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Bioactive peptides-derived from marine by-products: development, health benefits and potential application in biomedicine

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Abstract

Increased fisheries products have raised by-products that are discarded due to low economic value. In addition, marine by-products are still rich in protein and nutritional value that have biological activities and give benefits to human health. Meanwhile, there is raised pressure for sustainability practices in marine industries to reduce waste and minimize the detrimental effect on the environment. Thus, valorization by-products through bioactive peptide mining are crucial. This review focus on various ways to obtain bioactive peptides from marine by-products through protein hydrolysis, for instance chemical hydrolysis (acid and based), biochemical hydrolysis (autolysis and enzymatic hydrolysis), microbial fermentation, and subcritical water hydrolysis. Nevertheless, these processes have benefits and drawbacks which need to be considered. This review also addresses various biological activities that are favorable in pharmaceutical industries, including antioxidant, antihypertensive, anticancer, anti-obesity, and other beneficial bioactivities. In addition, some potential marine resources of Indonesia for the marine biopeptide from their by-product or undesired marine commodities would be addressed as well.

Keywords: Bioactive peptides, Bioactivity, Biomedicine, Marine by-product

Introduction

Total world fisheries and aquaculture from inland and marine in 2018 were 178.5 million tonnes, of which 87.6% were for human consumption (FAO, 2020). This number is estimated to rise each year due to the population growth, and changes in consumption habits due to the increasing knowledge about the health benefit effects of marine organisms. The fishing processing industries, however, create large amounts of processing by-products that include head, tail, skin, scale, viscera, and bone (Al Khawli et al., 2020; Zeller et al., 2018). It is estimated that 35% of the harvested fish is lost during the postharvest process, and then 70% of processed fish becomes by-products (FAO, 2020). The amount of marine processing by-products varies

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depending on species, size, season, and the fishing grounds (FAO, 2020; Villamil et al., 2017; Wang et al., 2019a). In salmon aquaculture, 41.5% of its biomass are by-products and only 15% of its by-products go to human consumption which has a full potential worth of almost 40 million USD (Stevens et al., 2018). Utilization of by-products can give more value to the fisheries and aquaculture industries such as biofilm packaging developed from skin collagen of a cartilaginous fish (*Mustelus mustelus*). This biofilm exhibited ultraviolet protecting properties and antioxidant activity which might be used to improve the shelf life of food or its perishable raw material (Azaza et al., 2022; Ben Slimane & Sadok, 2018). This can minimize environmental impact by reducing waste and pollution and also improve the economic gain of these industries (Marti-Quijal et al., 2020; Ucak et al., 2021).

Fish by-products have been utilized as raw material, not only in food industry, but also in pharmaceutical industries due to their bioactive compound (Abhari & Khaneghah, 2020; Dave & Routray, 2019; FAO, 2020). For many years, a great deal of interest has been developed by many research groups towards identification of bioactive materials from marine organisms including fish processing by-product. With this regard, it has been utilized in production of protein hydrolysate (Abhari & Khaneghah, 2020; Zamora-Sillero et al., 2018), fish oil (Jackson & Newton, 2016), therapeutants (Ashraf et al., 2020; Stevens et al., 2018) and even cosmetics (Nghia, 2020; Venkatesan et al., 2017). One of the valuable functional materials in marine processing by-products is the marine bioactive peptides, which have well documented beneficial health effect (Camargo et al., 2021; Daroit & Brandelli, 2021). However, there is a huge scope of using bioactive peptides from fish processing by-products as resources in the food and pharmaceutical industries; hence, further research is needed. Scientists should work out sustainable ways to refine fish by-products while governments and industries invest in using this abundant and cheap renewable resource. In this contribution, we focused on the current isolated bioactive peptides from marine processing by-products. In addition, their biological activities, as well as their potential as nutraceuticals were also discussed.

