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REVIEW ARTICLE

## Chinese herbal medicine for atopic eczema: an overview of clinical evidence

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### ABSTRACT

Atopic eczema (AE), or atopic dermatitis, is a common inflammatory skin disease. As conventional medicines for moderate and severe AE patients have been reported to be associated with unwanted side effects, many patients with AE have sought other therapies. Chinese herbal medicine (CHM) is one of the most commonly used complementary therapies with a long history of being applied for the treatment of AE. Clinical evidence for CHM for AE in systematic reviews and randomised controlled trials (RCTs) published from 2013 to 2016 was reviewed. Findings from the Cochrane systematic review suggested that oral use of a CHM formulation may improve health-related quality of life (HRQoL) of children with moderate or severe AE. The benefit on improvement of AE requires further high-quality clinical studies.

**Abbreviations:** AE: Atopic eczema; CDLQI: Children's Dermatology Life Quality Index; CHM(s): Chinese herbal medicine(s); CI: Confidence interval; CODs: Core outcome domains; COMI: Core outcome measurement instrument; EASI: Eczema Area and Severity Index; GRADE: Grading of Recommendations Assessment; Development and Evaluation; MD: Mean difference; NHMRC: National Health and Medical Research Council; HRQoL: Health-related Quality of life; RCT(s): Randomised controlled trial(s); RR: Risk ratio; SCORAD: Scoring Atopic Dermatitis; SMD: Standardised mean difference; TIS: Three Item Severity score; VAS: Visual analogue scale

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Atopic eczema; atopic dermatitis; Chinese herbal medicine; systematic review; randomised controlled trials

## Background

Atopic eczema (AE), or atopic dermatitis, is an itchy chronic inflammatory skin disease characterised by periods of remission and relapse of skin lesions. It occurs most frequently in infants and children and can also be seen in adults. AE is more prevalent in individuals with personal or family history of atopic conditions such as asthma and allergic rhinitis (1). Clinical features of AE differ in infants, children and adults, although pruritus, eczematous rashes, loss of sleep and impact on psychosocial wellbeing of patients are seen in all age groups (2–5).

The prevalence of AE has increased over the last three decades in both developed and developing countries, especially in those aged 6–7 years (6,7). A systematic review of epidemiological studies between 1990 and 2010 revealed that the incidence rate of AE has increased in Africa, Eastern Asia, Western Europe and parts of Northern Europe, such as the UK (8).

The causes of AE are yet to be fully understood, but risk factors associated with AE have been identified. These include deficiency of Vitamin D, climate factors such as combined high humidity and precipitation, prenatal or psychological stress and genetic hereditary alterations, in particular the loss-of-function mutations of the filaggrin gene (9–13).

## Current medical therapeutic options and limitations

Currently, there is no cure for AE. Conventional medical treatment for AE can be categorised into applications of topical

agents, systemic administration of medicines, or combination of both approaches (14). Topical or systemic immunosuppressive regimen is the mainstay of treatment for AE. Topical administration of corticosteroids with adequate potency or calcineurin inhibitors such as pimecrolimus and tacrolimus are the standard first-line treatment for mild AE (15). Systemic medications including oral corticosteroids or immunosuppressive drugs such as azathioprine, cyclosporine, mycophenolate and methotrexate are used for more difficult-to-treat or refractory moderate or severe AE (16,17). However, long-term use of oral corticosteroids can lead to unwanted adverse events such as suppression of the hypothalamic–pituitary–adrenal axis, osteoporosis, aseptic necrosis of the hip, hypertension, ocular changes and altered immune function (18). Side effects of immunosuppressive medications (e.g. azathioprine) include hepatosplenic T-cell lymphomas (19). Therefore, many AE sufferers have chosen to use other therapies such as Chinese herbal medicine (CHM) for the treatment of AE (20,21).

## The role of CHM for AE

“Si Wan Feng” is the comparable term used in Chinese medicine for AE. It appeared in classical Chinese medicine literature in A.D. 1665 and has been presented for any pruritic skin condition characterised by the involvement of fossae of the legs and ankles and relapses regularly since then. In 1994, it was approved as the

**Table 1.** AE Syndromes and formulae recommended in the Expert consensus 2013.

| AE                                        | Syndrome                                               | Formula              |
|-------------------------------------------|--------------------------------------------------------|----------------------|
| Infants                                   | Accumulation of heat in the Heart and Spleen           | San Xin Dao Chi Yin  |
| Acute relapse of AE in children           | Heart fire with Spleen deficiency                      | Qing Xin Pei Tu Fang |
| Remission of AE in infants and children   | Deficiency of the Spleen with accumulation of dampness | Xiao Er Hua Shi Tang |
| Remission of AE in adolescents and adults | Deficiency of blood with wind-dryness.                 | Dang Gui Yin Zi      |

standard Chinese medicine term for AE by the State Administration of Traditional Chinese Medicine in China (22).

