

# Topical herbal medicines for atopic eczema: a systematic review of randomized controlled trials\*

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## Summary

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Despite the availability of medicines with proven efficacy, many patients use complementary or alternative medicines (CAMs) to manage atopic eczema (AE). Due to the lack of objective information on topical CAMs, this systematic review evaluates the current evidence for the efficacy and safety of topical herbal preparations in AE. Using Cochrane systematic review methodology, PubMed, the Cochrane Library, the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL (via EBSCO), MEDLINE (via EBSCO), Proquest Health and Medical Complete, GREAT and CAM-QUEST were searched from inception until June 2014. Bibliographies of retrieved studies were hand searched for further relevant trials. All controlled clinical trials of topical herbal medicines for AE in humans of any age were included regardless of the control intervention or randomization. Only English-language publications were considered. Eight studies met the inclusion criteria. Seven investigated extracts of single plants and one an extract from multiple plants. Only two studies that showed a positive effect were considered to have a low risk of bias across all domains (those of liquorice gel and *Hypericum perforatum*). In these two, the test product was reported to be superior to placebo. Despite variations in diagnostic criteria and lack of validated tools for outcome assessments in one of these, the promising results may warrant continued research in better-designed studies. No meta-analysis was performed due to heterogeneity in all studies. There is currently insufficient evidence of efficacy for any topical herbal extract in AE. Many studies had methodological flaws and even those showing efficacy were single trials with small patient cohorts.

### What's already known about this topic?

- Patients use topical complementary or alternative medicines to manage atopic eczema.
- Objective evidence of efficacy and safety is lacking and is essential for clinicians and patients to make informed choices.

### What does this study add?

- Of six studies that displayed superiority of treatment over placebo, only two studies, of liquorice gel and *Hypericum perforatum*, were considered to have a low risk of bias across all domains.
- The promising effect of these two therapies for atopic eczema warrants continued research in well-designed studies.

Atopic eczema (AE) is a chronic, relapsing and frustrating condition, with marked effects on quality of life (QoL). Despite the availability of medicines with proven efficacy, many patients resort to complementary or alternative medicines (CAMs) to manage flare-ups.<sup>1–3</sup> Many of these CAMs have shown conflicting evidence of efficacy, and hence systematic reviews have sought to provide clarity on their role for AE. Previous systematic reviews have focused on oral CAMs,<sup>4–8</sup> and an overview of these concluded that there was currently no evidence of efficacy.<sup>9</sup>

Topical corticosteroids remain the mainstay of treatment for AE. Many patients are concerned about their long-term safety and seek evidence-based safer alternatives.<sup>10–12</sup> Many topical herbal preparations have been tested for AE, but few in controlled clinical trials.<sup>13–20</sup> We have found no systematic reviews of these trials, although systematic reviews of topical herbal extracts have been published for other chronic skin conditions, such as psoriasis.<sup>21–23</sup> In 2014, a Cochrane protocol was registered with the aim to review all randomized controlled trials (RCTs) of several forms of CAMs (including phytotherapy) and complementary techniques (including acupuncture).<sup>24</sup> No review based on this protocol has yet been published. Our systematic review focuses specifically on controlled trials of topical herbal preparations (whether randomized or not), and on evidence of efficacy and safety. The overall aims are to provide clarity to prescribers and patients, and to identify opportunities for future research.

## Methodology

### Data sources

This systematic review was conducted independently with reference to the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (no registered protocol).<sup>25</sup> The electronic databases searched from inception until June 2014 were PubMed, the Cochrane Library, the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL (via EBSCO), MEDLINE (via EBSCO), Proquest Health and Medical Complete. Subsequent searches were conducted in two additional databases (CAM-QUEST and GREAT). Bibliographies of retrieved studies were hand searched for other relevant trials.

Search terms were 'atopic eczema/atopic dermatitis' together with 'topical herbal', 'topical application', 'topical administration', 'plant extract', 'natural', 'cream', 'ointment' and their synonyms. These were adjusted according to suitability for each database. The corresponding author may be contacted for a list of the search terms per database. The search terms and strategy are summarized in Appendix S1 (see Supporting Information).

### Inclusion and exclusion criteria

All controlled clinical trials published in English that tested a topical herbal medicine for AE in human patients of any age were included, regardless of the control intervention or randomization.

Topical herbal medicines were defined as those containing extracts of multiple or single plants. These could include non-herbal ingredients used in the extraction process or in preparation of the test or vehicle. Preparations described as homeopathic were not excluded. Any preparations incorporating or combined with an active pharmaceutical ingredient, other bioactive ingredients, vitamins or minerals were excluded. Topical Chinese herbal medicines were also excluded, as a recent systematic review dealing specifically with these was published in 2014.<sup>26</sup>

All patients had to be clinically diagnosed with AE. Studies on other types of eczema (e.g. hand eczema) and where the type of eczema was not clearly classified (e.g. chronic eczema) were excluded. Case reports, case series and clinical trials not conducted within a controlled environment were also excluded.

### Data extraction and analysis

Titles and abstracts of the initial search were scrutinized by two reviewers (Y.T. and A.M.) and a selection of full texts was made. Discrepancies were clarified by two independent reviewers (J.B. and A.G.).

