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# Phytotherapy in paediatric skin disorders – A systematic literature review

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ABSTRACT

*Objectives:* Although skin disorders in children and adolescents are increasingly treated with phytotherapies in practice, there are very few studies investigating this topic, and no systematic review exists that summarizes the current state of research. This review examines which herbal medicines show to be effective to treat atopic dermatitis, diaper dermatitis, and skin lesions or wounds.

*Methods:* Clinical studies were searched according to PRISMA-guidelines in the medical databases of PubMed, EMBASE, and CINAHL and summarised in a systematic review.

*Results:* Among the 429 articles screened, 17 studies with a total of 2358 participants were identified that suited our inclusion criteria. Thereof seven studies each on the treatment of atopic dermatitis and skin lesions or wounds and three on diaper dermatitis. The phytotherapeutics investigated were based on the following herbs: Evening primrose, blackcurrant, polypodium leucotomos, calendula, aloe vera, chamomile, comfrey, hamamelis, olive, hypericum, neem, white oak, and myrrh. They have mainly been analysed in randomized controlled trials, but also in (long-term) observational studies, prospective trials and case series.

*Conclusions:* Based on the application of the Jadad score, eight out of 17 of the studies examined were of low quality. Yet we found some indication that evening primrose oil may be effective for treating atopic dermatitis in children, while comfrey appears to have a positive effect on wound healing. Interestingly, none of the studies found positive effects for treating skin disorders with aloe vera or chamomile.

## 1. Background

Skin disorders, like atopic dermatitis, diaper dermatitis, and skin wounds, are common in children and adolescents.[1] For atopic dermatitis, the prevalence in children is estimated at 20%, while diaper dermatitis affects about 25% of all children below the age of three.[2] Skin disorders are known to not only affect the physical state of children and adolescents, but they also impact their behaviour and emotion regulation.[3,4] Although skin disorders in early childhood and adolescence usually do not influence life expectancy, they can still cause a considerable amount of distress for both children and parents in everyday life.[5] This is especially true since the management of skin disorders in children and adolescents, especially atopic dermatitis, can be challenging, and many parents of affected children feel worried related to uncertainties about medication use and available treatment options.[5]

Conventional treatments recommended by classical medicine, such as topical steroids, can only be used for short periods due to possible side effects, such as skin atrophy, striae, telangiectasias, hypopigmentation, and rosacea and are therefore not recommended for long-term use.[6–8]

A high prevalence of complementary and alternative medicine (CAM) use can be observed among children suffering from skin disorders.[9] Research shows that over 50% of parents favour CAM products, such as herbal medicine or phytotherapy, in the belief that they are natural and therefore safe.[9] Although favoured by many parents, there are only a few studies on the use of herbal medicine (phytotherapy) in children. There are some studies on the use of phytotherapy in adults, but there are only a few studies that provide detailed information on the application of herbal medicines for skin diseases in children.[9] However, this research subject is of great importance because there are some specific diseases that mainly affect children, such as diaper dermatitis. This review aims to systematically summarize the available literature on the effectiveness and safety of phytotherapy for skin disorders in children and adolescents and attempts to highlight the gap in the current state of research.

*Abbreviations:* CAM, Complementary and alternative medicine; AD, Atopic dermatitis; SCORAD, Scoring atopic dermatitis; EASI, Eczema area and severity index; BCSO, Blackcurrant seed oil.

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## 2. Methods

### 2.1. Eligibility criteria

#### 2.1.1. Study selection

For this review, all types of clinical studies were included. Reviews, meta-analyses, case reports, and case series with less than five participants were excluded. Studies were only selected if they were peer-reviewed and published as full articles, written in English or German.

#### 2.1.2. Selection of participants

Children and adolescents (aged 0–18) diagnosed with any kind of skin disorder were included. Studies which reported results on both children and adults were excluded.

#### 2.1.3. Types of intervention

Studies that compared herbal medicines with no treatment, placebo, or any pharmaceutical medication, as well as case reports with more than 5 participants, were eligible. Studies were only included if the herbal drug was listed by the European Medicines Agency as an herbal drug to treat skin diseases or wounds. Furthermore, any type of medical outcome, at any type of measurement time was considered.

### 2.2. Search methods

PubMed, EMBASE, and CINAHL were searched by the two first authors from their inception to July 27, 2020. The review was not registered in any database.

The search strategy was constructed around the following search terms: “phytotherapy,” “skin disorders,” and “injuries,” as well as their synonyms, such as “herbal medicine” and “wound healing”. In a first step, titles were screened for eligibility, and selected studies were then judged by the abstract. The full text was assessed if inclusion criteria were met. The complete search strategy is depicted in Table 1.

### 2.3. Data extraction and management

Data was extracted independently by the two first authors. For each of the three disorders identified (atopic dermatitis, wound healing, and diaper dermatitis), a separate outcome-table was created. The data extracted involved the following: Year, study design, population, therapeutic agent, intervention, control, measurement, outcome and results of all studies on all three disorders.

