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Fish Allergy: Recent Advances in Diagnostics and Innovative Processing Technologies for Allergen Management

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Abstract

Background:
Fish allergy is a major immunological concern that affects sensitive individuals worldwide, primarily due to stable fish proteins such as parvalbumin. The allergenic potential differs across species and is influenced by environmental exposure and food processing.

Aims and Scope:
This review explores current diagnostic approaches, allergenic protein characterization, and recent innovations in fish processing technologies aimed at reducing allergenic risks.

Methods:
A critical evaluation of recent studies was conducted to assess immunological properties of fish allergens, diagnostic tools (e.g., IgE-based assays, species-specific PCR), and the impact of physical, enzymatic, and non-thermal processing on allergenicity .

Results:
Major allergens like Gad c 1 exhibit high heat stability, while those in tuna or salmon show reduced allergenicity after cooking. Diagnostic tools, including molecular assays, provide accurate identification of allergens and fish species, essential for risk management. Processing methods such as high-pressure treatment, thermal glycation, enzymatic hydrolysis, and washing can modify protein structures and reduce IgE-binding capacity. Additionally, poor-quality raw fish and improper fermentation may elevate histamine and biogenic amine levels, increasing allergic risk.

Conclusion:
Fish allergy management requires a combined understanding of allergen structure, reliable diagnostics, and processing interventions. Emerging technologies hold promises for developing hypoallergenic fish products and ensuring consumer safety through improved allergen detection and control strategies.

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INTRODUCTION

The concept of "allergy" was first introduced in 1906 by Austrian pediatrician Clemens von Pirquet (1874–1929) in the journal *Münchener Medizinische Wochenschrift*. In his work, von Pirquet coined the term "allergy" and drew a distinction between the term's "allergen" and "antigen." He explained that the prefix "allos" denotes a deviation from normal function or behavior, similar to its use in terms such as "allorhythmia" and "allotropism." While "antigen" refers specifically to a substance that elicits the formation of antibodies, the definition of "allergen" is broader. According to von Pirquet, allergens include not only true antigens but also a variety of proteinaceous compounds that do not necessarily induce antibody production, yet are capable of

provoking hypersensitivity reactions (Edwards, 2009). The prevalence of allergic disorders is influenced by intricate interactions between genetic predisposition and environmental exposures(Warner & Warner, 2014).

A limited number of food items account for the majority of food allergy cases globally. Common dietary sources known to trigger hypersensitivity reactions include various categories such as fish (both marine and freshwater finfish) and their derivatives; crustaceans like shrimp, prawns, crabs, lobsters, and crayfish; mollusks including snails, oysters, clams, squid, octopus, and cuttlefish; eggs and egg-based products; milk and dairy derivatives; and gluten containing cereals such as wheat, rye, barley, and their hybrid forms. Additionally, legumes such as peanuts and soybeans, a wide range of tree nuts such as almonds, walnuts, pecans, cashews, Brazil nuts, hazelnuts, pistachios, pine nuts, macadamia nuts, chestnuts, and hickory nuts as well as various seeds including sesame, poppy, sunflower, cottonseed, peas, and lentils, are recognized allergenic foods. In each of these, one or more specific proteins can act as the allergenic determinant responsible for eliciting an immune response (Danquah et al., 2010).

Fish is recognized as an excellent source of easily digestible proteins, along with significant levels of polyunsaturated fatty acids and fat-soluble vitamins. As a result, many healthcare professionals advocate for increased dietary intake of fish, which has contributed to the rising trend in fish consumption (Bugajska-Schretter et al., 1998).

Edible species from the animal kingdom that are relevant to food allergy studies primarily belong to the phylum Chordata, encompassing various vertebrate classes such as Amphibia (e.g., frogs), Aves (edible birds), Mammalia (marine mammals), Reptilia (e.g., turtles), Chondrichthyes (cartilaginous fishes like sharks and rays), and especially Osteichthyes (bony fishes). Within the bony fish class, Actinopterygii or ray-finned fishes constitute the majority of edible species, including key commercial orders such as Perciformes (tuna, mackerel), Gadiformes (cod, hake), Clupeiformes (herring, anchovy), Salmoniformes (salmon, trout), and others. This classification helps highlight taxonomic relevance when evaluating allergenic proteins like parvalbumin among different fish species. Although over 20,000 fish species are considered edible, the majority of global fish consumption is limited to a few species primarily within certain orders of the class Actinopterygii (ray finned fishes). In response to increasing consumer demand, the fisheries sector has undergone significant expansion, particularly through the growth of aquaculture and fish processing industries. Today, a substantial proportion of fish is not consumed in whole form but is instead incorporated into a variety of processed food products and nutritional supplements, including fish gelatin, fish oil, and omega-3 fatty acids (Faeste, 2010).

Proteins derived from fish, along with those found in eggs and dairy products, are among the most common triggers of immediate-type food hypersensitivity reactions. (Bugajska-Schretter et al.,1998) exposured to fish, either through consumption or inhalation of cooking vapors, is a well-documented cause of both immunoglobulin E (IgE)-mediated allergic responses and non-immunologic adverse effects. These reactions may result not only from the intrinsic properties of fish proteins but also from external factors such as contamination with scombroid toxins, marine or bacterial toxins, chemical additives, or potentially even spices incorporated during culinary preparation (O'Neil et al., 1993). In addition to the major known allergens, several other fish-derived compounds have been identified as potential allergens. These include vitellogenin, a reproductive hormone found in Beluga caviar, as well as collagen and gelatin extracted from fish skin tissue (Wong, 2015). Fish roe is recognized as a nutrient-dense food that is popular among consumers; however, it has also been shown to possess allergenic properties, particularly in salmonid species. In a study conducted by (Y. Y. Liu et al.,2014), the allergenic components of roe from the large yellow croaker (*Pseudosciaena crocea*) were investigated. Through mass spectrometry analysis, the primary allergenic protein was identified as the β'-component, with an estimated molecular weight of approximately 16 kDa. Fish gelatin is commonly derived from the skin of edible fish species, primarily cod. During its production, the process typically eliminates residual muscle tissue that may be present in the raw material. Given that parvalbumin, the principal allergen in fish, is highly soluble in water, it is expected to be effectively removed during gelatin extraction. While there have been no documented cases of allergic reactions linked to fish gelatin in processed food products, assessing its potential allergenicity remains important from a food safety perspective. Isinglass, a collagen-derived substance, is obtained from the swim bladders of certain fish species, notably sturgeon and cod. It is commonly utilized as a fining agent in the clarification process of alcoholic beverages (Danquah et al., 2010). According to (Vassilopoulou et al.,2011), trace amounts of isinglass that may remain in wine following the fining process pose minimal risk to individuals with fish-related food allergies. Collagen has been recognized as a fish-derived allergenic protein, as demonstrated in the findings of (Hamada et al.,2001). In certain cases, individuals may exhibit allergic reactions to Anisakis parasites present in fish and other seafood, which can be misinterpreted as an allergy to the seafood itself. Two distinct clinical manifestations have been identified: one involves the active penetration of the gastric mucosa by live larvae, leading to gastrointestinal symptoms, while the other presents as immediate hypersensitivity reactions, including urticaria, angioedema, and potentially life-threatening anaphylaxis (Wong, 2015).

Seafood consumption, including fish, shellfish, and related products, varies significantly across global regions, influenced by factors such as availability, economic accessibility, and cultural dietary preferences. However, advancements in global transportation and trade have led to the widespread distribution of these products, even in areas where seafood has not traditionally been a dietary staple. Consequently, the increased exposure to seafood has contributed to a growing prevalence of seafood-induced allergic reactions, emerging as a significant public health concern worldwide (Wong, 2015). A review of existing literature indicates that seafood allergy is highly prevalent in certain parts of the world (Hajeb & Selamat, 2012). A comprehensive knowledge of allergen types, exposure pathways, possibilities of cross-reactivity, underlying pathophysiological processes, and available treatment options is essential for effective management and control of seafood allergies in affected patients (Wong, 2015).

