Curr Allergy Asthma Rep (2012) 12:332–338
DOI 10.1007/s11882-012-0265-4

FOOD ALLERGY (D ATKINS, SECTION EDITOR)

Chinese Herbal Therapy for the Treatment of Food Allergy

Julie Wang · Xiu-Min Li

Published online: 12 May 2012
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Abstract Traditional Chinese medicine (TCM) has been widely used in China to treat various diseases for thousands of years. Given its reputed effectiveness, low cost, and favorable safety profile, TCM is attracting great interest in Western societies as a source of therapy for an array of illnesses, including allergies and asthma. Although food allergy has not been described in the TCM literature, a novel treatment for food allergy, named the food allergy herbal formula-2 (FAHF-2), was developed using TCM principles. Using a well-characterized murine model of peanut allergy, FAHF-2 has been shown to be highly effective in providing long-term protection against peanut-induced anaphylaxis, with a high safety margin. Phase 1 human trials have demonstrated the safety of FAHF-2 in food allergic individuals. Currently, a phase 2 trial examining efficacy of FAHF-2 is on-going. Other TCMs also show a potential for treating food allergies in preclinical studies.

Keywords Food · Allergy · Treatment · Chinese herbal medicine · Therapy · FAHF-2 · Food allergy herbal formula-2

Introduction

Food allergies appear to be increasing in incidence, with up to 8 % of the American population affected based on recent reports [1•]. The current standard of care remains strict avoidance and preparedness for allergic reactions since there is no definitive treatment available [2••]. However, efforts to develop effective methods to protect food allergic individuals from severe reactions and potentially cure them are underway. One approach that has recently been gaining interest is the use of complementary and alternative medicine (CAM). In fact, the 2007 National Health Interview Survey (NHIS) found that over 1/3 of adults and 12 % of children reported using some form of CAM (i.e. natural products, breathing exercises) in the prior year [3]. Traditional Chinese medicine (TCM) has a long history of human use and is one of the major types of CAM used in the United States. In China, TCM is routinely used as either monotherapy or complementary therapy to conventional Western therapy for a variety of chronic disorders. For example, TCM has been demonstrated to safely and effectively treat asthma in several randomized, controlled trials [4–8]. Unlike asthma, food allergy is a less frequent occurrence in China and as such, is not described in the TCM literature. Therefore, there is very little data regarding the use of TCM for food allergy. Given the reputed safety and efficacy of TCM to treat disorders such as asthma, the possibility of using a TCM herbal formula to treat food allergies is being explored.

Development of FAHF-2

Wu Mei Wan, a classical 10-herb formula, was the basis for the development of an herbal formula for food allergies. This formula is known to effectively treat intestinal parasite infections and gastrointestinal disorders with symptoms similar to food allergy and gastroenteritis [9]. Ling Zhi (*Ganoderma Lucidum*), a herb known to have significant anti-inflammatory and anti-allergy effects, was added [10,

J. Wang (✉) · X.-M. Li
Division of Allergy and Immunology, Department of Pediatrics, Mount Sinai School of Medicine,
One Gustave L. Levy Place, Box 1198, New York, NY 10029-6574, USA
e-mail: julie.wang@mssm.edu

X.-M. Li
e-mail: xiu-min.li@mssm.edu

11], and this 11-herb formula was named food allergy herbal formula-1 (FAHF-1). Subsequently, two herbs (Xi Xin [Herba cum radice asari] and Zhi Fu Zi [Radix lateralis aconiti carmichaeli praeparata]) that may be potentially toxic if improperly processed were removed. This final 9-herb formula was named food allergy herbal formula-2 (FAHF-2); the herbal constituents are shown in Table 1. Although FAHF-2 is a new herbal product, all herbs in FAHF-2 have a long history of human use and are widely used today in China, Japan, and Korea and are also currently marketed in the United States. Clinical studies have demonstrated the beneficial effects of *Wu Mei Wan* with or without modification on various diseases, including gastroenteritis and asthma, and no adverse effects were reported [12]. Ling Zhi has been shown to be beneficial for several chronic inflammatory conditions, including chronic bronchitis, bronchial asthma, and allergic rhinitis [13, 14].

All herbs originate from China and are inspected for identity and quality by licensed pharmacists in China. A standardized manufacturing process ensures the quality of the final product, which is analyzed for contaminants and monitored for consistency using HPLC fingerprinting (Fig. 1).

