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Regional Differences in Food Allergies

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Abstract
The prevalence of food allergies is increasing worldwide. To understand the regional specificities of food allergies and develop effective therapeutic interventions, extensive regional epidemiological studies are necessary. While data regarding incidence, prevalence, regional variation, and treatment in food allergies are available for western countries, such studies may not be available in many Asian countries. China accounts for almost 20% of the world's population and has a vast ethnic diversity, but large-scale meta-analyses of epidemiological studies of food allergy in China are lacking. A literature search revealed 22 publications on the prevalence of food allergy in Chinese populations. A review of these studies showed that the prevalence of food allergies in China is comparable to that in western countries, even though the Chinese diet is vastly different from that of the West and may vary even greatly within China, and finally, specific antigenic triggers of food allergy vary between China and the West and also within China. Current clinical management of food allergy in China includes allergen-specific immunotherapy, Chinese herbal medicine, acupuncture, and Western medicine. This study demonstrates an unmet need in China for a thorough investigation of the prevalence of food allergies in China, the specific foods involved, and characterization of the specific antigenic triggers of food allergy with respect to ethnicity, age, and diet in China.

Keywords Food allergy · Prevalence · Incidence · Type · Therapy · Immunotherapy

Introduction

Food allergies are much better appreciated throughout the world due to the increasing incidence, especially in developed countries. In Western countries, food allergies affect nearly 5% of adults and 8% of children [1]. The emotional, social, and financial toll of food allergies greatly affects the quality of life in patients with food allergy and their families [2]. In the USA, food-induced allergic reactions and anaphylaxis incur enormous health care costs [3]. The prevalence of food allergy is expected to rise with industrialization in many parts of the world, including China [4]. While there are many studies on the prevalence of food allergies, triggering foods, and treatment in Western countries, similar data is lacking in China. China is a vast country with an area of 9.6 million km^2 and over 1.3 billion inhabitants, comprising around 20% of the

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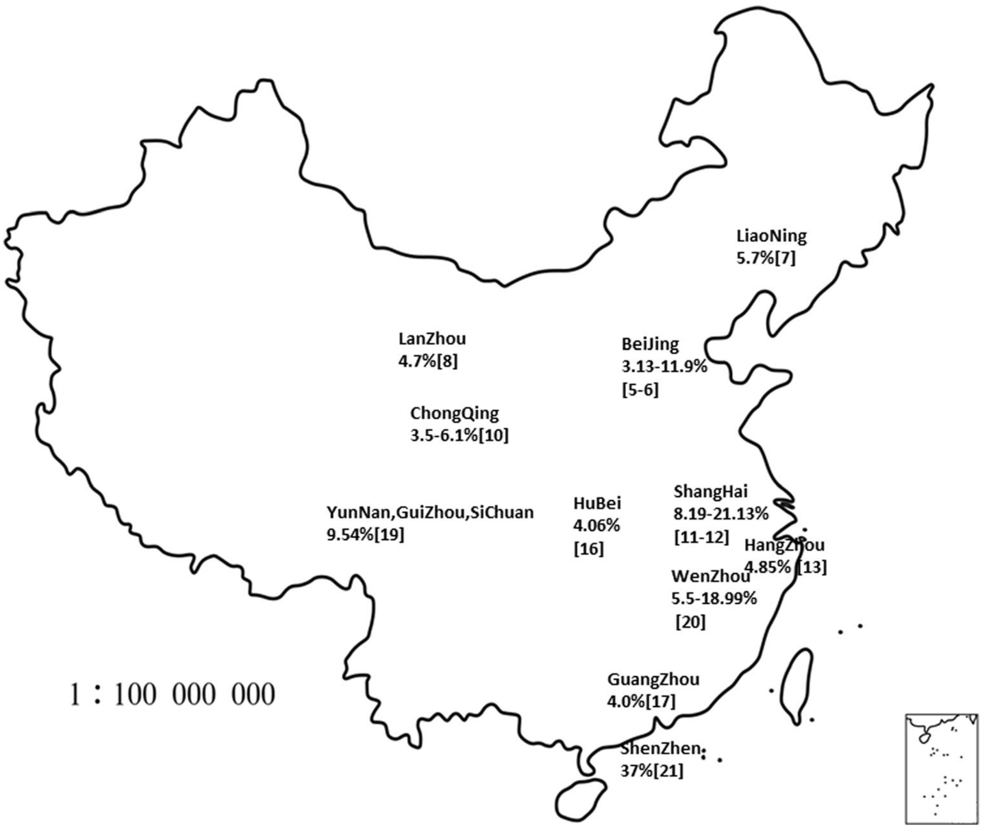

Fig. 1 Geographical distribution of the prevalence of food allergy in China

world's population. Knowledge of food allergy in China is an important factor in global public health.

