

Integrative Medicine as Adjunct Therapy in the Treatment of Atopic Dermatitis—the Role of Traditional Chinese Medicine, Dietary Supplements, and Other Modalities

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Abstract Atopic dermatitis (AD) is becoming increasingly prevalent in the pediatric population, with rates reportedly as high as 18–25 %. Westernized medicine has traditionally used a combination of emollients, antihistamines, corticosteroids, and immunomodulating agents to combat this often frustrating disease. Of late, integrative medicine has become the subject of more research as concerns grow regarding prolonged use of corticosteroids and their side effects in pediatric patients. Probiotics have been extensively studied to define their role in the treatment and prevention of AD in children. Unfortunately, results are varying showing significant improvement in some patients but not all. With regard to prevention, studies show that the use of probiotics during pregnancy does decrease the incidence of AD in children. Prebiotics and synbiotics are also a conceivable option for prevention of AD. A number of studies on Chinese herbal medicine have been performed, with a collective result of symptom improvement and decreased levels of inflammatory cytokines. However, there were reports of asymptomatic transaminitis in a few patients that warrant further testing. While the herbs tested in more recent randomized clinical trials were free from corticosteroids, a previous study showed high levels of dexamethasone in unlabeled herbal eczema creams. Vitamins and minerals have also been suggested as an alternative treatment of AD. Studies however have not yet demonstrated improvement of AD with vitamin or mineral supplementation. Topical vitamin

B₁₂ is the exception to this; however, no topical vitamin B₁₂ preparation is available for use. Finally, relaxation techniques are also being investigated as adjunctive methods of treatment, but well-designed scientific studies are lacking.

Keywords Atopic dermatitis · Eczema · Pediatrics · Alternative medicine · Prebiotics · Probiotics · Supplements · Traditional Chinese medicine

Abbreviations

AD	Atopic dermatitis
CAM	Complementary and alternative medicine
CDLQI	Children's Dermatology Life Quality Index
CS	Corticosteroid creams
DC	Dendritic cells
FOS	Fructo-oligosaccharides
GOS	Galacto-oligosaccharides
IGADA	Investigator's Global Atopic Dermatitis Assessment
PHF	Pentaherbs formulation
PUFA	Polyunsaturated fatty acids
RCT	Randomized control trial
RCU	Relative copy units
RDBPCT	Randomized double-blind placebo controlled trial
SCORAD	Scoring of Atopic Dermatitis
TCM	Traditional Chinese medicine
TLR	Toll-like receptor
XFS	Xiao-Feng-San

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Introduction

Atopic dermatitis (AD), or eczema, is the most common inflammatory skin condition seen in the pediatric population.

Its prevalence in the last two decades has increased with reported prevalence rates in certain developed countries as high as 18–25 % in children and adolescents [1]. AD is characterized by an itchy erythematous rash with a chronically relapsing and remitting course for which there is no known cure. Typical onset of the disease occurs in young infants and children. The dermatologic visibility and disruptive symptoms of severe AD can negatively affect the lives of both children suffering from AD and their families. Indeed, severe AD has been associated with significant psychosocial stress, anxiety, sleep deprivation, poor academic performance, social relationships, decreased self-esteem, and decreased sense of well-being [2].

Mild to moderate cases of AD commonly respond well to topical emollients, corticosteroid (CS) creams, and oral antihistamines, usually with few adverse effects. In Westernized medicine, the management of moderate to severe pediatric AD commonly includes the use of emollients, topical and oral CS, topical and systemic antimicrobials, and immunomodulating agents. Though such treatment can be beneficial, adverse effects have been reported. For instance, CS use has been associated with a wide range of effects such as deranged metabolism, growth suppression, increased susceptibility to infection, and suppression of the hypothalamic–pituitary–adrenal axis [3, 4]. While such treatments can sometimes offer patients better control of their AD symptoms, the clinical course of AD often remains chronic for many.

In an effort to avoid the potential adverse effects of systemic conventional AD treatments and also to attain better clinical outcomes, many patients and practitioners have sought alternative treatment modalities. Indeed, both practitioners and patients may use a variety of conventional, complementary and alternative (CAM), and integrative (both conventional and CAM) treatment modalities to treat pediatric AD. Popular examples of CAM treatments include traditional Chinese medicine (TCM), supplements such as vitamins, probiotics, omega-3 and omega-6 fish oil, as well as other integrative modalities such as massage and psychological intervention.

Historically, few randomized control trial (RCT) trials have been completed in pediatrics that have evaluated the safety and efficacy of using such CAM approaches integratively with conventional medicine for the treatment of AD. Recently, more scientific attention has been focused on the use of CAM approaches for AD in pediatrics. Several recent reviews have evaluated the safety and efficacy of TCM and probiotics in pediatric and adult populations suffering from AD [2, 3].

Pathogenesis of AD

The pathogenesis of AD is complex and incompletely understood (Fig. 1). AD is thought to result from a complex interaction between disruptions of the skin barrier (some of which have been associated with mutations within the filaggrin

gene), immune abnormalities, and environmental and infectious agents [5]. Cellular components involved with immune dysregulation include Langerhans cells, inflammatory dendritic epidermal cells, monocytes, macrophages, lymphocytes, mast cells, and keratinocytes. All of these factors interact to contribute to a biphasic cytokine imbalance that leads to a predominance of T helper type 2 (Th2) cells in the acute disease phase (dominated by IL-4, IL-5, IL-10, and IL-13) and T helper type 1 (Th1) in chronic disease (increased IFN- γ , IL-12 and IL-18) expression [5, 6]. In addition, The Th2 cytokine IL-5 as well as remodeling cytokines such as IL-11 and TGF- β 1 also predominates in the chronic form of the disease [7]. It is thought that dendritic cells have a central role in the predominance of Th2 cells via production of chemoattractants for Th2 cells, namely CCL17 and CCL27 [8]. AD patients also have an increased susceptibility to microbial skin infections due to defective cell-mediated immunity. Children with atopic dermatitis have decreased production of cathelicidin, a human antimicrobial peptide and a protease inhibitor that is able to destroy microbes via the innate immune system [9]. LL-37, a peptide domain on cathelicidin, destroys bacteria directly and indirectly through chemoattraction and recruitment of mast cells [9]. LL-37 has the potential to dismantle bacteria, viruses, and fungi [10, 11]. Decreased production of cathelicidins weakens this innate immunity leading to increased risk of superinfection. A variety of factors such as xerosis, bacterial colonization, foods, aeroallergens, and autoallergens, as well as mental stress [12], can all exacerbate or trigger AD [5].

