# A LITERATURE REVIEW OF ALLERGEN PROPERTIES IN FISH COLLAGEN AND ITS DERIVATIVE PRODUCTS

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**Abstract**

Fish are generally categorized as allergens that cause reactions mediated by Immunoglobulin E (IgE). Fish collagen is one of the causes of allergic reactions, ranging from mild symptoms such as nausea and itching to severe symptoms such as anaphylaxis across all ages. Previous research has not specifically or comprehensively explained the characteristics of fish collagen and its derivatives as allergens. This study aims to address this gap by explaining the properties, contributing factors, and potential hazards of fish collagen and its derivatives as allergens. This research employed a literature review summarizing several main studies to produce comprehensive findings. The structure of collagen, contaminant allergens, and fish type can affect the allergenicity of fish collagen. Processing methods, such as heating, acid or enzyme treatment, and washing, can determine allergenicity. The structure of fish collagen can change upon heating, but its allergenicity cannot be reduced. Fish collagen is also known to have good resistance to enzymes; therefore, it can easily bind to immune cells. Another factor was age, in which adults had a greater frequency of IgE binding to fish collagen than did children and adolescents. They were included as potential allergens based on research results and existing data regarding allergy cases and their potential hazards. Therefore, there is a need for further research on allergies to fish collagen and its derivatives, especially in countries that do not require the inclusion of allergens where food safety matters.

Keywords: collagen allergenicity, fish allergen, food safety, IgE reactivity, potential hazard

## Kajian Pustaka Sifat Alergen pada Kolagen Ikan dan Produk Turunannya

**Abstrak**

Ikan termasuk dalam makanan yang umum dikategorikan sebagai alergen yang reaksi alerginya termediasi oleh Immunoglobulin E (IgE). Kolagen ikan menjadi salah satu penyebab reaksi alergi, yang ditunjukkan dengan gejala ringan hingga berat seperti mual, gatal, hingga anafilaksis pada anak-anak, remaja, dan dewasa. Kajian dari penelitian-penelitian sebelumnya belum secara spesifik dan lengkap menjelaskan karakteristik kolagen ikan dan turunannya sebagai alergen. Penelitian ini bertujuan untuk menjelaskan secara mendalam sifat, faktor yang berkontribusi serta potensi bahaya pada kolagen ikan dan turunannya sebagai alergen. Metode penelitian yang digunakan adalah kajian literatur yang merangkum beberapa penelitian utama untuk menghasilkan temuan yang komprehensif. Struktur kolagen, alergen kontaminan, dan jenis ikan dapat memengaruhi alergenisitas kolagen ikan. Proses pengolahan seperti pemanasan, perlakuan asam maupun enzim, serta pencucian dapat menentukan alergenisitias kolagen ikan serta turunannya. Struktur kolagen ikan dapat berubah karena pemanasan, namun alergenisitasnya tidak dapat diturunkan. Kolagen ikan juga dinyatakan memiliki ketahanan yang baik pada enzim sehingga dapat dengan mudah berikatan dengan sel imun. Selain itu, usia menjadi faktor bagaimana kolagen ikan dan turunannya bersifat sebagai alergen. Orang dewasa memiliki frekuensi pengikatan IgE yang lebih besar pada kolagen ikan dibandingkan anak-anak hingga remaja. Melalui hasil penelitian serta data-data yang ada terkait kasus alergi dan potensi bahaya kolagen ikan dan turunannya sebagai alergen, kolagen ikan dan turunannya termasuk ke dalam alergen yang berpotensi. Perlu adanya penelitian lebih lanjut terkait alergi terhadap kolagen ikan dan turunannya khususnya di negara yang tidak mewajibkan pencantuman alergen kolagen ikan dan turunannya karena hal ini terkait dengan keamanan pangan.

Kata kunci: alergenisitas kolagen, alergen ikan, keamanan pangan, potensi bahaya, reaktivitas IgE

## INTRODUCTION

Fish is a source of animal protein, which provides vitamins, minerals, and omega-3 (Sarojnalini & Hei, 2019). Because fish has various functional properties, fish-derived products, such as collagen, were frequently added to food and beverage products. Given Indonesia's prominent role in the global fishery industry, the country has significant potential to capitalize on these benefits. In 2021, Indonesia's fishery production reached 21.87 million tons (The Ministry of Fishery and Marine, 2021), where 30-40% of the production weight is waste (skin, bones, scales, head). These parts have great potential in producing collagen and its derivative products.

Fish collagen is a protein with a triple helix structure consisting of three glycine-X-Y polypeptide chains where X and Y can be proline or hydroxyproline (Wijaya *et al*., 2020). Fish collagen that undergoes some denaturation and processing will produce product derivatives, such as gelatin, hydrolyzed collagen, and collagen peptides. Gelatin is formed through a heat process (Nurilmala *et al*., 2020). During the process, an enzymatic treatment will break the amino acid chains of fish collagen to produce collagen peptides or hydrolyzed collagen (Kouguchi *et al*., 2012).

Fish collagen is utilized as an alternative source of other collagen, particularly for individuals following halal and kosher dietary restrictions (Nurilmala *et al*., 2020). In addition, it mitigates the risk of livestock-related disease crises. Fish collagen hydrolysates are known for their strong antioxidant activity (Prastyo *et al*., 2020) making them a great potential for collagen supplementation. Hydrolyzed collagen is commonly used as a functional or daily food supplement where allergic cases are found (Fujimoto *et al*., 2016). Additionally, fish gelatin is increasingly used as an alternative to gelatin derived from livestock for processed food such as gummy jelly, marshmallows, yogurt, etc (Aziza *et al*., 2019; Ayati *et al*., 2022; Osiriphun *et al*., 2022). Fish gelatin has been shown to produce products with acceptable sensory quality and physicochemical characteristics compared to those made with commercial gelatin (Normah & Fahmi, 2015; Choobkar *et al*., 2018; Nur Kholis *et al*., 2023). Fish collagen derivatives can also enhance the nutritional value of the products (Choobkar *et al*., 2018; Ayati *et al*., 2022). Fish gelatin and its derivatives offers benefits to the food industry in terms of cost, given the abundant fishery resources and waste in Indonesia, as well as the sensory quality and nutritional value of the products which increase product values. Despite the fish collagen's benefits, there are potential risks associated with its use, including allergic reactions and sensitivities. Furthermore, it is crucial to consider the food safety of the products. Therefore, it is important to evaluate how fish collagen and its derivatives act as allergens, as they are classified as allergens.

Allergy is a response of hypersensitivity to some substances, which can occur from consumption, inhalation, or skin exposure. Allergy reactions can be mediated by IgE (Immunoglobulin E) and are called type 1 hypersensitivity (immediate hypersensitivity). Allergic reactions from fish collagen and its derivatives are stated as IgE-mediated allergy (Buyuktiryaki *et al*., 2021).

