



Alternative Treatments for Atopic Dermatitis: An Update

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Abstract

Atopic dermatitis (AD) is a chronic pruritic inflammatory skin disease in which management with topical anti-inflammatory agents during exacerbations remains the mainstay of treatment. With no cure in sight, a significant proportion of patients elect to incorporate complementary and alternative medicine (CAM) as an adjunct to conventional treatment. Many clinicians find it difficult to provide recommendations as the field covers an extensive number of very disparate therapies, with limited quality evidence to indicate efficacy. Since publication of the last review on this topic in the Journal that compiled and analyzed randomized controlled trials (RCTs) on CAMs in 2015, several new studies have surfaced. This update aims to aggregate and review these new data. A literature search was conducted in the PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and Global Resource for Eczema Trials (GREAT) databases for RCTs on complementary and alternative therapies in AD from March 2015 through May 2018, resulting in 15 studies being included in this review. The preliminary results for many treatments such as vitamin E, East Indian Sandalwood Oil (EISO), melatonin, L-histidine, and Manuka honey show positive clinical effects, but there is currently not enough evidence to recommend their use in AD therapy. Future investigative efforts should focus on reproducing some of these studies with a larger sample size whose clinical characteristics and demographics are more reflective of the general AD population, and standardizing the process to produce reliable data.

Key Points

Atopic dermatitis is a chronic inflammatory and pruritic skin disease that is difficult to manage, and there is growing interest in utilizing complementary and alternative medicines in its treatment.

Evidence for new alternative treatments have emerged in the last several years, with some demonstrating clinical effects seemingly on par with the efficacy of conventional approaches. Additional studies are needed to confirm the validity of the preliminary results.

1 Introduction

The prevalence of atopic dermatitis (AD) or eczema has been estimated to be as high as 25% in children and 3% in adults, accounting for approximately \$3.8 billion in annual national costs [1–3]. AD is a chronic, inflammatory, and often intensely pruritic skin disease characterized by cycles of exacerbations and remissions. Flares can be unrelenting, with significant effects on quality of life (QOL), causing anxiety, depression, sleep disturbances, attention difficulties, and social withdrawal, to name a few [4].

The pathogenesis of AD is not fully understood but is multifactorial, with the central tenets being immune dysregulation, impaired skin barrier integrity, genetic susceptibility, and environmental exposures [5]. The crux of current management is barrier protection and local anti-inflammatory control with emollients and topical corticosteroids (TCs) or calcineurin inhibitors, respectively. However, there are still unmet needs for safe, effective targeted therapies as conventional medications are not without side effects. Patients are often intrigued by, and tempted to try, complementary and alternative medicines (CAMs) based on anecdotal evidence from friends, family, or online sources,

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which can be fraught with unsubstantiated claims of therapeutic benefit and without the appropriate cautions.

While some clinicians may feel this to be irrelevant to their patient population, it is likely to affect everyone taking care of these patients; more than 50% of AD patients have used CAMs for primary or adjunctive AD treatment, citing frustration with the chronic nature of the disease and dissatisfaction with conventional medical treatment as reasons [6]. In some countries such as Korea, CAM use in AD is even more prevalent, with some studies reporting numbers as high as 84% [7, 8].

As a multifactorial disease, eczema management requires a multifaceted approach with a broad toolkit encompassing the gamut of conventional medical and alternative treatments integrated in a manner that optimizes clinical outcomes and is consistent with the lifestyle and health beliefs of each individual. Recommendations in CAM are inherently more difficult to make as there are no clear guidelines due to the lack of robust randomized controlled trials (RCTs). The field is tricky to navigate as it is riddled with many small, poorly designed studies that cannot be reliably used to base clinical treatment decisions on. The literature can be daunting to sift through, but a recent evidence-based medicine (EBM) review by Vieira et al. in 2016 does much of the leg work in filtering, compiling, and analyzing the literature, showing that evidence supporting some of these therapies does exist [9]. Since then, new alternative therapies have emerged, with promising pilot studies. This narrative review aims to add to and revisit the conclusions drawn in the review by Vieira et al. in light of new evidence.

2 Literature Search Methods

A systematic literature search was conducted in the PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and Global Resource for Eczema Trials (GREAT) databases using the following Medical Subject Heading (MeSH) terms: (randomized control trial) and (atopic dermatitis, atopic eczema, or eczema) and (complementary, alternative, integrative, traditional, homeopathic, natural, acupuncture, acupressure, massage, zinc, vitamin, pyridoxine, balneotherapy, hydrotherapy, cryotherapy, aromatherapy, hypnosis, biofeedback, phytotherapy, herb, herbal, oil, histidine, honey) and (treatment, medicine, therapy, therapies, management, or supplement). In their review, Vieira et al. included studies through March 2015, therefore we restricted our search to articles published between March 2015 and May 2018, yielding a total of 55 papers.

The contents of each article were manually reviewed and the article was subsequently included if it was published in English and was on human subjects with AD as the primary disease process and an alternative therapy as the primary

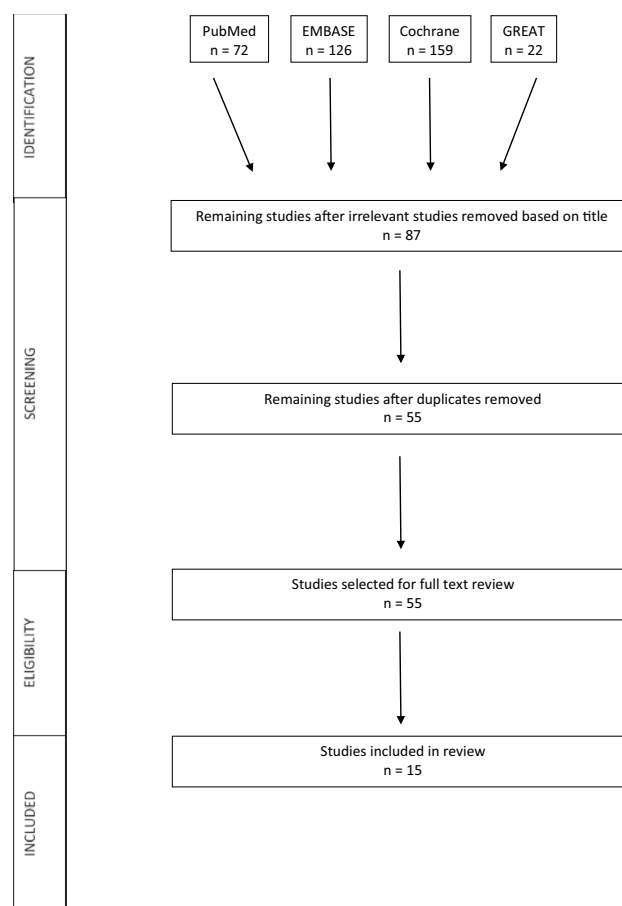


Fig. 1 PRISMA flowchart detailing the study selection process. *PRISMA* Preferred Reporting Items for Systematic Reviews and Meta-Analyses

intervention. Primary outcomes of interest included control of clinical signs and symptoms of AD and QOL. In keeping with the review by Vieira et al., studies on probiotics and diet were excluded as these areas of alternative medicine have substantial literature that warrant separate review and are considered mainstream by many. Additional studies were identified by reviewing the papers that have since cited the major trials discussed by Vieira et al., and reference lists in the trials found using the previously described MeSH headings. A total of 15 RCTs were included and are reviewed in this current article (see Fig. 1 for details on the study selection process).