Since 2000, there have been more than 2800 publications on food allergy in China (Fig. 1). However, studies on the prevalence rate of food allergy in China are scarce. We report our analysis of 22 studies published since 2000 on the prevalence of food allergy across China by region, age groups, and study methods. Firstly, the prevalence of food allergy was compared between northern and southern regions, which are divided by the Qinling Mountains and the Huaihe River. The studies included the following cities: Beijing, Shenyang, Lanzhou, Shanghai, Hangzhou, Chongqing, Chengdu, Wenzhou, Shenzhen, Zhuhai, Shaoguan, Suzhou, and Guangzhou. The provinces studied included Hubei, Yunnan, Guizhou, Sichuan, Liaoning, and Hebei. Secondly, populations were categorized into infants (0- to 1-year-old), toddler (1–3 years), preschool-aged children (3–6 years), school children (6–18 years), and adults (> 18 years). Data for infant populations was more abundant than that for older age groups. Thirdly, four different methods were utilized in these studies, including questionnaires (37%), skin prick tests (16%), food-specific IgE (11%), and food challenges (26%). Furthermore, data on the prevalence of food allergy by region, age group, and investigation method were analyzed to determine the major food allergens across the Chinese population. Common food allergens differ between the northern and southern regions of China due to differences in diet. Diets in the north are wheat-based, including coarse grains and mixed cereals (e.g., buckwheat, oat, corn, barley, purple rice). In the south, rice is the staple with a much more varied diet including seafood and tropical fruits. Finally, we also report on the current and upcoming treatment modalities for food allergies in China.

Geographical and Age Distribution of Food Allergies in China

The prevalence of food allergy varies greatly between different regions in China. Table 1 summarizes the prevalence of food allergies in China according to province, age group, investigational method, and allergenic food. The prevalence of food allergy ranges between 3.13–11.9% in the north [5–8] and 3.5–21.13% in the south [9–21]. The prevalence on a report of food allergy in three Chinese cities among children between 0 and 2 years old was 7.3%, 5.8%, and 5.6% with a mean prevalence of 6.2% [9], which is higher than the 3.5–5.2% among children in Chongqing [10]. The prevalence of food allergies also varies depending on the study method, for example, the prevalence of food allergy in Beijing was found to be 3.13% by skin prick test and 8.2–11.9% by questionnaire [5, 6], and in Shanghai, 8.19% by skin prick test and 21.13% by questionnaire [11, 12]. The food allergy prevalence rates also differ with age groups. It ranges from 3.5–18.99% in

Table 1 The prevalence of food allergies in China

	Province/city	Year	Age of subjects	Number of cases	Study population	Study method	Prevalence rate	Allergic food	Year of publication	Author
1 [9]	Chongqing, Zhuhai, Hangzhou	2009, 1-2; 2010, 1–5	0–2 years old	1687	Normal infant for physical examination	Questionnaire, prick test, challenge test	7.3%, 5.8%, 5.6%	Egg, milk, shrimp, fish	2012	Chen J, Liao Y
2 [10]	Chongqing	1999, 5–6	0–24 months old	314	Normal infant for physical examination	Questionnaire, prick test, exclusion test challenge test	3.5–5.2%, 6.1% for 0–12 months	Egg, milk, soybean, peanut, fish, orange	2000	Yan,H. Qi, H.
3 [5]	Beijing	2009	6–11 years of age	10,672	Random sampling	Questionnaire	8.2–11.9%	Shrimp, mango, crab, peach, egg, mutton, milk	2009	Ma Y, Fang JL
4 [6]	Beijing	2012	0–14 years of age	13,631	Cluster sampling	Questionnaire, prick test	3.13%	Mango, peach, pineapple, milk, egg	2012	Shao M. J, Liu C.H.
5 [7]	Liaoning	2005	15–24 years of age	4052	Random	Questionnaire, prick test	5.7%	Seafood, milk, egg	2005	Lu, X. Z, Liu X.M.
6 [8]	Lanzhou	2012	0–14 years of age	3802	/	Questionnaire	4.7%	/	2012	Lei H. Y, Xiao D.C.
7 [11]	Shanghai	2013	Senior high school student	2626	Random and cluster sampling	questionnaire	21.13%	Seafood, fruits	2013	Mo F, Tan Y.T.
8 [12]	Shanghai	2007–2008	2 months to 17 years of age	720	Atopic patients	Medical history, prick test, exclusion test, challenge test	8.19%	Egg, milk, shrimp, fish	2009	Zhang Z, Chen T.X.
9 [13]	Hangzhou	2010, 2–5	0–3 years of age	548	Normal infant for physical examination	Questionnaire, prick test, exclusion test, challenge test	4.85%	Egg white 2.80%, egg yolk 1.12%, milk 0.75%, shrimp 0.56%, fish 0.19%	2012	Zhao H, Li Z.Y.
10 [14]	Panzhihua	2010–2012	0–3 years of age	1387	Random	Questionnaire, physical examination, prick test, exclusion test, challenge test	7.58%	Egg, milk, fish, shrimp, peanut, walnut, orange	2013	Zou Y, Xu Y.L.
11 [15]	Wenzhou	2009	16–25	2042	Retrospective review	Questionnaire	5.5%	/	2010	Ye Z, Qian Y.
12 [16]	Hubei	2011, 6–12	6–9 months old	626	Medical examination and random sampling	Questionnaire, prick test, exclusion test	4.06%	Milk, egg, peanut, sea-fish, sea-shrimp, soybean	2012	Jin Y, Xiong Z.G.
13 [17]	Guangzhou	2012, 1–7	4.6 ± 1.1 years of age	2540	Random and cluster sampling	Questionnaire	4.0%	Shrimp, crab, mango, milk, egg, peanut, soybean, nut	2015	Zeng G. Q, Luo J.Y.
14 [18]	Shaoguan	2010	5–14 years of age	5596	Rural pupils	Questionnaire, prick test, EOS		Shrimp, crab, fish, oyster, mango	2010	Min H, Xiao P.W.
15 [19]	Southwest area Yunnan, Guizhou, Sichuan	2011, 3–7	6–24 months old	3344	Stratified and cluster random sampling	Questionnaire	9.54%	Fish, shrimp, egg, milk, fruit (mango, apple, orange, litchi)	2013	Wang Y, Rui S.