Data from included trials were extracted by one reviewer (Y.T.) and checked by the others. Study authors were contacted where clarity was required. Details of the extracted data and study descriptions are included in Table 1. The risk of bias in each study was assessed by three independent reviewers (Y.T., A.M. and A.G.) according to the Cochrane domain-based evaluation.<sup>27</sup> Table 2 includes this assessment.

## Results

### Literature search

The initial searches yielded 3813 potential studies. After removing duplicates, 2451 potential papers remained. Considering the inclusion and exclusion criteria, the full texts of 41 publications and three studies from reference lists were retrieved. Eight publications were finally selected. Subsequent searches of additional databases did not yield any studies that met the inclusion criteria. Figure 1 shows the results of the selection process.

All eight studies were RCTs conducted between 1990 and 2011. Four were conducted in Germany,<sup>15,16,18,19</sup> with the others in Spain,<sup>14</sup> the U.K.,<sup>17</sup> Iran<sup>13</sup> and the Philippines.<sup>20</sup> Five were intraindividual paired left–right comparison trials.<sup>15–19</sup> Participants ranged in age from 4 months to 65 years. The largest trial included 88 patients<sup>19</sup> and the smallest 12 patients.<sup>17</sup> Treatment duration ranged from 4 weeks<sup>15,19,20</sup> to 2 weeks.<sup>13,16–18</sup> The severity of AE varied. Three studies included patients with mild-to-moderate AE,<sup>13,17,19</sup> one with moderate AE<sup>18</sup> and another with moderately severe AE.<sup>16</sup> One study included patients with low-to-high/moderate objective Scoring Atopic Dermatitis (SCORAD) scores, implying a varied degree of AE severity.<sup>20</sup> One study

Table 1 Characteristics of the included studies

Study; location	Intervention	Control	No. and age of participants; duration of study	Study design	Outcome measures	Dropouts, adverse effects	Outcome	Diagnostic criteria
De Bellowsky 2011; Spain <sup>14</sup>	Sunflower 2% oleodisillate (Stelatopia <sup>®</sup> emollient cream)	Topical corticosteroid (hydrocortisone butyrate propionate)	Treatment: 40, control: 40. Children (4 months to 4 years); 3 weeks	Open, comparative, single-blind, randomized study	Primary: SCORAD days 0, 7, 21. Secondary: specific items of SCORAD – extent of AE lesions, erythema, oedema/papulation, oozing/crusting, excoriation/lichenification, dry skin in healthy areas, pruritus, sleep loss; investigator-rated GA on AE flare-ups at day 21; QoL at days 0 & 21 (IDQOL & DFI)	No ADRs or loss to follow-up in either group	Sunflower 2% oleodisillate demonstrated similar properties to topical steroid; SCORAD was identical at all evaluation points; QoL improved in both groups; tolerance was excellent	Clinical definition was based on presence of acute lesions in the folds of the elbows and/or knees, surfaces of limbs and cheeks. Severity was quantified by initial SCORAD as 15–60
Schempp 2003; Germany <sup>15</sup>	Cream containing hyperforin – a major constituent of <i>Hypericum perforatum</i> L. (St John's Wort)	Placebo (colour-matched vehicle) applied on other side (composition of the vehicle identical in the two creams)	21 patients age 12–59 years; 4 weeks	Prospective, randomized, double-blind, placebo-controlled study; half-side (within-patient left–right) comparison	Primary: modified SCORAD index based on extent and intensity of erythema, papulation, crust, excoriation, lichenification and scaling; intensity classified using a four-point scale (excludes subjective variables). Secondary: skin colonization with <i>Staphylococcus aureus</i> at days 0 and 28; cosmetic acceptability and skin tolerance of the creams (scored by the patients at visits 2–4)	Three dropouts, one due to missing efficacy data after 10 days of treatment and two because treatment lasted < 10 days (n = 18); four side-effects in three patients: acute episode of AD leading to withdrawal from study; one patient developed contact eczema. None of the side-effects was considered serious	<i>Hypericum perforatum</i> was significantly superior in efficacy and reduction of skin colonization with <i>S. aureus</i> vs. vehicle in the topical treatment of mild-to-moderate AD	Diagnosis of subacute AD of limited extent (SCORAD < 80). Score was calculated using the algorithm recommended by the European Task Force on Atopic Dermatitis <sup>29</sup>

(continued)

Table 1 (continued)