### 2.4. Risk of bias assessment

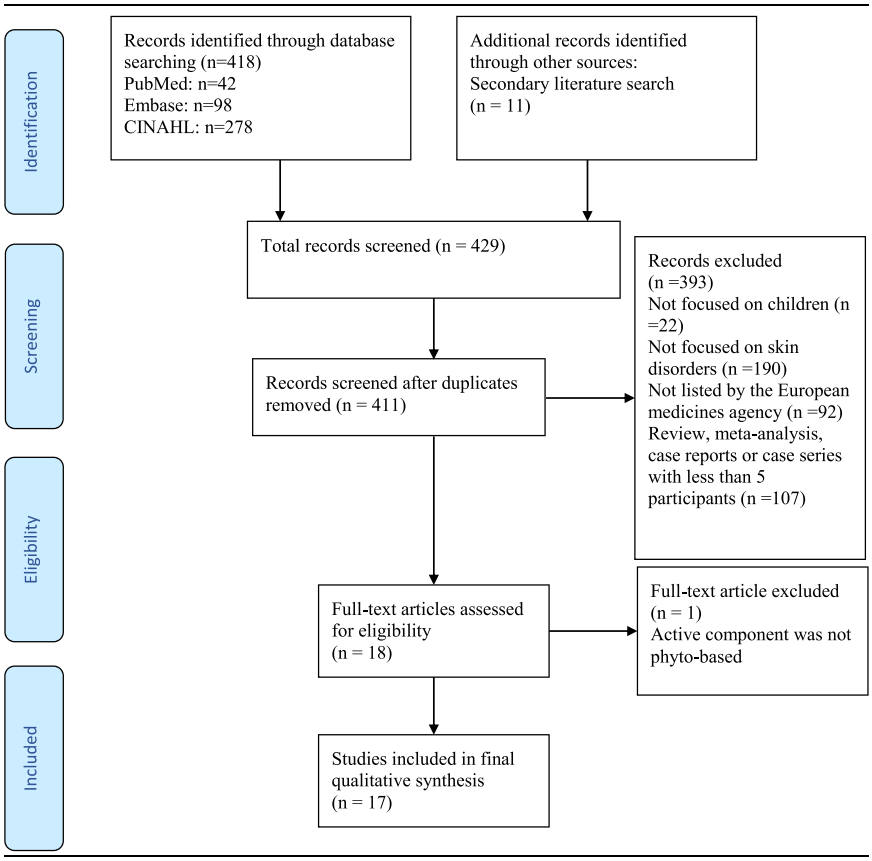
Each study was judged using the Jadad-score.[10] The assessment was carried out separately by the two first authors, then compared and in case of disagreement discussed. Criteria rated were randomization, blinding, and patient number. Only nine out of 17 studies reached three or more points.

## 3. Results

### 3.1. Literature search

The literature search in PubMed, EMBASE, and CINAHL resulted in 418 hits for the search term mentioned above. Of these, six studies were read as full text and all of them were included in the review. By scanning through their list of literature, 11 more studies could be identified. In total, 17 studies were included in the review.

**Table 1**
Prisma-flowchart of study selection.



### 3.2. Studies included

We explicitly searched for studies that investigated the treatment of any kind of skin disease with phytotherapy. However, we only found studies focusing on the following three skin disorders in children: atopic dermatitis, diaper dermatitis, and wound healing. For this reason, we grouped the included studies into these three categories.

Detailed information on the studies, such as study design, intervention, and measurements can be found in Table 2.

#### 3.2.1. Atopic dermatitis (AD)

Seven studies, namely Bordoni et al.,[11] Biagi et al.,[12] Hederos et al.,[13] Chung et al.,[14] Giordano et al.,[15] Linnamaa et al.,[16] and Ramirez-Bosca et al.,[17] analysed the treatment of atopic dermatitis with phytotherapy in a total of 630 children, aged from 0 to 17 years. The studies were carried out in Italy, Sweden, South Korea, France, Finland, and Spain. Six studies were randomized controlled clinical trials, only one (Biagi et al.) was a longitudinal observation study. In the studies of Hederos et al., Chung et al., and Ramirez-Bosca et al., the diagnosis of AD was based on the Hanifin-Rajka diagnostic criteria for atopic dermatitis.

The remaining publications did not mention their diagnostic criteria for AD. To test if there was any improvement regarding AD as compared to no treatment, the placebo, or the control group, the publications used the SCORAD score, EASI score, or a visual analogue scale as comparators. Regarding the Jadad-score only four out of the 7 studies reached three or more points.

The first five studies (Bordoni et al., Biagi et al., Hederos et al., Chung et al., Giordano et al.) focused on the effect of evening primrose oil, taken as capsules or applied as an emollient to relieve the symptoms of atopic dermatitis. The remaining two studies (Linnamaa et al. and Ramirez-Bosca et al.) examined the effect of blackcurrant seed oil and Polypodium leucotomos.

Bordoni et al. analysed whether an improvement in the symptoms of atopic dermatitis could be achieved by taking evening primrose oil capsules in addition to standard therapy, such as emollients or weak topical steroids. The results were compared to a placebo-treated group and showed that evening primrose oil indeed substantially improved the clinical symptoms of atopic eczema in two-thirds of the treated children after four weeks of therapy.[11]

The dosage of the evening primrose capsules and the treatment concept of Biagi et al. were identical to those of Bordoni et al. However, Biagi et al. was not a controlled study but a long-term observation over 20 weeks to assess effectiveness and safety of evening primrose capsules. The results after 4 weeks were almost identical to those of Bordoni et al., namely that the use of evening primrose capsules substantially improved the clinical symptoms of atopic eczema in two-thirds of the treated children after four weeks of therapy. However, after 20 weeks of therapy, no further significant improvement was detectable in the comparison of clinical status between 4 and 20 weeks of treatment.[12]

Hederos et al. conducted a double-blind, placebo controlled, parallel group study with 58 children with a 16-weeks treatment period with either evening primrose oil or placebo capsules. All participants were allowed to continue using their standard therapy, such as steroids or antihistamines. Overall, the symptoms of atopic dermatitis improved during the treatment period of 16 weeks; the study showed no clinical differences between active and placebo treatment.[13]

Chung et al. investigated whether a possible effect of evening primrose oil capsules is dose-related by treating participants with atopic dermatitis with two different dosages. Forty AD patients were randomly divided into two groups. One group received evening primrose oil 160 mg daily for 8 weeks, while the other received 320 mg of evening primrose oil twice a day for 8 weeks. The patients were not allowed to use other drugs such as topical steroids or emollients during the period of treatment. Symptoms improved in both groups after 8 weeks, but only the results of the patients who received a higher dosage were significant.[14]

Compared to the other studies investigating AD, Giordano et al. administered evening primrose extract in an emollient. Patients were not allowed to use other emollients as therapy, but they were allowed to use dermocorticoids during the study period. Results of this study showed that in AD patients, xerosis and pruritus were significantly improved by a twice-daily application of the emollient, compared to the control group, which solely used dermocorticoids.[15]