Probiotics

Probiotics are a diverse group of live microorganisms that when ingested modify intestinal microbial populations. This probiotic colonization confers a variety of therapeutic benefits to the host likely through immune modulation via the balance of pro- and anti-inflammatory cytokines in the gut [13]. The mainstay of probiotics is lactic acid bacteria, including *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*. There are a number of different theoretical models describing the proposed mechanism of probiotics. These mechanisms include (1) maintaining a mature and homeostatic gut barrier, (2) immunomodulation (cytokines, Th1/Th2 balance, IgE production, and serum inflammatory parameters), (3) development of tolerogenic dendritic cells leading to the production of more IFN- γ and IL-10, (4) downregulation of IL-4, (5) toll-like receptor (TLR) stimulation leading to IgA differentiation and IL-6 production, and (6) Treg production leading to increased TGF- β and suppressed IgE production [14].

Epidemiological studies have determined that the flora sampled from the stool of infants and children with AD

inhibit the release of inflammatory mediators. *E* XFS regulates the expression of Th1 and Th2 cytokines. *F* Relaxation techniques decrease stress that triggers AD cycle. *G* Vitamin B₁₂ decreases inflammatory cytokines to decrease NO₂, decreasing pruritis. *H* Vitamin B₆ is an important enzyme for various biochemical reactions. *I* PUFA restore stratum corneum and skin barrier. *J* Vitamin D decreases inflammatory cytokines, promotes cathelicidin expression to decrease superinfection, and increases synthesis of PDGF and promotes wound healing

AD. Since 2008, numerous reviews on the use of probiotics as treatment and prevention for pediatric AD have been published [13, 17–22]. Earlier reviews, including a Cochrane review published in 2008, found no clear benefit for the role of probiotics in treating pediatric AD and noted heterogeneous results which may have been related to differences in bacterial strains used [17, 20, 22]. Another review evaluated 13 RCTs, 10 of which evaluated probiotic use as treatment and 3 for prevention of pediatric AD [19]. In this study, administration of probiotics especially *Lactobacillus rhamnosus* GG to infants at high risk of atopy prenatally and postnatally seemed to be effective in preventing AD [19]. The authors noted that in about half the RCTs, treatment with probiotics for 1 or

Clinical research has been directed towards the use of ingested probiotic bacterial strains in the treatment of pediatric

2 months was also found to reduce the severity of AD, especially in children with high total or allergen-specific serum IgE and food allergy, although probiotics did not significantly change most of the inflammatory markers measured. They cautioned that most of the positive results had serious limitations in study design. A rigorous meta-analysis by Lee et al. partially supported these findings favoring the use of probiotics for prevention but not for treatment. They found a significant risk reduction by as much as 61 % associated with the use of prenatal and/or postnatal probiotics for pediatric AD prevention [21]. The authors concluded that prenatal and postnatal administration of probiotics appears to be a safe intervention for pregnant women with a personal or familial atopic history that may confer protection against AD for their infants. Pooled data suggest that probiotics significantly reduce the likelihood of having AD at the age of 2 years, but evidence for the therapeutic value of probiotics for established AD is equivocal.

More recent reviews have examined various probiotic combinations on the treatment and prevention of AD. A Chinese meta-analysis of 12 RCTs on the preventive effects of lactic acid bacteria as probiotics on infantile eczema found that 7 of the 12 RCTs reported the preventive effect of lactic acid bacteria on atopic eczema. The data from this meta-analysis suggest that lactic acid probiotics combined with other probiotics play a role in the prevention of infantile eczema. The authors found insufficient evidence to recommend the monotherapeutic use of lactic acid bacteria for the prevention of eczema [23]. On the other hand, a meta-analysis by Doege et al. reported on seven RCTs that assessed the later impact of prenatal probiotics on older children and found a significant risk reduction for atopic eczema in children aged 2–7 years by the administration of probiotics during pregnancy (reduction 5.7 %, $P = 0.022$). It should be noted that this effect was only significant for lactobacilli (reduction 10.6 %, $P = 0.045$) and not for a mixture of various bacterial strains as probiotics (difference 3.06 %, $P = 0.204$).

Overall, conflicting data suggest that probiotics may be effective for some, but not all, children with AD. Efficacy may depend on many factors such as genotype, phenotype, age, heterogeneity of disease, diet (formula vs breastfed), dose, particular species of bacteria, and overall number of bacterial species.

Prebiotics and Synbiotics

Prebiotics are indigestible microorganisms that provide a favorable environment for a host's gut flora by stimulating growth and activity of specific beneficial bacteria. As stated, breast-fed infants are known to have a lower incidence of atopic diseases. Breast milk has its own prebiotics, termed human milk oligosaccharides, to create this environment,

potentially leading to the bifidobacteria-rich gut found in breast-fed babies [24]. To date, there is one human RCT using prebiotics and two using synbiotics. Synbiotics are a combination of prebiotics and probiotics, which achieve a synergistic effect.

A prospective, randomized, double-blind, placebo-controlled trial (RDBPCT) was conducted to determine AD incidence in atopy risk, formula-fed infants who received prebiotics during the first 6 months of life [25]. Prebiotics were made from a combination of 90 % short-chain galacto-oligosaccharides (GOS) and 10 % long-chain fructo-oligosaccharides (FOS), a formula derived from human milk studies. Over 200 infants at risk for atopy were randomly split into placebo (hypoallergenic formula with maltodextrine placebo) and prebiotic groups (0.8 g GOS/FOS prebiotics per 100 mL hypoallergenic formula) and monitored monthly for 6 months. Skin symptoms were evaluated with the Scoring Atopic Dermatitis (SCORAD) index (Table 1). After 6 months, 9.8 % of infants from the prebiotics group and 23.1 % infants from the placebo group developed AD. Among this group with AD, the SCORAD scores were not notably different. This study is promising for the use of prebiotics as a well-tolerated and effective way to reduce AD incidence in a high-risk population.

Two prevention studies of AD have been performed on synbiotics. The first was a RDBPCT of 1,223 pregnant women and their highly atopic-risk infants examining the incidence of allergic disease at 2 years of age [26]. Mothers were given either a probiotic preparation or placebo 2–4 weeks prior to delivery. The probiotic preparation included bifidobacteria, two strains of lactobacillus, and propionibacteria. After birth,

Table 1 Scoring Atopic Dermatitis [27, 67]

	Score
Objective symptoms	
A) Extent	
a. Use rule of nines	1–100
B) Intensity (score each category below) ^a	
a. Erythema	0–3
b. Edema/papulation	0–3
c. Oozing/crusting	0–3
d. Excoriations	0–3
e. Lichenification	0–3
f. Dryness of the involved skin	0–3
Subjective symptoms ^b	
C) Pruritis	0–8
D) Sleep loss	0–8

Equation to calculate score: $A/5 + 7B/2 + C$. Interpretation of score: mild ≤ 15 , moderate 16–39, severe ≥ 40

^a Score range from this section is 0–18

^b Score range from the two sections is 0–16

infants were given synbiotics of the same probiotics plus GOS for the first 3 months of life. The authors divide eczema into eczema and atopic eczema, describing atopic eczema as those with positive skin prick test or elevated antigen-specific IgE levels. Eczema incidence in those given with synbiotics was found to be 26 vs 32.3 % in the placebo group, while for atopic eczema, incidence was 12.4 % as compared to 17.7 %. This study suggests the use of synbiotics as another possible means for the prevention of AD.