Study; location	Intervention	Control	No. and age of participants; duration of study	Study design	Outcome measures	Dropouts, adverse effects	Outcome	Diagnostic criteria
Korting 1995; Germany <sup>16</sup>	<i>Humamellis virginiana</i> distillate cream	Drug-free vehicle of <i>Humamellis</i> distillate (n = 36) or hydrocortisone 0.5% cream (n = 36) applied on other side of body	Treatment: 72, control: 36 (vehicle) and 36 (hydrocortisone cream). Age 18–62 years; 14 days	Double-blind, randomized, paired trial	Four-point scale rating for itching, erythema and scaling (basic criteria); oedema, papules, pustules, exudation, lichenification, excoriation and fissures (minor criteria); basic and minor criteria assessed at days 0, 7, 14; GA of therapeutic effect by physician and patient, and physician- and patient-assessed tolerability at days 7 and 14	Seven dropouts (one bronchitis, one non-compliance, five no cooperation); three dropouts from treatment group and one from hydrocortisone group	Low-dose hydrocortisone cream was found to be superior to <i>Humamellis</i> distillate, and the therapeutic outcome with <i>Humamellis</i> distillate was found to be no better than with the base preparation	Patients had moderately severe AE, diagnosis was established according to the criteria of Hanifin and Rajka (at least three basic and three minor features of AE). <sup>28</sup> Patients also had to present stable or acutely worsening flexural lichenification on both arms (test areas) with a sum score of 4–7 for the basic criteria (itching, erythema, scaling)
Anstey 1990; U.K. <sup>17</sup>	Topical evening primrose oil (EPO)	Placebo (E45 cream)	12 patients age 4–46 years; 2 weeks	Double-blind; placebo-controlled, paired trial (left–right comparison)	A 10-point self-assessment (patient) scoring system for redness, scaling, dryness, itch and overall impression on days 0, 7, 14, and physician assessments for dryness, scaling, erythema, infiltration/oedema, lichenification and overall impression on days 0 and 14	One dropout (due to flare in AE); no topical or systemic side-effects observed	A statistically significant difference between EPO and E45 cream was seen using patient self-assessments, concluding that topical EPO has potential for treating AE. No statistically significant difference in doctor-assessed scores	Patients had mild-to-moderate AE as defined by accepted criteria (Hanifin and Rajka 1980). <sup>28</sup>

(continued)

Table 1 (continued)

Study; location	Intervention	Control	No. and age of participants; duration of study	Study design	Outcome measures	Dropouts, adverse effects	Outcome	Diagnostic criteria
Patzelt-Wenzler 2000; Germany <sup>1,8</sup>	Chamomile extract (Kamillosan <sup>®</sup> ) cream	Vehicle cream (placebo) (n = 33) or hydrocortisone 0.5% cream (n = 36) applied on other side of body	72 patients, average age 45.5 years; 2 weeks	Partially double-blinded, randomized, half-side comparison (intraindividual left-right comparison)	All individual symptoms were assessed on a four-step scale, efficacy was determined with score and sum score consisting of pruritus, erythema and desquamation, oedema, vesicles, papules and pustules, lichenification, excoriation and fissures; investigator-rated GA based on a four-point scale; tolerability also assessed	Three dropouts, intolerance in one patient (from the Kamillosan/placebo group)	Kamillosan cream showed mild superiority over hydrocortisone 0.5% and a marginal difference vs. placebo	Patients had to exhibit a moderate degree of AE, i.e. a sum score of pruritus, erythema and desquamation of 3–7 (score range 0–9), distal on both arms
Saeedi 2003; Iran <sup>13</sup>	Liquorice 1% and 2% gel (extracted from <i>Glycyrrhiza glabra</i> L roots)	Placebo (base gel)	Treatment: 30 (liquorice 1%); 30 (liquorice 2%). Control: 30. Age > 15 years; 2 weeks	Randomized (simple random sampling), double-blind, prospective, placebo-controlled trial	Investigator-assessed four-point scale; effect on oedema, itching, erythema and scaling	No dropouts; no side-effects were mentioned in the study	Liquorice gel 2% was more effective than 1% in reducing the scores of erythema, oedema and itching over 2 weeks. Liquorice extract could be considered as an effective agent for treatment of AE	Patients with clinically diagnosed mild-to-moderate degrees of AD: 1, pruritus and scratching; 2, course marked by exacerbations and remissions; 3, lesions typical of eczematous dermatitis; 4, personal or family history of atopy; 5, clinical course lasting > 6 weeks

(continued)

**Table 1** (continued)

Study; location	Intervention	Control	No. and age of participants; duration of study	Study design	Outcome measures	Dropouts, adverse effects	Outcome	Diagnostic criteria
Klövekorn 2007; Germany <sup>19</sup>	Ointment containing alcohol-based plant extracts of <i>Mahonia aquifolium</i> , <i>Viola tricolor</i> and <i>Centella asiatica</i> and their ingredients	Vehicle alone (no active ingredients)	88 patients age 18–65 years; 4 weeks	Randomized, double-blind, vehicle-controlled, half-side comparison	Primary end points: four-point scale summary score for erythema, oedema, oozing and crusting, excoriation and lichenification. Secondary end points: assessment of pruritus severity (10-cm visual analogue scale) and a GA of effectiveness and tolerability	One excluded; 17 dropouts; well-tolerated, no serious adverse events	<i>Mahonia aquifolium</i> , <i>V. tricolor</i> and <i>C. asiatica</i> ointment could not be proven to be superior to a base cream for treatment of mild-to-moderate AE. A subanalysis indicated that the cream might be effective under conditions of cold and dry weather	Patients with mild-to-moderate AE, diagnosis was based on Hanifin and Rajka <sup>28</sup> and graded according to Rajka and Langeland <sup>30</sup>
Verallo-Rowell 2008; Philippines <sup>20</sup>	Virgin coconut oil (VCO)	Virgin olive oil	Treatment: 26. Control: 26. Age 18–40 years; 4 weeks	Randomized, double-blind, controlled trial	<i>Staphylococcus aureus</i> colonization, objective SCORAD severity index (OSI)	No dropouts; no adverse events were reported	VCO reduction in OSI and <i>in vitro</i> broad-spectrum activity against <i>S. aureus</i> may be useful in the proactive treatment of AD colonization	Diagnoses were based on the modified Hanifin major criteria of a history of a chronic and relapsing course, pruritus, a pattern of facial and extensor eczema and xerosis at a younger age, becoming flexural at adult age, frequent association with a family history of AD

AD, atopic dermatitis; ADR, adverse drug reaction; AE, atopic eczema; DEI, Dermatitis Family Impact questionnaire; GA, global assessment; IDQOL, Infant's Dermatitis Quality of Life Index; QoL, quality of life; SCORAD, Scoring Atopic Dermatitis.