Dietary Supplement and Botanical Drug Development

TCM therapy, including herbal medicines and acupuncture, is a part of mainstream medical practice in China, Japan and Korea and is being used more and more in the United States. Acupuncture needles have been approved by the U.S. FDA as medical devices. Chinese herbal medicines are currently viewed as dietary supplements, and their cost is not covered by medical insurance. However, this situation may change in the future. In recent years, the U.S. FDA has provided guidance for investigating botanical drug products, including complex formulas containing several herbs, focusing on efficacy, safety and consistency. The National Institutes of Health/National Center for Complementary and Alternative Medicine (NIH/NCCAM) provides grants to support clinical and basic research on CAM, including herbal medicines. Thus, some Chinese herbal medicines may become prescription botanical drugs if sufficient evidence on safety and efficacy is demonstrated in appropriate clinical trials. FAHF-2 has received approval as an investigational new drug (IND) by the U.S. FDA, and a phase 2 clinical trial is on-going. This review will focus on the evidence-based research investigating FAHF-2 for the treatment of food allergy. In addition, there are other TCM and TCM derivatives that show potential for treating food allergy.

Table 1 FAHF-2 herbal constituents. Organoleptic, macroscopic, and microscopically characterized herbal materials used in FAHF-2 were identified as the *Prunus mume* fruit (Wu-Mei), *Zanthoxylum schinifolium fruit skin* (Chuan-Jiao), *Angelica sinensis* root (Dang-Gui), *Zingiber officnale* rhizome (Gan-Jiang), *Cinnamomum cassia* twigs (Gui-Zhi), *Phellodendron chinense* bark (Huang-Bai), *Coptis chinensis rhizome* (Huang-Lian), *Panax ginseng root* (Hong-Shen), and *Ganoderma lucidum* fruiting body(Ling-Zhi)

Chinese Pinyin	Pharmaceutical name	Genus	Species
Wu-Mei	Fructus Pruni Mume	*Prunus*	*mume*
Chuan-Jiao	Percarpium Zanthoxyli Bungeani	*Zanthoxylum*	*bungearnum*
Dang-Gui	Radix Angelicae Sinensis	*Angelica*	*sinensis*
Gan-Jiang	Rhizoma Zingiberis	*Zingiber*	*officinale*
Gui-Zhi	Ramulus Cinnamomi Cassiae	*Cinnamomum*	*cassia*
Huang-Bai	Cortex Phellodendri	Phellodendron	amurense
Huang-Lian	Rhizoma Coptidis	*Coptis*	*chinensis*
Hong-Shen	Radix Ginseng	*Panax*	*gensing*
Ling-Zhi	Ganoderma	*Ganoderma*	*lucidum*

Pre-Clinical Studies of FAHF-2

Using a well-characterized murine model of peanut allergy, FAHF-2 treatment protected peanut allergic mice from anaphylaxis when orally challenged with peanut [15]. Similar efficacy was seen when FAHF-2 was administered to mice with established peanut allergy [16]. These clinical effects were persistent for 6 months after discontinuation of treatment, which represents about 25 % of the life-span of the mouse [17]. This was associated with suppression of peanut-specific IgE and enhancement of peanut-specific IgG2a levels. Furthermore, suppression of Th2 cytokine (IL-5 and IL-13) production and increased interferon-gamma production by splenocytes and mesenteric lymph node cells were found. These immunologic effects persisted for 6 months after FAHF-2 treatment was discontinued (Fig. 2).

The mechanisms underlying these protective effects are not yet fully understood. However, it is evident that FAHF-2 exerts multiple immunologic effects. Mechanistic studies have shown that up-regulation of interferon-gamma primarily by CD8+ T cells is associated with FAHF-2 induced tolerance [16, 17]. Mice receiving T-cell depleting antibodies or interferon-gamma-neutralizing antibodies did not show suppression of IgE and Th2 cytokine production after FAHF-2 treatment, but the protection from anaphylactic symptoms still persisted for 4 weeks, suggesting that additional immunologic effects are involved.

