

## Complementary therapy in atopic eczema: the latest systematic reviews

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Complementary and alternative medicines (CAM) are widely used for atopic eczema (AE) with user estimates as high as 63%. Despite the availability of effective conventional therapies, the chronic nature of AE and concerns about long-term steroid use lead many patients to seek alternative treatment. Evidence of the efficacy of these alternative therapies is inconsistent and available published data have shortcomings, making it difficult for clinicians to assess their role, if any, in management. To assess the evidence, systematic reviews of controlled studies have been undertaken for Chinese herbal medicines, homeopathy, evening primrose oil, borage oil, probiotics and certain dietary supplements. This overview summarises the findings from the most recent systematic reviews. Taken together, none of the alternative therapies evaluated demonstrated obvious and indisputable evidence of efficacy. Further studies are warranted with some therapies (Chinese herbal medicines, certain probiotic strains and fish oil), whereas homeopathy failed to show any treatment effect. Further studies on homeopathy, or evening primrose oil and borage oil, are difficult to justify. It must also be remembered that CAM products are currently under-regulated and may not meet the stringent quality standards of conventional medicines.

**Keywords:** alternative medicine, atopic eczema, complementary, dermatitis

### Introduction

Atopic eczema (AE) is the most common skin condition with a prevalence of 2–7% in adults and 7–20% in children, with an approximate doubling of the lifetime prevalence in South Africa over the last decade.<sup>1</sup> Numerous studies have demonstrated the popularity of complementary and alternative medicines (CAM) for AE.<sup>2–5</sup> Although effective conventional therapies exist, the nature of the disease, with remissions and relapses, its chronicity and the fear of long-term steroid use, especially in children, encourages patients to seek out CAM which they perceive to be safe. Despite limited evidence of efficacy, CAM is associated with considerable expense, and some patients spend more on certain alternative therapies than they do on conventional medicines.<sup>6,7</sup> Besides complicating overall management, this reduces funds that patients would otherwise invest in medication with proven reliability, thus delaying a positive clinical outcome.

Studies have indicated that CAM modalities, which are particularly popular for AE, include Chinese herbal medicines, herbal medicines and homeopathy.<sup>2,4</sup> Reports of the efficacy of these alternative therapies are contradictory,<sup>8</sup> and the vast literature is filled with shortcomings. This makes it difficult for clinicians to evaluate whether or not there is any role for them in management.<sup>9</sup> Systematic reviews of randomised controlled studies (RCTs) are central to any evidence-based practice of medicine. Systematic reviews have been undertaken for Chinese herbal medicines, homeopathy, oral herbal remedies, including evening primrose oil and borage oil, probiotics and certain dietary supplements.

This overview aims to summarise the findings from the most recently published systematic reviews in order to provide objective information to busy, often sceptical allopathic practitioners regarding the evidence of CAM in AE.

### Method

Literature searches were carried out using the following databases: Summon, EBSCO, PubMed, Google Scholar and Cochrane Library up to November 2013. Search terms were “eczema”, “dermatitis”, “review”, and “systematic review”, in combination with “Chinese herbal medicines”, “homeopathy”, “herbal therapy”, “probiotics”, “evening primrose oil”, “dietary supplements”, “complementary medicine”, “alternative treatment” and “adjunctive therapy”. Only English systematic reviews in peer-reviewed journals, involving controlled clinical trials with eczema patients of any age, were reviewed. This overview presents the findings from the most recent of these systematic reviews.

### Chinese herbal medicines

Three systematic reviews were identified, one of which, from 1999,<sup>10</sup> included only two RCTs that were dealt with in both subsequent systematic reviews. In 2010, the Cochrane Collaboration reviewed four RCTs of Zermaphyte<sup>®</sup> and concluded that it may be effective in AE, although the studies were small and heterogeneous. Interestingly, this product is no longer manufactured.<sup>11</sup> The most recent systematic review, published in 2013 by Tan et al, included RCTs of Zermaphyte<sup>®</sup>, as well as other Chinese herbal medicines. Among the inclusion criteria were studies published in English or Chinese, patients of all ages diagnosed with AE, and “placebo”, “pharmacotherapy” or “no treatment” as the control intervention. Outcome measures were disease or symptom severity scoring, quality of life, concurrent therapy use and adverse events. Other forms of Chinese herbal medicines, e.g. acupuncture, topical Chinese herbal medicines and other types of dermatitis were excluded.<sup>12</sup> Seven RCTs were selected, but as there were insufficient data for one, the authors included only six. The individual results of these are summarised in Table 1.

