

Complementary and Alternative Medicine for Atopic Dermatitis: An Evidence-Based Review

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Abstract

Background Complementary and alternative interventions are becoming increasingly utilized as adjuncts to conventional treatment of atopic dermatitis (AD). While the number of studies continues to grow, the vastness of the subject coupled with the relatively poor quality and small size of the studies limit their usefulness to clinicians.

Purpose Our aim was to comprehensively review randomized controlled trials (RCTs) of complementary and alternative therapies for AD.

Methods Searches were performed on PubMed, the Cochrane Central Register of Controlled Trials, EMBASE, and the Global Resource for Eczema Trial (GREAT) databases, focusing on RCTs of alternative or complementary AD therapies, with a sample size of ≥ 10 , through March 2015 and limited to the English language. A total of 70 manuscripts met the inclusion criteria and were included in the final analysis.

Results There is at least some level I evidence to support the use of acupuncture and acupressure, stress-reducing techniques such as hypnosis, massage, and biofeedback, balneotherapy, herbal preparations (with many important caveats), certain botanical oils, oral evening primrose oil, vitamin D supplementation, and topical vitamin B₁₂. Many other therapies either have sufficient data to suggest that they are ineffective, or simply do not have enough evidence to formulate a verdict.

Conclusions Careful review of the literature reveals several promising therapies in this domain; such findings may help direct further research that is necessary to bolster clinical recommendations for alternative or complementary treatments of AD.

Key Points

Atopic dermatitis can be difficult to treat, and some of the conventional medications have significant side effects. Many patients seek alternative treatments, often based only on anecdotes.

Although studies vary in quality and size, level I evidence exists for some alternative treatments that suggests clinically meaningful approaches may only require further confirmation.

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1 Introduction

Atopic dermatitis (AD) represents a chronic, relapsing, itchy, inflammatory skin condition that poses significant therapeutic challenges and has no known cure. One of the most common inflammatory skin diseases, AD has a prevalence exceeding 10 % of children in some populations [1]. Despite tremendous gains in understanding its pathogenesis and treatment, navigating the line between risks and benefits of conventional therapies such as topical corticosteroids, antibiotics, and systemic immunosuppressants remains fraught with difficulty. Many patients seek

alternative and complementary therapies, perhaps more so when diseases are incurable or when standard treatments have undesirable side effects, making AD a prime candidate for such exploration. Indeed, multiple studies converge on the conclusion that more than half of patients with AD utilize alternative medicine [2–4].

Alternative medicine can be difficult to define, as it encompasses a wide range of unconventional therapies, from snake oil sold on the Internet to ancient and complex healing systems. Generally speaking, it consists of treatments that have not been sufficiently tested to make conclusions about efficacy, as well as those that have accrued enough evidence to dismiss them completely [5]. In theory, any treatment that garners enough high-quality evidence will cease being alternative and graduate into the conventional canon. Herein we review the literature in order to make evidence-based conclusions about many of the most common alternative and complementary treatments for AD. In doing so, we hope to elucidate promising therapies that may be overlooked, and highlight those that are not beneficial so that time and money will not be wasted in fruitless pursuits. Moreover, by compiling a large number of studies, we hope to centralize these results in an accessible document to better inform clinicians and researchers.

2 Methods

A review of the medical literature was completed following the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement criteria [6]. In conjunction with a research librarian, a search of PubMed, EMBASE, the Cochrane Central Register of Controlled Trials and Cochrane Database of Systemic Reviews, and the Global Resource for Eczema Trials (GREAT) databases was conducted through March 2015 to identify all studies reporting complementary or alternative therapies of AD. Medical subject headings (MeSH) used in the literature search included atopic dermatitis or atopic eczema and complementary therapies, alternative medicine, therapies, integrative medicine, natural, diet therapy, diet modification, nutrition therapy, dietary supplement, pyridoxine, vitamins, zinc, herb therapy, herbal medicine, homeopathy, massage, acupuncture, balneotherapy, phytotherapy, traditional Chinese medicine, aromatherapy, naturopathy, hypnosis, acupressure, oil, vitamin D, cryotherapy, hydrotherapy, and biofeedback, as well as permutations of these words found in the title or abstract.

The inclusion and exclusion criteria were prospectively limited to publications in the English language and

randomized controlled trials (RCTs) of ten or more human subjects, and included adults, adolescents, children, or infants with AD. We excluded trials that did not assess the alternative or complementary therapy as the primary intervention to which the experimental group was exposed. Trials assessing probiotics were also excluded; while controversies remain, they have their own robust and more conventional literature. The primary outcomes of interest included clinical signs and symptoms, long-term control of flares, and quality of life.

The authors conducted a manual review of the titles and abstracts identified from the search. Details were independently obtained about the patient population, study design, intervention, and outcome measure. A study met inclusion criteria for this review if it was determined to be an RCT with a sample size of ≥ 10 , if it evaluated an alternative therapy, and if it assessed clinical improvement of AD severity as the primary outcome; discrepancies were resolved by consensus. The authors obtained the full text of the studies for independent assessment and determined eligibility again after full-text review. Disagreements were resolved by discussion among all authors. The authors were not blinded to the names of authors, journals, or institutions.

Authors' conclusions are based on available evidence.

3 Results and Implications for Future Research

The initial search using medical subject headings (MeSH) and keywords as outlined above yielded a total of 883 articles from the four databases (379 PubMed, 231 Cochrane, 50 EMBASE, 223 GREAT database). Of these articles, 130 RCTs met the inclusion criteria for this review during preliminary analysis of titles and abstracts. Of the 128 full-text articles assessed for eligibility, 70 met the inclusion criteria and were included in the final analysis.

Convergence of multiple large-scale RCTs remains the gold standard for making sound evidence-based recommendations [7]. Accruing such evidence, however, requires significant resources—resources that are notably absent from the realm of alternative medicine. Alternatives lack the funding and organization of large pharmaceutical companies studying new drugs, and also lack the gravitas to warrant government-sponsored research on a large scale. Thus, many of these treatments remain on the fringes, often supported by small, sometimes poorly conceived studies that make analysis difficult. Despite these limitations, we present multiple studies that met our inclusion criteria and, when taken together, argue for consideration of some promising alternatives and for more research across the board.

3.1 Acupuncture and Acupressure

Itch is the major symptom of AD, and is central to its pathogenesis. Acupuncture has been shown to exhibit a significant effect on itch in other contexts, such as in an RCT for uremic pruritus, which demonstrated that acupuncture was significantly better at reducing pruritus in refractory cases than a sham acupuncture control ($p < 0.001$) [8].

In two studies of 30 and 20 patients, respectively, Pfab et al. demonstrated that acupuncture significantly reduced allergen-induced itch intensity when compared with placebo and no treatment [9], and that acupuncture was more effective than the antihistamine cetirizine when used abortively rather than preventatively [10]. While somewhat contrived from a clinical perspective, these studies suggest the possibility of direct modulation of pruritus and inflammation by acupuncture in atopic individuals, a population not previously examined (Table 1).

Lee et al. carried this forward with an investigator-blinded trial of 15 patients with moderate-to-severe AD and found

that acupressure (using a small titanium bead to massage an acupoint on the arm 3 times weekly) significantly improved pruritus ($p = 0.04$), lichenification ($p = 0.03$) and Investigator Global Assessment (IGA) ($p = 0.03$) scores compared with control group, though overall Eczema Area and Severity Index (EASI) scores remained unchanged [11]. This study was limited by small patient numbers, lack of placebo, and unmonitored application of acupressure. No adverse effects were reported in any of the studies.

The results of these studies are encouraging, but the numbers are small—thus, larger studies are needed to clarify a repeatable approach, as well as to further elucidate the possible mechanisms of such an effect.

3.2 Hypnotherapy, Relaxation, and Massage

Several lines of evidence suggest that stress plays a role in AD [12]. It then follows that stress-reduction techniques may be helpful in managing the disease.

In a study of 44 patients by Sokel et al., both hypnotherapy and biofeedback (a relaxation/awareness

Table 1 Acupuncture and acupressure

References	Treatment	Study design	Number of patients enrolled	Duration (weeks)	Baseline AD assessment	Assessment of AD improvement	Age range (years)	Results	Adverse effects
Lee et al. [11]	Acupressure	Ran, contr, sc, nb	15	4	AD, VAS, IGA, EASI	VAS, IGA, EASI	19–79	Acupressure significantly improved pruritus and lichenification scores compared with control group	None
Pfab et al. [9]	VA	Ran, sc, db, contr, triple crossover	30	Not listed	AD, SCORAD >18	EIQ, wheel and flare response size via laser Doppler	18–50	VA significantly reduced type I hypersensitivity itch compared with placebo and no treatment	Not listed
Pfab et al. [10]	VA vs. oral antihistamine (cetirizine)	Ran, sc, db, contr, crossover	20	Not listed	AD, physician diagnosed, SCORAD >20	VAS, EIQ	18–50	Both VA and cetirizine significantly reduced type I hypersensitivity itch compared with placebo and no treatment. Abortive VA was more effective than preventive VA or cetirizine	Not listed

AD atopic dermatitis, *contr* controlled, *db* double blinded, *EASI* Eczema Area and Severity Index, *EIQ* Eppendorf Itch Questionnaire, *IGA* Investigator Global Assessment, *nb* nonblinded, *Ran* randomized, *sc* single center, *SCORAD* SCORing Atopic Dermatitis, *VA* verum acupuncture, *VAS* visual analog scale

technique based on a physiological feedback device that measures galvanic skin resistance) groups exhibited significant reduction in surface damage and lichenification compared with the control group [13]. Neither treatment appeared to be superior to the other, however, suggesting that both techniques may benefit patients similarly through relaxation (Table 2). Results of another study of 33 patients demonstrated that patients who were trained to decrease skin conductance (generally associated with more relaxed states) using biofeedback showed significant improvement in disease severity, while those who were trained to increase skin conductance (generally associated with increased anxiety) showed worsened severity [14]. Of note, this study included only patients with dyshidrotic eczema.

A study of 28 patients over 14 weeks found that cognitive behavioral stress (CBS) management therapy showed no significant improvement in disease severity over the non-treatment group [15]. Patients with other atopic comorbidities were excluded from the study. Of note, CBS did reduce endocrine and psychological stress responses in AD patients, though no skin manifestations were noted during the study period.

A study comparing an educational program versus autogenic training versus cognitive behavioral treatment versus a combination of education and behavioral treatment determined that at 1 year follow-up, all psychological treatments decreased severity of the AD and the amount of topical steroids used more than the standard medical care control, or education alone [16].

Schachner et al. compared massage therapy to standard topical treatment and found that massage significantly improved redness, scaling, lichenification, excoriation, and pruritus compared with control in 20 children aged 2–8 years [17]. In a trial of 25 patients that examined standard of care with or without progressive muscle relaxation therapy, it was found that progressive muscle relaxation significantly reduced pruritus and loss of sleep when compared with baseline. However, there was no significant difference in EASI scores between treatment and control groups [18].

In a study by Anderson et al., 16 children with refractory AD were divided into groups that either received massage therapy in conjunction with essential oils (aromatherapy), or massage therapy alone [19]. The authors found no significant difference between the two groups, but both did show improvement following treatment from baseline. However, there was no untreated control. Of concern was that some patients may have become sensitized to the essential oils and actually worsened during the study, possibly negating any positive effects of the oils.

