

Alternative and Complementary Treatment for Food Allergy

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KEYWORDS

- Food allergy • Complementary and alternative medicine
- Traditional Chinese medicine • Acupuncture
- Immunotherapy • Peanut

Despite increased consumer interest in complementary and alternative medicine (CAM) for the treatment of food allergy, there remains a relative paucity of knowledge regarding the clinical efficacy, mechanisms of action, and safety of most CAM treatments available to consumers. A comprehensive review of CAM for food allergy shows that Food Allergy Herbal Formulation-2 (FAHF-2), the only herbal formulation currently in phase II clinical trials, is safe and has promise to induce tolerance in food-allergic patients. Several mechanisms of action may underlie the therapeutic effect of FAHF-2 on food-induced immune responses. These include a systemic shift in T-helper 1 (Th1)/Th2 effector responses, as well as direct effects on mast cell and basophil reactivity. FAHF-2 seems to promote tolerance to food allergens without systemic immune suppression that is associated with steroids and other immune-modulating pharmaceuticals used in mainstream treatment of allergic diseases. Other novel approaches to diagnosis and treatment of food allergy are reviewed, but have not been formally validated for clinical use.

FOOD ALLERGY AND CAM

Food allergy research is receiving increased attention because of the high prevalence and severity of food-related conditions.¹ Recent efforts to develop effective treatments for food allergy have incorporated concepts from CAM and other novel avenues of immunotherapy to reduce the prevalence of food allergy and morbidity

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caused by accidental food ingestions in sensitized individuals. Current trends in the availability of herbal supplements, acupuncture, and homeopathic remedies to Western health care consumers,^{2,3} combined with new interest in the potential immune-modulating effects of these products among Western physicians,^{4,5} have led to what has been referred to as a renaissance of complementary medicine.⁶ Approximately 6 in 10 Americans report using some type of dietary supplement, and 1 in 6 Americans report using herbal remedies on a regular basis.⁷ Patients who use CAM for their allergies are younger, more educated, motivated by the assumption of few side effects, and unsatisfied with conventional medicine.⁸ In 2001, 4 procedures accounted for most of the CAM use in Europe: homeopathy (35%), autologous blood injection (28%), acupuncture (17%), and bioresonance (10%). European medical doctors provided 60% of CAM therapies and received reimbursement from insurance companies for 50% of services at a median cost of €41 (range €15–205) per treatment and €205 (range €15–1278) for a 4-treatment course.⁸ The therapeutic mechanisms, safety, and clinical efficacy of these previously non-evidence-based therapies are being tested by standards of Western medicine.⁹ Within the subspecialty of allergy, the clinical efficacy and potential mechanism of action of specific CAM components have been reported and reviewed for treatment of asthma,^{10–13} atopic dermatitis,¹⁴ and hay fever.^{10,15–18} In 2002, remedies for the treatment of food allergy accounted for 11% of CAM use reported by CAM users with allergic conditions.⁸ In 2005, 18% of patients seen in United States food allergy clinics reported using CAM for treatment of their food allergies.¹⁹ This article focuses on recent advances in CAM for food allergy, including acupuncture, herbal medicine, probiotics, and alternative approaches to allergen immunotherapy. Whereas most patients who consult practitioners of alternative allergy seek alternative treatments for established allergic diseases, others seek alternative methods of allergy diagnosis to explain clinical symptoms when conventional allergy testing is negative.²⁰ This article therefore briefly discusses the evidence for alternative approaches to the diagnosis of food allergy, but focuses on alternative approaches to the treatment of food allergy. Other novel approaches to treatment, including anti-immunoglobulin E (IgE) therapy, have been reviewed recently.^{21–23}

CURRENT CONCEPTS IN MECHANISMS OF ORAL TOLERANCE AND A ROLE FOR CAM

Food allergy results from the failure to establish oral tolerance or loss of preexisting tolerance-sustaining mechanisms. Factors central to the development of food allergy include those that promote and amplify Th2 responses in the gut, such as thymic stromal lymphopoietin (TSLP),²⁴ and factors that bypass normal gut mucosal tolerance, such as exposure to allergens through the skin or respiratory track.²⁵ Effector molecules and cellular pathways involved in oral tolerance remain areas of active investigation.^{26,27} Scientists interested in CAM have begun to investigate how CAM therapies may interact with these complex pathways to either enhance tolerant responses or reduce Th2 responses to ingested food antigens.

