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Seafood-Associated Shellfish Allergy: A Comprehensive Review

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ABSTRACT

Shellfish are diverse, serve as main constituents of seafood, and are extensively consumed globally because of their nutritional values. Consequently, increase in reports of IgE-mediated seafood allergy is particularly food associated to shellfish. Seafood-associated shellfish consists of crustaceans (decapods, stomatopods, barnacles, and euphausiids) and molluskans (gastropods, bivalves, and cephalopods) and its products can start from mild local symptoms and lead to severe systemic anaphylactic reactions through ingestion, inhalation, or contact like most other food allergens. Globally, the most commonly causative shellfish are shrimps, crabs, lobsters, clams, oysters, and mussels. The prevalence of shellfish allergy is estimated to be 0.5–2.5% of the general population but higher in coastal Asian countries where shellfish constitute a large proportion of the diet. Diversity in allergens such as tropomyosin, arginine kinase, myosin light chain, and sarcoplasmic binding protein are from crustaceans whereas tropomyosin, paramyosin, troponin, actine, amylase, and hemoyanin are reported from molluskans shellfish. Tropomyosin is the major allergen and is responsible for cross-reactivity between shellfish and other invertebrates, within crustaceans, within molluskans, between crustaceans vs. molluskans as well as between shellfish and fish. Allergenicity diagnosis requires clinical history, in vivo skin prick testing, in vitro quantification of IgE, immunoCAP, and confirmation by oral challenge testing unless the reactions borne by it are life-threatening. This comprehensive review provides the update and new findings in the area of shellfish allergy including demographic, diversity of allergens, allergenicity, their cross-reactivity, and innovative molecular genetics approaches in diagnosing and managing this life-threatening as well as life-long disease.

KEYWORDS

Allergy; characterization; cross-reactivity; occupational allergy; seafood-associated shellfish; tropomyosins

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Introduction

It is well known throughout the world that seafood (fish and shellfish) plays a very important role in human nutrition. The urge for a healthier diet, and the hence substitution of meat with seafood, has resulted in higher demands for both fish and shellfish. Because of this increasing demand, adverse reactions due to seafood consumption have also become common and have acquired higher chances of causing many types of symptoms that are difficult to be defined. The reactions, which include allergy as well as toxic reactions, are

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variable and can also cause infectious diseases (Schmid and Wuthrich, 1997). Typically, there are three types of illnesses which are associated with ingestion of contaminated seafoods, i.e., allergic, toxic or infectious illness. A large number of seafood-related illnesses often fall into the allergic or toxic type. Seafood allergies are the most common and widespread types of food allergies. In fact, they are among the most dangerous of food allergies, hospitalization, and emergency conditions.

Shellfish allergy can be classified as a type of seafood allergy, which is specifically an adverse immune response to any food protein found in shellfish. Just like other food allergies, the allergies with seafood are caused due to the presence of IgE-mediated Type I hypersensitivity from shellfish (Leung and Chu, 1998). Such hypersensitivities, to proteins in shellfish, cause overreaction of the immune system, which in turn leads to severe physical symptoms. Symptoms involve itching as well as swelling of the mouth and throat, i.e., oral allergy syndrome (OAS), and also life-threatening anaphylaxis. Allergic symptoms are caused not only when a susceptible person consumes the allergenic substance but also when exposed to vapors arising from the cooking of shellfish. It is estimated that 75% of individuals who are allergic to one type of crustacean (shrimp, lobster, crawfish, or crab) would also be allergic to other types. Crustaceans and mollusks (oysters, squid, and scallops) contain similar type of proteins. Hence, people might react equally to both types of foods.

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Seafood-associated shellfish

The terms, 'shellfish" and "seafood", are often used interchangeably by the common people. However, seafood is a general term which refers to any kind of edible marine organism. Seafood is composed of diverse groups of sea organisms which are mainly categorized as fish and shellfish. The term "shellfish" is used for both crustacean and mollusks, which have shells or shell-like exoskeleton on their body. They are heterogeneous group of invertebrates found in terrestrials, saltwater, and freshwater habitats.

Crustaceans generally inhabit in the marine ecosystem, diversifying themselves into the oceans. They also live on land, notably as woodlice or slaters, and hoppers. They are even found in freshwater habitats. Between 50,000 and 67,000 of these species are known worldwide. However, scientists estimate that the total number of crustaceans might include 10–100 times greater than the known value. The crustaceans of greater importance are the larger species from the decapods. Fisheries in many parts of the world often capture shrimps, prawns, spiny lobsters, King crab (*Paralithodes*), and centolla. Many species of true crabs, like the Blue crab, Dungeness crab, and the Stone crab, the edible crabs of Europe, are valuable sources of food (Food and Agriculture Organization, 2000).

Mollusks are the largest marine phylum, which comprise around 23% of the named marine organisms. There are around 85,000 described molluskan species, making them the second most diverse phylum of animalia. They are an important food source for humans and are consumed all over the world. The coastal regions of Asia are among the major consumers of mollusks. In many countries mollusks are eaten occasionally rather than as a part of their staple diet. People of southern Europe, especially Spain, consume more cephalopods and shellfish than the people

of northern Europe. Japanese consume higher quantity of squid while the French, Italians, Spainiards, and Portugese consume large quantities of terrestrial snails.

As in crustaceans, adverse reactions have been described in mollusks such as cuttlefish, abalone, limpet, and squid (Shibasaki et al., 1989; Morikawa et al., 1990; Carrillo et al., 1991; Carrillo et al., 1992; Carrillo et al., 1994). Due to the diversity of shellfish and the different common names used to describe them, patients allergic to shellfish fail generally in identifying the offending species.

Classification of shellfish

The edible marine shellfish, which causes an allergic reaction, belong to two main phyla (Woo and Bahna, 2011). The first one is the Athropoda consists of class crustacean, which comprises decapods (crabs, lobstersand shrimps), prawns, brine shrimp, barnacles, stomatopods (mantis shrimp), euphausiids (krill). The second phylum is the molluska consists of class gastropoda comprising abalones (*Haliotis* spp.), conchs, limpets (lapas, opihi), periwinkles, sea slugs, snails (escargot), snail (*Helix aspersa*), whelks (turban shell); class bivalvia comprises clams (cherrystone, geoduck, littleneck, pismo, quahog, *Ruditapes* spp.), cockles, mussels, Blue mussel (*Mytilus edulis*); scallop (*Pecten* spp.), oyster (*Ostrea edulis*) and the other class cephalopoda comprising cuttlefish, squid (calamari), squid (*Loligo* spp.), Pacific squid (*Todarodes pacificus*); octopus (*Octopus vulgaris*).

The most extensive IgE-mediated seafood allergies that cause severe reactions are the allergies caused due to crustacean shellfish (Crespo and Rodriguez, 2003; Villalta et al., 2010). In fact, shrimp, which are broadly consumed as nutritional seafood, are among the crustacean shellfish that contribute significantly to allergy (Lu et al., 2007).

Molluskan shellfish allergies have been documented with all classes of mollusks including gastropods (limpet, abalone), bivalves (clams, oysters, mussels), and cephalopods (squid, octopus). Bivalves, snails, and octopi (mollusks) are also allergenic for which the EU regulation board are currently in the process of evaluating to include into the list of important food allergens that must be specially labeled in line with fish and shellfish (Lopata et al., 2010).