Allergic reactions to food are a serious problem in developed and developing countries. Fish allergy is one of the common allergies found in cases of food allergies. In Asia, increasing fish consumption makes allergic reactions to fish a serious health problem. Allergies to fish were reported to be more common than other allergies, such as nuts or wheat, especially in Asian countries close to or connected to the coast (Boye, 2012).

Fish collagen was declared an allergen in early 2000 in Japan (Sakaguchi *et al*., 2000; Hamada *et al*., 2001). The fish collagen and its derivatives contain parvalbumin, a contaminant allergen (Koppelman *et al*., 2012). The parvalbumin levels can be affected by the washing and processing of the fish and its body parts used in collagen extraction (Kuehn *et al*., 2010; Koppelman *et al*., 2012; Kobayashi *et al*., 2016c).

Plenty of research has investigated the topics of fish collagen and its derivatives as allergens. The research typically discusses allergic cases, variations in allergen content, the effect of various treatments on allergen characteristics, potential allergen hazards, and risk management (Wang & Sicherer, 2005; Kuehn *et al*., 2010; Pan *et al*., 2012; Koppleman *et al*., 2012; Kiew & Mashitah, 2013; Veeruraj *et al*., 2013; Chikazawa *et al*., 2015; Chen *et al*., 2016; Fujimoto *et al*., 2016; Kobayashi *et al*., 2016b; Sotelo *et al*., 2016; Tamura *et al*., 2018; Ahmed *et al*., 2019; Blanco *et al*., 2019; Abe *et al*., 2020; Ueno *et al*., 2020; Wijaya *et al*., 2020). Those studies found several cases of allergic reactions to fish collagen and its derivatives and their derivative products after consumption. Allergic reactions are followed by symptoms such as nausea, itching, and anaphylaxis and occur in children, adolescents, and adults (Wang & Sicherer, 2005; Kuehn *et al*., 2010; Chikazawa *et al*., 2015; Fujimoto *et al*., 2016; Tamura *et al*., 2018; Abe *et al*., 2020; Ueno *et al*., 2020).

Up to the present, studies on fish collagen allergens and their derivatives are dominated by empirical research and rarely in the form of published reviews. There have not been any review studies specifically discussing fish collagen as an allergen. Hence, further studies are needed to determine the potential of fish collagen and its derivatives as allergens in fish. Previous review studies only discussed the types of allergens commonly found in fish (Virginie, 2020; Kalic *et al*., 2021). They did not specifically and completely explain the characteristics of fish collagen and its derivatives as allergens (thermostability, water solubility, enzyme resistance, allergenicity), human factors, analysis and detection, and existing labeling standards. Moreover, most regulatory standards in several countries, including Indonesia, do not yet have standards regarding fish collagen and its derivatives as allergens. This research aims to explain the properties, contributing factors, and potential hazards of fish collagen and its derivatives as an allergen.

## MATERIALS AND METHODS

### Search of Literatures

The keywords used in this review are fish gelatin allergy/allergen, fish collagen allergy/allergen, and fish parvalbumin allergy/allergen. Literature searches were conducted using internet resources, specifically Google Scholar, as a source of national and international journal or article data. The journals and research articles used come from reputable publishers such as PubMed, Elsevier, Taylor & Francis, and others. The publication years of the articles used range from 2012-2023. Literature other than research articles (regulations and standards) was obtained through Google searches.

### Gap Research Analysis Inclusion and Exclusion

The inclusion and exclusion criteria include publication year, type of publication, language used, research subjects, and the theme or topic of the literature. The publication years used are from 2012-2023, the languages used are Indonesian and English, the research subjects are individuals with allergies (fish, fish collagen, fish gelatin) and fish collagen and its derivatives themselves, and the theme or topic is related to allergens in fish collagen and its derivatives.

### Research Literature Selection Scheme

Figure 1 shows the steps in selecting research literature, starting from keyword searches to the total number of research articles to be reviewed. A total of 13 articles were obtained from the selection process using the inclusion and exclusion criteria. The 13 articles used as the main data for this review consist of research on fish collagen allergy cases, the thermostability of fish collagen and its IgE reactivity, detection and diagnosis of fish collagen allergy, also research on how parvalbumin influences the allergenicity of fish collagen derivatives.

Table 1 Gap research analysis
Tabel 1 Analisis kesenjangan penelitian

| Aspect | Current condition | Desired condition | Gap | Actions taken |
|---|---|---|---|---|
| Review research on fish collagen allergy and derivatives | Existing review research generally discusses fish allergens | Increased publication of review research specifically addressing fish collagen and its derivatives as allergens | There is no review research specifically addressing fish collagen and its derivatives as allergens | Review research on fish collagen and its derivatives, covering allergen characteristics and potential allergen hazards by the author |
| Cases of fish collagen allergy and derivatives publications | Allergy cases related to fish collagen and its derivatives are mostly reported in Japan and the U.S. | Awareness of allergy cases related to fish collagen and its derivatives in other countries | Cases of fish collagen allergy and its derivatives are still minimal and may have the potential of false diagnoses | More accurate and specific diagnosis of allergens to avoid false diagnoses between fish collagen and its derivatives with common fish allergens |
| Research on fish collagen allergy and derivatives in Indonesia | Most research comes from Japan and the U.S. | Research can be conducted in Indonesia to support food safety | No research on fish collagen and its derivatives as allergens in Indonesia | Research explaining the potential hazards of fish collagen and its derivatives as allergens to support further studies and inform regulatory standards and food safety considerations in Indonesia |
| Regulatory standards and labeling of fish collagen allergy and derivatives in Indonesia | Regulatory standards addressing fish collagen and its derivatives as allergens are only in Japan and the U.S. | Regulatory standards for labeling fish collagen and its derivatives as allergens in Indonesia can be updated | No regulatory obligation for labeling fish collagen and its derivatives as allergens in Indonesia | |

## RESULTS AND DISCUSSION

### Properties and Characteristics of Fish Collagen and Its Derivative Products As Allergens

Collagen is basically a protein because it has a triple helix structure composed of three polypeptide chains (tripeptides) (Alhana & Tarman, 2015). As shown in Figure 2, it has a molecular weight of 97-244 kDa with a triple helix structure composed of three glycine-X-Y polypeptide chains, where X and Y can be proline or hydroxyproline. Collagen in fish, later declared an allergen (Kobayashi *et al.*, 2016a), is known as type 1 collagen. It consists of α1, α2, β, and γ chains with a molecular weight of 97-244 kDa (Wijaya *et al.*, 2020).