Table 1 (continued)

	Province/city	Year	Age of subjects	Number of cases	Study population	Study method	Prevalence rate	Allergic food	Year of publication	Author
16 [20]	Wenzhou	2012–2013	0–36 months old	237	Child patients with digestive diseases	Questionnaire, sIgE, exclusion test	18.99%	Milk, egg	2015	Lu H. J, Zhao Z.Y.
17 [21]	Shenzhen	2007–2011	3.5–4 years of age (median age)	2986	Suspected allergic children patients	sIgE	37%	Egg, milk, wheat, peanut, soybean	2014	Wang H. P, Zheng Y.J.
18 [23]	9 areas (Beijing, Suzhou, Guangzhou, Zhengzhou, Chengdu, Lanzhou, Shenyang) and Nanhe county and Xingtai county of Xingtai City in Hebei	2015	3–12 years of age	1792	Multiple-stage cluster sampling	Questionnaire	8.4%	Seafood, fish, egg, fruit, milk	2015	Zhang Y. R, Chen Y.
19 [24]	China	2015	3–12 years of age	5190	Serum bank of Survey on nutrition and health status of Chinese residents	IgE checked by enzyme immunosorbent assay, sIgE checked by immunoblotting	3.2%	Milk, egg white, beef, nut	2015	Hu Y. C, Wang R.

children between 0 and 3 years old [9, 10, 13, 14, 16, 19, 20], 4.0–37% in children between 3 and 6 years old [17, 21], and 5.5–21.13% among those 6–18 years old [5, 7, 11, 15]. The wide range of results indicates the geographical variation of food allergy in China. Data in adults was not available. As tolerance to certain foods increases with age, food allergy disorders generally become less frequent [22]. The development of tolerance is a complex process involving both host and food factors and may be affected by timing, other exposures, and genetic predisposition.

The prevalence rates of food allergy can also vary greatly by study method. The prevalence of food allergy was 4.0–21.13% when determined by questionnaires, which accounted for 37% of the publications [5, 8, 11, 15, 17, 19, 23]. The prevalence rate determined by skin prick tests was 3.13–5.7%, which constituted 16% of the studies [6, 7, 18]. The prevalence rate was 3.2–37% by food-specific IgE test, which comprised 11% of the studies [21, 24]. The prevalence rate was 3.5–8.19% by food challenge tests, which accounted for 26% [9, 10, 12–14]. The prevalence rate determined by the questionnaire was higher than that by the prick test, serum IgE, and oral challenge tests, a finding that is inherently intuitive and confirmed in many studies from other countries as well. Self-reporting tends to overstate the prevalence of food allergies, resulting in a higher prevalence rate [25]. Since food allergy is the result of a dysfunctional immune response, it is likely to be more common in atopic individuals.

The prevalence of food allergy in some other Asian communities has been reported (Table 2). For example, the prevalence of food allergy is 4.62% in Hong Kong, 3.44–7.65% in Taiwan, 5.26% in Korea, 4.9% in Japan, and 1.11% in Thailand [26–31]. For comparison, the overall prevalence of food allergy is reported to be 6.3–8.6% in the USA, 2.26% in Denmark, and 2.9% in the UK [32–34]. As expected, the prevalence rates vary greatly due to differences in study design, population, and diet. The wide discrepancies in prevalence rates in China could be related to its vast territory, large population, and diverse food cultures.

Allergenic Foods in China

China is a country of nearly 3,700,000 mi^2 with a population of over 1.410 billion and enormous diversity in ethnic groups, culture, and dietary practice. Here, we will highlight the most studied food allergens and their occurrence among the diverse Chinese populations. Allergenic foods in China differ by age group and region. Globally, the most common food allergens among children are eggs, milk, and peanut. As children grow to consume greater variety of foods, they may develop nut and seafood allergies as well. Accordingly, seafood, fruit, and mutton allergies are more typical among adults. The situation is similar in China. For example, in China, the prevalence of fish allergy is relatively higher in adults (1.17%) than in children (0.17–0.49%) [9, 27]. Egg allergy is more common in younger children, simply because the majority of pediatric patients with egg allergy develop tolerance to egg over time [35].

Egg

A food challenge-confirmed allergy study conducted in three cities in China reported that the prevalence rate of egg allergy ranges from 3 to 4.4% in children under 2 years old [9]. This is higher than the challenge-confirmed prevalence rate for egg allergy in western countries, which ranged from 1 to 1.6% [36]. The higher prevalence in this study may be explained by the inclusion of non-IgE-mediated food sensitivity.

Cow's Milk

Cow's milk allergy (CMA) is the second leading source of food allergy in younger children. The oral food challenge (OFC)–proven prevalence rate in large cities was 1.3% in children below 1 year old and 0.83–3.5% in children under 2 years old. However, these studies included non-IgE-mediated reactions to cow's milk [37] as well as symptoms that were reported up to 72 h after the challenge test. An expert-screened questionnaire survey in Taiwan estimated that the prevalence of IgE-mediated CMA was 1.1% in children under 3 years old [27], and another study in Hong Kong reported CMA is present in 0.9% of children from 2 to 7 years old [38].