From the limited evidence, it appears that massage, hypnosis, and perhaps other stress-relieving techniques could play at least an adjunctive role in managing AD

given their minimal side effects. Sleep disruption continues to be a major problem for many patients, and the notion that something safe and inexpensive like progressive muscle relaxation could be of value is compelling and worthy of more research [20]. Aromatherapy oils do not appear to add any therapeutic value to massage, and may even pose a problem by acting as sensitizers.

3.3 Balneotherapy

Increased transepidermal water loss (TEWL) is one of the key characteristics of AD. Thus, it is not surprising that certain AD interventions involve water and bathing. Balneotherapy (bath treatments) are ancient practices, but emerged as modern treatment modalities in the 1800s in Europe [21]. Although it has been suggested that ‘hard water’ (water rich in minerals such as magnesium, calcium, and bromide) can provoke AD [22], in a recent RCT of 336 children, Thomas et al. demonstrated that ion-exchange water softeners provide no additional benefit to traditional AD therapy (Table 3) [23]. Togawa also evaluated the efficacy of ion-exchange water softeners in a sample of 12 children in Japan with mild to moderate eczema (EASI ≤ 20) [24]. Their results suggested that ultra-pure soft water does not significantly improve the EASI score; however, patients reported a significant reduction in pruritus and an increase in satisfaction.

In an RCT of 180 AD patients, Heinlin et al. found that synchronous balneophototherapy—a simulation of Dead Sea treatment conditions in terms of mineral bath content and ultraviolet light exposure—significantly reduced AD severity when compared with narrow-band UVB monotherapy ($p < 0.001$), with only mild and comparable adverse effects noted in both groups [25]. Finally, an open RCT of 104 children found that both balneotherapy and topical corticosteroids significantly improved disease severity. Topical corticosteroids proved to be more effective than balneotherapy regarding SCORing Atopic Dermatitis (SCORAD) ($p < 0.03$); however, IGA, Patient’s Self Global Assessment (PSGA), Children’s Dermatology Life Quality Index (CDLQI), and Family Dermatitis Impact Questionnaire (FDIQ) score improvements were similar. Interestingly, at 4 months, the incidence and duration of relapse were both significantly reduced in patients treated with balneotherapy compared with those treated with topical corticosteroids ($p < 0.0001$) [26].

From the evidence, it is reasonable to conclude that water softeners are likely not a useful adjunct for most patients with AD. Conversely, a large, high-quality trial by Heinlin et al. suggests that the supplementation of hypertonic, magnesium-rich salt baths in addition to phototherapy does confer an additional therapeutic benefit [25]. The corroboration by Farina et al. is helpful here, warranting

Table 2 Hypnotherapy, relaxation, and massage

References	Treatment	Study design	Number of patients enrolled	Duration (weeks)	Baseline AD assessment	Assessment of AD improvement	Age range (years)	Results	Adverse effects
Anderson et al. [19]	Massage therapy with or without aromatherapeutic essential oils	Ran, db, contr	16	8	Refractory AD, NS	Day-time irritation scores, night-time disturbance score, assessed by mother; general improvement scores by therapist, mother and GP	3–7	General improvement scores showed no significant difference between essential oil group and massage only control group	Worsening of night-time disturbance in essential oil group after subsequent sessions beyond 8 weeks
Bae et al. [18]	Standard of care with or without progressive muscle relaxation therapy	Ran, sc, contr, nb	25	4	At least moderate extrinsic AD, HRC	EASI, VAS, LOS	12–40	Progressive muscle relaxation significantly reduced pruritus and LOS from baseline. No significant difference in improved EASI scores between groups	Not listed
Ehlers et al. [16]	Educational program (DE) vs. autogenic training (AT) vs. cognitive-behavioral treatment (BT) vs. combined DE and BT (DE/BT)	Ran, contr, sc, ib, parallel	113	52	AD, HRC	Standardized disease severity score, amount of corticosteroids used, patient self-reported itching, Marburg Atopic Dermatitis Questionnaire, patient global disability rating	17–55	AT, BT, and DE/BT significantly reduced disease severity and amount of topical steroids used far greater than DE alone or standard medical care control	Not listed
Miller and Cogger [14]	Training for increasing vs. decreasing skin conductance	Ran, parallel, ib, sc	33	4	Diagnosis of dyshidrotic eczema	Investigator assessment using 6-point standard clinical scale, skin conductance, anxiety levels via STAI	Male: mean 28.7; female: mean 32.5	Patients who were trained to decrease skin conductance showed significant improvement in disease severity, while patients trained to increase skin conductance showed worsened severity	Eczema exacerbations
Schachner et al. [17]	Standard topical care with or without massage therapy	Ran, contr, sc, ib, parallel	20	4	AD, HRC	Behavior Observation Assessments, global/focal dermatologist assessments	2–8	Massage significantly improved redness, scaling, lichenification, excoriation, and pruritus compared with control	Not listed
Schut [15]	Cognitive behavioral stress management therapy	Ran, sc, ib, contr	28	14	AD, HRC	SCORAD, salivary cortisol, Multidimensional Mood Questionnaire	Not listed	Cognitive behavioral stress management therapy showed no significant improvement in disease severity over non-treatment group	None
Sokol et al. [13]	Hypnotherapy vs. biofeedback	Ran, ib, sc, parallel, contr	44	20	Refractory AD, NS	Scoring sheets for erythema, surface damage, and lichenification assessed by dermatologist	5–15	Both hypnotherapy and biofeedback groups had significant reduction in surface damage and lichenification compared with control group. Neither treatment group was better than the other	Not listed

AD atopic dermatitis, *contr* controlled, *db* double blinded, *EASI* Eczema Area and Severity Index, *GP* general practitioner, *HRC* Hanifin and Rajka's criteria, *ib* investigator blinded, *LOS* loss of sleep, *nb* nonblinded, *NS* not specified, *Ran* randomized, *sc* single center, *SCORAD* SCORing Atopic Dermatitis, *STAI* State-Trait Anxiety Inventory, *VAS* visual analog scale

Table 3 Balneotherapy

References	Treatment	Study design	Number of patients enrolled	Duration (weeks)	Baseline AD assessment	Assessment of AD improvement	Age range	Results	Adverse effects
Farina et al. [26]	Balneotherapy vs. TCS	Ran, nb, sc, parallel	104	2	Mild to moderate AD, SCORAD, IGA, PSGA, CDLQI, FDIQ	SCORAD, IGA, PSGA, CDLQI, FDIQ	1–14 years	Both treatments significantly improved disease severity. TCS showed significant improvements in SCORAD; however, no significant difference between groups in IGA, PSGA and CDLQI and FDIQ. Balneotherapy patients had fewer relapses post-treatment at 4 months	Mild erythema and burning sensation
Heinlin et al. [25]	Synchronous balneophototherapy vs. narrow-band UVB monotherapy	Ran, mc, nb, contr	180	24	AD, dermatologist-diagnosed, SCORAD >35	SCORAD, Sickness Impact Profile, 6-step Likert scale, FLQA	≥18 years, mean 41	Synchronous balneophototherapy significantly reduced AD severity compared with narrow-band UVB monotherapy	Erythema, light dermatoses, gastrointestinal diseases, infections and parasitic diseases, sunburn. Tolerability comparable among both groups
Thomas et al. [23]	Normal eczema care with or without ion-exchange water softeners	Ran, mc, contr, crossover, ib	336	16	AD, physician diagnosed, SASSAD ≥10	SASSAD score, POEM, Dermatitis FDIQ, EQ-5D, flaggrin saliva sample	6 months–16 years	Ion-exchange water softeners provide no additional benefit to normal eczema care	Not listed
Togawa [24]	Ultra-pure soft water	Ran, db, pc, crossover	12	14	Mild to moderate AD, EASI score ≤20	EASI, VAS, TEWL, serum biomarkers, out-in skin transparency	3–6 years	Ultra-pure soft water significantly improved pruritus and out-in skin transparency compared with placebo, but not eczema severity	Not listed

AD atopic dermatitis, *contr* controlled, *db* double blinded, *CDLQI* Children's Dermatology Life Quality Index, *EASI* Eczema Area and Severity Index, *EQ-5D* European Quality of Life-5 Dimensions, *FDIQ* Family Dermatitis Impact Questionnaire, *FLQA* Freiburg Life Quality Assessment, *ib* investigator blinded, *IGA* Investigator Global Assessment, *mc* multicenter, *nb* nonblinded, *pc* placebo controlled, *POEM* Patient-Oriented Eczema Measure, *PSGA* Patient's Self Global Assessment, *Ran* randomized, *SASSAD* Six Area, Six Sign Atopic Dermatitis Severity Score, *sc* single center, *SCORAD* SCORing Atopic Dermatitis, *TCS* topical corticosteroids, *TEWL* transepidermal water loss, *VAS* visual analog scale

some enthusiasm for balneotherapy, keeping in mind that the effect itself may be modest [26].

3.4 Herbal Therapy

Herbal therapy encompasses an enormous, complicated, and somewhat confounding area of alternative medicine. While many of these studies fall under the rubric of traditional Chinese medicine (TCM), others appear to focus more directly on the pharmacological aspects of the plants involved. Even those studies claiming to investigate aspects of TCM must be reviewed with caution: while TCM is a beautiful, intricate system of health and disease that has very ancient roots, its many variations and schools make any proclamations about the “efficacy of TCM” rather tenuous [27]. In addition, as with conventional medications, herbal therapies may have adverse effects—both intrinsically from the pharmacological effects of the herbs themselves, as well as from extrinsic contaminants like heavy metals that may adulterate some herbal preparations [28].

There are a number of small- and medium-sized RCTs that show significant improvements in AD with TCM herbal preparations over placebo (Table 4). A systematic review in 2013 examined seven RCTs and concluded that TCM herbal medicine significantly improved AD severity including erythema, pruritus, and sleep over placebo ($p < 0.0001$, $p < 0.0001$, and $p < 0.00001$, respectively) and was well-tolerated, but that the poor quality and heterogeneity of the studies did not allow for meta-analysis or “valid conclusions” [29].

Looking at some of these studies more closely, an RCT of 71 patients found that *Xiao-Feng-San* herbal preparation significantly ameliorated disease severity, itch, and sleep loss compared with placebo [30]. *Hwang-Yeon-Hae-Dok-San* (TJ-15) and *Ou-Ryung-San* (TJ-17) are two other oral herbal formulas that have been used to treat AD. Choi et al. determined that treatment with TJ-15 alone and TJ-15 plus TJ-17 reduced symptom severity in a study of 24 patients; however, there was no significant difference between the two groups, and there was no placebo group. The authors reported that both formulations provide safe and effective treatment for patients with the “dampness-heat pattern” type of AD [31].

TCM herbs have also been used in combination with acupuncture. The results of a study of 60 patients with mild-to-severe disease suggested that adjunctive treatment with combined “flying needle” acupuncture and TCM herbal medicine may be more effective than herbal medicine alone ($p < 0.05$) [32]. Adverse effects were minimal and included nausea, dizziness, vomiting, fatigue, and headaches. This supports the aforementioned conclusion that acupuncture appears to have a small, but measurable

effect in treating AD, but unfortunately does not give us much insight into the effect of the herbal medicine given the structure of the trial.

Sheehan and colleagues conducted a double-blinded, placebo-controlled study of TCM, which demonstrated positive effects on AD in both adults and children [33, 34]. Using a crossover study design, Sheehan et al. recruited 40 adults and 47 children with refractory AD and demonstrated that a TCM preparation (a mixture of ten plant extracts, referred to as “Zemaphyte”) significantly improved erythema and surface damage, as well as subjective itching and loss of sleep when compared with placebo. In contrast, results from a subsequent randomized trial of the same mixture conducted by Fung et al. failed to show a significant treatment effect over placebo. However, the authors importantly acknowledge that the latter study’s lower dosing, shortened dosing schedules, and distinct patient population could have contributed to these divergent findings given the known differences in drug bioavailability and metabolism [35].