Linnamaa et al. examined if blackcurrant seed oil processed into capsules has a protective effect on the occurrence of atopic dermatitis and if it has the potential to be used preventively. Three hundred and thirteen pregnant mothers were randomly assigned to receive blackcurrant seed oil capsules or olive oil as a placebo. The first doses were administered at 8–16 weeks of pregnancy and were continued until the cessation of breastfeeding, followed by feeding it to the children until the age of 2 years. Atopic dermatitis and its severity were evaluated with the SCORAD index, and skin tests were performed at the ages of 3, 12, and 24 months. According to SCORAD, atopic dermatitis was less severe in the actively treated group when compared with the placebo group at the age of 12 months (33.0% vs. 47.3%, $P = 0.035$). SCORAD was also lower in the BCSO group than in the olive oil group at 12 months of age ($P = 0.035$). No significant differences were observed in the prevalence of atopic dermatitis between the two groups at the age of 24 months ($P = 0.18$).[16]

Ramirez-Bosca et al. investigated whether the administration of orally taken Polypodium leucotomos (PL) extract would lead to a reduction in the use of topical corticosteroids and antihistamines for treating moderate atopic dermatitis. The results of their randomized, double-blind study showed that Polypodium leucotomos extract did not significantly reduce the mean percentage of days on which topical corticosteroids were used (11% [12%] vs 12% [11%] for placebo). However, a significant reduction for oral antihistamine use was observed (median percentage of days, 4.5% in the Polypodium leucotomos group and 13.6% in the placebo group [$P = 0.038$]).[17]

All seven studies investigated safety and tolerance of the active substances. Neither the treatment with evening primrose oil nor the treatment with blackcurrant seed oil, or polypodium leucotomos, caused any serious side effects.

#### 3.2.2. Diaper dermatitis

Three studies (Adib-Hajbaghery et al.,[18] Panahi et al.,[19] and Badelbuu et al.[20]) analysed the treatment of diaper dermatitis with phytotherapy in a total of 215 children, aged from 0 to 3 years. All three studies were conducted in Iran, and all of them were randomized-controlled, double-blind trials. Diaper dermatitis was diagnosed either in the hospital or by a paediatrician or general practitioner. The researchers investigated the impact of calendula, aloe vera, and chamomile in the treatment of diaper dermatitis. To evaluate the severity of complaints before and after treatment, a checklist and a 0–4 visual analogue scale were used. Regarding the Jadad-score all three studies reached three or more points.

Adib-Hajbaghery et al. compared the therapeutic effect of two different creams, one containing calendula and one containing bentonite for the treatment of diaper dermatitis. The findings of the study showed that the onset of improvement in the first six hours was significantly higher in the bentonite group than in the calendula group. Also, the total improvement in the first three days was significantly higher in the bentonite group.[18]

Panahi et al. compared the therapeutic efficacy of topical aloe vera and calendula officinalis on diaper dermatitis in children. Although the severity of diaper dermatitis was significantly decreased in both groups by the end of the trial, the reduction rate was found to be significantly greater in the group treated with calendula officinalis.[19]

The third study by Badelbuu et al. again compared the effect of two different ointments—one containing chamomile, the other one aloe vera—to each other and also to routine treatment. According to the results, there was an improvement in the severity of dermatitis during

**Table 2**
Characteristics of the studies included for the systematic literature review "Phytotherapy in paediatric skin disorders".

| | Year | Study design | Population | Therapeutic agent | Intervention | Control group | Measurements | Results | Jadad Score (0–5) |
|---|---|---|---|---|---|---|---|---|---|
| **Atopic dermatitis** | | | | | | | | | |
| Evening primrose | | | | | | | | | |
| Bordoni et al. 1988<br>Evening primrose oil (Efamol) in the treatment of children with atopic eczema. Drugs under experimental and clinical research. | 1988 | Double-blinded randomized placebo-controlled trial | Children with atopic dermatitis<br>N = 24<br>Age: 2–4 years<br>Gender (m/f): 14/ 10<br>Evening primrose group: 12<br>Placebo group: 12 | Evening primrose oil (Efamol) | N = 12<br>Evening primrose oil capsules<br>6 × 0,5 g per day for 4 weeks | N = 12<br>Olive oil capsules<br>6 × 0,5 g per day for 4 weeks | Pre and after 4 weeks treatment clinical evaluation for 10 clinical features (erythema, oedema, vasiculation, crusting, excoriation, scaling, lichenification, pigmentation, pruritus, loss of sleep)<br>on a 4 - point rating scale | After 4 weeks the symptoms of patients treated with evening primrose significantly improved ($p < 0.01$). Symptoms of the children in the placebo group remained largely unchanged. | 1 point for randomization<br>2 points for blinding<br>1 point for patients account<br>Total = 4 points |
| Biagi et al. 1988<br>A long term study on the use of evening primrose oil (Efamol®) in atopic children. Drugs under experimental and clinical research. | 1988 | Longitudinal observation study | Children with atopic dermatitis<br>N = 12<br>Age: 2–4 years<br>Gender (m/f): 8/ 4<br>Efamol group: 12 | Evening primrose oil (Efamol) | N = 12<br>Evening primrose oil<br>6 × 0.5 g capsules per day for 20 weeks | N = 0 | Pre and after 4 weeks treatment. Clinical evaluation for erythema, oedema, vasiculation, crusting, excoriation, scaling, lichenification, pigmentation, pruritus, loss of sleep, on a 4 - points rating scale, done by one blinded doctor.<br>Plasma, lymphocytes and neutrophils fatty acid percentage composition | Good results within 4 weeks<br>longer treatment (20 weeks) seems to maintain the improved clinical situation without side-effects<br>Basal: slight = no child; moderate = 2 children; marked = 7 children; severe = 1 child<br>after 4 weeks:<br>slight = 5 children; moderate = 3 children; marked = 1 child;<br>severe = 1 child<br>after 20 weeks:<br>slight = 6 children; moderate = 2 children; marked = 2 children; severe = no child | 0 points for randomization<br>0 points for blinding<br>0 points for patients account<br>Total = 0 points |
| Hederos et al. 1996<br>Epogam evening primrose oil treatment in atopic dermatitis and asthma. | 1996 | Double blinded, randomized, placebo controlled trial | Children with atopic dermatitis<br>N = 60<br>Age: 1–16 years<br>Gender (m/f): 13/ 17<br>Epogam-group: 30<br>Placebo- group: 30 | Evening primrose oil (Epogam) | N = 30<br>Epogam capsules (500 mg evening primrose oil /10 mg vitamin E) for 16 weeks. Dosage: Children from 1 to 12 years: 4 capsules twice daily. Children from 12 to 16 years: 6 capsules twice daily | N = 30<br>Placebo (500 mg sunflower oil / 10 mg vitamin E) for 16 weeks. Dosage: 1–12 years: 4 capsules twice daily. 12–16 years: 6 capsules twice daily | Clinical and parental assessment of eczema using a visual analogue scale (0 = normal, 100 = worst ever seen) for redness, dryness, crusts, excoriation/ itch, scaling, lichenification, fidget, overall impression of condition, area of involvement. Clinical measurements at baseline and every fourth week. | Significant improvement in atopic dermatitis during the 16 weeks treatment, but no significant difference between placebo and intervention group. | 2 points for randomization<br>1 point for blinding<br>1 point for patients account<br>Total = 4 points |

