Füller and Müller-Goymann 2018). The extracts of this plant have been reported to decrease the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) (Bezakova, Psenak, and Kartnig 1999), linked to a borad-spectrum inhibition of NF-κB (Bork et al. 1999), interleukin-6 (IL-6) (Gobbi et al. 2004), T lymphocyte (Schempp et al. 2002) and the accumulation of inflammatory cells. Its constituents, such as hypericin, quercin and amentoflavone, also demonstrated a downregulation in activity of tumour necrosis factor alpha (TNFα) or its production (Askari et al. 2012). However, some scientists suggested that there was a difference in the potency of anti-inflammatory effects between different extracted solvents and single molecules (Sosa et al. 2007). Hence, like most herbals, the synergistic interactions of constituents in *H. perforatum* need to be assessed further. On the other hand,

(Najafizdeh et al. 2012b; Boiy et al. 2008) assumed that the photodynamic activity of *H. perforatum* exhibited similar mechanisms as UV phototherapy (Najafizadeh et al. 2012a). If the hypothesis is successfully supported experimentally, it can be the model of potential topical psoriasis therapeutic mechanisms and create a new method in the search for new anti-psoriasis agents.

Turmeric, the radix and rhizome of *C. longa*, has been extensively used as a food, spice and wound treatment (Araujo and Leon 2001). The major component of this plant, curcumin (Chattopadhyay et al. 2004), was suggested to be used in many skin disorders linked to antioxidant (Ruby et al. 1995) and anti-inflammatory properties (Araujo and Leon 2001; Chattopadhyay et al. 2004; Thangapazham, Sharma, and Maheshwari 2007). From the point of view of psoriasis treatment, curcumin, with the effective downregulation of pro-inflammatory cytokines, in particular TNFα, interleukin 1, 6 and 8 (IL-1, IL-6 and IL-8) cytokines and enzymes (cyclooxygenase-2 (COX-2) and 5-lipoxygenase (5-LOX)), could reduce the symptoms of inflammation and redness (Aggarwal, Surh, and Shishodia 2007; Rahman et al. 2012). Moreover, the property of hyperproliferation suppression also supports the view of its psoriasis therapy. The phosphorylase kinase (PhK) activity showed a higher expression in psoriasitic than normal skin (Heng, Song, and Heng 1994). Curcumin as a selective PhK inhibitor, therefore, could decrease its level, leading to a lower expression of keratinocyte transferrin receptor and parakeratosis severity (Aggarwal, Surh, and Shishodia 2007; Heng et al. 2000). In short, both the inhibition of pro-inflammatory cytokines and cell proliferation could be the reasons that curcumin is a remarkable anti-psoriatic agent.

To sum up, regardless of any mechanisms involved in the treatment of psoriasis, the issues of chemical complexity around herbals, along with their combined usage and

the association with excipients in formulations should not be ignored when discovering new anti-psoriasis agents.

4.3 Quality of RCTs and Recommendations for Further Studies

Although much more attention is being paid to the quality of RCTs and their adherence to standard procedures, there still remains methodological issues not immediately apparent in the selected studies. Moreover, the rates of studies adherent to the CONSORT statement (Schulz et al. 2010) were relatively low. However, these trials do demonstrate specific effects on the topical treatment of psoriasis and could be an important reference point for the further improvement of RCTs.

All selected RCTs were non-compliant with the CONSORT statement because of the vague description of specific items in their abstract section (Hopewell et al. 2008). For example, most of the selected RCTs only offer the English name without the scientific name of the plants. Some studies related to TCM or herbal products, which included a long list of plants, may also fail to present the scientific name of each plant in the abstract. These problems should be addressed, and standards should be set in the further CONSORT statement.

Apart from the deficiency in the abstract section, a lack of description compliant with the CONSORT statement for herbal medicine interventions (Gagnier et al. 2006) in the method section of studies also points to limitations. Commonly, the chemical profile of the extract or the formulation are missing (Heinrich et al 2022). This makes such trials non-reproducible. Another concern are problems with the design of the study, like in the trial by Li et al. (2017). Here the lack of positive results may have been caused by the therapeutic effects of the excipients in both the treatment and the placebo group. Accordingly, both groups showed similar results in the reduction of psoriasis symptoms. Moreover, different formulations may influence the skin penetration rate of compounds,

resulting in the various effects of the same active compound and some of the safety concerns regarding products (Yu Heng et al. 2015). In short, the report of chemical composition for both plants and their final products plays a significant role in validating the results of RCTs.