Prevalence and epidemiology of shellfish allergy

Approximately 3.5–4.0% of the world population is affected by food allergies (Taylor, 2008), of which shellfish allergies are common. This can at times be serious. The prevalence of allergies due to shellfish is estimated to be approximately 0.5–2.5% of the general population. It mainly depends on the degree of consumption, age, and geographic locations (Woo and Bahna, 2011). The occurrence of occupational contact dermatitis due to shellfish ranges from 3% to 11% (Jeebhay et al., 2001).

The prevalence of shellfish allergy is higher in Asian countries compared to western countries (Chiang et al., 2007). In a study conducted on children residing in Singapore (Shek et al., 2010), allergy was found to be more common in native children (4–6 years, 1.19%; 14–16 years, 5.23%) compared to that of expatriate children (4–6 years, 0.55%; 14–16 years, 0.96%). Hence, it can be said that each allergy is caused by the species of shellfish consumed regionally. The instances of shellfish allergy in America are estimated to be higher than 7 million; in fact, 2 out of 100 Americans are allergic to shellfish. Around

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40% of the shellfish reactions in the United States, as corroborated by the telephone survey, are severe enough that they need evaluation by physician (Greenwood and Winnard, 1998).

In France, a study by Andre et al., 1994 showed that out of 580 patients who showed adverse reactions to food, 34% of them demonstrated specific IgE only to crabs. A study by Crespo et al., 1995 in Spain has reported that among 355 children, 6.8% showed reactions to proteins of crustaceans by skin prick test (SPT). Also, a study in South Africa, conducted on 105 individuals, has reported perceived adverse reactions to seafood. It was confirmed that sensitization to prawns and rock lobster was observed in 47% and 44% of individuals, respectively (Zinn et al., 1997). Thus, shellfish is among the leading causes of food allergy in most of the adults and is also a common cause of food-induced anaphylaxis. An international survey based on a questionnaire administered to 17,280 adults in the age group of 20-44 years from 15 countries showed that 2.3% of the symptoms were related to shrimp, 2.3% to oyster, and 2.2% to fish (Woods et al., 2001).

Only a few studies have evaluated the actual history of shellfish allergy and have reported it to be long-lasting (Wood, 2003). In a study conducted on 11 subjects for shrimp hypersensitivity, shrimp-specific IgE levels in all subjects were constant for 24 months of the study. They were not affected by shrimp challenge (Daul et al., 1990). Another study has however revealed that children allergic to shrimp had higher specific IgE antibody levels, which showed intense binding to shrimp peptides and greater epitope diversity than in adults. This suggests that sensitization to shrimp could have chances of decreasing with age (Ayuso et al., 2010).

Although shellfish allergy occurs quiet often in adults and in older children, it can also appear at any age, and can be caused by foods which have not shown any allergic reaction previously. Many people who exhibit shellfish allergy will remain allergic to it life-long.

Crustacean shellfish allergy is widely spread across diverse geographical locations due to its availability (Table 1). Prawns and shrimp are the frequent causes of shellfish allergy which are mediated by IgE antibodies. Molluskan shellfish allergies are also seafood allergies but they do not appear as frequently as that of crustaceans (Taylor, 2008). Occupational allergies are reported in workers who are exposed to molluskan shellfish products either by respiratory or by cutaneous routes. Allergies caused due to mollusks are more frequent in France, Spain, Hong Kong, Singapore while they are less frequent in the United Kingdom and Germany. Mollusks have caused approximately 5.6% and 11.7% of serious reactions in France in the years 2002 and 2003 and are reported to have caused 36% cases of anaphylaxis in Singapore during the same time.

A retrospective analysis was performed on seafood-allergic patients in three clinics in the Texas Medical Center between January 1, 1997 and January 30, 2010. Of the 5,162 patients, 159 showed allergy to seafood as diagnosed by physicians (average age of diagnosis was 50.2 (18-81 years) years. Shellfish allergies (59.1%) were more frequent than fish allergies (13.8%). Crustacean allergies (82.6%) were more frequent than mollusk allergies (7.2%). Among all these allergies, those caused by shellfish, shrimp (72.5%), crab (34.8%), and lobster (17.4%) were the common types of allergies (Khan et al., 2011). In a study conducted on nine Orthodox Jews, who observe Kosher dietary laws which prohibit

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Table 1. Global prevalence of shellfish allergy.

Countries	No. of individuals investigated	Prevalence (%)	Class	% of implicated species (common name)	Reference(s)
Philippines	11,158	5.12	Crustacean	–	Shek et al. (2010)
Singapore	30	66.7	Crustacean	30% (prawn, crab, lobster)	Thong et al. (2005)
			Mollusks	gastropods [36.7% (limpet, abalone)]	
Hong Kong, China	7,393	37.8	Crustacean	–	Ho et al. (2012)
			Mollusks	–	
South Africa	105	55	Crustacean	prawn 47% and lobster 44%	Zinn et al. (1997)
			Mollusks	–	
Spain	355	6.8	Crustacean	6.8% crustacean	Crespo et al. (1995)
			Mollusks	–	
France	580	34	Crustacean	14% shrimp, 34% crabs	Andre et al. (1994)
			Mollusks	–	
USA	14,948	2	Crustacean	38%	Sicherer et al. (2004)
			Mollusks	49%	
USA	5,162	59.1	Crustacean	82.6% [shrimp (72.5%), crab (34.8%), and lobster (17.4%)]	Khan et al. (2011)
			Mollusks	7.2%	

– = data deficiency.

eating of shellfish, the presence of IgE sensitization to shrimp was seen (Fernandes et al., 2003). All the nine subjects had perennial respiratory allergies, and showed a positive HDM skin test.

Clinical presentations of shellfish allergy

The clinical manifestations of shellfish allergy could at times be life-threatening "anaphylactic" reactions that vary within an individual and between individuals (Thalayasingam and Lee, 2015). The likelihood of having an anaphylaxis (32%) was statistically different in cases of shellfish and fish allergic subjects.

Shellfish allergy is a type of IgE-mediated immune response (class 1 food allergy). Patients may get exposed to the allergen through the gastro-intestinal tract during ingestion or through the respiratory system by shellfish aeroallergens or through skin contact. At times, breathing difficulties could also occur when one inhales fumes that arise during cooking of shellfish and also in shellfish processing factories. Symptoms could vary from mild rashes and hives (urticaria), swelling (angioedema), gut reactions (vomiting, diarrhea). Other reactions might include gastrointestinal (nausea, abdominal cramping, diarrhea), respiratory (laryngospasm, wheezing), and ocular (conjunctivitis) symptoms. Life-threatening reactions might occur in the case of sensitized individuals. Symptoms include urticaria, angiodema, palate itching, generalized pruritus, difficulty while swallowing, upper airway obstruction, and hypotension with slight sensation of faintness and can cause loss of consciousness in serious cases.

Shellfish allergies are different from other allergies, i.e., allergic reactions due to shellfish being unpredictable, and sometimes occur long after consuming the allergen. They do not show any symptom during the consumption. Food-dependent exercise-induced anaphylaxis is also caused due to shellfish (Maulitz et al., 1979; Tokunaga et al., 1995). In certain subjects, anaphylaxis occurs due to the synergistic effect of non-steroidal anti-inflammatory drugs with shellfish intake (Vidal et al., 2007).