In addition to the rare—but real—pharmacotoxic effects of some TCM herbs (including herb–drug interactions, variability in contents, and potential contaminants), many of these preparations have also proven to be unpalatable, particularly for children. To address this treatment barrier, Henderson et al. compared two different preparations of Zemaphyte and found that freeze-dried preparations were more palatable and equally as effective at improving erythema and surface damage when compared with traditional preparations. However, this study is limited by a lack of placebo [36].

In animal models, the orally administered herbal preparation *Hochu-ekki-to* has demonstrated various immunopharmacological effects, especially anti-allergy activity. Kobayashi et al. conducted a multicenter RCT with 91 patients to evaluate this treatment, and found that *Hochu-ekki-to* reduced the amount of topical steroids and/or tacrolimus used for AD treatment without aggravating the disease [37].

There are also studies that did not find significant improvement with oral herbal therapy. Hon et al. found that a formulation containing five herbs based on a commonly used concoction (*Flos lonicerae*, *Herba menthae*, *Cortex moutan*, *Rhizoma atractylodis*, and *Cortex phellodendri*) did not significantly decrease disease symptoms or severity compared with placebo [38]. Another study that investigated an oral herbal combination of *Eleutherococcus senticosus*, *Achillea millefolium*, and *Lamium album* found a similar lack of efficacy [39]. Despite finding no improvement in AD symptoms or severity, Hon et al. did find a >30 % improvement in the CDLQI ($p = 0.008$) and a significant reduction in topical corticosteroid use compared with placebo [38].

Table 4 Herbal therapy

References	Treatment	Study design	Number of patients enrolled	Duration (weeks)	Baseline AD assessment	Assessment of AD improvement	Age range (years)	Results	Adverse effects
Cheng et al. [30]	Chinese herbal product (oral <i>Xiao-Feng-San</i>)	Ran, db, pc, sc	71	8	Refractory AD, HRC	Standardized disease scoring system, patient self-reporting of itch and sleep loss	Mean 13.1	<i>Xiao-Feng-San</i> significantly lessened disease severity, itch, and sleep loss compared with placebo	None other than unpalatability
Choi et al. [31]	Oral herbal formula TJ-15 with and without herbal formula TJ-17	Ran, db, parallel, sc	24	4	Dampness-heat pattern AD, physician-diagnosed, HRC	SCORAD, EASI	5–32	Both SCORAD and EASI results showed more improvement in treatment group vs. control, but difference not of statistical significance. Symptom severity decreased in both groups, changes were similar and not significant	None
Fung et al. [35]	Traditional Chinese oral herbal medicine (Zemaphyte)	Ran, pc, crossover, db, double-center	40	20	Moderate to severe, refractory AD, HRC	Unspecified standardized disease scoring system	7–50	Zemaphyte did not result in a significant treatment effect over placebo	Minor transient dizziness, gastrointestinal upset
Henderson et al. [36]	Chinese herbal infusion vs. freeze-dried preparation of Chinese herbal infusion (oral)	Ran, nb, sc, parallel, no control	32	8	Moderate to severe refractory AD, NS	Standardized disease scoring system, CD4/CD8 circulating lymphocytes	17–60	Both herbal preparations were similarly effective in reducing eczema symptoms, but study was performed without control	Bad taste, nausea, dizziness, mild abdominal discomfort, loose bowels, flatulence
Hon et al. [38]	Traditional Chinese oral herbal medicine (5 herb extracts)	Ran, db, pc, sc	85	12	Moderate to severe AD, SCORAD >15	SCORAD, Allergic Rhinitis Score, serum biomarkers, CDLQI, corticosteroid use	5–21	Traditional Chinese herbal medicine did not significantly decrease disease symptoms or severity, but did improve the CLDQI and decrease corticosteroid use compared with placebo	None
Klovekorn et al. [45]	Topical herbal ointment with <i>Mahonia aquifolium</i> , <i>Viola tricolor</i> , and <i>Centella asiatica</i>	Ran, db, vehicle-controlled, sc	88	4	Mild to moderate AD, HRC with RLC	Standard severity scale, VAS, IGA	18–65	Herbal ointment did not significantly reduce symptoms compared with vehicle control	None
Kobayashi et al. [37]	<i>Hochu-ekki-to</i> oral herbal medicine	Ran, db, pc, mc	91	24	Patients with Kikyo and moderate-severe AD, physician-diagnosed with JDA	JDA scoring system, amount of topical agents used per day (TEA)	20–40	<i>Hochu-ekki-to</i> significantly reduced dose of topical steroids and/or tacrolimus without aggravating AD	Nausea, diarrhea, stomach discomfort in both groups, without statistical difference
Patzelt-Wenzler and Ponce-Poschl [43]	Topical Kamilloosan cream vs. 0.5 % hydrocortisone	Ran, partially db, vehicle-controlled, sc, phase III	72	2	Moderate to severe AD, NS	Standardized disease severity score, IGA	Mean 45.5	Kamilloosan produced mild symptom improvement compared with 0.5 % hydrocortisone, but only marginal difference compared with placebo	Not listed

Table 4 continued

References	Treatment	Study design	Number of patients enrolled	Duration (weeks)	Baseline AD assessment	Assessment of AD improvement	Age range (years)	Results	Adverse effects
Ramirez-Bosca et al. [41]	Oral <i>Polypodium leucotomos</i> (PL) extract	Ran, db, pc, mc, phase IV	105	24	AD, HRC, SCORAD between 20 and 40 inclusive	Amount of additional corticosteroid use, IGA, SCORAD, frequency of and time to first flare-up	2–17	Oral PL extract significantly reduced oral antihistamine use, but did not significantly reduce use of corticosteroids compared with placebo	Mild and moderate adverse effects were more common in placebo group than PL extract group
Saeedi et al. [44]	Topical 2 % licorice extract vs. 1 % licorice extract vs. placebo	Ran, db, pc, sc	108	2	Mild to moderate AD, NS	IGA	16–53	Both 1 and 2 % licorice extract significantly reduced erythema, edema, and itching compared with placebo. 2 % extract was more effective than 1 % extract	None
Shapira et al. [39]	Tri-herbal combination of oral <i>Eleutherococcus senticosus</i> , <i>Achillea millefolium</i> , and <i>Lamium album</i>	Ran, db, pc, sc	49	2	Moderate AD	SCORAD, body surface area, intensity score, subjective score	>1	Herbal combination group demonstrated no significant difference in disease compared with placebo	None listed
Schempp et al. [42]	Topical St. John's wort cream	Ran, db, half-side comparison, vehicle-controlled, sc	21	4	Mild to moderate AD, SCORAD <80	SCORAD, bacterial colonization of skin lesions, skin tolerance	12–59	St. John's wort cream significantly reduced disease intensity compared with vehicle control. <i>Staphylococcus aureus</i> skin colonization reduction was greater in treatment group, but did not reach statistical significance	Acute episode of AD, contact eczema
Sheehan and Atherton [33]	Traditional Chinese oral herbal therapy (Zemaphyte)	Ran, db, pc, crossover, sc	47	20	Moderate-severe refractory AD, NS	Unspecified disease scoring system	1.5–18.1	Zemaphyte resulted in significant improvement in erythema, surface area of involvement and subjective itching and loss of sleep when compared with placebo	Unpalatable but no hematological, renal or hepatic toxicity
Sheehan et al. [34]	Traditional Chinese oral herbal therapy (Zemaphyte)	Ran, db, pc, crossover, sc	40	20	Refractory AD, HRC	Standardized disease scoring system, serum biomarkers, patient self-reports	16–65	Zemaphyte resulted in significant improvement in erythema and surface damage, as well as subjective improvement in itch and loss of sleep compared with placebo	Unpalatable, mild abdominal distension, headaches
X et al. [32]	Chinese oral herbal medicine with and without flying needle acupuncture	Ran, sc	60	12	Mild to severe AD, NS	SCORAD	12–65	Both treatments resulted in significant improvement in disease severity. No significant difference in improvement between groups	Nausea, dizziness, vomiting, fatigue, headaches

AD atopic dermatitis, db double blinded, CDLQI Children's Dermatology Life Quality Index, EASI Eczema Area and Severity Index, HRC Hanifin and Rajka's criteria, IGA Investigator Global Assessment, JDA Japanese Dermatological Association, mc multicenter, nb nonblinded, NS not specified, pc placebo controlled, Ran randomized, RLC Rajka and Langeland criteria, sc single center, SCORAD SCORAD Atopic Dermatitis, TEA total equivalent amount, TJ-15 Hwang-Yeon-Hae-Dok-San, TJ-17 Ou-Ryung-San, VAS visual analog scale

Outside of the TCM rubric, *Polypodium leucotomos* (PL) extract, an antioxidant derived from a Central American fern, has been used to treat several inflammatory and atopic diseases in addition to its role as a photoprotective agent [40]. In Spain, PL extract has been available for many years as a drug product licensed for treatment of adults and children with AD. In an RCT of 105 patients designed to evaluate whether daily administration of oral PL extract would reduce topical corticosteroid use in children with AD, PL extract significantly reduced oral antihistamine use, but did not significantly reduce corticosteroid use compared with placebo [41]. While the significance here is somewhat marginalized given the fairly minor role of oral antihistamines in the treatment of AD, these results suggest that PL extract may offer some itch relief, and thus may warrant further study.

Beyond oral preparations, topical applications of herbal formulations also exist. One such topical herbal preparation used for treating AD is *Hypericum perforatum* (St. John's wort extract). This herb contains hyperforin, a compound with suspected anti-inflammatory properties that has traditionally been used to treat burns and other wounds. A randomized, double-blind, placebo-controlled, split-body comparison study of 21 patients with mild-to-moderate AD demonstrated that 1.5 % hyperforin cream was significantly better than vehicle control upon assessment with a modified SCORAD at weeks 1, 2, and 3 ($p < 0.05$) [42]. Notably, reduction in skin colonization of *Staphylococcus aureus* trended towards the hyperforin group (but did not reach significance), and no serious adverse events were reported. Although these are very limited data, these results undoubtedly warrant further study, and remain promising.

In another split-body comparison study, Kamillosan cream (which contains chamomile extract) was tested against 0.5 % hydrocortisone cream and a vehicle placebo. After a 2-week treatment period, Kamillosan cream demonstrated modest superiority over 0.5 % hydrocortisone cream, but showed only a marginal difference against placebo [43]. Results from another RCT of 108 patients suggested that both 1 and 2 % licorice extract significantly reduced erythema, edema, and pruritus compared with placebo, with 2 % extract proving more effective than 1 % extract [44]. On the other hand, a topical ointment containing *Mahonia aquifolium*, *Viola tricolor*, and *Centella asiatica* extract did not significantly reduce symptoms compared with vehicle control in a study of 88 patients with mild-to-moderate AD [45].

While heterogeneous, these studies are fairly large and numerous by the standards of AD trials, and their collective results make it difficult to dispute that herbal preparations can have real effects in the treatment of AD. However, the complexity of these preparations and their potential risks make this area inscrutable for most practitioners without

formal training in herbology. There remains an important asterisk as well: while there is real evidence of positive effect, there are simply too many unanswered questions to warrant routine clinical use of such herbs, and significant further research is needed before widespread clinical adoption can occur.

