

Complementary and Alternative Interventions in Atopic Dermatitis

Joohee Lee, MD^a, Leonard Bielory, MD^{b,c,*}

KEYWORDS

- Complementary and alternative medicine • Atopic dermatitis
- Chinese herbal therapy • Herbal medicine
- Biologically based therapies

Ever since the 1997 landmark study by Eisenberg,¹ there has been a growing awareness of the prevalence of CAM use by the general population. In December 2008, the National Center for Complementary and Alternative Medicine (NCCAM) released updated findings regarding CAM use based on the 2007 National Health Interview Survey. Of the 23,393 adults older than 18 years and 9417 children younger than 17 years, approximately 38% of adults and approximately 12% of children in the United States use some form of CAM (<http://nccam.nih.gov/news/camstats.htm>). The 2007 National Health Statistics Report has identified the use of a common group of nonvitamin, nonmineral natural products for therapy (17.7% of all CAM use) (<http://nccam.nih.gov/news/2008/nhsr12.pdf>).

A wide range of herbal products is available to the consumer/patient with allergic diseases. About 15 years ago, the herbal industry was in essence deregulated by the passage of the congressional Dietary Supplement Health and Education Act of 1994, which restricted the role of the US Food and Drug Administration in classifying herbal products.² Critical reviews of the available literature on herbal medicines have concluded that published data on the therapeutic effects of herbals on allergic

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^a Department of Internal Medicine, Mayo Clinic, 200 First Street South West, Rochester, MN 55905, USA

^b Rutgers University, Center for Environmental Prediction, 14 College Farm Road, New Brunswick, NJ 08901-8551, USA

^c STARx Allergy and Asthma Center, 400 Mountain Avenue, Springfield, NJ 07081-2515, USA

* Corresponding author. STARx Allergy and Asthma Center, 400 Mountain Avenue, Springfield, NJ 07081-2515.

E-mail address: drbielory@gmail.com

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diseases are conflicting and riddled with deficiencies in quality of design.^{3,4} However, for the clinician, it is important to recognize that consumption of CAM interventions continues to thrive despite the lack of strong clinical evidence of efficacy. Epidemiologic data indicate that the use of complementary interventions is common in atopic disorders, especially atopic dermatitis (AD), allergic rhinitis, and asthma.⁵ In a study performed in Scandinavia, 227 of 444 (51.1%) patients with AD reported previous or current use of one or more forms of complementary interventions. The most common forms were homeopathy, health-food preparations, and herbal remedies.⁶ In a 2007 survey of alternative medicine use in AD, it was found that herbal remedies and homeopathic products were given by parents of 34 of 80 pediatric patients with AD.⁷

The above-mentioned epidemiologic studies have identified motivating factors for CAM use. Among adults, disease duration, severity of the disease, and the perceived ineffective treatment of standard therapy were cited as common reasons for trying CAM interventions. In pediatric patients, parents commonly tried specific interventions based on recommendation from others (47%). A fear of steroid side effects (26.4%) and dissatisfaction with conventional treatment (17.6%) were also common driving factors.⁷ For the clinician, such data emphasize the importance of careful medication history-taking, easing fears regarding topical steroids by educating patients and caregivers, and making sure that conventional treatments are used appropriately.⁸

In the aforementioned survey of the parents of 80 patients with AD, most alternative treatments were perceived to have no therapeutic effect, and clinical worsening of AD was reported in 2 instances.⁷ There are several reported adverse effects associated with CAM use, which makes a strong case for the importance of a more systematic approach for establishing and maintaining patient-physician dialogue on both allopathic and alternative therapeutics. Of great concern are the potentially serious organ-specific side effects from alternative therapies for AD, including death, published in case reports. Other adverse effects include severe bilateral cataract formation in an 11-year-old boy after 8 months of treatment with an unidentified herbal medicine, although he had normal results on ophthalmologic examination 1 year before presentation.⁹ Lenses of both eyes had severe posterior subcapsular and posterior capsular opacification. Correction of visual acuity was achieved after extensive surgery and lens implantation. Severe cardiomyopathy has been reported in association with a 2-week course of Chinese herbal medicine.¹⁰ The connection between the 2 conditions was not made until 2 weeks after presentation when the patient was specifically asked if she had ingested any unusual substances. A review article of the potential harms of herbal medicines used for AD identified arsenic- and mercury-containing remedies that can produce eczematous lesions.¹¹ This article offers helpful tables delineating the various dermatoses reported in association with a wide range of popular herbal remedies, including kava, aloe vera, as well as adulterated therapeutic products.

Population-based research regarding CAM use for allergic diseases underscores the increasing challenge for health care providers with respect to identifying CAM use and ensuring safe use of allopathic and complementary medicines in disease management. A recent review by Engler and colleagues¹² provides a timely overview on this topic, proposing a practical 10-step approach to establishing patient-physician cooperation with regards to CAM use. Furthermore, Engler and colleagues acknowledge the challenge of synthesizing available data on specific alternative therapies and they identify 2 trustworthy and active databases for physicians and specialists. One is the website of the NCCAM branch of the National Institutes of Health (<http://nccam.nih.gov/>), which provides data formatted for patients and physicians. In addition,

the Natural Medicines Comprehensive Database (<http://www.naturaldatabase.com>) offers practical assessments of the research behind almost 1100 natural ingredients and more than 30,000 commercially available brand name products. It accounts for key quality markers such as randomization, allocation concealment, adequate blinding, and other factors using the principles from the Cochrane Collaboration. Furthermore, the database is regularly maintained and updated. It serves as a valuable tool for the clinician, as it integrates not only grading of efficacy but also that of safety and product quality/purity from international regulatory bodies.