Peanut

Although peanut allergy is common in western countries, it is much less observed in China. The estimated prevalence of peanut allergy was reported to be 0.52% in Hong Kong, 0.48–1.1% in Taiwan, and only 0.17% in Zhuhai [9, 26, 27]. These rates are significantly lower than in the USA (0.6–2.7%) [39] and the UK (1.2–3.3%) [34]. One reason for the lower prevalence in China is that peanuts are not commonly consumed throughout the country. In addition, differences in the preparation of peanut may account for the lower prevalence of peanut allergy in China [40]. Chinese generally boil or fry whole peanuts, which can destroy their allergenicity. On the other hand, roasting peanuts, such as for peanut butter in western countries, can increase allergenicity via the Maillard reaction [40]. It is also likely that Chinese parents tend to expose their children to peanuts at an older age (> 1 year old) when their intestinal immune barrier is better developed. This seems to run counter to the newest recommendation in the Western world to encourage early introduction of peanuts to prevent the development of allergy to peanuts, but the fact is that the development of tolerance is not simply a matter of early introduction. There are many other factors that can dictate whether or not an individual may acquire tolerance including the timing of first introduction, genetic factors, how the food is prepared, and concurrent exposures.

Wheat

Wheat is a dietary staple in northern China [41] and is also increasingly consumed as a health food in this region. Wheat allergy is common in northern China and fatal anaphylaxis has been reported [42]. Buckwheat is an unconventional food allergen in the west. Although the prevalence of wheat allergy is low in many regions of China [24], wheat is one of the most important causes of food-dependent exercise-induced anaphylaxis (FDEIA) in China [42, 43]. Similar to wheat, buckwheat can lead to allergy through three routes: inhalation of the allergen from a pillow filled with buckwheat husk, ingestion of buckwheat, and skin contact with buckwheat flour [44].

Seafood and Others

Seafood allergy is a common food allergy in older children and adults [45]. It is also the predominant cause of food-induced anaphylaxis in Taiwan [46] and Hong Kong [47]. In an expert-screened questionnaire survey, the prevalence rate of shellfish allergy in Taiwan was reported to be 7.71% in children 4–18 years of age and 7.05% in adults [27]. In this study, criteria for food allergy included a convincing history of IgE-mediated allergy and a skin prick test (SPT) and/or serum-specific IgE tests, but not oral food challenge (OFC) tests. In southern China, shrimp, crab, lobster, and scallop are common seafood allergens, and mango allergy is a common tropical fruit allergen. "Bird's nests" are noted as a common allergen in Hong Kong [48]. As fried insect and bird's nest are popular in some provinces in China, allergic reactions developing after dietary consumption of these delicacies have been reported. For example, 36 patients were reported to suffer from anaphylaxis after eating locust (grasshopper) [49–57]. A Chinese delicacy made from the saliva of swallows was also reported to be a potential trigger for anaphylaxis [48]. Surprisingly, anaphylactic reaction due to consumption of wheat flour contaminated by dust mites [58, 59] and unexpected delayed type anaphylactic response to red meat, associated with tick bites and IgE antibodies against galactose-α-1, 3-galactose (α-gal), have also been reported in China [60].

Finally, it is interesting to note that China shares many common food allergens with other Asian countries, including egg, milk, wheat, and buckwheat. The most commonly reported food allergens in the European and North American populations are cow's milk, egg, peanuts, tree nuts, wheat, crustacean shellfish, fish, and soy [61].

Treatment Modalities of Food Allergy

Avoidance

At present, there is no permanent curative therapy for food allergy [62]. The current standard clinical management of food allergy includes avoidance of the allergenic food and treating symptoms with appropriate medications such as antihistamines and anticholinergic agents [63, 64]. Although there is little data to support the use of corticosteroids in the acute treatment of food allergies, these drugs are used in China, as they are in Western countries. Unfortunately, food avoidance is not an ideal long-term solution for food allergy, as it is not foolproof, and the risk of anaphylaxis due to unexpected or accidental exposure remains. Thus, more proactive measures are needed. In China, other modes of therapy besides avoidance are gaining acceptance.

Immunotherapy

The objective of immunotherapy to treat food allergy is to achieve a state of complete or partial desensitization to that food, or to induce clinical tolerance in the patient [65]. Desensitization is the increase of the clinical reactivity threshold through continuous immunotherapy. Clinical tolerance is strictly defined as the achievement of a permanent state of non-reactivity, or the retention of a high reactivity threshold after treatment termination [66, 67]. Current allergen-specific immunotherapy approaches in food allergy include allergen-specific oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT). Allergen-directed immunotherapy tends to be more effective than any form of non-specific immunotherapy [68]. The most promising non-allergen-specific immunotherapies are anti-IgE therapy and Chinese herbal medicine [69, 70].