Subsequent experiments showed that FAHF-2 also has effects on mast cells and basophils [18]. Not only was a reduction in the number of peripheral blood basophils and peritoneal mast cells found, but there was also a notable decrease in percent of degranulated cutaneous mast cells in

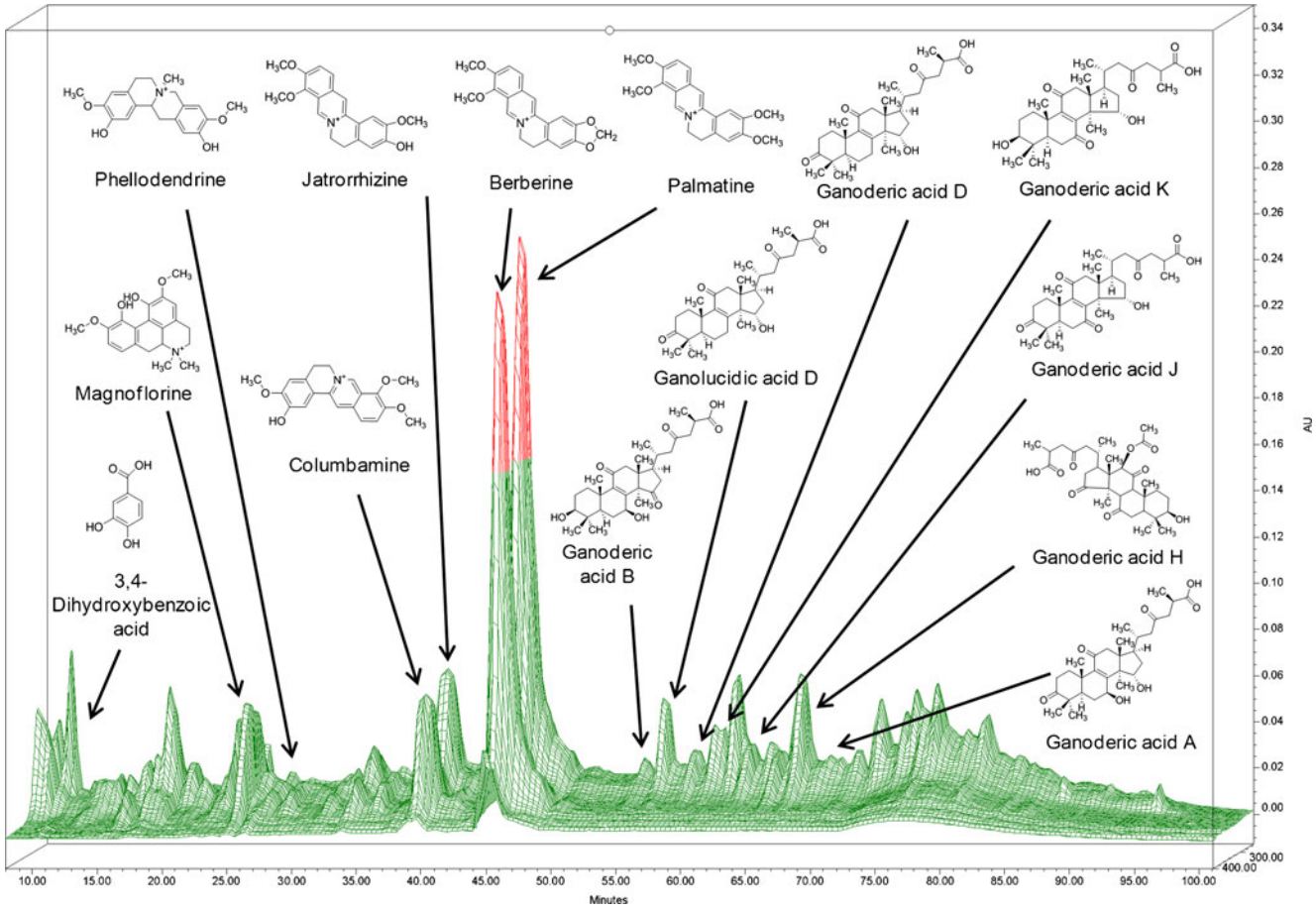

Fig. 1 A 3D HPLC fingerprint of B-FAHF-2. Thirteen components were characterized by LC-MS analysis based on molecular weights as compared to the references (Reprinted from [25], with permission John Wiley and Sons)

skin samples following oral peanut challenge 4 weeks post-FAHF-2 therapy, demonstrating suppression of IgE-mediated mast cell activation. Decreased expression of the high affinity IgE receptor (FcεRI) by peritoneal mast cells, but not basophils, was also observed. Since monomeric IgE binding to the FcεRI has been shown to promote murine mast cell and basophil survival and function, the decrease in mast cell numbers may be in part due to suppression of IgE production via interferon-gamma related mechanisms since interferon-gamma is known to reduce IgE production [19] and Th2 cytokine production [20]. Additional studies using a mast cell line (MC/9 cells) demonstrated that FAHF-2

