



Advances in Shellfish Allergy Therapy: From Current Approaches to Future Strategies

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Abstract

Shellfish allergy, triggered by immune reactions to crustacean and mollusk proteins upon consumption/inhalation, is one of the most severe and persistent food allergies, affecting approximately 1%–3% of the general population worldwide. Shellfish is among the “big nine” food allergens responsible for over 90% of food allergy cases worldwide. Its diagnosis poses major challenges due to regional species diversity and a lack of reliable diagnostic tools. Management strategies generally emphasize strict avoidance and provision of emergency adrenaline autoinjectors; however, these approaches are inconvenient and insufficient for both patients and healthcare providers. Given the rising prevalence of shellfish allergy, there is an urgent need for targeted therapies that focus on key allergens, particularly tropomyosin—a major pan-allergen. As the primary target in current immunotherapy approaches, tropomyosin plays a central role in driving shellfish-induced immune responses. Recent advancements in immunotherapy are exploring alternatives beyond avoidance, aiming for long-term desensitization. This review discusses progress with allergen-specific immunotherapy, hypoallergenic allergen variants, DNA-based vaccines, and innovative approaches involving immunoregulatory peptides and probiotics. These strategies collectively strive to desensitize patients, reduce allergic symptoms, and enhance quality of life. Although some therapies are in active trials, most are in the investigational stages and offer promising directions for effective, patient-centered long-term management of shellfish allergy.

Keywords Shellfish allergy · Food allergy · Crustacean · Allergen-specific immunotherapy · Tropomyosin

Introduction

Food allergies markedly reduce quality of life and place a significant economic burden [1–3] on approximately 8% of children [4] and 11% of adults, as reported in the USA [5]. Unlike many other food allergies, shellfish and fish (seafood)

allergy is rarely outgrown, and a high risk of severe allergic reactions persists throughout life, significantly impacting quality of life [5–8]. In regions such as the Asia–Pacific, where shellfish consumption is high, shellfish allergy is not only more prevalent and clinically significant, but symptoms may also develop at an earlier age compared to Western countries [9, 10]. Managing shellfish allergy is particularly challenging due to the major allergen, tropomyosin (TM), which exhibits significant cross-reactivity not only among various types of shellfish—such as crustaceans, mollusks, and cephalopods—but also with mites and other arthropods. This high degree of cross-reactivity can complicate skin testing, often necessitating multiple oral food challenges to accurately identify true clinical sensitivity. Furthermore, shellfish allergies may be specific to certain species [11, 12]. The primary approach for managing shellfish allergy remains strict avoidance [13]. Oral immunotherapy (OIT), a form of allergen-specific desensitization that increases the threshold for allergic reactions upon exposure, has been recommended by the European Academy of Allergy and

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Clinical Immunology (EAACI) for certain food allergies such as peanut, egg, and milk, primarily to reduce the risk of reactions from accidental exposure [13]. However, OIT is not without limitations, including adverse effects and variability in treatment outcomes depending on the criteria used to define success [14, 15]. However, it has not been developed for shellfish allergy. Most of the existing literature concentrates on peanut immunotherapy, resulting in the peanut allergen becoming the first and only treatment for food allergy approved by the United States (US) Food and Drug Administration [16]. The urgent need for effective treatments to mitigate these risks has driven advancements in immunotherapy, biologics, and other innovative therapies, paving the way for safer and more effective food allergy treatments [17]. This review will highlight key advancements in the immunotherapy of shellfish allergies.

Overview of Shellfish Allergy

Shellfish allergy is one of the most prevalent food allergies worldwide, with region-specific high rates of severe (fatal) allergic reactions, including nearly half of affected US children experiencing life-threatening episodes [18]. The prevalence of shellfish allergy appears to range from 0.5% to 2.5% in the general population, with significant variations across different regions and age groups, and consumption habits [19, 20]. A systematic review by Moonesinghe et al. highlights a broad variation in the prevalence of shellfish allergies, ranging from less than 1% to 10.3%, depending on the method of diagnosis [21]. Unlike peanut and egg allergies, which arise in early childhood, shellfish allergy typically develops later in life [22]. In the USA, shellfish allergy affects approximately 3% (2.9%; 95% CI, 2.7%–3.1%) of adults, making it the most common food allergy among adults, affecting an estimated 7.2 million US adults [5]. In Europe, shrimp allergy prevalence rates vary, with a high of 10% in Italy and 7% in France [23], and as low as 0.3% in Denmark [24]. Additionally, shellfish allergy is a major contributor to food allergies in several regions of Asia, including Thailand, Taiwan, Hong Kong, Vietnam, and Singapore, where shellfish is a dietary staple [19, 25].

Shellfish generally refers to both groups of edible crustaceans (shrimp, crab, and lobster) and mollusks (oyster, mussels, snails, octopus, squid) [26] and is one of the “big nine” food categories that account for more than 90% of all incidents of food allergies [27, 28]. Among shellfish, shrimp is the most frequently reported allergenic species [29]. Shrimp and prawn are often used interchangeably, with prawn common in the UK and Australia, and shrimp in the USA and Europe [29]. Crustacean allergy is generally more common than mollusk allergy, with some studies reporting rates as high as 10% among Italian adults [23]. In contrast,

the prevalence of mollusk allergy appears lower, particularly when confirmed through objective diagnostic methods. Nevertheless, co-allergy to both groups has been documented, with a combined prevalence of 6% among French children and 9% among American adults [21]. Similarly, a cross-sectional study in Vietnamese children reported self-reported crustacean and mollusk allergy at 3.8% and 1.3%, respectively [30]. In a physician-diagnosed adult population, seafood was identified as the predominant food allergen [31]. The increased awareness of the nutritional value of seafood has led to a surge in its consumption, reaching a global average of 20.5 kg per capita in 2020 [32] and 20.7 kg per capita in 2022 [33], according to the Food and Agriculture Organization (FAO). This increase has been associated with more frequent reports of allergic reactions. Shellfish-allergic individuals are suffering from a wide spectrum of symptoms, ranging from mild oral allergy syndrome (with limited oral symptoms of pruritus, rash, and swelling) to life-threatening anaphylaxis. Shellfish anaphylaxis stands as the leading cause of food-related fatalities in Australia, as reported by the Australian Bureau of Statistics, and has exhibited a concerning increase over the past decades [34, 35]. In Singapore [36, 37], Hong Kong [38], and Thailand [39], shellfish is the main food-related cause of anaphylaxis in adults. Shellfish allergies tend to be persistent, with low rates of resolution in the few studies available on the natural history of shellfish allergy [29, 40].

The primary allergen in shellfish is TM, a highly conserved muscle protein across species. This conservation results in considerable clinical, serological, and skin prick test (SPT) cross-reactivity among different shellfish types, complicating allergy diagnosis and management for affected individuals. Assessment of TM-specific IgE levels in shrimp-allergic individuals has shown that 72%–98% of patients have positive IgE binding to purified TM [11, 29, 41–43]. Despite being recognized as the primary allergen among shrimp-sensitized individuals, recent findings have reported sensitization rates to Pen m 1 of less than 50%, including 31% in Australian infants [44], 37% in Japanese [45], 42% in Austrian [46], 41.2% in Chinese [47], and 41% in Italian [48] shrimp-allergic populations. Additionally, studies on TM cross-reactivity with mites and insects underscore TM's role in IgE cross-reactivity, although recent research indicates that T-cell cross-reactivity is limited and appears to depend more on protein structural stability than on amino acid sequence identity [49]. While TM is recognized as a pan-allergen, the presence of other allergens, such as arginine kinase (AK), sarcoplasmic calcium-binding protein, and hemocyanin, may influence individual clinical reactivity, as some patients may react solely to these allergens rather than the pan-allergen [46]. Identifying such novel allergens further facilitates the development of specific animal models through molecular cloning and recombinant

allergen production [50–53]. Table 1 provides general information about all shrimp and crab allergens listed by the World Health Organization (WHO) and the International Union of Immunological Societies (IUIS) allergen nomenclature databases (www.allergen.org). Compared to crustaceans, knowledge of major allergens in mollusks remains limited. TM, a key allergen identified in mollusks such as abalone [54], shows a sequence identity of only 55% to 65% with TM from crustaceans, insects, mites, and fish [29]. While TM-crustacean exhibits strong immunological cross-reactivity due to a 91% conservation of IgE epitopes, mollusks display less than 20% conservation, resulting in minimal cross-reactivity between this group [55]. Additionally, we previously demonstrated in a murine model that mollusk TM can independently induce a strong IgE response, even without prior sensitization to crustacean allergens. However, this was achieved using intraperitoneal injections with alum adjuvant, which likely contributed to the observed immunogenicity [56].

