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# Clinical Implications of Cross-Reactive Shellfish Allergens

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**Abstract:** Patients with specific seafood allergies are commonly sensitized to related foods, for example, crab with other Crustaceans and Squid with other mlluscs. In some instances, this represents a true allergy to the related seafood, defined as CR (cross-reactivity), while in other instances, it represents a positive skin or IgE test only, in a patient who can eat the related food without difficulty. This is defined as cross-sensitization. It is extremely important that the clinicians recognize these patterns of cross-sensitization and CR, both to counsel patients on foods that should be avoided and to make sure that foods are not unnecessarily restricted from the diet. In fact, it is very common for patients to be instructed to avoid entire shellfish groups based just on positive tests, which leads to unnecessary dietary restrictions with effects on seafood choices, nutrition, and quality of life.

**Key words:** Cross-reactive, allergen, shellfish.

## 1. Introduction

The diagnosis of clinical hypersensitivity to a particular food allergen is attained through careful history, physical examination, a priori reasoning concerning clinical and epidemiologic features of food allergy, and judicious selection and interpretation of tests, including skin tests, RASTs (radioallergosorbent test), elimination diets, and OFCs (oral food challenges) [1, 2]. Allergists are painfully familiar with the pitfalls of these evaluations, some of which are related to the limitations of tests for food-specific IgE antibody. Compounding the clinical challenge of identifying particular causal food allergens is the phenomenon of CR (cross-reactivity) among various plant and animal proteins. Exposure to homologous proteins can trigger reactions or may be clinically silent while provoking positive test responses for food specific IgE antibody. Is the patient with peanut, fish, or apple allergy likely to react to related foods? The molecular basis of CR was recently reviewed [3, 4] and will not be highlighted in this article. Rather, this review will focus on the clinical data regarding cross-reacting food allergens with the goal of providing a framework to approach these difficult clinical questions.

CR between species of the shellfish group is frequent, but CR between shellfish and other invertebrates is common too [5, 6]. Shrimp-allergic patients have also reported reactions to mites, and clinically relevant CR between crustaceans and HDMs (house dust mites) allergens has been extensively studied [7]. It is well known that HDMs are implicated in detectable IgE to shrimp, even in individuals not exposed to shrimp [8]. Tropomyosin was the first shrimp allergen to be detected and identified as major allergen responsible for ingestion-related allergic reactions [9, 10], and its CR has been well-defined in invertebrates [11, 12]. In recent years, several other shrimp allergens have been described, including AK (arginine kinase) [13], SCBP (sarcoplasmic calcium-binding protein) [14-16], and myosin light chain [17, 18], although little is known of the clinical relevance of these allergens and their role in CR.

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Concerns about possible CR among foods are a common clinical issue in patients with food allergy. In fact, for some food families, such as tree nuts, fish, and shellfish, true CR is very common, while for other related foods, such as legumes and grains, CR is less common even though cross-sensitization is frequently identified [19, 20]. While there is some confusion in the literature, for this review, we will refer to cross-sensitization as a positive test, by either skin or IgE testing, to a related food to which the patient is clinically tolerant, while CR will be used to define true clinical reactivity. This distinction is extremely important, both to be aware of foods that may pose a high risk of reaction and to avoid unnecessary food restrictions. For example, while the patient with cashew allergy is extremely likely to be allergic to pistachio, most patients with peanut allergy will test positive to other legumes but be able to eat them with no difficulty. Here we will review specific food groups with the intent of providing a clinical perspective regarding CR related to a variety of common food allergens, hopefully enabling the clinician to clearly distinguish CR from cross-sensitization, with the ultimate goal of keeping patients safe without any unnecessary dietary restrictions [21, 22]. We will focus on food-to-food CR and not discuss pollen associated food allergies in any detail, aside from some discussion regarding the important relationship of peanut to birch pollen. A summary of each of the major seafood groups will be discussed in this review.

## 2. General Concepts

In human nutrition and health aspects, the human significantly requires seafood. Seafood is denoted to all edible aquatic animals, which specifically refer to numerous types of edible aquatic animals of different species. Seafood is divided into two common categories known as flipper fish and shellfish. Flipper fish comprises of two main subgroups which are bony (> 95%) and cartilaginous while shellfish comprises of two main subgroups which are crustaceans and mollusks. Due to its palatability and promoted nutritional advantages, seafood has been popularly consumed globally. It was reported that the highest consumption rate of seafood happened to be in Asia, or specifically in China, subsequently Japan and the US. According to Refs. [23, 24], data in 2009 discovered that the Americans consumed approximately around 15.8 lb (pound) of finfish and shellfish each person. Specifically, the top choice of seafood is the shrimp, which weighs with an average of 4.1 lb.

Globally, the increase in the international trading of seafood products has led to wider varieties and choices across many countries. Indirectly, it also increases the popularity and frequency of seafood consumption among the consumers. In reference to the data from FAO (Food and Agriculture Organization) (2010), Europe happened to be the largest seafood consumers, specifically in Iceland with an average per capita of crustaceans and seafood absorption roughly around 91 kg. This then followed by Spain with 43 kg, the United Kingdom (UK) with 19 kg, and Germany with 13 kg. In contrast, the US consumed about 8 kg and Australia 11 kg.

### *2.1 Cross-Reactions among Various Shellfish*

Shellfish comprises of different species which are commonly known as crustaceans and mollusks. These types of shellfish have different types of allergens and they often belong to eight parts of food groups, which causes allergy that does not fade out during childhood period, and they are common food allergens among adults. Additionally, several pan-allergens have been discovered and they were grouped in detail. It was mentioned that these pan allergens are accountable towards the CR with other inverted-borate allergen sources. These allergens include the mites, insects and the parasites. Presently, it was reported that there are at least seven types of shellfish allergens and mostly originated from the crustaceans. However, only three allergens are available for the IgE-based routine diagnostic. These three allergens are AK, sarcoplasmic $Ca^{2+}$ binding protein, and tropomyosin. In the meantime, other allergens such as actin, myosin, and light chain are studied to summarize the existing advances on the molecular characters in shellfish allergens, their CR, and available diagnostic approach to manage these allergens [25, 26].

The shellfish class of seafood is comprised of crustaceans and mollusks, and the major allergen responsible for allergic reactions is the muscle protein, tropomyosin [27, 28]. In a US telephone survey, the prevalence of reported shellfish allergy was 2% overall and the rate of reactions to multiple crustacean species was 38%, 49% for mollusks, and 14% with crustacean allergy reported also having a mollusk allergy [29, 30]. Cross-sensitization among shellfish species is extremely common, ranging from 70% to 100% for crustaceans and from 17% to 100% between crustaceans and mollusks [31, 32]. Unfortunately, however, the incidence of true CR is not clear due to a lack of comprehensive studies. Based upon the available data and clinical experience, we estimate that almost all patients with an allergy to one crustacean will be sensitized to other crustaceans, and at least half will react clinically upon ingestion. Similarly, among mollusk allergic patients, approximately 50% report reactions to more than one type of mollusk. Importantly, however, avoidance of all shellfish may not be necessary because the majority of patients—possibly as high as 80%-90%—with a crustacean allergy are not allergic to mollusks, and vice versa [33, 34].

### *2.2 Crustaceans*

In a marine ecosystem, there is a type of shellfish known as crustaceans. They can be found on land and fresh water habitats. About 50,000 to 67,000 of crustaceans can be discovered around the world. However, scientists claimed that the total number of crustaceans can be up to 10 to 100 times greater than the estimated number. According to Refs. [35, 36], crustaceans have significant impact on the human's nutrition as well as the world's economy. It was claimed that the greatest importance of the crustaceans was from the decapods species such as shrimps, prawns, lobster and King crab (Paralithodes). Additionally, FAO (2000) mentioned that species like crabs (blue crab, stone crab) and edible crabs Europe have rich source of food [37, 38].

Crustaceans, particularly crabs, are highly allergenic foods that are responsible for food-induced reactions in both children and adults [39, 40]. Despite its high prevalence, knowledge of the allergen profile of crustaceans is still limited might have IgE-reactivity to other identified shrimp allergens, such as myosin light chain, AK and SCBP; or to the other different shrimp IgE-binding protein bands that remain unidentified. First, we identified several proteins as potential allergens from the frequently consumed shrimp *S. melanto*. Identified proteins were tropomyosin, AK, SCBP, -actin, FBPA, -actinin, and ubiquitin, most of which are abundant in shrimp muscle and are involved in muscle contraction or energy metabolism. Among the new identified shrimp proteins, -actinin is a new shrimp allergic protein involved in muscle contraction too. Until today, -actin had not been identified as an allergen; only Rahman et al. [41] had identified an -actin in crab *Chionoecetes opiolo*, but they did not demonstrate it as a crab allergen.