THE SCOPE OF CAM

Complementary medicine encompasses treatments beyond the scope of conventional allopathic medicine, including acupuncture, homeopathy, Chinese herbal medicine, Ayurveda, and other ancient Eastern traditions, as well as household remedies such as probiotics and nonpharmaceutical supplements.²⁸ In 2005 chiropractors, homeopaths, and acupuncturists provided most of the therapies for food-allergic patients seeking alternative treatments.¹⁹ CAM is currently not emphasized in the

curriculum of Accreditation Council for Graduate Medical Education–accredited training programs in allergy and immunology, even though this is a field where patients often seek or use CAM for treatment of allergic disease.^{4,5} The intrinsic barriers to measuring the efficacy of complementary medicine using evidence-based medicine include large placebo response rates, sampling error, and reduced within-group variation.²⁹ Central to understanding the medicinal benefit of many of these alternative treatments is acceptance of the relationship between the mind and body, which influence health and illness. Activation of neuroimmunomodulatory pathways has been reported to have dramatic effects on immunity, and has been suggested to explain the mechanism by which placebos exert their effects.³⁰ However, without extensive supporting data to support this mechanism, CAM treatments have been shown to improve quality-of-life scores in patients with allergic disease.³¹ This article focuses on the best scientific evidence supporting the safety, therapeutic benefit, and other plausible mechanisms of action of alternative therapies.

ALTERNATIVE APPROACHES TO DIAGNOSIS OF FOOD ALLERGY

Complementary diagnostic techniques are used mainly in food-allergy intolerance.³² At present, the only noninvestigational treatment for food allergy is strict food-allergen avoidance and prescription medicines to treat symptoms caused by accidental exposures.³³ Because strict avoidance is mandated, children with multiple food allergies can develop vitamin and other nutritional deficiencies.³⁴ These children also suffer from social isolation at school age, and psychological problems resulting in poorer overall health and limitations in social activities.³⁵ Given the known risk for social, psychological, and nutritional side effects of food avoidance, the use of unproven diagnostic tools for food allergy diagnosis is highly controversial^{19,36–39} but, nonetheless, appealing to some families. Immunoglobulin G (IgG) antibodies to food allergens likely reflect normal and potentially protective immune responses to food intake. Moreover, the measurement of food-specific IgG levels in blood as a diagnostic tool for food allergy has been disproved by double-blind placebo-controlled food challenge (DBPCFC), where no correlation was found between symptoms resulting from ingestion of the food antigens and levels of food-specific IgG or IgG4 antibodies.³⁸ Similar unproven tests in allergy diagnosis include cytotoxic food-allergy testing, leukocytotoxic testing, the provocation/neutralization sublingual or subcutaneous test, the heart-ear reflex test, hair analysis, iridology, bioresonance, electrodermal testing (electroacupuncture), reflexology, and applied kinesiology.^{32,36–38} Despite being costly to administer, these tests lack scientific rationale, are not reproducible, and do not correlate with clinical evidence of allergy.³⁸ The gold standard for food-allergy diagnosis remains positive skin-prick testing or detectable food-allergen-specific IgE antibodies in parallel with a positive food challenge or documented allergic symptoms within 2 hours of food ingestion.³³ The only evidenced exception to this is with regard to delayed IgE-mediated food allergies caused by sensitization to galactose- α -1,3-galactose (α -gal).⁴⁰ These food-allergic patients are diagnosed by positive intradermal skin tests (often negative skin-prick tests), IgE antibodies to α -gal, and clinical allergic symptoms within 3 to 6 hours of food ingestion.⁴⁰ Other established food-related conditions that cannot be tested by detection of IgE antibodies, but do improve with food-avoidance diets, include eosinophilic gastrointestinal disease, food protein-induced enterocolitis syndrome, and celiac disease.⁴¹ Although the molecular basis of food intolerance remains poorly defined, existing alternative diagnostic tests such as those mentioned earlier are unlikely to lead patients and physicians in the right direction. Rather, they may cause additional

confusion and place patients at an increased risk for the nutritional side effects associated with strict avoidance diets.