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**Table 2** (*continued*)

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|---|---|---|---|---|---|---|---|---|---|
| Chung et al. 2013<br>Dose-dependent effects of evening primrose oil in children and adolescents with atopic dermatitis. | 2013 | Randomized trial | Children with AD who met the Hanifin and Rajka criteria<br>N = 40<br>Age: 2–15 years<br>Gender (m/f): 24/16<br>Group 1: 20<br>Group 2: 20 | Evening primrose oil (EPO) (Evoprim soft capsule 40 mg) | N = 20 Group 1<br>160 mg EPO<br>(2 capsules twice daily for eight weeks)<br>N = 20 Group 2<br>320 mg EPO<br>(4 capsules twice daily for eight weeks) | N = 0 | Eczema Area Severity Index (EASI) scores at weeks 0, 2, 4 and 8<br>. In addition, measurement of the levels of serum fatty acids at week 0 and 8 | The serum fatty acid levels C18: 3 n and C20: 4 were higher in the 320 mg group than in the 160 mg group.<br>EASI scores were reduced in the 2 groups. The improvement in EASI scores was greater in the 320 mg group (from 6.250 ± 1.713–3.475 ± 1.175 at week 8) than in the 160 mg group (from 5.850 ± 1.548–4.525 ± 3.581 at week 8).<br>There were no side effects seen in either group during the study. | 1 point for randomization<br>0 points for blinding<br>0 points for patients account<br>Total = 1 point |
| Giordano-Labadie F et al. 2006.<br>Evaluation of a new moisturizer (Exomega milk®) in children with atopic dermatitis. | 2006 | Controlled, randomized and multicentric with two parallel groups | Children with mild to moderate AD<br>N = 76<br>Age: 6 months-12 years<br>Gender: not mentioned<br>Exomega milk group: 37<br>Control group: 39 | Exomega milk contains: evening primrose oil, rhealba oat extract, chlorphenizine, phenoxyethanol, butyl hydroxy toluene, glycols, paraffin jelly, paraffin oil, shea butter | N = 37<br>Application of moisturizing milk twice a day for 2 months over the whole body and use of a standard cleansing bar | N = 39<br>Using only the cleansing bar | Measurements at baseline and at day 28 and 56. The number of applications of dermocorticoids per class of activity was evaluated (class 2 moderate or class 3 strong). Quality of life questionnaire at day 0 and day 56, filled by the families. It totals the scores of 10 questions, with a max. of 30 and a min. of 0 points. The higher the CLQI, the greater the handicap. | The global Scorad index decreased significantly for both groups by day 28. Between D28 and D56 there was no significant change in none of the groups. With regard to xerosis, by day 56 there was a highly significant improvement in the treated group, while there was no significant improvement in the non-treated group.<br>On day 28 and day 56, tolerance of the moisturizer was evaluated as 1 (satisfactory) or 0 (excellent) in 97% of the treated patients.<br>The Children's dermatology life quality index (CLQI) variables were scored at baseline and at day 56.<br>Analysis of the results showed that there was | 1 point for randomization<br>0 points for blinding<br>0 points for patients account.<br>Total = 1 point |

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**Table 2** (*continued*)

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| | | | | | | | | a significant improvement of the CLQI in children after 2 months of treatment with emollient milk), while there was no significant difference in the non-treated group. | |
| Polypodium leucotomos | | | | | | | | | |
| Ramirez-Bosca et al. 2012 Polypodium leucotomos extract in atopic dermatitis: A randomized, double-blind, placebo-controlled, multicentre trial. | 2012 | A phase IV randomized, double-blind, placebo controlled, multicentre trial | Children with moderate AD that requires topic corticosteroids for treatment<br>N = 105<br>Age: 2–17 years<br>Gender (m/f): 36/69<br>PL group: 52<br>Placebo group: 53 | Polypodium leucotomos (PL) Extract | N = 52<br>PL extract capsules (120 mg)<br>< 6 years: 2 capsules in a single dose<br>6–12 years: 3 capsules in 2 doses<br>> 12 years: 4 capsules in 2 doses<br>To treat affected areas: Application of Methylprednisolone aceponate 0.1% in emulsion. To treat pruritus: Desloratadine. Systemic corticosteroids if needed: deflazacort at a dosage of 0.25–1.5 mg/kg/d | N = 53<br>Placebo capsules | Visits every 2 weeks (in total 13.)<br>SCORAD and investigator's global assessment (IGA) were measured 1, 2, 3, 4, 5, and 6 months after the start of treatment. | Reduction of corticosteroids:<br>PL group: Use of corticosteroids on 11% of the days. After the fifth month a significant reduction of 36% was observed, compared to month 1.<br>Placebo group: Use of corticosteroids on 12% of the days. No significant reduction of coritcosteroid use during 6 months.<br>Reduction of antihistamines:<br>PL group: Use of antihistamines on 14% of the days. (significantly lower compared to placebo group). Significantly lower overall proportion of patients who required antihistamines after month 3 compared to placebo group.<br>Placebo group: Use of antihistamines on 21% of the days.<br>SCORAD index: similar in both groups<br>Fewer flares: no significant differences<br>adverse effects: 463 adverse effects were reported (similar numbers in both groups), most of them were classified as mild. | 2 points for randomization<br>2 points for blinding<br>1 point for patients account<br>Total = 5 points |
| Blackcurrant | | | | | | | | | |
| Linnamaa et al. 2010 Blackcurrant seed oil for | 2010 | double-blind, randomized, | Mothers and their babies | Blackcurrant seed oil (BCSO) | N = 151 Mothers<br>N = 112 Babies | N = 162 Mothers | Measurements at 3, 12 and 24 months, | Prevalence of atopic dermatitis at 3 | 2 points for randomization, |