Another considerable concern is that the dosage and treatment time were poorly described in all selected articles. Unlike oral treatment with well-defined information on dosage, for topical application, it is hard to determine the amount used in each application, also because of differences in the size and severity of the affected area. The description of "twice daily" without a specific time point is likely to cause variation in outcomes. Therefore, to establish the general guidelines for topical treatment (Altman et al. 2001), the dosage needs to be given unambiguously. An unclear description such as ‘one fingertip unit each time’ for ointment is insufficient.

Despite the fact that all the selected trials stated that participants were randomised to intervention groups, only five of them reported the allocation concealment (Alex et al. 2020; Li et al. 2017; Cheng, Wu, Wang, et al. 2017; Choonhakarn et al. 2010; Kolahdooz et al. 2018). One of these had an imbalanced baseline between the intervention and control group (Alex et al. 2020), leading to some risk of bias in this domain. Both the randomisation process and the baseline balance could affect the result of the risk of bias in trials. The loss of follow up on some of the patients during the treatment did not raise the risk of bias due to the intra-patient study design. However, the potential percutaneous absorption seems to lead the active compound to expose from one side to the contra-lateral, resulting in the possibility of therapeutic effects in both intervention and control groups (Lin et al. 2008). Hence, the separation of treatment and control groups into different patients may be better for further similar RCTs. In addition, most of the included RCTs applied self-formulated drugs, which may

also suggest an interest-related bias. Future trials should adhere to the CONSORT statement and correctly report the randomisation and blinding information to reduce the risks of bias.

Consistent and standardised diagnosis and outcome measures could also enhance the quality of evidence in RCTs. According to traditional Chinese medicine theory, blood heat, blood dryness and blood stasis psoriasis are three separately diagnosed conditions, whereas the biomedical system classifies this skin disease by its stage and type, such as mild and moderate plaque psoriasis. The standardization of these two systems is necessary to further integrate the evidence in the treatment of this skin disorder. In terms of outcome measures, PASI is recommended by the FDA (Food and Administration 1998; Mease et al. 2000) and the European Medicines Agency (EMA) (Weger 2010), However, considering the link between mental health and psoriasis, psychological investigating and QoL should also be considered in RCTs (Carlin et al. 2004). In the selected studies, only five trials reported the improvement of QoL (Alex et al. 2020; Boca et al. 2019; Choonhakarn et al. 2010; Lin et al. 2014; Li et al. 2017). Therefore, outcome measures including both physical and psychological aspects should play an essential role in future RCTs of psoriasis.

4.4 Limitations

A noticeable limitation in this review is that only English databases were used, meaning some potential efficacious Chinese medicines and herbal medicines used in other traditions, were omitted. Additionally, although studies have already been selected ranging from nearly a decade, a lack of standardisation of the RCTs implemented showed a bias in these trials, decreasing the reliability of results. Similarly, the various methods used in outcomes measurement hindered the comparison of trial results and the use of meta-analyses, reducing the number of included studies, suggesting a

potential bias in the meta-analyses results. Group 1, with only two studies, in particular, provided completely different intervention and control groups. Here the conclusion that herbal medicines are more beneficial than standard drugs in topical psoriasis treatment is less robust.

5. Conclusion

The results of this review suggest that topical herbal formulations may have some benefit for psoriasis as a topical treatment and are relatively safe in short-term application. The pharmacological actions of three herbal medicines - Indigo naturalis, *H. perforatum* and *C. longa* (turmeric), including their anti-inflammatory activity and the control of growth factors, might explain the reduction in symptoms and provide directions for studies in chemical and pharmacological fields. However, the weaknesses of methodology and reporting in the selected RCTs limited the reliability of the results. Therefore, higher quality RCTs, with a larger number of patients and more extended visits, are necessary for the development of topical psoriasis medicines.

Funding: None. WST was a self-funded MSc student in ‘Medicinal Natural Products’ at the UCL School of Pharmacy

Declaration of Competing Interest: No conflicts to declare.

Appendix A. Supplementary data

Supplementary material related to this article can be found in the online version.

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Conflict of Interest Statement

To the best of our knowledge, the named authors have no conflict of interest, financial or otherwise.