METHOD

Research Design

This study employed a narrative and systematic literature review design. The approach involved identifying, analyzing, and synthesizing peer-reviewed scientific articles on the topic of fish allergy, particularly focusing on immunological mechanisms, allergen identification (e.g., parvalbumin), diagnostic methods, and innovative food processing technologies for allergen mitigation.

Participant

As a literature review, this study did not involve human participants or direct data collection from subjects. Instead, it reviewed data and findings from prior research involving various sample groups, including allergic individuals, in vitro models, and animal studies as reported in the reviewed literature.

Population and the methods of sampling, Instrumentation (sample of questions, scoring method, and psychometric properties [validity and reliability]): No primary population was sampled in this study. The "population" consisted of published research articles retrieved from databases such as PubMed, ScienceDirect, Scopus, and Google Scholar. The inclusion criteria included peer-reviewed articles published primarily between 1981 and 2024 that focused on:

1. Fish allergens (e.g., parvalbumin),
2. Diagnostic tools for allergy detection (e.g., ELISA, PCR, skin prick test), and
3. Processing methods to reduce allergenicity (e.g., enzymatic hydrolysis, thermal and high-pressure processing).

The reliability and validity of findings are based on the methodological rigor and quality of the studies cited. Evaluation of study quality was conducted informally through assessment of peer-review status, sample size, research design, and consistency of findings across studies.

Instrument

No survey or experimental instruments were used in this study, as it relied entirely on secondary data from previous research. The data were extracted from journal articles, and no questionnaires, psychometric scales, or direct measurement tools were administered.

Procedures and if relevant, the time frame: The review process consisted of four main stages:

1. Systematic literature search using defined keywords;
2. Screening and selection based on inclusion and exclusion criteria;
3. Extraction and synthesis of relevant data; and
4. Critical analysis of findings based on relevance and contribution to the understanding of fish allergy and mitigation technologies.

RESULTS AND DISCUSSION

FISH ALLERGY

Throughout human history, aquatic environments, particularly marine ecosystems, have been vital sources of food and nutrients for both humans and other animals. Recent years have witnessed a rise in seafood consumption, driven by its high nutritional content and recognized health advantages. Beyond traditional commercial fishing, aquaculture has expanded production to supplement wild fish harvests. Despite these benefits, exposure to fish can provoke allergic responses in susceptible individuals. Indeed, seafood which includes fish, shellfish, and edible seaweeds is among the most frequent dietary allergens. Research indicates that even minimal exposure to seafood proteins can elicit severe allergic reactions in sensitized persons (Danquah et al., 2010).

Fish handling and processing encompass a variety of activities, including heading, gutting or evisceration, skinning, mincing, trimming, filleting, cooking, salting, milling, and packaging, applied to both bony (finfish) and cartilaginous species. These procedures inevitably create conditions where workers are exposed either directly or indirectly to fish-derived substances, which have the potential to trigger allergic responses (Danquah et al., 2010; Droszcz et al., 1981).

Allergic reactions triggered by the ingestion of seafood products resemble those caused by a wide range of other allergenic foods. The recognized health advantages of consuming fish and shellfish have driven a consistent rise in their per capita intake. This upward trend is anticipated to persist, partly due to increasing consumer apprehensions regarding the consumption of beef, pork, and occasionally poultry. As a result, there is a growing development of novel food items containing fish ingredients, which heightens the concern over allergic responses among sensitized individuals (Danquah et al., 2010).

In individuals with severe food allergies, allergic symptoms can occasionally be provoked through indirect exposure. (Caiaffa et al. (2008) documented a case of a pronounced IgE-mediated fish allergy triggered by multiple forms of indirect contact, including inhalation of airborne particles generated during fish cooking, both affectionate and non-affectionate kissing, as well as consumption of chicken that had been fed with fish-based feed. (van der Ventel et al.,2011) established a murine model to study inhalant fish allergy, providing a platform to evaluate various recombinant allergens for their potential application in specific immunotherapy targeting fish induced respiratory symptoms. Additionally, their research identified glyceraldehyde-3 phosphate dehydrogenase as a novel fish allergen implicated in occupational sensitization among workers exposed to fish. Immunotherapeutic approaches for fish allergy may offer a means to desensitize individuals employed in fish processing who experience allergic airway reactions due to inhalation, and could also help mitigate allergic responses in food-allergic patients at risk of inadvertent exposure to aerosolized fish proteins. (Taylor et al.,2000) investigated the presence and concentration of airborne fish allergens in an open-air fish market. Utilizing air sampling combined with immunochemical analysis, they confirmed that fish allergens are detectable in the market's atmosphere. They concluded that effective avoidance of food allergens like fish should encompass measures to prevent inhalation exposure to aerosolized allergenic particles in pertinent settings.

FISH ALLERGENS

PARVALBUMIN

The phylum Chordata encompasses two primary groups: bony fish (Osteichthyes) and cartilaginous fish (Chondrichthyes). The majority of edible fish species are classified as bony fish. Although over 32,000 bony fish species exist, allergen research has predominantly focused on a limited number of species, notably cod, carp, and salmon (Wong, 2015).

Parvalbumin, a protein involved in calcium regulation within skeletal muscle cells, is recognized as the primary allergen in fish. Initially characterized through studies on Baltic cod, it was designated as Gad c 1. The majority of individuals with fish allergies exhibit sensitization to this protein. Due to the varying degrees of amino acid sequence homology among parvalbumins from different fish species, cross-reactivity occurs, explaining why many allergic patients respond to multiple fish types depending on the similarity of their parvalbumins (Wong, 2015).

A wide array of edible fish species has been identified to contain allergenic parvalbumins, each exhibiting species-specific isoforms. These allergenic proteins are named based on the standardized allergen nomenclature system established by the International Union of Immunological Societies (IUIS), ensuring uniformity in allergen classification across taxa. Among the Gadidae family, parvalbumins such as Gad c 1 and Gad m 1 are found in Baltic cod (*Gadus callarias*) and Atlantic cod (*Gadus morhua*), respectively. The Atlantic wolffish (*Anarhichas lupus*) expresses Ana l 1, while Ang a 1 and Ang j 1 are associated with the Atlantic eel (*Anguilla anguilla*) and Japanese eel (*Anguilla japonica*), respectively. The Atlantic herring (*Clupea harengus*) expresses the allergen Clu h 1, and Cyp c 1 is derived from common carp (*Cyprinus carpio*). In zebrafish (*Danio rerio*), Dan r 1 is the dominant parvalbumin. Several tilapia species also produce distinct allergens: Ore a 1 in blue tilapia (*Oreochromis aurea*) and Ore m 1 in Mozambique tilapia (*Oreochromis mossambicus*). The channel catfish (*Ictalurus punctatus*) has been identified to produce Ict p 1, while Kat p 1 is found in bonito (*Katsuwonus pelamis*). Additional allergenic parvalbumins include Lep i 1 from Indian salmon (*Leptomelanosoma indicum*), Pag m 1 from red seabream (*Pagrus major*), and Pam c 1 from Chinese pomfret (*Pampus chinensis*). Flatfish such as the Japanese flounder (*Paralichthys olivaceus*) and the European flounder (*Platichthys flesus*) express Par ol 1 and Pla f 1, respectively. In the Salmonidae family, the Atlantic salmon (*Salmo salar*) contains Sal s 1. Small pelagic fish such as the Japanese sardine (*Sardinops melanostictus*) and Indian anchovy (*Stolephorus indicus*) produce Sar m 1 and Sto i 1, respectively. Various species of mackerel harbor distinct parvalbumins: Sco a 1 in blue mackerel (*Scomber australasicus*), Sco g 1 in spotted Spanish mackerel (*Scomberomorus guttatus*), Sco j 1 in chub mackerel (*Scomber japonicus*), and Sco s 1 in Atlantic mackerel (*Scomber scombrus*). The yellowtail or Japanese amberjack (*Seriola quinqueradiata*) produces Ser q 1. Other important species

include the perch (*Stizostedion lucioperca*, Sti l 1), Alaska pollock (*Theragra chalcogramma*, The c 1), and three species of tuna: yellowfin (*Thunnus albacares*, Thu a 1), bigeye (*Thunnus obesus*, Thu o 1), and Atlantic bluefin (*Thunnus thynnus*, Thu t 1). The horse mackerel (*Trachurus japonicus*) expresses Tra j 1. This diversity in allergenic parvalbumins reflects the taxonomic variability among fish species and underscores the importance of molecular identification for accurate allergen profiling in fish allergy diagnostics and labelling (Faeste, 2010).