Diagnosis of Shellfish Allergy and Challenges

Effective diagnosis of shellfish allergy relies on obtaining a detailed medical history, including information on the type of shellfish consumed, the timing and nature of symptoms, and any treatments received [57, 58].

SPTs are commonly used as the initial diagnostic tool to assess sensitization by applying shellfish extract to the skin and monitoring for allergic reactions. While SPTs offer high sensitivity, their specificity can be limited due to cross-reactivity among shellfish species and variability in allergen

content among commercial extracts [29, 59]. Moreover, some commercial SPT extracts do not contain a sufficient amount or diversity of shellfish allergens, potentially leading to false-negative results in sensitized individuals [60]. When commercial extracts are unavailable or doubtful, SPT using fresh shellfish—either raw or cooked—has been shown to improve diagnostic sensitivity, as heat treatment can affect allergen stability and IgE reactivity. However, this approach may introduce variability and requires cautious interpretation [60–62]. Serum-specific IgE testing quantifies the immune response to whole shellfish extracts or single-component allergens such as TM. Elevated IgE levels suggest sensitization, though they may not always correlate with clinical reactivity [63]. Sensitization can occur directly to shellfish allergens or through cross-reactivity with similar allergens found in other invertebrates such as cockroaches and house dust mites.

Additionally, although shellfish and finfish are taxonomically distant, limited cross-reactivity has been reported, primarily due to structurally conserved proteins like TM [29]. This may result from overlapping IgE responses, highlighting the need for cautious interpretation of test results, particularly in individuals sensitized to multiple seafood types [58, 64].

The gold standard for diagnosis is an oral food challenge (OFC), ideally a double-blind placebo-controlled food challenge (DBPCFC). However, the risk of severe allergic reactions and the time-consuming nature of these treatments limit their routine use [65]. The diagnostic process is complicated by the diverse range of shellfish species and the potential for cross-reactivity between them, necessitating the need for multiple oral food challenges. Emerging techniques such as basophil activation tests (BAT) and component-resolved

Table 1 List of WHO-IUIS-registered shellfish allergens (www.allergen.org) on May 2025—allergic reactions have been reported after both ingestion and inhalation

	Biochemical name	Allergen (shrimp and crab)	Molecular weight	Function	Heat stable
1	Tropomyosin	Cra c 1, Mac r 1, Mel l 1, Exo m 1, Lit v 1, Met e 1, Pan b 1, Pen a 1, Pen i 1, Pen m 1	35–40 kDa	Muscle contraction	Stable
2	Arginine kinase	Cra c 2, Lit v 2, Pen m 2, Mac r 2	40–45 kDa	Energy metabolism	Labile
3	Myosin light chain 2	Lit v 3, Pen m 3	20 kDa	Muscle contraction	Stable
4	Sarcoplasmic calcium-binding protein	Cra c 4, Lit v 4, Pen m 4	20–25 kDa	Calcium ion binding	Stable
5	Myosin light chain 1	Art fr 5, Cra c 5	18 kDa	Muscle contraction	Stable
6	Troponin C	Cra c 6, Pen m 6	17–21 kDa	Muscle contraction	Unknown
7	Hemocyanin	Pen m 7	76 kDa	Oxygen transport	Labile
8	Triosephosphate isomerase	Cra c 8, Pen m 8	27–28 kDa	Glycolytic enzyme	Labile
9	Filamin C	Scy p 9	90 kDa	Cytoskeletal protein	Labile
10	Fructose bisphosphate aldolase	Cha f 10	41 kDa	Glycolysis	Unknown
11	Mitochondrial malate dehydrogenase	Para c 11	39 kDa	Citric acid cycle	Unknown
12	Cytosolic fatty acid binding protein	Lit v 13, Pen m 13	15–20 kDa	Lipid binding	Stable
13	Glycogen phosphorylase-like protein	Pen m 14	95 kDa	Glycogen breakdown	Unknown

diagnostics (CRD) show promise in improving diagnostic accuracy without the need for confirmatory OFC [66–69]. CRD enhances shellfish allergy assessment by identifying IgE responses to specific allergens, such as TM, which shows high specificity for shrimp allergy prediction [70]. Studies indicate that recombinant shrimp allergens, like rPen a 1, are highly effective in identifying shrimp-allergic patients [43]. CRD methods provide detailed sensitization profiles, with singleplex approaches demonstrating higher sensitivity than multiplex assays in detecting shrimp-specific IgE [71]. However, CRD still requires improvement; research has primarily focused on TM, leaving many other shellfish allergens poorly characterized. Additionally, only a limited number of shellfish species have been studied, representing just a small portion of the global variety consumed. Thus, while existing diagnostic methods for shellfish allergy offer valuable insights, ongoing research is needed to enhance their reliability and standardization, ultimately improving patient management and safety.

Current Treatments

The most recent guideline for diagnosing and treating shellfish allergy has been established by EAACI [13]. The primary strategy for managing shellfish allergy is currently strict allergen avoidance. Individuals diagnosed with shellfish allergy are advised to eliminate all forms of shellfish from their diet, including both crustaceans and mollusks [72]. Although the majority of individuals with shrimp allergies do not exhibit respiratory symptoms from exposure to cooking steam, highly sensitive individuals may experience severe reactions to airborne allergens [73]. Therefore, it is advisable for individuals to avoid inhaling cooking fumes, steam, and vapors containing shellfish proteins, as well as refrain from touching or handling shellfish. Awareness and education play crucial roles in promoting allergen avoidance. Patients and their families should receive comprehensive information about the condition, its implications, and how to recognize allergic reactions. They should also be informed about carefully reading food labels, as shellfish can be present in various processed foods, which must be thoroughly assessed by the food industry and regulators. In addition to dietary restrictions, it is recommended to have emergency action plans and to carry personal adrenaline auto-injectors in case of severe reactions [74–76].

Effects of House Dust Mite Immunotherapy on Shellfish Allergy

House dust mite (HDM) immunotherapy can affect shellfish allergy, highlighting the potential cross-reactivity between HDM and shellfish and the complexities in treating these overlapping sensitivities. Reports have emerged of patients

who developed shrimp allergies after undergoing HDM immunotherapy, confirmed by positive SPT and food challenges. Notably, the clinical symptoms in these cases were primarily limited to oral mucosa consistent with the oral allergy hypothesis [77].

Several studies have raised concerns about potential adverse or limited effects of HDM immunotherapy for shellfish-allergic individuals. Additional insights come from studies on allergies to snail, a mollusk with cross-reactivity to HDM [78, 79]. In some cases, HDM immunotherapy has exacerbated respiratory symptoms in snail-allergic patients, even leading to anaphylaxis in individuals who previously exhibited mild symptoms [79, 80].

