



Oral supplements in atopic dermatitis

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Abstract Atopic dermatitis (AD) is the most common chronic inflammatory skin disorder. The disease is typified by chronic pruritus, a series of signs and symptoms associated with immune dysfunction (eg, increased immunoglobulin E mediated allergies), and abnormal skin barrier dysfunction (eg, increased response to irritants). Due to the chronic itch and reactivity, patients and parents of affected children will seek therapy. Therapies range from emollients to topical medicaments, including topical corticosteroids, and immunosuppressive agents. Due to concerns about the side effects of the available agents, patients and their loved ones will often seek “natural” agents as therapy. Oral agents that have been tried in (AD) include probiotics, vitamins, oils, and such traditional therapeutics as Chinese herbals and Ayurvedic agents. At this time probiotics may be promising, but there are inadequate data to determine their efficacy. In addition, there are significant concerns for the risks associated with Chinese herbals, which may be associated with liver failure and death, and Ayurvedic agents, which may be tainted with heavy metals. The safest and most effective natural agents are topically applied emollients.

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Atopic dermatitis (AD) is a chronic inflammatory skin condition with a lifetime prevalence of approximately 20%.¹ Treatment is directed at prevention, as well as reduction of clinical manifestations during an acute exacerbation. Prevention therapy is centered on the use of creams and emollients to prevent drying of the skin in combination with the avoidance of aggregating agents, such as allergens, detergents, and noncotton clothing. The mainstay of treatment during an acute flare is topical steroid creams, with systemic immunosuppressive medications and ultraviolet therapy reserved for patients with severe disease.^{2,3} Both patient and physician fear of side effects from topical steroids has led many to turn to “natural” alternative medications.⁴ Unfortunately, many alternative treatments are explored by patients and physicians without evidence of efficacy and to their potential detriment.⁵ This may

lead to economic waste, dangerous side effects, and inadequate treatment. We have reviewed the published literature for the use of common oral supplements in the treatment of AD. Current evidence is insufficient to recommend any of the oral supplements discussed; however, we shall highlight the treatments that warrant further study and that may one day aid in the treatment of AD.

Probiotics

The role of probiotics in the treatment of AD is controversial. Probiotics are live microorganisms that, when given in appropriate doses, are meant to offer a health benefit to the patient.⁶ Microorganisms live in the intestines of humans and confer intestinal, immune, and nutritional benefits to the host and are collectively termed the intestinal microflora,

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although the composition of the intestinal microflora has been shown to be different in the atopic patients.⁷⁻¹⁰ The “hygiene hypothesis” suggests that increasing rates of AD in Western countries can be attributed to changes in the microbial exposure in children seen in Western culture, possibly affecting their intestinal microflora.¹¹ Probiotics have been shown to be helpful in treating other disorders involving disruptions in the intestinal microflora.^{10,12} These findings have led researchers to study whether changing the intestinal microflora by way of probiotics could treat and prevent AD.

Meta-analyses of the use of probiotics in the treatment of AD have published conflicting results.^{6,9,10,13-16} While a 2008 Cochrane systematic review did not reveal a population in which probiotics served as an effective treatment for AD,¹³ a later meta-analysis in 2014 found that probiotics may aid in the treatment of children and adults with moderate to severe AD. This report included 12 more randomized controlled trials, studying more than double the number of patients compared with the earlier Cochrane review. This newer study looked at the weighted mean difference (WMD) of SCORing Atopic Dermatitis (SCORAD) values and found that while the effects of probiotics were significant in children (WMD -5.74 , 95% confidence interval [CI] -7.27 to 4.20 , $P < .001$) and in adults (WMD -8.26 , 95% CI -13.28 to 3.25 , $P = .001$), the WMD in SCORAD value between probiotics and placebo was not significant in the infant population (WMD 0.52 , 95% CI -1.59 to 2.63 , $P = .63$).⁶ Subgroup analysis showed that the greatest effect was seen when a mixture of different bacterial species was used as opposed to solely *Lactobacillus* or *Bifidobacterium* species.⁶ Additionally, treatment duration longer than 8 weeks was noted to be of greater benefit than treatment durations of less than 8 weeks. Synbiotic use, defined as the use of probiotics and prebiotics (nondigestible sugars that encourage the growth of certain strains of bacteria in the intestine) decreased the SCORAD score more than probiotics alone in children.^{6,16,17}