(Moraes et al.,2014) conducted the first NMR analysis to elucidate the structure and dynamics of Gad m 1, the principal allergen from Atlantic cod (*Gadus morhua*), and compared it to other characterized parvalbumins. While the overall structure and the accessibility of presumed IgE-binding epitopes of Gad m 1 resemble those found in mackerel and carp parvalbumins, notable differences exist in the charge distribution at these epitope sites. The resolved structure of Gad m 1 enhances the understanding of cross-reactivity among fish parvalbumins. Furthermore, high pressure NMR coupled with temperature variation studies highlighted the significant role of the AB motif and additional regions in the protein's folding process. These structural insights may facilitate the future design of hypoallergenic, calcium free variants through targeted mutagenesis, potentially applicable in immunotherapeutic interventions.

(C. Y. Liu et al.,2014) reported the identification of nucleoside diphosphate kinase B as a novel allergen in largemouth bass (*Micropterus salmoides*), a commonly consumed freshwater fish species in China. (Pan et al.,2012)demonstrated that collagen and its subunits from tilapia (*Tilapia zillii*) possess allergenic potential. (Sharp et al., 2014) investigated the variation in IgE binding to isoallergens of barramundi (*Asian seabass: Lates calcarifer*) among children and adults. Their study highlighted the significance of both heat-labile and heat-stable epitopes in barramundi parvalbumin and demonstrated that the isoallergens exhibit differing IgE reactivity profiles. (Cai et al.,2010) successfully purified and characterized the parvalbumins from red stingray (*Dasyatis akajei*). (Rencova et al., 2013) employed polymerase chain reaction (PCR) to detect the allergenic parvalbumin in fish products derived from Atlantic herring (*Clupea harengus*) and Pacific herring (*Clupea pallasii*). (R. Liu et al.,2011) conducted the characterization of allergens isolated from the freshwater fish blunt snout bream (*Megalobrama amblycephala*).

Fish muscle parvalbumin is a small, acidic protein that binds calcium ions (Ca^{2+}) and exhibits high stability against heat, chemical denaturation, and enzymatic digestion. Amino acid sequence analyses have classified the parvalbumin family into two evolutionarily distinct groups: the α-group, which comprises less acidic parvalbumins with isoelectric points (pI) equal to or above 5.0, and the β-group, which includes more acidic parvalbumins with pI values at or below 4.5. Typically, fish muscle contains parvalbumins from either the α- or β-lineage. Given their nature as Ca^{2+}binding proteins, recent studies have shown that IgE-binding to specific Ca^{2+}-dependent plant allergens requires the presence of bound calcium. In contrast to parvalbumin, other fish allergens such as type, I collagen found in many species, a 41 kDa minor allergen identified in cod, allergens ranging from 35 to 90 kDa in snapper, and those between 94 and 105 kDa in tuna and marlin play a less significant role in eliciting allergic reactions (Li & Lin, 2012).

Parvalbumins are classified into two distinct isoform lineages: α and β, with the majority of allergenic parvalbumins belonging to the β lineage. Currently, the allergome database (www.allergome.org) lists 241 allergenic parvalbumin isoforms, nearly all of which are derived from fish species. Fish muscle is generally categorized into white and dark muscle types. White muscle, responsible for rapid bursts of swimming, contains higher concentrations of parvalbumins, thereby exhibiting greater allergenic potential. In contrast, more active fish species such as tuna and skipjack possess a greater proportion of dark muscle compared to bottom dwelling species like flounder and cod. Additionally, certain edible frog species also contain parvalbumins that may induce food allergies. Despite these findings, knowledge regarding the specific IgE binding epitopes of allergenic parvalbumins remains limited. Further research is essential to elucidate their amino acid sequences as well as their secondary and tertiary structures, which could enhance diagnostic accuracy for patients suspected of fish allergy (Wong, 2015). The heightened allergenic potential observed among parvalbumins exhibiting microheterogeneous isoforms may be attributed to variations in their IgE-binding capacities, either through direct interactions or via allosteric effects. In general, sequence microheterogeneity is an intrinsic characteristic of many parvalbumins and is likely a contributing factor to their allergenicity (Lapteva et al., 2013). The cloning and expression of recombinant parvalbumin isoforms can advance the detailed study of the mechanisms underlying fish allergies, enable precise mapping of ige-binding epitopes, and allow comprehensive evaluation of their allergenic potential and stability (N. Y. H. Leung et al., 2014). Employed the phage display technique to generate mimotopes that replicate epitopes on parvalbumin. Notably, their study represents the first to characterize IgE-binding epitopes on the major fish allergen parvalbumin while accounting for the conformational structure of the intact protein (Untersmayr et al., 2006).

(Yang et al.,2015) investigated the optimization of the Maillard reaction using ribose to enhance the anti-allergic properties of fish protein hydrolysates through response surface methodology. Their findings indicate that Maillard reaction products of fish protein hydrolysate (MFPH) exhibit superior antioxidant and anti-

allergic activities compared to untreated fish protein hydrolysate (FPH), suggesting their potential as an improved dietary ingredient.

Parvalbumin is predominantly found in the white muscle of numerous fish species, and the observation that approximately 70% of tested patients exhibit exclusive reactivity to parvalbumin highlights its role in cross-reactivity among fish allergens. Amino acid sequence homology between parvalbumins from different fish species ranges from 60% to 90%; however, studies on cross-reactivity have produced inconsistent results, and allergenic potency varies considerably among species. Notably, patients allergic to cod frequently display sensitization to salmon and other fish species. Among common fish, cod, salmon, pollack, herring, tuna, and mackerel are considered less allergenic. Recent investigations involving Cyp c 1 and Sco j 1 underline the significance of conformational IgE epitopes in fish parvalbumins. Consequently, IgE cross-reactivity among fish parvalbumins is likely predominantly mediated by conformational rather than linear epitopes (Li & Lin, 2012).

(Van Do et al.,2005) investigated the allergenic cross-reactivity among nine commonly consumed fish species: cod, salmon, pollack, mackerel, tuna, herring, wolffish, halibut, and flounder. Their study concluded that Gad c 1 (cod), Sal s 1 (salmon), The c 1 (pollack), as well as allergens from herring and wolffish, exhibited the highest cross-reactivity and allergenic potency. In contrast, halibut, flounder, tuna, and mackerel showed the lowest allergenicity and were likely tolerable for some of the patients tested (Bugajska-Schretter et al., 1998). (Bugajska-Schretter et al.,1998) characterized cross-reactive IgE-binding components in six fish species cod, tuna, salmon, perch, carp, and eel. They concluded that parvalbumin is a cross-reactive fish allergen containing IgE epitopes that are sensitive to periodate treatment and calcium (Ca^{2+}) depletion. (Beale et al.,2009) studied the cross-reactivity of parvalbumin from fish species commonly consumed in the Southern Hemisphere. They successfully identified and sequenced a highly cross-reactive allergenic isoform of parvalbumin. (Saptarshi et al.,2014) evaluated the cross-reactivity of parvalbumin across a broad range of bony and cartilaginous fish species from the Asia-Pacific region, alongside a molecular analysis of this major allergen. Using the monoclonal antibody PARV-19, they detected both monomeric and oligomeric forms of parvalbumin in all fish examined except for gummy shark, a cartilaginous fish. Heat processing significantly reduced antibody reactivity: for most bony fish, heating decreased reactivity to multimeric parvalbumins, while in cartilaginous fish, heat treatment caused a complete loss of antibody reactivity. Their molecular analysis indicated that cross-reactivity among fish species is linked to the phylogenetic relationships of parvalbumin.