3 Results

3.1 Herbal Therapy

This subset of alternative medicine remains complex given the wide variety of herbs and herbal mixtures believed to

Table 1 Statistically significant differences in SCORAD, QOL, and VAS scores in a study of the effects of Pei Tu Qing Xin Tang in moderate to severe atopic dermatitis [10]

	Treatment A ^a vs. control	<i>p</i> value	Treatment B ^b vs. control	<i>p</i> value
SCORAD				
Week 28	− 8.09 (− 13.18, − 3.00)	0.002	− 5.52 (− 10.67, − 0.38)	0.036
Week 36	− 10.28 (− 15.24, − 5.32)	0.000	− 7.86 (− 12.87, − 2.85)	0.002
QOL				
Week 36	− 2.58 (− 4.09, − 1.07)	0.000	− 2.89 (− 4.42, − 1.37)	0.000
VAS				
Week 20	1.11 (0.33, 1.89)	0.005	0.98 (0.19, 1.77)	0.015
Week 28	1.74 (0.95, 2.52)	0.000	1.33 (0.54, 2.12)	0.001
Week 36	2.49 (1.73, 3.26)	0.000	2.17 (1.39, 2.94)	0.000

PTQXT Pei Tu Qing Xin Tang, SCORAD SCORing Atopic Dermatitis, QOL quality of life, VAS visual analog scale

^aOral PTQXT vs. mometasone + water pill

^bOral PTQXT + external wash vs. mometasone + water pill

have pharmacologic properties, and the lack of adequately powered and appropriately designed RCTs. Of the studies reviewed by Vieira et al., only a few oral and topical herbal preparations showed statistically significant improvement in erythema, pruritus, and sleep [9]. Since then, six new RCTs have evaluated herbal therapies in AD.

Liu et al. conducted a multicenter, randomized, assessor-blind, placebo-controlled trial in China examining the effects of Pei Tu Qing Xin Tang (PTQXT)¹ in 275 patients aged 5–25 years with moderate to severe AD [10]. Subjects were recruited from six participating outpatient clinics in China and were included if the patient was diagnosed with AD based on the Hanifin and Rajka criteria, had moderate to severe disease as defined by the Rajka and Langeland scoring system, and had AD for more than 1 year, with a remission period of < 3 months within that year. Of the 275 patients assessed, 250 fitted the inclusion criteria and were randomized in a 1:1:1 ratio by a computer-generated random number code. Patients were placed into one of three groups (two treatment groups and one positive control group): oral PTQXT, oral PTQXT and external herbal wash² to be applied twice daily, or placebo pills composed of water and starch with topical 0.1% mometasone furoate once daily. Treatment lasted 12 weeks, with a 24-week follow-up period [11]. Baseline characteristics across all three groups were similar. Aside from a significant difference in sex ($p = 0.03$) among the three groups, there was no significant difference in age, duration of disease, and initial SCORAD, QOL, and

patient self-assessment. Group A had more male subjects, with a male:female ratio of 46:29; the reverse was true in groups B and C, with male:female ratios of 31:41 and 30:43, respectively.

Both PTQXT treatment arms showed statistically significant improvement, compared with the positive control, in self-assessed disease severity by week 20, reduction in SCORing AD (SCORAD) by week 28 (which persisted through the follow-up period), and QOL as measured by the Children's Dermatology Life Quality Index (CDLQI) and Dermatology Life Quality Index (DLQI) by week 36 [10] (see Table 1 for details on statistically significant changes). Although 9, 12, and 11 patients were lost to follow-up in groups A, B, and C, respectively, all randomized patients were included in the intention-to-treat (ITT) analysis. Including these patients in the analysis increases the reliability of the results, but still requires further validation since this is the first RCT to examine PTQXT in treating AD and there are other design flaws that reduce the quality of the study and its findings.

Although the sample size of this study was adequate with > 90% power, it would be stronger if there were fewer variables. Liu et al. do not provide an explanation for including the oral PTQXT and external herbal wash treatment arm. Neither oral PTQXT nor the herbal wash have been previously shown to improve AD symptoms, therefore introducing both of these treatments make it difficult to interpret the results as it is unclear how much each treatment contributed to clinical improvement. Removing the topical component would not only more clearly delineate the effects of oral PTQXT but would also enable the authors to make the study double-blind instead of assessor-blind, which would strengthen the study. Another limitation was the lack of detail provided on creating the PTQXT pill. The paper does not provide quantifiable measurements, stating “a dose of

¹ PTQXT is composed of nine herbs: *Radix pseudostellariae*, *Sorbus domestica*, *Ramulus Uncariae cum Uncis*, *Medulla Junci*, *Herba lophatheri*, *Semen coicis*, *Rhizoma dioscoreae*, *Concha ostreae*, and *Radix glycyrrhizae*

² External herbal wash is composed of *Rhizoma Polygonati*, *Flos Lonicerae*, *Radix Glycyrrhizae*, and *Herba Menthae*

herbs was decocted in water twice". Although PTQXT does seem to provide some benefit, the results require further validation and testing in a sample of patients that more closely resembles the clinical characteristics of the global AD population. The findings in this study cannot be generalized as the cohort was limited to Chinese patients aged 5–25 years and the proportion of men and women in each group was not similar. Regarding safety, liver damage and kidney failure have been reported in association with traditional Chinese medicines (TCMs) [12, 13]. Liu et al. monitored study participants using blood, urine, stool, hepatic and renal function tests, and electrocardiogram examinations at 0 and 12 weeks, with no adverse events reported. This study was supported by the National TCM Project Application. A preliminary randomized, controlled, open-label study by Yen and Hsieh that assessed Tzu-Yun ointment (TYO) in AD randomly assigned 33 patients to either TYO or topical betamethasone valerate for 8 weeks [14]. These patients were recruited from the Veterans General Hospital in Taichung, Taiwan, and all met the inclusion criteria of having AD for more than 5 years and aged 18–65 years (inclusive). Patients were excluded if they were pregnant or breastfeeding, had a bacterial infection, had an allergy to TYO or betamethasone, or were using systemic corticosteroids, antibiotics, immunomodulators, or phototherapy 8 weeks prior to commencement of the study. Seventeen patients were assigned to the TC group and 16 were assigned to the TYO group. There was no significant difference between both groups in demographic and clinical characteristics, including sex, age, time from disease onset, and initial Eczema Area Severity Index (EASI) and Three-Item Severity (TIS) scores. Throughout the study, one patient in each group was lost to follow-up, and these patients were subsequently excluded from the final analysis.

Percentage change in EASI and TIS scores were 0.67 ± 0.27 and 0.601 ± 0.28 , respectively, in the TC group and 0.82 ± 0.20 and 0.66 ± 0.32 , respectively, in the TYO group. There was no significant difference in the percentage change in EASI and TIS scores between the TC and TYO groups, with p values of 0.082 and 0.567, respectively.