3.5 Topical Oils

Dry skin and impaired barrier function are defining characteristics of AD, so it is not surprising that the topical application of different oils remains a popular alternative therapeutic modality. From a conventional standpoint, the very act of moisturizing is a mainstay of treatment—and there are some very promising plant oils that may confer additional therapeutic value on top of their emollient properties.

For example, sunflower seed oil (*Helianthus annuus*) contains high levels of linoleic acid, a compound that may improve the skin barrier and yield anti-inflammatory effects [46]. An open, randomized trial of 80 children with mild to moderate AD found that a 2 % sunflower oleodistillate cream exhibited significant improvement in disease severity and quality of life comparable to hydrocortisone butyrate-propionate at days 7 and 21 of treatment ($p < 0.01$) [47]. When compared with topically applied olive oil, sunflower seed oil was found to preserve stratum corneum integrity and improve skin hydration, while the latter significantly reduced stratum corneum integrity and induced erythema [48]. The results suggest that the use of olive oil in the treatment of dry skin and infant massage should be discouraged, as poor skin barrier is directly linked to greater allergen and irritant penetration, as well as onset and severity of AD (Table 5) [49]. More generally, these findings directly challenge the common claim that all natural oils are beneficial to the skin.

Skin colonization by *S. aureus* is abnormal, but is a well-known feature in patients with AD [50]. While initially thought to be mostly innocuous, more recent studies suggest that the bacteria secrete a toxin that can actually drive the skin disease, thus making anti-staphylococcus measures of rising importance [51]. An RCT with 52 patients compared virgin coconut oil to virgin olive oil and found that while both oils reduced *S. aureus* colonization and improved disease severity, coconut oil was significantly superior: 95 % of subjects in the coconut oil group were cleared of *S. aureus* versus 50 % of subjects in the olive oil group ($p = 0.004$) [52]. In another study, including 117 patients, virgin coconut oil was compared with mineral oil. Again, while both groups found significant improvement in clinical (SCORAD) and instrumental (TEWL and skin capacitance) assessments compared with baseline, the virgin coconut oil was significantly superior

Table 5 Topical oils

References	Treatment	Study design	Number of patients enrolled	Duration (weeks)	Baseline AD assessment	Assessment of AD improvement	Age range	Results	Adverse effects
Anstey et al. [55]	Topical evening primrose oil	Ran, db, pc, half-side comparison, sc	12	2	Mild to moderate AD, NS	Patient self-assessment, IGA	4–46 years	Evening primrose oil significantly improved subjective patient symptom scores. Improvement of physician-assessed symptoms did not reach significance	None
Danby et al. [48]	Olive oil vs. sunflower seed oil	Ran, half-side comparison, ib, sc, parallel	19	5	AD, NS	Skin-surface pH, stratum corneum hydration, erythema, TEWL	Cohort 1: mean 46 years; cohort 2: mean 34 years	Olive oil significantly reduced stratum corneum integrity and induced erythema. Sunflower seed oil preserved stratum corneum integrity and improved skin hydration	Olive oil: erythema
De Belilovsky et al. [47]	2 % sunflower oleodistillate cream vs. hydrocortisone butyrate propionate 1 mg/g	Ran, nb, sc, ib, parallel	80	3	Mild to moderate AD, SCORAD between 15 and 60	SCORAD, IGA, QoL questionnaire, Infant's DLQI, FDIQ	3 months–4 years	2 % sunflower oleodistillate cream exhibits improvement in disease severity and QoL comparable to topical steroid	None
Evangelista et al. [53]	Topical virgin coconut oil vs. mineral oil	Ran, db, sc, parallel	117	8	Mild to moderate AD, HRC	SCORAD, TEWL, skin capacitance	1–13 years	Both treatment groups significantly improved SCORAD, TEWL, and skin capacitance scores compared with baseline. Virgin coconut oil was significantly superior on all accounts compared with mineral oil after 8 weeks	Mineral oil: erythema, pruritus; virgin coconut oil: no events; however, no statistically significant difference in events between groups
Ferreira et al. [56]	Nioleol vs. Uriage vs. Atoderm: 3 emollients containing gamma-linolenic acid	Ran, contr, parallel, nb, sc	23	12	AD in clinical remission (no eczema), NS	Standard disease severity score, TEWL, cutaneous hydration	3–15 years	All 3 emollients with gamma-linolenic acid and control emollient improved symptom severity and TEWL, but no treatment group reached statistical significance vs. control. All 3 treatment groups did significantly improve cutaneous hydration vs. control	None listed
Kanehara et al. [57]	Undershirts coated with borage oil	Ran, db, pc, sc	32	2	Mild to moderate AD, HRC, standardized disease severity score	Standardized disease severity score, TEWL	1–10 years	Undershirts coated with borage oil significantly improved symptoms of erythema, itch, and TEWL compared with baseline, while placebo group not significantly different from baseline	None

Table 5 continued

References	Treatment	Study design	Number of patients enrolled	Duration (weeks)	Baseline AD assessment	Assessment of AD improvement	Age range	Results	Adverse effects
Korting et al. [58]	Pale sulfonated shale oil cream, 4 %	Ran, mc, vehicle-controlled, nb	99	4	Mild to moderate AD, standardized disease severity score <21	Standardized disease severity score	0–12 years	Pale sulfonated shale oil cream significantly improved disease symptoms compared with vehicle control	Bacterial superinfection, itch, erythema. Comparable effects in both treatment and vehicle
Verallo-Rowell et al. [52]	Virgin coconut oil vs. virgin olive oil	Ran, db, double center, parallel	52	4	AD, modified HRC, SCORAD (O-SSI)	SCORAD (O-SSI), <i>Staphylococcus aureus</i> cultures, photography	18–40 years	Both coconut oil and olive oil reduced <i>Staphylococcus aureus</i> colonies and improved disease severity, but coconut oil was significantly superior to olive oil	Olive oil: contact dermatitis; coconut oil: none

AD atopic dermatitis, *contr* controlled, *db* double blinded, *DLQI* Dermatology Life Quality Index, *FDIQ* Family Dermatitis Impact Questionnaire, *HRC* Hanifin and Rajka's criteria, *ib* investigator blinded, *JGA* Investigator Global Assessment, *mc* multicenter, *nb* nonblinded, *NS* not specified, *O-SSI* Objective-SCORAD Severity Index, *pc* placebo controlled, *QoL* quality of life, *Ran* randomized, *sc* single center, *SCORAD* SCORing Atopic Dermatitis, *TEWL* transepidermal water loss

on all accounts compared with mineral oil [53]. What is particularly compelling here is the dual functionality of coconut oil; having both emollient and anti-bacterial properties makes for a highly appealing therapy in AD.

Evening primrose oil (*Oenothera biennis*) contains high levels of gamma-linolenic acid (GLA) and omega-6 fatty acids, which may play a role in barrier repair and anti-inflammatory pathways [54]. A study comparing topical evening primrose oil to placebo using a split-body comparison in 12 patients demonstrated significant improvement in subjective patient symptoms. Physician-assessed clinical improvement was also noted, but did not reach significance [55]. Similarly, although a different study observed that three emollients enriched with GLA improved symptom severity and TEWL compared with placebo, none of these effects reached statistical significance [56].

Similarly, borage oil has been examined as a topical treatment for AD, as it also contains high levels of GLA and omega-6 fatty acids. Sixteen children wearing pure organic cotton undershirts coated with borage oil experienced significant improvement in erythema, itch, and TEWL after two weeks of treatment ($p = 0.048$), while 16 children wearing placebo undershirts demonstrated no such improvement during the study period [57]. Of note, the treatment and control groups were not compared with each other; each group was compared only to itself at baseline.

Finally, 99 children with mild to moderate AD were randomized to receive pale sulfonated shale oil cream (also known as “ichthyol,” and related to “ichthammol”; a mixture of many different compounds obtained by distillation of oil shale) or placebo. After 4 weeks, there were significantly improved AD symptoms in the shale oil cream group compared with vehicle control ($p < 0.0001$) [58].

These studies suggest that topical sunflower seed oil and virgin coconut oil hold promise for the treatment of AD, while olive oil should likely be avoided. Topical pale sulfonated shale oil has one positive study that clearly warrants follow-up, especially as tar preparations are known to have an effect in AD. Topically applied borage oil and evening primrose oil may have some benefits as well, but the somewhat mixed results suggest that the effect is either very small or that it is perhaps only applicable to a subset of patients—if it exists at all.

3.6 Oral Oils and Fatty Acids

The concept that a deficiency in essential fatty acids (EFAs) may contribute to the pathogenesis of atopic disorders dates as far back as 1937, when reduced plasma levels were measured in patients with eczema [59]. However, trials of EFA supplementation in patients with AD have since yielded inconsistent results.

GLA has been shown to correct deficiencies in skin lipids and improve inflammation and immunity in AD patients, but clinical studies have been mixed. The role of GLA in AD has been studied since the 1980 s, with commonly used sources including borage oil (containing 23 % GLA) and evening primrose oil (containing 8–10 % GLA). While there is at least some measurable effect with topical application borage and evening primrose oils (as discussed above), the same cannot be said for oral administration—at least, not in aggregate. Indeed, the Cochrane Review published a systematic review of borage and evening primrose oils and concluded that these concoctions are “not effective treatments for eczema” when administered orally [60].

Three prominent studies evaluated the effectiveness of orally ingested borage oil in the treatment of AD, and all reached similarly disappointing conclusions. In the first study, including 160 patients, several clinical symptoms improved in response to borage oil containing high proportions of GLA (minimum 23 %) when compared with placebo. However, overall improvement as measured by corticosteroid use did not reach statistical significance (Table 6) [61]. Similarly, in another study, including 151 patients, Takwale et al. determined that borage oil supplements did not provide any significant benefit over placebo in any outcome measure in either adult or pediatric patients [62]. Finally, a study of 31 patients with AD found that while borage oil significantly improved disease symptoms compared with baseline, these results failed to significantly differ from placebo outcomes [63]. These studies collectively suggest that although borage oil is well-tolerated, it does not consistently provide therapeutic benefits when taken orally.

Randomized trials of evening primrose oil have failed to come to a consensus. Bordoni et al. studied 24 patients and found that oral evening primrose oil significantly improved eczema symptoms compared with placebo [64]. Similarly, Schalin-Karrila et al. studied 25 patients and found that while both the evening primrose oil and placebo groups demonstrated improvement in disease severity and grade of inflammation compared with baseline, the evening primrose oil group did show a significantly greater improvement over placebo. Furthermore, the evening primrose oil group also demonstrated a statistically significant improvement in dryness, pruritus, and in the percentage of body involved in disease [65]. Humphreys et al. conducted a study of 58 moderate-to-severe AD patients and showed that evening primrose oil significantly improved erythema and surface damage (but not lichenification) compared with placebo [66]. Finally, in a study of 25 patients, evening primrose oil significantly improved all measured disease symptoms when compared with placebo [67].

Two relatively large studies also examined treatment with oral evening primrose oil. The first large trial, a double-blinded crossover trial of 154 patients with AD by Bamford et al. found that evening primrose oil did not significantly improve erythema, scale, excoriation, lichenification, or overall severity compared with placebo [68]. Importantly, this study was excluded from some earlier meta-analyses because of allegations that the placebo group and experimental groups were muddled [69]. In a sobering essay, Dr. Williams suggests that important data on evening primrose oil were not made publicly available, making such analyses impossible [69]. Another study of 123 subjects by Berth-Jones and Graham-Brown showed that evening primrose oil with and without fish oil did not significantly improve disease symptoms compared with placebo [70]. Both trials ultimately concluded that GLA-containing evening primrose oil did not show an effect superior to placebo.