Oral Immunotherapy—Allergen Specific

Oral immunotherapy (OIT) involves the oral ingestion of low doses of food allergens, followed by slow incremental increases in dosage over a period of time until desensitization and sustained unresponsiveness are achieved [66, 67]. OIT has effectively induced desensitization in several uncontrolled clinical studies over the past decade, involving mainly milk [71–73], egg [74], and peanut allergies [75]. However, the majority of subjects are unable to attain sustained unresponsiveness and the potential risk of adverse reactions from OIT poses a significant obstacle in treatment of both children and adults [76–79]. Thus, strategies to improve the safety of OIT in addition to its long-term efficacy are much needed. Promising attempts in recent years have included the use of adjunctive therapies while performing OIT, such as anti-IgE agents, prebiotics, and herbal medicines. Takahashi et al. found that anti-IgE agents, or omalizumab, in OIT could significantly improve clinical and immunological parameters and successfully induce desensitization in all children in the study with high-risk cow's milk allergy, along with potentially improving safety [80]. Other studies targeting cow's milk allergy and egg allergy reported that OIT with omalizumab can effectively reduce adverse reactions, but did not improve or induce a sustained unresponsiveness [81, 82]. An herbal formula BFAFH2 used with OIT in mice significantly improved rates of adverse reactions compared to sham treatment as well as immunological parameters [83]. Vonk et al. found that using non-digestible oligosaccharides in OIT enhanced suppression of the acute allergic skin response and induction of regulatory immune cells in mice [84].

Understanding the mechanism behind OIT in greater detail will be crucial to develop better strategies to optimize the safety of OIT as well as its long-term efficacy. Studies so far have found that antigen-specific regulatory T cells (Tr1, Th3, and Foxp3 Tregs) which are crucial to tolerance may be functionally impaired in allergic subjects, and that OIT can reverse the Th2-skewed immune program in order to enhance induction of Tregs and also restore their suppressive function [85, 86]. Such effects have been enhanced in OIT supplemented with omalizumab or prebiotics. Using an oral-sensitized Brown–Norway (BN) rat model of food allergy, Huang et al. demonstrated that oral sensitization was comparable with the natural sensitization process in food allergy patients [87]. While animal studies have been conducted in China to investigate the mechanisms of desensitization in OIT [88], this has not been translated into clinical practice. Multicenter, randomized, double-blinded, and placebo-controlled studies of OIT are thus warranted.

Sublingual Immunotherapy—Allergen Specific

Sublingual immunotherapy (SLIT) administers small, increasing amounts of food allergen under the tongue for 2 to 3 min. The dosing regimen of SLIT may provide greater safety since doses are approximately 1000-fold less concentrated than those of OIT. Studies have confirmed the effectiveness of SLIT in treating some food allergies, including peanut [67], milk [89], peach [90], and hazelnut [91] allergies. Symptoms observed in most SLIT trials are less frequent or severe than OIT, often limited to oropharyngeal itching, and are rarely systemic. However, safety comes at a price, and SLIT only induces mild desensitization resulting in tolerated doses that are far lower than those attained by OIT. In addition, fewer patients in SLIT are achieving sustained unresponsiveness compared to OIT [78, 92]. SLIT may be more preferable for extremely sensitive patients and perhaps as a pre-treatment prior to undergoing OIT, but the cost-effectiveness of undergoing SLIT is uncertain. Research on how to increase the efficacy of SLIT without compromising its safety is needed.

Table 2 Prevalence of food allergy in USA, Europe, other countries and areas

City/country	Year	Age of subjects (in years)	Number of cases	Study method	Prevalence rate	Allergic food	Reference
Hong Kong	2009	2–7	3677	Questionnaire, test	4.62	Shellfish (15.8%), egg (9.1%), peanut (8.1%), beef (6.4%), cow's milk (5.7%), and tree nuts (5.0%)	[26]
Taiwan	2012	< 3, 4–18, > 19	813; 15,169; 14,036	Medical history, skin prick test, sIgE	3.44, 7.65, 6.4	Seafood, including shrimp, crab, fish and mollusk, mango, milk, peanuts and eggs	[27]
Korea	2011	< 1	1177	Medical history	5.26	Hen's eggs (33/62), cow's milk (20/62), and peanut/nuts (8/62)	[28]
Japan	2017	0–18	374	Questionnaire, sIgE, challenge test	4.9	Egg, milk, crustaceans, fish eggs, and yams	[29]
Singapore	2012	4–6, 14–16	4115, 4390, 6342, 6450	Medical history		Shellfish	[30]
Thailand	2012	3–7	452	Questionnaire, skin prick test, challenge test	1.11	Shrimp, cow's milk, fish, chicken eggs, and ant eggs	[31]
USA	2011	0–2, 6–10, 14–18	5429; 9911; 10,514	Questionnaire	6.3 7.6 8.6	Peanut (25.2%), milk (21.1%), shellfish (17.2%)	[32]
Denmark	2005	< 3, 3, > 3, adult	111, 486, 301, 936	Questionnaire, skin prick test, sIgE, histamine release test, challenge test	2.26	Children: hen's egg (1.6%), peanut (0.4%) Adult: codfish (0.2%), shrimp (0.3%)	[33]
United Kingdom	2008	0–3	891	Questionnaire, prick test, challenge test	2.9	Milk, egg and peanut	[34]

Smaldini et al. demonstrated in a milk-allergic mouse model that SLIT combined with intraperitoneal injections of an anti-IL-2 monoclonal antibody reduced serum IgE and was accompanied by reduced IL-5 expression and elevated IL-10 and TGF-β production, effectively reversing IgE-mediated milk allergy [93].

