

Asian herbal medicine for atopic dermatitis: a systematic review

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Abstract

Asian herbal medicines have been known for decades, and some have been used to treat atopic dermatitis (AD). This chronic and persistent inflammatory skin condition causes severe morbidity and negatively impacts the quality of life. In numerous trials, traditional Chinese medicines have demonstrated clinical efficacy for AD. However, there is no well-documented summary of the wide

variety of Asian herbal medicines used in treating AD. We aimed to systematically summarize the use of Asian herbal medicine in AD. An English-language literature search was performed in three electronic medical databases: PubMed, Cochrane Library, and EBSCOhost using keywords [“(atopic dermatitis” OR “atopic eczema”) AND (“traditional” OR “herbal”)] and limited to references published between January 2015 and December 2022. The literature included newborns, infants, children, adolescents, and adults. The review was conducted using the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* extension to determine the main criteria. The content and inclusiveness of the search were filtered using relevant terms (MeSH/Emtree), keywords, titles, and abstracts. Thirteen articles (12 randomized clinical trial + 1 clinical trial) reported a variety of herbal medicine compounds to treat AD with various efficacy. Most studies reported significant improvement when comparing the herbal medicine with a placebo, but only 1 study reported substantial improvement of SCORAD compared to corticosteroids. Asian herbal medicines have been studied and may be used as an alternative treatment in treating AD with fewer adverse effects. However, its role did not change the position of standard treatment in treating atopic dermatitis.

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Introduction

Atopic dermatitis (AD) is a chronic and persistent inflammatory cutaneous disease characterized by complex immune dysregulation and skin barrier dysfunction with various clinical phenotypes.¹ The condition causes severe morbidity and negatively impacts the patient's quality of life,² not only because of the social stigma associated with a visible skin disorder but also because of the intense itching, contributing to skin trauma and severe sleep disruptions.³ Furthermore, AD is the first disease to occur in various allergic diseases, such as food allergy, asthma, and allergic rhinitis, indicating that it is part of a continuum that may lead to a more severe allergic disease on other epithelial barriers.⁴

Worldwide, atopic dermatitis affects between 2 to 20% of children, with significant regional and racial variations. Atopic dermatitis is more prevalent in African, Oceania, and Asia-Pacific nations than in nations on the Indian subcontinent and Northern/Eastern Europe.⁵ Adult prevalence rates of 10-14% have been reported in population-based research.⁶ While the incidence remains high in urban areas and high-income countries, an increasing trend in the incidence and prevalence of atopic eczema has been reported in Asia's last few decades.⁷

The development of AD is influenced by environmental factors such as climate, urban versus rural location, air pollution, microbiome dysbiosis, and genetic factors such as atopic history and loss-of-function Filaggrin gene. These elements contribute to immunological dysregulation and skin barrier disturbance, both leading to inflammation.⁸

AD has a wide range of disease severity and various treatment

approaches. Effective treatment strategies are urgently required due to AD's significant burden on adult and pediatric patients.^{9,10} Emollients and systemic corticosteroids were typically utilized in clinical practice to treat AD.¹¹ Although the use of corticosteroids for AD is widespread, specialists from the Asian Academy of Dermatology and Venereology believe that it is still necessary to educate patients or caregivers due to their adverse effects and danger of rebound. Due to the potentially frightening side effects of topical steroids and immunosuppressant use, there is great interest in finding alternative and complementary drugs to treat AD.¹²

AD presents a significant cost burden with a clear relation to the seriousness of the disease.³ In Asian countries, the average annual cost per child with AD was estimated to be \$7943, comprising \$6651; \$7935; and \$14,335 in 2017 (measured in US Dollars) for mild, moderate, and severe disease, respectively.³ In adult patients with AD, the annual healthcare costs in 2018 were \$4979 higher than adults without AD.¹³ Furthermore, healthcare utilization contributed around 17% of the total cost, of which 43% was for medications.³ In addition, the recent development of medical treatment for children over 12 years of age with moderate and severe AD was by dupilumab injection. This biological agent effectively reduced the severity of AD. Yet, it was expensive and possessed several side effects, including infection, tenderness, and tingling sensation.¹⁴