### *2.3 Crustaceans Allergens*

Allergies happened due to the presence of crustacean. They are present to extensive IgE-mediated shellfish allergies, which can lead to severe reactions [43, 44]. Due to its availability throughout the world, the allergy source from the crustacean shellfish allergy is rapidly spreading to various areas. Besides, the allergies from the Mollusca shellfish are also another contributor of seafood allergies. However, they are not frequently been reported and they do not appear as often as the crustaceans [45, 46]. According to Refs. [47, 48], an IgE-mediated or known to be type I allergy is a type of allergy that originated from the crustacean allergy. Additionally, other crustacean shellfish such as shrimp and prawn were claimed to be as a good source of nutritional seafood. Unfortunately, they are also the major contributor to the allergy throughout the world.

In Southeast Asia, crabs have been highly demanded due to the claim that they have large chelae and higher meat content. Thus, among crustaceans, crabs are the frequent causes of shellfish allergy in several countries. The FAO of the United Nations as well as the WHO (World Health Organization) highlighted that crab and shrimp are the common sources of food allergens as their allergic reactions can be induced by ingestion (FAO/WHO, 2001).

### *2.4 Mollusk Allergens*

Studies of mollusk allergens are focused mainly on the three edible classes of mollusks, namely Gastropoda (e.g., limpet and abalone), Bivalvia (e.g., scallop, clam, mussel, and oyster), and Cephalopoda (e.g., cuttlefish, squid, and octopus). Similar to crustaceans, tropomyosin was identified as allergens in a wide range of mollusk species, such as the Japanese flying squid Todarodes pacificus [48], the abalone Haliotis midae [49], the turban shell Turbo cornutus [50], the Pacific cupped oyster Crassostreagigas [51] and the brown garden snail Helix aspersa [52]. Chu et al. [53] demonstrated that IgE from patients with shellfish allergic patients recognized recombinant tropomyosins from mussel, scallop, and abalone, and thereby confirmed that tropomyosin is also a major mollusk allergen and further demonstrated by inhibition studies that the mollusk and crustacean tropomyosins are cross-reactive. Moreover, Emoto et al. [54] further reported the major allergen of four species of gastropods and seven species of bivalves as tropomyosin.

## 3. Clinical Implications

### *3.1 Prevalence and Epidemiology*

In different countries, the prevalence of food allergy (FA) varies as they are affected by many factors such as age, ethnicity, the frequency of dietary exposure, and the cooking method. In addition, other factors that may affect the outcome of the epidemiologic studies may be due to the methodology, type of FA, and the size of the study population [55].

Taylor [46] mentioned that of about 4.0% of the people around the world are affected by food allergies, which often sourced from shellfish allergies. Generally, seafood, or specifically the shellfish, is part of the leading factors to food allergy in adults. This is commonly due to the food-induced anaphylaxis. However, in comparison between children and adult, it was found that the allergy from the shellfish is lower in children than adult with 0.5% and 2.5% respectively. A study reported on the occurrence of allergies due to shellfish and estimated that the incident happens to occur between 0.5% and 2.5% throughout the world as they depend on the various factors such as the age of the consumer, the amount of consumption, and their geographic locations [56].

An international survey was conducted in 17,280 adults aged between 20 until 44. The questionnaires were distributed to 15 countries. The outcomes of the survey revealed that the symptoms related to seafood allergy mostly came from the shrimp with 2.3%, oyster with 2.3%, and fish with 2.2% [57, 58]. In the United States, a telephone survey was conducted on 14,948 individuals. From the survey, it was discovered that about 2% to 3% are diagnosed to encounter seafood allergy which specifically reported that 2.2% of the allergy is caused by the shellfish and 0.6% caused by fish [59, 60]. Meanwhile, in Spain, a study by Crespo et al. [60] was conducted on 355 children. Through the SPT (skin prick test), it was reported that 6.8% of the children displayed reactions towards the proteins of crustaceans. The outcome also revealed that the most frequent allergies are caused by Crustacean allergies with 82.6% whereas mollusk allergies only 7.2%. Specifically, among all these allergies, the common types of allergies are caused by shellfish, mainly shrimp with 72.5%, crab with 34.8%, and lobster with 17.4% [61, 62]. In a different study done by Andre et al. [1060, in France, the result revealed that 34% out of the 580 patients showed contradicting reactions to food, specifically with IgE only to crabs. According to Chiang et al. [107], it was found that the shellfish allergy is frequently happening in the Asian countries in contrast to the western countries. The claim reflected that the geographic consumption of shellfish might contribute to the occurrence rate. Meanwhile a study by Shek et al. [108], in Singapore was conducted on the children. The shellfish allergy was commonly seen among the native children ranging between the age of 4 to 6 years, with 1.19% and 14 to 16 years with 5.23% compared to expatriate children of similar age range with 0.55% and 0.96% respectively. Generally, the consumption rate of a particular species can be reflected based on the specific shellfish allergy [63, 64].

Although there have been many studies on seafood allergy, yet only a few studies managed to analyze the actual history of shellfish allergy [61]. Daul, et al., [110], conducted a study on 11 participants with positive shrimp hypersensitivity. The outcome revealed that the participants with specific shrimp IgE level remain constant throughout the 24 months of the study period. In contrast, a research by Ayuso et al.[111], revealed that specific IgE antibody levels tend to be higher in children with shrimp allergy. This had proven that children tend to have more of shrimp peptides and greater diversity of epitope than adults. It can be concluded that the level of sensitivity to shrimp decreases as the age increases.

The prevalence of shellfish allergy is often higher than that of fish allergy in the general population. Prawn and crab are the major causes of anaphylaxis in both children and adults. Combined crustacean and mollusc allergy reportedly affects as many as 5.5% (95% CI, 4.3-7.1) of French children (5-17 years old) and 9.0% (95% CI, 6.7-11.9) of American adults (Moonesinghe et al. [4]. The prevalence of crustacean allergy alone is considerably higher, with the highest reported prevalence of 10.3% (95% CI, 7.0-14.9) determined among Italian adults who were confirmed positive by SPT [65].

There are various reasons for the cause of hypersensitivity reaction to shellfish such as ingestion, contact, or inhalational exposures. These kinds of reactions have been described to have direct allergies to the consumers. In a double blind, placebo-controlled oral fish challenge study it was conducted to rectify that the emesis is commonly found in patients with positive reaction. In addition, Oropharyngeal symptoms or generalized pruritus leads the emesis in all patients [66, 67].

In occupational settings, the most common allergens are sourced from the fish and shellfish. These sources of allergens were claimed to be important allergens reactions that frequently happen via direct contact or inhalational exposures. According to Goetz and Whisman [109], it was found that the workers with hypersensitivity reaction were unable to handle the raw food, but once they are cooked, they are able to accept the food, which can lead to a heat-labile allergen.

From the SPT, the outcome revealed that the positive reactions were commonly from crab with 40% and shrimp with 20%. In one study, four workers were found to have positive reaction towards specific IgE to snow crab with 21%. Two of the workers have the same IgE levels with the similar symptoms to those with asthma. Work-related symptoms such as skin rashes, rhinitis, and conjunctivitis were reported to be commonly occurred. Based on this outcome, the combination of work-related symptoms and the results from the specific SPT highlighted that between 11% until 22% of the workers encountered occupational asthma. Meanwhile, 22% may have the possibility to get occupational dermatitis or rhinitis. According to Bu et al. [112], when they are occupationally exposed to these allergens, the Greenlander Inuit does not appear to be protective against the sensitivity of the snow crab or shrimp.

Zeng et al. [68] listed the variation of sources that may lead to various food reactions. Shrimp (4.4%), crab (3.2%), mango (2.3%), cow's milk and dairy products (1.9%), and eggs (1.4%) are among the factors that may cause adverse food reactions to its consumers. This was explained based on the logistic regression analysis, which mentioned that the history of FA and the history of allergic rhinitis are the main aspects that caused FA in children [68].