However, other studies have shown no significant impact of HDM immunotherapy on shellfish sensitization. For example, sublingual immunotherapy (SLIT) trials have reported no new sensitization to shrimp tropomyosin [81, 82]. One study examined the effect of immunotherapy with *Dermatophagoides pteronyssinus* extract on shrimp allergy. Among 35 patients with positive SPT, those receiving immunotherapy showed reduced skin reactivity and lower IgE levels for both mite and shrimp. After 1 year, four of ten patients with positive SPT converted to negative, and six of nine patients with shrimp-specific IgE became negative. However, no significant changes in clinical sensitivity to shrimp were observed, suggesting that mite immunotherapy may not substantially alter shrimp allergy sensitivity [83].

In contrast, some case reports and studies have highlighted potential benefits of HDM immunotherapy in improving shrimp tolerance. Evidence suggests that SLIT with HDM can increase shrimp tolerance in patients with prior anaphylaxis. This improvement was attributed to the higher dose of TM administered, as the patient received double the standard dose of SLIT [84]. Additionally, HDM SCIT has been linked to a reduction in specific serum IgE levels and, in some cases, a sustained resolution of shrimp and squid allergy symptoms, as confirmed by OFC, and maintained over a 4-year follow-up period [85]. A case report highlights a 40-year-old woman with combined allergies to mites and shrimp who underwent subcutaneous immunotherapy (SCIT) for *Dermatophagoides farinae*. After 6 months, she exhibited significant reductions in skin reactivity and serum-specific IgE levels, indicating that mite immunotherapy may aid in desensitizing patients with shrimp allergies [86]. However, the absence of a clinical challenge leaves the effect on shrimp tolerance unclear.

The opposing outcomes of HDM immunotherapy—worsening shellfish allergy in some individuals while improving it in others—highlight the need for further research to clarify the underlying pathophysiological and molecular mechanisms and to identify patient phenotypes that may benefit, before this approach can be considered a viable treatment for shellfish allergy.

Allergen-Specific Immunotherapy Approaches

Shellfish allergy immunotherapy aims to induce tolerance and minimize allergic reactions through strategies such as allergen-specific immunotherapy (AIT), hypoallergenic allergen variants, monoclonal antibodies, and DNA vaccines. These methods modulate immune pathways by enhancing regulatory T cells (Treg) and regulatory B cells, increasing IgG4 and IgA, and suppressing IgE-mediated activation (Fig. 1).

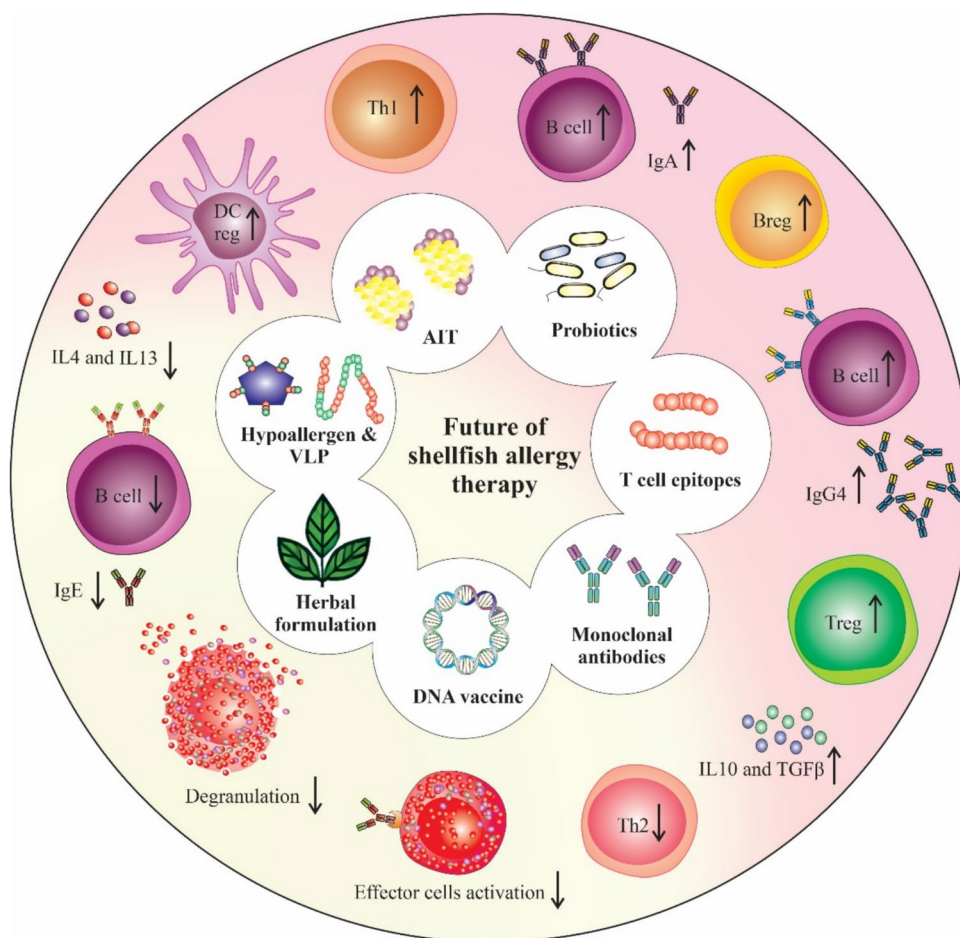
Allergen-Specific Immunotherapy

The concept of AIT originates in the early twentieth century and remained largely unexplored for several decades due to the high risk of severe reactions and anaphylaxis. However, recent advancements offer promising safe possibilities for achieving desensitization and long-term management of food allergies [87, 88]. AIT involves regular exposure to increasing doses of the allergen—in this case, shellfish proteins—to induce desensitization and tolerance. Initially,

allergen-specific IgE levels may rise, but they typically decline below baseline over time. The maintenance phase generally requires daily consumption of a target dose of the allergen, aiming to raise the threshold of reactivity and reduce the severity of allergic reactions in cases of accidental exposure. While the exact mechanism remains under investigation, current evidence suggests that AIT first suppresses basophils and mast cells, followed by a shift towards the formation of allergen-specific Tregs, the depletion of reactive mediators, and the stimulation of allergen-specific IgG production. Over time, Th2 cell activity diminishes, while regulatory cells, such as Tregs and Bregs that produce IL-10, become more prominent [87, 88]. Allergen-specific IgG, particularly IgG4, is believed to act as a “blocking antibody” by binding to the allergen before it interacts with IgE on effector cells, thereby preventing mast cell and basophil activation (Fig. 2).

Various administration routes and dosing strategies are considered in AIT for food allergies, including OIT, SLIT, SCIT, and epicutaneous immunotherapy (EPIT) [89, 90]. Among these, OIT has shown potential as a treatment for food allergies such as peanut and milk; however, concerns about its safety and tolerability remain major obstacles to

Fig. 1 Future directions in shellfish allergy therapy. This figure illustrates various therapeutic approaches being developed to manage shellfish allergy by promoting immune tolerance and reducing allergic reactions. These strategies aim to increase regulatory cells and the production of IgG4 and IgA to minimize allergic symptoms



its wider application [91, 92]. In comparison, SLIT offers a safer option with fewer side effects, though it is generally less effective [92, 93]. Currently, no clinical data currently exists for the use of SCIT or EPIT in shellfish immunotherapy. This review focuses on recent advancements in OIT and SLIT for shellfish allergy.

