Integrated Western and Chinese Medicine Interventions for Atopic Dermatitis: A Systematic Review and Meta-analysis

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Research

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Abstract

Background

Atopic Dermatitis (AD) is a chronic relapsing skin disease characterized by recurring episodes of itchiness with skin erythema and surface damages. Chinese medicine (CM) is widely used for the management of AD in China not only by its own, but also used in combination with conventional therapy (integrated Western-Chinese medicine, ICWM) in China. Although many clinical trials on the effectiveness of ICWM on AD have been reported; however, up to date, no sound evidence has been established on the clinical effectiveness and safety of ICWM for AD.

Objectives

To systematically review the currently available clinical evidence on the clinical effectiveness and safety of ICWM for AD.

Methods

Randomized and quasi-randomized controlled trials, which investigated ICWM interventions with at least one control group using the same conventional interventions, no treatment or placebo treatment, were included. Four English (CENTRAL, MEDLINE, EMBASE, AMED) and three Chinese (CNKI, CBM, WanFang Med) databases were searched. Risk of bias was assessed according to the Cochrane's tool. Meta-analysis were performed to pool the data.

Results

From 1473 database entries, 55 studies were included, of which 5953 participants aged between 35 days to 67 years old were involved. Duration of treatment ranged from 1 to 24 weeks. Only 2 studies were judged to be at low risk of bias, 3 studies at unclear risk of bias, and the other 50 studies at high risk of bias. The research findings suggested that ICWM was superior over WM alone in improving clinical severity of AD (measured by EASI, SCORAD), health-related quality of life (measured by CDLQI, DLQI), long term control of AD (recurrence rate), patients/ investigator global score (effectiveness rate), and serum IgE level. No more adverse events associated with ICWM was found when compared with WM alone.

Conclusion

Adopting ICWM may be superior to using WM alone in managing AD without risk of more adverse events. However, the current available evidence is still too weak to generate conclusive results.

Background

Since the 1997 handover, the Hong Kong Special Administrative Region Government has adopted an evidence-based approach in promoting the use of integrated western and Chinese medicine (ICWM). Clinical application of western medicine (WM) combined with Chinese medicine (CM) needs be supported

by scientific evidence on their safety and effectiveness. Atopic Dermatitis (AD) is a chronically relapsing skin disease and characterized by recurring episodes of itchiness with skin erythema and surface damages, such as dry skin, skin thickening and swelling [1, 2]. AD skin lesions usually appear on the face, neck, back of the hands and feet, and itchiness and sleep loss are the most significant clinical symptoms. It affects around 15% to 30% of children and 2% to 10% of adults worldwide [3, 4]. In Hong Kong, the incidence rate of AD was 15% to 20% of the general population [5]. Currently anti-inflammatory treatment with topical corticosteroids and/or topical calcineurin inhibitors is widely used for the management of AD; when uncontrolled, systemic immunosuppressive agents may be considered in severe cases [6]. Long-term topical corticosteroid use is associated with some side effects including stretch marks, small red or purple spots, telangiectasia (small, dilated blood vessels on the surface of the skin), skin thinning, atrophy and acne. Topical use of excessive corticosteroids can also cause hypothalamic-pituitary axis uppression. [1, 6] Tachyphylaxis is also associated with topical corticosteroid use [6]. Complementary and alternative medicine has been increasingly used for the management of AD worldwide [7].

Chinese medicine is nowadays widely used for treating AD in East Asia and provides a potential alternative treatment approach. Many clinical studies have been conducted to evaluate the effectiveness of Chinese herbal medicines (CHMs) for the treatment of AD in recent decades [8, 9]. Findings suggested that oral use of CHMs may improve health-related quality of life of children with moderate or severe atopic eczema. As ICWM is commonly used in mainland China, there are also large amounts of clinical studies on the effectiveness of ICWM on AD [10]. However, currently there is no solid evidence about the effectiveness and safety of ICWM for the treatment of AD.

