



Analysis of ethylene oxide and 2-chloroethanol in sesame seeds and other food commodities

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Ethylene Oxide (ETOX) is a gas that can be used as a fumigant on certain products intended for human consumption in order to reduce bacterial contamination, particularly salmonella. Several challenges are encountered when it comes to the analysis of ETOX and 2-CE in various food products: mainly due to the accumulation of high amounts of nonvolatile material in the liner, column, and possible interference with Acetaldehyde.

This webinar, in partnership with RLC, is intended for those who want to discover how to optimize the method for ETOX and 2-CE quantification. You will learn how to overcome the analytical challenges and how a novel, robust and automated method can be implemented in your lab.

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An overview of tropomyosin as an important seafood allergen: Structure, cross-reactivity, epitopes, allergenicity, and processing modifications

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Abstract

Tropomyosin (TM) is a major allergen in crustaceans, which often causes allergy and is fatal to some consumers. Currently, the most effective treatment is to avoid ingesting TM, although most adverse events occur in accidental ingestion. In this review, the molecular characterization, epitopes, cross-reactivity, and pathogenesis of TM are introduced and elucidated. Modification of TM by traditional processing methods such as heat treatment and enzymatic hydrolysis, and innovative processing technologies including high-pressure treatment, cold plasma (CP), ultrasound, pulsed electric field (PEF), pulsed ultraviolet, microwave and irradiation are discussed in detail. Particularly, enzymolysis, PEF, and CP technologies show great potential for modifying TM and more studies are needed to verify their effectiveness for the seafood industry. Possible mechanisms and the advantages/disadvantages of these technologies for the mitigation of TM allergenicity are also highlighted. Further work should be conducted to investigate the allergenicity caused by protein segments such as epitopes, examine the interaction sites between the allergen and the processing techniques and reveal the reduction mechanism of allergenicity.

KEYWORDS

cross-reactivity, epitopes, modification methods, seafood, tropomyosin

1 | INTRODUCTION

Seafood is generally referred to as fish, crustaceans, and mollusks. Fish mainly includes elasmobranchs (e.g., sharks) and Actinopterygii, such as bony fish. Crustaceans are classified as arthropods and include more than 50,000 species (shrimp, prawns, lobsters, and crabs). Mollusks are subdivided into bivalves, gastropods, and cephalopods, including nearly 100,000 different species (mussels, oysters, octopus, squid, abalone, and snails; Ruether et al., 2018). Seafood is favored internationally due to its valuable nutrition with high-quality proteins and physiologically active substances, such as docosa-

hexaenoic acid and minerals (Fu, Wang, et al., 2019; Kubota et al., 2016; Sicherer & Sampson, 2018). However, some consumers are highly allergic to seafood. Allergic reactions of these consumers include diarrhea, vomiting, or even life-threatening anaphylaxis (Kourani et al., 2019; Moonesinghe et al., 2016; Ruethers et al., 2018). Tropomyosin (TM) is an important allergic protein in seafood, especially in crustaceans. Therefore, the reduction of TM allergenicity or immunoreactivity at the source can effectively avoid allergic reactions (Davis et al., 2020).

The term of allergenicity or allergenic potential is usually applied to classify results simulating the elicitation

of an allergic reaction, referring to in vitro functional assays (rat basophilic leukemia, basophil activation test), in vivo assays (skin prick tests, open food challenge, and double-blind placebo-controlled food challenge), and animal allergy models (mice physiological responses, mice anaphylaxis; Costa et al., 2021; Verhoeckx et al., 2015). The allergenicity or allergenic potential describes the potential of a material to cause sensitization and allergic reactions, frequently associated with immunoglobulin E (IgE) antibody (Costa et al., 2021; Verhoeckx et al., 2015). In addition, immunoreactivity refers to the ability of a material to elicit an immune response (Costa et al., 2021; Verhoeckx et al., 2015). Immunoassays mainly include immunoblotting, enzyme-linked immunosorbent assay (ELISA), radioallergosorbent test, and enzyme allergosorbent test using animal antibodies (Costa et al., 2021). The data collected from the immunoassays with sera from allergic patients are usually described as IgE-binding ability. Epitopes are regions in the antigen or protein that bind to antibodies, resulting in the induction of an immune response. Epitopes usually are small linear fragments of amino acids or specific three-dimensional structures on the proteins (Chang et al., 2019).

The antigenicity of allergens mainly depends on their epitopes and is affected by the physicochemical properties of seafood proteins such as thermal stability and pH (C. Liu & Sathe, 2018). For the epitopes, they are regions in the antigen or protein that are bound to specific antibodies such as IgE or immunoglobulin G (IgG). They can be divided into linear epitope and conformational epitope according to their structures (Chang et al., 2019) or alternatively into B-cell epitope and T-cell epitope according to their binding with antigen receptor cells (Chinnappan et al., 2020; H. J. Huang et al., 2019). During processing, the changes in proteins may disrupt or mask the antigen epitope, thereby potentially reducing their allergenicity. Therefore, processing methods have been explored as a means for reducing TM allergenicity. Among them, thermal treatments have been shown to markedly increase the IgE reactivity of TM in crab (*Portunus pelagicus*; Abramovitch et al., 2013). Enzymatic deglycosylation of TM was found to be inefficient for altering the IgE-binding ability to bind to IgE (Ruan et al., 2013). Chemical treatment (such as glycation) can result in undesirable physicochemical changes in seafood products (Gavahian & Khaneghah, 2020; Lv et al., 2021).

For minimizing the negative effects of these traditional processing techniques, innovative techniques are needed to reduce or eliminate the allergenicity of TM. In recent years, high-pressure processing (HPP), cold plasma (CP), ultrasound, pulsed electric field (PEF), pulsed ultraviolet (PUV), and irradiation have been gradually studied for the control of TM and reduction of its allergenicity.

Jin et al. (2015) reported the effect of HPP technology on the structure of TM from squid (*Todarodes pacificus*) and observed a decrease in α -helix and a decline in the free sulfhydryl group after HPP treatment at 600 MPa for 20 min and suggested that HPP decreased the IgE- and IgG-binding ability of TM by protein unfolding and modification. Ekezie et al. (2019b) used CP technology to modify the TM in king prawn (*Litopenaeus vannamei*) and found that the amino acids residues were oxidized by the reactive species (e.g., electrons, ions, free radicals, excited atoms, and molecules), and the TM structure was unfolded, which jointly reduced IgE- (17.6%) and IgG (26.87%)-binding abilities. X. Li et al. (2011) experimented on boiled shrimp (*Penaeus vannamei*) and found that ultrasound treatment for 30 min at 0°C (800 W, 30 kHz) reduced binding to IgE obtained from the sera of shrimp allergic patients by 50%. All these studies confirmed the potential effectiveness of innovative processing technologies in the control of TM and the reduction of its allergenicity.

There are several relevant reviews published in recent years. Ekezie et al. (2018) and Dong et al. (2021a) reviewed the modification techniques and methods for food allergens (e.g., milk, shrimp, peanut, soybean, and egg) including HPP, pulsed light, PUV, PEF, CP, ultrasound, fermentation treatment, and enzymatic hydrolysis and showed the polarized impacts of PUV, CP, and enzymatic hydrolysis on different foods. Cabanillas and Novak (2019) summarized the effects of peeling, boiling, baking, frying, roasting, and microwave heating on potential allergenicity with antibody binding assays. They indicated that roasting increased the ability of peanut allergens (such as Ara h 1, Ara h 2, and Ara h 8) to bind to IgE antibodies, while frying, boiling, and pressure cooking decreased it. Rahaman et al. (2016) displayed the conformational changes related to allergenicity caused by thermal and nonthermal treatments and summarized that moist heat could reduce the antibody binding of food protein by changing the protein structures and conformational epitopes. In addition, Khan et al. (2019) highlighted the potentials of processing technologies (e.g., thermal, enzymatic, glycation, acid, HPP, ultrasound, PUV, and irradiation) for the reduction of the allergenicity of crustaceans allergens including TM.

However, the above reviews reported very little information on the systematic description of TM despite its great importance as a crustacean allergen. Therefore, this review is to give a comprehensive introduction of TM, including molecular characterization, epitopes, cross-reactivity, and pathogenesis. Especially, the modification of TM by traditional (heating, enzymatic) and innovative processing techniques related to HPP, ultrasound, CP, PUV, PEF, microwave, and irradiation are discussed. Also, the abatement effectiveness of these technologies is compared and future trends are finally presented.