Oral Immunotherapy

Despite the high prevalence of shellfish allergy, studies investigating shellfish OIT remain limited in scope and species (only shrimp). OIT has shown promise as a treatment for food allergies, including shellfish, but its application is constrained by safety concerns. While most reactions during OIT are mild, severe reactions can occur, particularly during the initial and buildup phase. Chronic symptoms, such as

abdominal pain potentially linked to eosinophilic esophagitis (EoE), are a common reason for discontinuation of therapy [91]. Recent advancements, such as combining OIT with biologics such as omalizumab, aim to enhance both safety and efficacy [94]. Evidence indicates that initiating treatment early, particularly in patients with high IgE levels, may enhance the likelihood of achieving long-term desensitization and remission [95]. Although new protocols have been developed to improve safety, further research is necessary to refine OIT and maximize its effectiveness for managing shellfish allergies.

Nguyen et al. examined the effectiveness of OIT for shrimp-allergic patients in a multi-food OIT trial that included omalizumab as an adjuvant [96]. This case series, which involved three patients—two of whom were children under 18—provided initial evidence suggesting that shrimp

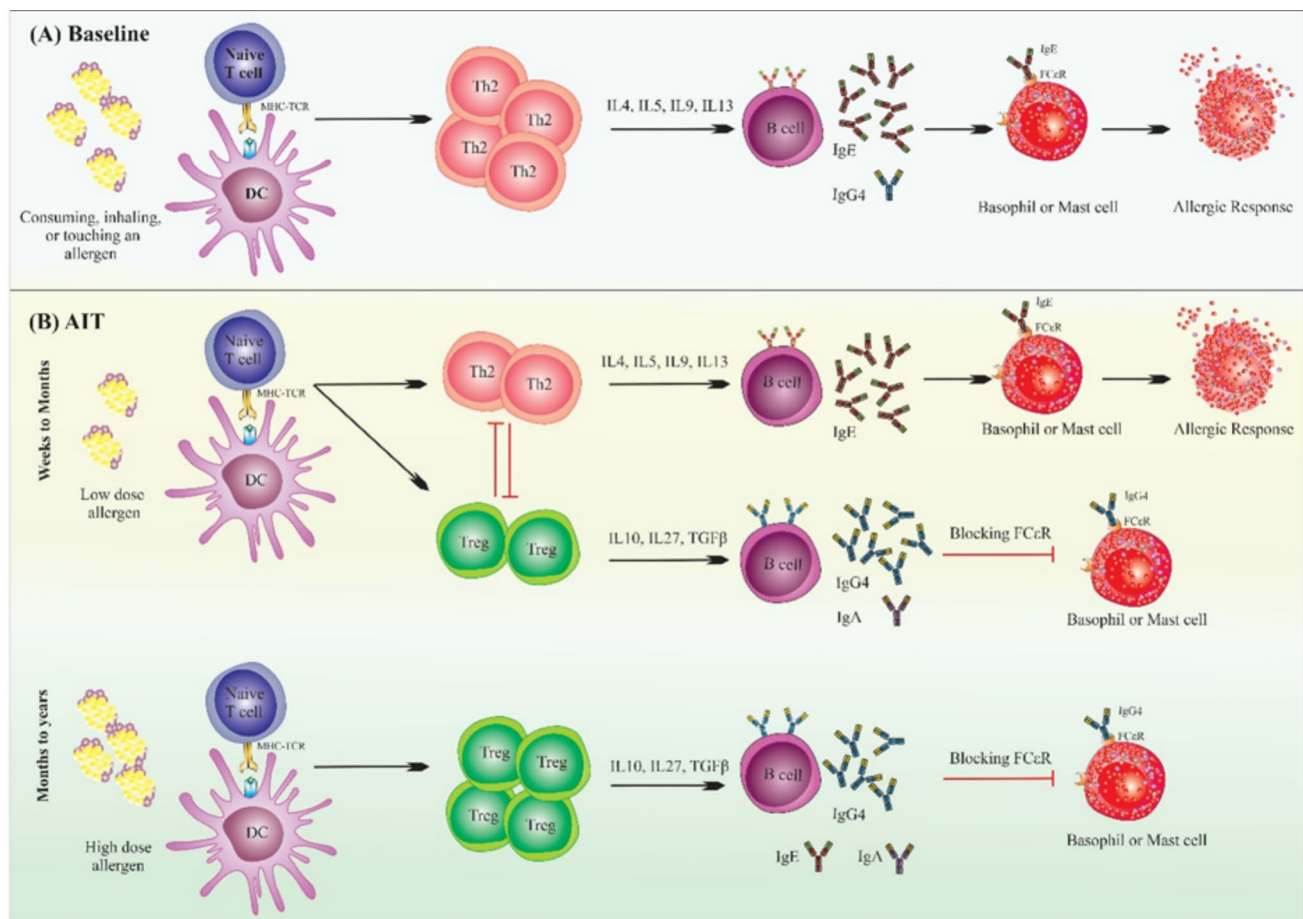


Fig. 2 Overview of immune responses in baseline allergy and allergen-specific immunotherapy (AIT). **A** At baseline, allergen exposure activates dendritic cells (DCs), which prime naive T cells towards a Th2 response. Th2 cells release cytokines (IL-4, IL-5, IL-9, IL-13), inducing IgE production by B cells. IgE binds Fcε receptors on mast cells and basophils, triggering degranulation and allergic reactions upon re-exposure. **B** During AIT, repetitive low-dose allergen exposure over weeks to months induces a shift towards Tregs that suppress

Th2 responses and increase IL-10, IL-27, and TGF-β production. B cells switch from IgE to IgG4 production, with IgG4 functioning as a blocking antibody that prevents IgE from binding Fcε receptors, thereby inhibiting mast cell and basophil degranulation. Prolonged high-dose allergen exposure over months to years further enhances Treg responses and stabilizes IgG4-mediated blocking, resulting in long-term tolerance and reduced allergic responses

OIT may be a viable strategy for managing shrimp allergies, despite the small sample size. In another recent study, a novel shrimp OIT approach was explored, which focused on bypassing the traditional build-up phase and proceeding directly to a maintenance dose [97]. This case series involved 17 mild shrimp-allergic or shrimp-sensitized pediatric patients, who were administered a maintenance dose of 300 mg shrimp protein (equivalent to 1.6 g of cooked shrimp) without the initial low-dose build-up phase. The study hypothesized that due to shrimp's higher reaction threshold compared to other allergenic foods, this approach could be safe for patients with mild shrimp allergies. A Phase 2 trial assessed the safety and efficacy of OIT for cashew and shrimp allergies by administering a 1000 mg maintenance dose over 52 weeks [98]. The trial demonstrated that OIT safely desensitized individuals with mild to moderate adverse reactions, primarily gastrointestinal symptoms. Mechanistic analyses showed significant increases in allergen-specific IgG4 and alterations in allergen-reactive CD4⁺ T cells, indicating effective desensitization.

New shrimp allergy models are being developed to improve the understanding of allergic mechanisms and advance diagnostic and therapeutic tools for shellfish allergy [99–101]. In a mouse model of gastrointestinal allergies, the potential of Pacific white prawn (*Litopenaeus vannamei*) as an allergen extract for immunotherapy was explored [102]. Mice were divided into groups and treated with varying doses—high, moderate, and low—of the shrimp extract, undergoing sensitization, desensitization, and subsequent oral challenges. Shrimp allergen extract (SAE) immunotherapy reduced systemic allergic symptoms across all dosages, with persistent effects after multiple challenges. Notably, high-dose treatment significantly increased IgG2a levels and IL-10 mRNA expression, highlighting a dose-dependent immunotherapy effect.

The lack of standardized allergen thresholds often creates confusion and risky decisions for individuals with food allergies. Without sufficient data on minimum doses unlikely to trigger reactions, developing effective allergen management strategies becomes challenging for both clinicians and patients [103].