During the period of planning the establishment of Hong Kong's first Chinese medicine hospital, high quality evidence regarding the use of ICWM in AD is in high need. We would therefore like to fill in the gap by conducting a systematic review focusing on the use of ICWM in AD, which might also help develop a pragmatic collaborative model for WM and CM practitioners in Hong Kong.

Methods

Eligibility criteria

We included randomised controlled trials (RCTs) or quasi-RCTs using a superiority design, which evaluated the use of investigated WM & CM interventions or its variants on the patients with atopic dermatitis. The herbal medicines included single herb, classical formulae, new formulae, herb-derived products and combination products. The control group should receive the same WM interventions, no treatment or placebo. The WM medicine included both oral and topical application of chemical drugs such as antihistamines, corticosteroids and other modalities such as UV light therapy.

Studies on "chronic eczema", "subacute eczema" and "acute eczema" were generally excluded, except when they use a recognized diagnosis of AD such as Hanifin and Rajka's criteria or UK working group criteria explicitly [11]. Studies on other types of eczema such as anal eczema, genital eczema,

dyshidrosis, eczema rhagadiforme, keratinized eczema were all excluded. Trials with co-morbidity other than allergy-related diseases (e.g. asthma) were also excluded.

The included studies should reported one or more of the primary and secondary outcomes.

The primary outcome is the clinical severity of eczema, measured by a validated or objective tool, such as eczema area and severity index (EASI), scoring atopic dermatitis (SCORAD), six area, six sign atopic dermatitis (SASSAD) severity score, investigators' global assessment (IGA), and affected body surface area (BSA). The secondary outcomes included participant-reported symptoms, health-related quality of life, long-term control of atopic dermatitis (defined as the status of disease control at least one week after end of intervention, such as recurrence rate), serum IgE level and adverse events. The percentage of trial participants with more than 50% improvement in terms of patients or investigator global score ("effectiveness rate", further explained in the "Results" section) was also accepted as one of secondary outcomes as it is widely used in studies conducted in China based on national guidelines.

Participant-reported symptoms should be measured by a validated tool, such as patient-oriented eczema measure (POEM) and Pruritus Visual Analogue Scale (pruritus VAS). Health-related quality of life should also be measured by a validated measure, such as Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI).

Search strategy

Literature search strategies were developed using medical subject headings and text words related to eczema. Various synonyms of the concepts of "eczema", "Chinese medicine", "integrative medicine" and "randomized controlled trials" are combined by "And" to construct the searching strategies. We searched the Cochrane Central Register of Controlled Trials (CENTRAL, via Cochrane Library, searched on 16 Oct 2019), MEDLINE (via Ovid, 1948 to 16 Oct 2019), EMBASE (via Ovid, 1974 to 16 Oct 2019) and AMED (via Ovid, 1985 to 16 Oct 2019). We also searched main Chinese databases including the China National Knowledge Infrastructure (CNKI, 1915 to 18 Oct 2019), the Chinese BioMedical Literature Database (CBM, via SinoMed, 1978 to 18 Oct 2019) and Wanfang Med Online (For dissertations and conference proceedings only, 1998 to 18 Oct 2019). The search strategy can be found in **appendix 1**.

Previous systematic reviews or meta-analyses on AD were examined to identify potential trials eligible to be included.

Data extraction

The systematic review was conducted and reported according to the Cochrane Handbook for Systematic Review of Interventions, version 5.1 and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [12, 13].

All titles and abstract of the entries returned by the search were imported into Covidence, an online collaboration tool designed to facilitate different stages in systematic reviews, to remove duplicates and

enable online screening. A review author (SCH) independently screened all the titles and abstracts against the original inclusion and exclusion criteria. That author (SCH) obtained full-texts of all entries which seem to match the inclusion criteria or if there was any uncertainty. Each of four reviewers (SCH, LMK, LCW, CPK) then screened part of the full text articles obtained and extracted selected characteristics of the studies. After preliminary analysis of the search data, we decided to narrow down the topic to AD only. Afterwards, another reviewer (LCW) rescreened the titles and abstracts classified as irrelevant to ensure completeness of inclusion, and a reviewer (SCH) rescreened the articles that are not explicitly on atopic dermatitis (e.g. those about “acute eczema”, “subacute eczema” or “chronic eczema”) to check whether AD’s criteria were actually used for those studies. All difficult cases were referred to a reviewer (LZX) for decision. The final list of included articles was determined afterwards.