Because of the lack of regulation, there is valid concern regarding the active ingredients in “natural” topical preparations, specifically potent corticosteroids. A study by Ramsay and colleagues¹³ found that the majority of effective herbal creams used by 19 pediatric patients contained potent steroids, as detected by high-performance liquid chromatography. The most common steroid was high-potency clobetasol propionate, which was found in 5 creams labeled Wau Wa and Muijiza. The remaining herbal creams contained clobetasol propionate and hydrocortisone, betamethasone valerate, clobetasone butyrate, and hydrocortisone. Parents were not aware that the creams contained steroids.¹³

Epidemiologic data have been stimuli for better elucidation of the efficacy of CAM interventions for allergic diseases. Despite the concern of the harms and risks associated with the use of alternative therapies, the research in this area continues to grow and offers some promising avenues for these frustrating and increasingly prevalent conditions. There have been hundreds of clinical trials looking at the effect of CAM on asthma, allergic rhinitis, and AD. Mainardi and colleagues⁴ have reviewed recent studies that have taken on a more sophisticated focus on mechanistic biochemical pathways of signal transduction and transcription of T-cell effectors and mediators by which anti-allergic effects of various nonconventional medicines might be achieved. The following discussion of complementary and alternative interventions that have been studied for AD treatment has been organized to reflect the classification system endorsed by NCCAM.

BIOLOGY-BASED PRACTICES

Probiotics

The intestinal microbiota plays an important role in immune development and may play a role in the development of allergic disorders. According to the revised hygiene hypothesis, the increase in prevalence of atopic diseases over the past several decades is considered as the immunologic consequence of a changed intestinal colonization pattern in infants. The microorganisms comprising endogenous flora of the normal gastrointestinal tract are believed to play a role in “educating” the neonate’s immune system. This education includes converting the T_H2-biased prenatal responses into “balanced immune responses,” which include tolerance to self-antigens and promoting the maturation of immune responses in other tissues.^{14,15}

There is increasing interest in the use of probiotics (live beneficial microorganisms, primarily of the *Lactobacillus* and *Bifidobacteria* genus, characteristic of the healthy infant gut microbiota) and prebiotics (nondigestible oligosaccharides that promote the selective growth of nonpathogenic strains of commensal bacteria), used alone or together (synbiotics), to influence intestinal microbiota and modulate immune responses *in vitro* and *in vivo*.¹⁶ It is not entirely surprising that promising observations at the bench have not neatly translated to benefit at the bedside. The landmark study by Kalliomaki and colleagues¹⁷ was the first report that the frequency of AD in neonates treated with *Lactobacillus rhamnosus* GG was half that of the placebo.

Sustained prevention was seen at 4 years out.¹⁸ However, numerous trials using strains of *Lactobacillus* reported negative results, with no difference in the development of AD between the intervention and placebo arms.^{19–21} It is worth noting that the study designs of these trials with negative results were not identical to those of the Kalliomaki study (prenatal and postnatal supplementation), as 2 of these trials started probiotic supplementation postnatally.

The heterogeneity of study design found among trials of prebiotics and probiotics poses a challenge to data synthesis. A recent review of randomized controlled trials of probiotics for AD reviewed 7 prevention studies and 12 treatment studies and found that overall results were conflicting.²² At present, there is not enough evidence to support the use of pro-, pre- or synbiotics for prevention or treatment of AD in children in clinical practice.²³ Furthermore, 2 trials in particular have raised the question of whether or not there may be a more insidious effect of predisposing children to developing allergic respiratory diseases with use.^{19,20}

It would be premature to dismiss the therapeutic potential of pro-, pre-, or synbiotics. Numerous review articles have suggested that the following details need to be addressed: (1) effective bacterial species/strains, (2) optimal dosing, (3) whether there is added benefit with synbiotics, (4) the optimal timing for intervention, and (5) the patient populations that would gain the most benefit.^{22,24} Effects may vary depending on the characteristics of the study population, such as whether the infant was delivered by caesarean section, and in the case of AD associated with elevated IgE.^{25,26} The same point can also be made when considering the limited study of prebiotics for AD prevention. One study found a significant reduction in the incidence of AD in infants who were at risk for developing AD.²⁷ Another study observed a higher incidence of AD associated with prebiotic use, but this study looked at formula-fed healthy infants.²⁸ In terms of AD treatment, a beneficial effect of probiotics has been observed in a trial of children with more severe AD.²⁹

A search of the literature revealed 1 article in a German publication that reviews ongoing research on topical preparations of probiotics, which is an intriguing notion to consider in light of our dominant medical paradigm of antibiotics.³⁰ It will be interesting to see if and how this approach will play a role in AD therapy.

Vitamin B₁₂

Use of vitamin B₁₂ in allergy is not a new therapeutic concept. However, in the past 10 years, in vitro investigation of inflammatory dermatoses, including AD, has drawn attention to the pathophysiologic role of overexpression of inducible nitric oxide synthase (iNOS). Lesional skin (upper dermal microvasculature) from AD has been demonstrated to have an increased expression of iNOS.³¹ Moreover, serum nitrate levels in Japanese children with AD have been shown to increase as compared with nonatopic controls and were found to correlate with disease severity and peripheral eosinophil counts.³² The reduction of pruritus and erythema observed in 15 patients with AD who were given a topical nitric oxide synthase inhibitor³³ inspired one group of German investigators to focus on vitamin B₁₂ on the basis of its ability to inactivate nitric oxide. In their prospective placebo-controlled randomized clinical trial of 41 adults with AD, topical vitamin B₁₂ was shown to be superior to placebo with respect to reducing the extent and severity of AD as assessed by the Modified Six Area Six Sign Atopic Dermatitis score.³⁴ In this trial, each patient applied the vitamin B₁₂-containing cream to lesions on one side of the body and the placebo preparation on lesions on the contralateral side. However, a fair amount of cutaneous reactions were reported, including AD flare and local irritation.