To reduce costs and potential side effects caused by modern medicine, Asian herbal medicine might help treat the condition. We described Asian herbal medicines as those that grow in Asia and have been used by people to treat diseases since ancient times. Studies from China, Malaysia, and Iran have demonstrated their herbal medicine's efficacy and safety in treating AD in adults and children.¹⁵⁻¹⁷ Compared to effective standard AD treatment, such as steroids and biological agents, herbal medicine is considered safer and less expensive.^{17,18} Nevertheless, there has not been a well-documented paper summarizing the wide variety of Asian herbal medicine in treating AD. This systematic review summarizes the Asian herbal medicine used to treat AD.

Methods

This systematic review was performed using the approach developed by Arksey and O'Malley: identify the research question, identify relevant studies, select studies, monitor data, and the collection, synthesis, and report results.¹⁹ The review was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension to determine the scope of the review criteria.²⁰

Identification of research topics

Research questions were identified using a brainstorming approach involving the entire research team. The research group identified the questions at the first meeting and decided on research strategies. The research topics were as follows "How can Asian herbals be used to treat atopic dermatitis?"

Study selection process

This systematic review was registered in the Open Science Framework on November 14, 2022. Following registration, an English-language literature search was performed in three electronic medical databases: PubMed, Cochrane Library, and EBSCOhost using keywords (("atopic dermatitis" OR "atopic eczema") AND ("traditional" OR "herb")). A literature search was limited to references published in English between January 2015

and December 2022 and comprised newborns, infants, children, adolescents, and adults. The scope and inclusiveness of the search were filtered using MeSH/Emtree terms, keywords, titles, and abstracts. The regional filter in search engines was set to include only countries in Asia. The study included only Asian countries, covering 26 countries and their WHO sub-regional classifications.

Initially, 81 articles were screened from the selected databases. After removing duplicates, there were 70 articles. Of the chosen articles, 28 were marked as irrelevant. Relevant studies (42 articles) were then determined. This process took place in three phases. In the first phase, two researchers (NV and SW) independently screened articles based on their titles. During article screening, researchers (NV and SW) made sure that the Asian herbal medicines mentioned in the article are herbal medicines that grow in Asia and are used by people to treat diseases. All disagreements were resolved in consultation with senior researchers (RS, RD). The search results were imported into Zotero Reference Manager, and duplicate records were identified and removed. Potential relevance was reviewed based on the titles and abstracts of the remaining articles, followed by full-text analysis. All research team members (NV, RS, SW, and RD) independently assessed each abstract in the second phase. Case reports, series, commentaries, reviews, qualitative studies, and *in vitro* studies were excluded. Twenty-nine articles excluded in this process were: i) review article (8 reports excluded); ii) animal studies (11 reports excluded); iii) research protocol (7 reports excluded); and iv) meta-analysis reports (1 report was excluded); and involvement of other eczemas (2 studies excluded). There were 68 articles excluded, and 13 were evaluated for full-text analysis. In the third phase, the full texts of 13 selected articles were critically reviewed.

Risk of bias analysis

The risk of bias analysis was also included in this study. It was analyzed according to the Cochrane domain-based evaluation by assessing selection, performance, detection, attrition, and reporting biases.²¹

Data extraction

Before data extraction, NV, RS, SW, and RD designed a data extraction form to expedite the entire process.

The following information was extracted from the included articles to answer the research question: author(s) name, publication date, study design, study population, country, the Asian herbs, the function of the herbs, ingredients of the herbal medicine, efficacy to AD, measured outcomes; study results, and adverse effect.

Results

Literature search

A flowchart of the PRISMA study is shown in Figure 1. There were 81 articles in total: 34 from PubMed, 27 from Cochrane Library, and 20 from EBSCOhost, which were retrieved and screened to meet the inclusion criteria. We eliminated 11 duplicate records, leaving 70 articles to be reviewed. Titles and abstracts were manually screened, and 28 irrelevant articles were excluded leaving 42 documents to be further filtered. There were 29 records excluded consisting of 8 review articles, 11 animal studies, seven protocol studies, one meta-analysis, and two studies involving other types of eczema because of the abovementioned reasons.