However, a reported clinical case highlights an instance of fish allergy where the primary sensitizing agent was identified as fish collagen, rather than the commonly implicated parvalbumin. Notably, the patient's sensitization developed through occupational exposure rather than dietary intake. This finding emphasizes the potential for fish collagen to act as an allergen via non-oral routes, particularly in occupational settings (Santos Vicente et al., 2023).

BIOGENIC AMINES

Not all adverse reactions to fish are immune-mediated; non-immunological reactions can also occur due to contaminants such as bacteria, toxins, parasites, and biogenic amines present in fish (Wong, 2015). Biogenic amines are non-volatile compounds formed by the decarboxylation of amino acids. While many biogenic amines have been detected in fish, only histamine, cadaverine, and putrescine are considered significant indicators for fish safety and quality assessment. Although histamine is widely associated with scombroid food poisoning, it alone may be insufficient to cause toxicity; putrescine and cadaverine are thought to potentiate histamine's toxic effects. Regarding spoilage, cadaverine serves as a useful marker for the early stages of fish decomposition. Specifically, histamine is produced from histidine, cadaverine from lysine, and putrescine from ornithine via enzymatic decarboxylation (Al Bulushi et al., 2009; Prester, 2011).

Scombroid poisoning, also known as histamine fish poisoning, is a form of food poisoning that presents symptoms and treatment similar to marine fish allergies. It results from consumption of improperly handled fish, where histamine (2-(1H-imidazol-4-yl) ethanamine) and other decomposition products are produced through bacterial enzymatic conversion of free histidine during time temperature abuse of raw fish. Scombroid poisoning remains a significant concern in marine fish safety. The precise role of histamine in causing scombroid poisoning is complex and not fully understood; dose response inconsistencies have led to several hypothesized toxicity mechanisms, none definitively proven. Regulatory actions currently use histamine threshold levels to manage safety risks pending further clarification. Victims typically respond well to antihistamines, and fish implicated in poisoning cases often show elevated histamine levels. Unlike other marine toxins, scombroid poisoning arises from post-harvest mishandling rather than contamination within the marine food chain. Inadequate cooling after harvesting encourages bacterial histidine decarboxylase activity, leading to histamine production and potential poisoning outbreaks. Bacteria involved include species such as *Proteus*, *Klebsiella*, *Aerobacter*, and *Escherichia coli*, which thrive on fish rich in free histidine, the substrate for histamine formation (Mclnerney et al., 1996), and are those most often implicated in scombroid

poisoning (Hungerford, 2010). (Kanki et al. (2004) identified *Photobacterium phosphoreum* as the causative agent of a histamine fish poisoning incident, isolated from iwashi maruboshi (dried sardine).

Symptoms of scombroid fish poisoning, caused by histamine release, closely resemble those of IgE-mediated food allergies. Typical manifestations include flushing, headache, dizziness, burning sensations in the mouth and throat, abdominal cramps, nausea, vomiting, diarrhea, urticaria, and generalized itching. In severe cases, bronchospasm and respiratory distress may occur. Histamine is produced by enzymatic decarboxylation of histidine, a process that occurs optimally between 20°C and 30°C and can be prevented by inhibiting bacterial growth through refrigeration or chemical means. Foods containing histamine levels above 50 mg per 100 g are generally considered hazardous. The illness has a short incubation period, ranging from minutes to a few hours (Sanchez-Guerrero et al., 1997).

Histamine exerts extensive effects on various cell types through activation of its four receptor subtypes (H1R–H4R). The specific effects depend on the receptor subtype involved and their patterns of expression. In the gastrointestinal tract, histamine is found at relatively high concentrations, especially during inflammatory responses (Smolinska et al., 2014).

The study by (Zare et al., 2013) demonstrated changes in urocanic acid, histamine, putrescine, and cadaverine levels in Indian mackerel (*Rastrelliger kanagurta*) during storage. The concentration of cis-urocanic acid (cis-UCA) increased nearly 13-fold after 15 days at 0 and 3 °C, decreased at 10 °C, and remained unchanged at 23 °C. Meanwhile, histamine, putrescine, and cadaverine levels increased significantly at all temperatures, with the most pronounced rise observed at 23 °C. Another study on tuna (Auxis thazard) showed that storage did not lead to elevated concentrations of trans- and cis-urocanic acid (UCA) (Zare et al., 2013, 2015a). Research indicates that high-hydrostatic-pressure treatments inhibit histamine production in mackerel (*Scomber japonicus*) muscle inoculated with *Morganella morganii* and *Photobacterium phosphoreum* (Kim et al., 2013).

Based on European Union legislation and FDA regulations, histamine levels in seafood, such as marine fish and shellfish, must not exceed 100–200 ppm and 500 ppm, respectively. However, the FDA recently lowered its caution level to 50 ppm. Histamine is resistant to thermal processing methods like freezing, cooking, and canning, making temperature control essential. The only effective way to prevent histamine accumulation is by storing fish below 4°C. Additionally, rapid removal of viscera and thorough washing of fish significantly reduce bacterial histamine production and are effective measures for lowering histamine levels in seafood (Akbari-Adergani et al., 2012). Another effective method to keep bacterial growth and histamine formation low is the rapid cooling of fish immediately after catching, coupled with maintaining proper refrigeration throughout handling and storage (Lehane & Olley, 2000). However, it is important to investigate not only mesophilic but also psychrophilic histamine-producing bacteria, as (Torido et al.,2014) reported the presence and distribution of both psychrophilic and mesophilic histamine-producing bacteria in retailed fish in Japan.

The decarboxylative conversion of histidine to histamine during fermentation by Enterobacteriaceae, lactic acid bacteria, and Photobacteria in scombroid fish, such as tuna, is the primary source of histamine accumulation in susceptible fish (Torido et al., 2014). (Naila et al.,2015) studied the histamine content in Rihaakuru, a cooked fish pastes from the Maldives commonly consumed as a condiment with rice and other foods. Their research confirmed that Rihaakuru contains up to 10 different biogenic amines, with histamine levels exceeding 500 ppm. Such high histamine content poses a risk of histamine poisoning, causing symptoms like skin rashes, vomiting, and fever, thus raising food safety concerns in the Maldives. Another study from our team developed a regression model to predict the rate and extent of histamine removal by diamine oxidase (DAO) under varying pH and salt concentrations in the tuna soup used for Rihaakuru production.

Found that, in addition to biogenic amines, both trans- and cis-urocanic acid (UCA) were present in food samples. Given the increasing evidence of cis-UCA's role in immunosuppression, they suggest that monitoring levels of both trans- and cis-UCA in foods is important alongside histamine and other biogenic amines. These compounds may act synergistically to cause scombroid fish poisoning (SFP) and related disorders. Therefore, new quality indices should be developed to incorporate the presence of both trans- and cis-UCA (Zare et al., 2015).

CURRENT DIAGNOSTIC APPROACHES

DIAGNOSTICS

Many individuals continue to consume fish due to personal preferences or health considerations; therefore, it is crucial to confirm whether any adverse reactions are truly IgE-mediated and to pinpoint the specific allergenic source. (O'Neil et al.,1993) outlined diagnostic approaches for fish allergy as follows: (1) Clinical history: As with most allergic conditions, obtaining a thorough and accurate patient history is fundamental. However, patients often misidentify the offending fish species, frequently using common names that may be ambiguous or misleading due to regional naming variations or marketing practices. Consequently, diagnostic testing is recommended to clarify the causative species. A detailed clinical history remains essential,

especially because specific IgE (sIgE) reactivity alone does not reliably predict cross-reactivity patterns among different fish species (Schulkes et al., 2014). (2) Skin testing: Since most individuals allergic to fish are atopic, initial evaluation commonly includes skin prick tests using standard inhalant and food allergens. Subsequently, skin tests with extracts derived from multiple fish species are conducted to assess sensitization patterns. (3) In vitro assays: Quantification of specific IgE antibodies can be performed using assays such as the radio allegro sorbent test (RAST) or enzyme linked immunosorbent assay (ELISA). These techniques are generally reserved for cases where skin testing is contraindicated, including patients with dermatographism, severe dermatological conditions, or those at risk of severe anaphylaxis. Additionally, these assays may serve as preliminary screening tools before employing advanced methods such as RAST or ELISA inhibition to evaluate cross reactivity between fish species. Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) combined with Western blotting further enables detailed characterization of antibody responses to specific allergenic components within complex antigen mixtures. (4) Elimination diet: Dietary exclusion is frequently applied to support diagnosis of food hypersensitivity. Nevertheless, in instances where the suspected allergen is clearly identified, such as fish, elimination diets may not always be necessary. When implemented, this approach is most appropriate for patients exhibiting non-life-threatening symptoms, like chronic urticaria or rhinitis. The suspected foods are removed from the diet; however, this method lacks blinding, has limited utility in patients with multiple food allergies, may require prolonged duration, and in pediatric populations, should be restricted to short-term use. (5) Double-blind placebo-controlled food challenge (DBPCFC): This method remains the gold standard for confirming food allergies, including fish allergy. It involves the controlled, blinded administration of the suspected allergen and a placebo in separate sessions to objectively assess clinical reactions. The DBPCFC minimizes bias and placebo effects, providing definitive evidence of allergenicity. However, due to its complexity, risk, and resource demands, it is typically reserved for cases where diagnosis remains uncertain after other testing modalities (O'Neil et al., 1993; Schulkes et al., 2014).