Participants in both groups saw decreased TIS and EASI scores, with no significant difference between the two at 0, 1, 2, 4, and 8 weeks (see Table 2), suggesting that TYO may be comparable to TCs in treating AD [14]. Since this was a preliminary study, statistical power and sample size were not calculated, therefore this study is likely underpowered to truly show non-inferiority. Additionally, study participants could use the antihistamine cetirizine adjunctively with their study-assigned treatment, which may have confounded the results. The results of this study require further validation with a larger sample size, double-blinding, inclusion of patients lost to follow-up in the analysis, and a more diverse subject group to increase the reliability and generalizability

Table 2 EASI and TIS scores at baseline and after treatment with topical corticosteroids and Tzu-Yun ointment, in the study by Yen and Hsieh [14]

	TC group ($n=16$)	TYO group ($n=15$)	p value
EASI			
Baseline score	3.46 ± 2.85	7.11 ± 7.05	0.078
End score	0.83 ± 0.53	1.01 ± 0.99	0.546
p value	0.001*	0.002*	
TIS			
Baseline score	5.25 ± 1.81	5.00 ± 2.10	0.729
End score	2.25 ± 1.69	1.73 ± 1.48	0.380
p value	0.000*	0.000*	

EASI Eczema Area and Severity Index, TIS Three-Item Severity, TC topical corticosteroid, TYO Tzu-Yun ointment

*Statistically significant values

of the results. Other than one patient in each group reporting a stinging sensation that resolved within 2 days from the start of treatment, no side effects were reported. This study was funded by a grant from the Chinese Medicine Research Center and China Medical University. Whey with *Cuscuta campestris* Yuncker, also known as aftimoun or dodder seed extract, is a traditional Iranian medicine commonly used in Iran for severe and refractory AD. *Cuscuta campestris* is a parasitic plant that possesses anti-inflammatory properties and is believed to aid in skin barrier function and reconstruction, accelerating skin healing, which could be beneficial in AD. Despite its common use in Iran, the randomized, double-blind, placebo-controlled trial by Mehrbani et al. in 2015 was the first to examine its efficacy [15]. In Iran, 52 adult patients with moderate to severe AD were recruited from Afzalipour Hospital of Kerman University of Medical Sciences. The study was designed to have 95% power despite an estimated 30% dropout rate. These patients were randomly assigned to receive either 15 g of freeze-dried whey powder with two 500 mg capsules of spray-dried water extract of field dodder or corn starch placebo to be taken twice daily for 15 days, with 26 subjects in each group. Inclusion criteria included a diagnosis of AD using the Hanifin and Rajka criteria, moderate to severe AD as indicated by SCORAD > 25, age > 18 years, poor response to conventional treatment, and symptoms for more than 6 months. Patients were excluded if they were pregnant, breastfeeding, taking systemic corticosteroids or immunosuppressants, receiving phototherapy, diagnosed with systemic disease, or had abnormal blood cell count, liver enzymes, or renal function tests. There was no significant difference between the two groups in baseline characteristics, including age, sex, duration of AD, and positive familial history of AD.

The intervention was noted to increase skin moisture and elasticity significantly more than placebo by 15 days of

Table 3 Skin moisture and elasticity, pruritus, and sleep disturbance in the whey with dodder seed extract and placebo groups at baseline, week 3, and week 5, in the study by Mehrbani et al. [15]

	Baseline	Week 3	Week 5
Skin moisture			
WaDSE	13.43 ± 2.08	20.97 ± 2.02	29.91 ± 1.68
Placebo	19.72 ± 2.59	19.44 ± 2.44	17.66 ± 2.20
<i>p</i> value	0.063	0.629	< 0.001*
Skin elasticity			
WaDSE	56.04 ± 5.32	70.97 ± 4.29	79.01 ± 2.96
Placebo	61.73 ± 5.76	63.48 ± 4.95	59.30 ± 4.99
<i>p</i> value	0.476	0.261	< 0.001*
Pruritus			
WaDSE	5.70 ± 0.45	2.75 ± 0.41	2.04 ± 0.32
Placebo	4.72 ± 0.39	4.83 ± 0.45	5.38 ± 0.45
<i>p</i> value	0.122	0.002*	< 0.001*
Sleep disturbance			
WaDSE	2.41 ± 0.57	0.79 ± 0.26	0.66 ± 0.20
Placebo	1.67 ± 0.24	1.50 ± 0.30	1.77 ± 0.32
<i>p</i> value	0.255	0.086	0.005*

WaDSE whey with dodder seed extract

*Statistically significant parameters

follow-up (all $p < 0.001$). The intervention also decreased pruritus scores more than placebo at 15 and 30 days ($p = 0.002$ and $p < 0.001$, respectively) [see Table 3 for details].

Whey with dodder seed extract (WaDSE) increased skin moisture and elasticity significantly more than placebo, even when the group's baseline levels were lower in comparison; however, it is not clear how reliable these results are. Two participants were excluded from the WaDSE group 1 due to poor compliance and another was excluded due to the use of a prohibited medicine), while eight participants were excluded from the placebo group (three due to poor compliance, one from disease progression, and four who were lost to follow-up). Not only were all of these patients excluded from the analysis, the placebo group lost four times more patients than the WaDSE group, creating an imbalance in the sample size of each group and likely affecting the outcome. Moreover, the device and software used to take these measurements (Multi Skin Test Center [MC1000] with Complete Skin Investigation [CSI] software) are not routinely used in clinical efficacy studies in AD. The validity of the measurements from this device have not been tested, and it is difficult to compare the results of this study with other clinical trials. Standardization in experimental methods and analysis has been a major issue in CAM research, and this study is an example of this. Although the results of this study suggest that there is clinical benefit to be gained from using WaDSE in AD therapy, there is insufficient evidence to recommend

its use because the method of analysis is a major weakness and the results will be difficult to validate.

In the study by Mehrbani, side effects included mild temporary gastrointestinal issues [15]. Thirteen patients in the WaDSE group reported temporary anorexia and four reported mild gastrointestinal problems such as dyspepsia and a feeling of heaviness in the stomach after drug administration. No other adverse effects were reported, and patients were assessed using liver and kidney function tests, blood cell counts, and blood pressure and weight measurements. The authors did not note any funding sources or conflicts of interest.

Fig extract, or *Ficus carica* L., is another common Iranian herbal remedy whose use in contact dermatitis has been documented in the literature [16]. It has anti-inflammatory, wound healing, immune modulating, antiviral, and antibacterial properties, with some studies showing activity against *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Proteus vulgaris*, *Escherichia coli*, and *Staphylococcus aureus* [17]. In Iran, Abbasi et al. conducted a randomized, double-blind, placebo-controlled clinical trial of 45 children aged 4 months to 14 years with mild to moderate AD recruited from Mofid Children's Hospital, Tehran, Iran [16]. Inclusion criteria were age < 15 years, AD diagnosed using the Hanifin and Rajka criteria, and mild to moderate AD defined as SCORAD < 50. Participants were excluded if they had severe AD defined as SCORAD > 50, a secondary skin infection, another skin disease, an immunodeficiency disorder, or used TCs or immunomodulators 2 weeks prior to, or systemic corticosteroids or immunosuppressive agents 4 weeks prior to, the commencement of the study. Of the 121 patients assessed for eligibility, 76 did not meet the inclusion criteria, resulting in 59 patients being randomized, with 20 subjects being randomized to both the Melfi cream and placebo groups and 19 being randomized to the hydrocortisone 1% group. Subjects were assigned, in a 1:1:1 ratio, to one of three groups via block randomization, and all interventions were cream-based and were placed in the same plastic container to ensure investigator and patient blinding. Each group lost patients to follow-up—five from the hydrocortisone group, four from the Melfi cream group, and five from the placebo group—and these patients were not included in the final analysis.

There was no significant difference in age and pre-intervention mean SCORAD, intensity, and pruritus across the three groups. However, there was a statistically significant difference in the distribution of sex across the groups ($p < 0.01$), with more females than males in the Melfi (male:female: 4:12) and hydrocortisone 1% (male:female: 5:12) groups, however, reverse results were reported in the placebo group (male:female: 13:2). For 2 weeks, participants applied a cream containing 8% fig extract (Melfi cream), 1.0% hydrocortisone, or a placebo base cream twice daily.