The potential allergenicity of fish collagen underlines the importance of

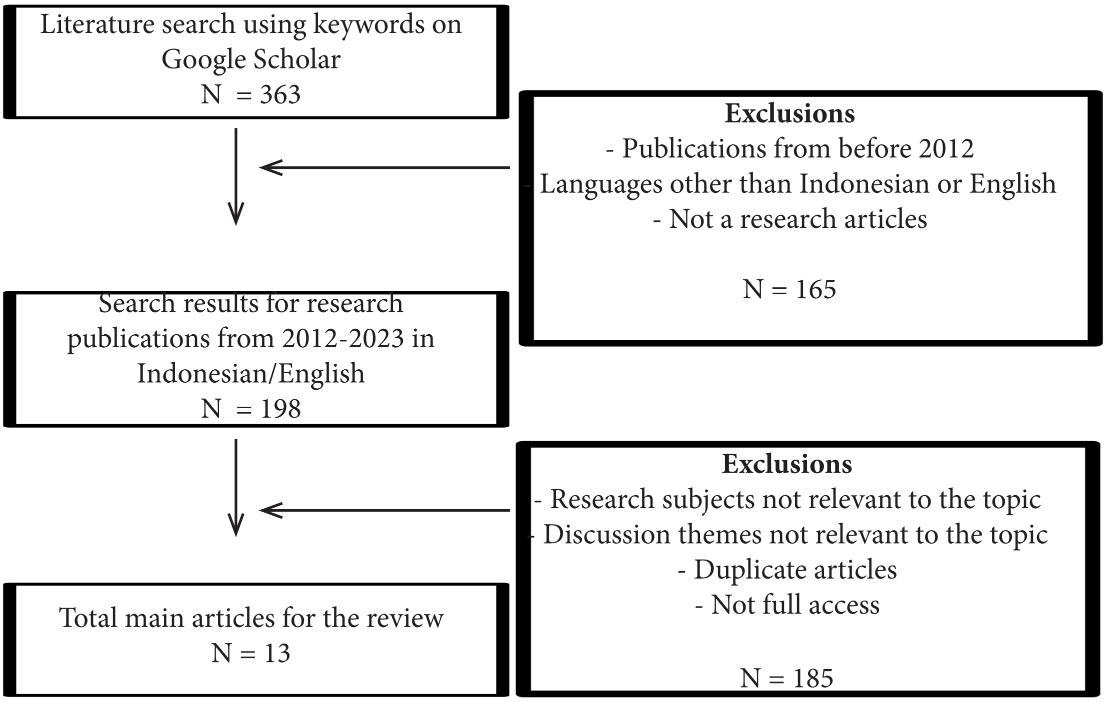


Figure 1 Scheme of literature selection
Gambar 1 Skema seleksi literatur

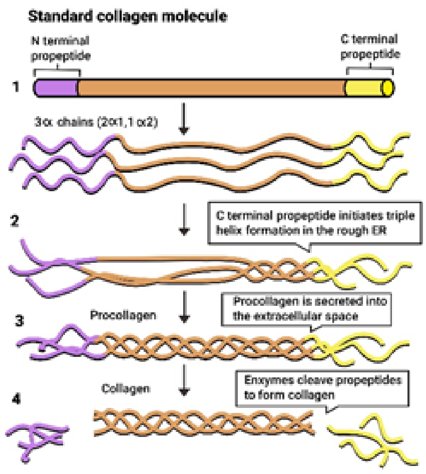


Figure 2 Collagen molecular structure (Mouw & Waever, 2014)
Gambar 2 Struktur molekuler kolagen (Mouw & Waever, 2014)

understanding its derivatives. Gelatin is one of them. It is a fish-derived product obtained from fish collagen processing. The structure of the gelatin is formed from the denaturation process experienced by collagen. Heat treatment causes the collagen triple helix structure to denature and form gelatin with a single-chain structure (Nurilmala *et al.*, 2020). The process continues when gelatin is given an enzymatic treatment that breaks the amino acid chains to produce collagen peptides or hydrolyzed collagen (Kouguchi *et al.*, 2012). Hydrolyzed collagen has been reported to cause allergic reactions in individuals who consume it either as a functional food or as a daily dietary supplement (Fujimoto *et al.*, 2016).

Figure 3 shows the different structures of collagen. Scholars argue that collagen, gelatin, and collagen peptides have different allergen characteristics (Chikazawa *et al*., 2015; Fujimoto *et al*., 2016; Wang *et al*., 2021). It was argued that heating does not affect the binding of the IgE (Immunoglobulin E) epitope of collagen (Chikazawa *et al*., 2015). The process of structure changing of collagen by heating it into gelatin or hydrolyzed collagen does not affect its reactivity to IgE. Nevertheless, the difference in structure still causes different levels of IgE reactivity due to its solubility in water (Chikazawa *et al*., 2015).

Understanding the role of amino acids in collagen can further explain these differences in allergenicity. The amino acid composition can determine the characteristics of collagen, especially its water solubility. Some amino acids are hydrophobic, meaning they are insoluble in water. According to Wijaya *et al*. (2020), the composition of amino acids in collagen is dominated by glycine, a hydrophobic amino acid. This high glycine content contributes to the hydrophobic characteristics of fish collagen. Studies have shown glycine is the most abundant amino acid in various fish species, further reinforcing the hydrophobic characteristics of fish collagen (Kiew & Mashitah, 2013; Veeruraj *et al*., 2013; Sotelo *et al*., 2016; Ahmed *et al*., 2019).

The solubility of an allergen in water can affect IgE reactivity. For example, Chikazawa *et al*. (2015) conducted a prick-to-prick test on a patient who experienced an allergic reaction after consuming baked eel. The patient's skin showed a positive reaction to heated fish samples but a negative reaction to raw fish samples, highlighting the influence of allergen solubility on IgE reactivity.

Collagen content is known to differ depending on the type and species of fish. Cartilaginous fish (Chondrichthyes) generally produce more collagen compared to bony fish (Osteichthyes) (Chen *et al*., 2016; Sotelo *et al*., 2016; Ahmed *et al*., 2019; Blanco *et al*., 2019). Furthermore, according to Veeruraj *et al*. (2013), the collagen content of fish can also be affected by the composition of the skin. For instance, the eel, which is a bony fish, has a high skin composition, resulting in substantial collagen production. This indicates that high collagen yields are not limited to cartilaginous fish but can also be found in fish with high skin composition.

## Contributing Factors Influencing The Allergenicity of Fish Collagen and Its Derivatives

### Contaminant allergen in fish collagen

The allergenicity of fish collagen and its derivatives can be influenced by contaminant allergens, with parvalbumin being a notable example. Despite the lack of published cases of allergy specifically caused by fish collagen, parvalbumin has been identified as a contaminant allergen in its production. Allergenicity and IgE reactivity of parvalbumin depends on the content, which varies according to the species and body part of the fish. Parvalbumin is most commonly

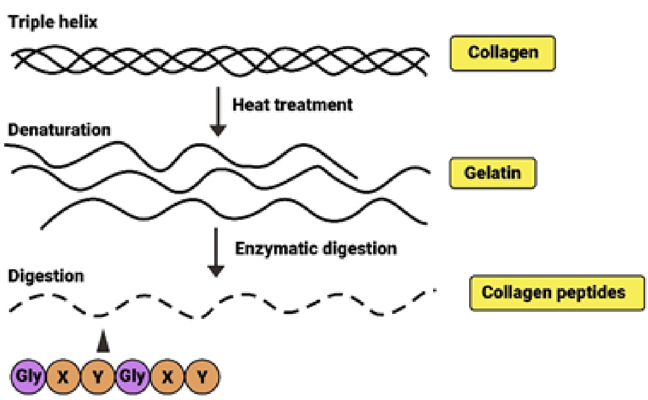


Figure 3 Collagen structure, denaturation and digestion (Kouguchi *et al*., 2012)
Gambar 3 Struktur, denaturasi dan pemotongan kolagen (Kouguchi *et al*., 2012)

found in fish muscles (Koppleman *et al*., 2012), with concentrations differing across the part of the muscle.