As mentioned previously, shellfish or crustaceans, which commonly comprise of shrimp, crab, and lobster, lead to the OAS reactions. From these sources, mild childhood asthma, allergic rhinitis, and eczema are among the atopic conditions that commonly occur in many individuals. This pattern of reaction was claimed to be similar to the shellfish or crustacean anaphylaxis. From 1 August 2015 to 31 May 2016, of about 120 pre-enlistees that reported food allergy symptoms were sent to the allergy clinic. Out of this number, 77 (64.2%) of the pre-enlistees were positive of food allergy with the mean age of 19 to 22 years old. Of this 77 people, they are mostly Chinese with 66.2% and Malays with 20.8%. In addition, the most commonly reported foods were shellfish or crustaceans with 78%, peanut with 15.6%, and egg with 6.5%. This then was trailed by anaphylaxis with $n$ = 23 (29.9%). One of the common methods to diagnose that positive result is the SPTs. It was found that the shrimp has OAS 87.1%, crab with OAS 95.8%, and lobster with OAS 91.7% [69].

### *3.2 Pathogenesis and Clinical Symptoms*

Pathogenesis is a complex interaction based on the environmental and genetic factors. In order for it to have immune response to the dietary allergens, it requires various roles from the antigen-presenting cells, dietary factors, effector cell function, homing receptors, humeral immune responces, T cells, signaling pathways, and many other aspects [70].

The immune system protects our body against pathogens and other foreign substances by producing a kind of glycoprotein known as immunoglobulin (Ig) or antibodies from plasma cells or B-cells (a type of lymphocyte). Antibodies are mainly of five types, each one having a different function; the type involved with allergy is immunoglobulin E (IgE). Immunoglobulin E (IgE) is overproduced during an allergic response. On the very first exposure to an allergen, an allergic person becomes sensitized by producing allergen specific IgE that binds with IgE receptors on mast cells (in tissues) and basophils (in circulation). If the sensitized person has another exposure to this specific allergen, then this allergen will bind to the antigenic determinant site (Fab) of IgE attached to the mast cells and basophils. Binding of two or more IgE molecules to mast cells (crosslinking) is required to activate the mast cells. These activated cells result in the release of certain chemicals, such as histamine, serotonin, proteoglycans, serine protease, leukotriene C4 and heparin, that will further bind with their receptors present in other cells (e.g., histamine receptors of blood vessels) and lead to inflammation, irritation, redness and other allergic symptoms. The primary function of our immune system is to defend against infection; however, during an allergic reaction the immune system responds against a substance that is harmless to most people. There are two subpopulations of T helper cells, Th1 and Th2. Th1 cells are helpful in protecting against invading microbes and other particles by producing interferon's and some cytokines. Th2 cells are responsible for triggering allergies by the overproduction of IgE, and are involved in the struggle against parasitic worms. Th2 cells produce cytokines like interleukins (such as IL-5) that enhance the production of specific IgE antibodies by B cells and result in hypersensitivity, eosinophil activation, mucus production and IgE secretion [71, 72]. The body's immune system involves the white blood cells, which produce antibodies. When the body is exposed to an antigen, a complex set of reactions begins. The white blood cells produce an antibody specific to that antigen.

This is called “sensitization”. The job of the antibodies is to detect and help destroy substances that cause disease and sickness. In allergic reactions, the antibody is called immunoglobulin E or IgE. This antibody promotes production and releases chemicals and hormones called “mediators”. Mediators have effects on local tissue and organs in addition to activating more white blood cell defenders. These effects cause the symptoms of the reaction. Histamine is one of the better-known mediators produced by the body. If the release of the mediators is sudden or extensive, the allergic reaction may also be sudden and severe, and anaphylaxis may occur. Allergic reactions are unique for each person. Reaction time to allergens can vary widely. Some people will have an allergic reaction immediately, for others it will take time to develop. Most people are aware of their particular allergy triggers and reactions [73, 74].

The mechanism of IgE-mediated allergic reaction is illustrated in Table. 1. The first exposure to a food allergen including crab will initiate the presence of the allergen by antigen-presenting cells. A T helper 2 ($T_H2$) lymphocyte then will response and interact with B cells, which stimulates the B cells to begin production of IgE antibodies against the allergen. The IgE will circulate in the blood and bind to Fcε receptor I (FcεRI), IgE-specific receptors on the outer part of the mast cells [41]. Subsequent disclosure to the same allergen will cause the connection of allergen to the IgE molecules on the exterior part of the mast cells, which eventually causes lysis of the membrane of mast cells. Additionally, histamine, leukotriene, platelet-activating factor, and prostaglandins are mediators that will be released from the granules and trigger the allergy reactions [75, 76].

According to Kurowski and Boxer [113], the symptoms of food allergy were listed in detail. Some of the symptoms to food allergy are abdominal pain, bloating, vomiting, diarrhea, and itchy skin. Besides that, flushing, generalized urticaria, pruritus, cramping, and swelling of the skin during hives are also among the common symptoms found in hypersensitivity individuals. Surprisingly, these food allergies do not often cause or trigger the respiratory (asthmatic) reactions or rhinitis. Additionally, shellfish allergy that often sources from crab allergy, displays that the symptoms may range from mild urticaria to life-threatening anaphylaxis. Moreover, these symptoms may also cause the symptoms of oral itching or burning sensation (oral allergy syndrome) as soon as they consumed the shellfish [77].

Allergy to shellfish including crab can manifest in the form of mild urticaria to life-threatening anaphylaxis. Most of these reactions are IgE-mediated and may be present in the form of respiratory, gastrointestinal, or cutaneous manifestations with rapid onset. In some cases, the symptoms may only be manifested within minutes of consuming the shellfish [78]. The clinical symptoms of shellfish allergy are presented in Table 1.

**Table 1 Symptoms of allergic reactions.**

| Class | | Name | System | Symptoms | Allergens |
|---|---|---|---|---|---|
| Crustaceans | | Prawns, lobster, rock lobster, crab, | Gastrointestinal | Nausea, Vomiting, Diarrhea, Abdominal cramping | Tropomyosin, AK, troponin, actin Hemocyanin, myosin light chain, SCBP |
| Mlluscs | Gastropods | Abalone, snail, limpets | Cutaneous | Pruritis, Dermatitis, Urticaria, Angioedema | tropomyosin |
| | Bivalves | Clam, oyster, mussels, cockles | Respiratory | Conjunctivitis, Rhinitis, Asthma, Laryngeal edema | tropomyosin |
| | Cephalopods | Squid, cuttlefish, octopus | Systemic | Anaphylactic shock, Hypotension | tropomyosin |

In general, the immunological mechanism in bivalve allergy is a type-I allergy, which is mediated by IgE antibodies. The IgE mediated response is divided into two phases, first allergic sensitization where no symptoms occur and later elicitation with clinical manifestations.

Recently, a 6-year-old boy was reported to have food protein-induced syndrome to shellfish after consuming the clam [79, 80]. This indicated that the food-dependent exercise-induced anaphylaxis has been described to be related to shellfish [81]. Generally, an individual will have anaphylaxis due to a synergistic effect of non-steroidal anti-inflammatory drugs with shellfish [82, 83].

*3.3 Diagnosis of Allergy*

Identifying the allergy involves investigating the medical past of the patients followed by diagnostic tests to identify the sensitivity allergen-specific immunoglobulin E (IgE), either through *in vivo* or *in vitro* assessments [84]. Numerous tests were conducted to search for the diagnostic methods of identifying a true seafood allergy. SPTs and blood IgE assays were conducted to study the possible unavailability of the exact species. It was mentioned that a clinical history of the patient should be presented as a support to the positive or negative result. Additionally, by implementing the *in vivo* and *in vitro* test to evaluate the shellfish, an accurate evaluation can be done to attain a less restricted dietary curtailment result. Below are some of the common methods and approaches that had been adopted [85].

*3.4 Medical History*

In the diagnostic process, a medical history of the patient must be presented in order to relate to the patient's recollection of the events that adjoins the establishment of the symptoms. However, Wild and Lehrer [29] mentioned that it is often that the patients will only be able to relate the symptom to the offending food.