Allergic reactions due to shellfish could affect the skin, respiratory tract, gastrointestinal tract, cardiovascular system. Affected patients might show a single symptom but quiet often there is multi-organs involvement. Severe reactions are likely to occur in the first hour of ingestion when compared to non-severe reactions ($p < 0.005$). Recently, a case of food protein-induced enterocolitis syndrome to shellfish has been reported in a 6-year old boy after ingestion of clam (Hayashi et al., 2010).

Shellfish allergy is common and persistent in adults. It is an important cause of food-induced anaphylaxis in both children and adults. Adults who are allergic to shellfish are more likely to experience respiratory symptoms compared to fish-allergic adults ($p < 0.05$). Shellfish, especially to crustaceans (shrimp, crab, lobster), are also rather common among adults (Lehrer and O'Neil, 1992).

There are some clinical studies that address the minimal eliciting dose for shellfish allergy. Doses are likely to vary from one allergic individual to another. However, a tiny bit can also be sufficient enough to give some people a very serious allergic reaction. Studies on shrimp conducted on double-blind placebo-controls have demonstrated allergic reactions after ingestion of two to four shrimps.

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Reactions caused due to shellfish allergy are immediate, and have been generally reported within 2 h; however, late reactions (particularly exercise-induced anaphylaxis) are also reported up to 8 h after ingestion, particularly with the consumption of Snow crab, cuttlefish, limpet, abalone (Lopata et al., 1997; Villacis et al., 2006).

Diagnostic approach

During the onset of the symptoms, it is important to understand that the adverse reactions are due to shellfish allergy or toxicity. Accurate diagnosis includes understanding the history and a careful interpretation of tests conducted *in vivo* and *in vitro*. Thus, diagnostic procedure mainly depends on the patient's clinical history, *in vivo* analysis of reactivity to skin, *in vitro* quantification of specific serum IgE and in few cases it also depends on oral provocation challenges.

Patient's clinical history

The initial evaluation begins with a thorough clinical history and a physical examination of the patient in order to consider a broad differential diagnosis. A detailed diagnosis, emphasizing the specific type of shellfish, the amount consumed, type of symptoms observed, time of onset of the symptoms and symptoms observed in other individuals who have consumed the same species, is of main priority. Symptoms of reaction shortly after exposure to shellfish could be an indication of shellfish allergy. However, conducting a test is the only sure way to confirm a shellfish allergy. Hence, clinical history and pathophysiology need to be conducted for obtaining better results.

In vivo analysis of skin reactivity

Testing is done usually with a SPT. The SPT requires puncturing in the forearm or back and introducing small amount of allergen found from shellfish. If an allergy is triggered an itchy, swollen, red-spot on the forearm appears in 15–30 minutes because of mast cells releasing histamine. Tests, which are not painful but are uncomfortable, can be positive if a wheal-like symbol develops at the test site. Although skin testing is known to be problematic, a study has demonstrated the high predictive probabilities using the mean wheal diameters to determine positive food challenges with shrimp. A diameter of 30 mm provides a predictive probability of 80 and 95% positive food challenge in patients allergic to Black tiger prawn (*Penaeus monodon*) and Giant freshwater prawn (*Macrobrachium rosenbergii*), respectively (Jirapongsananuruk et al., 2008).

In vitro quantification of specific serum IgE

A radioallergosorbent test (RAST), also known as the allergen-specific IgE antibody test, measures the immune system's response to shellfish proteins by measuring the amount of immunoglobulin E (IgE) antibodies in the bloodstream, where a certain amount of antibodies indicates an allergy. The immunoCAP is also an *in vitro* specific IgE test that generally shows superior sensitivity (Alonso et al., 1995) as well as a theoretical ideal assay defined by multiple analytical features (Williams et al., 2000). ImmunoCAP Specific IgE test results are rapid and do not require the patient to return to the physician's office for reading as do skin tests.

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Oral provocation challenges

Unless the allergic reaction is life-threatening in nature, verification by titrated oral challenge is required to be performed, in a blind, placebo-controlled manner (Bahna, 2007; Nowak-Wegrzyn et al., 2009). Double-blind, placebo-controlled food challenge is considered to be the gold standard, where the patient eats a small amount of the suspected food until he begins to show an allergic reaction. If the patient eats a normal serving without any kind of consequences, the doctor rules out an allergy to that particular food by the patient. Oral food challenge (OFC) is considered to be the standard method but it is laborious and time consuming. Attempts to predict OFC through specific IgE assays and through conventional skin tests have shown sub-optimal results.

Patient care

There is no single cure for allergies, but there are possible ways for getting relief from the symptoms. Many of the mild symptoms could be treated with over-the-counter antihistamines. Antihistamines are used for treating symptoms like hives, runny nose, abdominal pain associated with any allergic reaction. Patients under IgE-mediated reactions to shellfish receive epinephrine autoinjectors. Patients with severe reaction should be treated with a shot of epinephrine. Epinephrine (adrenalin) is the first-line treatment for anaphylaxis. If a child shows severe food allergies, the allergist recommends two epinephrine autoinjectors (EpiPens). It is recommended that patients keep epinephrine at home, in briefcase or purse, at relatives' homes and at the child's school.

Shellfish proteins can sometimes be hidden in non-shellfish foods that are prepared alongside shellfish. Fortunately, shellfish is an ingredient that is rarely "hidden" in foods. Shellfish has chances of being present in fish stock, seafood flavoring, sushi, and surimi. In the USA, if a packaged food contains shellfish, labeling regulations require the specific labeling of the particular shellfish. It is always advised to read ingredient labels to identify any shellfish ingredients. A patient showing allergic symptoms needs to be educated regarding food labeling and the hidden sources of foods. However, avoiding food that might have chances to be contaminated with shellfish ingredients is generally advised. In addition, it is also advised to avoid touching shellfish, going to fish markets or any area where shellfish are being cooked.

Immunotherapy approach

Immunotherapy reduces or eliminates allergic symptoms caused by the specific allergen (Liu et al., 2016). Freeman (1930) was first to report successful case of rush immunotherapy for fish allergy and poorly controlled asthma. In another study by Casimir et al., 1997 on a standard rush immunotherapy protocol with codfish was successfully desensitized. With regard to shellfish, it has developed a mutant tropomyosin with decreased allergenic potential for treatment of shellfish allergy (Reese et al., 2005). Mutant tropomyosin from crustaceans was produced with reduced allergenic potency as demonstrated by rat basophil mediator release assays, and reduced activation was much more pronounced in the murine model (Reese et al., 2005). Recently, immunization with hypoallergens of shrimp allergen tropomyosin inhibits shrimp tropomyosin-specific IgE reactivity by experimental evidence in Balb/

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c mice (Christine et al., 2014). Further, the effect of HDM immunotherapy on shellfish allergy due to tropomyosins (Wong et al., 2015) opens the possibility of novel therapeutic approaches for shellfish allergy.