A meta-analysis was attempted and although it favoured Chinese herbal medicines in three placebo-controlled trials, two of these

**Table 1:** Summary of randomised controlled trials of Chinese herbal medicines for atopic eczema.

Publication	Participants	Study rationale and design	Results
Sheehan MP & Atherton DJ. Br J Dermatol. 1992 126:179-84.	Children	<i>Double-blind crossover RCT</i> : Chinese herbal medicines (Zermaphyte®) (n = 47) versus placebo (n = 47)	Chinese herbal medicines more effective than placebo
Sheehan MP et al. Lancet. 1992 340: 13-7.	Adults (16–65 years)	<i>Double-blind crossover RCT</i> : Chinese herbal medicines (Zermaphyte®) (n = 40) versus placebo (n = 40)	Chinese herbal medicines more effective than placebo
Huang YQ et al. Shan Xi Zhong Yi. 2004 5:396-8.	Children (3–11 years)	<i>Single-blind RCT</i> : Chinese herbal medicines ( <i>Jian Pi Shen Shi</i> ) (n = 49) versus Western medicine (n = 49)	Chinese herbal medicines and Western medicine are more effective than Western medicine alone
Hon KLE et al. Br J Dermatol. 2007 157:357-63.	Children and adults (5–21 years)	<i>Double-blind RCT</i> : Chinese herbal medicines (pentaherbs) (n = 42) versus placebo (n = 43)	Chinese herbal medicines have significantly improved quality of life No significant difference in clinical scores
Kobayashi H et al. Evid Based Complement Alternat Med. 2010 7:367-73.	Adults (20–40 years)	<i>Double-blind RCT</i> : Chinese herbal medicines ( <i>Hochu-ekki-to</i> ) (n = 43) versus placebo (n = 48)	No significant difference in clinical scores
Cheng HM et al. Int Arch Allergy Immunol. 2001 155:141-8.	Age not specified	<i>Double-blind RCT</i> : Chinese herbal medicines ( <i>Xiao-Feng-San</i> ) (n = 47) versus placebo (n = 24)	Chinese herbal medicines more effective than placebo

RCT: randomised controlled trial

showed a high risk of bias. In addition, we noted that these two were crossover studies with short washout periods, which made any certainty about baseline equivalence impossible. There was also a high risk of bias in the WM study. Details on blinding and a lack-of-intention-to-treat analysis led to incomplete outcome data. Overall, the authors suggested that the results should be viewed with caution as there was a low risk of bias in only one study.

Although no severe adverse events were reported in any of the studies, their poor quality and heterogeneity meant that valid conclusions about the safety and effectiveness of Chinese herbal medicines in AE could not be made. The authors proposed that further studies with improved methodology are warranted.<sup>12</sup>

### Homeopathy

Homeopathy is based on two main beliefs, namely that “like cures like” and that remedies retain biological activity after repeated dilution and succussion.<sup>13,14</sup> Despite being of doubtful value, it is still popular for treating eczema.<sup>15</sup> Therefore, we were surprised to find only one systematic review. The author of this systematic review was equally surprised to find only three controlled clinical trials which met his inclusion criteria of testing homeopathic remedies, regardless of the control intervention or randomisation.<sup>15</sup> Table 2 summarises these trials. Only one was a

RCT and despite terminating in 2002, was only published in 2009. It contained serious shortcomings, and after dropouts, only 14 patients completed the trial.

It was concluded in the systematic review that the totality of evidence from the three trials failed to show a treatment effect. None of the published trials was rigorous, and selection bias in the two that were not randomised may have resulted in false positive results. Considering the lack of RCTs, with the only one published that was too small to produce reliable findings, Ernst concluded that homeopathy is not supported by sound evidence.<sup>15</sup>

### Probiotics

Intestinal microbiota have been shown to be altered in patients with eczema. While it is unknown whether or not this is causative or a result of the eczema, probiotics (live microorganisms) have been proposed to benefit eczematous patients.<sup>16</sup>

We found three recent systematic reviews, the latest published in 2009 by Boyle et al.<sup>16</sup> Being a Cochrane review, this was of high quality and according to the authors, superseded the previous two which had shown marginal and no clinical significance, respectively. This systematic review included 12 studies on live orally ingested bacteria, fungi or yeasts with participants who had doctor-diagnosed eczema. Control groups comprised “placebo”, “no treatment” or “another non-microbial intervention”, e.g. antibiotics, topical steroids