Atopic dermatitis, asthma, and allergic eosinophilic gastroenteritis are among the chronic disorders reactions that are commonly triggered by the food allergies. These reactions were claimed to have poor identification of food allergic in patients due to low predictive value. However, single foods like peanuts have higher predictive value with acute reactions [86]. It was clearly mentioned that the common methods used to diagnose food allergy are reference to patient's clinical history, physical evaluation, trial elimination diets, SPTs, and allergen-specific serum immunoglobulin E (IgE) test. However, due to scarce of diagnostic accuracy, the clinician-supervised OFCs is still the top method that has often been used to confirm the diagnosis [87].

In general, new and improved methods are required to determine the presence of the allergens and the possible resolutions to overcome the allergy. Thus, various studies had reported on the development and improvements that are available as diagnostic tools and new testing methods [87]. As mentioned previously, the diagnostic methods of establishing true seafood allergy require various *in vivo* and *in vitro* tests to demonstrate the presence of specific IgE antibodies. However, the positive and negative test results such as SPTs and blood IgE assays should be supported by a clinical history from the patient and/or oral challenge [88].

*3.5 In Vivo Test*

For patients with a past of IgE mediated to fish or shellfish sensitivity, SPT is said to be the best method in the *in vivo* test. It is crucial to prioritize the safety precautions when analyzing the skin test result if the history was poor. According to Fernandes et al. (2017), the cross-reacting allergens may have the potential to react to positive skin tests with unclear clinical relevance. A study demonstrated a diameter of the swelling after the SPT of about 30 mm. This revealed that the about 80% to 95% of the positive food challenge patients were allergic to black tiger prawn and the giant fresh water prawn [89]. However, Carnés et al. [89] mentioned that when using the cooked shrimp and the lobsters for the SPT, it was found that a total of 42 SPTs were successfully related to the positive food challenge.

*3.6 In Vitro Test*

The aim of the most of *in vitro* tests is to identify the type I hypersensitivity reactions of foods or aeroallergens in patients that have relative contraindications to SPT such as dermatographism, pregnancy or patients with high risk of anaphylaxis with antigen-specific antibodies such as IgE [90]. It was mentioned that the measurement of antigen-specific antibodies is advantageous information to assist in assessing the allergies, which particularly refers to foods. A study was done on young children. The outcome revealed that 62.5% of the children had specific IgG antibodies and while 22.9% had specific IgE antibodies. Meanwhile, the children without symptoms of food allergy had neither of the antibodies [91]. The most common *in vitro* tests are specific IgE test which includes an RAST, ELISA (enzyme-linked immunosorbent assay) and Immuno CAP.

RAST was introduced by Wide, Bennich & Johansson [92] in 1967 as an *in vitro* method to detect the specific antibodies of the IgE class in allergic disease. A close connection has been established between the results from the RAST and the clinical provocation tests [93]. In addition, the assessment of specific reaginic antibodies using *in vitro* methods including histamine was released from excised tissue slices and the outcome was closely parallel to the results from the RAST. In general, despite of its high cost procedure, this method has been reflected as a less sensitive technique for detecting food allergy compared to the skin-prick test. Additionally, the diagnostic IgE levels for fish allergy were identified at 20 kUA/L. At this level, it was claimed to be predictive to clinical reactivity with the certainty of more than 95% [92].

Another test to diagnose food allergy is called as a BAT (basophile activation test). It involves cytometry-based assay whereby the activation markers were measured on the outer part of the basophils which were then followed by the stimulation of the allergen [94]. Varieties of cell-surface markers lead to the identification of the basophils [94]. Recently, Santos and Lack [95] reported the efficiency of BAT to identify the peanut allergy in peanut sensitized and non-sensitized children. From this test, the outcome revealed a highly accurate result whereby 97% were diagnosed to have peanut allergy and a reduction up to 66% can be done in the number of OFC. Meanwhile, other studies investigated the effectiveness of BAT in diagnosing the allergies of different foods such as cow's milk, egg, shellfish, and peach. Overall, BAT was concluded to be effective in diagnosing food allergy [95].

*3.7 OFC*

When diagnosing an individual's reaction to food allergy, it requires high attention to the information related to the individual's medical history, the epidemiology to various food allergies and the outcomes of the test results. However, if these elements are not clearly confirmed or contradicting to the results, the allergy specialist or the clinicians may perform the clinician-supervised OFC [96]. According to Nowak-Wegrzyn et al. [114], OFC was introduced to control the suspected food in progressively increasing doses under a medical condition. In another word, it is a procedure that involves a single-blind food challenge whereby the patient is unaware of the presence of food allergen, but the observer knows. Meanwhile, another challenge known as a DBPCFC (double-blind placebo-controlled food challenge) refers to the procedure whereby both parties are unaware of the allergens [97].

OFC results that turned out to be positive have often been associated to inherent risks. This includes the acute allergic reactions that can be related to life-threatening anaphylaxis, exacerbation of atopic dermatitis, and emotional distress. These symptoms were claimed to be frequently occurring in older children, teenagers, and adults who are anxious and concerned about the food allergy. However, there have been no systemic studies on the prevention or delaying of food allergy yet. Based on the author's experience, patients with 1 or several positive OFCs because of the food will eventually lead to a negative OFC. The statement that positive OFC does not prevent or stop the food allergy instead has supported this; OFC was considered beneficial as it provides a comprehensive diagnosis to the food allergy. This indicates that the patients will need to attend continuous counseling related to food avoidance, avoidance to inadvertent exposure that can lead to risk, and confirmation of the patient's and families' effort to prevent the suspected food [98].

*3.8 CRD (Component-Resolved Diagnosis)*

Currently, progress in laboratory diagnostics is the use of CRD which implies determination of specific IgE against purified native and recombinant allergenic molecules was developed as a new approach for diagnosing allergy. The advantage of CRD over the current methods for determining the concentration of specific IgE is that CRD can distinguish the true allergen molecules from the cross-reactive allergen molecules. CRD enables the detection of the risk of severe symptoms and predicts the development of allergies for each individual patient. Thus, CRD provides a possibility for a personalized approach to the patient with allergy [99].

*3.9 Treatment and Management*

Based on the proven clinical reaction, it can be noted that the management of food allergy is crucial and must be conducted. However, due to CR, it was advisable to avoid consuming the crustacean. This is because, the CR among crustacean is incomplete, and hence the possibility for the allergy to be among the crustacean members is high. Therefore, patients need to be aware of the possible accidental exposure that may come from the food of crustacean members, especially in restaurants which the cooking appliances or utensils may have been used for different kinds of food. In contrast, it is not necessary for the patients to avoid the mollusks unless they are in tandem with the allergy [100].

Additionally, patients with a history of past reactions are advised to wear a medic alert identification and know how to use the epinephrine autoinjector. This is to prepare the patients for any future reactions that can be more severe than the past [101]. In a study done by Carnés et al. [89], a girl was desensitized with a standard rush of immunotherapy protocol with a codfish. As an outcome, the girl was succumbed to the uncooked codfish without any responses. Multiple injections were given in a single day or over few days to attain the maintenance dose rapidly. However, adverse reactions started to display and tend to be higher than with traditional allergens. It was concluded that the rush immunotherapy leads to greater risk for the children and the benefits as well as the risks should be investigated deeply [101].

There are numbers of medicinal reliefs to overcome food-induced disorders such as anti-histamines. It reacts partially to the oral allergy syndrome and IgE mediated symptoms. Besides that, anti-inflammatory therapies were claimed to be useful in overcoming allergic eosinophilic esophagitis or gastroenteritis [102]. In order to reduce the risk of food allergy, several potential therapies had been established whereby only the sensitized patients can tolerate the process. These therapies involved immunologic manipulation of the food-allergic subject or food alteration via genetic engineering of the production of hypoallergenic food [103].

There is no specific treatment for shellfish allergies. Intravenous fluids are often given to patients who have been vomiting. Standard allergic reaction therapy includes antihistamines (H1 and H2) and steroids [104]. In cases of anaphylaxis, intramuscular (IM) or intravascular (IV) epinephrine should be given immediately. Antihistamines, steroids and IV fluids should follow this. In rare cases, refractory to standard treatment intubation may be required to protect the airway [105]. The duration of symptoms and response to treatment is highly variable, and there is no one agreed upon period of observation. In general, benign presentations that respond to standard treatment and improve while in the emergency department can be safely discharged home with oral antihistamines and steroids with clear instructions to return for worsening symptoms. True cases of anaphylaxis should be admitted for further monitoring and close observation [55]. Following treatment, patients were reminded and instructed to prevent encountering or consuming any agent or food. For example, patients who have an allergic reaction triggered by crab should avoid other crustaceans. Despite avoidance, consideration of a prescription for an epinephrine auto-injector may be wise due to the potential for anaphylactic reactions and CR [105].