In 2011, through a collaboration between the World Health Organization (WHO) Western Pacific Regional Office and the China Academy of Chinese Medical Sciences, an evidence-based Chinese medicine guideline for the management of AE was published (23). The guideline recommended CHM, acupuncture, paediatric tuina, dietary therapies and life-style regimen for the management of AE. Details for CHM treatment of AE were further developed through expert consensus in 2013 (the Expert consensus 2013) (24). The consensus included categorisation of AE clinical syndromes according to Chinese medicine diagnostic framework which guided the selection of the four CHM formulae accordingly (Table 1).

Since the publications of the consensus, a study of 200 children with AE who were treated with CHM revealed that the most common Chinese medicine syndromes for AE are deficiency of the spleen syndrome (18.0%); deficiency of blood with wind-dryness syndrome (15.5%) and accumulation of dampness-heat syndrome (12.5%) (25). Such findings partially confirmed the recommendations in the Expert consensus 2013.

CHM is a complex intervention, as each of the formulae may involve the use of several herbs and each of them has multiple compounds (26). Evidence collated from systematic reviews is critical in the stage of development and reporting for investigating a complex intervention (27). Although findings from a randomised controlled trial (RCT) and retrospective cohort study suggested that oral ingestion of CHM may reduce the usage of topical corticosteroids for patients with AE (28,29), the specific benefit of CHM on reducing the severity of AE needs further determination through high-quality studies. As an expert consensus guideline of CHM for AE has been agreed in 2013 (24), this evidence update aims to review findings from systematic reviews and RCTs of CHM for AE since 2013.

## Method

We used key words *Chinese herbal medicine*, *atopic eczema*, *atopic dermatitis* and *systematic review* to search the following English databases: the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Library, EMBASE, Google Scholar, PubMed, ScienceDirect, SCOPUS and Chinese databases: China National Knowledge Infrastructure (CNKI), Chongqing VIP Information Co. Ltd (CQVIP), Wanfang Data. We also searched the main clinical trials registers including International Clinical Trial Registry Platform (ICTRP), ClinicalTrials.gov, Australian New Zealand Clinical Trials Registry (ANZCTR), Chinese Clinical Trial Registry (ChiCTR) and Global Resource of Eczema Trials (GREAT) database from January 2013 to June 2016. We retrieved papers of systematic reviews and RCTs. We excluded study protocols and RCTs that were unregistered or did not report approval from an institutional ethics review board.

## Evidence from systematic reviews

A Cochrane systematic review evaluated oral and/or topical application of CHM for AE in 2013 (30). A total of 28 studies published

from 1999 to 2011 involved 2306 participants were included. Eight studies used oral ingestion, six studies (including one arm of a 3-arm study) used topical intervention, and 14 studies combined oral ingestion and topical application. The sample sizes of the included studies ranged from 25 to 220, and participants aged from 12 days to 65 years. Interventions included CHM compared to placebo or CHM compared to conventional medications. The reviewers found promising evidence from one 12-week study which compared oral CHM capsules to placebo for participants with moderate to severe AE. A statistically significant difference between the two groups in score of Children's Dermatology Life Quality Index (CDLQI) (MD -2.50; 95%CI -4.77 to -0.23,  $n=85$ ) was observed. The finding of health-related quality of life (HRQoL) improvement was considered as moderate quality evidence according to the GRADE system (31). However, usage of the CHM capsules did not reduce the severity (the extent and intensity of skin lesions) of AE measured with objective Scoring Atopic Dermatitis (SCORAD) (MD 3.40; 95%CI -5.70 to 12.50). The CHM capsules (PentaHerbs) consisted of Jinyinhua (Flos Lonicerae Japonicae), Bohe (Herba Menthae), Mudanpi (Cortex Moutan), Cangzhu (Rhizoma Atractylodis) and Huangbai (Cortex Phellodendri).