After the full-text review, 12 randomized control trials and one

prospective control trial were eligible and included in this study. Iran, Korea, Pakistan, China, Thailand, and Taiwan contributed to these 13 studies. All studies reported different types of herbal medicine. We classified the 13 studies into four categories: single plant extract compared to placebo (n=4), single plant extract compared to corticosteroid (n=1), multiple plant extracts compared to placebo (n=4), multiple plant extracts compared to corticosteroid (n=3), and numerous plant extract compared to other (n=1). *Supplementary Table 1* shows the specific details of each study.

Risk of bias assessment

The evaluation of the risk of bias assessment by domain is summarized in *Supplementary Table 2* and illustrated in Figure 2. Regarding selection bias, randomization was performed in most studies except for one study by Chishti *et al.*²² A study by Yen and Hsieh did not mention the details of the randomization method. Regarding allocation concealment, nearly all studies created identical-appearing treatment and control drugs.²³ Nevertheless, a study by Liu *et al.* mentioned that developing the same taste for placebo drugs was challenging.²⁴ A study by Yen and Hsieh noted that they conducted an open-label study, which rendered allocation concealment impossible.²³

Regarding performance bias, all studies except for two (by Chishti *et al.*, and Yen and Hsieh) blinded the participants and personnel.^{22,23} Regarding detection bias, all studies except those by Chishti *et al.*, and Yen and Hsieh blinded outcome assessment.^{22,23} Concerning reporting bias, all studies reported the dropout rate and the reason for dropping out and analyzed all participant data.

Another type of bias was that four studies reported a small sample size, while five reported a brief follow-up period. A study by Liu *et al.* also revealed a non-uniform (oral and topical intervention), which may contribute to outcome bias.²⁴

Description of studies

Single plant extract compared to placebo (n=4)

Four studies used a single plant extract and compared it to a placebo. The four studies were conducted by Abbasi *et al.* in Iran,¹⁸ Lin *et al.* in Taiwan,²⁵ Mehrbani *et al.* in Iran,²⁶ and Meysami *et al.* in Iran.¹⁷ Extracts of *Ficus carica* L., *Baphicacanthus cusia*, *C. campestris* Yunck, and *Malus Sylvestris* were used, respectively. All four studies reported significant improvement in AD with different outcome measurements. There were improvements in Scoring Atopic Dermatitis (SCORAD); Eczema Area and Severity Index (EASI); skin moisture and pruritus; and SCORAD in those four studies. Both children and adult patients were included with only one exception, the study by Mehrbani *et al.*, which included only those aged 18 years and older. Three studies reported similar side effects of common cold and abdominal complaints, but no significant side effects were found.^{17,22,25} The study by Abbasi *et al.* did not mention any side effects.

Single plant extract compared to corticosteroid (n=2)

Two studies compared single plant extract to corticosteroids. The first study was conducted by Irajy *et al.* in Iran,²⁷ which stated that despite an improvement in SCORAD after applying *Fumaria officinalis*, there was no significant difference between the treatment group and the mometasone group. There were no adverse effects reported in this study. The second study was conducted by Abbasi *et al.* in Iran. The extract of *Ficus carica* L. was compared to a placebo and hydrocortisone 1% cream. There was a significant improvement in SCORAD and pruritus with $P=0.046$ and 0.004 , respectively.¹⁸

Multiple plants extract compared to placebo (n=4)

Four studies involving multiple plant extracts compared the use of these extracts to a placebo. These four studies were conducted by Ahn *et al.* in Iran,²⁸ Gu *et al.* in China,²⁹ Lee *et al.* in South Korea,³⁰ and Winayanuwattikun *et al.* in Thailand.³¹ The ingredients of the herbs are presented in *Supplementary Table 3*. A study by Ahn *et al.* reported a decrease in transepidermal water loss (TEWL) and an improvement in EASI and SCORAD.²⁸