A study examining parvalbumin levels of 22 fish species and different body parts using SDS-PAGE revealed that white muscles generally contain higher levels of parvalbumin compared to the dark muscles of fish. Notably, it was known that the highest parvalbumin levels existed in the Kinmedai fish sample with 11.2 mg/g whole fillet. On the other hand, the Bigeye tuna sample exhibited the lowest parvalbumin level at 0.234 mg/g whole fillet. Kinmedai fish, a sedentary fish, tend to have higher parvalbumin levels than migratory fish, like tuna (Kobayashi *et al*., 2016c).

Fish collagen can be extracted from the fish skin, bones, and muscles, and when treated with heat, it can form gelatin (Nurilmala *et al*., 2020). The production of collagen and gelatin from fish muscle can increase the risk of parvalbumin contamination. To minimize parvalbumin contamination in fish collagen and its derivatives, it is necessary to carefully select the production materials. Materials that may have minimal contamination risk during extraction, such as migratory fish species and dark muscle parts, are recommended. Further studies are needed to investigate the parvalbumin content in fish collagen and its derivatives from various species and muscle parts.

In addition to fish muscle, parvalbumin can also be found in fish skin, which is commonly used for gelatin production. Research by Koppleman *et al*. (2012) shows that parvalbumin derived from fish skin has different levels than that derived from fish muscle. Specifically, the parvalbumin level in fish muscle was 6.25 mg/g muscle, significantly higher than that from fish skin, which was only 0.4 mg/g. Therefore, to reduce allergen risk and potentially increase yield, it may be advantageous to use fish skin rather than muscle for collagen or gelatin production.

## Fish types influencing collagen igE reactivity

IgE reactivity to an allergen can be seen using ELISA (Enzyme-Linked Immunosorbent Assay) with the patient's serum. Measurements of patient IgE reactivity were carried out on collagen from bony fish (Osteichthyes) and cartilaginous fish (Chondrichthyes) (Kobayashi *et al*. 2016a).

The results indicate that bony fish exhibit higher reactivity than cartilaginous fish (Kobayashi *et al*., 2016a). In the fish collagen processing industry, the main objective is to obtain high yields. Thus, it is necessary to select the right type of fish and use the correct processing method. Based on previous studies, it can be concluded that the maximum collagen yield is produced by cartilaginous fish and fish with a large skin composition. Therefore, cartilaginous fish, which offer high collagen yield and low IgE reactivity, can potentially be considered for producing collagen and hypoallergenic fish products (Kobayashi *et al*., 2016a).

## Effect of Processing on The Characteristics of Fish Collagen and Its Derivatives as Allergens

### Extraction process of fish collagen and its derivatives

Collagen can be extracted from various parts of the fish's body, including the skin, bones, muscles, and fish scales (Pan *et al*., 2012; Sotelo *et al*., 2016; Luo *et al*., 2018; Kalic *et al*., 2020; Nurilmala *et al*., 2020; Srinivasan & Durairaj, 2021; Göçer, 2022). The extraction methods for fish collagen are generally classified into three categories: acid, base, and enzymatic extraction. Among these, acid and enzymatic extraction methods are the most commonly used. Acid extraction produces Acid Soluble Collagen (ASC), while enzymatic extraction produces Pepsin Soluble Collagen (PSC) (Wijaya *et al*., 2020; Srinivasan & Durairaj, 2021; Göçer, 2022).

The difference between PSC and ASC extraction is in the use of enzymes and acetic acid containing 1-1.5% pepsin. Both methods used low-temperature extraction (no more than 5°C) to prevent collagen degradation. Extremely high temperatures can convert collagen into gelatin by changing its amino acid triple helix structure. The process of making fish gelatin can be done by denaturing the collagen extract at a temperature of more than 50°C for a specified duration. The temperature used in the extraction of fish gelatin ranges from 60°C to 95°C depending on the ingredients and processing time (Koppleman *et al*., 2014; Pranoto *et al*., 2016; Nurilmala *et al*., 2020; Rafael *et al*., 2021). The conversion of collagen to gelatin affects its water solubility, where gelatin becomes hydrophilic (Chikazawa *et al*., 2015; Wang *et al*., 2022). Thus, it will affect the level of allergenicity of gelatin (Chikazawa *et al*., 2015).

Further processing, like the hydrolysis of collagen or fish gelatin, produces derivative products called hydrolyzed collagen or collagen peptides (Kouguchi *et al*., 2012). Despite these changes, hydrolyzed collagen and fish gelatin remain potential allergens due to their water-soluble nature, which can enhance allergenicity (Chikazawa *et al*., 2015; Fujimoto *et al*., 2016). Research showed that heating could not reduce the patient's IgE reactivity to gelatin (Chikazawa *et al*., 2015; Kobayashi *et al*., 2016b). Nonetheless, collagen and fish collagen extract without heating or hydrolysis also have potential, as proven in published allergy cases (Pan *et al*., 2012; Chikazawa *et al*., 2015; Kobayashi *et al*., 2016b; Kobayashi *et al*., 2016c; Tamura *et al*., 2018; Abe *et al*., 2020; Kalic *et al*., 2020; Ueno *et al*., 2020).

## Heating treatment

Heating process on fish collagen can affect its solubility level in the water. According to Chikazawa *et al.* (2015), collagen dissolves in water when subjected to heat treatment. This claim is supported by Wang *et al.* (2022), whose research on eel fish collagen found that heat treatment of fish collagen can reduce its hydrophobicity, increasing its solubility and leading to gelatinization or hydrolysis into gelatin or collagen peptides. The ability of collagen to dissolve in water is then related to IgE reactivity, that collagen which can dissolve in water due to heating shows positive results when tested on patients through a prick test (Chikazawa *et al*., 2015). Thus, collagen insolubility appears to influence allergenicity.

Using SDS-PAGE, the characteristics of collagen related to its resistance to heat were studied. It analyzed samples that went through various heat treatments for a certain time (Pan *et al*., 2012). At 70°C, collagen decomposition occurred, leading to the breakdown of α and β components into fragments (Pan *et al*., 2012). The thermostability of fish collagen was also investigated by Kobayashi *et al.* (2016a), arguing that collagen degrades at 140°C for 10 minutes and 100°C for 320 minutes. Both studies confirm that fish collagen is a protein that is unstable to heating.