TABLE 1 Summary of characteristics and functions for seafood allergens (Ruethers et al., 2018)

Allergens	Fish	Crustacean	Mollusk	Molecular weight (kDa)	Allergen nature and function
PV	✓			10–14	Muscle relaxation; two types: α , β ; heat stability and $\text{Ca}^{2+}/\text{Mg}^{2+}$ affinity
Collagen	✓			110–120	Insoluble in water of low temperature; easily convert to gelatin during heating; cannot be directly absorbed in human body
Aldehyde phosphate dehydrogenase	✓			41	Catalyzes oxidation of aldehydes
Aldolase A	✓	✓		~40	Enzyme in glycolysis
Creatine kinase	✓			~40	Energy metabolism
Beta-enolase	✓	✓		~37	Enzyme in glycolysis
Hemocyanin		✓		77	Enzyme in glycolysis
Ovary development-related protein		✓		28	Unknown ovary protein
Paramyosin			✓	100	Structural protein
Troponin C		✓		~20	Structural protein
Vitellogenin	✓	✓		18	Yolk protein
TM	✓	✓	✓	35–38	Major muscle protein with highly conserved amino acid structure; two identically coiled subunits; antibody binding increased after heating; heated denatured TM can refold; vertebrate TM seems to be nonallergic
AK		✓	✓	~40	Key enzyme in energy metabolism in invertebrates; unstable and form aggregates ($> 44^{\circ}\text{C}$) IgE-binding activity: $44\text{--}80^{\circ}\text{C}$ (increase) 80°C (decrease)
SCP		✓		~22	Calcium-binding muscle protein; EF-hand-type; stable in heat or thermal treatment
TIM	✓	✓	✓	28	Key enzyme in glycolysis; thermal and pH stable allergen; can be digested by pepsin and trypsin but still cause allergic reactions
MLC		✓		18–20	Two classes: MLC1 (the essential chain) and MLC2 (the regulatory chain); highly resistant to heat and digestion

Abbreviations: AK, arginine kinase; MLC, myosin light chain; PV, parvalbumin; SCP, sarcoplasmic calcium-binding protein; TIM, triosephosphate isomerase; TM, tropomyosin.

2 | TM: MOLECULAR CHARACTERIZATION, EPITOPES, AND CROSS-REACTIVITY

The main allergens present in seafood include parvalbumin, collagen, TM, arginine kinase, sarcoplasmic calcium-binding protein, triosephosphate isomerase, and myosin light chain. The different characteristics and functions of these seafood allergens are summarized in Table 1. Until now, TM is the only allergen found in all three types of seafood of fish, crustaceans, and mollusks.

2.1 | Structure of TM

TMs in different seafood are summarized in Table 2. Generally, based on the high sequence identity, the structures of TMs in different species are similar. For example, TM from wild boar (*Sus scrofa*) is a typical example that is often used as a template to study the structure of TM in other species. TM consists of two coiled subunits with a molecular weight of 35–38 kDa and an isoelectric point of about 4.5 (Peixoto et al., 2017). Structurally, TM has eight IgE-binding sites and each is composed of 5–14 amino acids.

TABLE 2 Summary of TM in seafood

Source of allergen	IUIS name	Molecular weight (kDa)
Shrimp		
<i>Crangon crangon</i> (North Sea shrimp)	Cra c 1	~38
<i>Exopalaemon modestus</i> (white-legged freshwater shrimp)	Exo m 1	38
<i>Litopenaeus vannamei</i> (white shrimp)	Lit v 1	36
<i>Metapenaeus ensis</i> (common shrimp)	Met e 1	34
<i>Panndalus borealls</i> (northern shrimp)	Pan b 1	37
<i>Penaeus aztecus</i> (brown shrimp)	Pen a 1	36
<i>P. indicus</i> (shrimp)	Pen i 1	34
<i>P. monodon</i> (black tiger shrimp)	Pen m 1	38
Prawn		
<i>Macrobrachium rosenbergii</i> (giant freshwater prawn)	Mac r 1	37
<i>Melicerus latisulcatus</i> (king prawn)	Mel l 1	38
Lobster		
<i>Homarus americanus</i> (American lobster)	Hom a 1	34
<i>Panulirus stimpsoni</i> (spiny lobster)	Pan s 1	34
Crab		
<i>Charybdis feriatus</i> (crab)	Cha f 1	40
<i>Portunus pelagicus</i> (blue swimmer crab)	Por p 1	39
<i>Scylla paramamosain</i> (mud crab)	Scy p 1	38
Other crustaceans		
<i>Oratosquilla oralia</i> (mantis shrimp)		37
<i>Euphausia superba</i> (Antarctic krill)		37
<i>E. pacifica</i> (Pacific krill)		38
<i>Balanus rostratus</i> (acorn barnacle)		38
<i>Capitulum mitella</i> (goose barnacle)		38
Gastropods mollusk		
<i>Buccium middendorffi</i> (Middendorff's buccinum)		37
<i>Haliotis diversicolor</i> (abalone)	Hal d 1	34
<i>H. discus discus</i> (Japanese abalone)		37
<i>H. midae</i> (perlemoen abalone)	Hal m 1	49
<i>Helix aspersa</i> (brown garden snail)	Hel as 1	36
<i>Neptunea polycostata</i> (whelk)		37
<i>Turbo cornutus</i> (turban shell)	Tur c 1	37
Bivalves mollusk		
<i>Chlamys(mimachlamys)nobilis</i> (scallop)	Chl n 1	38
<i>Crassostrea gigas</i> (Pacific cupped oyster)	Cra g 1	37
<i>Fulvia mutica</i> (Japanese cockle)		37
<i>Perna viridis</i> (green mussel)	Per v 1	38
<i>Placopecten magellanicus</i> (American sea scallop)		37
<i>Pseudocardium sachalinensis</i> (surf clam)		37
<i>Ruditapes (venerupis)phillipinarum</i> (Japanese carpet shell)		37
<i>Scapharca broughtonii</i> (bloody cockle)		37
<i>Solen strictus</i> (razor clam)		37
<i>Tresus keenae</i> (horse clam)		37

(Continues)

TABLE 2 (Continued)

Source of allergen	IUIS name	Molecular weight (kDa)
Cephalopods mollusk		
<i>Loligo bleekeri</i> (apesr squid)		35–38
<i>Loligo edulis</i> (swordtip squid)		35–38
<i>Octopus ocellatus</i> (ocellated octopus)		35–38
<i>O. vulgaris</i> (common octopus)	Oct v 1	31–34
<i>Ommastrephes bartrami</i> (neon flying squid)		35–38
<i>Paroctopus dofleini</i> (Pacific giant octopus)		35–38
<i>Sepia esculenta</i> (golden cuttlefish)		35–38
<i>Sepioteuthis lessoniana</i> (big fin reef squid)		35–38
<i>Todarodes pacificus</i> (Japanese flying squid)	Tod p 1	38
Fish		
<i>Salmo salar</i> (Atlantic salmon)	Sal s 4	37

Note: IUIS, International Union of Immunological Societies; TM, tropomyosin.

As a continuous coiled-coil parallel homodimer, TM follows a repetitive “abcdefg” heptamer pattern (Figure 1a). The entire structure of TM is made up of about 40 of these heptad repeats from “a” to “g,” where sites “a” and “d” are mostly occupied by nonpolar residues, and sites “b,” “c,” “e,” “f,” and “g” are mostly occupied by polar or ionic residues (James et al., 2018; Xie et al., 2020). Also, the acid residues are generally located at “e,” and the alkaline residues are located at “g.” The electrostatic interaction between acid and alkaline residues is beneficial to the stability of the coils. Meanwhile, in this double α -helix structure, the “a” residues in one helix can interact with the “d” residues in the other helix, which maintains the stability of the whole structure of TM. The remaining residues, “b,” “c,” and “f,” are located at external positions, facilitating interactions with other proteins (actin, troponin, etc.; Gonzalez-Fernandez et al., 2014; Sano et al., 2020). The secondary structures of TM are mainly composed of α -helix, which ensures its stability to endure heat and high pressure within bounds (Chinnappan et al., 2020; Kamath et al., 2013). Under extreme heat load, the denaturation of TM occurs, the heat-denatured TM can then be refolded upon cooling and the antigenicity remains after the heat processing (Z. Zhang et al., 2021). The antigenicity also remains after acid treatment (Lasekan et al., 2017).