Table 4 SCORAD, intensity, and pruritus scores at baseline and after treatment in the Melfi, hydrocortisone and base-cream groups, in the study by Abbasi et al. [16]

	Melfi	Hydrocortisone	Base cream
SCORAD			
Baseline	33.84 ± 10.05	29.53 ± 13.58	28.48 ± 10.34
After	14.85 ± 8.83	16.73 ± 9.44	34.30 ± 12.61
<i>p</i> value	< 0.0001*	< 0.001*	–
Intensity			
Baseline	6.75 ± 2.81	6.28 ± 2.84	5.60 ± 2.22
After	3.06 ± 1.80	3.28 ± 1.77	6.93 ± 2.89
<i>p</i> value	< 0.0001*	< 0.001*	–
Pruritus			
Baseline	5.31 ± 2.70	3.50 ± 2.76	5.0 ± 2.80
After	1.93 ± 1.91	2.35 ± 1.98	5.66 ± 2.92
<i>p</i> value	< 0.001*	< 0.004*	–

SCORAD SCORing Atopic Dermatitis

The *p* value for the placebo base cream was not provided

*Statistically significant values

SCORAD, intensity, and pruritus scores were all significantly reduced after 2 weeks in the Melfi cream ($p < 0.0001$, $p < 0.001$, $p < 0.001$, respectively) and 1.0% hydrocortisone groups ($p < 0.001$, $p < 0.001$, $p < 0.004$, respectively) [see Table 4 for details]. Both treatment arms also performed better than placebo in reducing SCORAD, intensity, and pruritus scores (all $p < 0.001$). Most notably, Melfi cream outperformed 1.0% hydrocortisone in reducing SCORAD and pruritus scores (mean difference of -4.959 and -1.640 ; p values < 0.046 and < 0.004 , respectively). These results suggest that a cream with a minimum of 8% fig extract could replace a low potency TC in mild to moderate AD; however, study limitations call into question the validity of the suggested conclusion [16].

Study limitations included the small sample size, short study duration, non-uniform demographics across the study groups, exclusion of patients lost to follow-up in the analysis, and the lack of generalizability due to the homogenous cohort. All subjects were < 15 years of age, had only mild to moderate AD, and were enrolled from a single site in Tehran, Iran. With only 2 weeks of treatment and two time points of measurement, the duration and full extent of clinical effect is not seen. The authors did not note any funding sources or conflicts of interest.

In Southern Asia, Indian pennywort, walnut, and turmeric are widely used traditional medicines. Khiljee et al. conducted a randomized, double-blind, placebo-controlled trial examining the efficacy of each of these items compared with placebo, in three formulations—microemulsion, gel, and ointment [18]. Participants were excluded if they had another skin disease, were taking other medications, were

Table 5 Number of patients (out of 30) showing improvement in the subcategories of erythema, edema, scaling, itching, and lichenification, in the study by Khiljee et al. [18]

	Erythema	Edema	Scaling	Itching	Lichenification
Indian pennywort					
Microemulsion	23	22	19	19	17
Gel	22	22	20	23	16
Ointment	19	20	21	18	23
Walnut					
Microemulsion	24	23	19	20	18
Gel	24	21	18	22	17
Ointment	22	21	22	20	24
Turmeric					
Microemulsion	23	19	22	21	20
Gel	22	18	20	22	21
Ointment	23	18	23	19	21

Each category was statistically significant at $p = 0.000$ vs. placebo

breastfeeding or pregnant, or had known hepatic disease, kidney disease, or drug hypersensitivities. A total of 360 patients with mild to moderate eczema were enrolled, with 30 patients in each group, and all randomized patients were included in the final ITT analysis. Patients were instructed to apply their assigned topical treatment twice daily for 4 weeks. The degree of erythema, edema, scaling, itching, and lichenification were measured on a scale of 0–3, from none to severe. Table 5 presents the number of patients (out of 30) experiencing symptom improvement in the areas of erythema, edema, scaling, itching, and lichenification.

Across all vehicles, Indian pennywort, walnut, and turmeric each showed statistically significant improvement compared with placebo ($p = 0.000$). However, Khiljee et al. did not provide details on the degree of symptom reduction in any of the categories and the amount of symptom improvement that qualified a patient to be considered as showing ‘improved symptoms’ [18], significantly compromising the reliability of the study. Inclusion into the group of patients who showed symptom improvement may not have required a statistically significant degree of symptom reduction, which would have inflated the reported proportion of patients showing improvement. The lack of transparency is compounded by the absence of validated measurements of symptom severity. The authors cite use of a 0–3 scale to measure symptom severity, but the numbers were not reported or discussed. When comparing mode of treatment delivery, Khiljee et al. stated that microemulsion was more effective in reducing erythema and edema, gel was more effective in relieving itch, and ointment was more effective in reducing scaling and lichenification, although, again, the lack of validated representation of this symptom

Table 6 SCORAD at baseline and days 29, 57, and 85 in the WO 3260 and control groups, in the study by Olah et al. [19]

	WO 3260			Imlan Crème Pur		
	Mean	Mean change from baseline	<i>p</i> value	Mean	Mean change from baseline	<i>p</i> value
Baseline	9.6	–	–	9.8	–	–
Day 29	7.2	– 2.4	< 0.001*	7.5	– 2.3	< 0.001*
Day 57	7.1	– 2.5	< 0.001*	8.2	– 1.6	0.008*
Day 85	7.9	– 1.6	0.013*	9.3	– 0.5	0.511

*Statistically significant values

improvement obscures the reliability of the results. Moreover, baseline characteristics of the cohort were not reported, limiting interpretation of the results. Without demographic data, it is unclear whether the results were skewed by unequal distribution of age, sex, initial disease severity, and other features. Furthermore, without understanding the makeup of the cohort, the results cannot be reliably applied to the general AD patient population. No loss to follow-up or adverse events were reported in the study [18], which was funded by the Higher Education Commission.

Echinacea purpurea is thought to have immunomodulating properties via direct cannabinoid 2 (CB2) receptor binding and increasing endogenous cannabinoid tone by partially inhibiting fatty acid amide hydrolase (FAAH), which degrades endogenous cannabinoids [19]. Cannabinoid receptors are largely found in immune tissue such as the tonsils and spleen, and the CB2 receptor has been shown to modulate immune cell functions [20]. The skin has an endocannabinoid system (ECS) and a study on the NC/Tnd mouse model for AD has shown worsened skin inflammation with loss of cannabinoid signaling, and significantly reduced skin symptoms with increased endocannabinoid tone [21].

Olah et al. conducted a randomized, double-blind, single-center, placebo-controlled study in Hamburg, Germany, to examine the effects of *Echinacea purpurea* on atopic skin [19]. Before *Echinacea extract* was applied to human skin, human repeat insult patch (HRIP) testing was performed to confirm that it had low sensitization potential. In 104 participants aged 18–75 years, the mean cumulative irritation score was 1.78 for *Echinacea extract* and 1.53 for the control (Linola body lotion); after 48 h of continuous occlusive application, neither product caused significant erythema.

For the clinical part of the study, 60 patients aged 10 years or older were enrolled. Participants were required to have two eczematous areas located contralaterally to each other and with a local SCORAD of at least 4 and a erythema and pruritus score of at least 1. Patients were excluded if they had other active skin disease, serious medical conditions potentially affecting the test reaction and assessment, and topical medication application on the test sites or use of systemic anti-inflammatory agents, analgesics, immunosuppressive

agents, antihistamines, or antibacterial agents the day before the commencement of the study or during the study period. *Echinacea extract* cream (WO 3260) was compared with Imlan Crème Pur, an emollient that has a smell similar to the characteristic odor of *Echinacea purpurea*. Patients applied the assigned topical treatment two to three times per day, on both sites, for 3 months. SCORAD was measured at baseline and at days 29, 57, and 85.