More recently, a 2016 meta-analysis of 6 studies (Table 1) of synbiotics in the treatment of AD found similar results. This new meta-analysis found a significant beneficial effect when mixed strains of bacteria were used in children 1 year and older.¹⁷

Meta-analyses studying probiotics and synbiotics in the treatment of AD encounter many problems, most notably the heterogeneity among studies. Heterogeneity exists in the type of probiotic strain, dose, timing, and duration of therapy. Future studies are needed to confirm these subgroup analysis findings and to elucidate optimal dosing, strain, and duration of treatment.

Currently, we are unable to recommend probiotics and synbiotics as AD treatment; however, they may be promising as a possible therapeutic intervention in the future. Probiotic treatment is generally considered safe, but adverse events have been noted in case reports, including sepsis and bowel ischemia. The risk of these events is difficult to quantify, but most likely the risk is very low for most patients.⁹ Proper dosing, choice of probiotic strain, and duration of therapy need to be established before they can be recommended, as noted in the guidelines for AD of the American Academy of Dermatology (AAD): “The use of probiotics/

prebiotics for the treatment of patients with established AD is not recommended due to inconsistent evidence.”¹⁸

Chinese herbal medications

Chinese herbal medications (CHMs) are one of the most commonly used alternative therapies in the treatment of AD. Typically, CHMs are derived from botanic sources, such as barks, seeds, flowers, or roots and can be administered orally, topically, or as a combination of both. Oral ingestion of CHM is generally adapted for the individual patient.¹⁹ Each component of CHMs is theorized to treat AD through modulation of the immunologic balance between Th1 and Th2 cells, as well as suppression of cytokine synthesis.²⁰

A recent Cochrane systematic review contained 28 studies with 2306 patients, comparing oral and topical CHM to either placebo or standard treatment. While several included studies found statistically significant differences in outcome measures in favor of CHM, recommendations could not be made because the trials were of very poor quality, due to a lack of blinding, inconsistency in formulation of CHMs, and a dearth of validated outcome measures.¹⁹ Use of CHMs has been linked to cases of liver damage and/or failure.^{19,21,22}

CHMs cannot be recommended in the treatment of AD. Despite some interesting results, larger well-designed and implemented studies are needed before recommendations can be made. The 2015 AAD guidelines stated: “Chinese herbal therapy and massage therapy have insufficient evidence for recommendation for AD treatment.”¹⁸

Dietary supplements

The combination of reluctance to use medicine and the belief that something is missing from their diet or their child’s diet has led patients and parents to turn toward dietary supplements in the treatment of AD.²³ Another Cochrane systematic review studied the use of several dietary supplements in the treatment of AD, including fish oil, vitamin D, vitamin E, vitamin B₆, zinc, selenium, docosahexaenoic acid, sea buckthorn oil, sunflower oil, and hempseed oil. Single randomized controlled trials were identified for vitamin B₆, zinc, selenium, docosahexaenoic acid, sea buckthorn oil, sunflower oil, and hempseed oil. These randomized controlled trials were generally of small size, contained methodologic flaws, and failed to show significance between the treatment group and placebo group. The 2015 AAD guidelines noted: “There is inconsistent to no evidence to recommend the use of fish oils, evening primrose oil, borage oil, multivitamin supplements, zinc, vitamin D, vitamin E, vitamin B₁₂ and B₆ for the treatment of AD,” summing up the paucity of data on these topics.¹⁸

Vitamin D

Vitamin D is a lipid-soluble vitamin synthesized predominantly in the skin. Aside from its role in immune function