(Carrera et al.,2012) proposed an innovative approach for the rapid and direct identification of the primary fish allergen, beta-parvalbumin (β-PRVB), in various food matrices. This method involves an initial rapid purification of β-PRVBs through thermal treatment, followed by enhanced in solution protein digestion using High Intensity Focused Ultrasound (HIFU). Subsequently, 19 specific peptide biomarkers are monitored via Selected MS/MS Ion Monitoring (SMIM) using a linear ion trap mass spectrometer. The described technique enables the detection of fish β-PRVBs within food products in under two hours. According to the authors, this represents the quickest available protocol for the direct identification of these allergens. (Hildebrandt, 2010) developed a multiplex assay for identifying multiple fish species through the detection of parvalbumin, utilizing a DNA-based multi-analyte profiling (xMAP™) technology. This approach has the potential to simultaneously detect up to 100 different species within a single sample.

Fish allergens have been identified and characterized using techniques such as immunoblotting, isoelectric focusing, and passive cutaneous transfer assays (Bugajska-Schretter et al., 1998). Immunoblotting represents a straightforward technique for the analysis of allergens in biological specimens. (Kanamori et al., 2011) developed an optimized extraction protocol tailored for immunoblotting of fish allergens, including both parvalbumin and collagen. Their study demonstrated that heating muscle homogenates of Japanese eel at 80 °C for 20 minutes yielded the most effective extraction of these proteins, as confirmed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE). This extraction procedure was also successfully applied to five additional fish species: rainbow trout, Japanese horse mackerel, crimson sea bream, Pacific mackerel, and Japanese flounder. Using the heated extracts prepared via this method, immunoblotting effectively identified parvalbumin and/or collagen as allergens across all six species. Consequently, this extraction method not only facilitates the immunoblotting analysis of fish allergens but also provides suitable antigen preparations for fish allergy diagnosis through radioallergosorbent test (RAST).

Various analytical techniques have been employed for the isolation, identification, and quantification of histamine and other biogenic amines in food and biological matrices. These include spectrophotometry, high-performance liquid chromatography (HPLC), gas chromatography-mass spectrometry (GC-MS), single or double-isotope radioenzymatic assays, capillary zone electrophoresis, electrochemical detection, and immunoassays. Despite their widespread use, these methods often suffer from high costs, limited specificity, and insufficient sensitivity. Since aliphatic amines lack distinct absorption features in the UV-Vis spectrum, conventional spectrometric detectors are generally ineffective for their direct analysis. To enhance detection sensitivity, derivatization protocols have been introduced; however, these procedures tend to be expensive, time-intensive, involve hazardous chemicals, require complex sample preparation, and result in low throughput. Although several coupled analytical systems have been developed to improve histamine quantification, there remains a need for more sensitive and reliable approaches applicable to real sample matrices. Enzymatic assays utilizing histamine oxidase or histamine dehydrogenase provide simple and rapid detection methods; nevertheless, their selectivity is compromised by cross-reactivity with structurally related amines such as putrescine and tyramine, which often co-elute with histamine. Immunochemical methods, including enzyme-linked immunosorbent assays (ELISA), are commonly employed due to their simplicity and

accessibility, and have been used for histamine measurement in products such as cheese. It is important to note, however, that ELISA results require validation through comparison with more precise analytical techniques (Akbari-Adergani et al., 2012).

The sandwich ELISA technique has been recognized as an effective method for detecting fish proteins in processed food products (Shibahara et al., 2013). (Y. T. Chen & Hsieh.,2014) developed a fish-specific sandwich enzyme-linked immunosorbent assay (sELISA) designed to detect fish muscle proteins in food, aimed at protecting individuals with fish allergies. This assay utilizes polyclonal antibodies raised against a 36 kDa heat-stable fish muscle protein. The sELISA demonstrated the ability to detect both raw and cooked fish, as well as fish products subjected to various processing methods such as salting, smoking, and canning. The detection limit of this method was 0.1 ppm for both raw and cooked fish. (Akbari-Adergani et al.,2012) employed an enzyme-linked immunosorbent assay (ELISA) to measure histamine levels in canned tuna fish and compared its performance with a fast Fourier transform stripping cyclic voltammetry (FFT-SCV) method. The ELISA kits served as a conventional approach to assess the histamine content in various brands of canned tuna available to retail consumers. The detection limit and mean recovery for the ELISA method were 2 mg/kg and 97%, respectively, while the FFT-SCV method demonstrated a detection limit of 3.5×10^{-7} mg/kg with a mean recovery of 99.2%.

Sensitized individuals may exhibit allergic reactions to a variety of allergenic foods in differing amounts, necessitating strict avoidance of such foods and making accurate product labeling essential. In this context, (Herrero et al.,2014) successfully developed a rapid in-house real-time polymerase chain reaction (PCR) assay capable of detecting fish allergens in diverse food matrices, including processed products. When compared to a commercial kit, this method demonstrated superior accuracy, sensitivity, specificity, and dynamic range, alongside a high throughput capacity and reduced contamination risk. Furthermore, it significantly shortened analysis time to 43 minutes. This rapid PCR assay serves as a valuable tool for ensuring food quality and safety, as well as for verifying compliance with labeling regulations to protect consumers. (Ishizaki et al., 2012) developed a specific Polymerase Chain Reaction (PCR) method for detecting allergenic residues of salmonid fish in processed food products. Since salmonid fish is listed among the allergens requiring mandatory labeling under the Japanese allergen-labeling regulations, this detection method addresses an important regulatory need. The PCR assay demonstrated a detection limit as low as 0.02 fg/µl of salmonid fish DNA, equivalent to approximately 10 DNA copies. Notably, due to the absence of an ELISA method for salmonid fish detection, this PCR technique currently represents the only reliable approach for identifying salmonid fish residues in processed foods.

(Zheng et al.,2012) developed a quantitative lateral flow immunoassay (LFIA) utilizing superparamagnetic nanoparticle (SPMNP) probes to detect the major fish allergen, parvalbumin (Pa). This method offers rapid, specific, and straightforward detection, which has the potential to greatly enhance efficiency in large-scale allergen screening and point-of-care testing for parvalbumin.

(Tao, Sato, Han, et al.,2011) developed a straightforward and rapid technique for histamine detection in fish and fishery products using thin-layer chromatography (TLC). This method allows simultaneous monitoring of histamine levels as low as 20 ppm (2.0 mg/100 g) across various fish products. Additionally, (H. C. Chen et al.,2010) validated a high-performance liquid chromatography (HPLC) method involving dansylation with dansyl chloride, which proved effective and simple for quantifying biogenic amines in fish meat. In related microbial analyses, Acetobacter baumannii strains were identified as weak histamine producers isolated from suspect fish samples. Furthermore, the species of fried fish cube was confirmed as *Tetrapturus angustirostris*. (Sato et al.,1995)introduced a novel pre-column derivatization technique for histamine analysis using high-performance liquid chromatography (HPLC), which involves the formation of a diazo-coupled histamine derivative. This method is characterized by its simplicity, efficiency, sensitivity, and specificity for histamine and related imidazole compounds, eliminating the need for prior sample clean-up. Application of this approach confirmed substantial histamine production in the muscle tissue of mackerel (*Scomber japonicus*) when incubated with the fish's intestinal contents.