A key consideration in OIT is the threshold at which allergic reactions are triggered. Previous studies have suggested that shrimp exhibits a higher reaction threshold compared to other allergenic foods, likely due to its relatively lower allergenic protein content (9,10). Houben et al. demonstrated that mustard is the most potent allergenic food, whereas soy and shrimp have the lowest allergenic potential [104], making shrimp allergies unique in the context of OIT protocols.

To further investigate this threshold, DBPCFCs were conducted with shrimp-allergic adults. Participants received increasing doses of shrimp mixed in a seasoned beef matrix, ranging from 100 µg to 4 g. The study revealed that the most

sensitive individuals reacted at 2.5 mg of shrimp protein. Additionally, the estimated dose predicted to provoke reactions in 5% of the shrimp-allergic population (ED05) was with 73.6–127 mg higher than those for other common food allergens, such as peanut, milk, and egg. These findings suggest that shrimp-allergic individuals generally have a higher reaction threshold, though further challenges are needed to confirm these results [105].

The importance of dose and threshold was also explored in a BALB/c murine model for shrimp hypersensitivity, where varying doses of a recombinant shrimp tropomyosin (rMet e 1) were administered to assess allergic responses and immune changes. While all treated mice were desensitized and protected during subsequent challenges, high-dose treatment caused severe systemic reactions. However, low and medium doses led to the upregulation of Treg-associated genes and an increase in Foxp3⁺ cells in gut tissues, suggesting that low-dose immunotherapy promotes local regulatory T cell induction and regulatory cytokine upregulation. This finding highlights the potential safety and long-term efficacy of low-dose immunotherapy in managing shrimp allergy [106].

Sublingual Immunotherapy

SLIT is another promising approach that involves placing allergen extracts under the tongue, allowing for absorption through the oral mucosa. It has emerged as a safer alternative to OIT for food allergy, offering a less invasive and lower-risk approach, albeit at the cost of reduced efficacy. A study conducted on 60 patients (aged from 5 to 50 years) with shrimp allergies evaluated the safety and efficacy of SLIT [107, 108]. Participants were divided into groups based on symptoms such as urticaria, rhinitis, and asthma and were treated with shrimp extract from two shrimp species (*Penaeus semisulcatus* and *Metapenaeus stebbingi*) administered sublingually. After 6 months of treatment, there was a significant reduction in allergic symptoms, accompanied by a decrease in specific IgE levels and an increase in IgG4 levels. While the study provides valuable insights, certain methodological aspects require careful consideration, such as the uncommon presentation of isolated rhinitis and the absence of oral food challenges to confirm outcomes. Future studies with comprehensive clinical assessments should further validate these findings.

A study conducted in a Midwest Allergy-Immunology practice included 66 patients with shrimp allergies, consisting of both children and adults, mainly presenting with systemic or localized reactions to shrimp. Patients were treated with serially diluted shrimp extracts, starting at doses of 64–320 ng and gradually increasing to 0.5 mg/dose three times a day over a treatment duration ranging from 5 to 72 months. A subset of patients (18/66) underwent

challenges, of whom 61% tolerated 42 g or more (~4 shrimp) of shrimp. While some localized reactions occurred, no severe adverse events were reported, underscoring that SLIT could be a safe and effective desensitization approach for shrimp allergy in select patients [109].

Hypoallergen-Based Immunotherapy

Oral desensitization has proven to be an effective strategy for achieving immune tolerance in individuals with food allergies. However, despite its effectiveness, conventional approaches using native allergens frequently lead to allergic reactions, underscoring the need for safer alternatives. One such approach involves the use of hypoallergenic allergens, which was first trialled for fish allergy [110]. Hypoallergens are designed to maintain immunogenicity while minimizing the risk of triggering allergic reactions, thus enhancing both the safety and efficacy of food allergy immunotherapy [111]. Modifying allergenic epitopes—regions of the protein that bind to IgE antibodies—has become a key area of focus for researchers and the food industry [112]. In shellfish allergies, much of this work has centered on modifying TM, the primary allergen in many shellfish species [63].

Effect of Digestion and Food Processing on Allergenicity

Epitopes can be classified into two types: linear and conformational [113]. Linear epitopes are continuous amino acid sequences, while conformational epitopes are composed of discontinuous sequences that fold together through the protein's three-dimensional structure [114]. It has been reported that most IgE epitopes are conformational; however, food processing and digestion often disrupt these structures, leaving linear epitopes more likely to reach the immune system in a reactive state. Nonetheless, under certain conditions, conformational epitopes may remain intact despite processing and digestion [115, 116].

Although digestion primarily influences the natural allergenicity of food proteins by altering their structural integrity, understanding how digestion affects these allergenic epitopes can provide valuable insights for designing hypoallergenic variants for immunotherapy. During digestion, proteins are broken down into smaller fragments, which can alter both conformational and linear epitopes that are crucial for immune recognition [117, 118]. It has been shown that even peptides, despite often being unstable during digestion, may still induce sensitization. Structural changes, such as protein unfolding and aggregation, can either disrupt existing epitopes or create new ones, influencing the protein's sensitivity or resistance to gastric and gastrointestinal enzymes [119]. For example, a study on shrimp (*Penaeus vannamei*) demonstrated that while gastric digestion reduces allergic reactions, gastrointestinal digestion can actually increase

the allergenic potential of shrimp proteins, likely due to the masking or exposure of specific epitopes during digestion [120]. TM from mud crab (*Scylla serrata*) demonstrated high resistance to digestion in simulated gastric and intestinal fluids, unlike other proteins like myosin heavy chain and actin, which were rapidly degraded [121]. Similarly, TM from shrimp (*Penaeus vannamei*) and Chinese mitten crab (*Eriocheir sinensis*) showed resistance to digestive enzymes, although partial reductions in allergenicity were observed. Their digestion-resistant fragments retained allergic activity, highlighting anti-digestion as a critical factor in allergenicity [122, 123].

The processing of food allergens is another factor that influences allergenicity, as thermal treatments and gastrointestinal digestion often destroy conformational epitopes. However, linear epitopes can persist, making them a key factor in the allergenicity of shrimp, even after processing [124]. Some shellfish allergens, such as TM and sarcoplasmic calcium-binding protein from *Litopenaeus vannamei*, retained its IgE and IgG-binding capacities even after undergoing various cooking methods [125]. One study found that roasting shrimp (*Penaeus vannamei*) increased allergenicity by exposing more linear epitopes. However, when roasting was combined with reverse-pressure sterilization, allergic responses were significantly reduced. This combination masked stable epitopes within protein aggregates and enhanced the gastrointestinal digestion of immunodominant epitopes. Mice treated with this combined method exhibited a weaker anaphylactic response, lower levels of specific antibodies, and reduced signs of cell degranulation compared to those treated with only roasted or reverse-pressure sterilized proteins [124]. Yadzir et al. investigated the effects of boiling, frying, and roasting on oyster allergenicity and found that thermal treatment generally reduced allergenicity by decreasing the number of IgE-reactive bands. Interestingly, allergenicity was highest in raw extracts, followed by boiled, with fried and roasted extracts showing similar levels of allergenicity [126]. More recently, it was demonstrated that boiling shrimp can increase IgE reactivity, likely due to the preservation of digestion-resistant allergenic fragments [127]. Consistently, research on TM in shrimp and oysters revealed that cooking does not significantly reduce allergenic risk, as TM remains intact after heat treatment, leading to higher IgE reactivity in roasted extracts compared to raw forms [128, 129]. Also, thermal processing affects T-cell reactivity, as cooked extracts increase IgE reactivity and reduce Treg levels compared to raw extracts, highlighting the immune-modulatory effects of cooking [130].