In addition, Kobayashi *et al.* (2016a) researched the relationship between collagen thermostability and IgE reactivity using patient serum using fish collagen extract via ELISA. The results indicated that patient serum IgE reactivity remains despite heating the collagen extract (100-140°C for 10 minutes, 100°C for 10 and 320 minutes). Therefore, the allergenicity of collagen cannot be easily reduced by heating even though it has been degraded into gelatin and collagen peptides. Consequently, the risk of collagen in processed fish and fish collagen, which mostly goes through a heating process, remains a concern for food safety.

## Acid and enzyme treatment

In the human digestive tract, food in the stomach meets extreme pH conditions and digestive enzymes. High stability under these extreme conditions is necessary for a protein to be a potential allergen. The allergenicity of an allergen depends on changes that occur in its matrix structure. One factor responsible for changes in allergenicity is the degree of acidity or pH (Khan *et al*., 2019). Using a pH buffer and SDS-PAGE analysis, it was found that tilapia collagen undergoes decomposition with fading bands at pH 2.0 but remains stable at pH 3.0 to 11.0 (Pan *et al*., 2012). This highlights the resilience of fish collagen in moderately acidic conditions.

Additionally, the allergenicity of fish collagen can also be seen through its digestibility in the stomach. Resistance to digestive enzymes determines the allergen allergenicity (Wang *et al*., 2017; Akkerdaas et al., 2018). To evaluate the digestive ability of fish collagen, SGF (Simulated Gastric Fluid) treatment was carried out. Pan *et al.* (2012) found that fish collagen could survive the SGF process for up to 30 minutes and begin to decompose in 60 minutes. According to this, collagen has a fairly high resistance to the pepsin enzyme, allowing it to maintain its protein structure in the digestive tract for an extended period. Consequently, this high resistance suggests that fish collagen has the potential to be a significant allergen to cause allergic reactions (Pan *et al.*, 2012).

## Effect of Processing on Contaminant Allergen Content

### Washing

Contamination of parvalbumin in the production of gelatin from fish skin can be minimized through an effective washing process. According to Koppleman *et al.* (2012), this washing process significantly reduces the risk of parvalbumin allergy in fish gelatin used in wine and beer. The study found that the washing process produces a high concentration of parvalbumin in the wash water (70 µg/mL of water). Given the low levels of parvalbumin, it can be said that fish gelatin in low concentrations is safe for consumption by individuals with fish allergies (Koppleman *et al.*, 2012). These results support the labeling standard by EU (European Union) regulation No 1169/2011, which exempts fish gelatin from the obligation of a nutritional label (European Parliament and Council, 2011).

However, it is important to note that the study did not specifically examine how fish gelatin acts as an allergen. Therefore, it cannot be concluded that consuming wine or beer containing fish gelatin is entirely allergy-safe.

### Heating and preservation

In their research, Kuehn *et al.* (2010) showed that parvalbumin is a heat-resistant allergen. They showed that simple boiling for 10-20 minutes at 95°C did not significantly affect parvalbumin levels. Parvalbumin levels in cooked fish are known to only decrease by 17-25% from raw fish. This resistance to heat can also be seen in the study of Pan *et al.* (2012). Even so, treatment at high temperatures can reduce the reactivity of IgE parvalbumin. For instance, heating parvalbumin to 80°C might decrease reactivity by more than 50% based on the absorbance at 450 nm. Furthermore, parvalbumin treated at 140°C almost completely loses its reactivity to the patient's IgE by ELISA. Another key finding is that heating at 140°C can remove the allergenic properties of parvalbumin, but the content does not show degradation (Kubota *et al.*, 2016).

Therefore, it can be said that there is still a risk of parvalbumin contamination in fish collagen or gelatin and that some people may experience allergies because the extraction process for collagen and fish gelatin extraction typically does not involve a high-temperature process (3°C-95°C), which are insufficient to degrade the content and reactivity of parvalbumin.

Further treatments, such as preservation processes (pickling, smoking, salting, and canning), can also significantly reduce parvalbumin levels. Compared to raw fish and fish that have undergone simple boiling, processed fish (canned fish, smoked fish, pickles) show up to 60% lower levels of parvalbumin. This reduction is presumably due to the modification or destruction of the parvalbumin epitope through various treatments. In addition, low pH and high pressure or temperature can also contribute to this effect (Kuehn *et al.*, 2010).

### Acid and enzyme treatment

Parvalbumin has stability at a certain pH so that its allergenicity and its content in food can be affected by pH (Tümerkan, 2022). Parvalbumin degrades into small fragments at pH 2.0, but at pH 3.0 to 11.0, it shows no change (Pan *et al.*, 2012). According to these findings, it can be said that parvalbumin is an allergen protein that is unstable to very acidic pH conditions but is stable at pH 3.0 to 11.0. This characteristic makes it important to consider pH conditions in the processing and consumption of fish products to manage allergenicity.

Unlike collagen, after 5 minutes of SGF digestion at a pH of 1.2, almost all parvalbumin components decompose into small fragments (Pan *et al.*, 2012). Parvalbumin can be stated to have low resistance to the pepsin enzyme, so it cannot maintain its protein form for a long time in the digestive tract. Therefore, while parvalbumin is stable at certain pH levels, its rapid degradation in the stomach suggests it poses a lower risk of causing allergic reactions once ingested and subjected to gastric digestion.

## Comparison of Allergen Characteristics by Processing

The solubility of fish collagen and its derivatives is stated differently, where fish collagen is hydrophobic, and fish gelatin is hydrophilic (Chikazawa *et al*., 2015; Wang *et al*., 2022). Paravalbumin itself has a higher ability to dissolve in water than gelatin (Koppleman *et al*., 2012). This difference in solubility is crucial when considering the allergenic potential of these proteins in various food products. Parvalbumin is more resistant to heat up to 100°C, whereas collagen decomposes at 70°C (Pan *et al*., 2012). In addition, parvalbumin's resistance to heat is also proven by treatment with temperatures up to 140°C, which cannot reduce the parvalbumin content (Kubota *et al*., 2016).