Development of Bioactive Peptides Derived from Fish By-Products

Protein plays various essentials parts, from structural and physiological support to improving health and body condition (Choy et al., 2021; Foegeding et al., 2017; Kumari et al., 2021; Ziegler et al., 2020). Nowadays greater recognition has been shown in developing proteins as dietary food since they provide a rich source of bioactive peptides (Chakrabarti et al., 2018; Foegeding et al., 2017; Gham et al., 2019; Karami & Akbari-Adergani, 2019). Bioactive peptides are peptide fragments of protein that have a beneficial impact on body function or conditions of living beings. That functional peptide fragments may contain from 2 to 20 amino acids residues and are encrypted within the protein sequence. Peptide sequences are released and then active after their parent protein is broken apart through protein hydrolysis reaction (Chakrabarti et al., 2018; Daroit & Brandelli, 2021; Karami & Akbari-Adergani, 2019). However, their function varies due to protein sources, a variation on amino acids sequence that builds those peptides, and even molecular weight (Chakrabarti et al., 2018; Karami & Akbari-Adergani, 2019; Pangestuti & Kim, 2017).

The oceans make up approximately 70% of earth's surface and contain around 243,000 described species (Jo et al., 2017; Wang et al., 2017). However, those numbers are 16% of from marine species. In addition, the marine ecosystem is more complex and diverse than the terrestrial because it considers being four-dimensional (latitude, longitude, depth, and time) (Costello & Chaudhary, 2017). Thus, it remains the largest source of bio-functional compounds, including bioactive peptides. Also, marine organisms live in complex habitat and expose to more extreme condition than the terrestrial, which make the marine bioactive peptides have significant different amino acid compositions and sequences from land bioactive peptides (Atef & Mahdi Ojagh, 2017; Jo et al., 2017; Ucak et al., 2021; Wang et al., 2017).

Recently, fish by-products rise rapidly each year from discarded fish body parts, such as head, viscera, skin, bones, and scales (FAO, 2020). For instance, in salmon (finfish), approximately 41.5% of its biomass is by-products such as heads, frames and viscera, and other small portions including belly flaps, trimmings, blood and skins. Those by-products parts contain bioactive protein and peptides (Stevens et al., 2018). Regarding the increase in by-product volume, the trend in the development of bio-functional ingredients from fish by-products has become a new focus to maximize the value of fish processing waste (Atef & Mahdi Ojagh, 2017; Coppola et al., 2021; Zamora-Sillero et al., 2018). A considerable amount of research has been done in this area. Interestingly, many researchers highlight the recovery of bioactive peptides from fish waste/by-products due to their quality proteins and outline their po-

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tential as candidate raw material for bioactive peptide mining (Villamil et al., 2017; Zamora-Sillero et al., 2018).

Method in Bioactive Peptide Production

Protein hydrolysate production can be performed using two methods. These methods are chemical methods that include acid and alkali hydrolysis, and biochemical methods that involve internal or external proteolytic enzymes (Petrova et al., 2018; Zamora-Sillero et al., 2018). However, there are other notable extraction methods, for instance microbial fermentation and subcritical water hydrolysis (Guo et al., 2019; Marti-Quijal et al., 2020a; Melgosa et al., 2020; Zamora-Sillero et al., 2018). The advantages and drawbacks of these extraction process are summarized in Table 1.

Chemical methods are the conventional hydrolysis methods which utilize chemical agents to break apart protein molecules into several peptide fragments. Those chemical agents can be acidic for the acid hydrolysis or alkaline for the alkali hydrolysis (Melgosa et al., 2020; Zamora-Sillero et al., 2018). Acidic hydrolysis employs hydrochloric acid or sulfuric acid under high temperature (up to 138℃) and high pressure (up to 310 MPa) for several hours during hydrolyzation (Melgosa et al., 2020; Petrova et al., 2018). After that, the mixture is neutralized and dehydrated. However, this process produces a high amount of NaCl that hinders the subsequent applications. In addition, due to intense heat and pressure, this process diminishes the product's functionality (Petrova et al., 2018; Zamora-Sillero et al., 2018). On the other hand, alkali hydrolysis uses calcium, sodium, or potassium hydroxide as alkaline agents to divide

Table 1. Benefits and drawbacks of bioactive peptide extraction from marine by-product