SLIT for peach allergy using peach extract enriched with Pru p 3 in patients led to decreased Pru p 3–specific effector cells. Rodriguez et al. took advantage of enhanced immunogenicity to a Pru p 3 T cell epitope through CpG motif-containing oligodeoxyribonucleotide (ODN) to develop immunotherapy against peach. This resulted in lower Pru p 3–specific IgE, along with lower IgG1, but increased Th1 cytokines, IgG2a, and Tregs. The treatment affords protection against anaphylaxis 3 weeks after treatment. Another interesting study found that Pru p 3 SLIT led to reduced skin prick test reactivity and increased the threshold dose not only for peach but also for peanut in patients with allergies to both [94].

Epicutaneous Immunotherapy—Allergen Specific

Epicutaneous immunotherapy (EPIT) uses skin patches to deliver whole antigens or specific antigenic peptides through the epidermis. The allergen is solubilized by moisture from the skin and taken up by dendritic cells in the outer dermal layer [95, 96]. EPIT is effective in animal models of food allergy [97–99] and has been investigated in clinical trials for food allergies in recent years [100]. One advantage of EPIT over other forms of immunotherapy is that the administration of small doses of allergen to the skin may decrease the likelihood of the systemic reactions that can occur with oral forms of immunotherapy. Patches containing doses typically in the range of 50 to 500 μg can be applied repeatedly in 24-h intervals for 1 year or more. Clinical trials are currently ongoing for peanut and milk allergies.

In a recently completed CoFAR study, a significantly greater number of participants given 250 μg peanut Viaskin® patch successfully passed a 5044-mg protein oral food challenge after 52 weeks, compared to the placebo group [101]. Successfully consumed doses increased by 0, 43, and 130 mg of protein in the placebo, 100 μg and 250 μg groups, respectively. Results were more significant among 4- to 11-year-old children. The treatment also increased peanut-specific IgG4 levels and reduced basophil activation and Th2 cytokine response. Preliminary results from a phase I/II trial for milk allergy show that 57.9% of children given a Viaskin® patch with 300 μg of cow's milk protein obtained a cumulative reactive dose of 1444 mg, compared to 32.5% of the placebo group. The trial did not observe any adverse reactions beyond local itching, inflammation, and, in a few cases, erythema.

Animal studies on EPIT have also shed much light on its tolerance-inducing mechanism. Dioszeghy et al. found that

Table 3 Chinese medicine prescriptions under development for treating food allergy

Name	Primary Chinese medicinal composition	Progress	Remarks
FAHF-1 [109]	Ganoderma lucidum, aconite root, Fructus Mume, Pericarpium zanthoxyli, *Asarum*, Coptis, *Phellodendron*, ginger, cassia, *Angelica*, red ginseng	Zoopery	FAHF-1 protected peanut-sensitized mice from anaphylactic reactions and significantly reversed established IgE-mediated peanut allergy.
FAHF-2 [111]	Ganoderma lucidum, Fructus Mume, Pericarpium zanthoxyli, Coptis, *Phellodendron*, ginger, cassia, angelica, red ginseng	Phase II	FAHF-2 is a safe herbal medication for food allergic individuals and shows favorable in vitro immunomodulatory effects.
FAHF-3 [114]	Ganoderma lucidum, Fructus Mume, Coptis chinensis, dried ginger, angelica, cicada, honeysuckle	Zoopery	Formula-3 stabilizes mast cells by suppressing FcεR1-induced Ca(2+) mobilization mainly through inhibiting Ca(2+) entry via SOCs, thus exerting a protective effect against OVA-sensitized food allergy.
CRFC-1 [112]	Angelica, Astragalus root, Mugwort leaf, Rhizoma Cyperi, Schizonepeta, ephedra, Scutellaria, Tangerine peel, Radix Codonopsis	Zoopery	The allergic symptoms, serum-specific IgE, IL-4, histamine levels and degranulation mast cells in the CRFC-1 and − 2 experimental groups were significantly lower than those in the control group; the difference was statistically significant ($P < 0.05$). CRFC-1 and − 2 can both antagonize the food allergy induced by peanut in the mouse model.
CRFC-2 [113]	Angelica, Radix Astragali, Rhizoma Cyperi, Schizonepeta, Ephedra, Tangerine peel, Radix Codonopsis, Coptis chinensis, Ganoderma lucidum	Zoopery	

EPIT induced a greater number of Foxp3 Tregs and expression of gut-homing receptors than OIT and SLIT in peanut-sensitized mice [102]. Most interestingly, only EPIT induced naive Tregs, which may potentially sustain suppression after discontinuation of treatment. Although OIT, and SLIT, to a lesser extent, induce greater immunological changes, they tend to be short-lived [103]. EPIT may thus have greater potential to induce long-term tolerance against the food antigen. Other studies have also supported a more efficient and sustainable induction of Tregs in EPIT, including the generation of LAP+Foxp3−Tregs which suppress mast cell activation directly without modulation by B or T cells, as well as the induction of Foxp3+CD62L+Tregs which can more potently inhibit effector T cells and have a low turnover rate compared to other types of Tregs [104]. The desensitization effect in EPIT is modest compared to OIT and even SLIT, but the method deserves further clinical investigation as it is relatively safer and investigations on its immunological mechanism suggest much potential for clinical use.