The second study differed from the previous in that the goal was treating AD as opposed to preventing it. It was also a RDBPCT performed to compare synbiotics with probiotics in children ages 2 to 12 with moderate to severe AD [27]. The probiotic used was a lactobacillus strain and the prebiotic contained bovine protein, lactose, and potato starch. AD grading was done via SCORAD (see Table 1) and Investigator's Global Assessment (IGA, an AD severity scale ranging from 0–6). Initial scores were obtained before the start of the trial then evaluated monthly for 3 months and again 6–12 months after completion of the study. The results indicated a significant decrease from the starting SCORAD and IGA scores in both groups. The mean total SCORAD score for synbiotic group at baseline was 39 which decreased to 21 after just 3 months of synbiotics. For the prebiotics alone group, the baseline score was 39 and 24 after 3 months of treatment. While there was no statistical significance in severity of atopy between the two groups, both groups improved significantly. Of note, the IGA scores showed similar findings with improvement after 3 months of treatment. As a follow-up, subjects continued to be scored after cessation of the synbiotic and prebiotic therapies. There was a notable increase in scores in only 2 to 4 months after completion of the trial. Although this study showed no statistical difference between the two groups, the improvement in both groups is a valuable piece of information. While this study lacked a placebo group, it is currently the only study of its kind to evaluate older patients and focus on the treatment of AD with prebiotics as opposed to prevention.

TCM

For many centuries, Asian cultures have used TCM to treat AD. Despite its popular use in Asian societies, studies examining the safety and efficacy of traditional Chinese herbal mixtures in children with AD have reported inconsistent results [2, 3]. Since standard TCM employs the use of many herbs combined in different forms and dosed differently depending on each individual patient, RCTs in this arena have been difficult to perform. Without the ability to analyze a standardized therapeutic product, bench studies isolating the potentially efficacious immunomodulatory components within such herbal products have also been difficult to perform. In fact, such standardization contradicts

the basic philosophies of TCM that treatment should be individualized for each particular patient. Nevertheless, two recent reviews of a limited number of RCTs that study Chinese herbal use AD have been published [2, 3].

A Cochrane review in 2004 [2] reports only four RCTs that met inclusion criteria [28–32]. The ages of the randomized participants ranged from 1 to 60 years. Overall, the authors concluded that Chinese herbal mixtures may be effective in the treatment of AD; however, results were heterogeneous. The authors called for larger clinical trials but noted that the product used in the four studies (Zemaphyte, a mixture of 10 traditional Chinese herbs), although potentially effective, is no longer being manufactured due to the inability of the manufacturer to obtain a license.

Only one of the four studies in the Cochrane review focused strictly on the pediatric population [31]. In the RDBPCT, conducted in England, 47 children with widespread, nonexudative AD each randomly received active treatment with Zemaphyte or placebo for 8 weeks, followed by a 4-week wash-out period. Thirty-seven completed the study. The authors noted there was no evidence of renal, hepatic, or hematologic toxicity in the short term but recommend prior routine monitoring for potential idiosyncratic renal, hematologic, and hepatic reactions. A 1-year open follow-up study undertaken by Sheehan et al. after their initial RDBPCT showed a sustained beneficial effect of Zemaphyte [33]. Asymptomatic elevation of serum aspartate aminotransferase to 7–14 times normal values was noted on one occasion in two children whose eczema was so well controlled that the therapy was stopped. Liver function tests were normal 8 weeks later. Although Sheehan et al. did report positive results in favor of Zemaphyte on doctor-rated outcomes of erythema and surface damage as primary outcomes, the trial did not use intention-to-treat analysis and drop-out rates exceeded 20 %. According to the 2004 Cochrane review, Sheehan's results were more likely to favor treatment [2]. Nevertheless, the authors concluded that the study herbs did provide a therapeutic option for treating refractory AD but noted that the possibility that it may provoke hepatic abnormalities requires further study.

Another review published in 2011 [3], which addressed RCTs of Chinese medicinal herbs on eczema for both adults and children with AD, noted three new pediatric studies on the use of TCM in pediatric AD. All three were conducted in Hong Kong and used a novel Pentaherbs formulation (PHF) [34–36]. The researchers conducted one pilot study on a PHF capsule, which showed beneficial results [35] and then a subsequent larger RDBPCT [34] assessing the efficacy and tolerability of PHF in children with long-standing, moderate-to-severe AD using both clinical scoring and quality of life scoring. The five herbs that were included in the capsule *Flos Lonicerae* (Jinyinhua) 2 g, *Herba Menthae* (Bohe) 1 g, *Cortex Moutan* (Danpi) 2 g, *Rhizoma Atractylodis* (Cangzhu) 2 g, and *Cortex Phellodendri* (Huangbai) 2 g (total 9 g of raw herbs

daily) were based on a widely used ancestral Chinese concoction.

In a separate study by the same authors, it was determined that none of the herbs in PHF contained corticosteroids [37]. The Institute of Chinese Medicine also tested the PHF for heavy metals, microbial products, and residual pesticides, and it was found to be safe. In the RDBPCT, following a 2-week run-in period, 85 children with long-standing moderate-to-severe AD were randomized to receive a 12-week treatment with PHF or placebo. The SCORAD score, Children's Dermatology Life Quality Index (CDLQI), allergic rhinitis score, and requirement for topical corticosteroid and oral antihistamine were assessed before and at weeks 4, 8, 12, and 16 after treatment. Adverse events, tolerability, hematological (complete blood cell counts, eosinophil counts), and biochemical (electrolytes and renal and liver function) parameters were monitored during the study. Data analysis used an intention-to-treat approach. Over 12 weeks, the mean SCORAD score fell from 58.3 to 49.7 in the treatment group ($n = 42$, $P = 0.003$) and from 56.9 to 46.9 in the placebo group ($n = 43$, $P = 0.001$), and there was no statistical difference between the two groups in the SCORAD or the component scores. However, the CDLQI in treated patients was significantly improved (over 30 % improvement) compared with the patients receiving placebo at the end of the 3-month treatment and 4 weeks after stopping the therapy ($P = 0.008$ and 0.059 , respectively). The total amount of topical corticosteroid used was also significantly reduced by one-third in the PHF group ($P = 0.024$). There was no significant difference in the antihistamine use or total allergic rhinitis scores and the majority of allergic rhinitis symptoms between the two groups. No serious adverse effects were observed between the groups. Researchers concluded that the PHF concoction is a palatable, well-tolerated treatment that is efficacious in improving quality of life and reduces topical corticosteroid use in children with moderate-to-severe AD.