Extraction method	Chemical agent	Drawback or benefit	By-product source	Hydrolysate result
Chemical hydrolysis: • Acidic hydrolysis • Alkali hydrolysis	Acidic hydrolysis: • Hydrochloric acid • Sulfuric acid	• High temperature (138℃) • High pressure (310 MPa) • Time consuming (hours) • High amount of NaCl by-product • Protein solubility • Removing heavy metal (Melgosa et al., 2020; Petrova et al., 2018; Shen et al., 2021; Surasani, 2018)	Mackerel whole body	Recovered protein 49.48% with HCl 0.1 M (Álvarez et al., 2018)
			Baltic herring whole body	Protein yield 30.0% at pH 2.5 (Nisov et al., 2022)
			Cod (head, tail, bones)	Protein yield 10%–30% at pH 2–3 (Abdollahi & Undeland, 2019)
			Salmon (head, tail, bones)	Protein yield 30%–50% at pH 2–3 (Abdollahi & Undeland, 2019)
			Herring (head, tail, bones)	Protein yield 30%–50% at pH 2–3 (Abdollahi & Undeland, 2019)
			Yellowfin tuna liver	Protein yield 57.22% at pH 2 (Shen et al., 2021)
	Alkali hydrolysis: • Calcium hydroxide • Sodium hydroxide • Potassium hydroxide	• Warm temperature (54℃) • Toxic by-product • Combination acid-alkaline to improve protein extraction • Improve protein solubility • Reduced bioactivity • Removing heavy metal (Álvarez et al., 2018; Melgosa et al., 2020; Petrova et al., 2018; Shen et al., 2021; Surasani, 2018; Villamil et al., 2017; Zamora-Sillero et al., 2018)	Mackerel whole body	Recovered protein 74.25% with NaOH 0.4 M (Álvarez et al., 2018)
			Baltic herring whole body	Protein yield 43.4% at pH 11.5 (Nisov et al., 2022)
			Cod (head, tail, bones)	Protein yield 40%–60% at pH 11.5–12.5 (Abdollahi & Undeland, 2019)
			Salmon (head, tail, bones)	Protein yield 60%–80% at pH 11.5–12.5 (Abdollahi & Undeland, 2019)
			Herring (head, tail, bones)	Protein yield 40%–70% at pH 11.5–12.5 (Abdollahi & Undeland, 2019)
			Yellowfin tuna liver	Protein yield 78.98% at pH 12 (Shen et al., 2021)

Biochemical: • Autolysis • Enzymatic hydrolysis	Autolysis (endogenous enzyme)	• Warm temperature (40℃–60℃) • 1–3 h • No additional enzyme • Various optimum working condition • Environmental friendly (de Silva & Senaarachchi, 2021; da Silva et al., 2017; Guo et al., 2019; Nikoo et al., 2021a; Nikoo et al., 2021b; Petrova et al., 2018; Vázquez et al., 2020)	Discarded mud crab *Scylla serrata*	Carotenoprotein content 8.1% (de Silva & Senaarachchi, 2021)
			Discarded tiger prawn *Penaeus monodon*	Carotenoprotein content 16.07% (de Silva & Senaarachchi, 2021)
			Pacific white shrimp (head, shells, appendix and tails)	TCA-soluble peptide ~20% (Nikoo et al., 2021b)
			Litopenaeus vannamei heads	Protein content 43.63% (da Silva et al., 2017)
			Salmon viscera	Protein solubilization 80%–85% (Lapeña et al., 2018)
			Rainbow trout (head, skin, bones and fins)	DH 12.6% (Nikoo et al., 2021a)
	Enzymatic hydrolysis: • Alcalase • Papain • Trypsin • Flavorzyme • Neutrase • Pepsin • Prolyve BS • Protamex • Subtilisin (Bui et al., 2021; Mongkonkamthorn et al., 2020; Saidi et al., 2018; Zhang et al., 2019b)	• High specificity • Lower to non-toxic chemical • Optimum working condition varied • Biological activity of extraction product varied between enzymes (Petrova et al., 2018; Villamil et al., 2017)	Skipjack tuna head	DH 25.76% with GI digestion (pepsin-trypsin) (Zhang et al., 2019b)
			Sarda orientalis dark muscle	DH 5%–20% with Protamex (Bui et al., 2021)
			Tuna *Katsuwonus pelamis* blood	• DH 26.5%–36.6% with Alcalase • DH 21.1%–41.7% with Neutrase • DH 21.7%–41.7% with Flavorzyme (Mongkonkamthorn et al., 2020)
			Salmon viscera	• DH 15%–20% with Pepsin • DH 15%–20% with Neutrase • DH ~15% with Alcalase • DH 10%–15% with Trypsin (Wang et al., 2020)
			Salmon frames	DH 10%–11.25% with Subtilisin (Valencia et al., 2021)
			Salmon heads	Protein soluble 61.0 g/L with Alcalase (Vázquez et al., 2020)
			Salmon frames and fins	Protein soluble 69.7 g/L with Alcalase (Vázquez et al., 2020)
			Rainbow trout heads	Protein soluble 47.8 g/L with Alacalase (Vázquez et al., 2020)
			Rainbow trout frames and fins	Protein soluble 53.9 g/L with Alcalase (Vázquez et al., 2020)
Fermentated hydrolysis	Lactic acid bacteria: • *Anoxybacillus kamchatkensis* • *Bacillus licheniformis* • *Lactobacillus plantarum* • *Pediococcus acidilactici* • *Pseudomonas aeruginosa* (Ghorbel-Bellaaj et al., 2018; Guo et al., 2019; Mechri et al., 2020; Nugroho et al., 2020; Rajendran et al., 2018)	• Bacterial growth • Warm temperature • Biological activity of extraction product varied between fermentation system • Optimum working condition varied • Sustainable • Efficient (Guo et al., 2019; Rajendran et al., 2018)	*Metapenaeus monoceros* by-product	Protein content 42% (Mechri et al., 2020)
			Shrimp head	Protein content 66.7% (Guo et al., 2019)
			Shrimp *M. monoceros* (head and appendix)	Protein content 47.01% (Ghorbel-Bellaaj et al., 2018)
			Atlantic salmon (head and gut)	Protein content 57% (Rajendran et al., 2018)
			Tuna viscera	Protein content 56.04% (Nugroho et al., 2020)