Table 1 Summary of synbiotics and outcomes in meta-analysis by Kim et al

Study	Synbiotic strain	Outcome
Passeron et al 2006 ⁵⁸	Probiotic: <i>L. rhamnosus</i> Lcr35 Prebiotic: Fermentation broth for <i>L. rhamnosus</i> Lcr35 skimmed milk powder, potato starch, and lactose	No statistically significant difference in reduction of SCORAD index between treatment and control groups Greater reduction in SCORAD (−14.2 [9.9] vs −7.8 [7.7]; $P = .001$), Infant Dermatitis Quality Of Life (33% vs 19%, $P = .013$) and Dermatitis Family Impact scores (35.2% vs 23.8%, $P = .010$) in the treatment group compared with placebo. Treatment group used on average 7.7 g less topical corticosteroids during the 8-week trial ($P = .006$).
Gerasimov et al 2010 ⁵⁹	Probiotic: <i>L. acidophilus</i> DDS-1, <i>B. lactis</i> UABLA-12 Prebiotic: Fructo-oligosaccharide	No statistically significant difference in reduction of SCORAD index between treatment and control groups.
Van der Aa et al 2010 ⁶⁰	Probiotic: <i>B. breve</i> M-16 V Prebiotic: Galacto-/fructooligosaccharide mixture	In a subgroup of infants with IgE-associated AD ($n = 48$), SCORAD score improvement was significantly greater in the treatment group at week 12 (−18.1 vs −13.5 points, $P = .04$)
Shafiei et al 2011 ⁶¹	Probiotic: 7 strains not specified Prebiotic: Fructo-oligosaccharide	No statistically significant difference in reduction of SCORAD index between treatment and control groups
Farid et al 2011 ⁶²	Probiotic: <i>L. casei</i> , <i>L. rhamnosus</i> , <i>S. thermophilus</i> , <i>B. breve</i> , <i>L. acidophilus</i> , <i>B. infantis</i> , <i>L. bulgaricus</i> Prebiotic: Fructo-oligosaccharide	Statistically significant reduction in SCORAD index at week 4 (−29.51 vs −11.06, 95% CI −33.78 to −25.24), $P = .01$ and between weeks 4 and 8 (−39.2 vs −20.10, 95% CI −44.61 to −33.79), $P = .05$) in treatment group compared with the control group.
Wu et al 2012 ⁶³	Probiotic: <i>L. salivarius</i> Prebiotic: Fructo-oligosaccharide	Statistically significant lower SCORAD index at week 8 (27.4 vs 36.3, $P = .022$) in treatment group compared with the control group.

AD, atopic dermatitis; CI, confidence interval; IgE, immunoglobulin E; SCORAD, SCORing Atopic Dermatitis.

and calcium homeostasis, vitamin D is known to be intimately involved in skin function, where it plays a role in normal keratinocyte development, wound healing, and skin protein production.²⁴ Vitamin D is also known to have immunomodulatory effects, with its receptors being present on macrophages, dendritic cells, B cells, and T cells.^{25–27} Vitamin D is also believed to inhibit type 1 helper T cells and to promote a shift to type 2 helper T cells.^{27,28} Additionally, vitamin D stimulates T regulatory cells and inhibits differentiation, maturation, and activity of dendritic cells.^{29–31} Epidemiologically, there is a higher prevalence of AD in higher geographic latitude, which correlates with less sun exposure and thus less vitamin D production.^{32,33} Additionally, a different study found that therapy with narrow-band ultraviolet B treatment, a routine therapy for AD, increased serum levels of calcidiol.^{32,34}