We resolved disagreement through discussion. We recorded the reasons for excluding articles/studies. The review authors were not kept blind to the journal titles or to the study authors or institutions.

One review author (SCH) extracted outcome data in the included studies and input them onto an excel spreadsheet. The means, standard deviations of continuous outcomes and the numbers of events of dichotomous outcomes were recorded. Other information including age range of the subjects, diagnosis and its diagnostic criteria, type of intervention (including constituent component and dose), randomization method, sample size, primary and secondary outcome types were also recorded.

Risk of bias assessment

Two review authors (SCH and LCW) independently assessed potential risks of bias in all included studies using the Cochrane’s tool for assessing the risk of bias [12]. They assessed all six domains (sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias) in each study and assigned a scale of high, low, or unclear risk of bias depending on each review author’s judgment. The discrepancy in judgment was resolved by another author (ZHW).

Data synthesis and statistical analysis

We used risk ratio (RR) with 95% confidence intervals (CI) to summarize dichotomous outcome data of individual studies, and used Mantel-Haenszel random-effects model to pool the results across studies. We used the mean difference to summarize continuous outcome data at the end of treatment or follow-up within studies, and used the inverse-variance random-effects model to pool the results. For meta-analysis, we used random-effects model because of the expected heterogeneity of the studies. RevMan 5.1 software was used for data analyses. Forest plots were made to visually assess the effect size and corresponding 95% CI using random-effects models. Heterogeneity was assessed using the I^2 test with the significance level set at I^2 over 50% or $P < 0.1$.

We planned to perform subgroup analyses based on patients’ age (whether they were lower or higher than the age of 12); however, this was eventually found to be infeasible as the majority of included studies (31

out of 56) contain patients of both age groups.. We assessed the possibility of publication bias by using funnel plots when at least 10 studies reported the outcomes. Sensitivity analyses were made to evaluate the influence of study methodological quality and that of using change from baseline data (with missing standard deviation imputed) instead of post-intervention data, if there is at least 1 included study reporting results in detail such that imputation of standard deviation is possible.

Results

Study selection

The electronic database search returned 1473 records. A total of 998 records remained after duplicates were removed. After title and abstract screening, 650 obviously irrelevant records were excluded and 348 full-text records were assessed for eligibility. And 6 additional records were identified from previous systematic reviews and trial summaries. On finalizing the scope of project, 55 trials (in 61 records) were included [14-74]. (Fig. 1 Flow of study selection)

Study characteristics

All included 55 studies were randomized controlled trials (RCTs). Among them, 5 studies were published in English and 50 in Chinese.

The included studies involved 5953 participants. The age of participants ranged from 35 days to 67 years old. Around 64% of the included studies (35 out of 55, involving 2987 participants) explicitly excluded people who had taken certain western medicine treatment within certain period (7 days to 2 months before screening) from participating in the trials (systemic corticosteroids: 35 studies, 2987 participants; immunosuppressives: 19 studies, 1680 participants; topical corticosteroids: 18 studies, 1256 participants; immunomodulators: 17 studies, 1577 participants; antihistamines: 16 studies, 1273 participants; antibiotics: 9 studies, 588 participants; phototherapy: 6 studies, 479 participants). Twenty-seven studies mentioned some types of Chinese medicine syndrome 证, and totally 15 syndromes were identified in those studies (Table 1). The most common four syndromes are dampness-heat 湿热 (566 participants), spleen deficiency with dampness accumulation 脾虚湿盛 (377 participants), spleen deficiency 脾虚 (309 participants) and blood deficiency and wind-dryness 血虚风燥 (304 participants).