In a subsequent study in 2011, Hon et al. tested the same concoction in syrup form for tolerability and efficacy in young children aged 4–7 years old with moderate-to-severe AD and found essentially similar results [36]. The therapeutic effects lasted 1 month after treatment cessation.

Since the 2011 review, we found two other Taiwanese studies that examine a variety of TCM herbal formulations for AD in the pediatric population [7, 38]. The first, an uncontrolled pilot case-series study, examined the clinical and immunomodulatory effects of a crude polysaccharide fraction isolated from *Dendrobium huoshanense* in 27 patients aged 4–18 years with severe, refractory AD for 4 weeks followed by a 4-week follow-up period [7]. Progression of AD was determined with the Lund–Browder chart for children, the Investigator's Global Atopic Dermatitis Assessment (IGADA), and the SCORAD at weeks 0, 2, 4, and 8. Serum levels of cytokines were also evaluated. Safety was determined with laboratory and clinical tests.

The lesion area, IGADA score, total SCORAD result, and score for sleeplessness decreased significantly from week 4 to week 8. Serum levels of IL-5, IL-13, IFN- γ , and TGF- β 1 decreased significantly between weeks 0 and 4 and between weeks 0 and 8. No significant difference in the levels of IL-10 was found. Though data was not shown, Wu et al. reported that the levels of total IgE and total eosinophil counts did not show significant changes throughout the study period.

The authors concluded that oral systemic treatment with the polysaccharide extract from *D. huoshanense* reduced the levels of some cytokines associated with AD and had significant beneficial effects on symptoms relative to baseline. No serious adverse effects occurred when it was administered orally for 4 weeks. Limitations of the study included the short-term nature of the study and the fact that patients' conditions were not categorized into subtypes or evaluated genotypically. Moreover, the individual active compound within the polysaccharide has not yet been isolated.

The second study, a prospective RDBPCT using intention-to-treat analysis examined the efficacy and safety of a Chinese herbal product (Xiao-Feng-San) for the treatment of severe, refractory AD in the pediatric population [38]. Xiao-Feng-San (XFS) is a standardized formulation of a Chinese herbal preparation containing 12 herbs that is commonly used to treat AD in Asian clinical practice. All study materials were tested for heavy metals and possible microbial contaminants and verified using thin-layer chromatography. Doses were stratified by age. Of note, XFS contains herbs that are unique from Pentaherb but contain three herbs (*Schizonepeta tenuifolia*, *Rehmannia glutinosa*, and *Glycyrrhiza uralensis*) in common with the formerly produced Zemaphyte product. Seventy-one patients were given an 8-week treatment with oral XFS or placebo. Total lesion score, erythema score, surface damage score, pruritis score, and sleep score were measured at 0, 4, 8, and 12 weeks. At each assessment, full hematologic, chemical electrolyte, renal, hepatic, and immunologic markers were measured, in addition to blood pressure, weight, and side effects. Immunologic markers, IgE, eosinophil count, eosinophilic cationic protein, IL-5, and IL-13 were above normal at baseline but demonstrated no difference during the 8-week treatment phase. The only abnormality observed was a transient elevation of AST in one patient, which reversed following 8 weeks of stopping treatment. Two patients in the treatment group noted transient gastrointestinal upset during the first week of treatment. The decrease in total lesion score in the treatment group at 8 weeks was significantly greater than that of the placebo group. Erythema, surface damage, pruritis, and sleep scores also improved significantly. The statistical difference between the two groups persisted for all outcome measures except erythema at the 12-week follow-up, 4 weeks after the 8-week treatment had ended. The

authors concluded that the traditional Chinese herbal medicine XFS may be an alternative therapy choice for severe, refractory, extensive, and nonexudative AD.

Potential Underlying Mechanisms of TCM

It has been postulated that Zemaphyte might work as an efficient antioxidant, capable of scavenging both superoxide and hydroxyl and preventing peroxidation of biological membranes. Zemaphyte may contribute to the downregulation of the activities of cells implicated in atopic eczema through its antioxidant activities [39]. Another theory by which the Zemaphyte drug may work is by profoundly affecting the morphology and phenotype of the developing dendritic cells (DCs), notably by losing their typical dendritic morphology and decreasing their expression of CD1a as well as the low-affinity IgE receptor CD23. TCM-exposed DCs also have been observed to exhibit a diminished stimulatory activity toward autologous antigen-specific and allogeneic T cells while secreting high amounts of IL-10 [40].

As was also reviewed in detail by Hon et al. [3], additional laboratory studies were undertaken in the Hong Kong studies to determine the possible underlying mechanisms of PHF on AD [5, 41, 42]. Several theories were formulated that could explain the clinical benefit of PHF in children with AD. In the first study, an in vitro downregulation of IL-4 that induced CD23 expression on peripheral blood monocytes was observed [41]. In this study, the authors postulated that suppression of the low-affinity receptors for IgE on antigen-presenting cells in patients with AD may partially account for the underlying clinical benefit following treatment with PHF. Another study concluded that PHF possessed both in vitro and in vivo immunomodulatory effects for five inflammatory mediators [5]. A third study, which investigated the actions of PHF on mast cell activation, concluded that individual herbs of PHF modulated mast cells and inhibited the inflammatory mediators from mast cells, a finding which may help explain the benefit seen clinically in the pediatric treatment subjects who received PHF [42]. Potential mechanisms cited by the authors in the *D. huoshanense* study suggest that decreased levels of IL-5, IL-13, and IFN- γ and suppression of TGF- β 1 could account for the observed improvement in symptoms or could be an indirect effect of alterations in other cytokines [7].

The authors of the XFS study admit that a limitation of their study is the lack of pharmacokinetic and pharmacodynamic data that could describe the underlying mechanism of their study drug. They do note that isolates from several of the individual herbs found within XFS have been postulated to affect immunomodulatory activity by inhibiting allergic skin reactions activated by anti-DNP IgE [7, 43], regulating the expression of Th1- and Th2-related cytokines [44] and

affecting macrophage activity [45]. Although they felt that immunomodulation is a likely part of the explanation, they saw no changes in serum levels of inflammatory markers and called for further investigations to delineate the exact biological mechanisms of XFS.