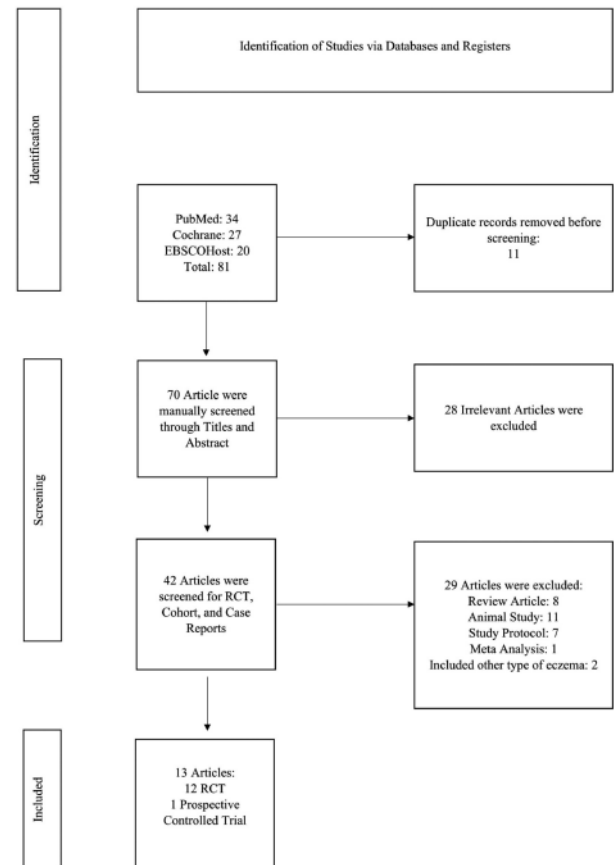


Figure 1. Flow diagram of review using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).²⁰

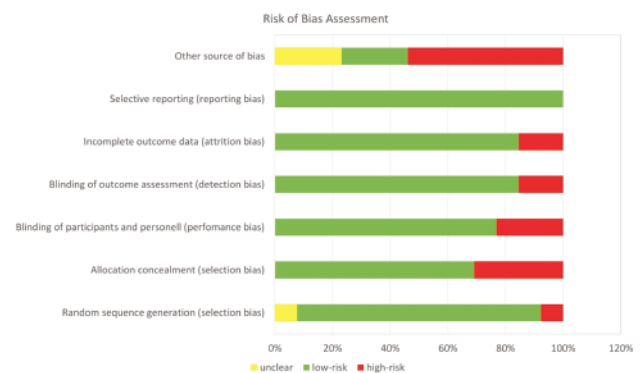


Figure 2. Risk of assessment bias.

Meanwhile, a study by Gu *et al.* revealed no significant improvement in EASI, Patient-Oriented Eczema Measure, and Children's Dermatology Life Quality Index (CDLQI) by the end of the treatment, even though the scores showed an improvement.²⁹ A study by Lee *et al.* showed improvements in SCORAD, CDQLI, and quality of life.³⁰ A study by Winayanuwattikun *et al.* reported improved skin hydration as evidenced by the decrease in TEWL.³¹ All studies reported no significant side effects.

Multiple plants extract compared to corticosteroids (n=3)

The three studies comparing multiple plant extracts to corticosteroids were studied by Chishti *et al.* in Pakistan,²² a study by Liu *et al.* in China,²⁴ and a study by Yen and Hsieh in Taiwan.²³ A study by Chishti *et al.* reported improvements in itching, pruritus, rashes, dry skin, and scale. Still, there was no significant difference between the treatment and corticosteroid group. A study by Liu *et al.* revealed that during the 12-week treatment, the mean SCORAD was decreased between the treatment and control groups, and the most significant decrease was found in the treatment group. However, the limitation of the study was that it used different forms of drugs. The herbal medicine was orally given, but the corticosteroid was topically given. On week 36, the treatment group's quality of life improved significantly. A study by Yen and Hsieh reported no significant difference in EASI and TIS scores between the treatment and corticosteroid groups. These three studies did not report any critical adverse events.²³

Multiple plants extract compared to others (n=1)

A study by Ma *et al.* in 2020 compared the use of Qinzhuiliangxue (QZLXD) decoction to Runzaozhiyang in treating atopic dermatitis.³² The results revealed that the treatment group's EASI score, itching score, and recurrence rate were lower. The adverse effects, such as abdominal pain and diarrhea, were similar between the two groups.