Table 1. CM syndromes identified in the included studies

CM Syndromes in Chinese	English translation	No. of participants
湿热	Dampness-heat	566
脾虚湿盛	Spleen deficiency with dampness accumulation	377
脾虚	Spleen deficiency	309
血虚风燥	Blood deficiency and wind-dryness	304
风湿热	Wind-dampness-heat	104
脾肾阳虚	Spleen-kidney yang deficiency	97
脾虚风燥	Spleen deficiency with wind-dryness	90
风湿湿盛	Wind-dampness accumulation in skin	72
心火亢盛	Hyperactive heart fire	60
湿滞	Dampness stagnation	60
脾虚兼阴虚 脾虚	Spleen deficiency accompanied by yin deficiency	60
脾虚心火	Spleen deficiency with heart fire	47
脾虚血燥	Spleen deficiency with blood dryness	47
胎热	Fetal heat	40
阴虚血燥	Yin deficiency with blood dryness	40

All the included trials compared the use of Chinese herbal medicine combined with Western medicine to the use of same Western medicine alone (baseline treatment). CHMs included oral and topical use of Chinese herbal medicine in the form of decoction or granules or proprietary Chinese medicine (pCm). From the Chinese medicine perspective, the herbs used in the formulae generally have at least one of the following functions:

1. 健脾益气 (Fortifying the spleen and replenishing qi (e.g. 白术 Baizhu (Atractylodis Macrocephalae Rhizoma), 太子参 Taizishen (Pseudostellariae Radix));
2. 利湿 (Inducing diuresis to drain dampness (e.g. 泽泻 Yiyiren (Coicis Semen), 茯苓 Fuling (Poria));
3. 清热燥湿 (Clearing heat and drying dampness (e.g. 黄芩 Huangbai (Phellodendri Chinensis Cortex), 黄芩 Scutellariae Radix));
4. 祛风清热 (Dispersing wind and discharging heat (e.g. 连翘 Lianqiao (Forsythiae Fructus, 白鲜皮 Baixianpi (Dictamni Cortex));

5. 清热凉血 (e.g. 牡丹皮 (Moutan Cortex), 玄参 (Scrophulariae Radix));
6. 养血 (e.g. 当归 (Angelicae Sinensis Radix), 白芍 (Paeoniae Radix Alba));
7. 滋阴 (e.g. 麦冬 (Ophiopogonis Radix), 天冬 (Asparagi Radix));
8. 活血 (e.g. 川芎 (Chuanxiong Rhizoma), 桃仁 (Persicae Semen)).

Western medicine treatment included oral and topical medicines (such as emollients, antihistamines, topical corticosteroids, topical calcineurin inhibitors, urea-containing cream, antibiotics, anti-septic solutions and vitamin C) or non-pharmacological therapy (UV light therapy, 2 trials). The duration of treatment ranged from 1 to 24 weeks.

For primary outcomes, the included studies reported EASI, SCORAD, SASSAD, IGA (Clinical severity of eczema), POEM and pruritus VAS (Participant-reported symptoms). The most commonly reported (count ≥ 5) primary and secondary outcomes among the selected domains were clinical effectiveness rate (49 RCTs), SCORAD (20 RCTs), recurrence rate (16 RCTs), IgE level (12 RCTs), EASI (8 RCTs), and pruritus relief in Visual Analogue Scale (5 RCTs).

Analysis on the use of Chinese herbs

The frequency of usage, functions and classifications of the top 20 most frequently used CHMs in the included studies were summarised in Table 2. These 20 CHMs can be classified into 11 categories according to their main functions in Chinese medicine. The main functions of these categories are, in descending order of the sum of the corresponding CHMs' frequency: qi-tonifying 补气, heat-clearing and dampness-drying 清热祛湿, water-draining and swelling-dispersing 利水消肿, wind-cold-dispersing 祛风散寒, dampness-resolving 祛湿, blood tonifying 养血, heat-clearing and blood-cooling 清热凉血, strangury-relieving diuretic 利尿通淋, qi-regulating 理气, liver-pacifying 疏肝, heat-clearing and detoxicating 清热解毒. These match well with the pathophysiology of AD in CM theory, i.e. accumulating dampness, heat and wind and the associated spleen qi deficiency that could result in blood deficiency if it persists into the chronic stage.