Safety of TCM

While in the reviewed studies no true adverse effects were found, caution must still be applied when considering the use of Chinese herbal medicine, especially in the pediatric population. Herbal preparations are available without a prescription and perceived as organic and chemical free to the public who is viewing a “natural” product. These herbs are largely unregulated by the FDA and often unlabeled.

A study done in London was inspired by the authors' patients praising their Chinese herbal medicine which was used to treat eczema [46]. The authors were suspicious for a steroid in the creams. They analyzed the creams used by 11 patients (aged 4 months to 36 years), using gas chromatography to determine the presence of topical steroids. Of note, the creams were in containers either unlabeled, or the ingredients were labeled in Chinese and none of them revealed the presence of a steroid. Eight of the 11 creams were found to include dexamethasone. The mean concentration was 456 $\mu\text{g/g}$ (range 64–1,500 $\mu\text{g/g}$), and the highest concentration was found in the 4-month old baby's eczema cream which was used on her face. By comparison, commercially available topical dexamethasone cream which is available in Western medicine to treat eczema is supplied at a potency of 0.1 % (or 1,000 $\mu\text{g/g}$).

These medications are easily accessed and not monitored by the FDA; therefore, the presence and/or concentrations of steroids are unknown, unregulated, and potentially hazardous, particularly in children. Patients are often using an herbal cream in addition to a topical/oral steroid, and the additive effect of steroids must be considered. Care must be taken to assure what patients are truly taking.

Vitamins and Minerals

Various supplements have been implemented in the treatment of AD. Studies have been done examining the efficacy of pyridoxine, unsaturated fatty acids, vitamin D, vitamin E, vitamin B₁₂, and zinc (Table 2).

Pyridoxine, or vitamin B₆, is an essential vitamin as well as a cofactor for many biochemical reactions in the body. While there is no specific mechanism linking vitamin B₆ deficiency and AD, a diet deficient in vitamin B₆ could theoretically increase the risk of AD [47]. In a RCT, either pyridoxine HCl or placebo was given to 48 children with

Table 2 Vitamins and minerals in atopic dermatitis [47, 48, 50–56, 59]

Vitamin/mineral	Effect on AD	Comments
Pyridoxine (B ₆)	Important cofactor for enzymes involved in biochemical reactions relating to the skin barrier. Deficiencies can cause pellagra like dermatitis	One RCT: No significant difference between B ₆ and placebo group on AD
Polyunsaturated Fatty Acids (PUFA)	↑ Stratum corneum repair and improves structure of skin barrier	Open trial is promising; however, no RCT has been done in the pediatric population
Vitamin D	↑ Differentiation of keratinocytes ↑ Synthesis of PDGF to promote wound healing ↑ Cathelicidin expression ↓ Synthesis of inflammatory cytokines	No RCT on using vitamin D as a treatment option Studies done showing significantly higher vitamin D levels in those with mild AD vs moderate or severe AD
Cobalamin (B ₁₂)	↓ Production of inflammatory cytokines ⇒ ↓ NOs ⇒ ↓ pruritis	One RCT in children with statistically significant results for topical B ₁₂ vs placebo One prospective cohort study in pregnant women showing association of higher vitamin B ₁₂ levels in early pregnancy with increased incidence AD in offspring.
Zinc	↓ Zinc levels have been observed in those with AD	A RCT proves no benefit to oral zinc supplementation

AD for 1 month to observe clinical effects on AD [47]. The dose of pyridoxine was 50 mg daily, greater than 30 times the recommended daily children's intake of pyridoxine. Symptoms were reported subjectively by parents and objectively by one objective investigator. Results showed no difference between these two groups, and it was concluded that vitamin B₆ is an ineffective treatment modality for AD.

Polyunsaturated fatty acids (PUFA), like those found in fish oil, primrose oil, and borage oil, have been employed in the restoration of the stratum corneum and the structure of the skin barrier [48]. For this reason, dozens of studies have tested the value of PUFA in AD. None of them have shown that PUFA is associated with improvements in clinical status of AD [49]. However, a more recent open trial showed some promise using a larger combination of PUFA [48]. Subjects aged 13 to 47 were split into two groups, receiving either a powder or capsule of supplements. Included in the supplements were five fatty acids, vitamin C, vitamin E, and zinc. After a 16-week trial, outcomes based on the SCORAD index and subjects' own subjective symptoms demonstrated a significant improvement of symptoms. Mean SCORAD of group 1 (powdered supplement) at the start of the trial was 65.1 and 24.4 after 16 weeks. Group 2 (capsule supplement) had a mean score of 60.8 at the start and finished at 29.1. Subjective symptoms correlated with SCORAD scores. Unfortunately, this was not a randomized control trial and there was no placebo group. These early results will hopefully prompt further high-quality research trials, and there may yet be an encouraging future for the use of PUFA in AD.

Vitamin D has recently become the subject of a considerable amount of research. Vitamin D is thought to be promising in the treatment of AD for several reasons,

including its ability to induce differentiation of keratinocytes, increase synthesis of platelet-derived growth factor, facilitate wound healing, decrease synthesis of inflammatory cytokines, and promote cathelicidin expression [50]. A recent study was performed evaluating vitamin D levels in children age 8 months to 12 years with different severities of atopic dermatitis [51]. Vitamin D levels as 25-hydroxyvitamin D (25(OH)D) were measured via chemiluminescence. IgE levels for *S. aureus* (*S. aureus*) enterotoxins and for *Malassezia furfur* (*M. furfur*) were also quantified via ImmunoCAP. Subjects with mild AD had 25(OH)D levels that were significantly higher ($P < 0.05$) than those with moderate or severe AD. The IgE levels showed a similar pattern for both *S. aureus* and *M. furfur*. This study warrants further testing of vitamin D as a treatment for children with AD.

Cathelicidin is known to be expressed through a complex pathway involving the active form of vitamin D (1,25-dihydroxyvitamin D) [52]. Oral vitamin D has been suggested as a way to increase the quantity of cathelicidin in order to decrease the risk of superinfection in those with AD. In a single-center, three-week long, controlled study of 14 individuals of unspecified age with moderate to severe AD and 14 without AD, subjects were all given 4,000 IU oral vitamin D3 daily [53]. These subjects were followed with punch biopsies of both uninvolved skin of both groups as well as the affected areas of the AD group. The punch biopsies were performed to examine the amount of cathelicidin expression pre- and posttreatment with vitamin D3. While not statistically significant, the biopsies of affected skin in those with AD showed a progression from a pretreatment level of 3.53 relative copy units (RCU) to 23.91 RCU posttreatment. The

effect was much more modest in the unaffected group with an increase from 1 to 1.78 RCU. While not a RDBPCT, this study suggests that vitamin D may have a beneficial role, via stimulation of cathelicidin production in those patients with AD to decrease the chances of cutaneous infections. In theory, vitamin D supplementation could reduce hospitalizations as well as antibiotic use and resistance. Currently, no RCTs of Vitamin D in the treatment of AD in children have been done.