2.2 | B-cell and T-cell epitopes in TM

Antigenic epitopes are special chemical groups that can activate allergic immune responses. Antigenic epitopes are regions in the protein. Antigenic epitopes located on the surface of allergens are easy to be recognized by IgE on the surface of mast cells. These epitopes determine the

whole protein allergenicity, and systematically studying these epitopes is the prerequisite for the study of allergic reactions (G. -Y. Liu et al., 2018).

T-cell epitopes refer to a peptide that binds to at least one major histocompatibility complex (MHC) molecule and is displayed on the surface of the antigen-presenting cell in the form of a peptide MHC (pMHC), and it can be recognized by T-cell receptors and trigger a T-cell immune response. The formation of pMHC can be classified into MHC I and MHC II, which are recognized by CD8⁺T and CD4⁺T cells, respectively. T-cell epitopes and MHC molecules can form pMHC complexes before they are recognized. The affinity between peptides and MHC molecules has a strong correlation with peptide immunogenicity. Thus, the epitopes can be indirectly predicted by the affinity of the pMHC complex (Ravkov et al., 2013). The epitopes recognized by B-cell receptors or specific antibodies secreted by B cells are called B-cell epitopes, which can be divided into linear epitopes and conformational epitopes (Xu et al., 2020). Linear epitopes and conformational epitopes are not completely independent and some linear epitopes are part of conformational epitopes. In other words, B-cell conformational epitopes are more complex than linear epitopes; thus, it is more difficult to predict B-cell conformational epitopes. The prediction of B-cell epitopes is mainly based on secondary structure and physicochemical properties of proteins, such as local hydrophilicity, surface accessibility, plasticity, antigenicity, and others.

The commonly used technologies to analyze the antigenic epitopes mainly include inhibitory ELISA, overlapping peptide library technology, bioinformatics, peptide library method, and phage display library, molecular cloning, and X-ray crystallography. Among them, the

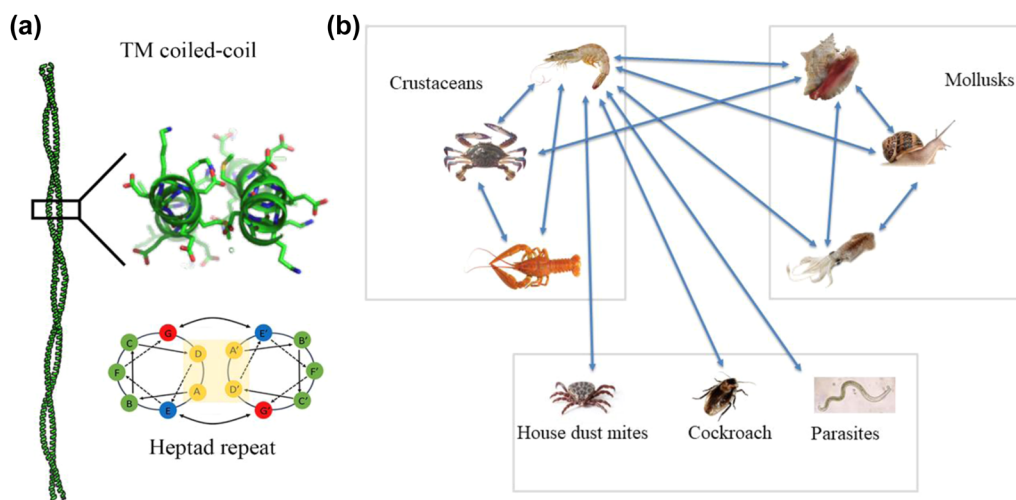


FIGURE 1 (a) The “abcdefg” heptamer pattern of tropomyosin (TM; Protein Data Bank (PDB): 1C1G). (b) Graphical representation of TM cross-reactivity among crustaceans, mollusks, and other invertebrates (mites, cockroach, and parasites; James et al., 2018; Lopata et al., 2016)

method of bioinformatics to predict epitopes avoids the limitation of cumbersome operation and low efficiency (De Groot et al., 2020; Xu et al., 2020). Combined with medical and computer science, information is easily available such as sequence analysis and function annotation and has been widely studied in recent years. Certainly, its accuracy has been verified, and studies have shown that the accuracy of bioinformatics is over 90% when applied to obtain binding peptide chips for identifying epitopes biomarkers (C. Wang et al., 2020). To be specific, software or websites include DNASTar (DNAS-TAR), AntheProt (Institute of Biology and Chemistry of Proteins, BepiPred 1.0 (<http://www.cbs.dtu.dk/services/BepiPred/>), Bioinformatics Predicted Antigenic Peptides system (<http://immunax.dfci.harvard.edu/Tools/antigenic.html>), ABCpred (<http://www.imtech.res.in/raghava/abcpred/dataset.html>), Immune Epitope Database Bank (IEDB) (<http://www.immuneepitopes.org>), and so on (X. L. Li et al., 2020).

In recent years, the potential epitopes in TM have been reported using bioinformatics. As reported above, epitopes can be divided into B- and T-cell epitopes. B-cell epitopes are generally located on the surface of antigens and could be directly recognized without processing, but T-cell epitopes need to be processed by antigen processing cells before they can be recognized. Thus, the B-cell epitopes are more meaningful, and the prediction results of B-cell epitopes are shown in Table 3 (Z. Zhang et al., 2020; Liu et al., 2021a). Generally, linear epitopes exist both in B-cell and T-cell epitopes, while conformational epitopes exist in B-cell epitopes. T-cell epitopes are linear epitopes and cannot bind to IgE. Typically, the predictions of linear epitopes are based on the primary or secondary structures of proteins. But the available data of conformational epitopes are few, and the prediction of conformational epitopes is nec-

essary to combine with the phage display library (Z. Zhang et al., 2020). Although the predicted results could provide related information for the localization and verification of antigen, more related studies are needed to further confirm the accuracy of the predicted results.

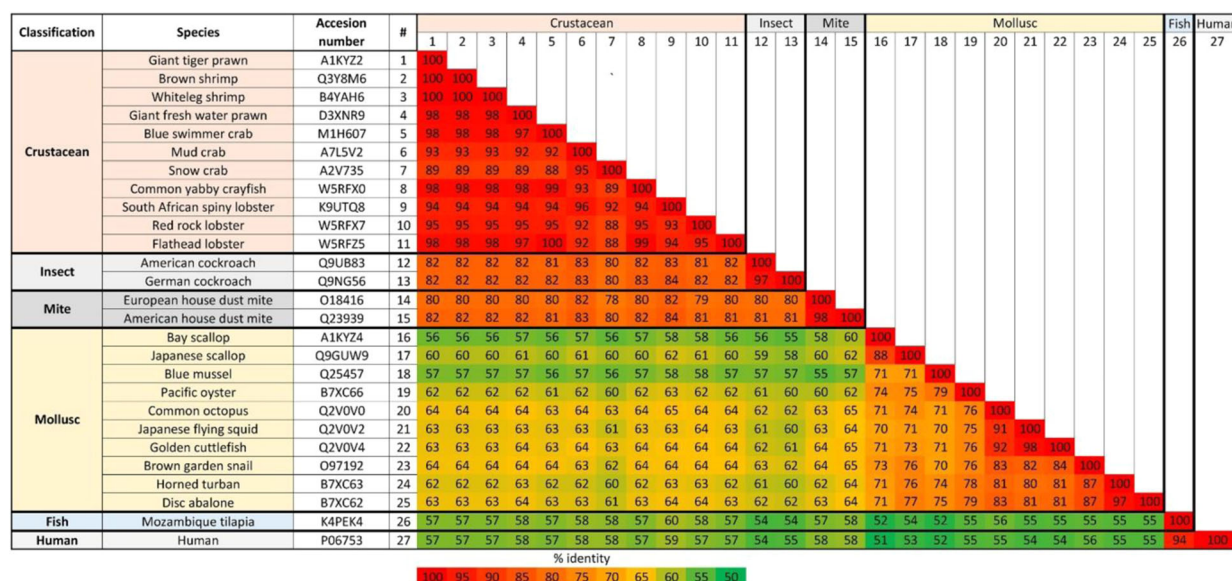
2.3 | Cross-reactivity of TM

Based on immune recognition, cross-reactivity means that if an antibody can react with two allergens, the two allergens are cross-reactive. Cross-reactivity is very common in IgE reactions. For most allergens, structural similarity requires similar folding, and the homology between allergens is related to a sequence of amino acids (Aalberse et al., 2001). TM is the important allergen in shellfish such as crustaceans and mollusks and some invertebrates such as house dust mites and insects (Peixoto et al., 2017; Rolland et al., 2018; H. Zhang et al., 2014). Significantly, only TMs in invertebrate species are major allergens, while TMs in vertebrate species are generally nonallergenic, although both of them show high homology. Klueber et al. (2020) reported that TM from shrimp and chicken showed no difference in the thermal stability and α -helix structures, but in simulated gastric digestion, chicken TM degraded faster, and only shrimp TM showed mostly positive in skin reactivity. In addition, the structural similarity of TM is high among different kinds of crustaceans and other species, and cross-activity can take place among different species (Figure 1b; Lopata et al., 2016; Zhou et al., 2020).