The reported average age and standard deviation, as well as male:female ratios, were comparable in both groups, although there was a female predominance—63.3% and 61.2% in the treatment and control groups, respectively. The treatment group averaged 30.2 ± 15.9 years, while the control group averaged 32.5 ± 16.4 years. Both WO 3260 and Imlan Crème Pur reduced local SCORAD at day 29 ($p < 0.001$) and day 57 ($p < 0.001$ and $p = 0.008$, respectively). At day 85, only WO 3260 showed significant improvement in local SCORAD compared with baseline ($p = 0.013$) [see Table 6 for details]. WO 3260 consistently yielded a greater absolute reduction in SCORAD compared with the control at each time point after treatment initiation, but only the difference measured on day 85 was statistically significant ($p = 0.047$). Moreover, the local SCORAD area under the curve (AUC) was significantly lower for WO 3260 compared with the control (654 vs. 708.5; $p = 0.021$). The effects of WO 3260 lasted longer than Imlan Crème Pur, suggesting that the effects were due to more than just emollient properties, although further studies are needed for confirmation. Of the 60 randomized patients, 11 were excluded from the analysis. One was lost to follow-up, four withdrew due to an AD flare, and five no longer met the inclusion and exclusion criteria. One subject withdrew. There were also two partial exclusions in the analysis for day 29 due to an adverse reaction, although details were not provided. Assessments were not collected for those two patients, but both completed the study. Although the results show a positive clinical impact, not including all randomized patients in the analysis likely affected the results. Moreover, the sparse demographic and clinical characteristic data reported in the study does not give enough insight into whether the cohort reasonably reflects the larger AD population. In addition, it

should be noted that the study was funded by an industrial research grant and three of the seven authors are employees of the sponsor and are on a patent application for a preparation containing *Echinacea* extract.

Overall, herbal therapies are economic, accessible, and relatively safe, although hepatic and renal toxicity have been reported from certain herbal preparations [12, 13]. Furthermore, while untoward effects are certainly possible, the aforementioned studies reported no adverse events and all yielded reductions in AD severity. All studies, with the exception of the study by Liu et al., were limited by small sample sizes. Although the study by Liu et al. had a large sample size, it lacked a placebo that matched the interventions and standardization with PTQXT dosing, as the amount of each component of the formula was tailored to individual patients. These flaws in study design obscure the clinical meaningfulness of the results. A meta-analysis by Shi et al. that evaluated 24 RCTs studying TCMs, through December 2016, drew similar conclusions [22]. The authors acknowledged that the analysis was limited by the lack of RCTs that could be included, small sample sizes, and significant heterogeneity, likely attributed to non-uniform controls and treatment dosing [22]. This is very representative of the landscape of the research in this field, underscoring the need for more quality evidence (Table 7).

3.2 Vitamins

Vitamin E is an essential nutrient with immune modulating activity. A randomized, double-blind, placebo-controlled trial by Jaffary et al. studied 70 patients aged 10–50 years, with mild to moderate AD in Isfahan, Iran [23]. Patients from two teaching hospitals were enrolled—Alzahra and Noor, affiliated with Isfahan University of Medical Sciences. Subjects were excluded if they had severe disease defined as SCORAD > 50, were pregnant or breastfeeding, had a coagulopathy or history of allergy to vitamin E, used systemic corticosteroids or immunosuppressants, or lived far from Isfahan. At baseline, both groups had a male:female ratio of 43:57% and no other characteristics were described.

These patients were administered 400 IU of vitamin E or placebo daily. After 4 months of treatment, patients taking vitamin E experienced greater improvement in their symptoms compared with those patients taking placebo in terms of reduced itching (− 10.85 vs. − 3.54), SCORAD (− 11.12 vs. − 3.89), and extent of lesion, which was characterized by erythema, edema, excoriation, and lichenification (− 10.85 vs. − 3.54) [all $p < 0.05$]. This was not sustained at 3 months of follow-up. In fact, 25% (7/28) and 22.2% (6/21) of patients relapsed in the treatment and placebo groups, respectively, with no significant difference between the two [23]. Five patients were lost to follow-up—two in the vitamin E group and three in the placebo group. Whether

these patients were included in the final analysis was not discussed in the study, affecting the reliability of the results. In addition, various clinical characteristics of the cohort may not have been equally distributed between the two groups and may have skewed the results, especially since the study lacks a detailed description of the demographic distribution. Another limitation is that patients were allowed to use topical hydrocortisone cream 1% and hydroxyzine tablets if needed, which may have also affected the validity of the results. Although there have been documented reports in the literature of contact dermatitis, burning, and itching with topical use of vitamin E, no side effects with low-dose oral vitamin E were reported in this study. The authors had no funding sources or conflicts of interest to disclose.

3.3 Amino Acids

Maintaining an intact skin barrier is essential to controlling AD. The most superficial layer of the skin is composed of terminally differentiated keratinocytes, structural proteins such as filaggrin (FLG), and lipids [5]. Profilaggrin is a large (> 400 kDa) polypeptide that is processed into 37 kDa FLG monomers [24]. FLG proteolysis releases L-histidine and other amino acids as natural moisturizing factors (NMFs) that maintain skin hydration [5, 24]. Lower levels of NMF and resultant transepidermal water loss (TEWL) have been implicated in AD pathogenesis [5]. Moreover, FLG mutations, especially loss-of-function mutations, are strongly associated with AD, but are found in only 15–50% of AD patients [5, 24]. In fact, many AD patients are wild-type FLG, and 40% of FLG mutation carriers never develop AD [4]. AD patients with wild-type FLG likely have epigenetic effects that reduce FLG processing and thus NMF levels, compromising skin hydration and barrier integrity.

A randomized, double-blind, placebo-controlled, crossover pilot study by Tan et al. examined the effects of 4 g of L-histidine or placebo (erythritol), to be taken once daily for 8 weeks, in 24 adult patients [24]. Patients were included if they were over 18 years of age and diagnosed with AD using the UK Working Party Diagnostic Criteria for Atopic Dermatitis, but were excluded if they were pregnant or breastfeeding, and had liver disease, exposure to natural or artificial ultraviolet radiation and immunosuppression from disease or medication, or used Chinese herbal medicines 3 months prior to commencement of the study. Participants were assigned groups via an online randomization tool. The average age in groups A and B was 25.9 ± 1.6 and 27.6 ± 1.6 years, respectively. All patients were Caucasian, except for one patient in each group, and group A was 55% female, whereas group B was 70% female.

L-histidine reduced SCORAD by 34% ($p = 0.0029$) and Patient Oriented Eczema Measure (POEM) scores by 39% ($p = 0.002$) after 4 weeks. At 8 weeks, the reduction in

Table 7 Studies of herbal therapies for atopic dermatitis

References	Treatment	Study design	Number of patients enrolled	Duration	Baseline AD assessment	Assessment of AD improvement	Age range	Results	Adverse effects
Liu et al. [10]	Oral PTQXT*, oral PTQXT + external TCM wash**, 0.1% mometasone furoate + water pills with starch	Ran, ab, pb	275	12 weeks tx, 24 weeks f/u	Mild to moderate AD, SCORAD	SCORAD, CDLQI, DLQI, VAS	5–25 years	Oral PTQXT and oral PTQXT + external wash significantly improved SCORAD, QOL, and VAS compared with mometasone + water pill	Mild cold or diarrhea with resolution upon discontinuation
Yen and Hsieh [14]	TYO, betamethasone valerate (TC)	Ran, contr, open-label	33	8 weeks	EASI, TIS	EASI, TIS	18–65 years	No statistically significant difference in EASI and TIS scores between TC and TYO	Stinging sensation that resolved within 2 days of starting treatment
Mehrbani et al. [15]	<i>Cuscuta campestris</i> Yuncker (afimoun, dodder seed extract) + whey powder (WadSE), placebo	Ran, db, pb	52	15 days tx, 15 days f/u	Moderate to severe AD (SCORAD ≥ 25)	Skin moisture, elasticity, pigmentation, surface pH, and sebum content as measured by the Multi Skin Test Center (MC1000); patient reported VAS pruritus and sleep disturbance	≥ 18 years	WadSE significantly increased skin moisture and elasticity and decreased pruritus and sleep disturbance at week 5. It also decreased pruritus at week 3	Temporary anorexia, dyspepsia, feeling of heaviness in the stomach after drug administration
Abbasi et al. [16]	Topical <i>Ficus carica</i> L. (fig) 8% extract (Melfi cream), hydrocortisone 1.0%, placebo cream	Ran, db, pb	59	2 weeks	Mild to moderate AD (SCORAD < 50)	SCORAD	4 months to 14 years	Melfi cream improved SCORAD and pruritus scores more than hydrocortisone and placebo by a statistically significant amount	No adverse effects reported