The question of a potential dose-dependent effect of evening primrose oil has been considered. Biagi et al. examined high dose evening primrose oil and found that it significantly reduced disease severity compared with placebo and low dose evening primrose oil [71]. Another study of children and adolescents—too recent for the latest Cochrane Review—also concluded that high dose evening primrose oil significantly improved disease symptoms compared with baseline ($p < 0.001$), while low dose evening primrose oil also improved symptoms, but not to a level reaching statistical significance ($p = 0.550$) [72]. Though these two studies were designed to evaluate a comparative dose-dependent effect, both were limited by lack of a placebo group. Finally, in a study of 39 children and 60 adults, high dose evening primrose oil significantly improved subjective evaluation of itch, scaling, overall severity, and physician-assessed overall severity, while low dose evening primrose oil significantly improved only itch [73].

In summary, despite the vehemence of the venerable Cochrane Review, more granular evaluations of the evidence on evening primrose oil (as well as the recent dose-response study) make it difficult to dismiss completely; evening primrose oil may yet be proven useful as an adjunct to the treatment of AD. It is possible, for example, that a particular sub-group may be identified for whom evening primrose oil will make a more consistent and clinically relevant difference. Nevertheless, further work needs to be done to standardize dosing regimens. The promise of potentially unconfirmed benefits, along with the minimal risk of adverse events suggests that oral evening primrose oil probably deserves further study, although this will probably frustrate those who have already fully dismissed it.

Table 6 Oral oils and fatty acid supplementation

References	Treatment	Study design	Number of patients enrolled	Duration (weeks unless otherwise stated)	Baseline AD assessment	Assessment of AD improvement	Age range	Results	Adverse effects
Evening primrose oil									
Bamford et al. [68]	Evening primrose oil	Ran, db, crossover, pc, sc	154	12	“Active” AD (specific criteria listed)	Standardized disease severity score, amount of topical steroid used, patient self-assessment of appetite and stress	2–66 years	Evening primrose oil did not significantly improve disease severity compared with placebo	Nausea, bloating, hyperactivity, eczema exacerbation
Berth-Jones and Graham-Brown [70]	Evening primrose oil with or without fish oil	Ran, pc, parallel, db, sc	123	16	AD, HRC, Leicester score (described)	Leicester score, Costa score, amount of topical steroid usage, patient self-assessment, VAS	7 months–60 years	Evening primrose oil with and without fish oil did not significantly improve disease symptoms compared with placebo	Eczema exacerbation, nausea, diarrhea
Biagi et al. [71]	High vs. low dose evening primrose oil	Ran, pc, db, sc	51	8	AD, HRC	Simple standardized disease severity score, erythrocyte microviscosity	2.2–8.5 years	High dose evening primrose oil significantly reduced disease severity compared with placebo and low dose primrose oil	None
Bordoni et al. [64]	Evening primrose oil	Ran, pc, db, sc	24	4	AD, NS, Assessed by simple physician scoring system	Simple physician scoring system	2–4 years	Evening primrose oil significantly improved eczema symptoms compared with placebo	None
Chung [72]	High vs. low dose evening primrose oil	Ran, parallel, sc, nb	40	8	AD, HRC, EASI score between 3 and 9	EASI	2–15 years	High dose evening primrose oil significantly improved disease symptoms. Low dose evening primrose oil improved symptoms, but failed to reach statistical significance	None
Humphreys et al. [66]	Evening primrose oil	Ran, db, parallel, pc, sc	58	16	Moderate-severe AD, HRC	Standardized disease scoring system, BSA, amount of topical corticosteroid used, serum biomarkers, patient self-assessment, VAS	16–64 years	Evening primrose oil significantly improved erythema and surface damage compared with placebo, but not lichenification	Diarrhea, worsening eczema, urticarial rash

Table 6 continued

References	Treatment	Study design	Number of patients enrolled	Duration (weeks unless otherwise stated)	Baseline AD assessment	Assessment of AD improvement	Age range	Results	Adverse effects
Schalinkarrila et al. [65]	Evening primrose oil	Ran, db, pc, sc	25	12	Moderate to severe AD, physician diagnosis (NS)	Standardized disease severity score, serum biomarkers	19–31 years	Both primrose oil and placebo significantly improved disease severity, inflammation, dryness, and itch. Response to treatment was significantly greater in every clinical parameter in the primrose oil group	None
Senapati et al. [67]	Evening primrose oil	Ran, sc, pc	25	20	AD, HRC, BSA, standardized disease severity scoring system	Intensity Item Score Aggregate score (described)	4 months–46 years	Evening primrose oil significantly improved all measured disease symptoms. Placebo also significantly improved some disease symptoms, to a lesser degree. The difference in outcome between groups was statistically significant	None
Wright and Burton [73]	High vs. low dose evening primrose oil	Ran, db, pc, crossover, sc	99: 39 children (20 low dose, 19 high dose; 60 adults (20 high dose, 20 moderate dose, 20 low dose)	24	Moderate to severe AD, HRC	VAS, IGA, patient self-assessment	0.7–14 years; 16–60 years	High dose evening primrose oil improved patients' subjective evaluation of itch, scaling, and overall severity, and physician assessment of overall severity. Low dose evening primrose oil significantly improved only itch	None attributed to treatment
Borage oil Henz et al. [61]	Borage oil	Ran, db, mc, pc	160	24	Stable, moderate AD, HRC, Costa score 20–36 points	Costa score, amount of corticosteroid usage until response, serum biomarkers	14–65 years	Overall response to borage oil did not reach statistical significance	Headache, nausea, diarrhea, vomiting, increased serum cholesterol and triglycerides
Takwale et al. [62]	Borage oil	Ran, db, pc, sc	151	12	AD, HRC, SASSAD score	SASSAD score, VAS, patient self-assessment, amount of corticosteroids used	>2 years	Borage oil did not provide any significant benefit over placebo in any outcome measure	Upper RTI, diarrhea, nausea, vomiting, abdominal pain, asthma, allergic rhinitis, urticarial, rash, musculoskeletal pains, skin sepsis, fever, headache

Table 6 continued

References	Treatment	Study design	Number of patients enrolled	Duration (weeks unless otherwise stated)	Baseline AD assessment	Assessment of AD improvement	Age range	Results	Adverse effects
Valsecchi et al. [63]	Borage oil	Ran, pc, nb, sc	31	14	AD, HRC	Standardized disease severity score, BSA, IgE levels	2–38 years	Both borage oil and placebo significantly improved disease symptoms compared with baseline. However, there was no statistically significant difference between treatment and placebo outcomes	None listed
Fish oil									
Bjorneboe et al. [75]	Eicosapentaenoic acid dietary supplementation	Ran, db, pc, sc	31	12	Moderate to severe AD, HRC	Standardized disease severity scale, patient self-assessment, amount of topical steroid used, serum biomarkers	16–56 years	Eicosapentaenoic acid supplementation significantly improved subjective manifestations of disease severity compared with placebo. Objective evaluation showed symptom improvement, but failed to reach statistical significance	Not listed
Mayser et al. [74]	n-3 (eicosapentaenoic acid) vs. n-6 fatty acid-based lipid IV infusion	Ran, db, pc, sc	22	10 days	Moderate to severe AD, HRC, BSA	Standardized disease severity scoring system, patient self-assessment	18–34 years	Both treatments showed improvement from baseline; however, change was significantly more pronounced in the n-3 group when compared with the n-6 group. Of note, patients who received n-3 treatment experienced greater relapse post-treatment when compared with the n-6 group, which showed nearly constant long-term improvement in post-treatment phase	Vertigo, whistling in ears, pallor, hypertriglyceridemia, oily taste
Soyland et al. [76]	Fish oil supplement	Ran, db, mc, pc, parallel	145	16	Moderate to severe AD, HRC	Standardized disease severity score, patient self-assessment, IgE levels	18–64 years	Fish oil and placebo both significantly improved disease symptoms. There was no statistically significant difference between treatment and placebo	Not listed

Table 6 continued

References	Treatment	Study design	Number of patients enrolled	Duration (weeks unless otherwise stated)	Baseline AD assessment	Assessment of AD improvement	Age range	Results	Adverse effects
Other oils									
Callaway et al. [77]	Dietary hempseed oil	Ran, ib, crossover, sc, contr	20	20	AD, HRC	Patient self-assessment of itch and loss of sleep, TEWL, amount of dermal medication used	25–60 years	Dietary hempseed oil significantly improved subjective evaluations of skin dryness and itching, and reduced dermal medication usage	Bad taste
Gimenez-Arnau et al. [79]	Linolenic acid vs. eicosapentaenoic acid with DHA	Ran, parallel, db, pc, sc	48	12	Chronic and severe AD, RLC ≥ 7	RLC, BSA, punch biopsy	Mean 24.2 years	Only linolenic acid significantly reduced symptom severity compared with placebo	Nausea, vomiting, bad taste, severe itch, eczema worsening
Koch et al. [78]	DHA supplementation	Ran, db, pc, sc	53	8	AD, HRC, SCORAD	SCORAD, IgE production	18–40 years	DHA supplementation resulted in significant clinical improvement. Placebo also improved symptoms compared with baseline, but did not reach significance	Slight gastrointestinal discomfort

AD atopic dermatitis, BSA body surface area, contr controlled, db double blinded, DHA docosahexaenoic acid, EASI Eczema Area and Severity Index, HRC Hanifin and Rajka's criteria, ib investigator blinded, IGA Investigator Global Assessment, mc multicenter, nb nonblinded, NS not specified, pc placebo controlled, Ran randomized, RLC Rajka and Langeland criteria, SASSAD Six Area, Six Sign Atopic Dermatitis Severity Score, sc single center, SCORAD SCORing Atopic Dermatitis, TEWL transepidermal water loss, VAS visual analog scale

In addition to GLA supplementation, a number of studies have investigated the efficacy of fish oil because of its potential anti-inflammatory properties. A randomized trial of 22 patients with moderate-to-severe AD compared infusions of 10 % fish oil (omega-3) to 10 % soybean oil (omega-6) and found that though both treatments showed improvement, change in disease severity score was more pronounced ($p < 0.05$) in the fish oil group than the soybean oil group. Of note, patients who received fish oil treatment experienced greater relapse post-treatment when compared with the soybean oil group, which showed nearly constant long-term improvement in the post-treatment phase [74]. Similarly, after 12 weeks of oral supplements with fish oil, Bjorneboe et al. reported improvement in disease severity compared with parallel oral placebo supplement [75]. However, these positive findings were undermined by the largest well-reported trial, which showed no significant difference between fish oil and placebo [76].

Other oral EFA supplements have been studied, but results have often been contradictory and weakened by a much smaller body of evidence. Hempseed oil is a rich source of omega-6 and omega-3 polyunsaturated fatty acids, both of which possess anti-inflammatory properties. One study of 20 patients found that dietary hempseed oil significantly improved subjective evaluations of skin dryness and itching, and reduced topical medication usage when compared with an olive oil control [77]. Additionally, docosahexaenoic acid (omega-3 fatty acid) supplementation resulted in significant clinical improvement, while improvement seen with placebo failed to reach significance [78]. In contrast, in a trial comparing linolenic acid (omega-6) versus eicosapentaenoic acid (omega-3) with docosahexaenoic acid (omega-3), only linolenic acid demonstrated significant symptom reduction compared with placebo [79].

As Bath-Hextall et al. concluded with their 2012 review, while there are some promising signals in these studies, convincingly positive results from larger, well-designed studies are necessary before clinical action can be recommended for oral oil and fatty acid supplementation. Given the reported positive outcomes and the good theoretical basis for their role in dampening the inflammatory pathway, we agree with Bath-Hextall et al. that further studies of fish oil might be worthwhile [80].