SAFETY OF CAM

Although the overall risk to public health seems to be low, certain groups of traditional remedies have been associated with potentially serious side effects.^{42,43} The Food and Drug Administration (FDA) has only recently provided a plan to begin to address issues related to manufacturing processes and quality control of the dietary supplement industry, which includes herbs and probiotics.⁷ Experience has shown that using herbal remedies without adequate thought about what the active drug components are, or their mechanism of action, may actually worsen rather than treat allergic disease.^{20,44} For example, injection of specific Chinese herbs for treatment of upper airway symptoms was reported to cause anaphylaxis,⁴³ and the use of several topical herbal remedies was reported to cause allergic contact dermatitis and, more rarely, IgE-mediated sensitization.⁴⁴ Royal jelly and propolis are honeybee products used in traditional medicine for their reported antioxidant and anti-inflammatory effects.^{45,46} Surveillance of toxicologic problems associated with the use of traditional and herbal remedies and herbal supplements between 1991 and 1997 at the Medical Toxicology Unit at Guy's Hospital, London, identified 785 adverse reactions attributed to herbal treatments among 1297 symptomatic enquiries.⁴² These complaints included liver problems after the use of traditional Chinese medicine (TCM) for skin problems, allergic reactions from royal jelly and propolis, and heavy-metal poisoning caused by remedies from the Indian subcontinent.⁴² Because of these past concerns, herbal remedies currently under investigation for the treatment of food allergy underwent extensive safety testing⁴⁷⁻⁴⁹ before attaining FDA approval for use in human clinical trials.^{50,51} Safety monitoring in murines and humans to date has shown no evidence of end-organ toxicity, heavy-metal contamination, or global immune suppression with FAHF-1 or FAHF-2 (**Tables 1 and 2**). Safety concerns regarding the health risks of acupuncture treatments in the United States, such as the potential for disease transmission through nonsterile needle use, were addressed in 1996, when the FDA removed the experimental status tag on acupuncture needles. The FDA reclassified acupuncture needles, regulating them as it does other medical devices such as surgical scalpels and hypodermic syringes. Acupuncture needles must now be manufactured according to single-use standards of sterility, and are regulated to be used by licensed practitioners. At least 40 states and the District of Columbia use an examination administered by the National Certification Commission for Acupuncture and Oriental Medicine. Studies of acupuncture for the treatment of asthma, atopic dermatitis, and allergic rhinitis remain conflicting with regard to efficacy; however, they have established the safety of acupuncture treatments by licensed practitioners, including safe use in children.^{18,52-57} In the authors' experience several patients with food allergy have anecdotally reported satisfaction and subjective benefits from acupuncture treatments, but they have not identified any published studies that formally investigate the use of acupuncture for the treatment of food allergy, nor was any published evidence identified for the use of homeopathy for the treatment of food allergy.

HERBAL MEDICINE FOR THE TREATMENT OF FOOD ALLERGY

One in 6 Americans report using herbal remedies on a regular basis,⁷ and remedies for food allergy account for 11% of CAM used for allergic conditions.⁸ Despite high consumer interest, wider acceptance into mainstream medicine has been hindered until more recently by a relative paucity of knowledge regarding the active ingredients

and mechanism of action of herbal formulations on food tolerance induction. Most of the herbal formulas studied include combinations of medical plants derived from TCM and, less often, ayurvedic medicine.⁵⁸ Food restriction for treatment of respiratory allergy has been a long-term practice in ayurvedic medicine,⁵⁹ and principles of ayurveda have been reported as beneficial for the treatment of food intolerance,⁶⁰ but the authors could not identify any study that evaluated the efficacy of ayurveda for the treatment of IgE-mediated food allergy. Based primarily on *in vitro* studies, numerous herbal formulations demonstrate the ability to modulate cytokine activity and alter both gene and protein expression, suggesting that their therapeutic efficacy may be related to such effects at a transcriptional level.⁵⁸ The most rigorous investigations of mechanism of action, identification of active compounds, and standardization of formula content for the treatment of food allergy have related to FAHF-1 and FAHF-2. Despite centuries of use of TCM for a variety of allergic conditions, modern definitions of food allergy are not described in the TCM literature.⁴⁷ Recent approaches to food-allergy treatment, which incorporate components of TCM, have shown promising results in preclinical trials in terms of both safety and efficacy. The first evidence-based report of TCM for food allergy tested in an animal model of peanut (PN) allergy was FAHF-1, developed in 2001 from a combination of herbs with anti-inflammatory and antiallergy properties.⁴⁷