For the herbal combinations used, 42 formulae with names were identified in the included studies. The most commonly used formulae was Danggui Yinzi 当归饮子, a blood tonifying and wind dispersing (养血祛风) formula designed to resolve blood deficiency and wind-dryness (血虚风燥, which is a common CM syndrome in the later chronic stage of AD), with 4 studies using it as part of intervention.

Risk of bias within studies

About a third of included studies described their ways of generating a random sequence and thus had low risk of bias in this domain. Only 3 studies described the allocation concealment method [14, 17, 19]. Five studies took measures to blind participants, study personnel and outcome assessors [14, 16, 17, 19, 21].

Most studies (47 out of 55) had low risk of bias in incomplete outcome data. Most studies (53 out of 55) had unclear risk of bias in selective reporting because no relevant information was available. Overall, 2 studies [14, 17] were judged to be at low risk of bias, 3 studies [16, 21, 26] at unclear risk of bias, and the other 50 studies at high risk of bias. (Fig. 2 Risk of bias graphs and summaries)

Effects of Interventions

Primary outcome

Thirty-three studies measured clinical severity of atopic dermatitis by validated measurement scales. Among these, 18 used SCORAD and 8 used EASI. Seventeen studies using SCORAD and 5 using EASI were included in meta-analysis based on the available data for analysis. In both measures, ICWM was superior to WM alone (SCORAD: MD = -11.06, 95% CI -16.53 to -5.60, participants = 1961, $I^2 = 99\%$, Fig. 3a Effects of ICWM on the clinical severity of AD measured by SCORAD when compared with WM alone; EASI: MD = -2.68, 95% CI -4.95 to -0.42, participants = 371, $I^2 = 94\%$, Fig. 3b Effects of ICWM on the clinical severity of AD measured by EASI when compared with WM alone). High heterogeneity was mainly due to the varied interventions involved.

Furthermore, sensitivity analysis was conducted to examine the effects of including only study of low risk of bias; and that of using the change of score from the baseline rather than post-intervention scores on the pooled results. The only study of low risk of bias (Gu 2018) [14] reported no significant difference was found between the ICWM and WM alone groups in terms of EASI change. When the change of score from baseline was used, with the missing SD of EASI imputed from figures report in Gu 2018 and that of SCORAD imputed from Chen 2016, ICWM was still superior to WM alone (SCORAD: MD = -8.15, 95% CI -12.89 to -3.41; EASI: MD = -2.59, 95% CI -4.48 to -0.70).

Other measures included IGA, SASSAD, Skin Severity Score by Japanese Dermatological Association and 3 different kinds of author-defined clinical lesion/symptom scores.

Secondary outcomes

Participant-reported symptoms

Six studies measured participant-reported symptoms by validated measurement scales. Among these, 5 used pruritus visual analogue scale (VAS), of which 3 were included in meta-analysis. The result of meta-analysis showed no significant difference between the ICWM and WM alone groups (MD = -1.21, 95% CI -2.45 to 0.02, participants = 203, $I^2 = 96\%$). Only 1 study [14] measured participant-reported symptoms by POEM. There was no significant difference between ICWM and WM alone group at the endpoint in this study.