**Table 2** Risk-of-bias assessment

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other potential biases/confounding factors
De Bellowsky 2011; Spain; sunflower 2% oleodistillate cream <sup>14</sup>	Unclear Patients were randomly selected (method of randomization not specified)	High risk Children randomized into the treatment and control groups following a chronological order of inclusion on a randomized attribution list. Unclear how the test packs were packaged and supplied in order to maintain blinding of observers	High risk Observer blinded (package identified by an individual code); patients (parents) not blinded (given different instructions as to how to apply the cream)	High risk Observer blinded. As the test and control were both commercial products, it was unclear how the test packs were packaged and supplied in order to maintain blinding of observers	Low risk No dropouts	Low risk All outcomes to be evaluated were reported	High risk All children were given a body hygiene product Stelatopia <sup>®</sup> milky bath oil to use at least once daily. No record as to which child used this regularly in conjunction with either control or treatment; unclear of washout periods of previously used systemics before beginning study; some children could have been on long-term antihistamines as these were not excluded
Schempp 2003; Germany; <i>Hypericum perforatum</i> L (St John's wort) cream <sup>15</sup>	Unclear Not stated	Low risk Treatment was randomly allocated to the left or right side of the body (detail of randomization not specified)	Low risk Double blinded (both treatment and placebo were similar in appearance)	Low risk Double blinded, therefore assessor also blinded: colour and content of additives were identical in placebo and treatment	Low risk Three dropouts (developed acute atopic dermatitis leading to withdrawal)	Low risk All outcomes to be evaluated were reported	Unclear

(continued)

**Table 2** (continued)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other potential biases/confounding factors
Korting 1995; Germany; <i>Hamamelis virginiana</i> distillate cream <sup>16</sup>	Unclear Not stated	Low risk To ensure randomized allocation of treatment each patient was given a medication pack with lowest number (from a predetermined randomization list)	High risk Double blinded (both treatment and controls were in neutral coded 50-g tubes). No mention was made of texture and appearance of meds being the same. It is also stated that patients had to be actively motivated to finish the treatment as they felt uncomfortable with the study medication (due to delayed onset of desired effect and having received more potent glucocorticoids in the past); blinding may not have been effective	Low risk Investigator blinded	High risk Seven dropouts (one bronchitis, one noncompliance and five no cooperation); four did not comply with protocol: three from treatment group and one from hydrocortisone group); side-effects of skin irritation seen in control and treatment	Low risk All outcomes to be evaluated were reported	Unclear
Anstey 1990; U.K.; evening primrose oil cream <sup>17</sup>	Low risk Randomized (method of randomization not mentioned)	Low risk Randomized (method of randomization not mentioned)	Low risk Double blind (treatment and control similar in texture, colour and smell)	Low risk Double blind (stated in abstract only)	Low risk One dropout (due to flare)	Low risk All outcomes to be evaluated were reported	High risk No restriction was imposed on usual topical treatments applied to sites other than test areas. Some systemic absorption of these could influence results
Patzelt-Wenzler 2000; Germany: chamomile (Kamillosan®) cream <sup>18</sup>	Low risk Randomized (carried out by biometrical department of Asta Medica, balanced after eight patient numbers each). Ambiguity exists in terms of randomization (patients allocated in chronological order according to patient number)	High risk Patients partially double blinded (blinded to control creams as these appeared the same, but Kamillosan appeared different in terms of colour and smell); with reference to Kamillosan the study had an open study character: both patients and personnel knew the treatment given	High risk Investigator was aware of the treatment cream. Open study character	Low risk Three dropouts (due to intolerance), in the Kamillosan/placebo group	Low risk Only main outcomes were reported on. Incomplete reporting of all symptoms	Low risk No statistical analyses. Only bold statements were made regarding the effect of placebo. Therefore, the claim that Kamillosan is superior to hydrocortisone cannot be supported by the data	High risk No restriction was imposed on usual topical treatments applied to sites other than test areas. Some systemic absorption of these could influence results

(continued)



Table 2 (continued)