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**Table 2** (*continued*)

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|---|---|---|---|---|---|---|---|---|
| prevention of atopic dermatitis in newborns: a randomized, double-blind, placebo controlled trial. | | placebo-controlled trial | N = 313 (mothers)<br>N = 241 (babies)<br>Age: 0–24 months<br>Gender (m/f): 113/128<br>BCSO group: 112<br>Placebo group: 129 | | BCSO was encapsulated in soft gelatine capsules, six capsules per day were taken by the mothers (3 g/day). The infants started receiving the same oil in the form of drops, dose 1 mL/day, when exclusive breastfeeding was ended, and the children continued receiving the oil until 2 years of age | N = 129 Babies Placebo (olive oil) taken in the same way as BCSO | evaluated by a specialist in dermatology, using SCORAD index. | months:<br>BCSO group: 13.4%<br>olive oil group: 12.4%<br>prevalence of atopic dermatitis at 12 months:<br>BCSO group: 33.0%<br>olive oil group: 47.3%<br>prevalence of atopic dermatitis at 24 months:<br>BCSO group: 38.8%<br>olive oil group: 48.9%<br>SCORAD<br>At 12 months AD was less severe in the BCSO group than in the olive oil group. | 2 points for blinding<br>1 point for patients account.<br>Total = 5 points |
| **Diaper dermatitis** | | | | | | | | |
| Calendula | | | | | | | | |
| Adib-Hajbaghery et al. 2014<br>The effects of bentonite and calendula on the improvement of infantile diaper dermatitis. | 2014 | Double-blinded randomized trial | Infants with mild to medium diaper dermatitis<br>N = 60<br>Age: 1–24 month<br>Gender (m/f): 19/41<br>Calendula group: 30<br>Bentonite group: 30 | Calendula or Bentonite | N = 30 Calendula cream<br>N = 30 Bentonite cream<br>Application of the cream on the affected area 4 times a day after changing the diaper. Washing the affected area only with lukewarm water. Repeating this work every 4–6 h. No Application of any other material on the affected area such as wet wipes, essence contained soaps or other medications was allowed. | N = 0 | The researcher followed the process of administrating the cream, following the treatment program and the effect of treatment 3 times a day by phone. Every other day (up to 3 times), the infants were visited and assessed by the physician and the researcher. | Start of recovery after 6 h: Bentonite 93,3%; Calendula 40%<br>Improved completely in first 3 days: Bentonite 90%; Calendula 36,7% | 2 points for randomization<br>2 points for blinding<br>0 points for patients account<br>Total = 4 points |
| Calendula and Aloe vera | | | | | | | | |
| Panahi et al. 2011<br>A randomized comparative trial on the therapeutic efficacy of topical Aloe vera and Calendula officinalis on diaper dermatitis in childern. | 2011 | Randomized comparative, double- blinded trial | Children with diaper dermatitis<br>N = 66<br>Age: 0–3 years<br>Gender (m/f): 32/34<br>Aloe vera group: 32<br>Calendula group: 34 | Calendula officinalis and Aloe vera | N = 34 Calendula group: 1.5% of total extract obtained from C. officinalis flowers mixed with base cream. Application 3x daily for 10 days.<br>N = 32 Aloe vera group: A.Vera gel and olive oil (3:2) mixed with base cream. Application 3x daily for 10 days. Both treatments were stopped at day 5 when complete health was reached. Otherwise it was continued until day 10. | N = 0 | Measurements at baseline and at days 5 and 10 | Although the severity of DD was clearly decreased in both groups, the reduction rate was found to be significantly greater in the Calendula group.<br>Calendula group: decrease from 3.15 ± 0.73–1.09 ± 0.7<br>Aloe group: decrease from 2.88 ± 0.86–1.69 ± 0.95 | 2 points for randomization<br>2 points for blinding<br>0 points for patients account<br>Total = 4 points |
| Aloe vera and Chamomile | | | | | | | | |
| Badelbuu et al. 2018<br>Evaluation of the effect of Aloe vera ointment with chamomile | 2018 | Double-blinded, randomized, clinical trial | Children with diaper dermatitis<br>N = 89 | Chamomile or Aloe vera | N = 30 Chamomile ointment for 6 days<br>N = 30 Aloe vera | N = 29 Routine skin care | Rash severity, assessed on a 0–4 scale (0 = none; 1 = mild | All three groups had an upward trend towards the relief of |

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**Table 2** (*continued*)