The structure and sequence similarity of TM is the foundation of cross-reactivity among different arthropod species. The high homology in the sequence is up to 98% among crustacean TMs, and 68%–100% among

TABLE 3 Prediction of B-cell epitopes in TM (Exo m 1) from prawn (*E. modestus*; Zhang et al., 2020)

Number	Sequence	Position	Length
Pre-epitope 1	LTCEQQNKKEANNRAEKSE	23–40	18
Pre-epitope 2	NLQKRMQQLENDLDQ	45–59	15
Pre-epitope 3	NRRIQLLEEDLERSEER	89–105	17
Pre-epitope 4	EASQAADESERMRK	115–128	14
Pre-epitope 5	ENRSLSDEERMD	131–142	12
Pre-epitope 6	ENQLKEARFLAEEADRKYDE	145–164	20
Pre-epitope 7	ERAEEAETGESKI	177–190	14
Pre-epitope 8	SEEKANQREEAYKEQ	210–224	15
Pre-epitope 9	ERSVQKLQKEVDRLDE	243–259	17
Pre-epitope 10	EKEKYKSITDELDQTFSE	263–280	18

**FIGURE 2** Comparison of amino acid sequence identities of TMs (Ruethers et al., 2018)

molluscan TMs (Duan et al., 2021; Palmer et al., 2020; Prester, 2016). Similarly, the high homology in the sequence is 80%–97% among crustaceans and house dust mite TMs and 78%–98% among crustacean and cockroach TMs. However, among the crustacean and vertebrate TMs, the sequence homology is only 54%–60% (Figure 2). Furthermore, the cross-reactivity among TMs might be due to similar epitopes within the eight epitopes in shrimp TM (Pen a 1), of which five are the same as cockroach TM (Per a 7), and four are the same as lobster TM (Hom a 1) and dust mite TM (Der p 10 and Der f 10; Hall & Liceaga, 2020; Tong et al., 2018). It was found that the cross-reactivity was 97.6% for raw TM between shrimp (*L. vannamei*) and clam (*Ruditapes philippinarum*; X. L. Li et al., 2020). Among seafood and other invertebrates, cross-reactivity was also reported with 71% of mite-allergic patients having a 55% chance of being allergic to shrimp TM (Matyushenko et al., 2020; Palmer et al., 2020). Such frequently encountered cross-

reactivity is probably due to TM from shellfish, insects, and mites, and they all belong to phylum arthropod (Loo et al., 2021; Wong et al., 2016).

3 | MECHANISM AND CLINICAL SYMPTOMS OF TM-INDUCED ALLERGIC REACTION

There are various types of allergic reactions, which can be divided into Type-I: anaphylaxis, Type-II: cytotoxic, Type-III: immune complex, and Type-IV: late-onset (Maker et al., 2019; Trautmann & Stoevesandt, 2019). In individuals susceptible to TM, IgE-mediated allergic reaction (Type-I allergic reaction) is the most common (Jianhua Wang et al., 2021). The IgE-mediated hypersensitivity reaction mainly covers two steps based on seafood allergy. Most notably, sensitization does not always translate into

elicitation, although it is widely believed that when sensitized, an individual is on a step forward to clinical allergy.

The first contact sensitization consists of three stages. First, the antigen-presenting cell processes the antigen after the initial exposure of TM and presents it by MHC II molecular. Then with the impact of cytokines (such as Interleukin (IL) - 10, IL-12, IL-4, and IL-6), T cells thereby are activated (Lei & Saltoun, 2019). Second, B-lymphocyte produces IgE. Third, the antibody binds to the surface of mast cells and basophilic cells, and the body becomes sensitized.

The second contact sensitization is when the body is exposed to TM again, TM binds to the IgE, which is adjacent to the surface of the sensitized target cell. As a result of the binding, the sensitized target cell is triggered to deregulate, release, or synthesize histamine and other bioactive media (W. Yu et al., 2016). Importantly, these bioactive substances can cause physiological phenomena such as cell migration, blood vessel dilation, and muscle contraction, which lead to an allergic reaction in the respiratory tract, digestive tract, and skin (Lozano-Ojalvo et al., 2019; Sicherer & Sampson, 2018).

Common clinical symptoms of the allergic reaction are respiratory symptoms such as asthma and cough, digestive symptoms such as nausea, abdominal cramping, vomiting, and diarrhea, and cutaneous symptoms such as urticaria, angioedema, pruritus, and rash. These clinical symptoms can be triggered by ingesting TM, or inhaling cooking vapors, or handling seafood (Carrera et al., 2020; Nugraha et al., 2021). Allergic reactions are commonly reported within minutes to 2 h (Khroa, 2016).

Therefore, allergic patients should be cautious in taking different seafood species simultaneously (Fu, Cherayil, et al., 2019). Consumers with a certain seafood allergy should be cautious even though consuming other different seafood species. A comprehensive understanding of the immunology mechanism among all the seafood species is thus necessary and more studies on allergen mitigation are required.

4 | MODIFICATION ON TM

Traditional and innovative processing technologies for crustaceans have been studied to modify and control TM allergenicity (Bassey et al., 2021; Fu, Cherayil, et al., 2019; Vanga et al., 2017). Table 4 summarizes the mechanisms, advantages, and disadvantages of these processing techniques for the reduction and control of seafood allergen.

4.1 | Traditional methods

4.1.1 | Heating

Common heating treatment methods include boiling, steaming, baking, frying, and so forth. Heating or thermal processing of foods is done to reduce the presence of microbial hazards, extend the shelf-life, and create specific quality and flavor attributes (He et al., 2021; Khan et al., 2019). Generally, for the heat-labile protein, heating can result in the destruction of conformational epitopes and unfolding and aggregation, thus reducing the IgE-binding ability of allergens (Costa et al., 2021). However for the heat-stable protein such as TM, a more compact structure is formed after heating, and the digestive stability of protein significantly increased, which may be due to the aggregation during heating (Cabanillas & Novak, 2019; Ruethers et al., 2020). Aggregation, cross-linking of disulfide, and noncovalent bonds result in the changes of allergic protein sensitization, such as the generation of neo-epitopes or the exposure of masked epitopes (Figure 3a). Besides, high temperature can also cause the Maillard reaction between proteins and reducing sugar, resulting in conformational changes of allergens, which to some extent maintain or increase the allergenic potential of allergens (M. Liu, Han, et al., 2021; Lin & Sun, 2019; Rahama et al., 2016).