Shellfish allergens

Shellfish allergens are mostly found in the flesh or as a part of the muscle protein system, while in shrimps, allergens are also reported from the shells. Hoffman et al. (1981), for the first time, isolated two allergens from raw and cooked shrimp (antigen I and antigen II). The heat stable antigen II showed specific IgE binding in the sera of 11 shrimp-allergic subjects. Subsequently, studies have confirmed that antigen II is the major shrimp allergen which was identified as tropomyosin (Daul et al., 1994; Leung et al., 1994). Along with tropomyosin, other allergens have also been identified and characterized from shellfish (Table 2). Tropomyosin and arginine kinase have been identified as crustacean allergens. Many other allergens also have been identified in crustaceans.

Tropomyosin (TM)

In shellfish, a muscle protein tropomyosin is known to be the major allergen which is responsible for ingestion-related allergic reactions. Tropomyosin belongs to the family of actin filament-binding proteins with different isoforms that can be expressed in muscle, and non-muscle tissues. A complex of tropomyosin and troponin regulates the calcium-sensitive interaction of actin and myosin. TM is relatively resistant to acidic digestion (Huang et al., 2010; Liu et al., 2010; 2011).

The open reading frame of cloned TM in invertebrates was reported to consist of 281 amino acids with a monomeric molecular weight of 38–41 kDa. The highly conserved amino acid sequence of tropomyosin is responsible for its identification as panallergen for cross-reactivity between crustaceans, insects, arachnids, and different classes of mollusks (Wild and Lehrer, 2005). The allergens in oyster (Cra g 1), abalone (Hal m 1), and in the squid (Tod p 1) have been identified as tropomyosin and some other species of crustaceans, e.g., Black tiger prawn (*Penaeus monodon*), Kuruma prawn (*Penaeus japonicas)*, Pink shrimp (*Pandalus eous*), King crab (*Paralithodes camtschaticus*), Snow crab (*Chionoecetes opilio*), and Horsehair crab (*Erimacrus isenbeckii*). Identification was done by immunoblotting and overall sequence identity has shown more than 90% homology (Motoyama *et al.*, 2007). TM shrimp allergen identified and termed as Pen a 1 (Brown shrimp, *Penaeus aztecus*) (Reese et al., 1997), Pen i 1 (Indian prawn, *Penaeus indicus*), Lit v 1 (Pacific white shrimp, *Litopenaeus vanamei*) (Gamez et al., 2011), and Cra c 1 (North Sea shrimp, *Crangon crangon*) (Woo and Bahna, 2011).

Arginine kinase (AK)

Arginine kinase is a monomeric phosphagen ATP phosphotransferase, generally found in invertebrates and is key to the energy metabolism (Yao et al., 2005). Arginine-kinase found in decapod crustaceans and HDM (Der p 20) have also been proposed as a probable pan-allergen with 78% sequence homology with shrimp allergen Pen m 2 (Binder et al., 2001). Arginine kinase is identified as a novel shrimp allergen (Yu et al., 2003) and subsequently reported from White shrimp: Lit v 2 (*Litopenaeus vannamei*) (García-Orozco et al., 2007), Chinese shrimp: Fen c 2 (*Fenneropenaeus chinensis*) (Yao et al.,

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Table 2. Specieswise allergenic proteins characterized in shellfish (crustacea and mollusks).

Shellfish	Sources of allergens	Allergens	Proteins	Mol. Wt	Seq. data	Recom protein	Reference(s)
Crustaceans	Mud crab (*Scylla serrata*)	Scy s 2	Arginine kinase	40	–	–	Shen et al. (2011)
	Red crab *(Charybdis feriatus)*	Cha f 1	Tropomyosin	34	cDNA	Yes	Leung et al. (1998a)
	Snow crab (*Chionoecetes opilio*)	Chi o 4	Sarcoplasmic binding protein	38	–	–	Abdel Rahman et al. (2011)
	North Sea shrimp (*Crangon crangon*)	Cra c 1	Tropomyosin	38	–	–	Bauermeister et al. (2011)
		Cra c 2	Arginine kinase	40	–	–	Bauermeister et al. (2011)
		Cra c 5	Myosin light chain	20	–	–	Bauermeister et al. (2011)
		Cra c 4	Sarcoplasmic binding protein	20	–	–	Bauermeister et al. (2011)
	Whiteleg shrimp (*Liptopenaeus vannamei*)	Lit v 1	Tropomyosin	36	–	–	Ayuso et al. (2010)
		Lit v 2	Arginine kinase	40	cDNA Library	No	Garcia-Orozco et al. (2007)
		Lit v 3	Myosin light chain	20	–	–	Ayuso et al. (2008)
		Lit v 4	Sarcoplasmic binding protein	20	–	–	Ayuso et al. (2009)
	Black tiger shrimp (*Penaeus monodon*)	Pen m 1	Tropomyosin	40	cDNA	No	Yu et al. (2003)
		Pen m 2	Arginine kinase	39.9	Yes	–	Yu et al. (2003)
		Pen m 3	Myosin light chain	20	–	–	Yu et al. (2003)
		Pen m 4	Sarcoplasmic binding protein	20	–	–	Shiomi et al. (2008)
		Pen m 6	Troponin C	16.8	cDNA	–	Garone et al. (1991)
	Sand shrimp (*Metpenaeus ensis*)	Met e 1	Tropomyosin	34	cDNA	Yes	Leung et al. (1994)
	Chinese shrimp (Feneropenasus chinensis)	Fen c 2	Arginine kinase Arginine kinase	40	_	_	Anas et al. (2012)
	Indian white shrimp (*Penaeus indicus*)	Pen i 1	Tropomyosin	38	No	No	Shanti et al. (1993)
	Neptune rose shrimp (*Parapenaeus fissurus*)	Par f 1	Tropomyosin	39	No	No	Lin et al. (1993)
	Gulf or Brown shrimp (*Penaeus aztecus*)	Pen a 1	Tropomyosin	36	cDNA	Yes	Deni et al. (1994), France et al. (1997)
	Kuruma prawn (*Penaeus japonicas*)	Pen j 2	Arginine kinase	40	–	–	Yu et al. (2003)
	Brine shrimp (*Artemia franciscana*)	Art fr 5	Myosin light chain	20	–	–	Woo and Bahna (2011)
	American lobster (*Homarus americanus)*	Hom a 1	Tropomyosin	34	Yes	–	Mykles et al. (1998)
		Hom a 3	Myosin light chain	34	cDNA	Yes	Leung et al. (1998b)
	Chinese spiny lobster (*Panulirus stimpsoni*)	Pan s 1	Tropomyosin	34	cDNA	Yes	Leung et al. (1998b)
	Acorn barnacle (*Balarus rustatus*)	Bal r 1	Tropomyosin	–	–	–	Suma et al. (2007)
	Japanese goose barnacle (*Capitullum mitella)*	Cap m 1	Tropomyosin	37	cDNA	No	Suma et al. (2007)
	Narrow-clawed crayfish *(Pontastacus leptodactylus)*	Pon l 4	Sarcoplasmic binding protein	20	–	–	Woo and Bahna (2011)
	Krill (*Euphausea superba*)	Eup s 1	Tropomyosin	38	Yes	Yes	Nakano et al. (2007)
	Krill (*Euphausea pacifica*)	Eup p 1	Tropomyosin	38	Yes	Yes	Nakano et al. (2007)

(*Continued*)

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Table 2. (Continued).