(Unterberger et al.,2014) developed probes for detecting DNA from allergenic fish, shellfish, and cephalopod species in food products using multiplex ligation-dependent probe amplification (MLPA). Testing on self-prepared sushi samples spiked with various analyte concentrations established detection limits of 20 mg/kg for scallop, fish, and bivalve species, and 100 mg/kg for cephalopods, gastropods, and crustaceans. This method offers a reliable approach for monitoring adherence to food allergen labeling regulations.

(Beale et al.,2009) investigated the cross-reactivity of parvalbumin among fish species commonly consumed in the Southern Hemisphere. The study evaluated antigenic cross-reactivity and the presence of parvalbumin oligomers and isoforms from five frequently eaten fish species in Southern Africa by immunoblotting with purified parvalbumin and crude fish extracts. Among ten fish-allergic individuals, pilchard (*Sardinops sagax*) parvalbumin exhibited the strongest IgE reactivity. The cDNA sequence of the β-form of pilchard parvalbumin was identified and designated Sar sa 1.0101 (accession number FM177701 in EMBL/Genbank/DDBJ databases). Oligomeric parvalbumin forms were detected across all fish species using both a monoclonal anti-

parvalbumin antibody and patient sera, with isoforms ranging from approximately 10 to 13 kDa. The study successfully identified and sequenced a highly cross-reactive allergenic isoform of parvalbumin, marking an important initial step toward developing recombinant proteins for diagnostic and potential therapeutic applications in fish-allergic individuals.

(Mukadam et al.,2001) demonstrated that autoinduction is an effective strategy to produce larger amounts of recombinant allergens. This approach facilitates the development of diagnostic tools, the quantification of allergens, and the production of immunotherapeutics targeting isoallergens. Hensley and Aronson discuss the management strategies for patients with suspected fish allergy undergoing cardiopulmonary bypass. (Nowak-Wgrzyn & Sampson, 2011) discuss emerging therapeutic strategies for food allergies, which encompass both allergen-specific and nonspecific approaches. Allergen-specific methods include oral, sublingual, and epicutaneous immunotherapy using native food allergens or mutated recombinant proteins with reduced IgE-binding capacity, often coadministered with heat-killed *Escherichia coli* to enhance immune response. Nonspecific strategies involve the use of monoclonal anti-IgE antibodies aimed at raising the allergen threshold dose in allergic patients, as well as a Chinese herbal formulation that prevented peanut-induced anaphylaxis in mouse models and is currently undergoing clinical trials. The diversity of these approaches offers promising prospects for developing effective food allergy treatments. (Arakawa et al., 2000) summarize that certain fish-allergic patients produce IgE antibodies reactive to fish gelatin. This suggests that fish gelatin, which is primarily type I collagen, may act as an allergen in individuals with fish allergy.

However, in the adult cohort studied, fish allergy typically manifested with severe symptoms. Although serological cross-reactivity was common, 41% of individuals tolerated at least one fish species. Clinical history played a critical role in evaluating fish allergy, as specific ige levels to fish extracts were not reliable indicators for predicting allergic responses to individual fish species (Schulkes et al., 2014).

CLINICAL FEATURES AND PATIENT CARE

Food allergy is defined as an abnormal immune response triggered by specific food substances. The components responsible for these reactions are known as allergens or antigens, which are naturally occurring proteins present in the foods (Danquah et al., 2010). Clinical symptoms of fish allergy can arise from ingestion, inhalation of fish proteins, or skin contact, and may include urticaria, dermatitis, angioedema, diarrhea, asthma, and anaphylactic reactions (Bugajska-Schretter et al., 1998). Fish allergy significantly impacts anxiety and stress levels not only in affected adults but also within families caring for allergic children (O'Neil et al., 1993). (Pellegrino et al.,2012) reported a case of a severe allergic reaction in a child previously diagnosed with asymptomatic codfish allergy. (Turner et al.,2011) demonstrated that seafood is a prevalent and significant cause of food allergy among Australian children, emphasizing the notably high incidence of anaphylaxis within this group. (Tao, Sato, Zhang, et al.,2011) demonstrated that fish sold in markets in certain countries pose a histamine-related risk to consumers, whereas other countries have implemented effective control measures to mitigate this risk.

The severity of fish allergic reactions varies from a minor itch of the skin or the mouth and lips to severe attacks of asthma or life-threatening anaphylactic reactions (Wong, 2015). Different routes and environments of exposures to fish species and allergens show in Table 1.

Filaggrin is an epidermal protein critical for maintaining skin barrier integrity. Loss of function mutations in the filaggrin gene (FLG-LOF) are well-established risk factors for eczema and atopic conditions. Found that FLG-LOF mutations are linked to food allergy (FA) in older children, mediated by early childhood eczema and food allergen sensitization (FAS). Their findings suggest that impaired skin barrier function plays a key role in the development and persistence of food allergies (Venkataraman et al., 2014).

(Pelé et al. 2013)concluded that there was no consistent association between maternal fish consumption during pregnancy and the development of childhood wheeze. However, they observed that maternal shellfish consumption before delivery may be linked to an increased risk of food allergy in offspring

Table 1. Routes of Fish Allergen Exposure and Associated Symptoms

Exposure Pathway	Mode of Allergen Contact	Domestic	Occupational	Clinical Manifestations	Common Fish Species
Oral	Consumption of raw, cooked, or processed fish products	✓		Angioedema, rhinitis, oral allergy syndrome, urticaria, anaphylaxis, nausea,	Sea bream, eel, pilchard, salmon, cod

				gastrointestinal symptoms	
Dermal	Skin contacts from unprotected fish handling or fish preparation	✓	✓	Urticaria, angioedema	Cod, herring, sardine, swordfish
Respiratory	Inhalation of moist aerosols during fish processing (e.g., heading, gutting, boiling)	✓ (boiling)	✓	Asthma, rhinitis, cutaneous rash	Plaice, salmon, hake, pilchard, anchovy, tuna, trout, sole, pomfret, yellowfin

[Adapted from (Saptarshi et al.,2014)]

(Miyata & Arita.,2015) explained that omega 3 fatty acids, specifically docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are abundant in fish oil, are widely regarded as anti-inflammatory agents with potential protective effects against inflammatory diseases such as asthma and allergies. While the precise mechanisms underlying these effects remain largely unclear, they are considered promising for therapeutic development. Numerous epidemiological and observational studies have explored the impact of fish consumption or omega-3 supplementation during various life stages, including pregnancy, lactation, infancy, childhood, and adulthood, on allergic and asthmatic outcomes. These studies generally suggest a protective effect and support the hypothesis that reduced fish oil intake in modern diets may be linked to the increasing prevalence of asthma and allergic conditions. Furthermore, specialized pro-resolving mediators (SPMs), including protectins, resolvins, and maresins, are derived from EPA and DHA through enzymatic pathways. These mediators actively regulate eosinophilic inflammation in the airways and facilitate the resolution of inflammation in vivo. Notably, impaired SPM biosynthesis has been observed in severe asthma cases, indicating that persistent lung inflammation may stem from a defect in the resolution phase of the inflammatory response. However, (Barman et al.,2014)found that serum fatty acid profile does not reflect seafood intake in adolescents with atopic eczema. Serum long-chain polyunsaturated fatty acids (LCPUFA) pattern was similar in allergic and nonallergic adolescents.

Advancements in molecular biology and a deeper understanding of the immunological mechanisms and allergenic epitopes of seafood proteins have opened new possibilities for the production of hypoallergenic or non-allergenic seafood. Gene transfer technology presents a powerful tool for altering the heritable traits of aquaculture species. Through DNA transformation, it is feasible to modify allergenic proteins by altering the amino acid sequences within specific epitopes, thereby reducing or eliminating their capacity to trigger allergic responses. This approach holds significant potential for improving the safety of seafood products for allergic individuals (Ka et al., 2005).