In the study of Gamez et al. (2015), the immunoreactivity of TM in shrimp (*Solenocera melanthero*) remained high after heat treatment (10 min at 60°C). To be specific, digested boiled shrimp extracts were immunized in rabbits, and IgG was produced. Then, such rabbit IgG was tested to inhibit the binding of allergic patients' IgE to boiled shrimp extract. ELISA competition experiments showed that the mean inhibition was 25.7%. In an earlier study, Kamath et al. (2013) boiled different mollusks and crustaceans for 20 min and found that TM in these sample extracts was more responsive to monoclonal anti-insect TM IgG than raw samples. Considering the potential impact of the food matrix on seafood allergens, they treated the prawn (*L. vannamei*) with shell in phosphate-buffered saline liquid by heating for 20 min (20°C) and then extracted the target protein TM. The result of immunoblot analysis indicated that the raw shrimp extracts showed no reactivity with a monoclonal antibody, but the reactivity of the heated shrimp extracts obviously increased. Also, the bands of TM got wider, which could be ascribed to the exposure of neo-epitopes and the occurrence of Maillard reactions. To be specific, TM was rich in lysine residues and reacted easily with sugar at high temperatures, and then the higher weight of TM was obtained, which was similar to the study result of Kamath et al. (2014). In addition, Fang et al. (2018) found

TABLE 4 Comparisons of different processing techniques

Technology	Key influence	Advantages	Disadvantages
Heating	Aggregation, cross-linking of disulfide and noncovalent bonds, changes of lipids and carbohydrates	Cheap and safe; no chemicals are added	Increasing the allergenicity; inefficient for heat-stable allergens; affecting the quality and flavor of food
Enzymolysis	Hydrolyzing protein into polypeptides or amino acids or other small molecular; promoting destruction of protein conformation	The processing condition is mild	Producing bitter peptides of food; not suitable for the protein insensitive to enzymes
HPP	Protein conformational changes; promoting enzymatic hydrolysis; denaturation; influencing noncovalent bonds	Less influence on nutritional value; pressure passes instantaneously and evenly through the food system	Food must endure the pressure; causing coagulation or gelation of proteins; low efficiency when used alone
CP	ROS and RNS, activates particles interact with protein; producing UV light or shock wave	Extensive application area; low effect on the flavor of food	Only suitable for liquid food and solid food surface
Ultrasound	Cavitation; explosion of sonication bubbles; high-shear stress; localized regions of high pressure and temperature	Simple and convenient; short processing time	Greatly influenced by temperature
γ - or EB-irradiation	Protein aggregation; protein conformational changes	Safety and no microbial hazard	Expensive equipment and high technical requirements; Increasing the allergenicity of shrimp with low dose irradiation
Microwave	Affecting the conformational structure of protein	Common; no chemicals are used	More work to do
PEF	Ionization or electrostatic interaction of chemical groups	Uniform transmission; short processing time; little influence on the characteristics of food	More work to do
PUV	Inducing chemical, instantaneous thermal, and physical effects	Extensive application area	Only affecting the surface of food; dose residual

Abbreviations: CP, cold plasma; EB-irradiation, electron beam irradiation; HPP, high-pressure processing; PEF, pulsed electric field; PUV, pulsed ultraviolet.

that after heating (boiling at 100°C and roasting at 180°C both for 10 min), the IgE-binding ability varied with the used methods of roasted > boiled > raw samples. This may be due to the temperature-dependent destroying of the hydrophobic interaction, and the hydrophobic surface may contain the hidden IgE-binding epitopes. After heating, the inward-oriented residues in TM become outward, and the inward linear epitopes become outward and then IgE-binding increased. Similar results showed that the IgE-binding ability of TM extract from the boiled shrimp (*L. vannamei*) was higher than the raw shrimp (G. -M. Liu et al., 2010). Similarly, Fasial et al. (2019) evaluated different processing techniques on the antigenicity of TM in banana prawn (*Fenneropenaeus merguensis*), and the results showed that the TM antigenicity of frying and boiling samples, respectively, increased by 6–8 times and 2–4 times, compared with raw prawn. The increase was due to the fact that frying or boiling destroyed the binding effect

in the original TM structure, leading to the unfolding of TM and the exposure of the masked epitopes in TM. In addition, Laly et al. (2019) kept flower tail shrimp (*Metapenaeus dobsoni*) in boiling water for 5–25 min, and the IgE-binding ability showed an increase of 18%–27%. Based on the above studies, it can be concluded that heating treatments alone are not effective for reducing the potential allergenicity of TM.

4.1.2 | Enzymolysis

The enzymatic hydrolysis process is mild and can destroy the original functional properties of proteins, which has been considered an appropriate option to reduce the allergenicity of proteins. The commonly used enzymes are hydrolytic enzymes such as trypsin and papain, while other enzymes including tyrosine, polyphenol oxidase,

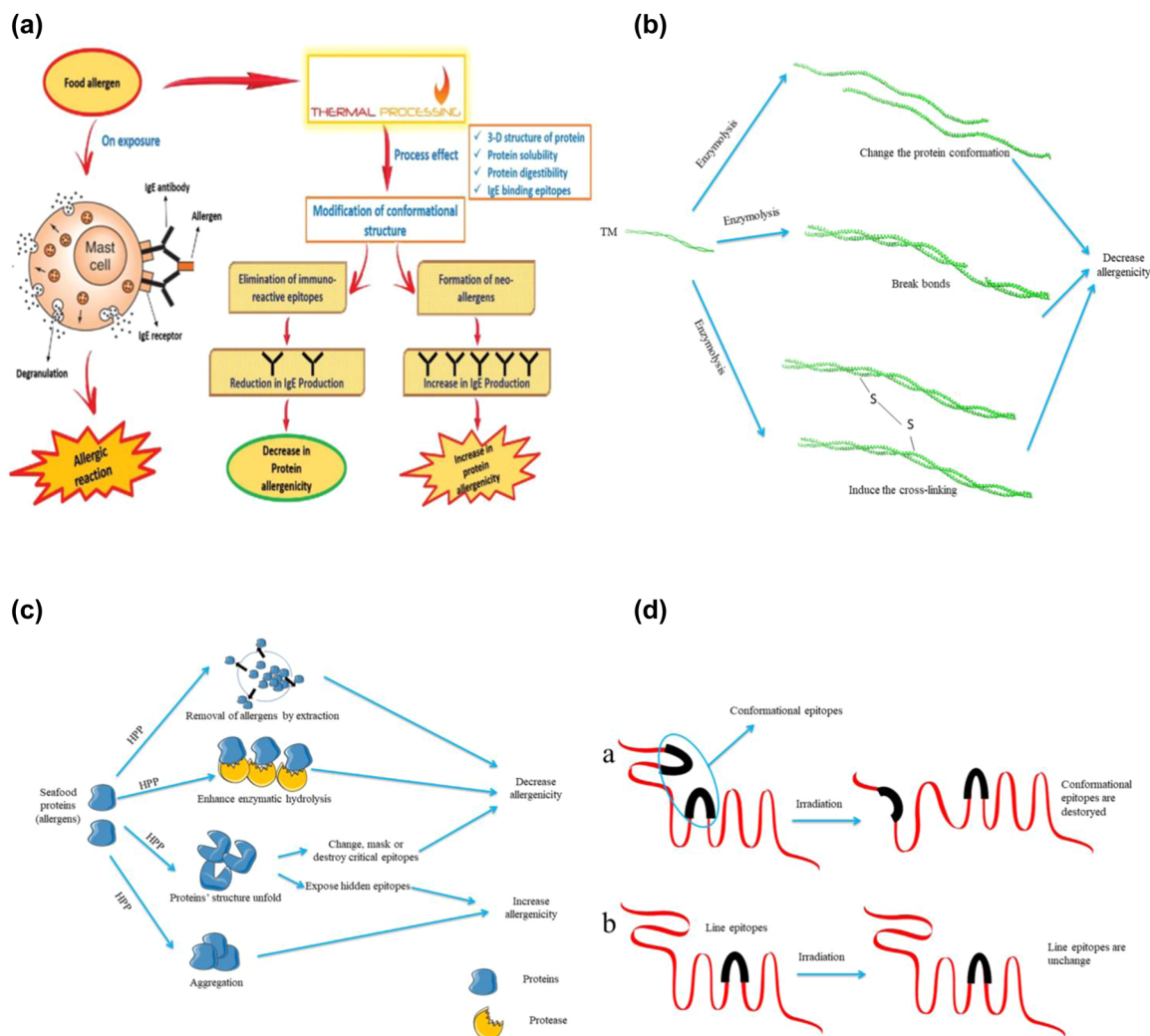


FIGURE 3 Schematic representation of different processing methods on physical/chemical changes to TM. (a) Heating; (b) enzymolysis; (c) high-pressure treatment; (d) γ -irradiation (Khan et al., 2018)

and laccase are mainly used for cross-linking in proteins. The corresponding mechanisms are mainly divided into two ways: (1) TM can be hydrolyzed by proteases into polypeptides or amino acids or other small molecular, thus changing the spatial conformation; (2) intermolecular or intramolecular cross-linking caused by enzymes results in the destruction of protein conformation (Figure 3b; Khan et al., 2019; Meng et al., 2020). In general, the enzymatic hydrolysis process seems to decrease the IgE-binding capacity of animal allergens (Costa et al., 2021).