There are conflicting studies about vitamin D levels in patients with AD, with some studies showing decreased vitamin D levels in patients^{35–37} and others revealing no such correlation.^{24,38–41} Most recently, a meta-analysis, including randomized controlled trials and case-control studies, found that pediatric AD patients had statistically significant lower vitamin D levels, while adult patients did not.⁴² Five single-center case-control studies were identified, with a combined total of 690 subjects. There was significant heterogeneity among studies, which spanned three continents, with one from Egypt, two from Korea, one from Hong Kong, and one from Italy. Studies included anywhere from 29 to 498 AD patients with a mean age between 4 and 15.5 years old. One study

did not report mean age and instead gave an age range from 12 months to 16 years. Two studies included equal men and women patients, one included more men (57.6%), and another included more women (63.6%). Three studies were conducted during the winter, one during the summer, and one did not report the season in which vitamin levels were measured.^{35–37,43,44}

Published studies on the relationship to vitamin D levels are also conflicting.^{24,32} A recent meta-analysis found that a low serum vitamin D level was associated with clinical severity of AD as measured by SCORAD scores.²⁴ This meta-analysis was in accordance with several other studies that found correlation between vitamin D levels and AD severity.^{37,44–46} Other reports have found no correlation between vitamin D levels and clinical severity of disease.^{36,39,47,48}

A few studies have tested vitamin D as treatment for AD, with controversial results. A 2012 Cochrane systematic review of two randomized control studies found no benefit of vitamin D over placebo in the treatment of AD.²³ A more recent meta-analysis included four double-blind randomized controlled trials of vitamin D as therapy in AD. Vitamin D benefited AD as measured by reduction in the SCORAD and Eczema Area and Severity Index (EASI) scores (mean difference = −5.85, 95% CI −7.66 to −4.05, $I < 50\%$). Two studies were conducted in Iran, one in the United States, and one in Mongolia. Two studies included patients 13 and older; the remaining two studied only children. Dosages of vitamin D varied (D_3 1600 IU in two studies, D_2 1000 IU and D_3 1000 IU each in one study) for 1 to 2 months. Two of the four studies included pediatric

patients who had flares in the winter, correlating with decreased sun exposure and theoretically lower vitamin D levels.⁴²

Vitamin D cannot be recommended as therapy for AD due to conflicting results. Despite the lack of evidence, it is still important that children and adults receive the US recommended dietary allowance dosage daily, and nutritional counseling can benefit the AD patient who has a diet modified or restricted for food allergy.

Fish oil

The imbalance of polyunsaturated fats may result in increased inflammation. Polyunsaturated fats can be divided into two groups: ω -6 and ω -3. The Western diet is rich in ω -6 fatty acids, resulting in an increased ratio of ω -6 to ω -3 compared with more traditional diets. Fish oil is particularly rich in ω -3 fatty acids, which are believed to compete with ω -6 fatty acids to decrease inflammation. A recent Cochrane review identified three small studies that suggested a modest benefit to the use of fish oil. Pooled data from two studies found that fish oil was associated with an increase in quality of life and a decrease in the area affected at the end of treatment. Both studies were composed of predominantly women with moderate to severe AD; the studies included 31 to 145 patients and ranged from 12 to 16 weeks. Unfortunately, both studies had poor methodology.²³

Vitamin E

Vitamin E is a potent antioxidant that may decrease serum levels of immunoglobulin E in atopic patients. Vitamin E has been explored as treatment for AD in several studies in combination with selenium and vitamin D. No significant difference in outcomes among patients treated with selenium and vitamin E versus selenium alone versus placebo or among vitamin E versus vitamin D versus vitamin E and D versus placebo were found. These studies were small and failed to conclude whether treatments were effective.²³ More recently, a randomized controlled trial of 70 patients, ages 10 to 50 years (43% women, 57% men), in Iran found significant diminution in all symptoms except sleeplessness in those receiving 400 IU/day of vitamin E for 4 months compared to controls. Reduced itching, SCORAD, and extent of lesions were seen in the vitamin E group. No significant differences were noted in 3-month relapse rates after discontinuation of the intervention.⁴⁹