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other potential biases/confounding factors
Saeedi 2003; Iran; liquorice gel <sup>13</sup>	Unclear Not stated	Low risk Randomized (simple random sampling)	Low risk Double blinded (details of concealment not specified)	Low risk Double blinded (details of concealment not specified)	Low risk No dropouts	Low risk All outcomes to be evaluated were reported	Unclear
Klövekorn 2007; Germany; <i>Mahonia aquifolium</i> , <i>Viola tricolor</i> , <i>Centella asiatica</i> ointment <sup>19</sup>	Unclear Not stated	Low risk Randomization using a computer-generated randomization code by a statistician not involved in the study	Low risk Double blinded (verum and vehicle were similar in appearance and dispensed in identical tubes)	Low risk Investigator was blinded	High risk One excluded (did not provide a valid postbaseline value), 17 dropouts due to lack of efficacy (~20%)	Low risk All outcomes that were to be evaluated were reported	Unclear
Verallo-Rowell 2008; Philippines; virgin coconut oil <sup>20</sup>	Unclear Not stated	Low risk Simple concealed random allocation (drawing rolled pieces of paper labelled 'A' and 'B')	High risk Double blinded. For preparation of bottles, randomization key and codes were done by a pharmacist and disclosed to investigators at end of study. Upon application of ether oil, the scent is notable. Appearance of oil is also different when poured onto the hand. Although the authors report that the scent disappears within few minutes, initial application compromises the blinding	Low risk Investigator was blinded. Preparation of the bottles and randomization key and codes were done by a pharmacist and only disclosed to investigators at the end of the study	Low risk No dropouts; no adverse effects reported	Low risk All outcomes to be evaluated were reported	High risk Small patient numbers with markedly unbalanced groups at baseline (20 vs. 12 positive <i>Staphylococcus aureus</i> colonies) makes the risk of chance finding high

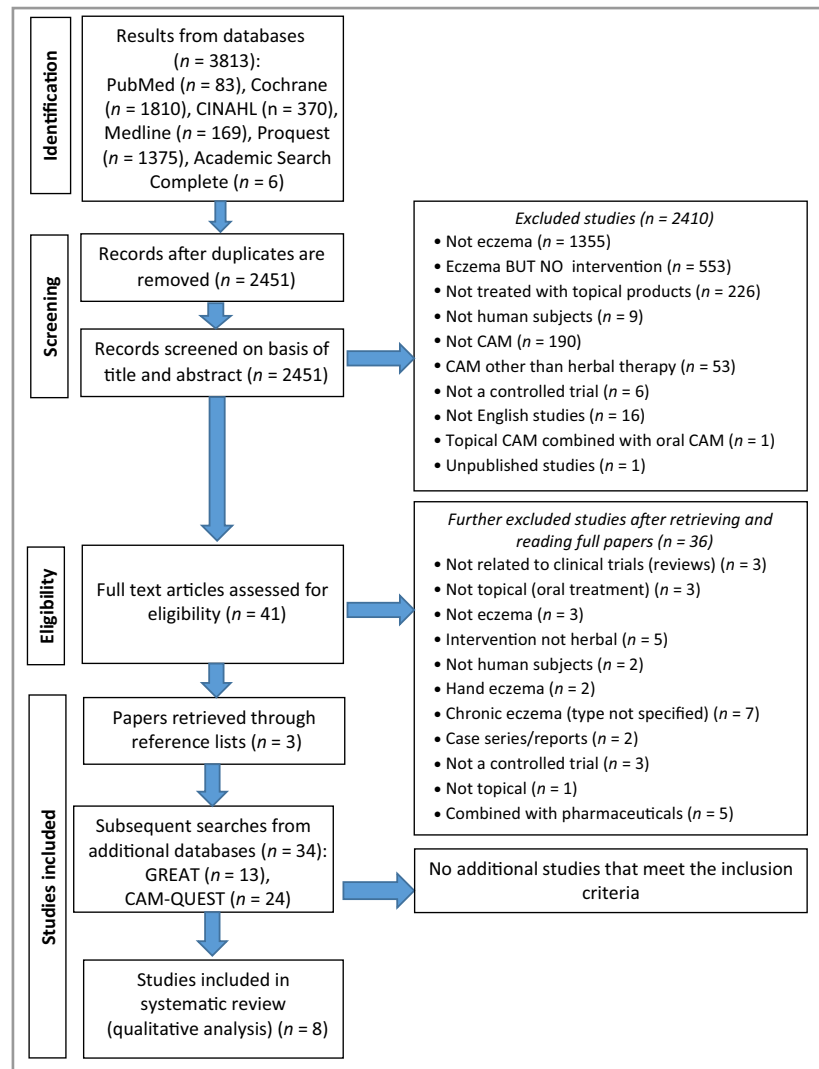


Fig 1. Flowchart showing the selection process of controlled clinical trials of topical herbal products for atopic eczema. CAM, complementary or alternative medicine.

included patients with SCORAD  $< 80$  and another, 15–60, hence there was a wide variation in severity.<sup>14,15</sup>

Primary outcome measures were a modified SCORAD using a four-point scale assessment in five studies,<sup>13,15,16,18,19</sup> SCORAD in one study,<sup>14</sup> objective SCORAD in one<sup>20</sup> and a 10-point self-assessment of symptoms in another.<sup>17</sup> *Staphylococcus aureus* colonization was measured in two studies<sup>15,20</sup> and tolerability was assessed secondarily in four studies.<sup>15,16,18,19</sup> Only one study assessed health-related QoL.<sup>14</sup>

Four studies compared a topical plant extract with a topical placebo.<sup>13,15,17,19</sup> Two trials were two-arm parallel studies (comparison with placebo and hydrocortisone 0.5%).<sup>16,18</sup> In another two, the test treatment was compared with a topical active control: hydrocortisone butyrate propionate<sup>14</sup> or virgin olive oil.<sup>20</sup>

Seven studies investigated single-plant extracts, and one studied extracts from multiple plants.<sup>19</sup> These were sunflower oleodistillate, *Hypericum perforatum* L (St John's wort), *Hamamelis virginiana* distillate, evening primrose oil (EPO), chamomile, *Glycyrrhiza glabra* L (liquorice gel), virgin coconut oil (VCO)

and an ointment containing extracts of *Mahonia aquifolium*, *Viola tricolor* and *Centella asiatica*.