## 4. Summary

The prevalence and magnitude of clinical allergy caused by cross-reacting proteins and pan allergens appears to be increasing and reflects an increase in atopy and allergen sensitization. The limitations that have plagued the evaluation of classical seafood allergens (egg, milk, wheat, soy, peanut, and seafood), such as the high false-positive rate of SPTs and RASTs, failure of oral challenges to confirm most clinical suspicions of reactivity, and inconsistent reaction rates to related foods, are magnified when dealing with cross-reactive proteins. Future studies are needed to address the clinical relevance, diagnosis, management, natural history, and treatment of these allergies. Such information can only be obtained from careful clinical studies that use blinded oral challenges.

## References

[1] Ferreira, F., Hawranek, T., Gruber, P., Wopfner, N., and Mari, A. 2004. “Allergic Cross-Reactivity: From Gene to the Clinic.” *Allergy* 59 (3): 243-67.

[2] Yong Jeong, K., Hong, C. S., and Yong, T. S. 2006. “Allergenic Tropomyosins and Their Cross-Reactivities.” *Protein and Peptide Letters* 13 (8): 835-45.

[3] Leung, P. S., and Chu, K. H. 1998. “Molecular and Immunological Characterization of Shellfish Allergens.” In *New Developments in Marine Biotechnology*, 155-64.

[4] Mudhafar, M., and Zainol, I. 2019. “Medical Values, Antimicrobial, and Anti-fungal Activities of Polyalthia Genus.” *International Journal of Pharmaceutical Research* 11 (1): 90-6.

[5] Popescu, F. D. 2015. “Cross-Reactivity between Aeroallergens and Food Allergens.” *World Journal of Methodology* 5 (2): 31.

[6] Mudhafar, M., and Alsailawi, H. A. 2019. “An Expression Study Profile of Proinflammatory Cytokines in Asthma Patient.” *Journal of Asian Scientific Research* 9 (12): 227-34.

[7] Gámez, C., Zafra, M. P., Boquete, M., Sanz, V., Mazzeo, C., Ibáñez, M. D., Sánchez-García, S., Sastre, J., and del Pozo, V. 2014. “New Shrimp IgE-Binding Proteins Involved in Mite-Seafood Cross-Reactivity.” *Molecular Nutrition and Food Research* 58 (9): 1915-25.

[8] Srinroch, C., Srisomsap, C., Chokchaichamnankit, D., Punyarit, P., and Phiriyangkul, P. 2015. “Identification of Novel Allergen in Edible Insect, *Gryllus bimaculatus* and Its Cross-Reactivity with *Macrobrachium* spp. Allergens.” *Food Chemistry* 184: 160-6.

[9] Leung, P. S., Chow, W. K., Duffey, S., Kwan, H. S., Gershwin, M. E., and Chu, K. H. 1996. “IgE Reactivity against a Cross-Reactive Allergen in Crustacea and Mollusca: Evidence for Tropomyosin as the Common Allergen.” *Journal of Allergy and Clinical Immunology* 98 (5): 954-61.

[10] Mudhafar, M., Zainol, I., Desa, S., Nor, C., and Jaafar, A. 2019. “Mini-review of Phytochemistry for *Polyalithia longifolia*.” *Eurasian J. Anal. Chem.* 14 (2): 119-47.

[11] Rolland, J. M., Varese, N. P., Abramovitch, J. B., Anania, J., Nugraha, R., Kamath, S., Hazard, A., Lopata, A. L., and O'Hehir, R. E. 2018. “Effect of Heat Processing on IgE Reactivity and Cross-Reactivity of Tropomyosin and Other Allergens of Asia-Pacific Mollusc Species: Identification of Novel Sydney Rock Oyster Tropomyosin Sac g 1.” *Molecular Nutrition and Food Research* 62 (14): 1800148.

[12] Sicherer, S. H., Wood, R. A., and Feldweg, A. M. 2011. “Seafood Allergies: Fish and Shellfish.” Accessed July 5, 2019.

https://www.uptodate.com/contents/seafoodallergies-fish-and-shellfish.

[13] Sicherer, S. H. 2001. "Clinical Implications of Cross-Reactive Food Allergens." *Journal of Allergy and Clinical Immunology* 108 (6): 881-90.

[14] Wang, B., Gong, Y. D., Li, Z. R., Yu, D., Chi, C. F., and Ma, J. Y. 2014. "Isolation and Characterisation of Five Novel Antioxidant Peptides from Ethanol-Soluble Proteins Hydrolysate of Spotless Smoothhound (Mustelusgriseus) Muscle." *Journal of Functional Foods* 6: 176-85.

[15] Yang, Y., Liu, G. Y., Yang, H., Hu, M. J., Cao, M. J., Su, W. J., and Liu, G. M. 2019. "Crystal Structure Determination of *Scylla paramamosain* Arginine Kinase, an Allergen That May Cause Cross-Reactivity among Invertebrates." *Food Chemistry* 271: 597-605.

[16] Mudhafar, M., Zainol, I., AizaJaafar, C. N., Alsailawi, H. A., and Majhool, A. A. 2020. "Two Green Synthesis Methods to Prepared Nanoparticles of Ag: Two Sizes and Shapes via Using Extract of *M. dubia* Leaves." *Journal of Computational and Theoretical Nanoscience* 17 (7): 2882-9.

[17] Kazatsky, A. M., and Wood, R. A. 2016. "Classification of Food Allergens and Cross-Reactivity." *Current Allergy and Asthma Reports* 16 (3): 22.

[18] Mudhafar, M., Zainol, I., Jaafar, C. N. A., Alsailawi, H. A., and Majhool, A. A. 2020. "Microwave-Assisted Green Synthesis of Ag Nanoparticles Using Leaves of *Melia dubia* (Neem) and Its Antibacterial Activities." *Journal of Advanced Research in Fluid Mechanics and Thermal Sciences* 65 (1): 121-9.

[19] Cox, A. L., Eigenmann, P. A., and Sicherer, S. H. 2021. "Clinical Relevance of Cross-Reactivity in Food Allergy." *The Journal of Allergy and Clinical Immunology: In Practice* 9 (1): 82-99.

[20] Mudhafar, M., Zainol, I., Jaafar, C. N., Alsailawi, H. A., Majhool, A. A., and Alsaady, M. 2020. "Phytochemical Screening and Characterization of Meliadubia Leaves Extract for Antimicrobial Activity against *Escherichia coli* and *Staphylococcus aureus*." *Indian Journal of Ecology* 47 (2): 493-6.

[21] Chan, E. S., Greenhawt, M. J., Fleischer, D. M., and Caubet, J. C. 2019. "Managing Cross-Reactivity in Those with Peanut Allergy." *The Journal of Allergy and Clinical Immunology: In Practice* 7 (2): 381-6.

[22] Skypala, I. J., Asero, R., Barber, D., Cecchi, L., Diaz Perales, A., Hoffmann-Sommergruber, K., Pastorello, E. A., Swoboda, I., Bartra, J., Ebo, D. G., Faber, M. A., Fernández-Rivas, M., Gomez, F., Konstantinopoulos, A. P., Luengo, O., van Ree, R., Scala, E., and Till, S. J. 2021. "Non-specific Lipid-Transfer Proteins: Allergen Structure and Function, Cross-Reactivity, Sensitization, and Epidemiology." *Clinical and Translational Allergy* 11 (3): e12010.

[23] Bahna, S. L. 2016. "Not Every Seafood 'Allergy' Is Allergy!" *Ann. Allergy Asthma Immunol.* 117 (5): 458-61.

[24] Majhooll, A. A., Zainol, I., Jaafar, C. N. A., Mudhafar, M., Ha, A., Asaad, A., and Mezaal, F. W. 2019. "Preparation of Fish Scales Hydroxyapatite (FsHAp) for Potential Use as Fillers in Polymer." *J. Chem.* 13: 97-104.