Collagen and parvalbumin both showed no change when treated with pH 3.0 to 11.0. However, when treated with a pH of 2.0, both of them were degraded into small fragments (Pan *et al*., 2012). It appears that collagen has better pepsin resistance compared to parvalbumin, where collagen can last up to 30 minutes while parvalbumin is completely degraded in 5 minutes (Pan *et al*., 2012). This higher pepsin resistance indicates that collagen might remain intact longer in the digestive tract, increasing its potential for allergenicity. The allergenicity of fish collagen

Table 2 Characteristics between fish collagen, gelatin, and parvalbumin as allergens
Tabel 2 Karakteristik kolagen ikan, gelatin, dan parvalbumin sebagai alergen

| Parameter | Fish Collagen | Fish Gelatin | Parvalbumin |
|---|---|---|---|
| Water Solubility | Insoluble | Soluble | Very soluble |
| Thermostability | Decomposition at 70°C | Not resistant to heat | Resistant to heat |
| Acid stability | - Stable at pH 3.0-11.0<br>- Degradation at pH 2.0<br>- Stable at pH 1.2 in SGF | - Stable at pH 3.0-11.0<br>- Degradation at pH 2.0<br>- Stable at pH 1.2 in SGF | - Stable at pH 3.0-11.0<br>- Degradation at pH 2.0<br>- Unstable at pH 1.2 in SGF |
| Enzyme resistance | - High resistance to pepsin<br>- Resistant to SGF digestion for up to 30 minutes | High resistance to pepsin | - Low resistance to pepsin<br>- Degraded after 5 minutes of digestion of SGF |
| Allergenicity | - Processing cannot reduce IgE reactivity<br>- Last longer in the digestive system → more likely to quickly bind to immune cells → High allergenicity | - Processing cannot reduce IgE reactivity<br>- Last longer in the digestive system → more likely to quickly bind to immune cells → high allergenicity | - Heating 140°C for 10 minutes reduced IgE reactivity, although levels did not decrease<br>- Does not last long in the digestive system → less likely to bind to immune cells → low allergenicity |

did not decrease in reactivity but instead increased its IgE binding ability when heated to gelatin or collagen peptides (Chikazawa *et al*., 2015; Kobayashi *et al*., 2016a). In contrast, parvalbumin, treated at extreme temperatures (140°C), experienced a decrease in IgE reactivity (Kubota *et al*., 2016). These findings highlight the different responses of collagen and parvalbumin to thermal treatments in terms of their allergenic potential.

If an allergen can maintain its form longer in the digestive system, the chance of an allergen bound to the immune system (IgE) and producing an allergic reaction will be higher. When compared with parvalbumin, collagen or fish gelatin has better resistance in the digestive system. It means that collagen or fish gelatin has a higher level of allergenicity than parvalbumin. Therefore, it can be indicated that fish collagen and its derivatives are allergens that have the potential to cause allergic reactions in a person.

## Identification of Hazard Risk Potential on Fish Collagen and Its Derivatives as Allergens

### Identification of allergen proteins in samples

To determine the presence of allergens in a food sample, an analysis was carried out. Identifying protein allergens can be done by separating proteins based on molecular weight. The instrument that supports this is SDS-PAGE, which is a semi-quantitative analysis based on protein separation using gel electrophoresis technique. The SDS-PAGE principle is based on the ability of protein molecules to move into the pores of the gel media due to the influence of an electric field. By using this method, protein size can be calculated by comparing the distance between migrations (Kumar & Roy, 2018).

Fish collagen is a protein that has a molecular weight of 115-400 kDa (Pan *et al*., 2012; Kobayashi *et al*., 2016a; Abe *et al*., 2020; Ueno *et al*., 2020). Meanwhile, fish gelatin has a molecular weight that ranges from 153.85-134.54 kDa for the α subunit and 226.65 kDa for the β subunit (Nurilmala *et al*., 2020). Fish collagen hydrolyzate shows a molecular weight of 2.94-30 kDa (Abe *et al*., 2020; Nurilmala *et al*., 2020). In addition to these points, it is also known that the molecular weight of the contaminant allergen (parvalbumin) is 10-12 kDa (Koppelman *et al*., 2012). Identification of an allergen-suspected protein is the initial step in allergen and allergy detection. Therefore, this step is important for determining the characteristics of a potential allergen, which is followed by analysis and other specific tests.

### Detection or diagnosis of allergy in patients and measurement of IgE reactivity

After protein separation, western blotting can be performed to see specific proteins or allergens using specific antibodies. To find out if a protein is an allergen, an immunoassay can be conducted by involving the antibody serum of a person who has an allergy to a specific protein (Kumar & Roy, 2018). Other instruments such as ELISA (Koppleman *et al*., 2012; Pan *et al*., 2012; Kobayashi *et al*., 2016a; Kobayashi *et al*., 2016c; Kalic *et al*., 2020), LC-MS/MS (Kalic *et al*., 2020), PCR (Polymerase Chain Reaction) (Kuehn *et al*., 2017; Daga *et al*., 2018), immunoCAP (Fujimoto *et al*., 2016), and CAP-RAST (radioallergosorbent) (Shimojo *et al*., 2021) can also be done. These methods provide comprehensive data that can help confirm the presence and concentration of allergenic proteins. ELISA can provide quantitative data in the presence of antibody concentration measurements by comparing standard curves from standard protein OD (Optical Density). The higher the antibody concentration, the higher the IgE reactivity. IgE-ELISA can also be used to measure specific IgE levels in serum (Kuehn *et al*., 2010). IgE-ELISA is more effective in replacing previous instruments, whereas previously, ImmunoCAP was used in measuring specific IgE levels (Fujimoto *et al*., 2016; Zhang *et al*., 2019).

Allergic reactions can be seen by performing skin prick tests (SPTs) and an oral challenge to confirm a protein as an allergen. SPTs are allergic tests carried out by placing some antigens or allergens on the forearm skin and then pricking or scratching them. This will cause wheals on the skin, which will be measured (Heinzerling *et al*., 2013; Frati *et al*., 2018). The advantage of this test is the short test time, which is around 15-20 minutes until it causes a reaction. SPTs are considered reliable and have a good correlation (85-95%) with in vitro tests (Frati *et al*., 2018). When compared with in vitro tests, SPTs can provide a visualization of a person's sensitivity (Heinzerling *et al*., 2013). Although it is low risk, some cases of anaphylaxis were reported after the SPTs. For this reason, in vitro tests are still preferred because they do not show the risk of allergic reactions (Frati *et al*., 2018).

Oral food challenge (OFC) can also be used to detect allergies in a person. OFC is performed to observe the threshold of allergic response. This test has high accuracy and is most effective in diagnosing allergies. OFC correlates with SPTs, where greater wheal on SPTs is associated with an increased likelihood of allergic reactions after ingestion (Cox & Nowak-Wegrzyn, 2018; Calvani *et al*., 2019). OFC is performed by observing allergic reactions, oxygen levels (SpO2), blood pressure, and/or histamine levels in blood plasma from time to time. Despite its advantages, OFC has the highest severity risk among all allergy tests (Calvani *et al*., 2019). Some cases of death were found due to acute anaphylaxis that occurred after OFC in children aged 3 years and 11 years (Smith, 2017; Upton *et al*., 2019). Due to the risk, it is recommended that SPTs be carried out first.

## Allergy mechanism of fish collagen and its derivatives

Allergic reactions from fish collagen and its derivatives include IgE-mediated reactions through skin contact, inhalation, and ingestion (Buyuktiryaki *et al*., 2021). The mechanism of allergy through ingestion is divided into two stages: the sensitization stage during the first exposure and the stage where the second exposure occurs. Sensitization to allergens can be divided into two: polysensitization, which means a person produces specific IgE for more than one type of allergen, and monosensitization, where a person has specific IgE for only one type of allergen. In the case of allergies to fish collagen and its derivatives, some people have polysensitivity to allergens other than fish collagen, where there is a cross-reactivity between parvalbumin and fish collagen (Kobayashi *et al*., 2016d). There are also people who are monosensitized only to fish collagen.