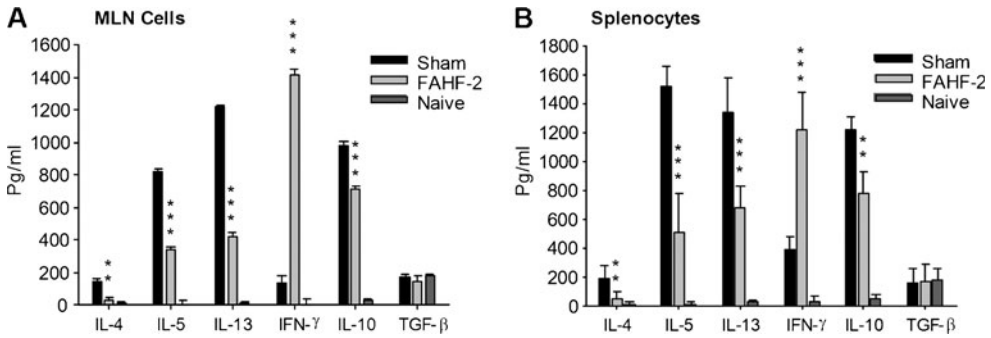

Fig. 2 FAHF-2 treatment reduced Th2 cytokine levels and increased IFN-γ secretion. Mesenteric lymph node (MLN) cells and splenocytes (SPC) were collected from each group of mice immediately following evaluation of clinical effect and blood drawing following the 7th challenge (week 50). Single MLN cells and SPCs were prepared and stimulated with crude peanut extract (CPE) for 72 hours. Cytokines in MLN culture supernatants (**a**) and SPC culture supernatants (**b**) were measured by ELISA. Data are shown as means ± SEM of pooled cultures from representative of one of two experiments measured in triplicate (n=5 mice per group). (Reprinted from [17], with permission from Elsevier)

treatment resulted in a significant reduction in IgE-induced FcεRI expression, FcεRI γ mRNA subunit expression, proliferation, and histamine release upon specific antigen challenge. These immunomodulatory effects likely contribute to the persistence of FAHF-2 protection against peanut-induced anaphylaxis.

The safety of FAHF-2 was demonstrated by administering 24 times the effective daily dose to mice (the maximal dose that could be fed to the mice) [14]. No signs of acute toxicity or abnormal laboratory values were seen within 2 weeks after the dose, and all mice appeared healthy. In addition, the histology of the major organs revealed no abnormalities.

Studies have also been performed to demonstrate the synergistic effect of using all nine herbs in this formula. In a series of experiments in which mice were treated with either the FAHF-2 formula or individual FAHF-2 herbs, mice treated with the individual herbs did not show the same level of protection from peanut-induced anaphylaxis as compared to those receiving the complete formula [21]. In addition, none of the individual herbs was as effective as FAHF-2 in suppressing Th2 responses (IgE, Th2 cytokines) and enhancing Th1 responses (IgG2a, interferon-gamma). A simplified formula using the three most effective herbs also did not achieve the same level of protection or immunomodulation as FAHF-2. These results demonstrated that the FAHF-2 formula, although more complicated, has advantages over using individual herbs or formulas with fewer herbs. Therefore, all subsequent studies used the nine-herb formula.

A major benefit of this formula is that, unlike immunotherapy, the effects are not allergen specific. In a murine model of multiple food allergies (peanut, codfish, and egg), similar protection from allergen-induced anaphylaxis was seen when the mice were challenged with these individual foods [22]. This protection was accompanied by a reduction in allergen-specific IgE, suppression of allergen-stimulated Th2 cytokine (IL-4 and IL-13) production, and increased levels of interferon-gamma by splenocytes and mesenteric lymph node cells from the FAHF-2 treated mice. If these effects also occur in humans, FAHF-2 may prove to be more advantageous than current oral or sublingual single food immunotherapy.