Anti-IgE Therapy—Non-Allergen-Specific

The use of anti-IgE agents, such as TNX-901 and omalizumab, for food allergies has been trialed [105–107]. As it is non-allergen-specific, anti-IgE therapy may be helpful for patients with multiple food allergies. Although not widely used for food allergies, when combined with allergen-specific therapies, anti-IgE agents may potentially provide additional safety benefits. In 2014, Lee et al. provided an overview of the literature on peanut immunotherapy and reported the successful treatment of a small group of children in Hong Kong using omalizumab combined with OIT [108]. At the end of the treatment, all children in the study were able to ingest a higher dose of peanuts than previously without reaction and were thus protected from severe allergic reactions after accidental ingestion. They concluded that using anti-IgE used with OIT may facilitate rapid and safe oral desensitization.

Traditional Chinese Medicine—Non-Allergen-Specific

Traditional Chinese medicine (TCM) has been used in China and neighboring countries for many years. The use of TCM in the form of herbal formulations in alleviating food allergy has gained attention in recent years. Due to different perspectives on medicine, the TCM literature does not address “food allergy” specifically, but rather a food allergy-like phenomenon. The identification and enrichment of active medicinal ingredients are gaining increasing attention in Chinese herbal medicine. More and more evidence-based studies are being done to validate the effectiveness and characterize the biochemical mechanisms present in TCM. As a result, there is increasing scientific evidence supporting the use of TCM in food allergy. Ultimately, this process will help to increase safety and long-term efficacy of the TCM medications.

The food allergy herbal formula-1(FAHF-1) contains 11 herbs derived from *Wu Mei Wan*, a classical 10-herb Chinese formula for treating intestinal parasite infection. Wu Mei Wan is effective for intestinal parasitic infections and gastrointestinal disorders with symptoms like food allergy and gastroenteritis. The clinical effect of FAHF-1 was consistent with *Wu Mei Wan* and Ling Zhi (*Ganoderma lucidum*), an herb known for its significant anti-inflammatory and anti-allergy effects. Medicinal ingredients of FAHF-1 are listed in Table 3.

In 2001, FAHF-1 was reported to protect peanut-sensitized mice from anaphylactic reactions and significantly reverse established IgE-mediated peanut allergy [109]. The food allergy herbal formula-2 (FAHF-2) is an improved version of FAHF-1 containing 9 herbs and is registered as a US FDA botanical IND. Two ingredients in the original formulation, Xi Xin (Herba cum radice asari) and Zhi Fu Zi (Radix lateralis

Table 4 Herbal composition in FAHF-2 and CRFC-2

	Ingredients	Pharmaceutical name
FAHF-2	Wu-Mei	Fructus Pruni Mume
	Chuan-Jiao	Percarpium Zanthoxyli Bungeani
	Dang-Gui	Radix Angelicae Sinensis
	Gan-Jiang	Rhizoma Zingiberis
	Gui-Zhi	Ramulus Cinnamomi Cassiae
	Huang-Bai	Cortex Phellodendri
	Huang-Lian	Rhizoma Coptidis
	Hong-Shen	Radix Ginseng
	Ling-Zhi	Ganoderma
CRFC-2	Dang-Gui	Radix Angelicae Sinensis
	Huang-Qi	Astragalus membranaceus (Fisch.) Bunge
	Xiang-Fu	*Cyperus rotundus* L
	Jing-Jie	*Nepeta cataria* L
	Ma-Huang	*Ephedra sinica* Stapf
	Chen-Pi	*Citrus reticulata* Blanco
	Dang-Shen	*Codonopsis pilosula* (Franch.) Nannf

aconiti carmichaeli praeparata), are potentially toxic if improperly processed and were removed in FAHF-2. The herbal constituents of FAHF-2 are shown in Table 4.

FAHF-2 may be a potentially effective and safe remedy for peanut allergy. Srivastava KD et al. demonstrated that treating peanut-allergic mice with FAFH-2 can eliminate anaphylaxis completely [110]. In another study, Wang et al. [111] found that FAHF-2 is safe and may have potent long-term efficacy for food allergies. In a randomized, double-blind, placebo-controlled study, patients allergic to peanut, tree nut, sesame, fish, and/or shellfish received either FAHF-2 or a placebo. Treatments were well tolerated with no serious adverse events. The limitation, however, was that 44% of subjects had poor drug adherence. Nonetheless, FAHF-2 has the potential to effectively alleviate multiple food allergies.

Another Chinese herbal formula, CRFC-2, was also studied in the treatment of food allergies. CRFC-2 is a 7-herb formula derived from CRFC-1 [112]. Man et al. [113] investigated the effects and mechanism of CRFC-2 for anaphylactic reactions induced by peanut in a mouse model. The mice were challenged with peanut and treated with CRFC-2 for 7 weeks. After the challenges, CRFC-2-treated mice showed no sign of anaphylactic reactions. They concluded that CRFC-2 can eliminate anaphylaxis in peanut-sensitized mice. Yang et al. also demonstrated in 2013 the antagonistic effect of CRFC-2 on peanut-induced food allergy [114].

In 2013, Yang et al. [114] used the OVA-sensitized food allergic model in Brown–Norway rats to investigate the effect of a modified Chinese herbal formula, Formula-3, on mast cell degranulation and anti-allergic activity. The direct effect of Formula-3 on mast cell stabilization was studied in a RBL-2H3 cell line. They showed that Formula-3 can stabilize mast cells by suppressing FcεR1-induced Ca2+ mobilization, mainly through inhibiting Ca2+ entry via store-operated Ca2+ entry, thus exerting a protective effect against OVA-sensitized food allergy. The authors concluded that Formula-3 can protect against OVA-sensitized food allergies.