Food Allergy Herbal Formula

FAHF-1 was the first TCM formulation proved to protect against PN-induced anaphylaxis in mice.⁴⁷ FAHF-2 is a refined version of FAHF-1 which lacks 2 herbs thought to be non-key herbs and potentially toxic in humans, if they are not processed correctly.⁴⁸ FAHF-2 was shown to be equally protective against anaphylaxis in PN-allergic mice⁴⁸ and is safe for food-allergic patients who are older than 12 years in clinical trials.^{50,51} The observed decrease in symptoms of anaphylaxis with FAHF-2 treatment is associated with suppression of Th2 cytokines, PN-specific IgE, histamine levels, numbers of peripheral blood basophils, and peritoneal mast cells, as well as diminished FcεRI expression on mast cells.^{48,61,62} Establishment of tolerance in PN-allergic mice was further associated with increased numbers of Th1 and mesenteric interferon-γ (IFN-γ)-producing CD8⁺ cells.⁶³ It was later shown that CD8⁺ T cells are the major source of IFN-γ and that neutralization of IFN-γ or depletion CD8 T cells attenuated the efficacy of FAHF-2.⁶¹ *In vitro*, FAHF-2 inhibits proliferation of IgE-producing B cells and mast cell activation. At the cellular level, 3 compounds in 1 of the herbs, berberine, palmatine, and jatrorrhizine, were shown to directly inhibit mast-cell degranulation by suppressing spleen tyrosine kinase phosphorylation.⁶² Because binding of monomeric IgE to FcεRI promotes mast-cell and basophil survival, the reduction in levels of PN-specific IgE associated with FAHF-2 treatment has been proposed as one explanation for the observed reduction in peripheral basophils and mast cells.⁶² Enhanced levels of IgG2a, which interfere with mast-cell degranulation by blocking FcεRI cross-linking via antigen interception, may further contribute to the FAHF-2 effects on mast cell and basophil reactivity.⁶¹ Because basophil numbers were reduced without effects on surface FcεRI expression, the potential effect of FAHF-2 on basophil survival has been proposed to be mediated through basophil survival factors, such as interleukin (IL)-3 and/or IL-33 signaling.⁶² Despite the dramatic effect of FAHF-2 on several effector immune cells, treatment with no single FAHF-2 herb alone provided full protection against anaphylaxis, indicating that the medicinal benefit of FAHF-2 likely depends on synergistic effects of each of its 11 component herbs.^{61,64} To reduce the size and dose of FAHF-2 pills for use in children, butanol extraction effectively decreased the dose by fivefold without altering its

Table 1
Preclinical trials in food-allergic mice treated with Chinese herbal medicine

Herbal Treatment	Evidence of Action	Duration of Action	Mechanism(s) of Action	Safety
FAHF-1 ^a (21 mg) given twice daily for 7 wk before oral challenge ⁴⁷	Protected mice from anaphylaxis induced by 10 mg of crude PN challenge	Single challenge at end of 7 wk therapy Peanut-specific IgE remained reduced at least 4 wk after discontinuing treatment	Reduced mast cell (MC) degranulation and histamine release Reduced peanut-specific IgE Suppressed Th2 cytokines	Therapeutic dose given for double the treatment course (14 wk) showed no damage to kidney, liver, blood cell lines, or other organs. No global immune-suppressive effect on B or T cells
FAHF-2 ^b (20 mg) given twice daily for 7 wk ⁴⁸	Protected mice from anaphylaxis induced by 200 mg of ground peanut	Protective response at 1 wk, persisted at 3 wk, and 5 wk post therapy	Blocked vascular leakage associated with anaphylaxis Suppressed Th2 responses to recall peanut stimulation	In a Lethal Dose 50 (LD50) protocol, mice were fed 12 times the daily therapeutic dose. LD50 was 24 times the therapeutic dose
FAHF-2 ^b (32 mg) given twice daily for 7 wk ⁶³	Protected mice from anaphylaxis induced by 200 mg of ground peanut	Protective response at 24 h, persisted at 4 wk post therapy	Increased peanut-specific IgG2a Increased numbers of mesenteric interferon (IFN)- γ ⁺ CD8 T cells	
Dry herb extracts equivalent to dose of herb present in the FAHF-2 ^b formula given twice daily for 7 wk ⁶⁴	FAHF-2, but none of the constituent herbs, protected 100% of mice from anaphylaxis <i>Huang bai</i> protected 25% of mice challenged	Full or partial protection was documented at 5 wk post therapy	<i>Huang bai</i> -treated mice showed reduced histamine release and Th2-cytokine production FAHF-2, but no constituent herb alone, induced a significant reduction in IgE and increase in IgG2a	