(Carrera et al.,2013) discussed the application of proteomic technologies in evaluating the quality and safety of fishery products. Proteomics, broadly defined as the large-scale analysis of the entire protein complement of a biological system at a specific time, encompasses not only the structure and function of proteins, but also their post-translational modifications, interactions, subcellular localization, and abundance. Mass spectrometry (MS), particularly matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) and electrospray ion trap (ESI-IT) MS, has become an essential tool in proteomic research. In the context of fishery products, proteomics plays a vital role in four key areas: (1) fish species authentication, (2) detection of allergens, (3) identification of spoilage organisms and foodborne pathogens, and (4) monitoring quality changes during storage and processing. These applications underscore the value of proteomics as a comprehensive approach for ensuring the authenticity, safety, and quality of seafood products.

(Nakamura et al. (2009) investigated the allergenicity of genetically modified (GM) amago salmon (*Oncorhynchus masou ishikawae*) that had been engineered to express growth hormone (GH). Their study aimed to determine whether the genetic modification altered the expression of endogenous allergens in the salmon. By comparing the allergenic protein profiles of GH-transgenic and non-transgenic amago salmon, they found no significant differences in allergen content between the two groups. The results suggest that the genetic modification for growth enhancement did not increase the expression of known allergens or introduce new allergenic proteins, supporting the allergenic safety of the GM amago salmon relative to its non-GM counterpart.

(Kuehn et al.,2014) summarized significant advancements in the understanding of fish allergy over recent decades. Key findings include: (1) Variable allergenicity among parvalbumins, especially between the beta-1 and beta-2 isoforms in salmon, highlighting differences in allergenic potential even within a single protein family, (2) Identification of new fish allergens, such as enolase, aldolase, and fish gelatin, which broaden the spectrum of proteins responsible for allergic reactions. These discoveries have critical implications. They: (1) Offer a more nuanced view of fish allergy, revealing it to be more clinically complex than previously thought, (2) Emphasize the need for incorporating these newly identified allergens into IgE-based diagnostic assays, which could improve the accuracy of allergy diagnosis and patient-specific management, (3) Support the development of novel immunotherapeutic strategies, potentially offering more effective treatment or desensitization approaches for fish-allergic individuals.

(Triantafyllidis et al.,2010) investigated the presence of allergenic fish species in commercial seafood products labeled with generic or ambiguous names in the Greek market. Their findings highlighted a significant risk for fish-allergic consumers, as these products often contained allergenic species that were not clearly identified on the label. Clinicians are advised to implement careful monitoring protocols when prescribing fish oil supplements to individuals with known allergies to fish or shellfish. To minimize the risk of adverse drug reactions, it is essential that both healthcare providers and patients maintain a current and comprehensive record of all allergens, encompassing pharmaceuticals, dietary components, and food additives, within the patient's medical documentation (Howard-Thompson et al., 2014).

Although cross-reactivity among fish species is common, some individuals with fish allergy can tolerate certain species, particularly those with low β-parvalbumin content. This study found that 40% of fish-allergic patients tolerated specific fish and highlighted inconsistencies between IgE sensitization and clinical reactions, especially in shellfish. The findings emphasize the need for precision-based approaches in diagnosing and managing seafood allergies (A. S.-Y. Leung et al., 2024).

Skin prick tests remain the primary method to detect allergen specific IgE in IgE-mediated allergies and are considered simple, safe, and reliable when performed by trained professionals. Emerging diagnostic tools like basophil activation tests (BAT), component-resolved diagnostics, and multiplex assays offer enhanced precision, though they are limited to certain allergens and not yet widely accessible. Standardization of allergen extracts and diagnostic procedures is essential for consistent results and improved clinical outcomes. Serum-specific IgE testing, using purified or recombinant allergens, is a useful alternative when skin testing is contraindicated. Multiplex IgE assays are particularly beneficial for young children, but current food panels require optimization to enhance specificity and cost-effectiveness. Clinical evaluation remains central to interpreting allergy test results accurately (Ansotegui et al., 2020).

Seafood allergies, encompassing both fish and shellfish, can cause serious reactions and are more frequent in adults, though children may also be affected. Diagnosis involves a thorough clinical history, supported by skin prick tests, serum specific IgE, and oral food challenges when necessary. Management includes strict avoidance of the allergen, prescribing epinephrine auto-injectors, and providing education on cross-contamination. Non-immunologic reactions should be considered to prevent unnecessary dietary restrictions. Further research is needed to refine diagnostic tools and improve management strategies (Davis et al., 2020).

Based on clinical history and supported by specific IgE or skin prick testing, fish-allergic individuals can be grouped into poly-sensitized (reacting to most fish via β-parvalbumin), mono-sensitized (reacting to specific species), or oligo-sensitized (reacting to several species). Key allergens include parvalbumin, enolase, and aldolase. Oral food challenges may help identify safe fish options, especially for mono and oligo sensitized patients. Even some poly sensitized individuals may tolerate low parvalbumin fish like tuna or mackerel, especially when processed. Allergen profiling can guide safe dietary reintroduction of certain fish species (Dijkema et al., 2022).

INNOVATIVE PROCESSING TECHNOLOGIES FOR ALLERGEN MANAGEMENT

RAW MATERIALS AND FOOD PROCESSING INCREASING ALLERGY RISK

Various food-processing methods can influence the allergenic properties of food proteins through multiple mechanisms. (De Jongh et al.,2013) examined how thermal glycosylation affects the digestibility and IgE-binding capacity of parvalbumin from codfish. Their findings indicate that glycosylation does not alter the protein's susceptibility to enzymatic digestion, and the resulting peptides exhibit minimal IgE binding activity regardless of glycosylation status. However, glycosylation was found to promote the formation of higher-order protein aggregates with enhanced IgE-binding potential compared to the native monomeric form. This suggests that certain processing conditions may intensify the allergenicity of fish proteins, even when digestibility remains unchanged. In a related study, (Hildebrandt & Garber.,2010) applied real-time polymerase chain reaction (PCR) techniques to assess the impact of baking and pressure cooking on the detectable levels of the parvalbumin gene in Atlantic salmon (*Salmo salar*). While questions remain about the quantitative accuracy of

this salmon-specific PCR assay, its sensitivity was on par with that of a widely used commercial kit, which lacks species specificity and exhibits cross-reactivity with more than 35 different fish species.

(Tsai et al.,2006) conducted an investigation into the histamine levels present in fermented fish products from Taiwan, alongside the isolation of histamine-producing bacteria. Their findings revealed that the majority of fermented fish samples contained histamine concentrations exceeding the 50ppm guideline established by the US Food and Drug Administration (USFDA), with 7.4% (2 out of 27) of samples exhibiting histamine levels above 1000 ppm. Such elevated concentrations pose a risk of scombroid poisoning upon consumption. Notably, only weak histamine-producing strains, *Bacillus coagulans* and *Bacillus megaterium*, were isolated from these products. This suggests that the accumulation of histamine and other biogenic amines may be primarily attributed to the use of substandard raw fish and inadequate handling practices during production.

INNOVATIVE FOOD PROCESSING TO REDUCE ALLERGY RISK

Processing methods have the potential to modify the solubility and structural conformation of fish proteins, which may result in either increased, decreased, or unchanged antigenic and allergenic properties (X. Jiang & Rao, 2021).

Various chemical alterations occurring during food processing can significantly influence the allergenic potential of proteins. One such modification involves non-enzymatic glycation, wherein carbonyl groups of reducing sugars react with the free amino groups of proteins, peptides, or amino acids, leading to the formation of advanced glycation end-products, including Amadori compounds. These glycations induced molecular cross-links may alter the spatial configuration of allergenic epitopes, consequently modulating their ability to trigger immune responses. Additionally, food proteins can undergo structural and chemical changes when exposed to processing techniques such as heating, irradiation, high-pressure treatment, or chemical exposure. These modifications often include protein unfolding, aggregation, and changes in tertiary and quaternary structures, which can either mask existing epitopes or create novel antigenic sites. Generally, heat-sensitive (labile) allergens show reduced immunogenicity upon thermal treatment, whereas heat-stable allergens tend to retain their allergenic properties. For instance, Gad c 1, a predominant allergen from codfish, is thermally stable and remains allergenic after cooking. In contrast, allergens present in fish species such as tuna and salmon exhibit decreased allergenicity following heat processing, with raw forms demonstrating greater allergic potential compared to their cooked or canned counterparts (Danquah et al., 2010).