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|---|---|---|---|---|---|---|---|---|---|
| ointment on severity of children's diaper dermatitis: a randomized, double-blind clinical trial. | | | Age: under 2 years<br>Gender (m/f): 50/39<br>Aloe vera group: 30<br>Chamomile group: 30<br>Control group: 29 | | ointment for 6 days. Washing the area, clearing the ointments used as routine treatments, rubbing the ointment on the dermatitis area, and covering the dermatitis area with chamomile or Aloe vera ointment, three times a day after changing the diaper and washing the area with warm water. | | erythema; 2 = moderate erythema; 3 = moderate erythema plus maceration; 4 = severe erythema plus pustules or ulceration).<br>Measurements at day 1, 3 and 6 | severity of dermatitis, no group was superior to another.<br>Alove vera group: from 1.8 ± 0.76 at day 1–0.76 ± 0.86 at day 6<br>Chamomile group: from 1.93 ± 0.83 at day 1–1.00 ± 1.110 at day 6<br>control group: from 1.70 ± 0.70 at day1 to 0.60 ± 0.67 at day 6 | blinding<br>0 points for patients account<br>Total = 4 points |
| **Wound healing**<br>Comfrey | | | | | | | | | |
| Grünwald et al. 2010<br>Anwendung und Verträglichkeit von Beinwellcreme (Symphyti herba) bei Kindern mit akuten stumpfen Traumen. | 2010 | Observational study | Children with bruise, strain and contusion<br>N = 196<br>Age: 4–12 years<br>Gender (m/f): 111/84<br>Traumaplant group: 196 | Traumaplant®Cream with a preparation of the aerial parts of symphytum × uplandicum Nyman 'Harras'(medicinal comfrey) | N = 196<br>Application of the cream min 3x daily on the affected area and massaging it in | N = 0 | Visits took place at the beginning of the study, as well as after 3–5 and after 7–9 days. | The improvement rates were:<br>pressure pain: 86.3% (84.7–92.5% for the individual symptoms, with the best results for distortions)<br>pain on movement: 86.7% (84.5-90.2%, with best results for strains).<br>functional disability: 89.7% (86.5–92.4%, best results for strains)<br>swelling: 94% (93.3–100%, best results for strains)<br>hematomas: 87.6% (86.4–93.8%, best results for sprains)<br>impairment of general condition: 90,1% (87,7–93,8%, best results for strains). | 0 points for randomization<br>0 points for blinding<br>1 Point for patients account<br>Total = 1 point |
| Barna M et al. 2012<br>Wound-healing effects of a symphytum herb extract cream (Symphytum×uplandicum Nyman) in children. | 2012 | Prospective, randomized, reference preparation-controlled double-blind, parallel-group study | Children with fresh (less than 24 h) abrasions<br>N = 108<br>Age: 3–12 years<br>Gender (m/f): 60/48<br>Verum (10%): 54<br>Control (1%): 54 | Symphytum Herb Extract | N = 54<br>Daily application of a cream with 10% extract of medicinal comfrey. | N = 54<br>Daily application of a cream with 1% extract of medicinal comfrey. | Measurements at baseline and at day 2–3 und day 7–9. | Wound area:<br>Verum: Wound area was reduced by 50% within an average of 1.8 days.<br>Control: Wound area was reduced by 50% within an average of 2.7 days.<br>Wound-healing rate:<br>Verum: 0.38 ± 0.18/day | 2 points for randomization<br>2 points for blinding<br>1 point for patients account<br>Total = 5 points |

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**Table 2** (*continued*)

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| | | | | | | | | Control: 0.26 ± 0.14/day<br>Significant difference<br>Complete wound-healing:<br>Verum: Average of 4.11 days.<br>Control: Average of 8.89 days.<br>Significant difference<br>Overall efficacy by physicians:<br>Verum: Efficacy was found to be good or very good in 90.7% after day 2–3 and in 92.6% after day 7–9.<br>Control: Efficacy was found to be good or very good in 55.6% after day 2–3 and in 74.0% after day 7–9.<br>In both groups overall efficacy by the patients correlated well with the findings from the physicians.<br>Safety and tolerance:<br>No adverse effects were observed. | |
| Kucera et al. 2018<br>Tolerability and effectiveness of an antitrauma cream with comfrey herb extract in paediatric use with application on intact and on broken skin. | 2018 | Open, non-interventional prospective trial | Children with blunt traumas with intact or broken skin<br>N = 712<br>Age: 4–12 years<br>Gender (m/f): 478/234<br>Intact skin: 386<br>Broken skin: 326 | Cream with comfrey herb extract | N = 712<br>Several times daily (2–4x) application of a cream with 10% extract of medicinal comfrey for 14 days | N = 0 | Measurements after week 1 and week 2 | Safety and tolerability:<br>Intact skin: No adverse effects<br>broken skin: One child showed severe local burning and reddening at the application site within 15 min after the first application.<br>Effectiveness of treatment by physicians:<br>Intact skin: Efficacy was found to be good or very good in 89.6% after week 1 and in 94.3% after week 2.<br>Broken skin: Efficacy was found to be good or very good in 81.2% after week 1 and in 91.1% after week 2.<br>In both groups efficacy by the patients correlated | 0 points for randomization<br>1 point for blinding<br>1 point for patients account<br>Total = 2 points |

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**Table 2** (*continued*)

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| | | | | | | | | well with the findings from the physicians. | |
| Hamamelis | | | | | | | | | |
| Wolff et al. 2006<br>Hamamelis in children with skin disorders and skin injuries: results of an observational study. | 2006 | Prospective, open-label, multicentre, observational study | Children with minor skin injuries or various skin diseases<br>N = 309<br>Age: 27 month - 11 years<br>Gender (m/f): 153/145<br>minor skin injuries: 72<br>(hamamelis: 48 / dexpanthenol: 24)<br>local inflammation: 142<br>(hamamelis:109/ dexpanthenol: 33)<br>diaper dermatitis: 97<br>(hamamelis: 75 / dexpanthenol: 22 | Hamamelis ointment | N = 232<br>Hamamelis ointment at a 3:1 ratio, external thin application several times a day for 8 days | N = 79<br>Dexpanthenol ointment at a 3:1 ratio, external thin application several times a day for 8 days | Measurements at baseline and at day 8. | Minor skin injuries:<br>Hamamelis group:<br>Score at baseline: 8.1 ± 3.0, significant change at day 8: −5.1 ± 3.9<br>(median −4.0)<br>Dexpanthenol group:<br>Score at baseline: 8.5 ± 2.6, significant change at day 8:<br>− 4.2 ± 2.8 (median −4.0)<br>Local inflammation:<br>Hamamelis group:<br>Score at baseline: 7.7 ± 3.5, significant change at day 8: - 5.2 ± 4.0<br>(median −5.0)<br>Dexpanthenol group:<br>Score at baseline: 7.4 ± 3.7, significant change at day 8:<br>− 4.7 ± 3.2 (median −4.0)<br>Diaper dermatitis:<br>Hamamelis group:<br>Score at baseline: 7.8 ± 5.1, significant change at day 8: - 6.0 ± 5.4 (median: −4.0)<br>Dexpanthenol group:<br>Score at baseline: 8.9 ± 5.9, significant change at day 8: - 6.6 ± 4.1 (median: −7.5) | 0 points for randomization<br>0 points for blinding<br>0 points for patients account<br>Total = 0 points |
| Olive | | | | | | | | | |
| Kiechl-Kohlendorfer et al. 2008<br>The effect of daily treatment with an olive oil/lanolin emollient on skin integrity in preterm infants: a randomized controlled trial. | 2008 | Randomized controlled trial | Children between 25 and 36 weeks of gestation<br>N = 173<br>Age: 25–36 weeks of gestation<br>Gender: (m/f): 93/80<br>Group A: 57<br>Group B: 58<br>Control group: 58 | Olive oil cream | N = 57 Group A:<br>10 g of Bepanthen (dexpanthenol and phenoxyethanol) per day, applied as thin coat on the skin, except face and scalp.<br>N = 58 Group B:<br>10 g of olive oil cream (30% olive oil and 70% lanoline) per day, applied as thin coat on the skin, except face and scalp.<br>In both groups therapy commenced within the first 24 h of life. | N = 58<br>Routine skin care without topical emollients | Evaluation at baseline and at weeks 1–4 | Skin condition:<br>Group A:<br>The score increased from 1.07 ± 0.29–2.00 ± 1.09<br>Group B:<br>The score increased from 1.10 ± 0.31–1.40 ± 0.81<br>Group C:<br>The score increased from 1.10 ± 0.31–2.70 ± 1.03.<br>In each Group the score increased, skin integrity got worse. | 1 point for randomization<br>1 point for blinding<br>1 point for patients account<br>Total = 3 points |