FAHF-2 ^c (32 mg) given twice daily for 7 wk ⁶¹	Protected mice from anaphylaxis induced by 200 mg of ground peanut	Full protection persisted up to 6 mo post therapy, including 6 separate oral challenges; partial protection lasted 9 mo post therapy	In vivo neutralization of IFN- γ abrogated protective effect of FAHF-2 on suppression of anaphylaxis, peanut-IgE, and Th2-cytokine production	
B-FAHF-2 ^d (12.8 mg) given daily for 7 wk ⁴⁹	Protected mice from anaphylaxis induced by 200 mg of ground peanut	Full protection persisted up to 8 mo post therapy, including 6 separate oral challenges; partial protection lasted 12 mo post therapy. A second treatment course restored protection	In vitro suppression of peanut-induced Th2-cytokine secretion and enhanced peanut-induced Th1-cytokine secretion Dose-dependent inhibition of IgE production by human B cells and inhibition of MCs	No physical, histologic, or laboratory evidence of toxicity to mice at 16 mo post treatment
FAHF-2 ^c (32 mg) given twice daily for 7 wk ⁶²	Protected mice from anaphylaxis induced by 200 mg of ground peanut	Protective response at 24 h, persisted at 4 wk post therapy	Reduced numbers of peripheral basophils, peritoneal MCs, and cutaneous MC degranulation	MC/9 mast cells remained viable with FAHF-2 (20 μ l/ml) in culture

^a Food Allergy Herbal Formula-1 (FAHF-1) contains 11 traditional Chinese medicinal herbs (*Latin name*), including fruiting body of Ling Zhi (*Ganoderma lucidum*), root of Fu Zi (*Radix lateralis aconite carmichaeli praeparata*), fruits of Wu Mei (*Prunus mume*), seed of Chuan Jiao (*Zanthoxyli bungeani*), whole Xi Xin (*Herba cum radice asari*), root of Huang Lian (*Coptis chinensis* or *Rhizoma coptidis*), bark of Huang Bai (*Phellodendron chinense*), rhizome of Gan Jiang (*Zingiber officinalis*), twigs of Gui Zhi (*Cinnamomum cassia*), roots of Ren Shen (*Panax ginseng*), and roots of Dang Gui (*Angelica sinensis*).⁴⁷

^b Food Allergy Herbal Formula-2 (FAHF-2) is a simplified formulation of FAHF-1 that lacks 2 components of the original formula, Fu Zi (*Radix lateralis aconite carmichaeli praeparata*), and Xi Xin (*Herba cum radice asari*).⁴⁸

^c On the basis of organoleptic and microscopic examination, the raw herbs used in FAHF-2 were confirmed to be 9 herbs (*Latin names*): (1) *Zanthoxylum schinifolium*, (2) *Ganoderma lucidum*, (3) *Prunus mume*, (4) *Coptis chinensis*, (5) *Phellodendron chinense*, (6) *Zingiber officinalis*, (7) *Cinnamomum cassia*, (8) *Panax ginseng*, and (9) *Angelica sinensis*. Note: *Zanthoxylum schinifolium* replaced *Zanthoxyli bungeani*.⁶¹

^d Butanol-extracted Food Allergy Herbal Formula-2 (B-FAHF-2) comprises the active ingredients in FAHF-2 concentrated to one-fifth of the effective daily dose of FAHF-2 (64 mg).⁴⁹

Table 2
Clinical trials in food-allergic patients and healthy controls treated with Chinese herbal medicine