Vitamin D

A role for vitamin D in atopic diseases including AD has been the subject of a growing number of studies (see the article by Searing and Leung elsewhere in this issue for further exploration of this topic). Recently, lack of vitamin D has been proposed as one of several environmental factors responsible for the increase in atopic diseases. Studies of maternal dietary intake of vitamin D have noted a lower frequency of atopic disease in the children of mothers with higher intake.³⁵ Conversely, a birth cohort study of 123 children sought to determine whether the estimated dose of dietary vitamin D₃ (recorded in a previous study) during the first year of life was associated with atopic diseases up to the age of 6 years, as determined by questionnaire-based survey.³⁶ Atopic manifestations were more prevalent in the group with higher intake of vitamin D₃. As more data are gathered, vitamin D supplementation may have a place in AD prevention in the prenatal period, whereas in the postnatal period, modified or limited vitamin D₃ supplementation will be necessary.

MASO63DP

MASO63DP (Atopiclair) is an emollient preparation that contains the active metabolite of *Glycyrrhiza glabra* (licorice) and *Vitis vinifera* (grapevine), a potential antioxidant. It has been recently approved for mild to moderate AD.³⁷ The efficacy of MASO63DP was established by a multicenter trial that looked at 60 pediatric patients (between ages 2 and 17 years) with mild to moderate AD treated for 6 weeks, with clinical evaluations at baseline and at days 8, 15, 22, 29, and 43. MASO63DP was associated with a statistically significant reduction in AD severity score at day 22 compared with vehicle. A statistically significant difference was sustained until the end of the study.³⁸

AOA

Severe AD can be associated with cataract formation. One Japanese group published the findings from clinical application of an oral antioxidant, named AOA, derived from numerous seeds (eg, soybean, sesame, wheat germ). The extract was heated with infrared rays (4–14 μ m wavelength), fermented with *Aspergillus oryzae*, and lipophilized with similarly heated sesame oil. This processing has been demonstrated to release low-molecular-weight antioxidants that are active and more bioavailable. Approximately half the patients with cataract-associated AD tested showed marked improvement.³⁹ An Internet search indicates that AOA has been evaluated in clinical use for AD as a topical preparation that also includes low levels of corticosteroids.

γ -LINOLENIC ACID

Evening primrose (*Oenothera biennis*) has been reported to have a potential benefit in AD, a property that is now linked to the plant's high content of γ -linolenic acid (GLA) as well as omega-6 fatty acids.⁴⁰ The immunologic basis for this property may be related to an abnormality in fatty acid metabolism in AD. The postulation is that atopic patients may have a deficiency in GLA, which is a precursor of prostaglandin E₁, an important component in normal T lymphocyte function.⁴⁰ Preliminary results of supplementation with 500 mg of evening primrose oil (EPO) containing 45 mg of GLA included data from 46 adults and 20 children. A subsequent report described improvement of itch with low-dose EPO and a 43% reduction in AD severity among the adults.⁴¹ However, other trials have reported negative findings^{42–44} as well as positive effects.^{45,46} Overall, the body of evidence for EPO has been evaluated to be rather weak, and it cannot be endorsed as an effective treatment.⁴⁷

Borage oil is another herbal agent with high GLA content that has been studied for treatment and prevention of AD. Published trials have evaluated therapy in adults and children. Adults were given 920 mg γ -linolenic acid, and children, 460 mg twice daily for 12 weeks. No significant benefit was noted with supplementation.⁴⁸ A later trial looked at supplementation with higher levels of GLA. Although it did not report statistically significant differences in therapeutic effect, significant differences favoring borage oil were observed when individuals who failed to show an increase in a serum surrogate marker and who were suspected of noncompliance were excluded from analysis.⁴³ Oral supplementation with 100 mg of GLA failed to show preventive benefit at 1 year of age in formula-fed infants with maternal history of atopic disease. However, GLA supplementation did show a favorable trend for AD severity. An increase in GLA concentrations in plasma phospholipids between baseline and 3 months of age was negatively associated with the severity of AD at 1 year.⁴⁹

ST JOHN'S WORT

Hyperforin, identified as a major component of St John's wort (*Hypericum perforatum*), has antiinflammatory and antibacterial properties. This herbal extract, standardized to a 1.5% hyperforin (verum) preparation, has been studied in 21 individuals with mild to moderate AD in a one-sided comparison study with an emollient vehicle. Eighteen patients completed the 4-week treatment period. Primary outcome was AD severity, determined by a modified Scoring Atopic Dermatitis (SCORAD) index. The intensity of the eczematous lesions improved with the intervention and with the placebo. Although the intervention was significantly superior to the vehicle at all clinical visits ($P < .05$), it is unknown how this compares with topical corticosteroids.⁵⁰

PERSIMMON LEAF EXTRACT

In vitro and in vivo studies have been published on the effects of persimmon leaf extract, which contains elements, including astragaloside, that have been shown to inhibit histamine release by the human basophil cell line KU812 in response to cross-linkage of high-affinity IgE receptors.⁵¹ Oral intake of both persimmon leaf and astragaloside in mice attenuated passive cutaneous reactions and suppressed scratching behavior and elevation of serum IgE levels. Histologic analyses revealed significant reduction in inflammation and transepidermal water loss.^{51,52}

BAMBOO STEM EXTRACT

Bambusae caulis in Liquefied (BCL) is a nutritious liquid extracted from heat-treated fresh bamboo stems, an herbal medicine that has been used to treat cough and asthma in East Asia. One group evaluated the antiinflammatory, antiallergenic, and immunoregulating properties of this extract in a murine model of 2,4-dinitrochlorobenzene-induced AD-like skin lesions in hairless mice.⁵³ BCL extract applied to the lesions inhibited the development of these lesions, with lower numbers of infiltrating leukocytes. BCL administration was also associated with suppression of serum IgE levels, attenuation of messenger RNA (mRNA) expression of interleukin (IL)-4, IL-13, and tumor necrosis factor (TNF) α , and induction of interferon (IFN)- γ expression in the spleen.⁵³

SYNERGY BETWEEN PROBIOTICS AND HERBAL MEDICINE?