Shellfish	Sources of allergens	Allergens	Proteins	Mol. Wt	Seq. data	Recom protein	Reference(s)
Mollusks	Tropical green mussel (*Perna viridis*)	Per v 1	Tropomyosin	38	Yes	–	Chu et al. (2000)
	Mediterranean black mussel (*Mytilus galloprovincialis*)	Myt g PM	Paramyosin	–	–	–	Anas et al. (2012), Galler (2008), Tsai et al. (2005)
	Pacific oyster *(Crassostrea gigas)*	Cra g 1.01	Tropomyosin	35	Peptide	No	Ishikawa et al. (1998b)
		Cra g 1.02	Tropomyosin	35	No	–	Leung and Chu (2001)
		Cra g 1.03	Tropomyosin	31	cDNA	–	Ishikawa et al. (1997, 1999)
	Noble scallop (*Mimachlamys nobilis)*	Mim n 1	Tropomyosin	–	–	–	González-Fernández (2014)
	Scallop (*Chlamys nobilis)*	Chl n 1	Tropomyosin	38	cDNA		Chu et al. (2000), Lu et al. (2004)
	Variously coloured abalone (*Haliotis diveriscolor)*	Hal d 1	Tropomyosin	38	Yes	–	Wang et al. (2008)
	Pacific abalone (*Haliotis discus*)	Hal d 1	Tropomyosin	38	Yes	–	Choi et al. (2003)
		Hal di	Paramyosin	103	–	–	Suzuki et al. (2011)
	South African abalone (*Haliotis midae*)	Hal m 1	Tropomyosin	49	No	No	Lopata et al. (1997)
	Red abalone (*Haliotis rufescens*)	Hal r 1	Tropomyosin	36	–	–	Chu et al. (2000)
	Common whelk *(Buccinum undatum)*	Buc u 1	Tropomyosin	36	–	–	Lee and Park (2004)
	Horned turban snail (*Turbo cornutus)*	Tur c 1	Tropomyosin	35	Peptide	No	Ishikawa et al. (1998b)
		Tur c PM	Paramyosin	–	–	–	Galler (2008)
	Brown garden snail *(Helix aspersa)*	Hel a 1	Tropomyosin	36	cDNA	Yes	Asturias et al. (2002)
	Fan shell *(Pinna atropurpuria)*	Pin a 1	Tropomyosin	–	–	–	Leung and Chu (1998)
	Razor clam *(Ensis macha)*	Ens m 1	Tropomyosin	–	–	–	Jimenez et al. (2005)
	Japanese common squid (*Todarodes pacificus)*	Tod p 1	Tropomyosin	38	12 residue	No	Miyazawa et al. (9196)
	Common octopus *(Octopus vulgaris)*	Oct v 1	Tropomyosin	31–34	–	–	Ishikawa et al. (2001)
		Oct v PM	Paramyosin	–	–	–	Galler (2008)

– = data deficient.

2005), Black tiger prawn: Pen m 2 (*Penaeus monodon*), and other shrimp species using a proteomics approach (Yu et al., 2003). It is identified in crab species: Mud crab (*Scylla serrata*) (Shen et al., 2011), and in Snow crab (*Chionoecetes opilio*) (Abdel Rahman et al., 2011), in some other invertebrates, such as the House-dust mite (*Dermatophagoides farinae*) (Bi and Chew, 2004), Indian-meal moth (*Plodia interpunctella*) (Binder et al., 2001), and Silkworm larvae (*Bombyx mori*) (Liu et al., 2009). And also in mollusks: Common octopus *Octopus vulgaris* (Oct v 2), Ocellated octopus *Octopus fangsiao* (Oct f 2) (Florin-Dan, 2015). AK obtained from shrimp which is anticipated to play an essential role as a cross-reactive crustacean allergen and in rousing hypersensitivity responses (Yu et al., 2003). Characterization of AK is done by Molecular genetics and Mass spectrometry techniques (Abdel Rahman et al., 2012).

Sarcoplasmic calcium-binding protein (SCP)

Immunoreactive band (20 kDa) was identified from Black tiger shrimp (*Penaeus monodon*) as SCP (Shiomi et al., 2008). It is a new crustacean allergen. SCP is found in Black tiger shrimp (Pen m 4), Kuruma shrimp (*Penaeus japonicus*), American lobster (*Homarus americanus*), Pink shrimp (*Pandalus eous*), King crab (*Paralithodes camtschaticus*), Pacific white shrimp (*Litopenaeus vannamei*), and Snow crab (*Chionoecetes opilio*) (Shiomi et al., 2008; Ayuso et al., 2009; Abdel Rahman et al., 2011). SCP is also known as Lit v 4 with 22 kDa allergen, 194 amino acids, and isoelectric point of 4.7 (Ayuso et al., 2009). It is an invertebrate EF-hand calcium buffering protein that fulfills a similar function in muscle relaxation as vertebrate major allergen parvalbumin (White et al., 2011). It is an important allergen in the pediatric population, as recombinant SCP was recognized by serum IgE from 20 of 52 (38.4%) shrimp allergic subjects, with a higher frequency in children (17 out of 23; 74%) than in adults (3 out of 29; 10%) (Ayuso et al., 2009). To characterize this allergen a few methods are employed such as ELISA, Edman, Western blotting, liquid chromatography-tandem mass spectrometry (LC-MS), mass spectrometry, or molecular genetics (Abdel Rahman et al., 2012).

Myosin light chain (MLC)

It is a muscle protein of 20 kDa (Ayuso et al., 2008). MLC from the Pacific white shrimp termed as Lit v 3 was recognized as a new shrimp allergen in the Pacific white shrimp (*Litopenaeus vannamei*) (Ayuso et al., 2008), and then it was also identified in Black tiger prawn (*Penaeus monodon*) (Abdel Rahman et al., 2010a). TM is known as the major allergen, but in some patients' sensitivity to MLC is seen. It has a similar molecular weight and similar isoelectric point to SCP, which causes difficulties to recognize. It is also found that patients with IgE binding to the boiled form of MLC appear to be greater in adults compared with children who tend to recognize the MLC in the raw extract with higher intensity (Ayuso et al., 2008).

Paramyosin (PM)

It is a 103 kDa cross-reactive muscle protein present in diverse invertebrates. Molluskan PM is responsible for "catch" mechanism which enables sustained contraction of the muscles with very little energy expenditure. House dust mite allergen Der p 11 (PM with 89% identity with Der f 11) presents significant homology with the PM of mollusks: Mediterranean black mussel *Mytilus galloprovincialis* (Myt g PM),

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Pacific abalone *Haliotis discus* (Hal d PM), Horned turban snail *Turbo cornutus* (Tur c PM), Common octopus *Octopus vulgaris* (Oct v PM) (Anas et al., 2012; Galler, 2008; Tsai et al., 2005).

Other IgE-reactive shellfish proteins

Other potent allergens such as myosin heavy chain (Martins et al., 2004), troponin, actine (Juji et al., 1990; Koshte et al., 1989; Maeda et al., 1991) are also reported in molluskan shellfish. Amylase and hemocyanin are other allergens found in mollusks and are possibly involved in cross-reactivity with House-dust mite aeroallergens. Alpha-amylase Der p 4 may be involved in *Dermatophagoides pteronyssinus* cross-reactivity in gastropod allergy (Florin-Dan, 2015). These allergens were identified and characterized in different species such as mussel, oyster, and crustaceans (Taylor, 2008). A high molecular weight protein of 75 kDa was found to be an additional major allergen in Black tiger prawn (*Penaeus monodon*) (Sahabudin et al., 2011; Kalyanasundaram and Santiago, 2015).