Clinical Trial	Clinical Outcome	Tolerability	Immunologic Outcomes	Overall Safety
Phase I clinical trial: food-allergic patients treated with FAHF-2 ^a or placebo for 7 days ⁵⁰	18 food-allergic patients completed the therapy (12 received FAHF-2 and 6 received placebo)	1 FAHF-2-treated patient reported loose stools 1 subject developed a flare of underlying eczema	No change in specific IgE or skin-prick tests Reduced IL-5 in in vitro allergen-stimulated PBMC cultures in FAHF-2 treated subjects	Levels of heavy metals, pesticides, and ethanol residues were below recommended limits No serious adverse events occurred
Phase I clinical trial: 3.3 g (6 tablets) FAHF-2 ^a taken three times a day for 6 mo ⁵¹	18 food-allergic subjects enrolled; 14 subjects completed the study. Dropouts were related to noncompliance (3) and pregnancy (1)	1 subject temporarily stopped FAHF-2 because of a recurrence of eosinophilic esophagitis	Significant reduction in basophil activation markers in response to ex vivo stimulation at 6 mo	No toxicity in kidney, liver, lungs, or heart in any subjects
Phase II clinical trial: 10 tablets FAHF-2 ^a taken three times a day for 6 mo (ClinicalTrials.gov identifier: NCT00602160)	FAHF-2 and placebo-treated groups will undergo DBPC food challenges and the beginning and after 6 mo of treatment	NA	NA	Ongoing study of 68 subjects aged 12–45 years expected to end by June 2012

Abbreviations: DBPC, double-blind placebo-controlled; NA, not available; PBMC, peripheral blood mononuclear cell.

^a FAHF-2 (0.55 g per tablet), produced by Xiyuan Chinese Medicine Research and Pharmaceutical Manufacturer (Beijing, China) and was approved by the FDA. The product is composed of 9 herbal extracts (*Latin names*): (1) fruits of Wu Mei [(*Prunus mume*) or Japanese apricot, 20.0%], (2) seed of Chuan Jiao [(*Zanthoxyli bungeani*) or Pricklyash peel, 2.0%], (3) roots of Dang Gui [(*Angelica sinensis*) or Angelica root, 6.0%], (4) rhizome of Gan Jiang [(*Zingiber officinalis*) or ginger, 6.0%], (5) twigs of Gui Zhi [(*Cinnamomum cassia*) or cassia cinnamon, 4.0%], (6) roots of Ren Shen [(*Panax ginseng*) or ginseng, 4.0%], (7) bark of Huang Bai [(*Phellodendron chinense*) or Phellodendron, 4.0%], (8) root of Huang Lian [(*Rhizoma coptidis*) or Goldthread, 6.0%], and (9) Ling Zhi [(*Ganoderma lucidum*) or Reishi mushroom, 46.0%].

protective benefit.⁴⁹ At present, the immune-modulatory capacity of FAHF-2 in PN-allergic mice seems temporary, lasting 6 to 12 months post treatment, but can be restored by a second treatment course.⁴⁹ In addition to providing safety information for treatment in humans, results of phase I clinical trials support evidence of an FAHF-2-mediated immune-modulatory effect similar to the effect seen in animal models. In phase I clinical trials, patients who received 3.3 g (6 tablets) of FAHF-2 3 times a day demonstrated a significant reduction in basophil activation markers in response to ex vivo stimulation, and a downward trend in total numbers of blood eosinophils and basophils at the end of a 6-month treatment course.⁵¹ Current evidence, summarized in **Tables 1** and **2**, suggests that several mechanisms may underlie the therapeutic effect of FAHF-2 on PN-induced immune responses. These include a systemic shift in Th1/Th2 effector responses, as well as direct effects on mast cell and basophil reactivity. FAHF-2 seems to promote tolerance to PN allergen without systemic immune suppression that is associated with steroids and other immune-modulating pharmaceuticals used in the mainstream treatment of allergic diseases.