[25] Lopata, A. L., Kleine-Tebbe, J. Ö. R. G., and Kamath, S. D. 2017. "Allergens and Molecular Diagnostics of Shellfish Allergy." In *Molecular Allergy Diagnostics*. Cham: Springer, pp. 399-414.

[26] Norbäck, D., and Wieslander, G. 2021. "A Review on Epidemiological and Clinical Studies on Buckwheat Allergy." *Plants* 10 (3): 607.

[27] Allen, K. J., Turner, P. J., Pawankar, R., Taylor, S., Sicherer, S., Lack, G., and Sampson, H. A. 2014. "Precautionary Labelling of Foods for Allergen Content: Are We Ready for a Global Framework?" *World Allergy Organization Journal* 7 (1): 1-14.

[28] Chatziefthimiou, A. D., Deitch, E. J., Glover, W. B., Powell, J. T., Banack, S. A., Richer, R. A., and Metcalf, J. S. 2018. "Analysis of Neurotoxic Amino Acids from Marine Waters, Microbial Mats, and Seafood Destined for Human Consumption in the Arabian Gulf." *Neurotoxicity Research* 33 (1): 143-52.

[29] Wild, L., and Lehrer, S. 2005. "Fish and Shellfish Allergy." *Current Allergy and Asthma Reports* 5 (1): 74-79.

[30] Majhooll, A. A., Zainol, I., Jaafar, C. N. A., Ha, A., Hassan, M. Z., Mudhafar, M., Majhool, A. A., and Asaad, A. 2019. "A Brief Review on Biomedical Applications of Hydroxyapatite Use as Fillers in Polymer." *J. Chem.* 13: 112-9.

[31] Yang, C. F. J., Kumar, A., Klapper, J. A., Hartwig, M. G., Tong, B. C., HarpoleJr, D. H., and D'amico, T. A. 2019. "A National Analysis of Long-Term Survival Following Thoracoscopic versus Open Lobectomy for Stage I Non-small-cell Lung Cancer." *Annals of Surgery* 269 (1): 163-71.

[32] Marwaha, N., Beveridge, M., Phillips, M. J., Komugisha, B. R., Notere Boso, D., Chan, C. Y., and Wiebe, K. 2020. *Alternative Seafood: Assessing Food, Nutrition and Livelihood Futures of Plant-Based and Cell-Based Seafood*. Penang, Malaysia: WorldFish. Program Report.

[33] ALsailawi, H. A., Mudhafar, M., Majhool, A. A., and Asaad, A. 2019. "Study of Cystatin C as Early Biomarker of Nephropathy in Patients with Type 2 DM and Risk Stratification in Tarnaka Hospital of Hyderabad City in India." *Journal of US-China Medical Science* 16: 232-41.

[34] Anupama, K. P., Nayak, A., Karunasagar, I., and Maiti, B. 2020. "Rapid VISUAL detection of *Vibrio*

*parahaemolyticus* in Seafood Samples by Loop-Mediated Isothermal Amplification with Hydroxynaphthol Blue Dye." *World Journal of Microbiology and Biotechnology* 36: 1-10.

[35] Castaño-Sánchez, A., Hose, G. C., and Reboleira, A. S. P. 2020. "Salinity and Temperature Increase Impact Groundwater Crustaceans." *Scientific Reports* 10 (1): 1-9.

[36] Huang, Y., and Ren, Q. 2020. "Research Progress in Innate Immunity of Freshwater Crustaceans." *Developmental and Comparative Immunology* 104: 103569.

[37] Wolfe, J. M., Breinholt, J. W., Crandall, K. A., Lemmon, A. R., Lemmon, E. M., Timm, L. E., and Bracken-Grissom, H. D. 2019. "A Phylogenomic Framework, Evolutionary Timeline and Genomic Resources for Comparative Studies of Decapod Crustaceans." *Proceedings of the Royal Society B* 286 (1901): 20190079.

[38] Ha, A., Misnan, R., and Mudhafar, M. 2021. "Major and Minor Allergen IgE Reactivity of Purple Mud Crab (*Scylla tranquebarica*) against a Cross-Reactive Allergen in Crustacean and Molluscs in Patients with a Seafood Allergy." *Research Journal of Pharmacy and Technology* 14 (1): 239-44.

[39] Hamilton, R. G. 2019. "Assessment of Human Allergic Diseases." In *Clinical Immunology*, 5th ed., pp. 1283-95.

[40] Štrus, J., Žnidaršič, N., Mrak, P., Bogataj, U., and Vogt, G. 2019. "Structure, Function and Development of the Digestive System in Malacostracan Crustaceans and Adaptation to Different Lifestyles." *Cell and Tissue Research* 377 (3): 415-43.

[41] Misnan, R., Sockalingam, K., Yadzir, Z. H. M., Abdullah, N., Bakhtiar, F., and Murad, S. N. 2019. "Characterization of Major Allergens of *Macrobrachium rosenbergii* and their Thermostability in Different Cooking Methods." *Jurnalteknologi* 81 (1): 163-70.

[42] Al Sailawi, H. A., Misnan, R., Mudhafar, M., Desa, S., and Abdulrasool, M. M. 2020. "Effects of Storage Period on Protein Profile and Allergenicity of Purple Mud Crab (*Scylla tranquebarica*) under Various Storage Conditions." *International Journal of Pharmaceutical Research* 12 (2): 4400-13.

[43] Nelson, K. 2020. "Scheduling of Reproduction in Relation to Molting and Growth in *Malacostracan crustaceans*." In *Crustacean Egg Production*. Boca Raton, FL: CRC Press, pp. 77-113.

[44] Villalta, D., Tonutti, E., Visentini, D., Bizzaro, N., Roncarolo, D., Amato, S., and Mistrello, G. 2010. "Detection of a Novel 20 kDa Shrimp Allergen Showing Cross-Reactivity to House Dust Mites." *European Annals of Allergy and Clinical Immunology* 42 (1): 20.

[45] Al Sailawi, H. A., Misnan, R., Yadzir, Z. H. M., Abdullah, N., Bakhtiar, F., Arip, M., and Ateshan, H. M. 2020. "Effects of Different Salting and Drying Methods on Allergenicity of Purple Mud Crab (*Scylla tranquebarica*)." *Indian Journal of Ecology* 47 (4): 1173-9.

[46] Taylor, S. L. 2008. "Molluscan Shellfish Allergy." *Advances in Food and Nutrition Research* 54: 139-77.

[47] Subramaniam, K., Behringer, D. C., Bojko, J., Yutin, N., Clark, A. S., Bateman, K. S., and Waltzek, T. B. 2020. "A New Family of DNA Viruses Causing Disease in Crustaceans from Diverse Aquatic Biomes." *MBio* 11 (1): e02938-19.

[48] Moonesinghe, H., Mackenzie, H., Venter, C., Kilburn, S., Turner, P., Weir, K., & Dean, T. (2016). Prevalence of fish and shellfish allergy: a systematic review. *Annals of Allergy, Asthma & Immunology*, *117*(3), 264-272.

[49] Nugraha, R., Kamath, S. D., Johnston, E., Karnaneedi, S., Ruethers, T., and Lopata, A. L. 2019. "Conservation Analysis of B-Cell Allergen Epitopes to Predict Clinical Cross-Reactivity between Shellfish and Inhalant Invertebrate Allergens." *Frontiers in Immunology* 10: 2676.

[50] Karnaneedi, S., Huerlimann, R., Johnston, E. B., Nugraha, R., Ruethers, T., Taki, A. C., Kamath, S. D., Wade, N. M., Jerry, D. R., andLopata, A. L. 2021. "Novel Allergen Discovery through Comprehensive De Novo Transcriptomic Analyses of Five Shrimp Species." *International Journal of Molecular Sciences* 22 (1): 32.

[51] Iason, T., Watts, T. J., Siew, L., Caballero, R. M., Till, S. J., and Rutkowski, K. 2019. "Clinical Relevance of *Mollusc sensitisation* in Crustacean-Allergic Patients." *Journal of Allergy and Clinical Immunology* 143 (2): AB256.

[52] Yu, C., Gao, X., Lin, H., Xu, L., Ahmed, I., Khan, M. U., Xu, M. Y., Chen, Y., and Li, Z. 2020. "Purification, Characterization, and Three-Dimensional Structure Prediction of Paramyosin: A Novel Allergen of Rapanavenosa." *Journal of Agricultural and Food Chemistry* 68 (49): 14632-42.