Health-related quality of life

Seven studies measured health-related quality of life by validated measure scales. Among these, 3 used only CDLQI, 3 used only DLQI, and one used a score combined from both CDLQI and DLQI. Two studies using only CDLQI and all studies using only DLQI were included in the meta-analysis. The study with combined score was not included for meta-analysis as the scores were combined in an unspecified way and not separately available. In both measures, ICWM was superior to WM alone (CDLIQ: MD = -2.12, 95% CI -3.93 to -0.31, participants = 125, $I^2 = 1\%$; DLQI: MD = -3.12, 95% CI -5.03 to -1.22, participants = 206, $I^2 = 94\%$). However, sensitivity analysis showed that using change from baseline instead of post-intervention data, with missing SD imputed from Gu 2018, would give a different conclusion that ICWM and WM alone groups had no significant difference in terms of CDLQI (MD = -1.41, 95% CI -3.84 to 1.02).

Long-term control of atopic dermatitis (defined as the status of disease control at least 1 week after the end of intervention)

Sixteen studies measured long-term control of AD. All were expressed in some forms of “numbers of recurrence” or “recurrence rate” with observing intervals from 1 week to 1 year. The pooled analysis of 16 studies showed that ICWM was superior to WM alone in reducing recurrence rate (RR = 0.47, 95% CI 0.38 to 0.58, participants = 1246, $I^2 = 0\%$).

Percentage of trial participants with more than 50% improvement in terms of patients or investigator global score (effectiveness rate)

Most included studies in Chinese (49 out of 50) reported a set of ordinal percentage measures, such as no effect rate, effective rate, significantly effective rate, or complete recovery rate, which are based on various patients or investigator global scores, either validated (like EASI, SCORAD or SASSAD) or self-defined. For each study, we grouped subjects with more than 50% improvement in terms of global scores into one category, and those lower than 50% grouped into another. Percentages of the former categories over the total sample sizes were defined as “effectiveness rates” in this review, and meta-analyzed as a dichotomous outcome.

There were 4, 15, 5 and 24 studies which adopted EASI, SCORAD, SASSAD and other measures, respectively, as their basis for calculating the percentages. Meta-analyses were performed separately for these four groups. All four groups showed that ICWM was superior to WM alone on improving effectiveness rate (EASI: RR = 1.30, 95% CI 1.13 to 1.51, participants = 307, $I^2 = 0\%$, Figure 4a; SCORAD: RR = 1.46, 95% CI 1.24 to 1.72, participants = 1547, $I^2 = 72\%$, Figure 4b; SASSAD RR = 2.50, 95% CI 1.79 to 3.49, participants = 311, $I^2 = 0\%$, Figure 4c; all other measures: RR = 1.35, 95% CI 1.23 to 1.49, participants = 2831, $I^2 = 77\%$, Figure 4d). The high heterogeneity in the SCORAD and other measures groups was probably due to the vast range of interventions involved.

Apart from the above, there was 1 English study [17] which reported “prominent efficacy rate” (defined as the rate of subject with skin severity scoring 0 at the end of study). The difference between ICWM and WM alone groups is not significant (ICWM: 19%, 7 of 37; WM alone: 5%, 2 of 40, $P = 0.06$)

Serum IgE Level

Twelve studies measured serum IgE level. Among them, 10 studies were included in the meta-analysis. Pooled analysis showed that ICWM was superior to WM alone in increasing IgE level (MD = -48.53 kU/L, 95% CI -79.67 to -17.38, participants = 884, $I^2 = 80\%$). Its high heterogeneity was possibly due to the different interventions involved. For sensitivity analysis, if change from baseline data were used instead of post-intervention data, with missing SD imputed from figures report in the study Zhou 2003[63], ICWM would still be superior to WM alone (MD = -45.69 kU/L, 95% CI -84.1 to -7.29).