As for use of hydrolytic enzymes in TM allergens, Y. -Y. Huang et al. (2010) studied the digestive stability of TM with pepsin and trypsin, respectively, in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). The results showed that actin and myosin heavy chains were rapidly degraded with pepsin in SGF, while TM showed a certain resistance to pepsin. However, in the SIF system,

the myosin heavy chain was rapidly degraded, and actin showed equally digestion resistibility as TM reacted with trypsin. The results were similar to the work of G. -M. Liu et al. (2011). In another study, Mejri et al. (2017) used pepsin (30 $\mu\text{g}/\text{ml}$) to treat the TM under the conditions ($\text{Ph} = 2$, $t = 2$ h), and the results showed that the recognition degree fell by 89.4% with 20 kinds of human serum IgE, while the recognition degree fell by 90.5% with rabbit IgG. When combined with heating (90°C), the maximum reduction of IgG-binding ability was 85.1%. However, Ruan et al. (2013) added glycosidase to cleave the O-linked disaccharides, and they found that enzymatic deglycosylation with this kind of enzyme did not affect the IgE-binding activity of TM.

When cross-linked with laccase, laccase/coffee acid, and transglutaminase, Ahemd et al. (2020) explored the TM antibodies binding decreased in greasy back shrimp (*M. ensis*), with the decrease of IgG/IgE-binding ability and the

increase of gastrointestinal digestibility. Also, in the mice model of allergy, the level of IgG1, IgE, and histamine in serum all reduced after cross-linking with enzyme, which revealed the great potential of laccase/cafeic and transglutaminase in decreasing TM antibodies binding by changing its conformational structures. Likewise, Guangyu Liu et al. (2017) studied the influence of polymer compounds forming from cross-linking caused by tyrosine or horseradish peroxidase on the sensitization of TM. The results showed that the cross-linking of tyrosinase and horseradish peroxidase reduced the IgE-binding ability of TM by 34.5% and 63.5%, respectively, and the IgG-binding ability of TM by 16.9% and 70.8%, respectively. Linked with horseradish peroxidase, TM was more easily digested into small fragments, and the degranulation of RBL-2H3 cells was reduced. These results suggested that the enzyme affected the TM structure, regulated the Th1/Th2 immune balance, and changed the way of antigen presentation, and then TM sensitization reduced. For the potency of transglutaminase, the results of Yuan et al. (2017) showed that the IgG-binding ability of TM to rabbit polyclonal antibody was decreased by 36.9% after enzyme treatment. The IgE-binding ability of TM to serum from patients with prawn allergy was also decreased by about 30%, which may be related to the observed unfolding primary and secondary structure and cleavage of some free amino groups. Specifically, glycosylation caused the cross-linking and changes in the linear and conformational structure of TM after treatment, which leads to the destruction of epitopes. Although enzymatic treatments can reduce antibody binding, clinical studies should be used ultimately for determining the effectiveness of treatments since antibody-binding studies and *in vitro* studies have limitations.

4.2 | Innovative methods

4.2.1 | HPP

In HPP, the pressure is added to food, which leads to the changes of the noncovalent bonds (Cuadrado et al., 2020; Pan et al., 2020a). HPP has been extensively employed to inactivate spoilage microorganisms and enzymes, and thus it has been investigated to reduce seafood allergenicity (Zhu et al., 2019).

The effects of HPP on protein structure and seafood allergens are shown in Figure 3c. To be specific, first, HPP can increase the penetration of surrounding solution into food when food is put in this airtight container filled with a liquid medium, which leads to the extraction of allergens in food, and then the food allergenicity decreases. Second, HPP can cause an irreversible or reversible modification of protein structures, which gives rise to the gelatiniza-

tion, aggregation, or denaturation of proteins (Guanchen Liu et al., 2020; Han et al., 2018). The aggregation of proteins may mask or destroy the critical epitopes, causing the reduction of allergenicity. Also, it may produce neo-epitopes, thus the allergenicity increases, especially for TM. Third, during HPP treatment, protease in solution diffuses into the inner of food, thereby reducing the allergenicity by hydrolyzing allergic proteins (Cuadrado et al., 2020). Finally, conformational changes of allergic protein caused by HPP also affect its allergenicity. On one hand, the unfolding of protein structure may change the conformational epitopes, reducing its allergenicity; on the other hand, the unfolding may expose hidden epitope especially in molecular internal, increasing its allergenicity.

Unlike heat treatment, HPP only affects the weak bonds including hydrogen, ionic, and hydrophobic bonds (Yan Zhang et al., 2018). In proteins, the primary, secondary, tertiary, and quaternary structures form different types of interactions. The primary structure is the basis of the spatial and specific biological function of the protein, whose bonds are peptide and disulfide belonging to covalent. The secondary structure refers to α -helix, β -sheet, β -turn, and random coil, and it changes only at extremely high pressure due to hydrogen bonding (Bolumar et al., 2021). The tertiary structure is related to the polypeptide chains arranged with each other to form a specific conformation. The quaternary structure is associated with the subunits held by noncovalent bonds. Among these four-level structures, HPP exercises considerable influences on the tertiary and quaternary structures maintained by noncovalent interaction, and changes in the structures determine the allergenicity of crustaceans' allergenic proteins such as TM. Table 5 lists the recent studies about the effects of HPP on TM.

H. -L. Yu et al. (2011) found that the IgE/IgG-binding of TM in crab (*Scylla paramamosain*) decreased after pressure treatment at 0.14 Mpa at 121°C for 20 min and demonstrated that high pressure could significantly destroy the structure of TM by affecting the noncovalent bonds. They also confirmed that HPP was the best way to decrease the IgE-binding of TM, compared with two other methods of boiling, and combined ultrasound and boiling. Likewise, Jin et al. (2015) observed that for TM in squid (*T. pacificus*), the α -helix decreased and the free sulfhydryl group dropped after treatment by HPP at a pressure of 600 Mpa for 20 min at 20°C. Based on the test of *in vitro* gastrointestinal digestion, the IgE-binding ability of TM was reduced by 38%–67%, as a consequence of protein unfolding and secondary structure modification. A similar investigation on the surface morphology, structure, and sensitization of TM in squid (*T. pacificus*) under HPP treatment (200–600 Mpa, 20 min, 25°C) was also performed. The results showed that HPP treatment changed the

TABLE 5 Recent studies conducted on the effect of HPP on TM

Type of seafood	Treatment conditions	Effects on allergenicity	Reference
Crab (<i>S. paramamosain</i>)	0.14 MPa, 20 min, 121°C	Decreased	Yu et al. (2011)
Squid (<i>T. pacificus</i>)	200–600 MPa, 20 min, 20°C	Decreased	Jin et al. (2015)
Squid (<i>T. pacificus</i>)	200–600 MPa, 20 min, 25°C	Decreased	Zhang et al. (2015)
Shrimp (<i>L. vannamei</i>)	500 MPa, 10 min, 55°C	Decreased	Long et al. (2015)
Shrimp (<i>L. vannamei</i>)	600 MPa, 10 min, 55°C	Increased	Long et al. (2015)
Banana prawn (<i>Micropterus salmoides</i>)	600 MPa, 5 and 10 min, 40 and 80°C	Increased	Faisal et al. (2019)
Banana prawn (<i>M. salmoides</i>)	600 MPa, 5 and 10 min, 120°C	Decreased	Faisal et al. (2019)

Abbreviations: HPP, high-pressure processing; TM, tropomyosin.

surface topography and resulted in the migration of related peaks, which were related to the observed reduction of IgE- (42%–70%) and IgG- (35%) binding capacity. In their study, HPP treatment had potential in commercial applications for reducing seafood allergens (Yifeng Zhang et al., 2015).

In another study, Long et al. (2015) found that the IgE-binding ability of TM in shrimp (*L. vannamei*) was completely lost with HPP treatment (500 Mpa, 10 min) assisted with heating (55°C). However, at 600 Mpa, the IgE-binding ability of TM increased, which was explained by the revealing of initial masked IgE-binding epitopes. In contrast, the antigenicity of TM in banana prawn (*F. merguensis*) increased with the treatment of HPP (600 Mpa) at 40 and 80°C, whereas it decreased by 65% at 120°C (600 Mpa, 20 min; Faisal et al., 2019). When high temperatures are applied together with HPPs, a generalized reduction effect is often obtained, contrary to treatments performed at high pressures with mild temperatures (Costa et al., 2021). The above contradictory results might be due to variation in samples and treatment parameters of temperature, pressure, and exposure time. In addition, processing parameters for certain samples should be optimized, and more animal and human testing are needed for confirming the feasibility of HPP.