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**Table 2** (*continued*)

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| | | | | | | | | But the olive oil could slow down the process the most. | |
| Burn & Wound Ointment and Burdock leaves | | | | | | | | | |
| Flurry et al. 2017<br>Salve and burdock: A safe, effective Amish remedy for treatment of traumatic wounds? | 2017 | Retrospective chart review | Amish or Mennonite patients with large open wounds<br>N = 6<br>Age: 4–29 years<br>Gender (m/f): 4/1 | Burn & Wound Ointment (honey, lanolin, olive oil, wheat germoil, marshmallow root, Aloe vera gel, wormwood, comfrey root, white oak bark, lobelia, vegetable glycerin, beeswax, and myrrh.) And Burdock leaves | N = 6<br>B & W Ointment is slathered thickly onto steeped burdock leaves by hand or with a tongue depressor. The combination is placed on the wound and wrapped in either additional cloth dressings or chuck pads. The dressing is changed at least 2–3 times per day, until the wound is fully healed. | N = 0 | Discussions with the patients and their families after wound healing was complete | Time to full epithelialization ranged from 1 to 7 months. Time to full wound healing was proportional to wound size.<br>Complications included one minor infection treated with antibiotics and wound contracture of a palmar wound with minor limitations to hand motion.<br>No major limb loss or death.<br>The families were all very pleased with the results | 0 points for randomization<br>0 points for blinding<br>0 points for patients account<br>Total = 0 points |
| Hypericum and neem | | | | | | | | | |
| Mainetti et al. 2013<br>An experience with paediatric burn wounds treated with a plantderived wound therapeutic. | 2013 | Retrospective, non-controlled study | Children with burn wounds<br>N = 9<br>Age: 1–11 years<br>Gender (m/f): 7/2 | Hypericum and Neem oil | N = 9<br>Daily cleansing of the wound with saline solution and application of 1 Primary wound dressing on the whole surface | N = 0 | Granulation tissue formation, epithelialization, wound area (using scaled digital photographs, pain relief and time of healing were recorded weekly by the same wound-care specialist). An external specialist processed the digital data. | Pain: decrease of initial pain rating of 7–8 out of 10–0 out of 10 on the VAS, after 3–5 days of treatment and remained at the same level for the second and third week of treatment.<br>Wound healing: 14 out of 15 wounds healed by secondary intention without any further interventions.<br>Time to complete healing: mean time was 16.6 ± 4.69 days.<br>Complications: no superficial or deep infection, none of the patients showed signs of allergic reaction an no other side effects were observed. | 0 points for randomization<br>0 points for blinding<br>0 points for patients account<br>Total = 0 points |

the six-day study in all three groups, but no group was superior to another.[20]

In all three studies, the treatments were described as safe without describing the process of side effect assessment in more detail.

#### 3.2.3. Wound healing

Seven studies (Grünwald et al.,[21], Barna et al.,[22], Kucera et al.,[23] Wolff et al.,[24], Kiechel-Kohlendorfer et al., [25] Flurry et al.[26] and Mainetti et al.[27]) analysed the effect of phytotherapy in treating blunt trauma and wounds on a total of 1513 children, aged from 25 weeks of gestation to 11 years. The studies were carried out in Germany, Czech republic, Austria, USA, and Bolivia. Among them were randomized controlled trials, open, non-interventional prospective trials, observational studies, and case series.

The studies investigated the impact of comfrey cream, hamamelis ointment, olive oil cream, hypericum and neem oil, as well as burn and wound ointment containing aloe vera, comfrey, white oak bark, and myrrh on wound healing. Regarding the Jadad-score only two out of the 7 studies reached three or more points.

Grünwald et al. examined the influence of traumaplant cream containing comfrey on wound healing. According to the results, comfrey can be regarded as a good and safe therapeutic option for the treatment of blunt traumas like strains, contusions or sprains in children, since the effect of the comfrey cream was judged by over 80% of parents and doctors to be good or very good.[21]

Barna et al. examined the effect of a cream containing comfrey on the wound healing in children. The control group received a cream containing 1% of the active agent instead of no treatment or a placebo due to ethical concerns, while the intervention group received a cream containing 10% of the active agent. The collected data shows an acceleration of the wound healing process for the intervention group and the effect was found to be good or very good in over 90%.[22]

Kucera et al. investigated the safety and tolerance of a comfrey cream as well. Their results support the findings of Barna et al., in that comfrey seems to be effective in the treatment of intact or broken skin in children.[23] In all three studies that focused on comfrey, possible side effects were investigated, but none were found.

Wolff et al. compared the effect of hamamelis ointment to dexpanthenol ointment for the following skin diseases in children: minor skin injuries, diaper dermatitis, and localized inflammation of skin or mucous membranes. The results showed that the effect of both treatments was similar, by leading to clinically relevant and significant improvements in the conditions.[24] The researchers also investigated safety and tolerance and found hamamelis to be safe for application in children.