A recent study presents an interesting concept of probiotic-fermented herbal medicine.⁵⁴ Select herbal extracts were fermented in *Lactobacillus plantarum* (FHE) for

anti-AD effects. The effects of FHE were evaluated using a murine model of AD induced by dust mite extract. The fermentation was demonstrated to increase bioavailability, and the end product exerted a dose-dependent inhibition of mitogen-induced splenic T- and B-lymphocyte proliferation. A reduction in plasma levels of IgE was also noted. Analysis of cytokine mRNA expression demonstrated suppression that was comparable to that seen with cyclosporine. Therefore, probiotic fermentation may have therapeutic advantages of increasing the bioavailability and immunosuppressive properties of herbal medicines.⁵⁴

WHOLE MEDICAL SYSTEMS

All of the published trials in this area of alternative medicine (eg, traditional Chinese medicine, Kampo) used herbal combinations. Much of the benefit observed with the following herbal medications has been as an adjunctive, as opposed to an alternative therapy.

Clinical Trials

Overall, there are few randomized controlled trials of Chinese herbal therapy with sufficient powering. A 1999 double-blind, placebo-controlled, crossover trial with 40 adult patients with recalcitrant AD looked at the efficacy of Zemaphyte, a Chinese herbal oral preparation containing licorice, along with 9 other herbs commonly used for treatment of AD.⁵⁵ A 2005 update of a Cochrane review of traditional Chinese herbal mixtures identified 4 randomized controlled trials (159 individuals aged 1 to 60 years), all looking at the proprietary herbal mixture Zemaphyte (no longer being manufactured), that met the inclusion criteria.⁵⁶ Three of these trials used crossover design, and reduction of erythema and surface damage was greater with Zemaphyte than with placebo in 2 of these studies. Quality of sleep was higher in the treatment arm. The fourth trial was an open-label study comparing Zemaphyte in 2 different forms. There was a reduction in erythema and surface damage with both formulations, but no comparison between the 2 formulations was reported. Some adverse effects were reported in all 4 trials, but none were regarded as serious.⁵⁶ Overall, the studies had poor reporting and results were heterogeneous. The withdrawal rates ranged from 7.5% to 22.5%, and no trial used intention to treat analysis.

PentaHerbs is a formulation of 5 herbs (*Cortex Moutan*, root bark of *Paeonia suffruticosa* Andr (Ranunculaceae), *Cortex Phellodendri*, bark of *Phellodendron chinensis* Schneid (Rutaceae), *Flos Lonicerae*, flower of *Lonicera japonica* Thunb (Caprifoliaceae), *Herba Menthae*, aerial part of *Mentha haplocalyx* Briq (Labiatae), and *Rhizoma Atractylodis*, rhizome of *Atractylodes lancea* (Thunb) DC; 2:2:2:1:2 composition) that has been under investigation for several years. The initial trial in 2004 was an open-label study and enrolled 9 children, treated for 4 months.⁵⁷ In a confirmatory study, the medication was verified to be free of steroids (hydrocortisone, prednisolone, fludrocortisone, and dexamethasone) by thin-layer chromatography, infrared spectrophotometry, and liquid chromatography mass spectrometry.⁵⁸ In 2007, this same group published the findings of the use of the 5 herbal ingredients (PentaHerbs formulation, PHF) in a randomized and placebo-controlled clinical trial of 87 children with moderate to severe AD.⁵⁹ Twice-daily PHF reduced topical corticosteroid use and improved the quality of life in children with moderate to severe AD. The adverse reaction profiles seen among these patients were comparable with those observed in the placebo group, most common effects being upper respiratory infections ($P = .828$), diarrhea ($P = .074$), and abdominal pain ($P = .381$).⁵⁹

Additional publications by this group focused on observable immunomodulatory effects to account for clinical benefit. Twenty-eight children with AD were treated

with PHF for 3 months, and their mean plasma concentrations of inflammatory mediators, brain-derived neurotrophic factor (BDNF), and thymus and activation-regulated chemokine (TARC) decreased significantly from 1798 and 824 pg/mL at baseline to 1378 and 492 pg/mL ($P = .002$ and $.013$, respectively) at study completion.⁶⁰ Cell cultures showed dose-dependent suppression of peripheral blood mononuclear cell (PBMC) proliferation, reduction of supernatant concentrations of BDNF, IFN- γ , and TNF- α in response to PHA, and reduction in levels of BDNF and TARC following staphylococcus enterotoxin B stimulation. At the mRNA level, PHF suppressed the transcription of BDNF, TARC, IFN- γ , and TNF- α .⁶⁰ PHF and 2 of its 5 components were also observed to significantly reduce histamine release and prostaglandin D₂ synthesis in rat peritoneal mast cells activated by anti-IgE and compound 48/80 ($P < .05$).⁶¹

A small-scale prospective uncontrolled trial examined the therapeutic benefits of acupuncture combined with Chinese herbal medicine.⁶² Twenty individuals aged between 13 and 48 years with mild to severe AD were treated with a 12-week course of twice-weekly acupuncture and a Chinese herbal formula taken 3 times daily. Primary end points were changes in the Eczema Area and Severity Index, Dermatology Life Quality Index, and patient assessment of itch measured on a visual analog scale. At the end of treatment, all patients had an improvement in AD severity when compared with the baseline. However, whether this score reduction was clinically relevant is uncertain. More than 75% of patients experienced a reduction in pruritus and improvement of quality of life. No adverse effects were observed.