### Risk-of-bias assessment

The judgement of risk of bias per domain is summarized in Table 2 and depicted in Figure 2. Selection bias in terms of sequence generation was unclear in all studies. Only one reported randomization<sup>14</sup> and none stated any method of sequence generation. All studies stated that participants were randomly allocated into treatment groups, hence allocation concealment was considered to be low risk in all but one study.<sup>14</sup> Although two did not provide any detail on the method of randomization, they were classified as low risk.<sup>15,17</sup>

Four studies demonstrated a high risk of performance bias,<sup>14,16,18,20</sup> with two also having a high risk of detection bias.<sup>14,18</sup> In the study of Patzelt-Wenczler and Ponce-Poschl (Kamillosan<sup>®</sup>), the participants and investigators, although blinded to the control, could identify the treatment cream due

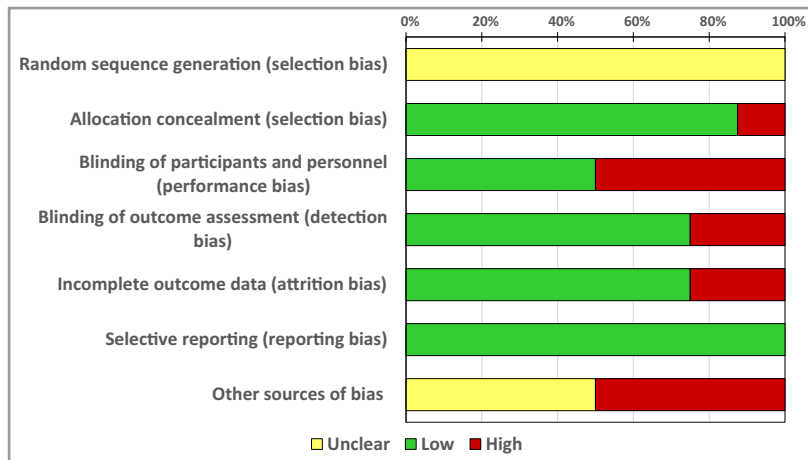


Fig 2. Risk-of-bias graphs presented as percentages across all included studies.

to its distinct colour and smell.<sup>18</sup> The study of De Belilovsky *et al.* (2% sunflower oleodistillate) was observer blinded.<sup>14</sup> Participants were unblinded and were given different instructions on application of the creams. Although they reported that this was unlikely to influence the outcome, the study was classified as having high risk of performance bias.<sup>14</sup> Unblinding of parents and carers may affect adherence, especially if the corticosteroid is known. Also, it was unclear how the commercial test and control products were packaged and supplied to maintain blinding. These factors generated a study with high risk of detection bias. In the study of Verallo-Rowell *et al.* (VCO), the creams were distinguishable by scent and appearance prior to application.<sup>20</sup> Despite the authors' claim that this was unlikely to have influenced the results, we considered the performance bias as being high.

In the study of Korting *et al.* (*Hamamelis* distillate), the treatment and control creams were dispensed in neutral, coded 50-g tubes; however, no mention was made of the similarity of texture, colour or smell, thus the double blinding may have been ineffective.<sup>16</sup> Also, patients had to be actively motivated to complete the trial as they felt uncomfortable with the medication due to delayed onset of desired effect and having received potent glucocorticoids previously. This study was thus regarded as having a high risk of performance bias.

Two studies had incomplete outcome data and were considered to have a high risk of attrition bias.<sup>16,19</sup> Korting *et al.* (*Hamamelis* distillate) had seven dropouts, in whom analysis was performed on intention-to-treat numbers and the last value obtained served for analysis.<sup>16</sup> These values were not mentioned, thus the missing data could have resulted in inaccuracies. Conflicting figures exist in this study, as an initial report of seven dropouts was inconsistent with another statement that four patients withdrew (three test and one control). Another discrepancy was a statement that 65 patients completed the trial, but a later statement said that 61 complied with the full trial protocol. Despite the poor-quality reporting, the results were not in favour of the test product.<sup>16</sup>

Approximately 20% of the sample dropped out in the study of Klövekorner *et al.* (multiple-plant extracts) due to lack of efficacy.<sup>19</sup> Analyses were performed on the intention-to-treat

data. The missing data could have led to inaccurate results. Attrition bias in the other studies was low, due to no dropouts,<sup>13,14,20</sup> small dropout numbers<sup>15,17,18</sup> or clear reasons for dropouts.<sup>15–18</sup>

All eight studies were considered to be at low risk for selective reporting, as all outcomes assessed as part of the trial objectives stated in the paper were reported in the results. One study did not report on additional symptoms investigated as part of the outcomes; however, the risk was low, as all major symptoms were reported.<sup>18</sup>

Other potential sources of bias exist in two studies.<sup>14,17</sup> In De Belilovsky *et al.* (2% sunflower oleodistillate), all children were given Stelatopia<sup>®</sup> milky bath oil for daily use. Compliance is uncertain and it is possible that its regular use could improve symptoms and bias the results. Also, no mention was made of washout periods with previously used systemic corticosteroids, antibiotics or immunosuppressants.<sup>14</sup> In Anstey *et al.* (EPO), no restrictions were given with any topicals used on other areas of the body.<sup>17</sup> The risk was considered high, as systemic absorption of these could potentially produce inaccurate outcomes.