Table 7 (continued)

References	Treatment	Study design	Number of patients enrolled	Duration	Baseline AD assessment	Assessment of AD improvement	Age range	Results	Adverse effects
Khiljee et al. [18]	Indian pennywort, walnut, turmeric	Ran, db, pb	360	4 weeks	Erythema, edema, scaling, itching, lichenification on a scale of 0–3 (none–severe)	Erythema, edema, scaling, itching, lichenification on scale of 0–3 (none–severe)	Pediatric and adult cohort, age range not provided	Indian pennywort, walnut, and turmeric each statistically significantly increased the proportion of patients experiencing improvement in each symptom compared with placebo	No adverse effects reported
Olah et al. [19]	<i>Echinacea purpurea</i> extract cream (WO 3260), Imilan Crème Pur	Ran, db, pb	60	12 weeks	SCORAD	SCORAD	≥ 10	Both treatments reduced SCORAD by a statistically significant amount at each time point. Mean SCORAD reduction was greater with WO 3260 than the control at each time point, but was only statistically significant on day 85	No adverse effects reported

ab assessor-blind, *AD* atopic dermatitis, *CDLQI* Children's Dermatology Life Quality Index, *contr* controlled, *db* double-blind, *DLQI* Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *f/u* follow up, *pb* placebo-controlled, *PTQXT* Pei Tu Qing Xin Tang, *QOL* quality of life, *Ran* randomized, *SCORAD* Scoring AD, *TC* topical corticosteroids, *TIS* Three-Item Severity, *tx* treatment, *TYO* Tzu-Yun ointment, *VAS* visual analog scale

SCORAD and POEM was sustained at 32% ($p = 0.0029$) and 39% ($p = 0.001$), respectively. L-Histidine had a profound effect on AD symptoms, an effect comparable to a mid-potency (group III) TC and one that persisted after discontinuing L-histidine supplementation. Although 24 patients were randomized, only 21 were analyzed as three patients were lost to follow-up, which occurred prior to receiving treatment. For a study with such a small sample size, excluding three patients from the analysis can significantly affect the results. Moreover, the findings of the study cannot be applied to the general population as this cohort consisted predominantly of Caucasian females. Participants were also allowed intermittent rescue therapy with TCs and non-medicated emollients. If and how frequently subjects used rescue therapy was not documented, and this would significantly confound the results. Based on this pilot study, L-histidine shows promise as an adjunctive treatment, but the sample size was small and an RCT with a larger cohort is needed to verify the results, the cohort demographics are very specific therefore findings may not be readily generalized, rescue therapy with TCs was allowed and not tracked, and not all randomized patients were analyzed. These are significant limitations that dilute the significance of the positive impact that, the authors are suggesting, L-histidine has on ameliorating AD symptoms, and preclude recommendation of its use in AD treatment for now. The authors also found L-histidine to be safe, with no adverse events noted during the study [24]. This study was funded by the Scottish Overseas Research Student Award, University of Edinburgh College of Medicine and Veterinary Medicine PhD Scholarship, and the University of Manchester.

A pilot study by Aranda et al. assessed the effects of isoleucine (ISL) on AD severity in 20 patients aged 5–18 years with mild to severe AD, in Brazil [25]. Patients were excluded if they had food allergies, kidney or liver disease, difficulty swallowing, and corticosteroid or immunosuppressive medication use. All patients were administered ISL 10–30 mg/kg/day for 60 days and were allowed to maintain their usual treatment regimen. Of the 20 patients enrolled, 19 completed the study. The average age was 9 years (range 5–17 years) and the cohort consisted of four (21%) males. The distribution of disease severity was four (21%) patients with mild disease, nine (47%) patients with moderate disease, and six (32%) patients with severe disease.

After 60 days, a reduction in SCORAD (-19.2 ± 11.4 , $p < 0.001$), objective SCORAD (-16.8 ± 10.7 , $p < 0.001$), and pruritus (-3.4 ± 1.5 , $p < 0.001$) was noted, independent of AD severity as there was no statistical difference in SCORAD or pruritus across the mild, moderate, and severe AD groups. Notably, serum ISL levels did not increase in a statistically significant amount and the initial (52 ± 12.7) and final (58.3 ± 21.5) ISL serum concentration in participants was in the normal range for the general

population. Although the results show a positive effect on AD, it is unclear if this was due to ISL supplementation or the participants' previously prescribed medications. This confounding factor and lack of placebo comparison compromises the results of the study, preventing the intervention from being accurately assessed [25]. The lack of randomization and blinding are also significant limitations. No side effects were reported, and no funding sources or conflicts of interest were reported.

3.4 Topical Oils

Vieira et al. have previously noted that sunflower seed, coconut, and evening primrose oil had evidence to support their therapeutic use in AD [9]. Furthermore, Sandalwood album oil (SAO) has recently come to light as another topical oil that may yield symptomatic improvement in AD [25]. SAO has anti-inflammatory and antioxidant properties mediated by inhibition of 5-lipoxygenase, proinflammatory cytokines, cyclooxygenase, and reactive oxygen species (ROS) formation [26]. SAO may also have activity against many fungi, viruses, and gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Staphylococcus aureus* (VRSA) [26]. It has a benign safety profile, and a recent phase II trial studying three topical East Indian Sandalwood oil (EISO) formulations with 0.1% colloidal oatmeal in 25 AD patients demonstrated a significant reduction in AD severity [27]. Sharma et al. performed a single-center, open-label, proof-of-concept study of 25 pediatric patients with mild, moderate, or severe eczema, with 22 patients completing the study [27]. No further details regarding the inclusion and exclusion criteria or baseline characteristics were given. Over 8 weeks, all but one patient showed improvement, with 87.5% of the cohort seeing a 25% reduction in EASI scores, 75% seeing a $> 50\%$ reduction in EASI scores, and 18.8% achieving complete remission [27]. While the results indicate symptom improvement with EISO treatment, it is not as clear how much of the improvement seen can be directly attributed to EISO. There was no mention of a control group and without at least a 0.1% colloidal oatmeal group for comparison, it cannot be said that the improvement seen was due to EISO. Moreover, a description of the preparation did not detail the ingredients included in each of the three formulations, hence other variables may have contributed to symptom reduction, confounding the results. Lack of randomization and blinding also contributed to the many limitations in this study. No adverse events were reported, and this study was funded by Santalis Pharmaceuticals, a company focused on developing dermatology drugs based on EISO.

3.5 Honey

A study by Al-Waili in 2003 showed a significant reduction in AD severity at 1, 2, and 3 weeks of topical treatment with a honey, beeswax, and olive oil mixture in 21 adult patients with mild to moderate AD that allowed for a 75% reduction in corticosteroid dose without clinical deterioration [28]. Although this study was small and it was unclear which ingredient(s) yielded the positive results, the review by Vieira et al. concluded that olive oil worsened AD outcomes, suggesting that the effect came from honey, beeswax, or both [9, 28]. Over a decade later, Alangari et al. found that topical Manuka honey had potential as a natural therapeutic in AD [32]. Honey has broad-spectrum antimicrobial properties in vivo and in vitro and has also been found to promote wound healing [29]. Furthermore, Manuka honey inhibits *S. aureus* proliferation, leukocyte infiltration, and inflammation [30, 31].