Cobalamin, or vitamin B₁₂, has also been theorized to have a role in treating AD. Vitamin B₁₂ is known to suppress the production of inflammatory cytokines [54]. These cytokines stimulate nitric oxide synthase, enzymes responsible for nitric oxide production and symptoms such as vasodilatation, erythema, and pruritis. Previous studies have shown that high nitric oxide synthase levels are present in the affected skin of those with AD and that they are thought to be a potential cause for some of the symptoms experienced by those with AD. Thus, if vitamin B₁₂ decreases the amount of inflammatory cytokines produced, nitric oxide synthase expression may be inhibited and symptoms may decrease. The first and only RDBPCT to date that was done on topical vitamin B₁₂ therapy in pediatric subjects shows promise [55]. Subjects between the ages of 6 months and 18 years were given topical vitamin B₁₂ cream on one side of the body and a placebo cream on the other. A modified SCORAD was used to grade the progress at baseline and at 2 and 4 weeks. Results showed a significant decrease in SCORAD value after both 2 and 4 weeks of treatment, on the treated side when compared to the placebo side. At 4 weeks, the score was decreased by 4.52 and 1.61 points for vitamin B₁₂ and placebo, respectively ($P = 0.011$).

Interestingly, a recent prospective cohort study was done on pregnant women to determine an association between elevated vitamin B₁₂ levels during pregnancy and atopic diseases in the infant [56]. Levels of B₁₂ were drawn during the first trimester of pregnancy, and atopic dermatitis was screened for with parental questionnaire and physician interview at ages 12, 24, 36, and 48 months. Vitamin B₁₂ levels >178 pmol/L were significantly associated with higher incidence of atopic dermatitis in infants in the first 4 years of life. The mechanism behind these results may include the role of vitamin B₁₂ as a methyl donor in DNA impacting the Th1/Th2 equilibrium. This is supported by a study in mice showing exposure to in utero vitamin B₁₂ and folate mutating this equilibrium to a Th2 predominance [57].

It has been suggested that children with atopic dermatitis have decreased serum zinc levels [58] and oral supplementation may improve the symptoms of AD [59]. The first RDBPCT to study oral zinc's effect on AD was an 8-week trial on patients aged 1–16 years [59]. Subjects were instructed to take placebo capsules or zinc capsules three times daily. The zinc capsules contained over three times the

recommended adult daily value of zinc. Changes in AD were measured subjectively by patients and parents as well as by an objective observer. Symptoms included itch, sleep disturbance, erythema, steroid application, emollient application, and the trimeprazine dose used. At the end of the trial, there were no significant changes in the mean symptom score with the exception of a significantly higher “mean itch” score in those taking the zinc capsule. Further studies must be done in order to demonstrate the efficacy of zinc oral preparations in AD.

Relaxation Therapies

Stress has been postulated to worsen AD through a variety of mechanisms such as increased histamine release and vasodilation, leading to redness and itching in atopic children [28], and central nervous system-mediated vasoconstriction secondary to chronically stressful situations [29]. Stress can negatively impact the immune system via increased cortisol levels and altered immune function [30]. Some researchers have explored stress reduction as an adjunct treatment for AD as a means to lessen the scratch–itch cycle that exacerbates symptoms of AD. Massage, biofeedback, progressive muscle relaxation, and hypnosis have been utilized as adjunct stress reduction therapies for children with AD. However, high-quality RCTs have not yet been performed.

To date, no RDBPCT has been conducted to study the effect of massage in children or infants with AD. We found only two very small studies of massage for treatment of AD in children in the literature [31, 32]. While both studies had notable limitations of study design, results seemed to indicate improvements in children's affect, activity level, parental anxiety, and atopic eczema in the short term. In the aromatherapy study, which compared regular massage with aromatherapy massage, there was a lack of increased efficacy on AD of the essential oils used in the aromatherapy massage group, which the authors note was a consistent finding in previous aromatic studies that evaluate dermatologic outcome parameters. Moreover, a worsening of AD occurred in subsequent sessions, which may be a result of an allergic contact dermatitis to the essential oils.

Discussion

AD is a complex disease with an intricate pathophysiology and a plethora of triggers, making treatment challenging. Integrated medicine is becoming more popular in use, and while much research has been done, more is needed to determine efficacy and safety of its use in the pediatric population.

Probiotics, while fairly well studied, are viable treatment and prevention options for some, but not all, patients. Both prebiotics and synbiotics show promise for the prevention of AD. However, it was not so effective as a treatment modality. Few studies have been done on prebiotics and synbiotics, and further research is recommended. Traditional Chinese medicine, an encompassing term of alternative medicine originating in China, consisting of herbal medicine as well as touch therapy and dietary modifications, is another well-studied form of CAM. Chinese herbal medicine is potentially more dangerous in the pediatric population, as adverse effects have been reported in the past. RCTs with several different herbal combinations show success with certain herbs to decrease AD symptoms, need for corticosteroids, and even inflammatory cytokines. The only side effect noted in these studies was asymptomatic transaminitis in a small number of patients. It is quite possible, and indeed, there are some preliminary data that show that Chinese herbal remedies may contain high levels of steroids, a fact that is unknown to most users of TCM [60].

RCT of relaxation therapies in pediatric AD is sparse; however, some uncontrolled studies show marked improvement in symptoms. Vitamins and minerals have been suggested as a treatment option for AD. Again, there is insufficient research done to show that supplementation with any vitamin or mineral can truly benefit a pediatric patient with AD. A RCT on topical vitamin B₁₂ shows statistically significant improvement; however, there are currently no topical vitamin B12 preparations available.

While the research in the use of integrative medicine for the treatment of AD has increased and shows much promise, there is still a need for more RCT to be done, especially those in the pediatric population. With regard to integrative medicine in atopic dermatitis, this review only touches the surface and much more literature is available on the subject. For additional material, the reader is directed to recent reviews and studies published in the Western [5, 7, 18, 36, 38, 61–64] and Chinese literature [3, 65, 66].

Acknowledgments The authors would like to thank Matthew T. Jones for his assistance with the illustrations.