Among thermal processing methods, high-pressure steaming has emerged as a particularly effective way to reduce the allergenicity of TM in *Penaeus monodon*, surpassing the effectiveness of other heat treatments [131]. Gamma radiation combined with heat significantly reduced

shrimp allergen immunoreactivity, with higher radiation doses showing greater effects [132]. High-intensity ultrasound at 50 °C significantly reduced the major shrimp allergen Pen a 1 and IgE binding, while no effect was observed at 0 °C [133]. This study evaluated the effects of three processing methods—boiling, combined ultrasound and boiling, and high-pressure steaming—on TM from crab. High-pressure steaming was the most effective in reducing TM's IgE/IgG reactivity and enhancing its degradation during gastrointestinal digestion, suggesting it as a promising method to lower crab allergenicity [134].

Glycation and Allergen Modification

Another promising approach to reduce allergenicity involves the glycation of shrimp TM. Glycation, the process of bonding a protein with a sugar molecule, has been shown to reduce the allergenicity of TM in several studies: In a study using a mast cell degranulation system and a murine model, glycated TM with smaller saccharides led to significantly lower histamine release, reduced IgE levels, and milder allergic symptoms. When combined with Al(OH)₃, glycated TM also promoted a shift towards regulatory and Th1 responses and milder anaphylactic symptoms after mice OFC, supporting its potential as a candidate for shrimp allergy immunotherapy. The study also showed that saccharide size was critical, with smaller saccharides producing greater glycation and allergenicity reduction, while TM glycated with maltose had no significant effect [135]. Further research demonstrated that glycation of shrimp TM from species such as *Penaeus aztecus* [136], *Litopenaeus vannamei* [137], *Exopalaemon modestus* [138], and *Penaeus chinensis* [139] with various saccharides also shows potential as a method for developing hypoallergenic candidates for immunotherapy.

A meta-analysis on OIT found that processing methods, including Maillard-treated allergens and slightly processed crustacean meat, significantly reduced anaphylactic symptoms in mice and improved oral tolerance in clinical patients, supporting their potential role in OIT strategies [140].

Enzyme Treatments

In addition to glycation, enzymatic hydrolysis is a promising method for producing hypoallergenic shrimp products. Enzyme treatments, such as transglutaminase (TG) and tyrosinase, have been explored for their ability to reduce the allergenicity of TM by altering its structure and reducing its IgE-inducing capacity. Furthermore, TG-treated TM has been shown to promote Treg proliferation, contributing to its hypoallergenic properties and potential use in food production and immunotherapy [141]. The use of papain, a common enzyme in the food industry, was shown to reduce the

TM allergenicity in shrimp [142]. The study found that treating shrimp meat with 20U of papain, combined with 3 min of heating, decreased TM levels by up to 80%. Additionally, Fourier-transform infrared spectroscopy analysis revealed alterations in the secondary protein structure, highlighting this processing method's potential to produce hypoallergenic shrimp products. In another approach, hypoallergenic variants of Cra g 1 were developed through epitope deletion and site-directed mutagenesis [143]. These variants showed significantly reduced IgE reactivity, degranulation, and allergic mediator secretion, suggesting their potential for use in clinical immunotherapy for shellfish allergies.

Innovative Strategies for Hypoallergens Under Investigation

Beyond these biological modifications, advancements in immunotherapy have extended to the development of novel delivery systems for hypoallergens. Recently, AP205-based virus-like particles (VLPs) were created using the SpyTag/SpyCatcher system combined with the Pen m 1 allergen. These VLPs have shown reduced allergenicity while enhancing the production of TM-specific IgG-blocking antibodies, further improving the safety profile of immunotherapy. Future studies are required to evaluate the efficacy of this method in preventing shrimp-induced anaphylaxis in animal models and eventually in human clinical trials [144, 145].

Efforts to create hypoallergenic variants of shrimp TM have also made significant progress. Research on shrimp TM, Met e 1, has identified specific IgE-binding epitopes and led to the development of two hypoallergenic variants, MEM49 and MED171. These variants exhibited significantly reduced IgE reactivity and allergenicity while inducing IgG antibodies that blocked IgE binding, making them promising candidates for shrimp allergy immunotherapy [146]. Epitope mapping studies on shrimp TM fragments revealed that the N- and C-terminal regions exhibit strong IgE-binding and receptor crosslinking, highlighting key allergenic domains that could inform hypoallergenic design strategies [147]. An evaluation of five Pen a 1 epitopes demonstrated that epitope 3 plays a crucial role in allergenicity, while epitope 5 remained stable across all treatment conditions, including irradiation and heat treatment [148]. Furthermore, Li et al. have shown that hypoallergenic derivatives of mud crab (*Scylla paramamosain*) allergens, specifically through the elimination of dominant linear epitopes in Scy p 1 and Scy p 3, could be promising candidates for immunotherapy [146]. The Pen a 1 mutant VR9-1, carrying 12 amino acid substitutions across major IgE-binding epitopes, demonstrated a remarkable 90%–98% reduction in allergenic potency, suggesting its potential as a therapeutic agent in shellfish immunotherapy [149]. These derivatives, including mutant allergens with deleted heat- and digestion-stable linear epitopes,

were unable to bind to IgE or induce basophil activation in some patients. Additionally, Chen et al. identified the allergen AK in *Oratosquilla oratoria* and developed an epitope-deleted derivative, mAK-L, which demonstrated reduced immunoreactivity compared to recombinant AK [150].

DNA Vaccine-Based Immunotherapy

DNA vaccines can trigger TH1-dominant immune responses, which makes them suitable for allergen-specific therapies. This TH1 bias can be further amplified by co-expressing TH1 cytokines alongside the vaccine antigens. IL-12, a robust TH1-inducing cytokine, has shown significant potential as a DNA vaccine adjuvant in both small and large animal studies and has proven to be safe and effective in humans [151–153]. This innovative strategy involves the administration of plasmid DNA encoding specific shellfish allergens, intending to modulate the immune response and induce tolerance.

Wai et al. introduced two shrimp hypoallergens, MEM49 and MED171, and evaluated their effectiveness as DNA vaccines in reducing shellfish allergy symptoms in mice. The intradermal administration of pMED171 resulted in a significant reduction of allergic responses, primarily through the induction of Treg, which are crucial for maintaining immune tolerance. This treatment notably decreased anaphylactic symptoms and intestinal inflammation following oral allergen challenges [154]. Another study utilized a DNA plasmid vaccine encoding shrimp antigens and a lysosomal-associated membrane protein, demonstrating its ability to suppress anaphylactic reactions by inducing a strong Th1 response characterized by increased levels of IgG2a, IL-10, and IFN- γ [155].

One of the most promising aspects of DNA vaccines is their ability to induce the production of allergen-specific IgG antibodies. These IgG antibodies play a dual role: (a) they can intercept allergens before they bind to cell surface-bound IgE or (b) engage inhibitory receptors like Fc γ RIIb on effector cells, thus mitigating the allergic response. DNA vaccines delivered via Gene Gun targeting shellfish allergens led to a significant increase in shrimp-specific IgG production across several mouse strains, with C3H/HeJ mice showing the highest response. Importantly, the vaccine also induced IgG responses against lobster and crab allergens, indicating its potential for broader cross-reactivity in crustacean allergies [152].

To enhance the efficacy of DNA vaccines, co-delivery of immunomodulatory molecules such as IL-12 has been explored. This method aims to further skew the immune response towards a TH1 phenotype, reducing the TH2-driven allergic response [156]. While DNA vaccines show great promise in preclinical studies, challenges remain in optimizing delivery methods and ensuring long-term

efficacy, particularly when translating findings from animal models to human clinical trials. Ongoing research is required to refine DNA vaccine strategies, addressing these issues to improve the safety and effectiveness of shellfish allergy treatments. Translating preclinical findings into effective patient treatments will necessitate further advancements in delivery methods and long-term efficacy.