3.7 Vitamins and Minerals

Vitamins are a bastion of the alternative medicine movement, and multiple vitamins have been studied as possible therapies in AD. Pyridoxine hydrochloride (vitamin B₆) did not significantly improve disease symptoms compared with placebo in 48 patients with moderate-to-severe AD

(Table 7); however, this study was limited by its short duration of 4 weeks [81]. Selenium (600 µg) with or without vitamin E (600 IU) was studied in 60 patients, but neither selenium nor the combination improved disease severity compared with placebo [82]. In a study of 50 children with AD, Ewing et al. examined daily administration of oral zinc sulphate and found that it did not significantly improve disease symptoms compared with placebo. Of note, the authors reported that some patients actually seemed to worsen or develop additional eruptions that may have been caused by zinc supplementation [83].

Vitamin D, on the other hand, has a much more robust—yet somewhat controversial—literature foundation behind its use. In fact, even recent guidelines for AD management disagree over the role of vitamin D supplementation: the American Academy of Dermatology's guidelines note that there are insufficient data to recommend it, while the Joint Task Force on Practice Parameters (representing several US-based allergy and immunology groups) supports its use [84]. Two RCT's by Amestajani et al. and Camargo et al. have indeed found that vitamin D supplementation significantly improved disease symptoms; however, the former study was limited by not comparing vitamin D with placebo, while the latter only examined a specific population of Mongolian children with winter-related AD [85, 86]. In contrast, two other well-designed studies found no significant improvement with supplementation [87, 88]. Notably, however, a double-blind, placebo-controlled RCT comparing 1600 IU per day of vitamin D with or without 600 IU of vitamin E (tocopherol) found that the combination supplementation resulted in greater improvement of AD severity versus vitamin D alone, as well as versus placebo [89].

Topical formulations of vitamins have also been studied. A trial of 0.05 % clobetasol with and without 2.5 % zinc sulphate in 47 patients with hand eczema found that while both treatments significantly improved disease symptoms, clobetasol with zinc sulphate was significantly more effective, and was also associated with significantly lower disease recurrence [90]. Topical vitamin B₁₂—thought to attenuate eczema-related symptoms by reducing nitric oxide levels—was found to significantly improve disease symptoms compared with placebo in both pediatric and adult populations ($p = 0.01$ and $p < 0.001$, respectively) [91, 92].

Studies of vitamin and mineral supplementation continue to be mired in controversy in many areas of medicine [93], and bring with them many limitations, including small sample sizes, relatively short study durations, and the mechanistic reality that their effect sizes will likely be modest. From the available data, it seems reasonable to assign oral vitamin D supplementation and topical vitamin B₁₂ as potential candidates that are worthy of more

Table 7 Vitamins and minerals

References	Treatment	Study design	Number of patients enrolled	Duration (weeks)	Baseline AD assessment	Assessment of AD improvement	Age range	Results	Adverse effects
Vitamin B									
Januchowski [91]	Topical vitamin B ₁₂	Ran, db, pc, half-sided comparison, sc	22	4	AD, modified SCORAD	Modified SCORAD	6 months–18 years	Topical vitamin B ₁₂ significantly improved disease symptoms compared with placebo	Localized skin reaction in 1 patient on both treatment and placebo arms
Stucker et al. [92]	Topical vitamin B ₁₂	Ran, pc, phase III, mc, half-sided comparison, db	49	8	Chronic AD, HRC, modified SASSAD score	SASSAD score, investigator assessment, patient self-assessment	18–70 years	Both topical vitamin B ₁₂ and placebo significantly reduced the extent and severity of disease, but topical vitamin B ₁₂ showed significant superiority over placebo	Burning, itching, redness, hyperthermia, formation, swelling
Mabin et al. [81]	Pyridoxine hydrochloride	Ran, db, pc, sc	48	4	Moderate to severe AD, HRC	BSA, standardized disease severity score, parental assessment, parental assessment of sleep quality	2.2–15.2 years	Pyridoxine hydrochloride did not significantly improve disease symptoms compared with placebo	Erythematous rash
Vitamin D									
Amestajani et al. [85]	Vitamin D (1600 IU/day) supplementation	Ran, db, pc, sc	60	8.67	Mild to severe AD, HRC, SCORAD	SCORAD, Three Item Severity Score	Mean 23.3 years	Vitamin D group showed significant improvement in disease symptoms compared with baseline, while placebo group showed no significant improvement. Groups not statistically compared	None listed
Camargo et al. [86]	Vitamin D (1000 IU/day) supplementation	Ran, db, pc, mc	107	4	Winter-related AD, EASI 10 to 72	EASI, IGA, parental assessment	2–17 years	Vitamin D significantly improved disease symptoms compared with placebo. Patients studied were Mongolian children, a population likely to be vitamin-D deficient in wintertime	None
Hata et al. [87]	Vitamin D (4000 IU/day) supplementation	Ran, mc, pc, db	Subset of 30 with AD	3	Moderate to severe AD, RLC from 4 to 9	EASI, punch biopsy, serum biomarkers	Mean 31.2 years	Vitamin D did not significantly improve disease symptoms	None related to treatment

Table 7 continued

References	Treatment	Study design	Number of patients enrolled	Duration (weeks)	Baseline AD assessment	Assessment of AD improvement	Age range	Results	Adverse effects
Javanbakht et al. [89]	Vitamin D (1600 IU/day) with and without vitamin E (600 IU/day)	Ran, db, pc, mc	45	8.5	AD, HRC, SCORAD 10–70	SCORAD, amount of topical steroid usage	13–45 years	Vitamin D alone, vitamin E alone, and vitamin D and E together all significantly improved disease symptoms compared with placebo. Combination vitamin D and vitamin E demonstrated greatest improvement	One event of eczema exacerbation with vitamin E alone
Sidbury et al. [88]	Vitamin D (1000 IU/day) supplementation	Ran, pc, sc, db	11	4	Mild AD to moderate AD, EASI from 10 to 18.6	IGA	2–13 years	Vitamin D did not significantly improve disease symptoms compared with placebo	None
Minerals									
Ewing et al. [83]	Oral zinc sulphate	Ran, db, pc, sc	50	8	AD, HRC	BSA, standardized disease severity score, amount of topical steroids and emollients used, patient self-assessment	1–16 years	Zinc sulphate did not significantly improve disease symptoms compared with placebo	Eczema exacerbation, itchy maculopapular rash
Faghihi et al. [90]	0.05 % clobetasol with and without 2.5 % zinc sulphate	Ran, db, parallel, double center	47	2	Patients with both-sided chronic hand eczema of similar severity for longer than 4 weeks	Standardized disease severity scale, VAS	17–74 years	Both treatments significantly improved disease symptoms. Clobetasol with zinc sulphate was significantly more effective on all assessments. Recurrence rate was significantly lower in patients treated with combination treatment	None
Fairris et al. [82]	Selenium with or without vitamin E supplementation	Ran, db, pc, parallel, sc	60	12	Moderate to severe AD, NS. Standardized disease scoring system	Standardized disease scoring system, skin biopsy	≥18 years	Neither selenium with vitamin E nor selenium alone significantly improved disease symptoms compared with placebo	None listed

AD atopic dermatitis, BSA body surface area, db double blinded, EASI Eczema Area and Severity Index, HRC Hanifin and Rajka's criteria, IGA Investigator Global Assessment, mc multicenter, NS not specified, pc placebo controlled, Ran randomized, RLC Rajka and Langland criteria, SASSAD Six Area, Six Sign Atopic Dermatitis Severity Score, sc single center, SCORAD SCORing Atopic Dermatitis, VAS visual analog scale

Table 8 Miscellaneous

References	Treatment	Study design	Number of patients enrolled	Duration (weeks)	Baseline AD assessment	Assessment of AD improvement	Age range	Results	Adverse effects
Kwon [96]	Cyclosporin with or without glucosamine	Ran, crossover without washout, sc, ib	12	24	Patients with refractory AD who required systemic cyclosporine. NS	SCORAD, serum biomarkers	13–41 years	Cyclosporin combined with glucosamine improved symptoms better than cyclosporine alone, but not to a statistically significant degree	None
Schoni et al. [94]	Bioresonance therapy	Ran, sc, pc, db	32	4	AD, HRC, Costa score	Costa score, parental and investigator assessment of pruritus intensity and sleep quality, serum biomarkers, general questionnaire	1.5–16.8 years	Bioresonance therapy showed no statistically significant improvement of disease severity compared with sham therapy	None
Tripodi et al. [95]	Topical furfuryl palmitate	Ran, db, vehicle-controlled, mc	117	2	AD, UK Working Party Diagnostic Criteria, SCORAD	SCORAD, parent questionnaire, physician questionnaire	3 months–14 years	Furfuryl palmitate and vehicle control both significantly improved symptoms. Vehicle control was more efficacious overall	Itching, burning
Vita et al. [97]	Ass's milk vs. goat's milk	Ran, crossover, single-blind, contr, sc	28	36	Mild to severe AD, SCORAD >20	SCORAD, VAS	6 months–3 years	Ass's milk significantly improved disease symptoms when compared with both placebo and goat's milk, whereas goat's milk (control) had no measurable clinical effect	Urticaria, angioedema, eczema exacerbation, wheezing, rhinitis, vomiting, abdominal pain, diarrhea

AD atopic dermatitis, *contr* controlled, *db* double blinded, *HRC* Hanifin and Rajka's criteria, *ib* investigator blinded, *mc* multicenter, *NS* not specified, *pc* placebo controlled, *Ran* randomized, *sc* single center, *SCORAD* SCORing Atopic Dermatitis, *VAS* visual analog scale

research. Their low cost, relatively safe side effect profile, and familiarity to patients make the risk–benefit ratio very favorable for vitamins, further underscoring the need for more studies.

3.8 Miscellaneous

There are some alternative interventions that defy easy classification or toe the line between conventional and unconventional therapies. One such example is bioresonance therapy, which purports to use electromagnetic waves to diagnose and treat disease. In a study involving 32 hospitalized Swiss children with AD, bioresonance therapy showed no statistically significant improvement of disease severity compared with sham therapy (Table 8). However, this study is limited in terms of external validity because of its very specific population [94].

Another trial, involving 117 patients, examined topically applied furfuryl palmitate—an antioxidant compound—in comparison to vehicle control. Though furfuryl palmitate and the vehicle control both showed significant clinical improvement from baseline, the vehicle control was more efficacious overall [95]. Additionally, an interesting trial demonstrated that cyclosporin with glucosamine improved symptoms better than cyclosporine alone—but not to a statistically significant degree [96].

A randomized, crossover, single-blinded study examined children with cow's milk allergy and AD who were assigned to drink goat's milk or donkey's milk for 6 months. The study found that the donkey's milk group had significantly improved AD symptoms ($p < 0.03$) compared with both the goat's milk group and with baseline [97]. However, multiple adverse effects were reported, including urticaria, angioedema, eczema exacerbation, wheezing, diarrhea, and abdominal pain.

Isolated studies like these are difficult to interpret and, unfortunately, must remain curiosities until further data can be obtained.

4 Discussion

Despite the heterogeneity among many of these trials, their typically small sizes, and the fact that their quality, on balance, is almost certainly lower than investigations of conventional medications supported by pharmaceutical companies, there is at least some evidence to support the use of selected complementary and alternative therapies. Importantly, many patients are already discussing or using alternatives and holistic practitioners have long been recommending them; as such, there is value to reviewing the evidence even if it is incomplete.