Further search of Chinese scientific literature revealed three additional formulas for the treatment of food allergy, namely, JinAoKang electuary [115], anti-allergic electuary [116], and external decoction [117]. Their main ingredients of each of these are listed in Table 5. JinAoKang electuary and anti-allergic electuary area administered orally, while external decoction is applied directly to skin lesions, such as eczema and urticaria. If patients have severe eczema and exudate, *Sophora flavescens* can be added to the formulation. Modern pharmacological studies indicate that jujube contains large amounts of active ingredients, including cyclic adenosine monophosphate which can inhibit IgE antibody formation, glycyrrhizic acid which has steroid-like effects, Perilla which can antagonize histamine release from mast cells, and Cortex lycii radicis and Fructus pruni mume, which both have inhibitory effects on IgE antibody.

Other Therapeutic Approaches in Food Allergy

Ren et al. [118] investigated the efficacy of genetically modified *Lactococcus lactis* for peanut allergy. Their study hypothesized that allergen-producing *L. lactis* strains modulated allergic immune responses and can be developed as promising mucosal vaccines for managing allergic diseases. Liu et al. [119] found that the hapten trinitrobenzene sulfonic acid

Table 5 Chinese medicine prescriptions post market for treating food allergy

Name	Primary Chinese medicinal composition	Curative	Effective	Invalid	Total effective rate
JinAoKang electuary [115]	The seed of Job's tears, Periostracum cicada, Fructus Mume, Liquorice, Fructus Ziziphi Jujubae, Fructus hordei germinatus, Concha ostreae, Schisandra chinensis	25	3	2	94%
Anti-allergic electuary [116]	Fructus Ziziphi Jujubae, Liquorice, Pokeberry root, *Perilla frutescens* crispa, Cortex lycii radicis, Fructus Mume	22	5	3	93%
External decoction [117]	Cortex dictam, Medicinal honeysuckle, Fructus Kochiae, *Tribulus terrestris*, Purslane, Gloden cypress, *Sophora flavescens*	23	24	1	98%

may facilitate initiation of a food antigen–related Th2 pattern inflammation and elevated OVA-specific IgE in ovalbulmin-sensitized mice upon exposure to food allergens.

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE) is an immune-mediated, chronic esophageal disease. EoE may be another form of food allergy with abnormal eosinophilic infiltration of the intestinal tract, although the identification of triggers has been elusive [120]. EoE may be triggered by foods and possibly by environmental allergens, but this is not always the case. Currently, there are no FDA-approved therapies for EoE and most cases are treated by food-restriction diets [121, 122]. However, the success of such elimination diets has been inconsistent. In general, amino acid diets are better than 6 food elimination diets, which are better than elimination of foods that test positive by various standard in vivo or in vitro food allergy testing techniques.

EoE can occur in children and adults. One study in China followed 22 children with EoE and found that EoE could occur at any age of children. The most common clinical manifestations reported in this study were vomiting and abdominal pain. The presentation of EoE in children is often different from that in adults. Adults generally present with dysphagia, food impaction, or regurgitation, whereas the signs and symptoms are more subtle in children. In adults, the prevalence of EoE is 0.34% in Guangzhou [123] and 0.4% in Shanghai [124].

There is a variety of treatment options for EoE including proton pump inhibitors, systemic topical corticosteroids, elimination diets, leukotriene receptor antagonists, anti-IL-5 antibody, and esophageal balloon dilation [125]. Researchers have suggested that in many cases, pediatric patients can achieve remission by proton-pump inhibitors and only a few children need further elimination diet or oral glucocorticosteroids [126].

Due to the complex and often widely variable presentation of EoE, and the lack of consensus on the underlying pathophysiology, there is no commonly accepted optimal therapy for EoE currently. Tan ND et al. performed a systematic review of 6 RCTs including 193 participants until 2015 and concluded that steroids are effective on decreasing the tissue eosinophil count in EoE patients [125].

Conclusion

Much remains to be understood regarding food allergies, including more details about its mechanism and the mechanisms behind non-IgE-mediated allergic disorders. Studies on geographic, dietary, ethnic, and demographic influences on the prevalence of food allergies may help us to better understand genetic and environmental factors in food allergy. Animal models are also imperative to understanding the mechanism of food allergies. Furthermore, continued research on various immunotherapy treatments including OIT, SLIT, and EPIT directed to address specific knowledge gaps on optimal dose, duration, mechanisms of actions, predictors of risk, and therapeutic response, as well as Chinese herbal medicine, which is used clinically in China, can bring about safe, personalized, and effective treatment modalities for food allergy patients in the future. As current data on food allergies in China focuses mainly on children, studies on other age groups across all regions and socioeconomic groups with a standardized format are needed to establish a solid database on the prevalence and incidence of various food allergies across this vast nation. A nationwide study on food allergies in China is greatly anticipated. The population in China is highly diverse in ethnicity and culture, making it a microcosm for the development of models or algorithms on management and treatment around the world. With increasing worldwide prevalence, food allergy is a global health issue for which early intervention and prevention techniques are urgently needed.

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Compliance with Ethical Standards

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