Peptide-Based Immunotherapy

Peptide-based immunotherapy (PIT) is an approach gaining considerable attention for allergic diseases. This method uses short synthetic peptides containing allergen-specific CD4+ T cell epitopes, which induce tolerance by stimulating Tregs and promoting a Th1 response [157]. These peptides have a significantly reduced capacity to crosslink IgE, and consequently, they do not activate mast cells or basophils, reducing the risk of allergic reactions [158, 159]. Recent research on TMs, including Pen m 1, demonstrated that T-cell cross-reactivity is influenced more by structural stability than by sequence similarity [49], providing insights for PIT development for shrimp allergies.

A key area of interest in PIT is to identify allergen-specific epitopes for different allergens. For instance, Ravkov et al. identified 17 epitopes from shrimp TM and validated them as capable of inducing T cell proliferation and cytokine release (IL-6 and IL-13) in shrimp-allergic individuals. These epitopes, restricted to common MHC class II alleles, are ideal candidates for PIT [160]. Similarly, Wai et al. evaluated immunodominant T cell epitopes of TM from *Metapenaeus ensis* (Met e 1) in a Balb/c mouse model. Mice treated with the peptide mixture exhibited reduced allergic symptoms, including a significant decrease in Th2-related antibodies and cytokines [161]. Furthermore, PIT using the T-cell epitope of AK encapsulated with the TLR9 agonist CpG-ODN in nanoparticles, demonstrated significant attenuation of Th2-mediated allergic responses, reducing anaphylactic symptoms and Th2 cytokines while enhancing Th1 cytokine expression in a shrimp allergy model [162].

Beyond synthetic peptides, another approach involves mimotopes—short peptides that mimic allergenic epitopes—which have been investigated for targeting shrimp allergens. A study used the one-bead-one-compound library to identify multiple mimotopes that bind TM-specific IgE. These mimotopes were validated through peptide ELISA, epitope mapping, and immunization in a Balb/c mouse model, demonstrating their ability to induce TM-specific IgG without triggering allergic reactions [163].

Monoclonal Antibody-Based Immunotherapy

Anti-IgE therapy has been under investigation for many years and has recently shown promising results in the

management of IgE-mediated food allergy. Omalizumab, a humanized monoclonal antibody targeting free IgE, has been evaluated for its ability to reduce allergic reactions following accidental food exposure [164]. Clinical trials have demonstrated that it can increase the tolerated dose of various food allergens (including peanut, milk, and egg) both as monotherapy and in combination with OIT [165]. Beyond omalizumab, other anti-IgE monoclonal antibodies such as talizumab and ligelizumab have also been investigated. Talizumab showed dose-dependent increases in reactivity thresholds in early peanut allergy trials but was not further developed [166]. Ligelizumab, a next-generation anti-IgE with higher affinity for IgE, has shown potential in early studies; however, it has not yet demonstrated superior clinical benefit to omalizumab in the context of food allergy [164, 167, 168]. To date, omalizumab remains the most extensively studied and the only anti-IgE biologic with Food and Drug Administration (FDA) approval for food allergy [164, 169].

However, data specific to shellfish allergy remain scarce. One pilot study involving 22 patients with asthma and concomitant IgE-mediated food allergy reported reduced reactions to various foods, including shellfish, after six doses of omalizumab, with improvement observed in symptoms such as atopic dermatitis, urticaria, rhinosinusitis, and anaphylaxis [170]. Additionally, a recruiting clinical trial (NCT06369467) is evaluating linvoseltamab—a novel anti-IgE monoclonal antibody—in combination with dupilumab in adults with severe IgE-mediated food allergies, including shellfish, offering a potential avenue for future targeted therapies.

Adjuvant/Complementary Therapies

Probiotics

Probiotics, defined as live microorganisms that confer health benefits to the host when administered in adequate amounts, have been increasingly studied for their role in regulating both the immune system and gut microbiota [171–173]. These microorganisms have demonstrated significant potential in providing preventive and therapeutic benefits for allergic conditions, including shellfish allergies [174]. Schiavi et al. investigated the effects of the VSL#3 probiotic mixture in a shrimp TM-induced mouse model. The results showed that VSL#3 reduced allergic reactions, such as anaphylaxis and histamine release, by shifting the immune response from a Th2-dominated profile to a more balanced Th1/T regulatory profile. This shift decreased pro-inflammatory cytokines like IL-4, IL-5, and IL-13, while increasing anti-inflammatory cytokines such as IL-10 and TGF- β [175]. Similarly, Fu et al. highlighted

the potential of yogurt-sourced probiotic bacteria, *Bifidobacterium longum* and *Bacillus coagulans*, in mitigating shrimp TM-induced allergic responses in a BALB/c mouse model by restoring gut microbiota balance and regulating immune responses [176]. In another shrimp allergy model, *Bifidobacterium infantis* was shown to increase Tregs and balance Th2/Treg ratios, suggesting that probiotics may play a valuable role in managing shellfish allergies through immune modulation [177].

Additionally, oxidative stress has been identified as a factor in the sensitization to allergens. Probiotics, which contain antioxidant enzymes such as glutathione peroxidase and superoxide dismutase, may help reduce oxidative stress by scavenging reactive oxygen species and regulating DCs. This modulation, in conjunction with immune regulation, positions probiotics as a promising therapeutic approach for shellfish allergies [178]. Studies indicate that children with shrimp or crab sensitization have significantly lower GPx activity, further linking oxidative stress to allergic responses [179].

Traditional Chinese Medicine

Research on traditional Chinese medicine (TCM) for treating food allergies remains relatively rare [180]. However, TCM is being explored as a therapeutic option for allergic diseases, including food allergies. Li et al.'s [181] study on a combination of 11 herbs in a mouse model of peanut allergy demonstrated promising results. Ongoing clinical trials are exploring the therapeutic use of Chinese herbal formulations for various food allergies, with encouraging findings reported for several types, including shellfish allergy [182]. The clinical investigation of Food Allergy Herbal Formula-2 (FAHF-2) began after its approval as an investigational new drug by the US FDA in 2007, based on successful murine studies. A phase I trial involving 18 participants with peanut, tree nut, fish, and shellfish allergies demonstrated that FAHF-2 was well tolerated and showed significant immune-modulating effects, including reduced IL-5 and increased IFN- γ . In the phase II trial, extended over 6 months, FAHF-2 continued to show long-term tolerability and BAT reduction. The main outcome was the change in reaction threshold during OFCs before and after treatment. Although the treatment was well tolerated and in vitro studies showed that FAHF-2 suppressed IL-5, induced IL-10, and increased Tregs, indicating a shift to a non-allergic immune response, the primary endpoint was not achieved, possibly due to poor adherence by 44% of participants [182–184]. In another study using a murine model of multiple food allergies, FAHF-2 also protected against allergen-induced anaphylaxis in multiple food allergies (peanut, fish, and egg) [180, 185].