Cross-reactivity of shellfish allergens

Cross-reactivity is the recognition of distinct antigens by the same IgE antibody demonstrable by *in vivo* and *in vitro* tests, and is clinically manifested as reactions caused by antigens homologous to different species (Torres et al., 2003). Cross-reactivity occurs because of shared similar IgE binding epitopes. Allergic consumers might sometimes experience cross-reactions between closely related seafood. As in the case of crustacean allergy, most of the sensitive individuals are allergic to various species of shrimp, crab, lobster, and crayfish (Lehrer, 1986). If a patient is allergic to one shellfish, they have approximately 75% chance of being allergic another shellfish. Because of common antigenic structures, different species show cross-sensitization especially between crustaceans and mollusks. In invertebrates, tropomyosins show greater homology in their amino acid sequence and are the panallergens responsible for cross-reactions between crustacea, insects, mites, nematodes, and various classes of mollusks (Table 3).

Between shellfish and other invertebrates

Allergic reactions in shellfish, as well as in mites and insects have been widely reported (Ayuso et al., 2002; Banzet et al., 1992; Crespo et al., 1995; Martins et al., 1999; Oneil and Lehrer 1995; Petrus et al., 1997, 1999; Reese et al., 1999; Lehrer and Reese, 1998). Such frequently encountered cross-reactivity is probably due to tropomyosins from shellfish, insects and mites, belonging to phylum arthropod (Jeebhay et al., 2007; Lopata et al., 2005; Wong et al., 2015). The cross-reactivity between mites (Der p 10) and shellfish is frequent, mainly with crustaceans and to a lesser extent with mollusks (Carrillo et al., 1992)) and insects. Clinically relevant cross-reactivity between crustacean and house dust mite allergens (Witteman et al., 1994) is sometimes termed as "mite-crustaceans-mollusks-syndrome".

Within crustaceans

Subjects with shrimp hypersensitivity usually react to other types of crustacean. A lower degree of cross-reactivity is observed between members of the crustacean family, such as barnacles, with amino acid sequence identity of only 61% when compared with that of shrimp.[28]

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Table 3. Shellfish allergen cross-reactivity.

Shellfish groups	Clinical reactivity (%)	Sensitization (%)	Comments	Reference(s)
Shrimp vs. other crustacean	38*		Tropomyosins are panallergens that also are responsible for cross-reactions to crustaceans in those with dust mite and cockroach allergy	Radauer et al. (2008) Beaudouin et al. (2006)
Mollusca vs Molluska	49*	47		Morita et al. (2007)
Crustacea vs Molluska	14*			Mansoor and Sharma (2011)

*Percentage based on reported clinical reactions and not systematically evaluated by using DBPCFCs (double-blinded placebo-controlled food challenges).

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It is observed that cross-reactivity frequently occurs in phylogenetically related family of crab, lobster, shrimp, etc. among the crustaceans (Ayuso et al., 2002, Lehrer and McCants, 1987; Lehrer et al., 1988; Motoyama et al., 2006; Reese et al., 1999; Zhang et al., 2006). Crustacean species have very high homologies up to 985 among the different shrimp, crab, and lobster species. Interestingly, an identified barnacle tropomyosin has also demonstrated a much lower sequence identity with only 58% (Suma et al., 2007). Inhalant arthropod-derived troptomyosins share high sequence identities to crustacean troptomyosins with up to 84%. These allergenic troptomyosins are found in two cockroaches (Per a 7 and Bla g 7) as well as in the House-dust mite (Der p10 and Der f 10). Cross-reactions with the related tropomyosin allergens in crustacean shellfish may also occur but this is less clearly defined.

Within mollusks

Cross-reactivity to tropomyosin from molluskan shellfish observed with sera from patients allergic to oysters, which suggested that individuals allergic to molluskan should avoid eating all species of mollusks (Taylor, 2008). Cross-reactions are found in mollusks within the same class (bivalves, cephalopods, or gastropods). As in patients with history of shellfish allergy, patients showing a positive skin test to clam had a 0.55 (55%) probability to show a positive skin test to scallop, while patients with negative result to clams had a 0.05 (5%) probability of a positive skin test to scallop. It was also reported that those testing positive to abalone had a 25% probability of positive skin test to scallop and a 79% probability of positive skin test to limpets. Hence, patients allergic to bivalves (clams, mussels, oysters, and scallops) are likely to react to other bivalves, while patients showing reactions toward gastropods (abalones, limpets, snails, winkles, and whelks) are likely to react to other gastropods. A case of fatal anaphylaxis on consumption of terrestrial snails has been reported of a patient who was diagnosed as allergic to abalone showing cross-reactions relating to biological families (gastropods) rather than to seafood versus land animals.

Between crustacean and mollusks

A study by Lehrer and McCants (1987) reported that crustacean sensitized sera had significant IgE antibody reactivity to oyster extract by RAST analysis, highlighting the cross-reactivity within shellfish. Crustacean allergic patients generally react to molluskan

species (Ishikawa et al., 1998a; Lehrer et al., 2003). Serological and clinical cross-reactivity are reported between crustaceans and the mollusk squid (*Todarode pacificus*) (Jeong et al., 2006; Miyazawa et al., 1996), the allergen being Tod p 1 which is also a tropomyosin and seems to cross-react with other squid (*Loligo vulgaris*) as well as shrimp, lobster, and crab. Crespo's group in Spain have reported that 9 among 10 children with sensitization to mollusks reacted by SPT and specific IgE to crustaceans (Crespo et al., 1995). Of the subjects with allergies to crustaceas and mollusks only 38% and 49%, respectively, reported reactions to multiple species, and only 14% cross-reactivity was reported between the crustacean and mollusks.

Tropomyosin is also demonstrated in a number of molluskan species (Leung et al., 1996) and is key to understanding the cross-reactivity existing between species of the same class of shellfish (crustaceans, bivalves, gastropods, and cephalopods), between crustaceans and mollusks (Uda et al., 2006). For example, squid contain an important allergen, tropomyosin, in some parts of Europe, as do oysters, mussels, scallops, and edible snails, and they cross-react with crustaceans. Significant RAST reactivity to oyster extracts has been found in sera from crustacean-sensitive subjects and form a number of patients having sensitivity reactions to both crustaceans and oysters. Moreover, there is a significant correlation of IgE reactivity to oyster with that of crustacean allergens suggesting that oyster and crustacean may share common antigenic epitopes (Lehrer and McCants 1987).

Between shellfish and fish

It is estimated that 50% of people who are allergic to some species of fish have risks of reacting adversely to another species, while those allergic to some crustacean species are at 75% risk due to the greater similarity among tropomyosins than among parvalbumins. Tropomyosins do not cross-react with those in vertebrate fish (parvalbumins). Hence, avoidance of both vertebrate fish and crustaceans is generally unnecessary on the basis of cross-reactivity (Torres et al., 2003).