Hochu-ekki-to is a traditional Japanese Kampo medicine which originated in China and is composed of 10 species of medicinal plants. In the framework of Kampo medicine, individuals are categorized as having a particular physiologic constitution. The premise of the study of Hochu-ekki-to for AD is that it has been considered effective for individuals with a Kikyo constitution, which includes atopsics. This herbal medicine has been studied in conditions of chronic fatigue (murine model) and chronic obstructive pulmonary disease, as well as in individuals undergoing chemotherapy. In vitro and in vivo studies of this herbal medicine have demonstrated some immunomodulatory properties, such as enhancing mucosal IgA production and attenuating proallergic cytokine IL-4 production.⁶³

In a placebo-controlled study, 91 individuals with AD and a Kikyo constitution underwent 24 weeks of intervention (herbal therapy or placebo).⁶⁴ All patients continued their regular treatments (topical steroids, topical tacrolimus, emollients, or oral antihistamines) during the study. Hochu-ekki-to or placebo was orally administered twice daily for 24 weeks. Seventy-seven of the initial group completed the trial. Only mild adverse events such as nausea and diarrhea were noted in both groups, without statistical difference. Outcomes included AD severity scores, efficacy, and exacerbation rates. There was no significant reduction in AD severity at the end of the trial. However, there were some promising trends. Although the rate of efficacy did not reach statistical significance ($P = .06$), it was higher in the Hochu-ekki-to group compared with placebo (19% vs 5%). Furthermore, the rate of exacerbation was significantly ($P < .05$) lower in the Hochu-ekki-to group (3%) than in the placebo group (18%). Because the use of topical steroids and tacrolimus was significantly lower at the end of 24 weeks of intervention in the Hochu-ekki-to group, the investigators concluded that this could be a useful adjunct to conventional treatments for patients with AD who have a Kikyo constitution.⁶⁴

Animal Model Studies

A Chinese herbal formula called Bakumijioogan (BJG) has been investigated in an NC/Jic mouse model of AD.⁶⁵ AD symptoms were induced by repeated injections of

Dermaphagoides farinae (Df) antigen into the ear auricle for 16 days. Daily oral administration of BJG from 7 days before to 16 days after the first injection significantly reduced ear swelling. BJG was also observed to suppress the total levels of IgE and Df-antigen-specific IgG1 at 17 days after first injection. Serum levels of the T_H1 cytokine IFN- γ and lesional IFN- γ mRNA levels were significantly higher, whereas lesional IL-1 α and TNF- α mRNA levels were lower in BJG-treated mice than in control mice.⁶⁵

A Korean herbal medicine called DA-9102 is currently in phase II of clinical investigation. Published data on this medicine are from a murine model (magnesium deficiency-induced AD in hairless rats). Oral administration of DA-9102 at a dose of 100 mg/kg for 16 days was observed to suppress the occurrence of spontaneous dermatitis.⁶⁶ Eczematous skin lesions, water loss, and scratching behavior were significantly decreased by DA-9102 in a dose-dependent manner. Results from flow cytometry analysis of PBMCs indicated that DA-9102 suppressed leukocyte activation. DA-9102 not only suppressed the mRNA expression of T_H2 cytokines including IL-4 and IL-10 in the lymph node but also decreased the levels of inflammatory mediators such as nitric oxide and leukotriene B_4 in the serum.⁶⁶

Homeopathy has recently increased in popularity among patients with skin disease. Unlike the traditional herbal medicines discussed under this section of whole medical systems, outcomes for homeopathy are difficult to quantify because the treatments are individualized. A meta-analysis of 89 placebo-controlled trials of homeopathic medicine concluded that the clinical effects of homeopathy in a variety of medical conditions were not placebo effects.⁶⁷ Despite this, the researchers surmised that insufficient evidence existed to show that any one type of homeopathic remedy was specifically effective in any clinical condition. A study of individualized homeopathic treatments focused on patients' own assessments of 7 elements (overall impression, improvement of skin condition, reduction of itchiness, reduction of sleep disturbance, satisfaction in daily life, fulfillment at work, and satisfaction in human relations) using a 9-point scale similar to the Glasgow Homeopathic Hospital Outcome Scale.⁶⁸ Of the 60 patients, 25 with chronic skin disease had AD. Another 20 had a nonspecific eczema other than AD. Treatment periods ranged between 3 and 31 months. About 50% of individuals with AD reported greater satisfaction in daily life, greater fulfillment at work, and greater satisfaction in human relations.⁶⁸

MIND-BODY

Manipulative and Body-Based Practices

As suggested by observations with homeopathy, there is an inextricable tie between chronic skin conditions and psychological/psychosomatic symptoms. A parasympathetic tone-skewed autonomic balance has been described in atopic diseases, but there are studies refuting this notion.⁶⁹ A recent case-control study sought to reevaluate the autonomies in 30 adults with AD.⁷⁰ Findings included decreased resting autonomic "set point" (assessed by heart rate variability during 5 minutes at rest) and increased parasympathetic tone in patients with AD when compared with normal controls. Furthermore, individuals with AD had higher values for parasympathetic modulation than healthy controls in response to deep breathing but not in response to postural changes. The investigators interpreted these findings to be consistent with the concept of an altered autonomic set point, while similar tone in the setting of postural change indicated that autonomic function to defined tasks remained intact.⁷⁰ Whether these alterations are disease inherent or counterregulatory remains uncertain. Furthermore, there are 2 factors to take into account before attempting to interpret this potential autonomic dysregulation observed in AD. One is the impressive