While not always practical for conventional medical practitioners, and often with unknown variables, the following treatments and modalities emerge as potential therapies for AD: acupuncture and acupressure, stress-reducing techniques (such as hypnosis, massage, and biofeedback), balneotherapy, herbal preparations (with many important caveats), sunflower seed oil, coconut oil, pale sulfonated shale oil, oral evening primrose oil, vitamin D supplementation, and topical vitamin B₁₂. Many other therapies either have sufficient data to suggest that they are *not* effective, or simply do not have enough evidence to make any reasonable conclusion at this time.

As a group, the adverse events associated with these treatments were rare and tended to be mild, but all were not necessarily completely safe. The risk that essential oils may cause allergic contact dermatitis, the possibility olive oil may actually damage the skin barrier, and the warning that evening primrose oil could cause increased bleeding in some patients all represent possibilities for harm. These, too, must be kept in mind when integrating such therapies into practice.

5 Conclusions

AD remains a challenging disease that causes significant morbidity. With its complex etiology and many remaining pathophysiological mysteries, there is ample room for innovative therapies to emerge. While conventional treatments offer significant relief for many patients, risks—both real and perceived—and personal preference may lead to explorations of alternative and complementary treatments. While evidence in this realm is relatively sparse and of lesser quality than that of most conventional medications, well-designed trials do indeed exist, with occasional agreement between studies. Undoubtedly, more RCTs and comparative efficacy studies are necessary for these alternative treatments; with luck, some of them may well become mainstream in time.

Compliance with Ethical Standards

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References

1. Shaw TE, Currie GP, Koudelka CW, Simpson EL. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. *J Invest Dermatol*. 2011;131(1):67–73.
2. Jensen P. Use of alternative medicine by patients with atopic dermatitis and psoriasis. *Acta Derm Venereol*. 1990;70(5):421–4.

3. Simpson EL, Basco M, Hanifin J. A cross-sectional survey of complementary and alternative medicine use in patients with atopic dermatitis. *Am J Contact Dermat*. 2003;14(3):144–7.
4. Aguiar Júnior N dos R, Costa IMC. The use of alternative or complementary medicine for children with atopic dermatitis. *An Bras Dermatol*. 2011;86(1):167–8.
5. Strom MA, Lio PA. Alternative medicine in pediatric dermatology: what is the evidence? *Curr Derm Rep*. 2014. doi:[10.1007/s13671-014-0086-x](https://doi.org/10.1007/s13671-014-0086-x).
6. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6(7):e1000100.
7. Silverberg JJ. Atopic dermatitis: an evidence-based treatment update. *Am J Clin Dermatol*. 2014;15(3):149–64.
8. Che-Yi C, Wen CY, Min-Tsung K, Chiu-Ching H. Acupuncture in haemodialysis patients at the Quchi (LI11) acupoint for refractory uraemic pruritus. *Nephrol Dial Transplant*. 2005;20(9):1912–5.
9. Pfab F, Huss-Marp J, Gatti A, et al. Influence of acupuncture on type I hypersensitivity itch and the wheal and flare response in adults with atopic eczema—a blinded, randomized, placebo-controlled, crossover trial. *Allergy*. 2010;65(7):903–10.
10. Pfab F, Kirchner MT, Huss-Marp J, et al. Acupuncture compared with oral antihistamine for type I hypersensitivity itch and skin response in adults with atopic dermatitis: a patient- and examiner-blinded, randomized, placebo-controlled, crossover trial. *Allergy*. 2012;67(4):566–73.
11. Lee KC, Keyes A, Hensley JR, et al. Effectiveness of acupressure on pruritus and lichenification associated with atopic dermatitis: a pilot trial. *Acupunct Med*. 2012;30(1):8–11.
12. Shenefelt PD. Biofeedback, cognitive-behavioral methods, and hypnosis in dermatology: is it all in your mind? *Dermatol Ther*. 2003;16:114–22.
13. Sokel B, Kent CA, Lansdown R, et al. A comparison of hypnotherapy and biofeedback in the treatment of childhood atopic eczema. *Contemp Hypnosis*. 1993;10(3):145–54.
14. Miller RM, Cogger RW. Skin conductance conditioning with dyshidrotic eczema patients. *Br J Dermatol*. 1979;101(4):435–40.
15. Schut C. Psychophysiological effects of stress management in patients with atopic dermatitis: a randomized controlled trial. *Acta Derm Venereol*. 2013;93(1):57–61.
16. Ehlers A, Stangier U, Gieler U. Treatment of atopic dermatitis: a comparison of psychological and dermatological approaches to relapse prevention. *J Consult Clin Psychol*. 1995;63(4):624–35.
17. Schachner L, Field T, Hernandez-Reif M, Duarte AM, Krasnegor J. Atopic dermatitis symptoms decreased in children following massage therapy. *Pediatric dermatology*. 1998;15(5):390–95.
18. Bae BG, Oh SH, Park CO, et al. Progressive muscle relaxation therapy for atopic dermatitis: objective assessment of efficacy. *Acta Derm Venereol*. 2012;92(1):57–61.
19. Anderson C, Lis-Balchin M, Kirk-Smith M. Evaluation of massage with essential oils on childhood atopic eczema. *Phytother Res PTR*. 2000;14(6):452–6.
20. Fishbein AB, Vitaterna O, Haugh IM, et al. Nocturnal eczema: review of sleep and circadian rhythms in children with atopic dermatitis and future research directions. *J Allergy Clin Immunol*. 2015;136(5):1170–7.
21. Matz H, Orion E, Wolf R. Balneotherapy in dermatology. *Dermatol Ther*. 2003;16:132–40.
22. McNally NJ, Williams HC, Phillips DR, et al. Atopic eczema and domestic water hardness. *Lancet*. 1998;352(9127):527–31.
23. Thomas KS, Koller K, Dean T, et al. A multicentre randomised controlled trial and economic evaluation of ion-exchange water softeners for the treatment of eczema in children: the Softened Water Eczema Trial (SWET). *Health Technol Assess (Winchester, England)*. 2011;15(8):v–vi, 1–156.
24. Togawa Y. Ultrapure soft water improves the skin barrier function of child atopic dermatitis: the first report. *J Investig Dermatol*. 2012;132:S68.
25. Heinlin J, Schiffner-Rohe J, Schiffner R, et al. A first prospective randomized controlled trial on the efficacy and safety of synchronous balneophototherapy vs. narrow-band UVB monotherapy for atopic dermatitis. *J Eur Acad Dermatol Venereol JEADV*. 2011;25(7):765–73.
26. Farina S, Gisondi P, Zanoni M, et al. Balneotherapy for atopic dermatitis in children at Comano spa in Trentino, Italy. *J Dermatol Treat*. 2011;22(6):366–71.
27. Zhang GG, Lee W, Bausell B, et al. Variability in the traditional Chinese medicine (TCM) diagnoses and herbal prescriptions provided by three TCM practitioners for 40 patients with rheumatoid arthritis. *J Altern Complement Med*. 2005;11(3):415–21.
28. Zhang J, Onakpoya IJ, Posadzki P, Eddouks M. The safety of herbal medicine: from prejudice to evidence. *Evid Based Complement Alternat Med*. 2015;2015:316706.
29. Tan HY, Zhang AL, Chen D, et al. Chinese herbal medicine for atopic dermatitis: a systematic review. *J Am Acad Dermatol*. 2013;69(2):295–304. doi:[10.1016/j.jaad.2013.01.019](https://doi.org/10.1016/j.jaad.2013.01.019).
30. Cheng HM, Chiang LC, Jan YM, et al. The efficacy and safety of a Chinese herbal product (Xiao-Feng-San) for the treatment of refractory atopic dermatitis: a randomized, double-blind, placebo-controlled trial. *Int Arch Allergy Immunol*. 2011;155(2):141–8.
31. Choi IH, Kim S, Kim Y, Yun Y. The effect of TJ-15 plus TJ-17 on atopic dermatitis: a pilot study based on the principle of pattern identification. *J Altern Complement Med (New York, N.Y.)*. 2012;18(6):576–82.
32. Xq X, Cheng S, Ma H, et al. Combination of flying needle with Chinese herbal medicine in the treatment of atopic dermatitis: a clinical trial. *Pak J Pharm Sci*. 2014;27(5 Suppl):1687–90.
33. Sheehan MP, Atherton DJ. A controlled trial of traditional Chinese medicinal plants in widespread non-exudative atopic eczema. *Br J Dermatol*. 1992;126:179–84.
34. Sheehan MP, Rustin MH, Atherton DJ, et al. Efficacy of traditional Chinese herbal therapy in adult atopic dermatitis. *Lancet*. 1992;340(8810):13–7.
35. Fung AY, Look PC, Chong LY, et al. A controlled trial of traditional Chinese herbal medicine in Chinese patients with recalcitrant atopic dermatitis. *Int J Dermatol*. 1999;38(5):387–92.
36. Henderson CA, Morris A, Wilson A, Ilchyshyn A. An open study comparing the efficacy of two different Chinese herbal therapy formulations in atopic eczema and their effects on circulating activated T-lymphocytes. *J Dermatol Treat*. 2000;11(2):91–96.
37. Kobayashi H, Ishii M, Takeuchi S, et al. Efficacy and safety of a traditional herbal medicine, hochu-ekki-to in the long-term management of Kikyo (Delicate Constitution) patients with atopic dermatitis: a 6-month, multicenter, double-blind, randomized, placebo-controlled study. *Evid Based Complement Altern Med*. 2010;7(3):367–73.
38. Hon KL, Leung TF, Ng PC, et al. Therapeutic effect and safety of a traditional Chinese medicine for atopic dermatitis in children: a randomised, double-blind, placebo-controlled study. *Hong Kong Med J = Xianggang yi xue za zhi/Hong Kong Academy of Medicine*. 2011;17(Suppl 2):38–40.
39. Shapira MY, Raphaelovich Y, Gilad L, et al. Treatment of atopic dermatitis with herbal combination of *Eleutherococcus*, *Achillea millefolium*, and *Lamium album* has no advantage over placebo: a double blind, placebo-controlled, randomized trial. *J Am Acad Dermatol*. 2005;52:691–3.
40. Winkelmann RR, Del Rosso J, Rigel DS. Polypodium leucotomos extract: a status report on clinical efficacy and safety. *J Drugs Dermatol*. 2015;14(3):254–61.
41. Ramirez-Bosca A, Zapater P, Betlloch I, et al. Polypodium leucotomos extract in atopic dermatitis: a randomized, double-blind,