Enzymatic hydrolysis has shown variable impacts on the allergenicity of food proteins. In the case of codfish, the major allergen Gad c 1 exhibits considerable resistance to enzymatic degradation, necessitating the use of a combination of four distinct proteolytic enzymes to effectively eliminate its IgE binding capacity (Danquah et al., 2010). Research by (Unterberger et al.,2014)indicated that physiological gastric digestion significantly diminishes the allergenic potential of codfish proteins, with degraded allergens demonstrating a markedly reduced ability to elicit allergic responses in the intestine. This suggests that compromised digestive function may lower the threshold required to trigger allergic reactions in sensitized individuals. Additionally, (De Jongh et al.,2011) explored how the Maillard reaction affects the aggregation behavior of heat-treated codfish parvalbumin under food relevant conditions. Their findings reveal that controlled pre-processing treatments, such as thermal exposure and glycation, could serve as strategic interventions to reduce the risk of allergenic responses associated with fish protein consumption.

Various food-processing methods can influence the allergenic properties of food proteins through multiple mechanisms. (Huang et al.,2014) examined the impact of high-pressure processing (HPP), an emerging nonthermal food preservation technique, on the allergenic potential of food proteins. HPP utilizes ultra-high pressures exceeding 100 MPa at ambient temperature to inactivate spoilage microorganisms and endogenous enzymes, thereby extending shelf life while preserving the sensory and nutritional attributes of food products. This innovative method offers a promising alternative to conventional thermal processing. Current research findings have not indicated any adverse microbiological, toxicological, or allergenic effects associated with high-pressure treatment. Moreover, available evidence suggests that HPP has the potential to selectively reduce the allergenicity of certain protein groups, highlighting its application in the development of hypoallergenic food products. (R. Liu & Xue.,2010)examined the impact of high-pressure processing on the proteins of silver carp (*Hypophthalmichthys molitrix*) and their allergenic properties. They concluded that while high-pressure treatment did not alter the subunit composition, molecular weight, or overall allergenicity of silver carp allergens, it induced structural modifications in these allergenic proteins.

(W. Jiang et al.,2014) reported the presence of biogenic amines in Yulu, a traditionally fermented Chinese fish sauce available on the commercial market. Their findings emphasize the necessity for routine monitoring of biogenic amine levels to ensure the safety and quality of such fermented fish products. The concentration of biogenic amines in fish muscle tissue can be effectively minimized. Experimental evidence indicates that treatment with high hydrostatic pressure significantly decreases biogenic amine levels in vacuum-packaged trout (*Oncorhynchus mykiss*) fillets (Matějková et al., 2013). (Ezzat et al.,2015)concluded that ikan pekasam, a traditional fermented fish product, can be safely consumed, as the total biogenic amine content remained below

the 1000 ppm threshold commonly associated with scombroid fish poisoning in humans. Notably, histamine was not the predominant amine detected; rather, cadaverine and putrescine were the major components. This finding suggests that the combined levels of cadaverine and putrescine may serve as a more appropriate indicator for evaluating the safety and acceptability of fermented fish products.

(Koppelman et al. (2012) investigated the impact of washing procedures on the production of fish gelatin. Their findings indicate that washing cod skin effectively reduces the parvalbumin concentration to approximately 0.5 μg per gram of skin, a level considered below the threshold capable of eliciting allergic responses in individuals with fish allergies. As a result, parvalbumin levels in commercially manufactured fish gelatin are typically minimal and generally fall below detectable limits.

Processing steps involved in producing seafood products such as EI (baby eel imitation) and CI (crab stick imitation) from Alaska Pollock significantly reduce the content and allergenic properties of β-parvalbumin (β-PV), the main fish allergen. Washing, heating, and additive incorporation not only lower β-PV levels and ige-binding, but also diminish its stability and aggregation. These products may be better tolerated by fish-allergic individuals; however, the presence of other allergens like milk or egg additives must be considered (Pérez-Tavarez et al., 2021).

Sensitization patterns to fish allergens differ across Asian populations, indicating the need for region-specific diagnostic components. Nonetheless, parvalbumin and collagen consistently serve as key allergenic markers. Thermal processing, particularly baking and frying, tends to preserve a broader range of fish proteins including heat-sensitive allergens compared to boiling or steaming, potentially affecting the severity of allergic responses (Wai et al., 2023).

Discussion

Treatment of fish allergies today cannot rely solely on conventional clinical diagnoses, but requires an integrated approach that includes molecular identification of allergens, innovations in food processing technology, as well as knowledge related to biogenic amines. Research shows that parvalbumin is a major allergen that is highly stable to heat and enzymes, but the influence of fish species, processing conditions, and bacterial contamination greatly affects the allergenicity's potential. Despite advances in techniques such as ELISA, PCR, and proteomics, the complexity of cross-reactions between species as well as indirect exposure through air or skin contact remains a major challenge.

Implications

The results of this study have important implications for the development of safer seafood products, particularly for individuals with allergies. The food industry can adopt technologies such as high-pressure processing (HPP), intensive washing, and enzymatic hydrolysis as methods of allergen mitigation. In addition, food labeling policies and quality control of processed fish products need to be strengthened with a scientific evidence-based approach to ensure consumer safety.

Research Contribution

This study contributes to a comprehensive understanding of fish allergy from immunological, molecular, and food technology perspectives. It includes an up-to-date summary of allergen profiles (especially parvalbumin), innovative diagnostic approaches, as well as food processing that has the potential to reduce IgE binding. In addition, this study introduces the discourse of proteomics integration and protein engineering for immunotherapy purposes and hypoallergenic food production.

Limitations

As a literature review study, this study relies on the quality and availability of data from previous publications. No primary data or direct experimental tests were conducted, so the findings are highly dependent on the accuracy, methodology, and scope of previous studies. In addition, the available data are more from developed countries, so they may be less representative of Asian or African populations with different fish consumption habits.

Suggestions

1. Further Research: Further clinical and immunological trials are needed on the effect of processing technologies on the reduction of apparent allergenicity in humans.
2. Diagnostic Standardization: There needs to be the development and standardization of specific diagnostic tools that can distinguish between cross-reactions and species-specific allergies.
3. Labeling Regulations: Governments and the food industry need to update allergen labeling policies based on parvalbumin-based approaches and potential cross-reactions between species.

4. Education: Increased public awareness of the risks of fish allergens and the importance of carefully reading labels is essential to prevent fatal allergic reactions.

CONCLUSION

This review demonstrates that effective fish allergy management depends on an integrated approach involving allergen identification, precise diagnostics, and innovative processing technologies. Key allergens such as parvalbumin and Gad c 1 vary in stability and immunogenicity across fish species, requiring accurate detection through ige assays and molecular diagnostics like PCR. Compatibility between these diagnostics and processing outcomes is evident, as treatments such as enzymatic hydrolysis, high-pressure processing, and washing techniques have shown potential in reducing allergenic proteins' structure and ige-binding capacity. Furthermore, mitigating risks from biogenic amines through proper fermentation and raw material handling is crucial. These insights pave the way for developing hypoallergenic fish products, offering future prospects in personalized nutrition and safer seafood manufacturing for allergic individuals.

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AUTHOR CONTRIBUTION STATEMENT

RL, as the first and corresponding author, conceptualized the study framework, synthesized the literature, and finalized the manuscript. HR and WB assisted in collecting and analyzing relevant research articles, contributed to the data interpretation, and participated in drafting specific sections. AS provided critical insights on allergen management and reviewed the technical accuracy of the processing technologies discussed. EI contributed to editing the manuscript for clarity and consistency and helped refine the structure and language. All authors reviewed and approved the final version of the manuscript.

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