[53] Kamath, S. D., Nugraha, R., and Lopata, A. L. 2017. "Recent Advances in Diagnosis and Management of Shellfish Allergy." In *Food Allergy*, pp. 122-54.

[54] Alsailawi, H. A., Mudhafar, M., and Abdulrasool, M. M. 2020. "Effect of Frozen Storage on the Quality of Frozen Foods—A Review." *J. Chem.* 14: 86-96.

[55] Kim, M., Lee, J. Y., Jeon, H. Y., Yang, H. K., Lee, K. J., Han, Y., and Ahn, K. 2017. "Prevalence of Immediate-Type Food Allergy in Korean Schoolchildren in 2015: A Nationwide, Population-Based Study." *Allergy, Asthma and Immunology Research* 9 (5): 410-6.

[56] Woo, C. K., and Bahna, S. L. 2011. "Not All Shellfish 'Allergy' Is Allergy!" *Clinical and Translational Allergy* 1 (1): 3.

[57] Woods, R. K., Abramson, M., Bailey, M., and Walters, E. H. 2001. "International Prevalences of Reported Food Allergies and Intolerances. Comparisons Arising from the European Community Respiratory Health Survey (ECRHS) 1991-1994." *European Journal of Clinical Nutrition* 55 (4): 298-305.

[58] Ali, A. H., and Rosmilah, M. 2019. "Effects of Food Processing on the Stability and Quality of Shellfish Allergens." *Journal of US-China Medical Science* 16: 149-63.

[59] Sicherer, S. H., and Leung, D. Y. 2015. "Advances in Allergic Skin Disease, Anaphylaxis, and Hypersensitivity Reactions to Foods, Drugs, and Insects in 2014." *Journal of Allergy and Clinical Immunology* 135 (2): 357-67.

[60] Crespo, J. F., Pascual, C., Burks, A. W., Helm, R. M., and Esteban, M. M. 1995. "Frequency of Food Allergy in a Pediatric Population from Spain." *Pediatric Allergy and Immunology* 6 (1): 39-43.

[61] Khanaruksombat, S., Srisomsap, C., Chokchaichamnankit, D., Punyarit, P., and Phiriyangkul, P. 2014. "Identification of a Novel Allergen from Muscle and Various Organs in Banana Shrimp (*Fenneropenaeus merguiensis*)." *Annals of Allergy, Asthma and Immunology* 113 (3): 301-6.

[62] Ha, A., Rosmilah, M., Keong, B. P., and Ateshan, H. M. 2019. "The Effects of Thermal and Non-thermal Treatments on Protein Profiles of *Scylla tranquebarica* (Purple Mud Crab." *Plant Archives* 19 (2): 813-6.

[63] Potter, P. C., Fenemore, B., and Lopata, A. L. 2017. "Crustacean Allergy in South Africa." *Current Allergy and Clinical Immunology* 30 (4): 234-8.

[64] Carr, T. F., Shreffler, W. G., Griffin, N. M., Rosén, K., Zawadzki, R., Matthews, J., and Jones, S. M. 2019. "Longer-Term Safety and Efficacy Measures of AR101 Oral Immunotherapy for Peanut Allergy: Results from a Phase 3 Follow-On Study." *Journal of Allergy and Clinical Immunology* 143 (2): AB256.

[65] Burney, P., Summers, C., Chinn, S., Hooper, R., Van Ree, R., and Lidholm, J. 2010. "Prevalence and Distribution of Sensitization to Foods in the European Community Respiratory Health Survey: A EuroPrevall Analysis." *Allergy* 65 (9): 1182-8.

[66] Qureshi, T. A., Beigh, A. H., Jan, I., Kawoosa, F., Baba, S. M., Gull, A., and Wani, R. R. 2021. "Clinical History Matters, Skin Prick Test (SPT) Results Are Not the Be-All and End-All for Allergy Diagnosis." *Front Med Case Rep* 2 (4): 1-3.

[67] Mudhafar, M. 2019. "Review of Photochemistry for *Polyalithia longiflia*." *Discovery Phytomedicine* 6 (2): 33-55.

[68] Zeng, G. Q., Luo, J. Y., Huang, H. M., Zheng, P. Y., Luo, W. T., Wei, N. L., and Sun, B. Q. 2015. "Food Allergy and Related Risk Factors in 2540 Preschool Children: An Epidemiological Survey in Guangdong Province, Southern China." *World Journal of Pediatrics* 11 (3): 219-25.

[69] Thong, B. Y. H., Arulanandam, S., Tan, S. C., Tan, T. C., Chan, G. Y. L., Tan, J. W. L., and Leong, K. P. 2018. "Shellfish/Crustacean Oral Allergy Syndrome among National Service Pre-enlistees in Singapore." *Asia Pacific Allergy* 8 (2): e18.

[70] Kumar, S., Singh, J., Rattan, S., DiMarino, A. J., Cohen, S., and Jimenez, S. A. 2017. "Pathogenesis and Clinical Manifestations of Gastrointestinal Involvement in Systemic Sclerosis." *Alimentary Pharmacology and Therapeutics* 45 (7): 883-98.

[71] Drouin, S. M., Corry, D. B., Kildsgaard, J., and Wetsel, R. A. 2001. "Cutting Edge: The Absence of C3 Demonstrates a Role for comPlement in Th2 Effector Functions in a Murine Model of Pulmonary Allergy." *The Journal of Immunology* 167 (8): 4141-5.

[72] Mudhafar, M., Zainol, I., Jaafar, C. N. A., Alsailawi, H. A., and Desa, S. 2021. "A Review Study on Synthesis Methods of Ag Nanoparticles, Considering Antibacterial Property and Cytotoxicity." *International Journal of Drug Delivery Technology* 11 (2): 635-48.

[73] Mastrangelo, A., Bonato, M., and Cinque, P. 2021. "Smell and Taste Disorders in COVID-19: From Pathogenesis to Clinical Features and Outcomes." *Neuroscience Letters* 748: 135694.

[74] Ouassou, H., Kharchoufa, L., Bouhrim, M., Daoudi, N. E., Imtara, H., Bencheikh, N., ELbouzidi, A., andBnouham, M. 2020. "The Pathogenesis of Coronavirus Disease 2019 (COVID-19): Evaluation and Prevention." *Journal of Immunology Research* 2020 (10): 1-7.

[75] Abbas, A. K., Lichtman, A. H. and Pillai, S. 2012. *Cellular and Molecular Immunology*. Amsterdam: Elsevier Saunders, p. 426.

[76] Majhooll, AlhusseinArkan, Ismail Zainol, SaripahSalbiah Syed Abdul Azziz, Che Nor Aziza, and Mustafa MudhafarJahil (2010). Mechanical properties improvement of epoxy composites by natural hydroxyapatite from fish scales as a filler. "International Journal of Research In Pharmaceutical Sciences." (2018)

[77] Schmoyer, C. J., Saidman, J., Bohl, J. L., Bierly, C. L., Kuemmerle, J. F., and Bickston, S. J. 2021. "The Pathogenesis and Clinical Management of Structuring Crohn Disease." *Inflammatory Bowel Diseases*. https://doi.org/10.1093/ibd/izab038.

[78] Liu, N., and Abell, T. 2017. "Gastroparesis Updates on Pathogenesis and Management." *Gut and Liver* 11 (5): 579.

[79] Hayashi, D., Aoki, T., Shibata, R., and Ichikawa, K. 2010. "Case of Food Protein-Induced Enterocolitis Syndrome

Caused by Short-Neck Clam Ingestion." *Allergy* 59 (12): 1628-33.

[80] Fani, M., Teimoori, A., and Ghafari, S. 2020. "Comparison of the COVID-2019 (SARS-CoV-2) Pathogenesis with SARS-CoV and MERS-CoV Infections." *Future Virology* 15 (5): 317-23.

[81] Wójciak, P., and Rybakowski, J. 2018. "Clinical Picture, Pathogenesis and Psychometric Assessment of Negative Symptoms of Schizophrenia." *Psychiatr. Pol.* 52 (2): 185-97.

[82] Vidal, C., Bartolome, B., Gonzalez-Quintela, A., Rodriguez, V., and Armisen, M. 2007. "Prawns, Barnacles, and Nonsteroidal Anti-inflammatory Drugs: Effect Modifiers or Interaction?" *Journal of Investigational Allergology and Clinical Immunology* 17 (2): 113.