In the open-label pilot study by Alangari et al., 16 adults with bilateral, similarly affected eczematous areas were enrolled [32]. Subjects were excluded if they had severe, extensive AD or other skin disease. Of the 16 subjects recruited, 14 completed the study and 2 withdrew due to worsening symptoms. The average age of the cohort was 33 ± 10 years, with a male:female ratio of 6:8. Fourteen adults with bilateral antecubital fossae lesions applied Manuka honey on one site overnight for 7 consecutive days, leaving the contralateral side untreated. After 7 days, the treatment site showed a significant pre- to post-reduction in TIS score (mean difference of -2 , $p < 0.001$), with no significant change in the control lesions (mean difference of -0.7 , $p = 0.15$) or staphylococci isolates from days 0 to 7 [32]. Although local symptom reduction was seen, the results require validation with a larger cohort. In addition to increasing the sample size, this study would also benefit from including other measures of AD symptom improvement, such as POEM and DLQI, to provide additional objective data points and to assess other areas affected by AD. Moreover, while TIS has been correlated with SCORAD, SCORAD is now considered inferior to POEM or EASI, both of which are thought to be better suited to capture the effects of clinical treatment of AD in clinical trials [33]. Randomization and investigator and patient blinding would be prudent design measures to add if future RCTs are to assess the effects of Manuka honey on AD as these factors were also significant limitations of this study. No adverse effects were reported. This study was funded by the Deanship of Scientific Research at King Saud University, and one of the authors has received consultation and presentation fees from Derma Sciences Inc., which produces a product, Medihoney, using Manuka honey.

A similar study by Henatsch et al. evaluated 15 patients with recurrent eczematous external otitis treated with

medical honey ear drops three times daily for 2 weeks. Inclusion in the study only required patients to have eczematous external otitis that had not been treated 2 weeks prior to commencement of the study [34]. Baseline characteristics included average age of 63 years (range 46–89) and a male:female ratio of 12:3. Discomfort, itching, and combined redness and scaling were measured using visual analog scale (VAS) scores. After treatment, there was a significant reduction in discomfort (5.3 – 3.6 , $p < 0.01$) and itching (5.5 – 1.8 , $p < 0.01$) and combined redness and scaling score (4.4 – 3.1 , $p = 0.02$). The honey drops also eradicated commensal bacteria in 4 of 10 patients, although *S. aureus* colonization remained unchanged [34]. No losses to follow-up and no adverse reactions were reported. Limitations of this study include the small sample size and lack of a placebo-control group, randomization, blinding, and more rigorous inclusion criteria. The authors had no funding sources to disclose; however, they note that Dos Medical BV provided honey eardrops for the study but made no other contributions.

3.6 Melatonin

Skin barrier function, keratinocyte proliferation, inflammatory response, blood flow, and facial sebum production have all been reported to operate in a rhythmic pattern, with defined peaks and troughs in a 24-h day [35]. At night, circulating naïve T cells, proinflammatory cytokines, skin blood flow, and TEWL are at their peak, whereas facial sebum production is at its trough [35, 36]. Sebum forms a lipid layer on the skin to prevent TEWL, and greater blood flow yields greater skin permeability and histamine release. Decreased sebum lipid layer and increased blood flow, skin permeability, histamine release, and TEWL all contribute to worsening night-time pruritus [35].

High levels of proinflammatory cytokines, night-time pruritus, and abnormal melatonin production contribute to sleep disturbances, leading to low energy, behavior problems, mood disturbances, learning difficulties, and shifts in the immune system towards a T-helper (Th) 2 response, which further perpetuates AD [35, 37]. Higher nocturnal melatonin is associated with less sleep disturbance and less severe AD symptoms in children [37].

In a randomized, double-blind, placebo-controlled study by Chang et al., 48 children aged 1–18 years who were seen at the National Taiwan University Hospital pediatric and dermatology departments from 1 August 2012 through 31 January 2013 were enrolled [38]. Eligibility criteria included having physician-diagnosed AD involving more than 5% of body surface area (BSA) with sleep problems, defined as any difficulty with sleep initiation or maintenance that leads to impaired QOL or interferes with daytime activities of the child or family more than 3 days per week in the 3 months

Table 8 SCORAD, objective SCORAD, and sleep onset latency at baseline and after treatment with melatonin versus placebo, in the study by Chang et al. [38]

	Melatonin			Placebo			Difference in effect ^a	<i>p</i> value
	Before	After	Change	Before	After	Change		
SCORAD	49.1	40.2	− 9.9	48.0	46.8	− 0.7	− 9.1	< 0.001
Objective SCORAD	38.6	31.3	− 8.2	37.4	37.6	− 0.6	− 8.7	< 0.001
Sleep onset latency	44.9	21.6	− 23.4	31.5	29.6	− 1.2	− 21.4	0.02

SCORAD SCORing Atopic Dermatitis

^aDifference in effect between melatonin and placebo, as estimated by a linear mixed-effects model, adjusted for age and sex

preceding the study. Subjects were excluded if they had a documented sleep disorder, any other medical condition that might cause sleep issues, or use of medications for insomnia or antidepressants within 4 weeks prior to the participant's baseline assessment visit. Patients were randomized by a computer-generated sequence monitored by special personnel with no other involvement in the trial. Participants were assigned in a 1:1 ratio to receive either 3 mg of melatonin or placebo every night for 4 weeks, followed by a 2-week washout period then crossover for 4 weeks. The melatonin and placebo tablets were identical in appearance. Patient characteristics were comparable between the two groups, with an average age of 7.6 ± 4 years in the 'melatonin first' group and 7.3 ± 3.5 in the 'placebo first' group. There were slightly more females in the melatonin group compared with the placebo group, i.e. 13 (54%) and 10 (42%), respectively. Baseline SCORAD was also similar at 49.1 and 48.0 in the melatonin and placebo groups, respectively.

Melatonin shortened sleep latency 21.4 min more than placebo ($p=0.02$). It also decreased the SCORAD index and objective SCORAD index more than placebo by a statistically significant amount (see Table 8), with no significant carryover effect ($p=0.67$). Of the 48 participants who were randomized, 10 withdrew prior to study completion (six in the melatonin group and four from the placebo group), resulting in 38 participants being included in the analysis. Although the study only required 48 randomized subjects to have a power of 80%, given an alpha of 5% and estimated withdrawal rate of 33%, and the 10 subjects who withdrew still fell within the 33% allowance, excluding those subjects from the analysis may still affect the results. No adverse effects were reported.

Melatonin may affect AD by decreasing wake time at night, reducing scratching opportunities, and modulating the immune system. Both Th1 and Th2 cells have melatonin receptors that produce interleukin (IL)-2, IL-6, IL-12, and interferon- γ when acted upon, driving the body primarily towards a Th1 response. Despite the small sample size, Chang et al. demonstrated benefit in AD symptoms derived from melatonin supplementation; however, further validation with larger sample sizes is still required. If the trajectory

of future studies is comparable to that of Chang et al., melatonin may prove to be a useful adjunctive treatment in AD, especially in patients with associated sleep disturbance; however, at present, evidence to support its current use in AD is lacking [38]. The authors reported funding from the National Taiwan University Hospital and the Yonghe Cardinal Tien Hospital.