Table 2 Summary of clinical trials of shellfish immunotherapy listed by ClinicalTrials.gov (www.clinicaltrials.gov)

Study details	NCT	Phase	Status	Condition	Intervention type	Sample size	Age (years)	Purpose	Location/duration	Findings
Immunotherapy approaches										
Short-Term Linvoseltamab Treatment on Top of Chronic Dupilumab Treatment for Adults With Severe IgE-Mediated Food Allergy	NCT06369467	1	Recruiting	Food allergy (including shellfish)	Linvoseltamab and dupilumab	6	18–50	Evaluate the effects of Linvoseltamab in patients undergoing Dupilumab treatment for severe food allergy	USA (2024–2025 Estimated)	Not submitted
Open-label Extension Study of ADP101	NCT05243719	1 and 2	Completed	Food allergy (including shellfish)	ADP101 OIT	45	4–57	Evaluate the safety and efficacy of ADP101 for OIT	USA (2022–2024)	Not submitted
Multi OIT to Test Immune Markers After Minimum Maintenance Dose	NCT03181009	2	Completed	Food allergy (multiple allergens)	Omalizumab and multi-Food OIT	60	2–25	Explore if Omalizumab can enhance safety and enable lower maintenance doses in OIT	USA (2017–2019)	–70% showed changes sIgG4/sIgE ratio –Early plasma marker changes occur even at a 300 mg dose with mOIT and omalizumab [187]
Randomized Double-Blind Placebo-Controlled Crab or Shrimp Allergy Reduction Study Using Nambudripad Allergy Elimination Techniques	NCT02208414	N/A	Unknown	Crab or shrimp allergy	NAET ¹	80	> 20	Evaluate NAET with acupuncture techniques over 6 months for shellfish	Taiwan (2012–2014)	Not submitted

Table 2 (continued)

Study details	NCT	Phase	Status	Condition	Intervention type	Sample size	Age (years)	Purpose	Location/duration	Findings
ADP101 for Oral Immunotherapy in Food-Allergic Children and Adults	NCT04856865	1 and 2	Completed	Food allergy (including shellfish)	ADP101 OIT	73	4–55	Evaluate the safety and efficacy of ADP101 for food allergy	USA (2021–2022)	Advisor and Patient Advisory Committee feedback improved ADP101 palatability, refined trial materials, and ensured timely enrollment, with plans to expand patient input in phase 3 [188]
Food Allergen OIT for Shrimp and Cashew	NCT03504774	2	Completed	Shrimp and cashew nut allergy	OIT	52	7–55	Assess desensitization and sustained unresponsiveness to shrimp and cashew allergens	USA (2019–2023)	-Shrimp OIT was safe, with mainly mild (90%) and some moderate (10%) adverse events -Increased sIgG4 [98]
Immunological Response After Shrimp Oral Immunotherapy Treatment	NCT04552522	N/A	Not yet recruiting	Shrimp allergy	OIT	20	12–40	Investigate immune responses (sIgE and IgG4) and tolerance post-oral immunotherapy	Thailand (2020–2024)	Not submitted
Jak Inhibition in Food Allergy	NCT05069831	1	Recruiting	Food allergy (including shellfish)	Abrocitinib (JAK Inhibitor)	40	18–50	Examine the potential of abrocitinib, a JAK1 inhibitor, to reduce food allergy symptoms by measuring BAT, SPT, and sIgE changes over 4 months	USA (2022–2024)	Not submitted

Table 2 (continued)

Study details	NCT	Phase	Status	Condition	Intervention type	Sample size	Age (years)	Purpose	Location/duration	Findings
Adjuvant/complementary approaches										
Therapeutic Effect of Chinese Herbal Medicine on Food Allergy	NCT00602160	2	Unknown	Food allergy (including shellfish)	FAHF-2 herbal formula	68	12–45	Assess FAHF-2 for food allergy, targeting multiple allergens	USA (2007–2012)	-FAHF-2 was safe and well-tolerated, with favorable in vitro effects (e.g., reduced IL-5, increased IL-10, Tregs) -Placebo showed a higher eliciting dose in DBPCFC, with no differences in IgE/IgG4 or epinephrine use [182]
Pilot study on traditional Chinese medicine and food allergy	NCT02490813	N/A	Completed	Allergy to cod, shrimp, crab	Chinese herbal formula-X	18	> 8	Assess allergic tolerance after 8-week treatment with Chinese herbal formula-X	Hong Kong (2015–2023)	Not submitted

¹NAET, Nambudripad Allergy Elimination Techniques

Clinical Trials

Multiple clinical trials have investigated potential immunotherapy treatments for shellfish allergies, as summarized in Table 2. This table includes 10 trials on shellfish immunotherapy, encompassing OIT, Chinese herbal formulas, monoclonal antibodies, and alternative techniques. Key findings suggest that OIT is generally safe, with mild to moderate adverse events, and shows promise for desensitization and increased IgG4 levels. Chinese herbal formulas, such as FAHF-2, demonstrated favorable *in vitro* effects but require further clinical validation. Monoclonal antibodies such as linvoseltamab and omalizumab are being studied for their potential to enhance safety and efficacy. In contrast, alternative approaches like Nambudripad's Allergy Elimination Techniques—a non-conventional method combining acupuncture and muscle testing—have been proposed but lack scientific validation or robust clinical evidence [186]. These studies demonstrate progress in shellfish immunotherapy but underscore the need for continued research to establish long-term safety and efficacy.

Future Directions

The future of shellfish immunotherapy will likely be shaped by advancements in precision diagnostics and personalized treatment strategies, aimed at enhancing both safety and efficacy for patients with severe allergies. Shellfish OIT is a promising option; however, several key questions remain unsolved, including optimal dosing, the duration of maintenance, and how to optimize treatment for patients who are allergic to multiple species of shellfish. Currently, most allergen-specific immunotherapy research for shrimp and shellfish allergy are largely confined to animal models and proof-of-concept studies, limiting their progression to clinical trials and practical application in clinical settings. A major challenge in advancing these therapies is the absence of standardized protocols and comprehensive safety data, both of which are critical for ensuring the reproducibility, scalability, and clinical effectiveness of treatments in human patients.

Given the significant cross-reactivity observed between crustaceans and mollusks, modifying key allergens, such as TM, may offer the potential for broader desensitization across various shellfish species. However, further research is essential to fully elucidate the structural and molecular characteristics of major shellfish allergens. This includes identifying specific T- and B-cell epitopes and analyzing the interactions of IgE with their allergen binding sites. Precision medicine approaches, such as diagnostic tests that assess an individual's specific allergen recognition profile, could enhance the understanding of

shellfish allergies and improve the efficacy of therapeutic interventions.

Another key challenge is the considerable diversity of shellfish allergens. As noted, most allergen-specific immunotherapy strategies focus on TM, despite its variable prevalence across different geographical regions, where it is not always the dominant allergen. This variability complicates the development of universal immunotherapy approaches, as they must account for regional and individual differences in allergen sensitization patterns.

Advances in allergen modification, such as the development of hypoallergenic variants through epitope deletion or structural alterations, hold promise for inducing tolerance without triggering severe allergic reactions. The combination of immunotherapy with biologic agents, including anti-IgE, anti-IL4, and anti-IL13 antibodies, may further enhance both safety and efficacy, particularly in patients with multiple allergies. Emerging strategies, such as microbiome modulation and targeted delivery systems, also show significant potential for reshaping immune responses. Altering the microbiome through interventions such as probiotics may help promote tolerance, while novel approaches such as virus-like particles or DNA vaccines could offer targeted, long-term desensitization with minimal side effects.

Conclusion

Shellfish allergy continues to present ongoing challenges due to its severity, lifelong persistence, and the diversity of allergenic proteins across various species. Although strict avoidance remains the primary management strategy, emerging immunotherapeutic approaches such as allergen-specific immunotherapy, hypoallergenic variants, DNA vaccines, and microbiome-based interventions are reshaping future treatment paradigms. These innovations hold promise for inducing long-term tolerance, but their clinical application is limited by regional variability, insufficient standardization, and a lack of human trials. Advancing shellfish immunotherapy will require the integration of precision diagnostics, targeted interventions, and robust clinical validation to ensure safe, effective, and individualized care.

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Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflicts of interest The authors declare no competing interests.

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