Kiechl-Kohlendorfer et al. treated 173 neonates between 25 and 36 weeks of gestational age admitted to a neonatal intensive care unit. Infants were randomly assigned to daily topical treatment with water-in-oil emollient cream ("Bepanthen"), olive oil cream (70% lanoline, 30% olive oil), or to a control group (no treatment). Each neonate was continuously treated for a maximum of four weeks. Skin condition (skin score reflecting degree of dermatitis) in the three groups was compared at weeks 1, 2, 3, and 4. Findings revealed that neonates treated with olive oil cream showed statistically less dermatitis than did neonates treated with emollient cream, and both had a better outcome than neonates in the control group ($p < 0.001$ in weeks 2–4).[25]

Flurry et al. studied an ointment called "Burn & Wound ointment" used by the Amish. It contains, among others, honey, aloe vera, comfrey, white oak bark, and myrrh. The treatment also included the application of burdock leaves. Since this explorative study was a non-controlled case series with only five children, no general statements can be made about the effectiveness of the treatment. Results showed that the treatment had no harmful side effects. In the conclusion, it was stated that supervised applications of these wound dressings could allow healthcare providers to ensure a low-cost treatment and to foster trust with members of the Amish community.[26]

Mainetti et al. examined the impact of hypericum and neem oil called "1 Primary Wound Dressing" on the time of complete wound healing and the extent of pain in burnt soft tissue. As this study was a case series, no conclusive statements can be made about treatment effectiveness. However, the results of the nine children examined suggest that the plant-derived wound spray "1 Primary Wound Dressing" is potentially effective in treating burnt soft tissue.[27]

## 4. Discussion

### 4.1. Summary of evidence

This systematic review aimed to examine the efficacy of herbal medicines for children affected by skin disorders, such as atopic dermatitis, diaper dermatitis, or skin wounds.

In total, 17 studies were included, seven each examined atopic dermatitis or wound healing, three investigated diaper dermatitis. For the treatment of atopic dermatitis, evening primrose capsules were found to be the most safe and effective phytotherapeutical treatment, based on the evidence of one double-blind randomized and placebo-controlled trial,[11] one randomized trial investigating dose-dependent effects,[14] and one longitudinal observation study over 20 weeks.[12] Interestingly, the study of Hederos et al.[13] could not replicate the positive effect of evening primrose capsules as seen in the other studies, although the same dosage of evening primrose capsules was used. Likewise, the extract of polypodium leucotomos was found to be safe and effective in treating atopic dermatitis.[17] However, as this is the only study that exists on polypodium leucotomos that was eligible for this review, the positive results await replication by further studies. The prevention of atopic dermatitis with blackcurrant seed oil did not provide clear evidence.[16]

Contrary to atopic dermatitis, no clear recommendation can be provided for the best phytotherapeutical treatment of diaper dermatitis in young children. Findings of Kiechl-Kohlendorfer et al. revealed that neonates treated with olive oil cream showed statistically less dermatitis; however, the results of this controlled clinical trial would benefit from replication.[25] Panahi et al.[19] also found that calendula has a significant impact on the symptoms of diaper dermatitis, however, Adib-Hajbaghery et al.[18] disproved this results in their study. For Aloe vera and chamomile, none of the publications found significant results. To accelerate wound healing in children, comfrey was found to be effective and safe in both a randomized controlled trial by Barna et al.,[22] as well as in an open, non-interventional, prospective trial with 712 children by Kucera et al.[23] A third study, by Grünwald et al.,[21] investigated comfrey for treating internal injuries, and showed positive results for it as well. In all studies, comfrey-based treatments showed no or only mild side effects. Finally, the use of hamamelis ointment was found to be effective in the treatment of minor skin injuries, local inflammation and diaper dermatitis.[24] Since the results await replication, no final conclusions can be made on this agent.

### 4.2. Limitations

We searched for studies that investigated the treatment of any kind of skin disease in children by phytotherapy. However, we only found studies on the following three skin disorders that met our inclusion criteria: atopic dermatitis, diaper dermatitis, and wound healing. The children affected by these disorders had typically already been treated with standard therapies before the studies started. In some studies, this initial treatment was continued during the trial, and it was not always clarified what kind of drugs the standard therapy was composed of. Therefore, it remains unclear what confounding effects the initial treatments might have had on the final study outcomes.

Moreover, the length of the treatment period in the studies varied greatly depending on the disorder. For disorders requiring a longer treatment period, such as atopic dermatitis, all studies were designed for at least four weeks, so that long-term effects could be observed. For

disorders requiring shorter treatment periods, such as diaper dermatitis, the studies lasted for a maximum of ten days, which renders comparisons difficult. Furthermore, all examined phytotherapeutics were classified as low-risk treatments, even if recordings of side effects/adverse events were not provided.

Our quality rating showed that most of the included studies were of poor quality, with only nine out of 17 studies reaching three or more points on the Jadad-score.

Another limitation results from the data collected on the populations in each study. For the studies, children with skin diseases in Asian, European, North, and South American countries were examined. Based on the origin of the cited studies, it only can be assumed, that BIPoC were included in the studies. However, the studies did not provide detailed information. Future studies, that provide detailed information on effectiveness, safety, and dosage of herbal medicine to treat skin diseases in the form of randomized controlled trials will be of great importance.

### *4.3. Conclusion*

Based on the application of the Jadad score, eight out of 17 of the studies examined were of low quality. Yet we found some indication that evening primrose oil processed in capsules may be effective for the treatment of atopic dermatitis in children. To accelerate wound healing in children, comfrey processed in an ointment appears to have a positive effect. Since no or only mild side effects have been reported, both primrose oil capsules and treatments containing comfrey can be considered as low-risk treatment for skin disorders in children and adolescents. For Aloe vera and chamomile, none of the studies found positive results.

## Declarations

none.

## Ethics approval and consent to participate

Not applicable.

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## Consent for publication

Not applicable.

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### *Competing interests (include appropriate disclosures)*

The authors declare that they have no competing interests.

### *Authors' contributions*

Authors FA and EK carried out the systematic literature review, quality rating, data extraction and writing of the main body of the manuscript, RS aided in the composing, editing and submission of the paper. UW provided the idea and conceptualization, supervised, reviewed and funded this research.

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