3.7 Alpine Climate

Fieten et al. published the first study on alpine climate treatment in AD, a therapy akin to other types of climatotherapy historically used in Europe for difficult-to-treat AD [39]. In this trial, 77 children aged between 8 and 18 years with difficult-to-treat AD received 6 weeks of personalized treatment from a multidisciplinary team, as an inpatient in the alpine Switzerland climate, 1560 m above sea level, or as an outpatient in the moderate maritime climate of The Netherlands [39]. According to the authors, the alpine climate is characterized by dry air, low allergen exposure, and increased exposure to ultraviolet radiation [40]. Subjects were included if they had moderate to severe AD, were aged between 8 and 18 years, were fluent in Dutch, had internet access at home, and were able to stay in Davos, Switzerland, for 6 weeks. Eighty-four patients were randomized in a 1:1 ratio by an external data manager via a random sequence generated by a covariate adaptive randomization method that controls for imbalance between various characteristics.

Of the 84 patients who were randomized, 74 completed follow-up, but all 84 were included in the ITT analysis. There was a 12% dropout rate, including three subjects from the alpine group and seven from the maritime group. The authors reported that there was no difference in baseline characteristics of children who completed and dropped out of the study, but the data are not shown. EASI and CDLQI scores both improved more in the alpine group by a statistically significant amount right after ending treatment and 6 weeks after, although this effect was lost 6 months out (see Table 9) [39].

Alpine climate treatment may be useful when immediate drastic results are required, but many design flaws preclude

Table 9 EASI and CDLQI scores in the alpine versus maritime climate groups, in the study by Fieten et al. [39]

	Alpine	Maritime	Difference ^a	<i>p</i> value
EASI				
Baseline	28.2	28.3	–	
6 weeks	3.0	14.5	– 10.1	0.000
12 weeks	8.5	14.1	– 8.4	0.000
6 months	11.9	15.1	– 3.4	0.185
CDLQI				
Baseline	8.7	7.9	–	
6 weeks	2.9	4.8	– 1.9	0.008
12 weeks	4.7	5.1	– 1.5	0.019
6 months	4.4	4.8	– 0.3	0.707

CDLQI Children's Dermatology Life Quality Index, *EASI* Eczema Area Severity Index

^aEstimated difference corrected for baseline scores

meaningful use of the results. The variation in the clinical setting may have been a confounding factor. Children in the alpine climate group were also in an inpatient setting and had daily interactions with and assistance from medical personnel, likely yielding better compliance. Returning home, children in the alpine inpatient arm likely had more difficulty adapting to implementing treatments on their own, whereas the moderate altitude outpatient group developed those skills during the study [39]. Moreover, the lack of blinding is another significant limitation and one that would be difficult to address in future studies as the treatment modalities are very different and impossible to disguise. There is insufficient evidence to recommend alpine climate treatment in AD. This study was supported by grants from the European Allergy and Asthma Center Davos, Merem Dutch Asthma Center Davos, and patient support groups.

3.8 Other

MD2011001 is a non-steroidal topical cream containing vitamin E, epigallocatechin gallate (EGCG) and grape seed procyanidins. EGCG is the most abundant catechin in green tea, but all are antioxidant and emollient ingredients widely used in cosmetics. Patrizi et al. performed a single-center, double-blind, randomized controlled study in Bologna, Italy, to evaluate the safety and efficacy of MD2011001 [41]. Patch testing was performed first to establish a safety profile and determine sensitizing potential. This study randomized 44 patients who were at least 6 years of age and had mild to moderate AD localized on the head and neck, at the University of Bologna, Italy. AD severity was determined using the Investigator's Global Assessment (IGA) and patients were included if their IGA score was 2 or 3. However, patients were excluded if they had moderate to severe

AD, other skin disease, skin infections, systemic drug use, a medical condition that interfered with study participation, hypersensitivity to the product ingredients, or were pregnant or breastfeeding. At baseline, the majority of the cohort were Caucasian (41/44 subjects) and were predominantly female (male:female ratio of 15:29), with an average age of 22.6 years (range 6–69). Placebo was a topical cream that did not contain vitamin E, EGCG, and grape seed procyanidins. Patients applied the assigned cream to the affected areas twice daily for 4 weeks. Participants were evaluated at days 0, 7, and 28 using the IGA and the Patient's Global Assessment (PGA). IGA was recorded as a score of 0 or 1 for treatment failure or success, and failure was set at an IGA score ≥ 2 . Severity of erythema, edema/papules, vesiculation/crusting, excoriation, lichenification/prurigo, and xerosis were also measured on day 7 [41].

Although 44 patients were randomized, only 39 were included in the final analysis. Two subjects had an inadequate washout period prior to starting the study, two were withdrawn due to rescue TC use between days 0 and 7, and one never applied the assigned product. There was no significant difference in IGA or PGA scores in terms of average value reduction or rate of therapeutic success within and between the MD2011001 and placebo groups. By day 7, MD2011001 significantly reduced the affected surface area in the face and neck compared with baseline. All symptom severity was reduced compared with baseline in both the MD2011001 and placebo groups. The change was statistically significant for all signs and symptoms, except papules and vesicles on day 7 and vesicles on day 28. However, there was no statistically significance difference in symptom reduction between MD2011001 and placebo, indicating that this topical cream performs no better than the regular emollient in alleviating AD symptoms. Limitations of this study include the lack of generalizability due to an homogeneous cohort that was predominantly Caucasian, female, and young. In addition, although the authors attempted to perform a double-blind study, the two creams had a different color and smell due to their composition. Even with packaging and labeling by study personnel uninvolved in patient assessment, patients and/or the investigators could very likely have uncovered the group assignments during the trial. Adverse events included irritant contact dermatitis, AD flare, and impetigo in both groups, as well as one case of flu-like syndrome in the MD2011001 group [41]. This study was funded by Panin S.r.l.

4 Discussion and Conclusion

AD is a chronic, relapsing pruritic disease that can be rather difficult to control. Patient frustration with symptom control coupled with hopes of avoiding long-term TC use and its side

effects leaves much to be desired in AD treatment. The review by Vieira et al. suggests that acupuncture and acupressure, hypnosis, massage, biofeedback, balneotherapy, sunflower seed oil, coconut oil, pale sulfonated shale oil, oral evening primrose oil, vitamin D supplementation, topical vitamin B₁₂, and select herbal preparations have some evidence to suggest therapeutic benefit in ameliorating clinical signs and symptoms of AD [9].

The recent RCTs on new herbal therapies add to the growing body of evidence in this area, but there is undeniably a lack of quality and consistency in these studies that gives pause in accepting the results at face value. Similar to the conclusions drawn by Vieira et al., there is a positive signal with select therapies, but there are important caveats. With the current state of evidence, herbal therapies have no place in conventional AD management, but with more standardized, larger, placebo-controlled clinical trials, this position may be re-assessed at a later point.

Although the stance on herbal therapy remains the same, vitamin E, EISO, L-histidine, Manuka honey, and melatonin have shown some benefit in improving AD symptoms. However, even with these agents, there is still more to be desired regarding the quality of evidence. The vast majority of the alternative interventions studied have not had initial results reproduced and verified, and most of the initial pilot RCTs had small sample sizes, opening the door for chance and other factors to affect the results. To some extent, this is to be expected as alternative medicines receive significantly less attention and funding compared with conventional pharmacologic therapies.

Although there are currently no evidence-based recommendations that can be made from the available literature, what remains compelling about CAMs is that many of the studies included in this review have reported no adverse events and patients have an interest in exploring alternative avenues in treating their eczema. Research in this area needs to be better and generate reliable data to guide the clinician and patient in crafting individual treatment plans. As the number of trials with larger sample sizes, appropriate controls, and standard parameters grows, it is plausible that some CAMs will graduate into the conventional mainstream.

Compliance with Ethical Standards

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