Adverse events

Thirty-six studies reported the occurrence of adverse events (AEs). Among these, 17 studies stated that no AEs were observed. For the other 19 studies, the reported adverse events for the ICWM group mainly included skin discomfort (such as rashes, pruritus, irritation, urticaria, local edema, xerosis) and gastrointestinal disturbance (like nausea, diarrhea, stomach discomfort, abdominal distension, epigastralgia, anorexia, loose stools). Other AEs included feeling of sleepiness, insomnia, dizziness, headache, conjunctivitis, common cold, upper respiratory infection, scabies, right hypochondriac pain, malaise, rhinitis, feverish thirst, dental caries, eosinophilia, GPT elevation, IgE elevation, blood urea nitrogen (BUN) attenuation and serum potassium elevation. Pooled analysis of 19 studies found no significant difference between ICWM and WM groups in the rate of adverse events (RR = 0.91, 95% CI 0.61 to 1.35, participants = 1416, $I^2 = 47\%$, Fig. 5 Effects of ICWM on the rate of adverse events when compared with WM alone)

Funnel plots were made for the outcomes that have at least 10 studies included in the meta-analysis. The pooled data on SCORAD, the percentages of trial participants with more than 50% improvement in terms of SCORAD or “other measures” as defined above, and serum IgE level were examined by funnel plots. Apart from the one with SCORAD, the plots were all highly asymmetrical, suggesting a significant risk in publication bias. (Fig.6 Funnel plots)

Table 2 The top 20 most frequently used Chinese medicinal herbs in the included studies

Chinese pinyin and name	Latin name	Frequency of usage	Classification based on main functions (Chinese Materia Medica 7 th edition)
Fuling 茯苓	Poria	32	water-draining and swelling-dispersing 利水渗湿
Baizhu 白术	Atractylodis Macrocephalae Rhizoma	26	qi-tonifying 健脾
Gancao 甘草	Glycyrrhizae Radix et Rhizoma	26	qi-tonifying 补虚
Baixianpi 白鲜皮	Dictamni Cortex	25	heat-clearing and dampness-drying 清热燥湿
Huangqi 黄芪	Astragali Radix	20	qi-tonifying 补气
Cangzhu 苍术	Atractylodis Lancea Rhizoma	19	dampness-resolving 祛湿
Danggui 当归	Angelicae Sinensis Radix	18	blood tonifying 补血
Yiyiren 薏苡仁	Coicis Semen	17	water-draining and swelling-dispersing 利水渗湿
Shengdihuang 生地	Rehmanniae Radix	16	heat-clearing and blood-cooling 清热凉血
Difuzi 藜蘆	Kochiae Fructus	15	strangury-relieving diuretic 利水通便
Jingjie 荆芥	Schizonepetae Herba	15	wind-cold-dispersing 祛风散寒
Fangfeng 防風	Saposhnikoviae Radix	14	wind-cold-dispersing 祛风散寒
Kushen 苦参	Sophorae Flavescentis Radix	14	heat-clearing and dampness-drying 清热燥湿
Chenpi 陈皮	Citri Reticulatae Pericarpium	13	qi-regulating 理气
Huangbai 黄柏	Phellodendri Chinensis Cortex	12	heat-clearing and dampness-drying 清热燥湿
Huangqin 黄芩	Scutellariae Radix	12	heat-clearing and dampness-drying 清热燥湿
Jili 薤白	Tribuli Fructus	11	liver-pacifying 理气
Dangshen 党参	Codonopsis Radix	10	qi-tonifying 补虚
Zexie 泽泻	Alismatis Rhizoma	10	water-draining and swelling-dispersing 利水渗湿
Lianqiao 连翘	Forsythiae Fructus	9	heat-clearing and detoxicating 清热解毒

Discussion

The research findings suggested that ICWM was superior over WM alone in improving clinical severity of AD (measured by EASI, SCORAD), health-related quality of life (measured by CDLQI, DLQI), long term control of AD (recurrence rate), patients/ investigator global score (effectiveness rate), and serum IgE level. We found no more adverse events associated with ICWM when compared with WM alone. However, some issues related to study quality, such as most studies at high risk of bias and conflicting results in some sensitivity analyses, and potential publication bias weaken the strength of evidence.