Evening primrose oil and borage oil

Evening primrose oil (EPO) and borage oil are considered to be natural sources of gamma-linolenic acid (GLA) and have been studied extensively in the treatment of AD.⁵⁰ GLA is an ω -6 fatty acid that, unlike most ω -6 fatty acids, decreases inflammation. A deficiency in GLA of the skin is proposed to

be one mechanism contributing to AD development.^{50,51} EPO is believed to contain 8 to 10% GLA, while borage oil contains at least 23% GLA. Thorough evaluation of these natural sources of GLA is disappointing.³²

A 2013 Cochrane systematic review evaluated 27 studies with 1596 patients, reporting on EPO and borage oil in the treatment of AD. EPO was studied in 19 reports and borage oil in 8 reports. This review had difficulty in pooling studies due to variations in methods of reporting outcome data. A meta-analysis of seven studies of EPO found no difference in patient-reported symptoms between EPO and placebo. A second meta-analysis of eight studies of EPO found no difference in physician-reported assessment of symptoms between EPO and placebo. Borage oil did not show any benefit over placebo in the treatment of AD; however, meta-analysis of borage oil was impossible due to differences in reporting outcomes among studies. Additionally, these studies did not allow researchers to evaluate quality of life differences among patients in the treatment and placebo group.⁵⁰

Adverse events associated with EPO and borage oil are limited to case reports. EPO was previously linked to seizures, which has been disproven. There are case reports of lipoid pneumonia, inflammation, thrombosis, and immunosuppression with prolonged EPO therapy. Borage oil is also associated with the side effects of headache and minor gastrointestinal upset.⁵⁰

This meta-analysis provides persuasive evidence against the use of EPO or borage oil over placebo in AD. Limitations include lack of generalizability as only one included study involved developing countries, as well as inability to perform meta-analysis of all studies due to differences in methods of reporting outcome. Additionally, this study did not evaluate long-term treatment with either EPO or borage oil as duration of treatment ranged from 3 to 24 weeks.

Ayurveda

Ayurvedic medicine is one of the oldest traditional medicine systems and is used by the majority of India's population.^{52,53} Ayurveda employs a holistic approach, focusing on rejuvenation of the body, cleansing, and enhancing longevity.⁵² Often topical, oral, and aromatized medications are used to detoxify patients.⁵² A 2014 US population-based study found that 0.28% of American children with AD were being treated with Ayurveda.⁵ While we were unable to identify any studies investigating the use of oral Ayurvedic medications in the treatment of AD, it is important for physicians to be aware that families may use these potentially dangerous medications as they are readily available via the Internet. While no oral Ayurvedic medication trials were found, one trial focusing on the principle of *Suśruta*, in which bloodletting is considered the best treatment for skin disease, was identified.⁵⁴ In this open-labeled clinical trial study without a control group, 27 patients were treated with leech application. After a

minimum of four treatments the total EASI score was reduced by 54.45% ($P < 0.01$) and the SCORAD index by 55% ($P < 0.01$). Additionally, the life quality of the patient, calculated by the Dermatology Life Quality Index, improved significantly by 62.36% ($P < 0.01$). While these results are interesting, it is important to note that there was no control group and that the placebo effect cannot be ignored.

The risk of heavy metal poisoning with Ayurvedic medicines far outweighs the benefit at this time. Several studies have demonstrated that these medications contain lead, mercury, and arsenic in levels exceeding US Environmental Protection Agency limits by 3 to 4 orders of magnitude.^{53,55} Furthermore, over 80 case reports have demonstrated lead poisoning in patients taking these supplements.^{53,56,57} It is clear that well-designed trials with medical-grade supplements would be needed to safely assess the benefits of this type of care.

Conclusions

Most studies about oral supplements in the treatment of AD are of small scale and are often conflicting, with poor methodologic quality. Meta-analyses of these studies more often than not were unable to draw conclusions, or the analyses suggested no use of oral supplements in the treatment of AD. Some oral supplements, such as probiotics, synbiotics, and CHMs, may prove to be efficacious, but they need to be subject to larger and more controlled clinical trials.

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