During the sensitization process, usually no allergic reactions occur. Allergic reactions will occur when a sensitized person experiences a second exposure. Allergic reactions can occur due to the binding of specific IgE to allergens. In the second exposure, there will be binding and cross-linking between allergens and specific IgE on basophils and mast cells. This binding causes the degranulation of basophils and mast cells, causing a release of preformed granules and mediators such as histamine, prostaglandin tryptase, and leukotrienes, followed by an allergic reaction.

## IgE binding to specific allergens

A person can experience both polysensitization and monosensitization. Research shows that 62% (13 of 21 people) experienced polysensitization to parvalbumin other than fish collagen. However, there were also 38% (8 of 21 people) who experienced specific IgE binding only to fish collagen (Kalic *et al*., 2020). In a study by Kobayashi *et al*. (2016b) regarding fish collagen allergy in the Japanese population, it was found that 14% (5 of 36 patients) had specific IgE to parvalbumin and fish collagen. Additionally, 36% of patients experienced monosensitization only to fish collagen.

Another case of monosensitization was also investigated by Kobayashi *et al*. (2016d) through ELISA, where as many as 50% (8 of 16 patients) had increased levels of IgE to fish collagen but not to parvalbumin. In another case, a patient who experienced anaphylaxis after consuming yogurt containing hydrolyzed collagen was found to have specific IgE levels for fish gelatin but not for parvalbumin (Fujimoto *et al*., 2016). This highlights the varying immune responses individuals can have to different fish-derived proteins. Through ELISA and SPTs, Chikazawa *et al*. (2015) stated that a patient had specific IgE and gave a positive reaction to fish collagen but negative to parvalbumin. From these studies, it can be stated that fish collagen is a specific allergen for some people with monosensitivity. This distinction is crucial for understanding individual allergic profiles and managing dietary restrictions effectively. This, of course, can increase the potential danger of fish collagen, where it can act as its allergen. In addition, it is known that the presence of specific IgE for fish collagen and its derivatives can be an indicator of the severity of the fish allergic reaction (Shimojo *et al*., 2021).

## Age factor

The process of sensitization can occur at any time and is not affected by age, but the frequency and severity of allergens can be affected by it. Cases of anaphylaxis after ingestion of allergens are known to be more common among infants and children than adolescents and adults (Lee *et al*., 2017; Jiang *et al*., 2021). However, it is known that adolescents and adults have a higher risk of severity of anaphylactic reactions (Turner *et al*., 2022). Kalic *et al*. (2020) conducted an ELISA test to determine IgE reactivity among 101 patient sera (76 children and 25 adults). The results revealed 21 patients who reacted positively to fish collagen. Of these patients, 18% (14 of 76) were children's serum and 28% (7 of 25) were adult patient's serum. This suggests that the frequency of IgE binding to fish collagen is higher in adults than in children. This finding still needs support from other studies specifically discussing the age factor on the prevalence of allergies and their reactivity to fish collagen.

Table 3 shows several published cases of allergy to fish collagen and its derivative products. The majority of sufferers of fish collagen allergy and its derivatives are adults, with 3 cases of allergy in children aged 9, 12, and 17 years (Kuehn *et al*., 2010; Tamura *et al*., 2018; Ueno *et al*., 2020) and 5 cases of allergies in adults aged 20-31 years (Chikazawa *et al*., 2015; Kobayashi *et al*., 2016a; Fujimoto *et al*., 2019; Abe *et al*., 2020). Currently, no published cases fish collagen and its derivative products have been found in Indonesia.

## Potential hazard

Collagen derivatives and processed products can still maintain their potential as an allergen (Pan *et al*., 2012; Chikazawa *et al*., 2015; Kobayashi *et al*., 2016a). When compared to other allergens such as parvalbumin, IgE reactivity from fish collagen has better resistance to processing and digestion (Pan *et al*., 2012; Kubota *et al*., 2016). Derivative products such as processed fish through heating (Chikazawa *et al*., 2015; Kobayashi *et al*., 2016a; Tamura *et al*., 2018), marshmallows (Kuehn *et al*., 2010), food supplements (Fujimoto *et al*., 2016), candy (Abe *et al*., 2020; Ueno *et al*., 2020), and other products containing gelatin or collagen peptides have the potential to cause allergic reactions. Allergens with low allergenicity are usually digested quickly upon entering the stomach and only cause reactions in the mouth or skin, and have a low risk of anaphylaxis (Wang *et al*., 2017; Akkerdaas *et al*., 2018). Based on its resistance to enzymes, fish collagen has a high level of allergenicity (Pan *et al.,* 2012). A person with monosensitivity or polysensitivity to parvalbumin also has the possibility of experiencing an allergic reaction when consuming fish collagen and its derivative products.

Through various cases, it is stated that some people may experience monosensitization to fish collagen (Chikazawa *et al*., 2015; Fujimoto *et al*., 2016; Kobayashi *et al*., 2016b; Kobayashi *et al*., 2016d; Kalic *et al*., 2020). Monosensitivity to fish collagen contributes to the potential danger of fish collagen as an allergen. Allergic reactions due to the consumption of fish collagen and its derivatives range from mild allergic symptoms to serious symptoms, namely anaphylaxis (Kuehn *et al*., 2010; Chikazawa *et al*., 2015; Kobayashi *et al*., 2016b; Tamura *et al*., 2018; Fujimoto *et al*., 2019; Abe *et al*., 2020; Ueno *et al*., 2020).

## Risk management

Risk management of fish collagen allergens and their derivative products can be carried out starting from the production process, labeling, and post-consumption actions. Based on the above data, it can be concluded that the material with minimal allergic risk in the production of fish collagen and its derivatives is the skin or dark muscle

Table 3 Cases of fish collagen allergy and its derivative products
Tabel 3 Kasus alergi kolagen ikan dan produk turunannya

| Age/Gender | ImmunoCAP (class*) | **SPTs (+)** | **OFC (+)** | **ELISA** | Allergen | Symptoms |
|---|---|---|---|---|---|---|
| 9/F | Flatfish (3), salmon (3), mackerel (2), fish gelatin (3), parvalbumin (2) | - | Fish collagen gummy | | Fish collagen | Anaphylaxis after gummy ingestion[a] |
| 17/F | Eel (3), cod (2), salmon (4), sardine ( 2), fish gelatin (2) | - | Baked eel | Fish collagen (+), heated fish (+), parvalbumin (-) | Eel collagen | Anaphylaxis after baked eel ingestion[b] |
| 25/F | Gelatin (0), tuna (2), cod (1) | Gummy, fish collagen peptide | | | Fish collagen peptide | Anaphylaxis after gummy ingestion[c] |
| 12/M | Tuna (5), salmon (4), cod (3) | Fish gelatin | | Fish gelatin (+), parvalbumin (+) | Fish gelatin | Anaphylaxis after marshmallow ingestion [d] |
| 30/F | Fish gelatin (4), bovine gelatin (3), parvalbumin (0) | Fish gelatin, hydrolyzed collagen | | | Hydrolyzed fish collagen | Anaphylaxis after yogurt ingestion[e] |
| 20/F | Tuna (3), salmon (6) | Heated fish | | Fish collagen (+), parvalbumin (-) | Fish collagen | Nausea after eating baked fish[f] |
| 24/F | Salmon (5), tuna (5), cod (4), flatfish (3), sardine (3), mackerel (2) | | Mackerel | Fish collagen (+), parvalbumin (-) | Fish collagen | Anaphylaxis after jelly ingestion[g] |
| 31/F | Gelatin (3), mackerel (2) | Fish gelatin | | Fish collagen (+), parvalbumin (-) | Fish collagen | Dyspnea after collagen drink ingestion[g] |