4.2.2 | CP

Plasma is the fourth state of matter and gas with an ionization degree of more than 0.1%, which contains active particles such as electrons, ions, free radicals, excited atoms, and molecules, forming active oxidation system waves of reactive oxygen species (ROS) and reactive nitrogen species (Charoux et al., 2021; Gavahian & Khaneghah, 2020; Han et al., 2019). Plasma can also induce other physical effects including Ultraviolet (UV) light or shock waves (Sarangapani et al., 2017; Ali et al., 2021a; Ali et al., 2021b; Pan et al., 2020b; Pan et al., 2019a; Zhu et al., 2021). Low temperature makes CP an alternative to thermal treatment, and CP has thus been increasingly used

for food processing such as sterilization and degradation of fungal toxins and pesticide residues (Jiang et al., 2020; Chen et al., 2020; Zhu et al., 2022; Pan et al., 2021; Pan et al., 2019b; Wu et al., 2021). For food allergen, CP has been studied for reducing the immunoreactivity of soybean (Meinlschmidt et al., 2016), peanuts (Venkataratnam et al., 2019), wheat (Sun et al., 2020), and house dust mite (Gavahian et al., 2014).

In particular, the current studies on CP treatment of seafood mainly focus on the modification of the configuration of proteins, thus reducing the allergenicity. It was reported that exposure to free radical of CP, the secondary structure of proteins changed, such as the decomposition of α -helix, β -sheet, amide bonds, and side chains of protein, which might mask or break the conformational binding epitopes, leading to the decrease of allergenicity (Venkataratnam et al., 2019). On the other hand, the compositions of CP would also induce the cross-linking, etching, and depolymerization of proteins (Cheng et al., 2021; Esua et al., 2021a; Sarangapani et al., 2018). It is believed that the hydroxyl radicals produced by CP have the capacity of oxidization and could disrupt the binding sites of antibodies, thus resulting in the reduction of allergenicity (Gavahian et al., 2014).

In a recent study, Ekezie et al. (2019a) pointed out that CP might oxidize the amino acids residues, causing the unfolding of the structure of TM in king prawn (*L. vannamei*). In another study by Ekezie et al. (2019b), the structural changes and allergic reactions of TM in king prawn (*L. vannamei*) induced by cold argon plasma jet (7 Kv, 50 Hz) was evaluated. It was found that with a longer time of treatment, surface hydrophobicity increased and free sulfhydryl decreased, which jointly affected the antibody binding ability of TM, causing reductions in IgE- (17.6%) and IgG- (26.87%) binding capacities. In addition, Shriver (2011) found that under the treatment conditions of 30 Kv, 60 Hz, and 5 min, the dielectric barrier discharge plasma reduced the hypersensitivity of TM in prawn (*L. setiferus*) by 67%. It might be explained by the changes in protein configuration caused by active particles, followed

by changes in conformational structures of epitopes, leading to that the IgE could no longer recognize them and could not provide any conditions for the immune response. Nevertheless, more studies are needed to confirm the effectiveness of CP and optimize processing parameters.

4.2.3 | Ultrasound

The ultrasound wave is a mechanical oscillation with a frequency higher than 20 kHz, which can cause the breaking of chemical bonds and the occurrence of the redox reaction of free radical, leading to covalent bonds breaking and molecular degradation (D. Huang et al., 2020; Esua et al., 2021b). The applications of ultrasound can be divided into high frequency and low power intensity (frequency: 100–1000 kHz, power intensity $<1 \text{ W/cm}^2$), and low frequency and high power intensity (frequency $<100 \text{ kHz}$, power intensity: $10\text{--}1000 \text{ W/cm}^2$). The former is widely used in nondestructive measurements for food products, while the latter is often applied to modify food physical and chemical properties (Alarcon-Rojo et al., 2019; Ali et al., 2022; Bhargava et al., 2020; Esua et al., 2021c).

Due to the compression and rarefaction of mechanical waves, cavitation occurs, which generates bubbles. When the bubbles reach the critical size, they eventually burst (Nayak et al., 2017), causing local high pressure ($>1000 \text{ atm}$) and high temperature ($>5000 \text{ K}$). Such local high pressure and temperature can provide enough motivation to cause the physical and chemical changes of proteins and result in the conformational alteration of allergens, especially the destruction or concealment of the epitopes existing on molecular surface (Bhargava et al., 2020; Z. Li et al., 2006). Also, ultrasound treatment could lead to the polymerization of protein, which may result from intermolecular disulfide bonding cross-linking. Such polymerization can mask the epitopes on the surface of allergic proteins, ultimately reducing the probability of the binding between antigens and antibodies, and then decrease the allergenicity of proteins (Jin Wang et al., 2021). Contrarily, the polymerization could also promote the formation of complex structures with new conformational epitopes, leading to the increased allergenicity of protein (Costa et al., 2021).

Z. Li et al. (2006) reported that high-intensity ultrasound treatment for 15 min (0°C , 800 W, 30 Hz) had no effect on the IgE-binding ability of TM from shrimp (*P. vannamei*), but the IgE-binding ability was decreased by 20% for ultrasound treatment for 1.5 h at 50°C , confirming the synergism between ultrasound and heating. Moreover, the synergism could be explained by the results that heating reduced the viscosity of the liquid, resulting in a better penetration for the ultrasound. Thus, the better penetra-

tion of ultrasound might enhance the reduction of seafood allergens after heating. In order to improve the treatment effectiveness, Z. Li et al. (2011) experimented on boiled shrimp (*P. vannamei*) and found that after ultrasound treatment for 30 min with 0°C (800 W, 30 kHz), the IgE-binding ability was decreased by 50%. On the other hand, Z. Zhang et al. (2018) investigated the effect of ultrasound (800 W, 20 kHz) combined with other methods (pepsin and trypsin) on the digestibility and IgE-binding ability of TM in shrimp (*Exopalaemon modestus*) and found that the IgE-binding ability was significantly decreased by more than 70% with treatment for 15 min. Despite the above-limited studies, the information available shows that ultrasound is an effective and nonthermal treatment method to reduce the immunoreactivity of TM and other seafood allergens. It should be noted that ultrasound might not be considered as a nonthermal processing technology due to the generation of thermal energy during sonication, it is believed that cavitation plays a key role in reducing TM allergen. At present, few studies were reported on the effect of ultrasound on reducing TM allergenicity, and thus more related studies are needed.

4.2.4 | Gamma or electron beam (EB) irradiation

Gamma irradiation is usually used as a preservation technology by inactivating fungi and bacteria. The ionizing irradiation can destroy or modify the antibody-binding sites to reduce food allergens (Pi et al., 2021). There are two ways for irradiation to affect the allergens: Irradiation directly cleaves the covalent bond on the protein by photon energy, and ROS are produced by irradiating water that causes protein damage. ROS can extract hydrogen from the amino acid chains and residual rings. Fragmentation, cross-linking, aggregation of protein caused by irradiation can also result in the destruction of the secondary and tertiary structure (Gaidau et al., 2021). Figure 3d shows the conformational and line alterations of seafood antigenic epitopes caused by γ -irradiation. Recently, Muanghorn et al. (2018) found that γ -irradiation caused the loss of protein band density in immunoblot analysis (with polyclonal anti-TM produced in rabbit) of TM in giant freshwater prawn (*Macrobrachium rosenbergii*) with doses of 10 and 15 kGy at a dose rate of 0.5 kGy/h . Specifically, γ -irradiation changed epitopes structure in allergens, causing the unrecognition by IgG.

γ -irradiation can have better control effectiveness if combined with heating. Z. Li et al. (2007) combined γ -irradiation at 1–15 kGy with heat treatment, and such treatment effectively reduced the IgE-binding ability of crude protein in shrimp (*P. vannamei*) by 5–30 times as

compared with that using heat treatment alone. On the other hand, Mou et al. (2014) discovered that γ -irradiation at 7 kGy together with heat displayed an enhanced damaging effect on the pure protein (TM) as compared with γ -irradiation alone. The above phenomena can be explained by the exposure of critical epitopes in natural proteins due to γ -irradiation, followed by the destruction of the exposed epitopes by heating.