**Table 2:** Summary of controlled trials of homeopathy for atopic eczema

Publication	Participants	Study rationale and design	Results
Keil T, et al. Complement Ther Med. 2008 16:15-21.	118 children (1–16 years)	Homeopathic (n = 54) versus conventional medicines (n = 64) Comparative cohort, open and non-randomised assessment at 0, 6 and 12 months	Similar improvement in perception of symptoms and quality of life (patient and parent) Ratings by physicians favoured homeopathy
Witt CM, et al. Dermatology. 2009 219:329-40.	135 children (1–14 years)	Homeopathic (n = 48) versus conventional medicines (n = 87) Comparative cohort, open and non-randomised assessment at 0, 6 and 12 months	No significant difference at 6 and 12 months Costs higher in the homeopathy group
Siebenwirth J, et al. Forsch Komplementarmed. 2009 16:315-23.	14 adults (18–35 years)	Homeopathic (n = 5) versus placebo (n = 11) <i>Double-blind RCT</i> : Treatment and monitoring for 32 weeks	No significant difference in any of the parameters, e.g. clinical score and quality of life

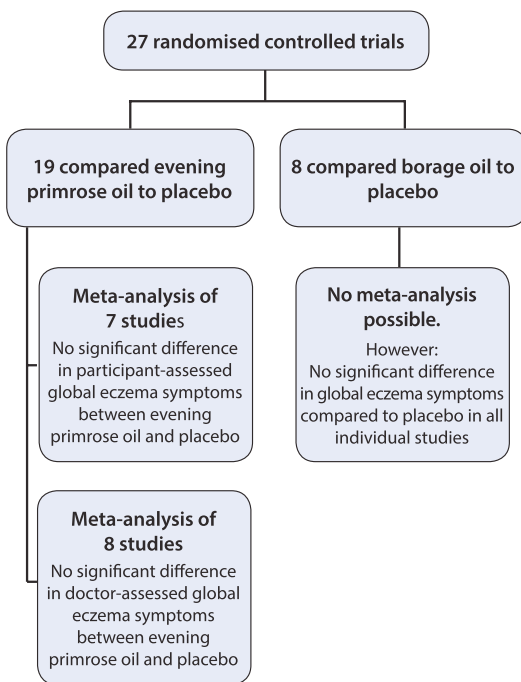


Figure 1: Summary of evening primrose oil and borage oil studies

or exclusion diets. The outcome measures were self-reported symptoms, quality of life, need for other eczema treatment, investigator-rated eczema severity and number of days lost from school or work due to eczema.<sup>16</sup> Seven trials assessed investigator-rated eczema severity at the end of treatment. They were all double-blind RCTs lasting between four and 12 weeks, and

included between 48 and 252 children. Pooled data analysis of these showed no benefit for probiotic treatment for this outcome. Data from five of the studies suggested that probiotics do not reduce symptoms, such as itching and sleep disturbance. An analysis of studies in which quality of life or the need for other eczema treatment were reported, also found no benefit with probiotics.

A subgroup analysis comparing three studies using *Lactobacillus rhamnosus* GG with four others using other *Lactobacillus* strains found opposite results in the SCORAD (scoring atopic dermatitis) scores, suggesting a strain-specific effect. As a result, the reviewers concluded that research into as yet unstudied, probiotic strains may be warranted in eczema.<sup>16</sup>

When searching for adverse events, the authors found cases of bowel ischaemia and sepsis. Although these were not in studies on AE, it is clear that probiotics should not be used without a good indication and that AE is not an indication.

### Evening primrose oil and borage oil

As natural sources of the essential fatty acid gamma-linoleic acid (GLA), it has been considered likely that evening primrose oil and borage oil improve eczema by favouring the synthesis of relatively non-inflammatory eicosanoids. Because of conflicting results regarding the efficacy and safety of GLA, including the findings of two systematic reviews published in 1989 and 2006, respectively, Bamford et al carried out a Cochrane review in 2013.<sup>17</sup> Twenty-seven RCTs were considered worthy of inclusion. Of parallel or crossover design, they investigated oral evening primrose oil or borage oil for doctor-diagnosed eczema in adults and children. Samples sizes ranged from 12-160 patients, and together involved 1 596 participants from 12 countries. The

Table 3: Summary of included randomised controlled trials of dietary supplements for eczema