Discussion

Our data show that there are a variety of Asian herbal plants which can be used as a treatment for AD. Herbal medicines can be used as a treatment for AD because they have long been known to suppress inflammatory reactions. Another systematic review on topical herbal medicine for atopic eczema was developed and reported in 2017. However, the results of those studies were not limited to Asian herbal medicine in the analysis.³³

From 13 studies,^{17,18,22-32} almost all declared significant results, especially when the herbal medicines were compared to placebo. However, there were conflicting results in studies that compared herbal medicines to corticosteroids. From 5 studies that compared herbal medicine to corticosteroids (3 multiple plant extracts and two single plant extracts),^{18,22-24,27} 4 mentioned no significant result.^{22-24,27} Only one study by Abbasi *et al.* mentioned significant improvements in SCORAD and pruritus in those who received the herbal medicine Melfi cream 8% (*Ficus carica* L.) compared to hydrocortisone 1% cream.¹⁸ This means corticosteroids are still a mainstay therapy of AD and cannot be replaced by herbal products. Nevertheless, from other perspectives, it can be stated that those herbal medicines are as good as corticosteroids in managing atopic dermatitis.

From many different herbal extracts, the *Glycyrrhiza* genus became one of the ingredients used by Gu *et al.*,²⁹ Lee *et al.*,³⁰ Liu *et al.*,²⁴ and Ma *et al.*³² Interestingly, the *Glycyrrhiza* genus can be found not only in Asia but also in Australia, Europe, and America,

making it possible to be used in other parts of the world.³⁴ However, a study by Gu *et al.* revealed insignificant results, while the study by Lee *et al.*,³⁰ Liu *et al.*,²⁴ and Ma *et al.*³² revealed significant results. However, these four studies used different comparisons. Gu *et al.* compared the herbal medicine Pei Tu Qing Xin (PTQX) containing *Glycyrrhiza* to placebo in oral form. In contrast, Liu *et al.* compared the herbal medicine containing *Glycyrrhiza* (PTQXT) to topical mometasone furoate.²⁴ Lee *et al.*³⁰ also used *Glycyrrhiza*, but the herbal medicine formulation differed from Gu *et al.*²⁹ and Liu *et al.*²⁴. Lee *et al.* used Soshiho tang orally and compared it to a placebo.³⁰ Ma *et al.* also used *Glycyrrhiza* in different formulations, QZLXD, and compared it to another traditional Chinese medicine called Runzaozhiyang. This lack of uniformity in comparing treatments makes it hard to draw clear conclusions.³²

Glycyrrhiza isolated compounds vary with around 400 chemical compounds, including triterpene saponins, flavonoids, coumarins, pterocarpan, phenolics, and others. Among these compounds, flavonoids and triterpenes constitute the most significant proportion of all chemical compounds.³⁵ The pharmacological activities of glycyrrhiza as anti-inflammation and immune-regulatory effects have been evaluated as the most potential compound scientifically studied on cells, mice, and rat models. Studies have shown that Glycyrrhizin could down-regulate interleukin-10 and tumor growth factor-beta by enhancing the expression of iNOS2 and the inhibition of COX-2.³⁶

These studies show that oral or topical herbal extracts potentially affect the body's immune responses to inflammation. However, further research must be addressed to evaluate herbal medicine's efficacy solely in treating AD.

Conclusions

Asian herbal medicines have been studied and may be used as an alternative treatment in treating AD with fewer adverse effects. However, its role did not change the position of standard treatment in treating atopic dermatitis.

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Online supplementary material:

Supplementary Table 1. Summary of the papers/studies examined.

Supplementary Table 2. Risk of bias assessment.

Supplementary Table 3. Ingredients, functions and efficacy of the herbal medicine.