EB irradiation is another irradiation way, but it is less penetrable than γ -irradiation at the same dose. It is worth noting that the general use of EB-irradiation treatment for seafood cannot exceed 10 kGy, below which the irradiation should have no negative impact on food (Y. Liu et al., 2017b).

Guan et al. (2018) used EB-irradiation for TM reduction in shrimp (*S. melantho*) at a dose rate of 1 kGy/s. The results showed that the IgG-binding ability of TM was decreased by 59% at 7 kGy. As for the allergen mitigation, the conformational changes of TM were caused by EB-irradiation, leading to the reduction of allergenicity. Y. Liu et al. (2017b) studied the effects of EB-irradiation on frozen shrimp (*M. ensis*) and found that the trend of changes of IgE-binding ability was increased at 0–3 kGy and then decreased at 3–10 kGy. It could be explained by that the energy of the EB-irradiation was not able to penetrate the frozen shrimp. With increasing the dose to 10 kGy, the IgE-binding ability of TM was reduced to about 20%. Recently, Mei et al. (2020) reported that the α -helix, β -turn, β -sheet, and random coil were changed in TM of crab (*Ovalipes punctatus*) after EB-irradiation at a dose between 1 to 9 kGy at a rate of 1 kGy/s. With an increase in the dosage, the surface hydrophobicity was increasingly enhanced, while the free sulfhydryl group content of TM was decreased. The study also showed that EB-irradiation had little effect on the thermal stability of the TM. The above studies were consistent with the conclusions reported by Costa et al. (2021), which showed that structural changes caused by high doses of radiations (unfolding) and long periods of exposure (formation of aggregates) reduced the IgE-binding ability of TM, while small doses of radiations increased it. It should be noted that EB-irradiation seems not to be an ideal control technology for crustacean allergens, as EB-irradiation at low doses might increase its allergenicity.

4.2.5 | Other innovative methods

Except for the innovative techniques above, other methods to mitigate TM allergenicity have also been studied. For microwave, Dong et al. (2021b) applied microwave to treat TM in shrimp (*L. vannamei*) with the condition of 125°C for 15 min. They found that anti shrimp the IgG-binding

ability of TM with rabbit antiserum decreased by 75%, with the loss of turn structure and increase of β -fold induced by microwave. Microwave treatment is widespread around the world for home food processing, but more work is needed to further verify its feasibility in reducing TM allergenicity.

As for PEF, which is a technology widely used for sterilization, filtration, homogenization, extraction, and enzyme inactivation in the food industry with advantages of uniform transmission, short-time processing, less heat production, low energy consumption, and little influence on the nutrition and sensory characteristics of food (Arshad et al., 2020; Dong et al., 2021a). The mechanism of PEF treatment is to cause the ionization or electrostatic interaction of chemical groups that can seep into the structure of food (Dong et al., 2021a). There are few studies on the use of PEF for eliminating the allergen of seafood, and limited studies available only focus on protein modification. M. Li et al. (2016) carried out exploratory experiments and found that PEF (0–20 kV/cm, 0–800 μ s)-assisted enzymatic hydrolysis was more effective for extraction of abalone (*Haliotis discus hannailno*) viscera protein than simple enzymatic hydrolysis. This assisted treatment could change the properties of abalone viscera protein with an increase in solubility and emulsibility but a decrease in the foaming ability and viscosity. Likewise, more studies are needed to verify the effectiveness of mitigating TM allergenicity by PEF.

Besides, as for PUV, its system mainly consists of a power unit to provide high voltage and current, and an inert gas lamp to emit ultraviolet light. It discharges high-intensity ultraviolet light at a high pulse rate, which can induce instantaneous chemical, thermal, and physical reactions, influencing the structure and IgE-binding ability of allergens (Shriver et al., 2011). Although the peptide bonds in amino acids cannot be broken by PUV treatment, the absorption of photons can ionize proteins. Especially, aromatic amino acids such as tyrosine absorb UV and recombine, leading to cross-linking of allergic proteins with other heat-sensitive proteins, and then the proteins' allergenicity decreases (Singh & Huppertz, 2020).

In an earlier study, Shriver et al. (2011) used PUV treatment with a pulse width of 360 μ s and rate of 3/s to control the allergenicity of crude protein extract in Atlantic white shrimp (*L. setiferus*). They found that the IgE-binding ability was approximately reduced by 25% for 4 min, and the PUV treatment led to the modification of TM or cross-linking between TM and other proteins, reducing the allergic reactions. Yang et al. (2012) compared the allergic reaction of shrimp (*L. setiferus*) extracts with and without PUV treatment at a pulse width of 360 μ s and rate of 3/s for 4 min using simulated intestinal fluid and gastric fluid. The results showed that the IgE-binding ability was decreased

by 20% after the treatment. In addition, Shen et al. (2014) treated the TM in octopus (*Fangsiao*) with PUV (15 W, 60 min) and found that the IgE/IgG-binding ability was decreased by no more than 3%. However, PUV light can only destroy the contaminant on the surface. Contaminants inside the food are not affected and are likely to be present after treatment. Also, PUV treatment may leave dose residual, and more researches are needed to verify the safety of PUV in treating seafood.

5 | CHALLENGES AND FUTURE WORK

Allergic reactions caused by TMs are a topic of widespread concern in the world, which is expected to be addressed by innovative nonthermal processing techniques. Compared with the traditional technologies, the treatment conditions of innovative nonthermal processing techniques are mild, green, efficient, and have few negative effects on the quality properties of seafood (Vanga et al., 2017). Nevertheless, some limitations and challenges exist in allergens mitigation with these innovative technologies.

- (1) Effects of protein segments such as epitopes should be investigated. Current researches mostly focus on the whole protein (TMs) rather than specific protein segments such as epitopes. Epitopes are peptides located in a specific region of a protein that is usually recognized by the receptor cells and can activate the lymphocytes to trigger an immune response (Ruethers et al., 2018); thus, they are the actual cause for allergic reaction (Fu et al., 2018). Therefore, in subsequent studies, interdisciplinary techniques and biological approaches such as overlapping synthetic peptides, phage display, surface plasmon resonance, protein chip, and bioinformatics methodology can be applied to identify these specific chemical groups. Emerging processing technologies should be studied about their effects on epitopes modification for making seafood suitable for consumption by allergic patients.
- (2) The exact mechanism by which these technologies influence the allergenic potential of proteins is unknown. In general, several mechanisms are suggested to explain the mitigation of seafood allergenicity with processing techniques such as protein aggregation, masking, or destroying the epitopes or unfolding the protein structure. However the identification of the exact mechanism of each processing technique is a challenge, and the explanation of the reduction of seafood allergenicity mostly relies on the changes in proteins structures (Yifeng Zhang et al., 2019). More investigations can thus be carried out on

the relationship between the structures and the allergenicity in the future.

- (3) “Hurdle technology” can be applied. At present, the allergenicity of TM cannot be totally eliminated by a single technology. Hurdle technology utilizes the advantages of different processing methods. Therefore, combining several processing techniques might provide a solution to the complete elimination of allergenicity, while maintaining the sensorial and functional properties of seafood (Khan et al., 2019). In addition, processing parameters should be optimized. These can thus be the topics in future studies.
- (4) Toxicology analysis is needed. Allergic patients may have totally different responses to processed seafood due to individual variation (Armentia et al., 2020). More animal and human testing are needed for confirming the feasibility of these innovative nonthermal techniques in the future, and the ethical aspects of human testing should also be seriously considered.

6 | CONCLUSION

Seafood allergens affect the quality of human life. As a major category of seafood, the risk of allergic reactions induced by crustaceans should not be underestimated. TMs are the main cause of allergic sensitization to crustaceans and important panallergens among different animal species, namely, crustaceans and mollusks. The current review introduces the structure, epitopes, cross-reactivity, and clinical symptoms of TM, and discusses its reduction and control by traditional and innovative processing techniques. Innovative processing techniques have been applied for allergen mitigation with few negative effects on nutrients and sensory of seafood, compared with traditional methods. Among them, HPP, CP, ultrasound, PEF, and irradiation show great potential in reducing TM by promoting the aggregation, cross-linking, or denaturation of proteins, modifying the conformational epitopes or altering the structures of amino acid chains and residues. The review also presents the possible mechanisms and the advantages/disadvantages of these technologies in reducing TM allergenicity. Future work should focus on the study of allergenicity caused by protein segments such as epitopes, the examination of the interaction sites between the allergen and the processing technique, and the identification of the reduction mechanism of allergenicity.

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