Publication	Participants	Intervention and study design	Results
Bjorneboe A, et al. J Intern Med. 1989 225(731):233-6. Soyland E, et al. Br J Dermatol. 1994 130(6):757-64. Gimenez-Arnau A, et al. Adv in Exp Med Biol. 1997 433:285-9.	31 adults 145 adults 48 adults	Fish oil versus placebo Fish oil versus placebo Linoleic acid (sunflower oil) versus fish oil versus placebo	No significant difference for any primary outcomes in all three studies Significant difference in quality of life and area affected at the end of treatment with fish oil (pooled analysis of Bjorneboe and Soyland) Significant difference in improvement of itch with fish oil (Bjorneboe) No significant difference in any outcomes (Soyland) Significant difference in scores in favour of sunflower oil over both fish oil or placebo (but participant numbers in each arm unavailable) (Gimenez-Arnau)
Ewing CI et al. Eur J Clin Nutr. 1991 45(10):507-10.	50 children	Zinc versus placebo	No significant difference in severity at 8 weeks Parental-rated itch better in placebo
Fairris GM, et al. Acta DermVenereol. 1989 69(4):359-62.	60 adults	Selenium versus selenium plus vitamin E versus placebo	No significant difference in global severity scores No benefit for either treatment over placebo
Sidbury R, et al. Br J Dermatol. 2008 159(1): 245-247. Javanbakht MH, et al. J Dermatol. Treatm. 2011 22(3):144-50.	11 children 52 adults	Vitamin D versus placebo Vitamins D plus E versus two placebos versus vitamin D plus placebo versus vitamin E plus placebo	No significant difference of vitamin D over placebo in both studies No significant difference of vitamin E over placebo and significant difference in SCORAD at the end of treatment in favour of vitamin D and vitamin E over placebo (Javanbakht)
Mabin DC, et al. Br J Dermatol. 1995 133(5):764-7.	48 children	Pyridoxine hydrochloride versus placebo	No significant difference in global severity scores
Yang B, et al. J Nutr Biochem. 1999 10(11): 62-630.	78 adults	Sea buckthorn seed oil versus sea buckthorn pulp oil versus placebo	No significant difference in SCORAD at four weeks or four months between either group and placebo
Callaway J, et al. J Dermatol Treatm. 2005 16(2):87-94.	20 adults	Hempseed oil versus placebo (crossover study)	No benefit of hempseed oil over placebo Significant difference in skin dryness and itchiness (although subjective) in favour of hempseed oil
Koch C, et al. Br J Dermatol. 2008 158(4): 786-792.	53 adults	DHA versus isoenergetic control of saturated fatty acids	Significant decrease in SCORAD from baseline to eight weeks for DHA

DHA: docosahexanoic acid, SCORAD: scoring atopic dermatitis

Primary outcomes: symptom improvement at six weeks, decrease conventional treatment or flare ups

studies varied in duration of follow-up and assessed outcomes.<sup>17</sup> Primary outcome measures were firstly, the global degree of improvement in participant or doctor-rated signs and symptoms, and secondly, an improvement in quality of life. The results could be pooled for meta-analysis from studies where these end-points were reported in a similar manner. However, a meta-analysis was not possible in the borage oil studies because the results were reported in different ways. The main findings are summarised in Figure 1. Two studies of evening primrose oil measured quality of life, with only one reporting results, and these did not favour evening primrose oil over placebo.

Although the adverse events were largely minor, with no significant differences between the oils and placebo, long-term safety could not be assessed. The authors cautioned that evening primrose oil was reported in one study to increase bleeding in patients on warfarin. In another case report, prolonged use was associated with potential risk of inflammation, thrombosis and immunosuppression.<sup>17</sup>

The authors concluded that neither evening primrose oil nor borage oil had any benefit in eczema and that more studies would be difficult to justify because the narrow confidence intervals between active and placebo treatments excluded the possibility of any clinically useful difference.<sup>17</sup>

### Dietary supplements

Dietary supplements are sometimes chosen by patients who believe that something lacking in their diet is aggravating their eczema.<sup>18</sup> A Cochrane review published by Bath-Hextall et al in 2012 is the most recent systematic review to evaluate the RCTs of an extensive range of dietary supplements for the treatment of doctor-diagnosed atopic eczema. Dietary supplements were compared with “placebo”, “no treatment” or “another active intervention” in studies which were of various design, including two-, three- and four-arm parallel studies and one crossover study.<sup>18</sup> Eleven RCTs (596 patients) met the inclusion criteria and their individual results are summarised in Table 3.

The authors were not surprised that most of the studies found no significant differences as they were generally too small. Many of them were of poor methodological quality and some combined various products with possibly opposing, beneficial or harmful effects. Owing to these limitations, it is not possible to conclude that all of the examined supplements are ineffective. However, the absence of evidence means that currently, they cannot be recommended for clinical practice. It is also important to remember that not all supplements are safe and that high doses of certain vitamins can pose serious risks. The positive outcomes seen in the two studies on fish oil, and its theoretical role in suppressing inflammation, mean that further investigation with a larger placebo-controlled, well-designed study might be justifiable.<sup>18</sup>

### Conclusion

None of the discussed alternative therapies have demonstrated evidence of efficacy as assessed by rigorous systematic reviews. Further studies may be warranted with some (Chinese herbal medicines, certain probiotic strains and fish oil), whereas they may be difficult to justify for others, e.g. evening primrose and borage oil. Despite no evidence for homeopathy, long and empathetic consultations with homeopaths may be a possible reason for its popularity. Practitioners also need to remember that CAM products are currently under-regulated and may not meet the stringent quality standards of conventional medicines.

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