Although the mechanisms of CHMs in treating AD are not well understood, the research findings in some herbs or compound herbal preparations could help us to some extent. Some herbs, such as Poria (山藥), Atractylodis Macrocephalae Rhizoma (白朮), and Angelicae Sinensis Radix (當歸), have anti-inflammatory and immunomodulatory effects [75-77]. Atractylodis Lancea Rhizoma (白朮) and Dictamni Cortex (白芷), also has anti-bacterial effects [77, 78]. Danggui Yinzi, a commonly used herbal preparation, was shown to inhibit delayed allergic reaction [79].

The possible interaction between Chinese medicines and WM is one of most concerns about clinical safety. We found no significant difference in the occurrence of AEs between ICWM and WM. This finding is similar to previous reports that the combination

of ICWM did not evoke additional adverse events [80]. It has been also reported that adding CHMs might have reduced the occurrence of adverse events of conventional pharmacotherapy such as skin dryness, skin itchiness, dry mouth/lips, and dry/scaly skin [81]. Different herbs and pharmacotherapies may be involved in the possible interaction. As CHMs can affect the pharmacokinetic properties of WMs, we need to pay much attention to the possible interactions between CHMs and WMs.

This review is the first one to systematically summarise and analyse the ICWM for AD. The comprehensive search strategy and scientifically rigid way to assess risk of bias and conduct meta-analysis made the generation of findings more reliable. The low methodological quality and poor reporting are the main problems that weakened the evidence. No proper blinding is one of main problems with included studies. As the main outcomes for evaluating the treatment effect for AD are most subjective, the blinding is a very important measurement to reduce possible bias and subjective influences. Additionally, no clear description of random generation and allocation concealment is also one of main problems in most included studies. Further clinical studies with high methodological quality are needed to consolidate the evidence.

Conclusion

Adopting ICWM may be superior to using WM alone to help improve clinical symptoms and quality of life, and reduce the recurrence rate in the patients with atopic dermatitis. It seems that the adding of CHMs

present no more harm than WM alone. However, due to the overall low quality of the studies and possible publication bias, more methodologically rigorous research is needed to generate a conclusive result about the routine use of ICWM in the treatment of atopic dermatitis.

Abbreviations

AD: Atopic dermatitis; ICWM: Integrated Western-Chinese medicine; WM: Western medicine; CHM: Chinese herbal medicines; RCT: Randomised controlled trials; EASI: Eczema area and severity index; SCORAD: Scoring atopic dermatitis; SASSAS: Six area, six sign atopic dermatitis; IGA: Investigators' global assessment; BSA: Body surface area; POEM: Patient-oriented eczema measure; VAS: Visual analogue scale; DLQL: Dermatology life quality index; CDLQI: Children's dermatology life quality index; RR: risk ratio; CI: Confidence intervals; pCm: proprietary Chinese medicine; AEs: Adverse events; BUN: Blood urea nitrogen.

Declarations

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Authors' contributions

CJ, LS, YCL and LZX organized and conceived the study. SCH, LCW, LMK, CPK, and LZX searched and screened the studies. SCH, LCW, and ZHW assessed the risk of bias. SCH, CJ, LS, and ZHW performed the data analysis. SCH, CJ, LZX and ZHW drafted the manuscript.

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Consent for publication

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Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Flow of study selection

(2a)

(2c)

Figure 2

(a) Risk of bias graph; (b) Risk of bias summary

(a)

(b)

Figure 3

Effects of ICWM on the clinical severity of AD measured by (a) SCORAD and (b) EASI when compared with WM alone

Figure 4

Effects of ICWM on the percentage of trial participants with more than 50% improvement in terms of (a) EASI, (b) SCORAD, (c) SASSAD and (d) all other measures when compared with WM alone

Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias

Figure 5

Effects of ICWM on the rate of adverse events when compared with WM alone

Figure 6

Funnel plots for the meta-analysis of (a) SCORAD, (b) percentage of trial participants with more than 50% improvement in terms of patients or investigator global score (SCORAD), (c) percentage of trial participants with more than 50% improvement in terms of patients or investigator global score (all other measures), and (d) serum IgE level.