complexity of the efferent signaling pathways of the parasympathetic system.⁷¹ For instance, although the physiologic cholinergic pathway has been described as overall antiinflammatory,⁷² increased cholinergic tone does not necessarily equate with purely antiinflammatory effects, as acetylcholine has been shown to promote histamine release from mast cells.⁷³ Secondly, one cannot discount the influence and interplay of associated psychiatric symptoms/conditions, such as depression and anxiety, which are often associated with decreased vagal tone. The limited volume of literature in this area includes a study of 12 patients with AD who were exposed to a fixed sequence of treatment phases (no treatment, nonspecific treatment factors, electromyographic feedback and relaxation). Significant remission of disease was noted but could not be attributed to a specific phase in the above-mentioned sequence.⁷⁴ From the perspective of safety, this area of CAM is less concerning.

SUMMARY

The burden of atopic diseases, including AD, is significant and far-reaching. In addition to cost of care and therapies, it affects the quality of life for those affected as well as their caretakers. Complementary and alternative therapies are commonly used because of concerns about potential adverse effects of conventional therapies and frustration with the lack of response to prescribed medications, be it due to the severity of the AD or the lack of appropriate regular use. Despite the promising results reported with various herbal medicines and biologic products, the clinical efficacy of such alternative therapies remains to be determined. Physicians need to be educated about alternative therapies and discuss benefits and potential adverse effects or limitations with patients. A systematic approach and awareness of reputable and easily accessible resources are helpful in dealing with CAM.

REFERENCES

1. Eisenberg DM. Advising patients who seek alternative medical therapies. *Ann Intern Med* 1997;127(1):61–9.
2. McNamara SH. FDA regulation of ingredients in dietary supplements after passage of the Dietary Supplement Health and Education Act of 1994: an update. *Food Drug Law J* 1996;51(2):313–8.
3. Bielory L. Complementary and alternative interventions in asthma, allergy, and immunology. *Ann Allergy Asthma Immunol* 2004;93(2 Suppl 1):S45–54.
4. Mainardi T, Kapoor S, Bielory L. Complementary and alternative medicine: herbs, phytochemicals and vitamins and their immunologic effects. *J Allergy Clin Immunol* 2009;123(2):283–94 [quiz 295–86].
5. Bielory L, Lupoli K. Herbal interventions in asthma and allergy. *J Asthma* 1999;36(1):1–65.
6. Jensen P. Alternative therapy for atopic dermatitis and psoriasis: patient-reported motivation, information source and effect. *Acta Derm Venereol* 1990;70(5):425–8.
7. Hughes R, Ward D, Tobin AM, et al. The use of alternative medicine in pediatric patients with atopic dermatitis. *Pediatr Dermatol* 2007;24(2):118–20.
8. Anderson PC, Dinulos JG. Atopic dermatitis and alternative management strategies. *Curr Opin Pediatr* 2009;21(1):131–8.
9. Kang KD, Kang SM, Yim HB. Herbal medication aggravates cataract formation: a case report. *J Korean Med Sci* 2008;23(3):537–9.
10. Ferguson JE, Chalmers RJ, Rowlands DJ. Reversible dilated cardiomyopathy following treatment of atopic eczema with Chinese herbal medicine. *Br J Dermatol* 1997;136(4):592–3.

11. Ernst E. Adverse effects of herbal drugs in dermatology. *Br J Dermatol* 2000; 143(5):923–9.
12. Engler RJ, With CM, Gregory PJ, et al. Complementary and alternative medicine for the allergist-immunologist: where do I start? *J Allergy Clin Immunol* 2009; 123(2):309–16.
13. Ramsay HM, Goddard W, Gill S, et al. Herbal creams used for atopic eczema in Birmingham, UK illegally contain potent corticosteroids. *Arch Dis Child* 2003; 88(12):1056–7.
14. Smits HH, Engering A, van der Kleij D, et al. Selective probiotic bacteria induce IL-10-producing regulatory T cells in vitro by modulating dendritic cell function through dendritic cell-specific intercellular adhesion molecule 3-grabbing nonintegrin. *J Allergy Clin Immunol* 2005;115(6):1260–7.
15. Prescott SL, Dunstan JA, Hale J, et al. Clinical effects of probiotics are associated with increased interferon-gamma responses in very young children with atopic dermatitis. *Clin Exp Allergy* 2005;35(12):1557–64.
16. Rautava S, Kalliomaki M, Isolauri E. New therapeutic strategy for combating the increasing burden of allergic disease: Probiotics-A Nutrition, Allergy, Mucosal Immunology and Intestinal Microbiota (NAMI) Research Group report. *J Allergy Clin Immunol* 2005;116(1):31–7.
17. Kalliomaki M, Salminen S, Arvilommi H, et al. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. *Lancet* 2001;357(9262): 1076–9.
18. Kalliomaki M, Salminen S, Poussa T, et al. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. *Lancet* 2003;361(9372):1869–71.
19. Kopp MV, Hennemuth I, Heinzmann A, et al. Randomized, double-blind, placebo-controlled trial of probiotics for primary prevention: no clinical effects of *Lactobacillus GG* supplementation. *Pediatrics* 2008;121(4):e850–6.
20. Taylor AL, Dunstan JA, Prescott SL. Probiotic supplementation for the first 6 months of life fails to reduce the risk of atopic dermatitis and increases the risk of allergen sensitization in high-risk children: a randomized controlled trial. *J Allergy Clin Immunol* 2007;119(1):184–91.
21. Soh SE, Aw M, Gerez I, et al. Probiotic supplementation in the first 6 months of life in at risk Asian infants—effects on eczema and atopic sensitization at the age of 1 year. *Clin Exp Allergy* 2009;39(4):571–8.
22. Tang ML. Probiotics and prebiotics: immunological and clinical effects in allergic disease. *Nestle Nutr Workshop Ser Pediatr Program* 2009;64:219–38.
23. van der Aa LB, Heymans HS, van Aalderen WM, et al. Probiotics and prebiotics in atopic dermatitis: review of the theoretical background and clinical evidence. *Pediatr Allergy Immunol* 2009;21(2):e355–67.
24. Kopp MV, Salfeld P. Probiotics and prevention of allergic disease. *Curr Opin Clin Nutr Metab Care* 2009;12(3):298–303.
25. Kuitunen M, Kukkonen K, Juntunen-Backman K, et al. Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort. *J Allergy Clin Immunol* 2009;123(2):335–41.
26. Kukkonen K, Savilahti E, Haahtela T, et al. Probiotics and prebiotic galacto-oligosaccharides in the prevention of allergic diseases: a randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2007;119(1):192–8.
27. Moro G, Arslanoglu S, Stahl B, et al. A mixture of prebiotic oligosaccharides reduces the incidence of atopic dermatitis during the first six months of age. *Arch Dis Child* 2006;91(10):814–9.