Occupational exposure to shellfish allergens

The allergic symptoms not only appear from ingestion of seafood, but could also be triggered from inhaling cooking vapors and by handling seafood in occupational environment (Goetz and Whisman 2000; Jeebhay et al., 2001; Taylor et al., 2000) (Table 4). Occupational exposure to shellfish could trigger allergy as in Snow crab (*Chionoecetes opilio*) processing plants *de novo* sensitization could also occur (Weytjens et al., 1999). The reported estimation for prevalence of occupational asthma caused in shellfish-processing workers is about 2–36% (Jeebhay et al., 2001; Moscaa et al., 2015). Exposure through the skin contact occurs more in occupational cases and its manifestations are mostly cutaneous in the form of urticaria or allergic contact dermatitis (Rašković et al., 2014).

Workers could get exposed occupationally through manual or automated processing of crabs, prawns, mussels, fish, and fishmeal production. Aerosolization of shellfish and cooking fluid during processing are potential occupational situations that could result in sensitization through inhalation. There is great variability of aerosol exposure within and among various jobs with reported allergen concentrations ranging from 0.001 to 5.061 μg/m^3. Studies have even documented the aerosolization of seafood (muscle, visceral organs, skin /mucin) during canning and fishmeal operations resulting in highly variable levels of

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Table 4. Shellfish and their agents that induce occupational reactions in seafood workers (Adapted from Lehrer et al., 2003).

Shellfish	Agent(s)	Exposure	Disease	Reference(s)
Crustacea	Shrimp	Fish market workers	Allergic contact urticaria	Fisher (1988)
	King crab	Processing	Asthma	Orford and Wilson (1985)
	Lobster, shrimp	Processors	Asthma	Lemiere et al. (1996)
	Shrimp-meal	Aquaculture	Asthma	Carino et al. (1985)
	Crab	Processing	Asthma	CDC (1982)
	Snow crab	Processing	Asthma	Cartier et al. (1984) and (1986)
	Prawns	Processing	Asthma, dermatitis	Gaddie et al. (1980), McSharry and Wilkinson (1987)
	Gammarus shrimp	Fish factory worker	Asthma	Baur et al. (2000)
	Shrimp	Caterers	Contact urticaria, dermatitis	Cronin (1987), Maibach (1986)
	Shrimp, scallop	Restaurant workers	Asthma	Goetz and Whisman (2000)
	Lobster	Cooks	Contact urticaria, asthma	Goransson (1981), Patel and Cockcroft (1992)
	Shellfish	Food handlers	Contact dermatitis	Hjorth and Roed-Pertersen (1976)
Mulluska	Oysters	Oyster shuckers	Dermatitis	Yamura and Kurose (1966)
	Oysters	Culturing	Asthma	Nakashima (1969), Wada et al. (1967)
	Mother of Pearl	Button factory workers	Asthma	Tas (1972)
	Clam, scallop	Food company workers	Asthma	Desjardins et al. (1995)
	Seashells	Shell grinders	Asthma	Kim et al. (1982)
	Mussels	Mussel processors	Dermatitis	Zhoutyi and Borzov (1973)
	Cuttlefish	Contact	Dermatitis	Burches et al. (1992)

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airborne particulate (0.001–11.293 mg/m^3) and allergens (0.001–75.748 μg/m^3). Occupational asthma to shellfish is reported in fisherman, processing workers, shell grinders, cooks and also in restaurant workers (Cartier et al., 1986; Droszca et al., 1981; Gaddie et al., 1980; Hudson et al., 1985). The prevalence of occupational asthma ranges from 7% to 36%, and occupational protein contact dermatitis from 3% to 11%. Allergic reactions to shellfish are of significant concern in shellfish industry and from environmental health view point.

By crustaceans

Exposure value among crustacean-processing environments is relatively less well established, but exposures of about 3 mg/m^3 seems to induce severe allergic reactions. Inhalational route seems to be common particularly in the workplace, as it is estimated that up to 15% of the asthmatic population in the USA and Europe have occupational asthma. Lobster, shrimp, and crab have been documented to cause occupational dermatitis, rhinitis, and conjunctivitis (Goransson, 1981; Lehrer and O'Neil, 1992; Orford and Wilson, 1985; Nagano et al., 1984; Liu et al., 2016). At least one case of contact urticaria to shrimp is reported to be caused by the protein in the shell and not to the meat itself (Nagano et al., 1984). The range of allergic disease associated with occupational exposure to crab is well characterized (Jeebhay et al., 2001). Occupational exposure, such as in Snow crab processing plants, not only can cause symptoms in highly allergic subjects, but can

also cause de novo sensitization. Symptoms may be limited to the respiratory tract or affect other systems such as the skin or systemic anaphylaxis.

The aeroallergen levels of Snow crab and Northern shrimp in harvesting vessels and processing plants were measured using tandem MS techniques. TM and the AK were detected in aerosolized forms in the processing plants; however, the only allergen to be detected aboard the vessels holds and decks was TM (Abdel Rahman et al., 2012; 2011; 2010c). The results of the various exposure characterization studies conducted demonstrate the wide range of total inhalable airborne particulate (0.001–11.293 mg/m^3), protein (0.001–6.4 mg/m^3), and allergen (0.001–75.748 mg/m^3) levels (Jeebhay and Cartier, 2010). Particulate and allergen levels reach very high levels in the processing operations aboard vessels at sea in the case of crab processing and during fishmeal operations.

By mollusks

Occupational allergies have also been described in workers exposed to molluskan shellfish products via respiratory and cutaneous routes. Most of these reactions are attributed to the same proteins that cause food allergic reactions. Occupational sensitizations have also been reported to mollusks such as scallops among restaurant workers (Goetz and Whisman, 2000), scallop processers (Barraclough et al., 2006), inhalation of wet aerosols from oyster "shucking", washing dermal contact from unprotected handling of mollusks. Aside from increased consumption worldwide, more than 45 million workers are also involved in seafood production and hence exposed to shellfish allergens in different contexts (Food and Agriculture Organisation, 2010).

Characterization and quantification of shellfish allergens

Molecular genetics-based methods are followed for the characterization of the primary structure of shellfish allergens. To characterize them, it is necessary to profile their crude extracts by separating the protein content by gel electrophoresis and western blotting. Further, molecular characterization is carried out using molecular cloning or MS techniques. The allergen bands are cut and introduced to Edman sequencing for identification of the amino acid sequence of the *N*-terminal protein region. Allergen analysis can be performed in MS by peptide mass fingerprinting (PMF) or by tandem MS for *de novo* sequencing. Mass spectrometry serves as a characterization technique of shellfish allergens for determining the molecular weight, primary structure, and quantity of the intact allergenic protein.

Allergen can be routinely detected in radio-allergosorbent test (RAST), enzyme allergosorbent test (Dearnaley et al., 2010), rocket immuno-electrophoresis (RIE), immunoblotting, and enzyme-linked immunosorbent assay (ELISA). The choice of the protocol depends on the availability of the antibody, the target of the analysis, and the detection limit and precision. TM and AK are simultaneously measured using MRM-MS/MS in air samples collected from crab processing plants (Abdel Rahman et al., 2010; 2012). The most common shellfish allergens and the used method(s) for the characterization and quantification are summarized in Table 5.

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Table 5. The common known shellfish allergens and the method of their characterization and quantification (Adapted from Anas et al., 2012).