*Class 0: 0 < 0.35 kUA/L; 1: 0.35 < 0.7 kUA/L; 2: 0.70 < 3.5 kUA/L; 3: 3.50 < 17.5 kUA/L; 4: 17.5 < 50 kUA/L; 5: 50 < 100 kUA/L; 6: ≥ 100 kUA/L ,
[a]Ueno *et al.*, 2020 ; [b] Tamura *et al.*, 2018; [c] Abe *et al.*, 2020; [d]Kuehn *et al.*, 2010; [e]Fujimoto *et al.*, 2019; [f] Chikazawa *et al.*, 2015; [g] Kobayashi *et al.*, 2016a

of cartilaginous migratory fish (Koppleman *et al*., 2012; Kobayashi *et al*., 2016a; Kobayashi *et al*. al., 2016c). The washing process is proven to reduce parvalbumin levels in fish skin. As a result, the production materials are suggested to be washed beforehand (Koppleman *et al*., 2012). Regarding processing, there has been no research on methods that can reduce the IgE reactivity of fish collagen and its derivative products. The main solution for someone with an allergy is to avoid consuming fish collagen and its derivatives. For this reason, food labeling standards are needed to inform consumers about the presence of these allergens. Finally, if a person experiences an allergic reaction, a treatment like giving anti-allergic drugs according to the severity is needed (Tamura *et al*., 2018; Ueno *et al*., 2020).

## Fish Collagen Derivatives and Processed Products

Fish collagen in the form of gelatin includes stabilizers, gelling agents, binding agents, clarification agents, emulsifiers, and encapsulants (Ktari *et al*., 2014; Aziza *et al*., 2019; Lestari *et al*., 2019; Ayudiarti *et al*., 2020; Rafael *et al*., 2021; Osiriphun *et al*., 2022). Meanwhile, fish collagen in hydrolysates is also widely used as a food supplement or functional food as a bioactive compound (Astre *et al*., 2018; Shori *et al*., 2020; Ayati *et al*., 2022). These hydrolysates are often utilized in various nutritional products. Some processed products that contain fish collagen and its derivatives are marshmallows (Kuehn *et al*., 2010; Aziza *et al*., 2019), ice cream (Lestari *et al*., 2019; Ayudiarti *et al*., 2020), gummy candy and jelly (Kobayashi *et al*., 2016b; Abe *et al*., 2020; Ueno *et al*., 2020; Osiriphun *et al*., 2022), food supplements (Astre *et al*., 2018), yogurt (Fujimoto *et al*., 2016; Shori *et al*., 2020; Ayati *et al*., 2022), and collagen drinks (Kobayashi *et al*., 2016b).

Examples of processed fish collagen products and their derivatives in the market include the “Paskesz Kosher Marshmallow” and “Campfire” marshmallows, “Diva” and “Jele Collagen” collagen drinks, and “Hemaviton C1000+Collagen” health drinks. In Indonesia, “Diva”, “Jele Collagen”, and “Hemaviton C1000+Collagen” already have BPOM (Badan Pengawas Obat dan Makanan) distribution permits. This regulatory approval indicates compliance with local safety and quality standards. Based on published cases of allergy to fish collagen and its derivatives, several processed products cause mild to severe allergic reactions (Kuehn *et al*., 2010; Fujimoto *et al*., 2016; Kobayashi *et al*., 2016a; Abe *et al*., 2020; Ueno *et al*., 2020;). This potential hazard can be considered for food labeling standards concerning processed products containing fish collagen and its derivatives. Proper labeling and clear allergen information are crucial to ensure consumer safety and informed choice.

## Food Labeling Standards Regarding Fish Collagen and Its Derivatives as Allergens

Based on EU regulation No 1169/2011 on labeling standards, fish gelatin is exempted from nutritional label obligations (European Parliament and Council, 2011). Food Standards Australia & New Zealand (FSANZ) (2022) also exempt fish gelatin from nutritional label obligations. In Japan, the Japanese Consumer Affairs Agency (CAA) (2015) stipulates that gelatin is included in products that are not mandatory but are recommended for allergen labeling. The Food and Drug Administration (FDA) (2022) states that an ingredient derived from an allergenic source, such as fish, must be stated on the label, so fish gelatin is required to be included in the nutritional label as an allergen.

Likewise, Indonesia is one of the countries that does not require allergen information on fish gelatin because it is considered purified (BPOM, 2019). Indonesia also does not yet have a labeling standard related to fish collagen and its derivative products other than gelatin. The lack of publication of cases of fish collagen allergy in Indonesia has resulted in exceptions to the standard for labeling fish collagen and its derivatives as allergens. Therefore, future studies are needed to become a consideration for the establishment of food labeling standards. Such studies would help ensure that labeling standards are both scientifically informed and protective of consumer health.

## CONCLUSION

In conclusion, this research confirms that type 1 fish collagen and its derivative products, such as gelatin and collagen peptides, are declared as allergens to cause mild to serious allergic reactions, such as anaphylaxis. This review reveals that the allergenicity of fish collagen can be influenced by fish types, parvalbumin contamination, fish material, and processing. Selecting specific fish materials may help reduce allergenic risks. Fish collagen is unstable to heat but able to maintain and even increase its allergenicity due to water solubility. Future research on how to reduce its IgE reactivity by processing methods may be needed.

The allergic potential of fish collagen can be seen by its resistance to processing and digestion, as it remains stable and easily binds to immune cells. The research also found adults have a higher frequency of IgE binding to fish collagen than children and adolescents. Cases were also found in people with monosensitivity to fish collagen, which increases its potential as an allergen. Derivative products and processed products from fish collagen have the potential to cause an allergic reaction. Many regulatory standards including BPOM do not yet have a standard for labeling allergens related to fish collagen and its derivatives, as well as excluding the labeling of fish gelatin as an allergen which represents a regulatory gap. The lack of published cases of fish collagen allergy in Indonesia is certainly a factor in the absence of allergen labeling standards. It is hoped that future studies can consider these topics to establish food labeling standards.

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