28. Ziegler E, Vanderhoof JA, Petschow B, et al. Term infants fed formula supplemented with selected blends of prebiotics grow normally and have soft stools similar to those reported for breast-fed infants. *J Pediatr Gastroenterol Nutr* 2007;44(3):359–64.
29. Weston S, Halbert A, Richmond P, et al. Effects of probiotics on atopic dermatitis: a randomised controlled trial. *Arch Dis Child* 2005;90(9):892–7.
30. Volz T, Biedermann T. [Outside-in: probiotic topical agents]. *Hautarzt* 2009; 60(10):795–801 [in German].
31. Rowe A, Farrell AM, Bunker CB. Constitutive endothelial and inducible nitric oxide synthase in inflammatory dermatoses. *Br J Dermatol* 1997;136(1):18–23.
32. Taniuchi S, Kojima T, Hara Mt K, et al. Increased serum nitrate levels in infants with atopic dermatitis. *Allergy* 2001;56(7):693–5.
33. Morita H, Semma M, Hori M, et al. Clinical application of nitric oxide synthase inhibitor for atopic dermatitis. *Int J Dermatol* 1995;34(4):294–5.
34. Stucker M, Pieck C, Stoerb C, et al. Topical vitamin B12—a new therapeutic approach in atopic dermatitis-evaluation of efficacy and tolerability in a randomized placebo-controlled multicentre clinical trial. *Br J Dermatol* 2004;150(5):977–83.
35. Erkkola M, Kaila M, Nwaru BI, et al. Maternal vitamin D intake during pregnancy is inversely associated with asthma and allergic rhinitis in 5-year-old children. *Clin Exp Allergy* 2009;39(6):875–82.
36. Back O, Blomquist HK, Hernell O, et al. Does vitamin D intake during infancy promote the development of atopic allergy? *Acta Derm Venereol* 2009;89(1): 28–32.
37. Patrizi A, Raone B, Neri I. Atopiclair. *Expert Opin Pharmacother* 2009;10(7): 1223–30.
38. Patrizi A, Capitanio B, Neri I, et al. A double-blind, randomized, vehicle-controlled clinical study to evaluate the efficacy and safety of MAS063DP (ATOPICLAIR) in the management of atopic dermatitis in paediatric patients. *Pediatr Allergy Immunol* 2008;19(7):619–25.
39. Niwa Y, Tominaga K, Yoshida K. Successful treatment of severe atopic dermatitis-complicated cataract and male infertility with a natural product antioxidant. *Int J Tissue React* 1998;20(2):63–9.
40. Lovell CR, Burton JL, Horrobin DF. Treatment of atopic eczema with evening primrose oil. *Lancet* 1981;1(8214):278.
41. Wright S, Burton JL. Oral evening-primrose-seed oil improves atopic eczema. *Lancet* 1982;2(8308):1120–2.
42. Bamford JT, Gibson RW, Renier CM. Atopic eczema unresponsive to evening primrose oil (linoleic and gamma-linolenic acids). *J Am Acad Dermatol* 1985; 13(6):959–65.
43. Henz BM, Jablonska S, van de Kerkhof PC, et al. Double-blind, multicentre analysis of the efficacy of borage oil in patients with atopic eczema. *Br J Dermatol* 1999;140(4):685–8.
44. Skogh M. Atopic eczema unresponsive to evening primrose oil (linoleic and gamma-linolenic acids). *J Am Acad Dermatol* 1986;15(1):114–5.
45. Biagi PL, Bordonni A, Masi M, et al. A long-term study on the use of evening primrose oil (Efamol) in atopic children. *Drugs Exp Clin Res* 1988;14(4):285–90.
46. Schalin-Karrila M, Mattila L, Jansen CT, et al. Evening primrose oil in the treatment of atopic eczema: effect on clinical status, plasma phospholipid fatty acids and circulating blood prostaglandins. *Br J Dermatol* 1987;117(1):11–9.
47. Stonemetz D. A review of the clinical efficacy of evening primrose. *Holist Nurs Pract* 2008;22(3):171–4.