Twenty-one studies used "total effectiveness rate" (percentage of trial participants with the sum of "recovery" and "significant improvement" reported by the trial investigators, a higher rate indicated better result) as their primary outcome measure. The rate in CHM groups was significantly higher than that in the control groups where conventional medications were used (RR 1.43; 95%CI 1.27-1.61; 21 studies;  $n=1868$ ). Itching visual analogue scale (VAS) was used by seven studies as their primary outcome measure. The overall itching VAS in the CHM groups was lower than the conventional medication groups (SMD -0.83, 95%CI -1.43 to -0.22; 7 studies;  $n=465$ ). No severe adverse events have been reported by all included studies.

Tan et al. conducted a systematic review of CHM for AE in 2013 (32). Seven RCTs published from 1992 to 2011 with a total of 432 participants were evaluated for safety and efficacy of orally administered CHM. Tan's review included three studies which used Zemaphyte and one study that used Hochu-ekki-to, a Kampo medicine product modified from a CHM formula Bu Zhong Yi Qi Tang (33) to compare with placebo. The reviewers reported that the overall effect could not be tested due to insufficiency of data and differences in measurement of the primary outcome measures across the seven studies. Three studies used a standardised scoring system to measure the extent and severity of erythema and skin surface damage. A positive effect favouring CHM when compared to placebo with the outcome of erythema score (SMD -0.76; 95%CI, -1.05 to -0.47) and surface damage scores (SMD -1.08; 95%CI, -1.59 to -0.56) was found. However, it was not conclusive that that oral CHM was efficacious for AE because of the poor quality of most included studies.

A systematic review with meta-analysis of topical application of CHM for AE was published in 2014 (34). Ten studies published from 2003 to 2012 were included with a total of 1058 participants aged from 12 days to 27 years old. Interventions included topical application of cream, ointment, moist dressing with lotion, powder and oil on the affected skin for one to three weeks. All studies

**Table 2.** Summary of systematic reviews.

| Title                                                                                                             | Included studies and participants | Intervention                                                 | Results                                                                                                        |
|-------------------------------------------------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|
| Chinese herbal medicine for atopic eczema (Review) (2013)                                                         | 28/2306                           | Oral, topical or combination of oral and topical application | Limited evidence that oral usage of a CHM formulation can improve HRQoL in children with moderate or severe AE |
| Chinese herbal medicine for atopic dermatitis: a systematic review (2013)                                         | 7/432                             | Oral application                                             | Inconclusive                                                                                                   |
| Topical application of Chinese herbal medicine for atopic eczema: a systematic review with a meta-analysis (2014) | 10/1058                           | Topical application                                          | Inconclusive                                                                                                   |

reported on the outcome “total effective rate”. The overall effect in topical CHM groups was higher than control groups where conventional medications were used (RR 1.19; 95% CI, 1.04 to 1.36; 10 studies;  $n=997$ ). Nevertheless, high heterogeneity ( $I^2 = 66\%$ ) was also detected in the meta-analysis. Table 2 summarises the main findings from systematic reviews.

### Evidence from RCTs

An outcome-assessor blinded, placebo-controlled, 3-arm design RCT was reported in 2015 (35). The study included 250 participants aged from 5 to 25 years old who were diagnosed with moderate to severe AE. Participants were randomised to receive oral PTQXT (group A,  $n=83$ ), oral PTQXT plus external wash with CHM lotion (group B,  $n=83$ ), or oral placebo pills plus oral ingestion of loratadine or cyproheptadine hydrochloride and topical usage of 0.1% mometasone furoate cream (group C,  $n=84$ ) for 12 weeks with a 24-week follow-up. PTQXT was composed of nine CHMs: Taizishen (*Radix Pseudostellariae*), Lianqiao (*Fructus Forsythiae*), Gouteng (*Ramulus Uncariae cum Uncis*), Dengxincao (*Medulla Junci*), Danzhuye (*Herba Lophatheri*), Yiyiren (*Semen Coicis*), Shanyao (*Rhizoma Dioscoreae*), Muli (*Concha Ostreae*) and Gancao (*Radix Glycyrrhizae*). The CHMs for external wash composed of Jinyinhua (*Flos Lonicerae Japonicae*), Huangjing (*Rhizoma Polygonati*), Bohe (*Herba Menthae*) and Gancao (*Radix Glycyrrhizae*). The trial investigators reported that the mean SCORAD in the three groups was reduced within the groups, but no statistical significant difference across the three groups at the end of 12 weeks treatment. However, oral PTQXT alone (MD  $-8.09$ ; 95%CI,  $-13.18$  to  $-3.00$ ) or with external CHMs (MD  $-5.52$ ; 95%CI,  $-10.67$  to  $-0.38$ ) resulted in a greater reduction in SCORAD than conventional medicine at week 28 of the follow-up period. The HRQoL was also improved at week 36 of the following-up period when the mean of QoL score where oral PTQXT alone or with external CHMs was compared with placebo plus conventional medicine. No severe adverse events were reported.