Herbal Formulations Implicated for Possible Treatment of Food Allergy

The safety of herbal agents other than FAHF-2 for the treatment of food allergy has not been tested in humans, but several reports have identified alternative formulations with potentially beneficial immune-modulatory benefits. Investigation of more than 210 crude herbal compounds used in traditional Japanese medicines (Kampo medicine) revealed only 2 functionally immune-suppressive herbs, *Notopterygii Rhizoma* and *Saussureae Radix*. Isolation of the active components of *Saussureae Radix* proved this herb to be cytotoxic; however, in an epicutaneous sensitization model, topical treatment with *Notopterygii Rhizoma* suppressed delayed-type hypersensitivity to ovalbumin (OVA). The anti-inflammatory effect of *Notopterygii Rhizoma* seems to occur via suppression of expression of inducible nitric oxide synthase and inhibition of lipopolysaccharide (LPS)-induced dendritic-cell (DC) maturation by its active component faltarindiol.⁶⁵ Kakkonto is one of the most common traditional Japanese herbal medicines, comprising seven constituents and widely used for the treatment of cold, headaches, and myalgia⁶⁶ and, more recently, proposed to be beneficial for the treatment of food allergy.⁶⁷ Pretreatment with Kakkonto of OVA-sensitized mice suppressed development of allergic diarrhea when mice were challenged with OVA. Decreased symptoms were associated with reduced mucosal mast-cell numbers and reduced Th1 and Th2 cytokines in the colon, suggesting that Kakkonto has the potential to interfere with infiltration of mast cells in the colon of food-allergic mice.⁶⁷ Quercetin, a flavonoid polyphenolic compound, was also recently proposed to have immune-modulatory effects similar to FAHF, and is being investigated as another novel therapeutic for food allergy.⁶⁸ Pentagalloylglucose (PGG) is a natural polyphenolic compound and major constituent of plant-derived tannins from *Phyllanthus emblica* L, a subtropical tree located in China, India, and Indonesia. The fruit and juice that contain PGG are reported to have anti-inflammatory properties, and have been used by local people for treatment of eczema and diarrhea.⁶⁹ In another mouse model of food allergy, PGG was shown to reduce allergic symptoms on challenge via suppression of FcεRI on mast cells in the gut.⁷⁰ Although most studies have focused on identifying the effects of herbal formulations on global Th1/Th2-cytokine-mediated effects or directly on mast cells and basophils, evidence also suggests that certain herbal formulations may exert direct effects on airway smooth muscle cells and attenuate airway constriction that accompanies food-induced anaphylaxis, a mechanism most relevant to food-allergic patients with underlying asthma.⁷¹ Herbal formulations developed specifically

for the treatment of asthma have entered clinical trials,⁷² but are beyond the scope of this article.

ALTERNATIVE IMMUNOTHERAPY

Conventional immunotherapy with food allergens has a significantly higher rate of adverse events compared with those associated with aeroallergen and insect venom, thus making the injection of crude allergen extract unsafe for the treatment of food allergy.⁷³ Current investigational approaches to food-allergen immunotherapy have begun to address this problem by creating formulations of food allergens that induce cellular mechanisms of tolerance without cross-linking IgE on the surfaces of effector cells. Suggested alternatives to the classic subcutaneous injection of whole allergen extracts include oral⁷⁴ or sublingual administration of whole allergen,⁷⁵ engineered food-allergen proteins,⁷⁶ synthetic allergen peptides,⁷⁷ and adjuvant therapy.⁷⁸

Central to understanding the mechanism of oral immunotherapy is the notion that administration of crude extracts of raw⁷⁴ or cooked⁷⁹ food allergens somehow engages the natural mechanisms of oral tolerance via the gut mucosa. The enhanced safety and efficacy of cooked food allergens for the treatment of food allergy are thought to occur because the process of heating alters allergen epitopes, making the cross-linking of IgE less efficient than in the raw form. A more refined way to reduce food-allergen reactivity is to engineer food-allergen proteins, which contain altered amino acid residues within epitope regions and thereby reduce the efficiency of the food allergen to cross-link IgE. These engineered proteins have been shown to lack the capacity to bind to IgE and, when injected subcutaneously, partially desensitize PN-allergic mice.⁸⁰ Despite the inability to cross-link IgE, these engineered proteins maintained their ability to interact with T cells and to promote tolerance via suppression of Th2 cytokines and induction of IFN- γ and transforming growth factor β .⁸⁰

Adjuvants have long been used in vaccination to promote long-term immunity against infectious diseases. More recently, their immune-activating properties have been explored for enhancing tolerant immune responses to food allergens. In the first approach, PN-sensitized mice treated with modified PN allergens in the presence of *Listeria monocytogenes* or *Escherichia coli* showed enhanced protection against anaphylaxis compared with treatment with modified PN allergen alone.⁸⁰ In the second approach, when heat-killed *E coli* (HKE) overexpressing modified PN allergens were administered to PN-allergic mice before oral food challenge, the mice showed reduced anaphylaxis symptoms and reduced plasma histamine levels that were associated with a reduction of PN-specific IgE and Th2 cytokines.⁷⁶

The mechanism by which these bacterial adjuvants enhance tolerogenic responses to food allergens likely involves activation of innate signaling pathways via toll-like receptors (TLRs) expressed on the surface of professional antigen-presenting cells. Recent work suggests that the induction of tolerance to PN using a bacterial adjuvant system depends on the ability of HKE to engage TLR signaling pathways, and that blocking TLR signaling abrogates the effect of HKE.⁷⁸