48. Takwale A, Tan E, Agarwal S, et al. Efficacy and tolerability of borage oil in adults and children with atopic eczema: randomised, double blind, placebo controlled, parallel group trial. *BMJ* 2003;327(7428):1385.
49. van Gool CJ, Thijs C, Henquet CJ, et al. Gamma-linolenic acid supplementation for prophylaxis of atopic dermatitis—a randomized controlled trial in infants at high familial risk. *Am J Clin Nutr* 2003;77(4):943–51.
50. Schempp CM, Windeck T, Hezel S, et al. Topical treatment of atopic dermatitis with St. John's wort cream—a randomized, placebo controlled, double blind half-side comparison. *Phytomedicine* 2003;10(Suppl 4):31–7.
51. Kotani M, Matsumoto M, Fujita A, et al. Persimmon leaf extract and astragalin inhibit development of dermatitis and IgE elevation in NC/Nga mice. *J Allergy Clin Immunol* 2000;106(1 Pt 1):159–66.
52. Matsumoto M, Kotani M, Fujita A, et al. Oral administration of persimmon leaf extract ameliorates skin symptoms and transepidermal water loss in atopic dermatitis model mice, NC/Nga. *Br J Dermatol* 2002;146(2):221–7.
53. Qi XF, Kim DH, Yoon YS, et al. Effects of *Bambusae caulis* in Liguamen on the development of atopic dermatitis-like skin lesions in hairless mice. *J Ethnopharmacol* 2009;123(2):195–200.
54. Joo SS, Won TJ, Nam SY, et al. Therapeutic advantages of medicinal herbs fermented with *Lactobacillus plantarum*, in topical application and its activities on atopic dermatitis. *Phytother Res* 2009;23(7):913–9.
55. Fung AY, Look PC, Chong LY, et al. A controlled trial of traditional Chinese herbal medicine in Chinese patients with recalcitrant atopic dermatitis. *Int J Dermatol* 1999;38(5):387–92.
56. Zhang W, Leonard T, Bath-Hextall F, et al. Chinese herbal medicine for atopic eczema. *Cochrane Database Syst Rev* 2005;(2):CD002291.
57. Hon KL, Leung TF, Wong Y, et al. A pentaherbs capsule as a treatment option for atopic dermatitis in children: an open-labeled case series. *Am J Chin Med* 2004;32(6):941–50.
58. Hon KL, Lee VW, Leung TF, et al. Corticosteroids are not present in a traditional Chinese medicine formulation for atopic dermatitis in children. *Ann Acad Med Singapore* 2006;35(11):759–63.
59. Hon KL, Leung TF, Ng PC, et al. Efficacy and tolerability of a Chinese herbal medicine concoction for treatment of atopic dermatitis: a randomized, double-blind, placebo-controlled study. *Br J Dermatol* 2007;157(2):357–63.
60. Leung TF, Wong KY, Wong CK, et al. In vitro and clinical immunomodulatory effects of a novel Pentaherbs concoction for atopic dermatitis. *Br J Dermatol* 2008;158(6):1216–23.
61. Chan BC, Hon KL, Leung PC, et al. Traditional Chinese medicine for atopic eczema: PentaHerbs formula suppresses inflammatory mediators release from mast cells. *J Ethnopharmacol* 2008;120(1):85–91.
62. Salameh F, Perla D, Solomon M, et al. The effectiveness of combined Chinese herbal medicine and acupuncture in the treatment of atopic dermatitis. *J Altern Complement Med* 2008;14(8):1043–8.
63. Nakada T, Watanabe K, Matsumoto T, et al. Effect of orally administered Hochu-ekki-to, a Japanese herbal medicine, on contact hypersensitivity caused by repeated application of antigen. *Int Immunopharmacol* 2002;2(7):901–11.
64. Kobayashi H, Ishii M, Takeuchi S, et al. Efficacy and safety of a traditional herbal medicine, Hochu-ekki-to in the long-term management of Kikyo (delicate constitution) patients with atopic dermatitis: a 6-month, multicenter, double-blind,

- randomized, placebo-controlled study. *Evid Based Complement Alternat Med* 2008. [Epub ahead of print].
65. Makino T, Hamanaka M, Yamashita H, et al. Effect of bakumijogan, an herbal formula in traditional Chinese medicine, on atopic dermatitis-like skin lesions induced by mite antigen in NC/Jic mice. *Biol Pharm Bull* 2008;31(11):2108–13.
 66. Choi JJ, Park B, Kim DH, et al. Blockade of atopic dermatitis-like skin lesions by DA-9102, a natural medicine isolated from *Actinidia arguta*, in the Mg-deficiency induced dermatitis model of hairless rats. *Exp Biol Med (Maywood)* 2008;233(8):1026–34.
 67. Linde K, Clausius N, Ramirez G, et al. Are the clinical effects of homeopathy placebo effects? A meta-analysis of placebo-controlled trials. *Lancet* 1997;350(9081):834–43.
 68. Itamura R. Effect of homeopathic treatment of 60 Japanese patients with chronic skin disease. *Complement Ther Med* 2007;15(2):115–20.
 69. Murphy GM, Smith SE, Smith SA, et al. Autonomic function in cholinergic urticaria and atopic eczema. *Br J Dermatol* 1984;110(5):581–6.
 70. Boettger MK, Bar KJ, Dohrmann A, et al. Increased vagal modulation in atopic dermatitis. *J Dermatol Sci* 2009;53(1):55–9.
 71. Tracey KJ. Physiology and immunology of the cholinergic antiinflammatory pathway. *J Clin Invest* 2007;117(2):289–96.
 72. Wang H, Yu M, Ochani M, et al. Nicotinic acetylcholine receptor alpha7 subunit is an essential regulator of inflammation. *Nature* 2003;421(6921):384–8.
 73. Masini E, Fantozzi R, Conti A, et al. Immunological modulation of cholinergic histamine release in isolated rat mast cells. *Agents Actions* 1985;16(3–4):152–4.
 74. Haynes SN, Wilson CC, Jaffe PG, et al. Biofeedback treatment of atopic dermatitis: controlled case studies of eight cases. *Biofeedback Self Regul* 1979;4(3):195–209.