Clinical Studies of FAHF-2

Given the efficacy and safety of FAHF-2 in the murine model, the U.S. FDA approved FAHF-2 as an investigational new drug (IND 77,468) in 2007. The first human study was an acute phase 1 trial investigating the safety of FAHF-2 in food allergic individuals [23•]. Eighteen subjects between 12 and 45 years of age with allergies to peanut, tree nut, fish, and/or shellfish were enrolled in this double-blind, placebo-controlled dose escalation trial. Subjects received 4, 6, or 12 tablets three times a day for 7 days. All doses of FAHF-2 were well-tolerated, and no significant adverse effects were observed.

Long-term safety and tolerability were then assessed in an extended phase 1 trial [24•]. In this open label study, subjects received six tablets three times a day for 6 months. Eighteen food allergic individuals were enrolled and 14 completed 6 months of treatment. FAHF-2 was well-tolerated, and no significant adverse effects were seen. Four subjects withdrew from the study—one for pregnancy, two for difficulty with adherence, and one for transient abdominal complaints without vomiting or diarrhea.

Although these phase 1 studies investigated only safety, correlative studies were performed to determine whether evidence of immunomodulation could be detected with FAHF-2 treatment. While no significant changes in prick skin test wheal sizes or allergen-specific IgE levels were seen, suppression of allergen-stimulated basophil activation was observed after 6 months of FAHF-2 treatment. Trends for decreased percentages of basophils and eosinophils in the peripheral blood were observed as well.

Currently, a multi-center phase 2 clinical trial to investigate the efficacy of FAHF-2 in the treatment of food allergies is ongoing (Clinicaltrials.gov identifier: NCT00602160).

Future Directions

Refined FAHF-2

A major limitation of the current formulation of FAHF-2 is the inconveniently high daily dose. Therefore, a refined FAHF-2 formula using butanol purification (B-FAHF-2) has been developed [25•]. Using the previously described murine model of peanut allergy, B-FAHF-2 achieved the same level of protection from peanut induced anaphylaxis in treated mice while using 20 % of the dose of the original FAHF-2. The protective effects persisted up to 6 months after discontinuation of treatment, and the protection was re-established with a second course of treatment (Table 2 and Fig. 3). Furthermore, the safety and immunologic profiles were comparable to FAHF-2. Given these promising results, studies investigating the safety and efficacy of B-FAHF-2 in humans are planned.

Identification of Active Compounds

Another method to decrease the daily dose of FAHF-2 would be to identify and administer the individual active compounds. B-FAHF-2 was separated into four fractions based on polarity by preparative high performance of liquid

Table 2 B-FAHF-2 provided prolonged protection against anaphylaxis to multiple peanut challenges *in vivo*. Anaphylactic reactions were scored 30 minutes following each oral peanut challenge. Data are shown as number of reactions/total and group score medians with range in parenthesis. Challenges up to week 50 (36 weeks post B-FAHF-2 therapy) indicate responses after the first course of treatment. Challenge at week 65 was administered 4 weeks after the second course of B-FAHF-2 treatment. (Reprinted from [25], with permission from John Wiley and Sons)

Course of Treatment	Challenge (time-point)	PNA/sham		PNA/B-FAHF-2		Naive	
		N/total	Score [median (range)]	N/total	Score [median (range)]	N/total	Score [median (range)]
First	1st (W14)	8/8	3 (2–4)	0/8	0 (0)*	0/10	0, (0)
	2nd (W18)	8/8	3.5 (3–4)	0/8	0 (0)*	NC	NS
	3rd (W22)	8/8	3.5 (3–4)	0/8	0 (0)*	NC	NS
	4th (W28)	8/8	4 (3–4)	0/8	0 (0)*	NC	NS
	5th (W34)	8/8	4 (3–4)	0/8	0 (0)*	NC	NS
	6th (W40)	8/8	4 (3–4)	1/8	0 (0–2)*	NC	NS
	7th (W50)	8/8	4 (3–4)	4/8	0 (0–2)*	0/10	0 (0)
Second	8th (W65)	8/8	4(3–4)	0/8	0 (0)*	0/10	0 (0)

NC not challenged, *NS* not scored, *PNA* peanut allergic

*$p<0.05$ vs sham

chromatography (prep-HPLC): fraction 1 = water soluble compounds, fraction 2 = mainly alkaloids, fractions 3 and 4 = mainly flavonoids and terpenoids [18]. Using the β-hexosaminidase assay to assess RBL-2 H3 mast cell degranulation, fraction 2 was found to significantly inhibit degranulation. Experiments were also performed using human skin mast cells; fraction 2 significantly inhibited human skin mast cell degranulation triggered by IgE cross-linking and C5a.