References

1. Stensen L, Thomsen SF, Backer V (2008) Change in prevalence of atopic dermatitis between 1986 and 2001 among children. *Allergy Asthma Proc* 29:392–396
2. Zhang W, Leonard T, Bath-Hextall F, Chambers CA, Lee C, Humphreys R et al (2004) Chinese herbal medicine for atopic eczema. *Cochrane Database Syst Rev* :CD002291
3. Hon KL, Chan BC, Leung PC (2011) Chinese herbal medicine research in eczema treatment. *Chin Med* 6:17
4. Ellison JA, Patel L, Ray DW, David TJ, Clayton PE (2000) Hypothalamic-pituitary-adrenal function and glucocorticoid sensitivity in atopic dermatitis. *Pediatrics* 105:794–799
5. Leung TF, Wong KY, Wong CK, Fung KP, Lam CW, Fok TF et al (2008) In vitro and clinical immunomodulatory effects of a novel Pentaherbs concoction for atopic dermatitis. *Br J Dermatol* 158:1216–1223
6. Leung DY, Bieber T (2003) Atopic dermatitis. *Lancet* 361:151–160
7. Wu KG, Li TH, Chen CJ, Cheng HI, Wang TY (2011) A pilot study evaluating the clinical and immunomodulatory effects of an orally administered extract of *Dendrobium huoshanense* in children with moderate to severe recalcitrant atopic dermatitis. *Int J Immunopathol Pharmacol* 24:367–375
8. Yoo J, Omori M, Gyarmati D, Zhou B, Aye T, Brewer A et al (2005) Spontaneous atopic dermatitis in mice expressing an inducible thymic stromal lymphopoietin transgene specifically in the skin. *J Exp Med* 202:541–549
9. Gallo RL, Nizet V (2003) Endogenous production of antimicrobial peptides in innate immunity and human disease. *Curr Allergy Asthma Rep* 3:402–409
10. Braff MH, Gallo RL (2006) Antimicrobial peptides: an essential component of the skin defensive barrier. *Curr Top Microbiol Immunol* 306:91–110
11. Lopez-Garcia B, Lee PH, Yamasaki K, Gallo RL (2005) Antifungal activity of cathelicidins and their potential role in *Candida albicans* skin infection. *J Invest Dermatol* 125:108–115
12. Schmid-Ott G, Jaeger B, Meyer S, Stephan E, Kapp A, Werfel T (2001) Different expression of cytokine and membrane molecules by circulating lymphocytes on acute mental stress in patients with atopic dermatitis in comparison with healthy controls. *J Allergy Clin Immunol* 108:455–462
13. Williams HC, Gindlay DJC (2008) What's new in atopic eczema? An analysis of the clinical significance of systemic reviews on atopic eczema published in 2006 and 2007. *Clin Exp Dermatol* 33:685–688
14. Ozdemir O (2010) Various effects of different probiotic strains in allergic disorders: an update from laboratory and clinical data. *Clin Exp Immunol* 160:295–304
15. Kalliomaki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E (2001) Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. *J Allergy Clin Immunol* 107:129–134
16. Oz O (2009) Gut flora development in infancy and its effect on immune system. *J Pediatr Inf* 2009:202–203
17. Boyle RJ, Bath-Hextall FJ, Leonardi-Bee J, Murrell DF, Tang ML (2009) Probiotics for the treatment of eczema: a systematic review. *Clin Exp Allergy* 39:1117–1127
18. Batchelor JM, Grindlay D, Williams HC (2010) What's new in atopic eczema? An analysis of systemic reviews published in 2008 and 2009. *Clin Exp Dermatol* 35:823–828
19. Betsi GI, Papadavid E, Falagas ME (2008) Probiotics for the treatment or prevention of atopic dermatitis: a review of the evidence from randomized controlled trials. *Am J Clin Dermatol* 9:93–103
20. Boyle RJ, Bath-Hextall FJ, Leonardi-Bee J, Murrell DF, Tang ML (2008) Probiotics for treating eczema. *Cochrane Database Syst Rev* 4:CD006135
21. Lee J, Seto D, Bielory L (2008) Meta-analysis of clinical trials of probiotics for prevention and treatment of pediatric atopic dermatitis. *J Allergy Clin Immunol* 121:116–121 e11
22. Michail SK, Stolfi A, Johnson T, Onady GM (2008) Efficacy of probiotics in the treatment of pediatric atopic dermatitis: a meta-analysis of randomized controlled trials. *Ann Allergy Asthma Immunol* 101:508–516
23. Zhu DL, Yang WX, Yang HM (2010) Meta analysis of lactic acid bacteria as probiotics for the primary prevention of infantile eczema. *Zhongguo Dang Dai Er Ke Za Zhi* 12:734–739