[83] Tarlinton, R. E., Khaibullin, T., Granatov, E., Martynova, E., Rizvanov, A., and Khaiboullina, S. 2019. "The Interaction between Viral and Environmental Risk Factors in the Pathogenesis of Multiple Sclerosis." *International Journal of Molecular Sciences* 20 (2): 303.

[84] Sastre, J. 2010. "Molecular Diagnosis in Allergy." *Clinical and Experimental Allergy* 40 (10): 1442-60.

[85] Hilger, C., van Hage, M., and Kuehn, A. 2017. "Diagnosis of Allergy to Mammals and Fish: Cross-Reactive vs. Specific Markers." *Current Allergy and Asthma Reports* 17 (9): 1-12.

[86] Sampson, H. A., Aceves, S., Bock, S. A., James, J., Jones, S., Lang, D., and Randolph, C. 2014. "Food Allergy: A Practice Parameter Updated 2014." *Journal of Allergy and Clinical Immunology* 134 (5): 1016-25.

[87] Huang, H. J., Campana, R., Akinfenwa, O., Curin, M., Sarzsinszky, E., Karsonova, A., Riabova, K., Karaulov, A., Niespodziana, K., Elisyutina, O., Fedenko, E., Litovkina, A., Smolnikov, E., Khaitov, M., Vrtala, S., Schlederer, T., and Valenta, R. 2021. "Microarray-Based Allergy Diagnosis: Quo Vadis?" *Frontiers in Immunology* 11: 3611.

[88] Fernandes, A., Pereira, C., Antonio, A. L., and Ferreira, I. C. F. R. 2017. "Food Irradiation Chemistry." In *Food Irradiation Technologies,* pp. 210-36.

[89] Carnés, J., Ferrer, Á. Huertas, Á. J., Andreu, C., Larramendi, C. H., and Fernández-Caldas, E. 2007. "The Use of Raw or Boiled Crustacean Extracts for the Diagnosis of Seafood Allergic Individuals." *Annals of Allergy, Asthma and Immunology* 98 (4):349-54.

[90] Sicherer, S. H., and Sampson, H. A. 2018. "Food Allergy: A Review and Update on Epidemiology, Pathogenesis, Diagnosis, Prevention, and Management." *Journal of Allergy and Clinical Immunology* 141 (1): 41-58.

[91] Hofman, T. 1995. "IgE and IgG Antibodies in Children with Food Allergy." *Roczniki Akademii Medycznej Bialymstoku* 40 (3): 468-73.

[92] Wide, L., Bennich, H., and Johansson, S. G. O. 1967. "Diagnosis of Allergy by an *in-Vitro* Test for Allergen Antibodies." *The Lancet* 290 (7526): 1105-7.

[93] Berg, T., Bennich, H., and Johansson, S. G. O. 1971. "In Vitro Diagnosis of Atopic Allergy. I. A Comparison between Provocation Tests and the Radioallergosorbent." *Test. Int. Arch. Allergy* 40: 770.

[94] Ebo, D. G., Bridts, C. H., Hagendorens, M. M., Aerts, N. E., De Clerck, L. S., and Stevens, W. J. 2008. "Basophil Activation Test by Flow Cytometry: Present and Future Applications in Allergology." *Cytometry Part B: Clinical Cytometry* 74 (4): 201-10.

[95] Santos, A. F., and Lack, G. 2016. "Basophil Activation Test: Food Challenge in a Test Tube or Specialist Research Tool?" *Clinical and Translational Allergy* 6 (1): 10.

[96] Muraro, A., Werfel, T., Hoffmann-Sommergruber, K., Roberts, G., Beyer, K., Bindslev-Jensen, C., and Fernandez Rivas, M. 2014. "EAACI Food Allergy and Anaphylaxis Guidelines: Diagnosis and Management of Food Allergy." *Allergy* 69 (8): 1008-25.

[97] Rancé, F., Deschildre, A., Villard-Truc, F., Gomez, S. A., Paty, E., Santos, C., and Dupont, C. 2009. "Oral Food Challenge in Children: An Expert Review." *European Annals of Allergy and Clinical Immunology* 41 (2): 35.

[98] Chung, B. Y., Cho, Y. S., Kim, H. O., and Park, C. W. 2016. "Food Allergy in Korean Patients with Chronic Urticaria." *Annals of Dermatology* 28 (5): 562-8.

[99] Dodig, S. and Čepelak, I. 2018. "The Potential of Component-Resolved Diagnosis in Laboratory Diagnostics of Allergy." *Biochemica Medica* 28 (2): 020501.

[100] Stiefel, G., Anagnostou, K., Boyle, R. J., Brathwaite, N., Ewan, P., Fox, A. T., and Clark, A. T. 2017. "BSACI Guideline for the Diagnosis and Management of Peanut and Tree Nut Allergy." *Clinical and Experimental Allergy* 47 (6): 719-39.

[101] Atkins D. 2008. "Food Allergy Diagnosis and Management." *Prim Care* 35 (1): 119-40.

[102] Atanaskovic-Markovic, M., Gomes, E., Cernadas, J. R., du Toit, G., Kidon, M., Kuyucu, S., and Caubet, J. C. 2019. "Diagnosis and Management of Drug-Induced Anaphylaxis in Children: An EAACI Position Paper." *Pediatric Allergy and Immunology* 30 (3): 269-76.

[103] Syed, A., Kohli, A., and Nadeau, K. C. 2013. "Food Allergy Diagnosis and Therapy: Where Are We Now?" *Immunotherapy* 5 (9): 931-44.

[104] Taslakian, B., Sebaaly, M. G., and Al-Kutoubi, A. 2016. "Patient Evaluation and Preparation in Vascular and Interventional Radiology: What Every Interventional Radiologist Should Know (Part 2: Patient Preparation and

Medications." *Cardiovascular and Interventional Radiology* 39 (4): 489-99.

[105] VandenHoek, T. L., Morrison, L. J., Shuster, M., Donnino, M., Sinz, E., Lavonas, E. J., and Gabrielli, A. 2010. "Part 12: Cardiac Arrest in Special Situations: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care." *Circulation* 122 (suppl. 3): S829-61.

[106] André, F., André, C., Colin, L., Cacaraci, F., & Cavagna, S. (1994). Role of new allergens and of allergens consumption in the increased incidence of food sensitizations in France. *Toxicology*, *93*(1), 77-83.

[107] Chiang, C. H., Tang, Y. C., Lin, M. W., & Chung, M. Y. (2007). Association between the IL-4 promoter polymorphisms and asthma or severity of hyperresponsiveness in Taiwanese. *Respirology*, *12*(1), 42-48.

[108] Shek, J. K., Macpherson, D. E., Mueller, M. A., & Xiang, J. (2007). Reaction force control of a linear electrical generator for direct drive wave energy conversion. *IET renewable power generation*, *1*(1), 17-24.

[109] Goetz, D. W., & Whisman, B. A. (2000). Occupational asthma in a seafood restaurant worker: cross-reactivity of shrimp and scallops. *Annals of Allergy, Asthma & Immunology*, *85*(6), 461-466.

[110] Daul, C. B., Morgan, J. E., & Lehrer, S. B. (1990). The natural history of shrimp hypersensitivity. *Journal of allergy and clinical immunology*, *86*(1), 88-93.

[111] Ayuso, E., Mingozzi, F., Montane, J., Leon, X., Anguela, X. M., Haurigot, V., & Wright, J. F. (2010). High AAV vector purity results in serotype-and tissue-independent enhancement of transduction efficiency. *Gene therapy*, *17*(4), 503-510.

[112] Bu, Q., Wang, B., Huang, J., Deng, S., & Yu, G. (2013). Pharmaceuticals and personal care products in the aquatic environment in China: a review. *Journal of hazardous materials*, *262*, 189-211.

[113] Kurowski, K., & Boxer, R. W. (2008). Food allergies: detection and management. *American family physician*, *77*(12), 1678-1688.

[114] Nowak-Węgrzyn, A., Assa'ad, A. H., Bahna, S. L., Bock, S. A., Sicherer, S. H., & Teuber, S. S. (2009). Work Group report: oral food challenge testing. *Journal of Allergy and Clinical Immunology*, *123*(6), S365-S383.