NUTRITION

The most marked change in paradigm with regard to dietary intake and food allergy is that avoidance of food allergens during pregnancy, lactation, or infancy is no longer believed to prevent allergic disease.⁸¹ Although rigorous studies of the role of nutrition and allergic disease are lacking, specific nutrients, including antioxidants, oligosaccharides, polyunsaturated fatty acids, folic acid, retinoic acid, probiotics, and other vitamins, have documented effects on immune function.⁸² A recent systematic review of evidence-related

nutritional supplements and allergic disease found epidemiologic evidence to support intake of vitamins A, D, E, and zinc; fruits and vegetables; and the Mediterranean diet for prevention of asthma.⁸³ A birth cohort of 2423 Swedish children, who started taking multivitamins before age 4 years, had a decreased risk for sensitization to food allergens, measured in blood at the age of 8 years.⁸⁴ Similarly, adults who reported higher levels of vitamin E intake had lower levels of food sensitization.⁸⁵ No prospective studies have evaluated these nutritional components for the prevention or treatment of food allergy.

PROBIOTICS AND SOY ISOFLAVONES

An extension of the use of nutrition and bacterial adjuvants for the treatment of food allergy is the use of probiotics to enhance the gut's natural microflora and engage innate signaling pathways that promote tolerance. The therapeutic benefit of soy products to protect against food-induced anaphylaxis was first demonstrated in a PN-allergic mouse model, in which oral administration of a fermented soy product (processed by a koji fungus *Aspergillus oryzae*) called ImmuneBalance reduced anaphylaxis scores in parallel with reduced plasma histamine and PN-specific IgE levels.⁸⁶ The major active isoflavones present in soybean (genistein, daidzein, and glycitein) are examples of naturally derived immunologically active compounds alleged to combat a wide variety of diseases. The role of soy in the treatment of PN allergy poses interesting questions because, in addition to the known immune-regulatory effects of isoflavones, soybean proteins share significant amino acid sequence homology to PN allergens. Nonetheless, the incidence and severity of soy allergy are far less compared with PN, and the active components of soy may prevent initiation of PN allergy or otherwise diminish responsiveness of effector cells in models of PN anaphylaxis. Dietary intake of high levels of soy has been associated with improved lung function in asthmatics.⁸⁷ In mice, genistein and daidzein supplementation before oral sensitization reduced symptoms of anaphylaxis caused by PN oral challenge by 35% to 40%.⁸⁸ In this model, the reduction in symptoms was associated with significantly reduced skin mast-cell degranulation, β -chymase release by intestinal mucosal mast cells, and allergen-specific IgE production. Furthermore, soy isoflavones were shown to inhibit human DC maturation in vitro.⁸⁸ The immune-regulatory effects of soy may include both a primary regulatory response to PN allergen and a secondary suppression of responsiveness to PN allergen exposure in sensitized patients, by attenuating the responsiveness of effector cells.

SUMMARY

Historically most of the medicines we use originate from natural products and their synthetic derivatives.¹⁵ It is not surprising, therefore, that traditional herbal formulations would contain immune-modulating characteristics and the ability to alter or suppress allergic disease at a cellular level. Compared with the long history of ancient traditions, such as TCM for a variety of other illnesses, alternative herbal therapy and immunotherapy for food allergy remains in its infancy. As evidence favoring CAM strengthens, the distinction between CAM and other novel approaches to the treatment of food allergy becomes clouded. This gray area is likely to transform into a modern era of truly integrative medicine. It is insufficient to investigate the clinical efficacy of CAM without giving priority to elucidating the mechanistic actions of these therapies. In food-allergy research, as we struggle to define the roles of specific immune cells, portals for allergen sensitization, and the role of food allergy in setting the stage for more severe allergic diseases later in life, it is important to incorporate what we learn from CAM into this paradigm.

The scope of CAM for the treatment of food allergy is slowly increasing. In addition, the scope of potential use for agents that promote oral tolerance extends beyond treatment of food allergy.⁸⁹ Similarly, health care expenditures have increased in this sector. As health care practitioners we have an obligation to our patients to understand their reasoning and interest in complementary treatments and to help them to make educated decisions about the potential risks and benefits of each. For patients with severe disease and limited conventional therapeutic options, or for those who have suffered from unwanted side effects of conventional therapies, we should break the cultural and social barriers to accessing complementary therapies that have been proved to be safe and beneficial.

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