24. Coppa GV, Bruni S, Soldi S, Gabrielli O (2001) The first prebiotics in humans: human milk oligosaccharides. *J Clin Gastroenterol* 38: S80–S83
25. Moro G, Arslanoglu S, Stahl B, Jelinek J, Wahn U, Boehm G (2006) A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. *Arch Dis Child* 91:814–819
26. Kukkonen K, Savilahti E, Haahtela T, Juntunen-Backman K, Korpela R, Poussa T et al (2007) Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 119:192–198
27. Passeron T, Lacour JP, Fontas E, Ortonne JP (2006) Prebiotics and synbiotics: two promising approaches for the treatment of atopic dermatitis in children above 2 years. *Allergy* 61:431–437
28. Barankin B, DeKoven J (2002) Psychosocial effect of common skin diseases. *Can Fam Physician* 48:712–716
29. Fung AY, Look PC, Chong LY, But PP, Wong E (1999) A controlled trial of traditional Chinese herbal medicine in Chinese patients with recalcitrant atopic dermatitis. *Int J Dermatol* 38:387–392
30. Henderson CA, Morris A, Wilson A, Llichyshyn A (2000) 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* 11:91–96
31. Sheehan MP, Atherton DJ (1992) A controlled trial of traditional Chinese medicinal plants in widespread non-exudative atopic eczema. *Br J Dermatol* 126:179–184
32. Sheehan MP, Rustin MH, Atherton DJ, Buckley C, Harris DW, Brostoff J et al (1992) Efficacy of traditional Chinese herbal therapy in adult atopic dermatitis. *Lancet* 340:13–17
33. Sheehan MP, Atherton DJ (1994) One-year follow up of children treated with Chinese medicinal herbs for atopic eczema. *Br J Dermatol* 130:488–493
34. Hon KL, Leung TF, Ng PC, Lam MC, Kam WY, Wong KY et al (2007) Efficacy and tolerability of a Chinese herbal medicine concoction for treatment of atopic dermatitis: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 157:357–363
35. Hon KL, Leung TF, Wong Y, Lam WK, Guan DQ, Ma KC et al (2004) A pentaherbs capsule as a treatment option for atopic dermatitis in children: an open-labeled case series. *Am J Chin Med* 32:941–950
36. Hon KL, Lo W, Cheng WK, Leung TF, Chow CM, Lau CB et al (2012) Prospective self-controlled trial of the efficacy and tolerability of a herbal syrup for young children with eczema. *J Dermatol Treat* 23:116–121
37. Hon KL, Lee VW, Leung TF, Lee KK, Chan AK, Fok TF et al (2006) Corticosteroids are not present in a traditional Chinese medicine formulation for atopic dermatitis in children. *Ann Acad Med Singap* 35:759–763
38. Cheng HM, Chiang LC, Jan YM, Chen GW, Li TC (2011) 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* 155:141–148
39. Chung LY (2008) Antioxidant profiles of a prepared extract of Chinese herbs for the treatment of atopic eczema. *Phytother Res* 22:493–499
40. Novak N, Haberstick J, Kraft S, Siekmann L, Allam JP, Bieber T (2001) Standardized extracts from Chinese herbs induce IL-10 production in human monocyte-derived dendritic cells and alter their differentiation in vitro. *J Allergy Clin Immunol* 108:588–593
41. Latchman Y, Bungy GA, Atherton DJ, Rustin MH, Brostoff J (1995) Efficacy of traditional Chinese herbal therapy in vitro. A model system for atopic eczema: inhibition of CD23 expression on blood monocytes. *Br J Dermatol* 132:592–598
42. Chan BC, Hon KL, Leung PC, Sam SW, Fung KP, Lee MY et al (2008) Traditional Chinese medicine for atopic eczema: Penta-Herbs formula suppresses inflammatory mediators release from mast cells. *J Ethnopharmacol* 120:85–91
43. Kim H, Lee E, Lee S, Shin T, Kim Y, Kim J (1998) Effect of *Rehmannia glutinosa* on immediate type allergic reaction. *Int J Immunopharmacol* 20:231–240
44. Yang T, Jia M, Meng J, Wu H, Mei Q (2006) Immunomodulatory activity of polysaccharide isolated from *Angelica sinensis*. *Int J Biol Macromol* 39:179–184
45. Cheng A, Wan F, Wang J, Jin Z, Xu X (2008) Macrophage immunomodulatory activity of polysaccharides isolated from *Glycyrrhiza uralensis* fish. *Int Immunopharmacol* 8:43–50
46. Keane FM, Munn SE, du Vivier AW, Taylor NF, Higgins EM (1999) Analysis of Chinese herbal creams prescribed for dermatological conditions. *BMJ* 318:563–564
47. Mabin DC, Hollis S, Lockwood J, David TJ (1995) Pyridoxine in atopic dermatitis. *Br J Dermatol* 133:764–767
48. Eriksen BB, Kare DL (2006) Open trial of supplements of omega 3 and 6 fatty acids, vitamins and minerals in atopic dermatitis. *J Dermatol Treat* 17:82–85
49. van Gool CJ, Zeegers MP, Thijs C (2004) Oral essential fatty acid supplementation in atopic dermatitis—a meta-analysis of placebo-controlled trials. *Br J Dermatol* 150:728–740
50. Searing DA, Leung DY (2010) Vitamin D in atopic dermatitis, asthma and allergic diseases. *Immunol Allergy Clin N Am* 30:397–409
51. Peroni DG, Piacentini GL, Cametti E, Chinellato I, Boner AL (2011) Correlation between serum 25-hydroxyvitamin D levels and severity of atopic dermatitis in children. *Br J Dermatol* 164:1078–1082
52. Schaubert J, Gallo RL (2008) Antimicrobial peptides and the skin immune defense system. *J Allergy Clin Immunol* 122:261–266
53. Hata TR, Kotol P, Jackson M, Nguyen M, Paik A, Udall D et al (2008) Administration of oral vitamin D induces cathelicidin production in atopic individuals. *J Allergy Clin Immunol* 122:829–831
54. Stucker M, Pieck C, Stoerb C, Niedner R, Hartung J, Altmeyer P (2004) 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* 150:977–983
55. Januchowski R (2009) Evaluation of topical vitamin B(12) for the treatment of childhood eczema. *J Altern Complement Med* 15:387–389
56. Kieffe-de Jong JC, Timmermans S, Jaddoe VW, Hofman A, Tiemeier H, Steegers EA et al (2012) High circulating folate and vitamin B-12 concentrations in women during pregnancy are associated with increased prevalence of atopic dermatitis in their offspring. *J Nutr* 142:731–738
57. Hollingsworth JW, Maruoka S, Boon K, Garantzios S, Li Z, Tomfohr J et al (2008) In utero supplementation with methyl donors enhances allergic airway disease in mice. *J Clin Invest* 118:3462–3469
58. David TJ, Wells FE, Sharpe TC, Gibbs AC (1984) Low serum zinc in children with atopic eczema. *Br J Dermatol* 111:597–601
59. Ewing CI, Gibbs AC, Ashcroft C, David TJ (1991) Failure of oral zinc supplementation in atopic eczema. *Eur J Clin Nutr* 45:507–510
60. Klinsunthorn N, Petsom A, Nhujak T (2011) Determination of steroids adulterated in liquid herbal medicines using QuEChERS sample preparation and high-performance liquid chromatography. *J Pharm Biomed Anal* 55:1175–1178
61. Zhang W, Leonard T, Bath-Hextall F, Chambers CA, Lee C, Humphreys R et al (2005) Chinese herbal medicine for atopic eczema. *Cochrane Database Syst Rev* 2:CD002291
62. Hoare C, Li Wan Po A, Williams H (2000) Systematic review of treatments for atopic eczema. *Health Technol Assess* 4:1–191
63. Williams HC, Grindlay DJ (2010) What's new in atopic eczema? An analysis of systematic reviews published in 2007 and 2008.

- Part 1. Definitions, causes and consequences of eczema. Clin Exp Dermatol 35:12–15
64. Simpson EL (2010) Atopic dermatitis: a review of topical treatment options. Curr Med Res Opin 26:633–640
 65. Luo W, Wu C (2001) Fifty-six cases of stubborn eczema treated by oral administration and topical application of herbal medicine. J Tradit Chin Med 21:259–260
 66. Sung YY, Yoon T, Jang JY, Park SJ, Jeong GH, Kim HK (2011) Inhibitory effects of *Cinnamomum cassia* extract on atopic dermatitis-like skin lesions induced by mite antigen in NC/Nga mice. J Ethnopharmacol 133:621–628
 67. Pucci N, Novembre E, Cammarata MG, Bernardini R, Monaco MG, Calogero C et al (2005) Scoring atopic dermatitis in infants and young children: distinctive features of the SCORAD index. Allergy 60:113–116
 68. Lieberman P, Anderson J (2000) Allergic diseases: diagnosis and treatment. Humana, Totowa
 69. Brandt EB, Sivaprasad U (2011) Th2 cytokines and atopic dermatitis. J Clin Cell Immunol 2:110