- placebo-controlled, multicenter trial. *Actas Dermosifiliogr*. 2012;103(7):599–607.
42. Schempp CM, Windeck T, Hezel S, Simon JC. Topical treatment of atopic dermatitis with St. John's wort cream—a randomized, placebo controlled, double blind half-side comparison. *Phytotherapy*. 2003;10(Suppl 4):31–7.
 43. Patzelt-Wenczler R, Ponce-Poschl E. Proof of efficacy of Kamillosan(R) cream in atopic eczema. *Eur J Med Res*. 2000;5(4):171–5.
 44. Saeedi M, Morteza-Semnani K, Ghoreishi MR. The treatment of atopic dermatitis with licorice gel. *J Dermatol Treat*. 2003;14(3):153–7.
 45. Klovekorn W, Tepe A, Danesch U. A randomized, double-blind, vehicle-controlled, half-side comparison with a herbal ointment containing *Mahonia aquifolium*, *Viola tricolor* and *Centella asiatica* for the treatment of mild-to-moderate atopic dermatitis. *Int J Clin Pharmacol Ther*. 2007;45(11):583–91.
 46. Eichenfield LF, McCollum A, Msika P. The benefits of sunflower oleodistillate (SOD) in pediatric dermatology. *Pediatr Dermatol*. 2009;26(6):669–75.
 47. De Belilovsky C, Roo-Rodriguez E, Baudouin C, et al. Natural peroxisome proliferator-activated receptor- α agonist cream demonstrates similar therapeutic response to topical steroids in atopic dermatitis. *J Dermatol Treat*. 2011;22(6):359–65.
 48. Danby SG, AlEnezi T, Sultan A, et al. Effect of olive and sunflower seed oil on the adult skin barrier: implications for neonatal skin care. *Pediatr Dermatol*. 2013;30(1):42–50.
 49. Cork MJ, Danby SG, Vasilopoulos Y et al. Epidermal barrier dysfunction in atopic dermatitis. *J Invest Dermatol*. 2009;129:1892–1908.
 50. Lio PA, Lee M, LeBovidge J, et al. Clinical management of atopic dermatitis: practical highlights and updates from the atopic dermatitis practice parameter 2012. *J Allergy Clin Immunol Pract*. 2014;2(4):361–9.
 51. Nakamura Y, Oscherwitz J, Cease KB, et al. Staphylococcus δ -toxin induces allergic skin disease by activating mast cells. *Nature*. 2013;503(7476):397–401.
 52. Verallo-Rowell VM, Dillague KM, Syah-Tjundawan BS. Novel antibacterial and emollient effects of coconut and virgin olive oils in adult atopic dermatitis. *Dermatitis*. 2008;19(6):308–15.
 53. Evangelista MT, Abad-Casintahan F, Lopez-Villafuerte L. The effect of topical virgin coconut oil on SCORAD index, transepidermal water loss, and skin capacitance in mild to moderate pediatric atopic dermatitis: a randomized, double-blind, clinical trial. *Int J Dermatol*. 2014;53(1):100–8.
 54. Lee J, Bielory L. Complementary and alternative interventions in atopic dermatitis. *Immunol Allergy Clin N Am*. 2010;30(3):411–24.
 55. Anstey A, Quigley M, Wilkinson JD. Topical evening primrose oil as treatment for atopic eczema. *J Dermatol Treat*. 1990;1(4):199–201.
 56. Ferreira MJ, Fiadeiro T, Silva M, Soares AP. Topical-linolenic acid therapy in atopic dermatitis. A clinical and biometric evaluation. *Allergo J*. 1998;7(4):213–16.
 57. Kanehara S, Ohtani T, Uede K, Furukawa F. Clinical effects of undershirts coated with borage oil on children with atopic dermatitis: a double-blind, placebo-controlled clinical trial. *J Dermatol*. 2007;34(12):811–5.
 58. Korting HC, Schollmann C, Cholcha W, Wolff L. Efficacy and tolerability of pale sulfonated shale oil cream 4 % in the treatment of mild to moderate atopic eczema in children: a multicentre, randomized vehicle-controlled trial. *J Eur Acad Dermatol Venereol*. 2010;24(10):1176–82.
 59. Brown WR, Hansen AE. Arachidonic and linoleic acid of the serum in normal and eczematous human subjects. *Proc Soc Exp Biol Med*. 1937;36:113–7.
 60. Bamford JT, Ray S, Musekiwa A, et al. Oral evening primrose oil and borage oil for eczema. *Cochrane Database Syst Rev*. 2013;4:CD004416.
 61. Henz BM, Jablonska S, van de Kerkhof PC, et al. Double-blind, multicentre analysis of the efficacy of borage oil in patients with atopic eczema. *Br J Dermatol*. 1999;140(4):685–8.
 62. Takwale A, Tan E, Agarwal S, et al. Efficacy and tolerability of borage oil in adults and children with atopic eczema: randomised, double blind, placebo controlled, parallel group trial. *BMJ (Clinical research ed.)*. 2003;327(7428):1385.
 63. Valsecchi R, Di Landro A, Pansera B, Reseghetti A. Gammalinolenic acid in the treatment of atopic dermatitis. *J Eur Acad Dermatol Venereol*. 1996;7(1):77–9.
 64. Bordonì A, Biagi PL, Masi M, et al. Evening primrose oil (Efa-mol) in the treatment of children with atopic eczema. *Drugs Exp Clin Res*. 1988;14(4):291–7.
 65. Schalin-Karrila M, Mattila L, Jansen CT, et al. Evening primrose oil in the treatment of atopic eczema: effect on clinical status, plasma phospholipid fatty acids and circulating blood prostaglandins. *Br J Dermatol*. 1987;117 (1):11–19.
 66. Humphreys F, Symons JA, Brown HK, et al. The effects of gamolenic acid on adult atopic eczema and premenstrual exacerbation of eczema. *Eur J Dermatol*. 1994;4 (8):598–603.
 67. Senapati S, Banerjee S, Gangopadhyay DN. Evening primrose oil is effective in atopic dermatitis: a randomized placebo-controlled trial. *Indian J Dermatol Venereol Leprol*. 2008;74(5):447–52.
 68. Bamford JT, Gibson RW, Renier CM. Atopic eczema unresponsive to evening primrose oil (linoleic and gamma-linolenic acids). *J Am Acad Dermatol*. 1985;13(6):959–65.
 69. Williams HC. Evening primrose oil for atopic dermatitis. *BMJ*. 2003;327(7428):1258–9.
 70. Berth-Jones J, Graham-Brown RA. Placebo-controlled trial of essential fatty acid supplementation in atopic dermatitis. *Lancet*. 1993;341(8860):1557–60.
 71. Biagi PL, Bordonì A, Hrelia S, et al. The effect of gamma-linolenic acid on clinical status, red cell fatty acid composition and membrane microviscosity in infants with atopic dermatitis. *Drugs Exp Clin Res*. 1994;20(2):77–84.
 72. Chung B. Dose-dependent effects of evening primrose oil in children and adolescents with atopic dermatitis. *Ann Dermatol*. 2013;25(3):285–91.
 73. Wright S, Burton JL. Oral evening-primrose-seed oil improves atopic eczema. *Lancet*. 1982;2(8308):1120–2.
 74. Mayser P, Mayer K, Mahloudjian M, et al. A double-blind, randomized, placebo-controlled trial of n-3 versus n-6 fatty acid-based lipid infusion in atopic dermatitis. *JPN J Parenter Enteral Nutr*. 2002;26(3):151–8.
 75. Bjorneboe A, Soyland E, Bjorneboe GE, Rajka G, Drevon CA. Effect of dietary supplementation with eicosapentaenoic acid in the treatment of atopic dermatitis. *Br J Dermatol*. 1987;117(4):463–9.
 76. Soyland E, Funk J, Rajka G, et al. Dietary supplementation with very long-chain n-3 fatty acids in patients with atopic dermatitis. A double-blind, multicentre study. *Br J Dermatol*. 1994;130(6):757–64.
 77. Callaway J, Schwab U, Harvima I, et al. Efficacy of dietary hempseed oil in patients with atopic dermatitis. *J Dermatol Treat*. 2005;16(2):87–94.
 78. Koch C, Dolle S, Metzger M, et al. Docosahexaenoic acid (DHA) supplementation in atopic eczema: a randomized, double-blind, controlled trial. *Br J Dermatol*. 2008;158(4):786–92.
 79. Gimenez-Arnau A, Barranco C, Alberola M, et al. Effects of linoleic acid supplements on atopic dermatitis. *Adv Exp Med Biol*. 1997;433:285–9.

80. Bath-Hextall FJ, Jenkinson C, Humphreys R, Williams HC. Dietary supplements for established atopic eczema. *Cochrane Database Syst Rev*. 2012;2:CD005205.
81. Mabin DC, Hollis S, Lockwood J, David TJ. Pyridoxine in atopic dermatitis. *Br J Dermatol*. 1995;133(5):764–7.
82. Fairris GM, Perkins PJ, Lloyd B, Hinks L, Clayton BE. The effect on atopic dermatitis of supplementation with selenium and vitamin E. *Acta Derm Venereol*. 1989;69(4):359–62.
83. Ewing CI, Gibbs AC, Ashcroft C, David TJ. Failure of oral zinc supplementation in atopic eczema. *Eur J Clin Nutr*. 1991;45(10):507–10.
84. Mohan GC, Lio PA. Comparison of dermatology and allergy guidelines for atopic dermatitis management. *JAMA Dermatol*. 2015. doi:10.1001/jamadermatol.2015.0250.
85. Amestehani M, Salehi BS, Vasigh M, et al. Vitamin D supplementation in the treatment of atopic dermatitis: a clinical trial study. *J Drugs Dermatol JDD*. 2012;11(3):327–30.
86. Camargo CA Jr, Ganmaa D, Sidbury R, et al. Randomized trial of vitamin D supplementation for winter-related atopic dermatitis in children. *J Allergy Clin Immunol*. 2014;134(4):831–835.e831.
87. Hata TR, Audish D, Kotol P, et al. A randomized controlled double-blind investigation of the effects of vitamin D dietary supplementation in subjects with atopic dermatitis. *J Eur Acad Dermatol Venereol JEADV*. 2014;28(6):781–9.
88. Sidbury R, Sullivan AF, Thadhani RI, Camargo CA Jr. Randomized controlled trial of vitamin D supplementation for winter-related atopic dermatitis in Boston: a pilot study. *Br J Dermatol*. 2008;159(1):245–7.
89. Javanbakht MH, Keshavarz SA, Djalali M, et al. Randomized controlled trial using vitamins E and D supplementation in atopic dermatitis. *J Dermatol Treat*. 2011;22(3):144–50.
90. Faghihi G, Iraj F, Shalingohar A, Saidat A. The efficacy of ‘0.05 % clobetasol + 2.5 % zinc sulphate’ cream vs. ‘0.05 % clobetasol alone’ cream in the treatment of the chronic hand eczema: a double-blind study. *J Eur Acad Dermatol Venereol JEADV*. 2008;22(5):531–6.
91. Januchowski R. Evaluation of topical vitamin B(12) for the treatment of childhood eczema. *J Altern Complement Med (New York, N.Y.)*. 2009;15(4):387–89.
92. Stucker M, Pieck C, Stoerb C, et al. Topical vitamin B12—a new therapeutic approach in atopic dermatitis—evaluation of efficacy and tolerability in a randomized placebo-controlled multicentre clinical trial. *Br J Dermatol*. 2004;150(5):977–83.
93. D’Aurizio F, Villalta D, Metus P, et al. Is vitamin D a player or not in the pathophysiology of autoimmune thyroid disease? *Autoimmun Rev*. 2015;14(5):363–9.
94. Schoni MH, Nikolaizik WH, Schoni-Affolter F. Efficacy trial of bioresonance in children with atopic dermatitis. *Int Arch Allergy Immunol*. 1997;112(3):238–46.
95. Tripodi S, Di Rienzo Businco A, Panetta V, et al. Lack of efficacy of topical furfuryl palmitate in pediatric atopic dermatitis: a randomized double-blind study. *J Investig Allergol Clin Immunol*. 2009;19(3):204–209.
96. Kwon H. Combination of glucosamine improved therapeutic effect of low-dose cyclosporin A in patients with atopic dermatitis: a pilot study. *J Dermatol*. 2013;40(3):207–10.
97. Vita D, Passalacqua G, Di Pasquale G, et al. Ass’s milk in children with atopic dermatitis and cow’s milk allergy: crossover comparison with goat’s milk. *Pediatr Allergy Immunol*. 2007;18(7):594–8.