Only three studies measured compliance. Two collected and weighed tubes<sup>14,15</sup> and one collected tubes and documented application frequencies.<sup>19</sup> Follow-up was mentioned in only one study, which ceased after 2 weeks.<sup>13</sup>

Diagnostic criteria varied among studies.<sup>13,14,18</sup> Three reported the use of the Hanifin and Rajka criteria.<sup>16,17,19,28</sup> One used the modified Hanifin and Rajka criteria,<sup>20</sup> and another used the criteria recommended by the European Task Force on Atopic Dermatitis (1993).<sup>15,29</sup>

Of five studies that used a four-point scale to measure outcomes,<sup>13,15,16,18,19</sup> only four used the same scale, with erythema being the only common symptom assessed. Three were placebo controlled and two included two comparator arms (placebo and hydrocortisone 0.5% cream). Four were half-sided intraindividual comparisons. Due to these differences, a meta-analysis was not considered feasible.

Six studies reported on adverse events,<sup>14–19</sup> of which three reported that there were none,<sup>14,17,19</sup> and the others reported that none was serious.

## Description of studies

### Topical single-plant extracts compared with placebo ( $n = 4$ )

Published in 2003, a randomized, placebo-controlled, double-blind trial was conducted by Schempp *et al.*<sup>15</sup> In this intraindividual bilateral comparison, the effects of St John's wort cream, containing hyperforin (a major constituent of *H. perforatum*) on AE intensity were compared with placebo using a modified SCORAD of objective variables. Secondary outcomes were *S. aureus* colonization and tolerability. The investigators found that St John's wort cream significantly improved the intensity of AE and reduced *S. aureus* skin colonization compared with placebo. Tolerability was good, with only a few nonserious adverse effects reported.<sup>15</sup>

A randomized, double-blind, placebo-controlled, intraindividual bilateral comparison trial with topical EPO was published in 1990.<sup>17</sup> In this pilot study, the effects of topical EPO on eczema severity were assessed by patients and physicians using a 10-point scale. A statistically significant difference only in patient scores (not doctor's) was noted, concluding that despite uncertainty of emollient or anti-inflammatory effects, topical EPO has the potential to improve eczema.<sup>17</sup> No published main study following this pilot was found.

Published in 2003, Saeedi *et al.* investigated the effect of liquorice gel 1% and 2% (extracted from *G. glabra* L roots).<sup>13</sup> This was a randomized, double-blind, placebo-controlled three-arm trial. Symptoms were assessed using a four-point scale. Itching, oedema, erythema and scaling were reduced more effectively with liquorice 2% gel compared with 1%. Both were more effective than placebo. The investigators concluded that liquorice 2% extract could be considered in AE management.<sup>13</sup>

### Topical multiple-plant extracts compared with placebo ( $n = 1$ )

In 2007, Klövekorn *et al.* compared an ointment containing extracts of *M. aquifolium*, *V. tricolor* and *C. asiatica* with placebo.<sup>19</sup> This was a bilateral intraindividual comparison. Efficacy was based on a modified SCORAD four-point-scale investigator assessment of objective parameters. Subjective variables were assessed by the patient. A global assessment of effectiveness and tolerability was also assessed. The investigators concluded that this extract was not superior to placebo. Considering the study was conducted over a period of varying climatic conditions, a subanalysis over similar climatic conditions concluded that the cream might be effective.<sup>19</sup>

### Topical single-plant extracts compared with topical corticosteroids ( $n = 3$ )

Three studies compared topicals from single-plant extracts with topical corticosteroids.<sup>14,16,18</sup> Two were three-arm studies (comparison with corticosteroid and placebo).<sup>16,18</sup>

Sunflower oleodistillate 2% (Steltopia<sup>®</sup> emollient cream) was compared in an open, single-blind RCT with hydrocortisone butyrate propionate by De Belilovsky *et al.* in 2011.<sup>14</sup> Both the SCORAD index and individual symptoms improved significantly compared with baseline in both groups, but with no differences compared with each other. However, xerosis was significantly better with the extract. The lesions decreased to a greater extent and sooner with the topical corticosteroid. Investigator-rated global assessment, flare-ups and QoL were similar. The investigators concluded that sunflower oleodistillate 2% cream is comparable with topical corticosteroid, and if used repeatedly on the whole body it is an appropriate first-line treatment for children with AE.