Three major alkaloid compounds were identified using liquid chromatography mass spectrometry, jatrorrhizine, palmatine, and berbine [18]. These compounds were individually tested using the β-hexosaminidase assay, and significantly inhibited degranulation in a non-toxic, dose-dependent manner. Additional studies were performed to determine the combined effect of these three compounds on Syk signaling, an IgE-mediated FcεRI early signaling event required for degranulation. Decreased Syk phosphorylation was seen in antigen-stimulated RBL-2 H3 cells, which was not due to inhibition of IgE binding to cells.

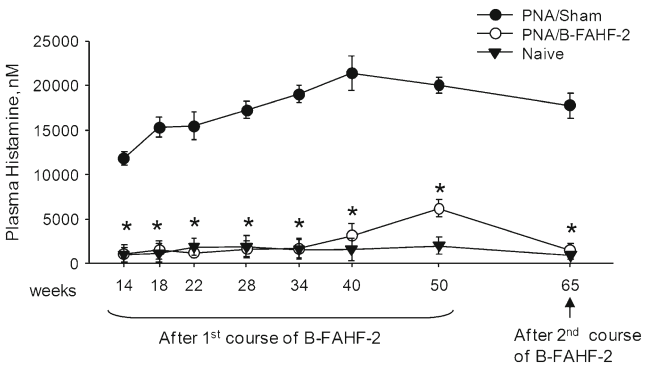

Fig. 3 B-FAHF-2 blocked histamine release following multiple peanut challenges. Blood were collected 30 min following each challenge as indicated. Plasma histamine levels were determined by ELISA (B). Initial B-FAHF-2 was administered from week 8 to week 14, and retreatment was from week 52 to week 62. Data shown as means ± SEM of each group; n=8–10. *$P<0.05$ vs sham. (Reprinted from [25], with permission from John Wiley and Sons)

Other Preclinical Studies of Potential Herbal Medicine Therapies for Food Allergy

Kakkonto

Kakkonto is a Japanese-Chinese herbal formula composed of seven medicinal plants (based on Kampo medicine). Yamamoto et al. [26] tested the effect of kakkonto in a murine model of food allergy (ovalbumin [OVA]) with gastrointestinal symptoms. Kakkonto treated mice had a significant reduction in OVA-induced diarrhea. Although no difference in OVA-specific IgE levels were observed between mice receiving kakkonto and untreated mice, the number of mucosal mast cells was reduced in the proximal colons of mice that received kakkonto.

Qian Cao (*Rubia cordifolia)* and Qu Mai *(Dianthus superbus)* Extracts

Seventy herbal extracts were tested for their ability to reduce IgE secretion by the human B-cell line (U266). *Rubia cordifolia* and *Dianthus superbus* extracts potently inhibited IgE production in vitro in a non-toxic manner [27]. Potential effects of both extracts were then tested in a murine model of peanut-induced anaphylaxis. Both extracts reduced

peanut-specific IgE levels in a dose-dependent manner, but not peanut specific IgG_1 levels. *Rubia cordifolia* and *Dianthus superbus* treated mice also exhibited significantly lower anaphylaxis symptom scores and reduced plasma histamine levels following peanut challenge [27].

Conclusions

Recently, interest in TCM as potential alternative or complementary treatments for various diseases has been increasing. The food allergy formula (FAHF-2) has demonstrated a very promising role as a novel treatment for food allergy. Clinical trials examining the efficacy of this treatment and the mechanisms of these effects are on-going. Furthermore, efforts to identify the active components and simplify the formula are also under way. FAHF-2 and perhaps other TCMs may have the potential to be safe and effective treatments for food allergies.

Acknowledgments Julie Wang, MD is funded in part by a grant from the National Institutes of Health/National Institute of Allergy and Infectious Diseases (K23 AI083883).

Xiu-Min Li, MD is funded in part by grants from the National Institutes of Health/National Center for Complementary and Alternative Medicine (1R01AT001495-01A1 and 2R01AT001495-05A1), Food Allergy Initiative, and the Winston Wolkoff Integrative Medicine for Allergy and Immunology Foundation.

Disclosure No potential conflicts of interest relevant to this article were reported.

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