Shellfish	Allergen/code	Techniques		Reference(s)
		Characterization	Quantification	
Mollusks	Tropomyosin/Hel as 1, Hal a 1, Tod p 1	WB, ELISA	N/A	Asturias et al. (2000), Suma et al. (2007)
	Hemocyanin /Meg c	Microarray	N/A	Oyelaran and Gildersleeve (2010)
	Paramyosin/Hal di, Myt g, Oct v, Tur c	MG, WB, ELISA	N/A	Suzuki et al. (2011)
	Hal r 49kD	RAST, ELISA	N/A	Lopata et al. (1997)
Crustacea				
[Shrimps]	Tropomyosin/Cra c1, Lit v1, Met e1, Pan b1, Pen a1, Pen i1, Pen m1	RAST, MG, MS	ELISA, MS	Abdel Rahman et al. (2010a), Leung et al. (1994), Motoyama et al. (2008, 2007)
	Arginine kinase/Cra c2, Lit v2, Pen m 2, Met e 2, Met j 2	MG, MS	MS	Abdel Rahman et al. (2010a), García-Orozco et al. (2007), Yoon et al. (2004), Yu et al. (2003)
	Sarcoplasmic calcium-binding protein/Cra c4, Pen e4, Pen m 4, Lit v4	ELISA, Edman, WB, LC-MSMS, MG	N/A	Ayuso et al. (2009), Shiomi et al. (2008)
	Myosin light chain /Art fr 5, Cra c 5, Lit v 3, Pen m3	MS, Edmand, MG, WB, Peptide microarray	N/A	Ayuso et al. (2008, 2010)
	Troponin C/Pen m6, Cra c6	MG	N/A	WHO-IUIS Allergen DB
	Triosephosphate isomerase/Cra c8	MG	N/A	WHO-IUIS Allergen DB
[Crabs]	Tropomyosin/Cha f 1, Chi o1, Can p 1, Eri i 1, Par c 1, Por s 1, Por tr 1, Ran ra 1, Scy o 1, Scy pa 1, Scy s 1	MG, ELISA, RAST, WB, MS	ELISA, LC-MSMS, RAST	Huang et al. (2010), Kunimoto et al. (2009), Leung and Chu (1998), Liang et al. (2008), Motoyama et al. (2007), Shibahara et al. (2009), Werner et al. (2007), Yu et al. (2010)
	Argine kinase/Chi o2, Scy s 2, Lim p 2	MG, WB, RAST, MS	MG, WB, RAST, MS	Abdel Rahman et al. (2011), Bobolea et al. (2010), Werr et al. (2009), Yu et al. (2003)
	Troponin /Chi o 6	MS	N/A	Shiomi et al. (2008), Abdel Rahman et al. (2011)
	Sarcoplasmic calcium-binding protein/Chi o 4	MG, MS	N/A	Abdel Rahman et al. (2011), Shiomi et al. (2008)
[Lobsters]	Tropomyosin/Hom a1, Hom g 1, Jas la 1, Met ja 1, Nep n 1, Pan h 1, Pan j 1, Pan s 1	MG, WB, RAST, MS	ELISA	DeWitt et al. (2004), Leung et al. (1996), Leung and Chu (1998), Motoyama et al. (2007), Mykles et al. (1998), Shibahara et al. (2009), Werr et al. (2009)
	Arginine kinas Argine kinase /Hom g 2	WB, MS, MG, ELISA	N/A	Werr et al. (2009), Yu et al. (2003)
	Myosin light chain 2/Hom a3	MG	N/A	Towle and Smith (2006)
	Troponin C/Hom a6	MG	N/A	Garone et al. (1991)
	Sarcoplasmic calcium-binding protein/Hom a 4	MG	N/A	Shiomi et al. (2008)
[Crayfish]	Tropomyosin/Pro cl 1	WB, MG	LC-MSMS	Faeste et al. (2011)
	Sarcoplasmic calcium-binding protein/Pon i 4	MS	N/A	Jauregui-Adell et al. (1989)
	Ast f	WB	ELISA	Lopata and Jeebhay (2007)
	Troponin I/Pon l7	Edman	LC-MSMS	Faeste et al. (2011), Kobayashi et al. (1989)
[Krill]	Tropomyosin/Eup p1, Eup s 1	MG, WB	N/A	Motoyama et al. (2008), Nakano et al. (2007)

MG: Molecular genetics, WB: Western blotting, MS: Mass spectrometry, ELISA: Enzyme-linked immunosorbent assay, LC-MS/MS: Liquid chromatography-tandem mass spectrometry, RAST: Radio allegro sorbent test, N/A: Not available.

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Non-allergic reaction

Adverse reactions to shellfish do not always show genuine allergy. In filter-feeding shellfish such as black mussels and oysters, toxins are produced by toxic algal blooms "Red Tide" along the coasts at certain times of year. This can cause illnesses such as amnesic, diarrhetic, paralytic, and neurotoxic shellfish poisonings. It is crucial to distinguish between shellfish allergy and toxicity as their presentations mimic each other. However, the evaluation of a patient can be difficult if the adverse reaction to a particular shellfish is caused by a non-allergic reaction. It is also important to differentiate shellfish toxic syndromes frequently masquerading as allergic reactions (Woo and Bahna, 2011).

There has been some confusion in recent years regarding the relationship between shellfish allergy and iodine. Many people falsely believe that iodine may trigger an allergic reaction in people with a shellfish allergy. A study published in the *Journal of Emergency Medicine* reports that iodine is not an allergen. According to the researchers, "Allergies to shellfish, in particular, do not increase the risk of reaction to intravenous contrast any more than that of other allergies". Non-immunological reactions to seafood can be triggered by contaminants such as parasites, bacteria, viruses, marine toxins, and biogenic amines (Prester, 2015).

Conclusion

Shellfish consumption is increasing globally, consequently causing widespread instances of shellfish allergies. It occurs most commonly in Asia and Scandinavia where seafood is part of the staple diet. Shellfish is one of the leading causes of food allergy in adults and it is also the common cause of food-induced anaphylaxis. Allergies are more frequently caused due to shrimp, crab, lobster, clam, oyster, and mussel. A group of mollusks are designated as commonly allergic foods in the European Union. Tropomyosin has been identified as the major allergen among shellfish; at times, argentine kinase may be the causative allergen in a few important allergenicities. Tropomyosin seems to be the major allergen responsible for molecular and clinical cross-reactivity between crustaceans and mollusks. However, newly discovered allergens and the subtle differences in the structures of tropomyosin between different species of shellfish could account for the differences between cross-reactivity and true clinical reactions. Further research is needed for identifying allergens with improved clinical sensitivity and also with species specificity, which could aid in proper diagnosis. Shellfish allergy can be chiefly managed by its avoidance. Patients who have immunodeficiency should eat only cooked shellfish because it reduces the risk of severe infections from ingesting raw shellfish contaminated with infectious organisms.

Further research on the molecular structure of tropomyosins with focus on the immunological and clinical reactivity could improve management of such life-threatening allergy, and is essential for future immunotherapy. The advances in the characterization of shellfish allergens will not only enhance our understanding on the physiological basis of shellfish allergy but also lay the groundwork for the development of diagnostic and therapeutic design in food allergies.

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Declaration of interest

The author reports no conflicts of interest. The author alone is responsible for the content and writing of the paper.

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