Korting *et al.* investigated the effects of *H. virginiana* distillate cream against hydrocortisone 0.5% cream and placebo in a double-blind RCT in 1995.<sup>16</sup> While all patients received the test cream, the two controls were randomly allocated to the left-right side of the body. *Hamamelis* distillate cream failed to show superiority over the topical corticosteroid and achieved similar results to placebo using the four-point scale to measure symptoms. Patient- and physician-assessed global efficacy and tolerability also failed to show any positive effect.

In 2000, Patzelt-Wenzler and Ponce-Poschl compared a chamomile extract (Kamillosan<sup>®</sup>) against hydrocortisone 0.5% cream and placebo.<sup>18</sup> This study was only partially double blinded because the colour and smell of chamomile extract easily distinguished it from placebo and corticosteroid. A four-point assessment of symptoms and investigator global assessment were the main outcomes. A marked superiority of the chamomile extract over hydrocortisone 0.5% and a marginal superiority over placebo on assessment of pruritus, erythema and desquamation were reported. No reports were given regarding the other symptoms assessed.<sup>18</sup>

### Topical single-plant extracts compared with other pharmaceuticals ( $n = 1$ )

In a 2008 double-blinded RCT by Verallo-Rowell *et al.*, the effects of VCO on objective symptoms of SCORAD and *S. aureus* colonization were compared against virgin olive oil.<sup>20</sup> Both oils improved severity scores, but improvement was better with VCO. VCO was also superior in reducing *S. aureus* colonization. The investigators concluded that VCO and its key ingredient monolaurin may be useful in the proactive treatment of AE.

## Discussion

This systematic review reports on trials conducted over the past 25 years. Despite this lengthy period, evidence regarding the use of topical plant extracts still remains unclear. Objective information rather than complete rejection is essential for any clinician treating patients who may be using or wanting to consider CAMs.

Of eight RCTs included in this review, two reported no efficacy.<sup>16,19</sup> The Korting *et al.* study (*Hamamelis* distillate) had a

high risk of performance bias, possibly leading to inaccurate results.<sup>16</sup> The Klövekorn *et al.* study (multiple-plant extracts) reported a high dropout rate due to lack of efficacy and thus had a high risk of attrition bias.<sup>19</sup> The intention-to-treat analysis revealed negative results. It is therefore unlikely that a better-designed study would show any positive effect.

Six studies reported that the extracts tested were effective.<sup>13–15,17,18,20</sup> However, there were no common data that were suitable for a meta-analysis. Of these, the Patzelt-Wenzler and Ponce-Poschl study (Kamillosan<sup>®</sup>), which reported that chamomile extract was mildly superior to topical corticosteroid, was considered to be at high risk of performance and detection bias, lending itself towards a positive effect.<sup>18</sup> No statistical analysis or follow-up was reported. Considering this, the claim of superiority over a topical corticosteroid cannot be supported by the data in this trial. Following this 2000 publication, we have found no other trials with a chamomile extract for AE. Another better-designed study ensuring complete blinding would be useful.

The De Belilovsky *et al.* study (sunflower 2% oleodistillate) had selection, performance and detection biases.<sup>14</sup> Other potential biases were uncertainty of washout periods with prior medicines and the concurrent use of a milky bath oil, which may have led to a false positive result. Results of comparability of the test cream with a topical corticosteroid and its consideration as first-line treatment for mild-to-moderate AE were reported in this 3-week observer-blinded trial. A longer trial, with double blinding, addressing the flaws in this study may be warranted.

The Anstey *et al.* study (EPO) did not mention any validated instrument for assessing outcomes. A positive outcome was documented by patients only, with no statistical differences in doctors' assessments.<sup>17</sup> This study was considered to be at high risk of bias, as patients were allowed to use other topicals. A study excluding other medicines may be warranted.

Although the study of Verallo-Rowell *et al.* (VCO) showed a positive effect, it had a high risk of detection bias.<sup>20</sup> The reduction in *S. aureus* colonization in this study is of limited clinical significance, as it was a cross-sectional study in a small number of patients (unbalanced at baseline), thus posing a high risk of a chance finding.

Only two studies that showed superiority over placebo had low risk of bias across all domains.<sup>13,15</sup> Despite variations in diagnostic criteria and a lack of validated tools for outcome assessments in one study,<sup>13</sup> its promising effect in the treatment of mild-to-moderate AE may warrant continued research using larger patient cohorts, in better-designed, longer-duration, possibly three-armed trials (with topical corticosteroids and placebo).

Although a thorough literature search was conducted, some studies may have been missed. No information was obtained on unpublished studies. Despite every effort to use a wide array of databases, EMBASE and AMED were inaccessible. Studies published in languages other than English were not considered.

The heterogeneity among studies in terms of the tested product, age of participants, sample sizes, outcome measures and

degree of eczema severity precluded the performance of a meta-analysis. The development of a minimum core outcome set to be used in future studies should be considered, as this would make it easier to compare results across trials and thus establish firm conclusions.

In conclusion, there is currently insufficient evidence of efficacy with any of the topical herbal extracts explored in this review. Many of the included studies were pilot studies and had methodological flaws, and even those that did show efficacy were single trials. Further trials with larger patient cohorts and longer follow-up to assess efficacy and record adverse effects may be warranted with those topical herbal extracts – *H. perforatum* extracts, liquorice gel 2% and EPO – that did show some promise.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

**Appendix S1.** Search strategy.

**Video S1.** Author video.