A report from an open-label parallel pilot RCT testing topical application of Tzu-Yun ointment for AE was published in 2016 (36). Tzu-Yun ointment contains Zicao (*Radix Arnebiae*), Danggui (*Radix Angelicae Sinensis*), Fengla (*Cera Flava*) and Heizhimayou (*Oleum Semen Sesami Nigrum*). A cream with 0.6 mg/g betamethasone valerate was used as a control intervention. Data from a total of 31 adults who had history of AE for at least 5 years and completed 8-week treatment with topical application of CHM ointment or corticosteroid cream were analysed. Oral cetirizine (a second generation H1 antihistamine) was also supplied to both the groups. Decrease of Eczema Area and Severity Index (EASI) and Three Item Severity (TIS) score was observed in both groups at the end of the study with no statistical significant difference between the two groups (EASI score: MD  $-0.18$ ; 95%CI,  $-0.74$  to  $0.38$ ;  $n=31$ ; TIS score: MD  $0.52$ ; 95%CI,  $-0.60$  to  $1.64$ ;  $n=31$ ; the effect estimate was re-calculated with data extracted from Table 2

of the Yen and Hsieh’s study 2016). The trial investigators claimed that efficacy of the CHM ointment was equivalent to the corticosteroid cream for AE, but a RCT with larger scale of sample size is needed to confirm the effect.

### Discussion

This paper reviews recent evidence of CHM for the treatment of AE from three systematic reviews and two RCTs up to June 2016. The three systematic reviews have included studies published from 1992 to 2012. There was limited evidence that oral intake of a CHM formulation (PentaHerbs capsule) could improve HRQoL for children with moderate to severe AE (30). The CHM formulation contained five CHMs. They were within the range of most frequently used CHMs for the treatment of AE. The range was found from a government-funded study using data mining method on 186 papers published from 1978 to 2012 in China (37).

Findings from the other systematic reviews published in 2013 and 2014 were inconclusive. No severe adverse events were reported from the three systematic reviews. Most of the included studies in systematic reviews have shown promising benefit of CHM when compared with the control groups. Such findings are limited due to quality concerns of the included studies, such as high risk of bias due to sequence generation; allocation concealment; lack of blinding of participants and outcome assessors.

The results from the Liu et al. trial in 2015 need to be interpreted with caution due to the lack of blinding of both participants and investigators, which may have resulted in an overestimation of the treatment effect (38).

The Yen and Hsieh’s trial was a pilot study without blinding. Effect of topical application of the Tzu-Yun ointment needs to be confirmed by an adequately powered and appropriately designed RCT to minimise risk of bias.

Most of the included studies in systematic reviews used a non-validated outcome measure, “total effectiveness rate”, as the primary outcome measure. To be meaningful, outcome measures for RCT in AE should include the following core outcome domains (CODs): clinician reported signs, patient reported symptoms, HRQoL and long term control of flares (39,40). Each of the CODs should be measured by a core outcome measurement instrument (COMI) (41). EASI is recommended as a validated COMI for measuring clinician-reported signs and the POEM is a COMI for measuring patient reported symptoms (42). COMIs for measuring of HRQoL and long-term control of flares are under development (<http://nottingham.ac.uk/homeforeczema/research/index.aspx> accessed on 1 June 2016). We suggest that all RCTs for AE in CHM should use these COMIs for their outcome measures.

### Conclusion

A Cochrane systematic review in 2013 found limited evidence that oral ingestion of a CHM formulation could improve HRQoL for

children with moderate to severe AE, but no conclusive finding on the benefit of CHM for the reduction of AE severity. Findings from the other two systematic reviews and RCTs were inconclusive. The quality of RCTs in CHM for AE needs urgent attention. More high-quality RCTs are warranted.

### Disclosure statement

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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