Subcritical water hydrolysis	Water	• High temperature (100℃–374℃) • High pressure (0.10–22.00 MPa) • Fast (< 60 min) • Protein degradation at higher temperature (Ab Rahman et al., 2019; Ahmed & Chun, 2018; Lee et al., 2021)	Fish viscera	Protein content 1.705 g/L BSA at 180℃ (Ab Rahman et al., 2019)
			Tuna skin	DH 14.47% at 250℃ (Ahmed & Chun, 2018)
			Abalone viscera	Protein content 68.5% at 230℃ (Hao et al., 2019)
			Penshell viscera	Protein content 36.14 mg/g BSA at 230℃ (Lee et al., 2021)
			Sardine waste (heads, spines and viscera)	Protein content 73.2% at 190℃ (Melgosa et al., 2020)

TCA, tricarboxylic acid; DH, degree of hydrolysis; GI, gastrointestinal; BSA, bovine serum albumin; BS, Prolyve BS. A neutral enzyme composed of metalloprotease produced by fermentation using a selected strain of *Bacillus subtilis*.

protein molecules. In contrast to acidic hydrolysis, alkali hydrolysis requires a less extreme working environment, for instance 54℃ (Melgosa et al., 2020; Petrova et al., 2018). Despite lower temperature than the acidic process, this alkali method also has problematic issues, such as toxic by-products and reduced functionality (Petrova et al., 2018; Villamil et al., 2017; Zamora-Sillero et al., 2018). Nevertheless, this alkali hydrolysis is still considered in fish protein extraction to obtain bioactive protein hydrolysates (Petrova et al., 2018).

Biochemical extraction methods consist of autolysis and enzymatic hydrolysis. The autolysis process utilizes enzymes in the substrate to digest its protein molecules (Petrova et al., 2018; Zamora-Sillero et al., 2018). Thus, the autolysis does not require additional enzymes to put into the mixture. During hydrolysis warm working temperature between 40℃ to 60℃ for up to 3 h is milder than the chemical methods (Nikoo et al., 2021a ; Nikoo et al., 2021b; Vázquez et al., 2020). Moreover, this process results in better nutritional value. However, since this process utilizes its endogenous enzyme, thus the optimum condition and products might be inconsistent, driven by body part, species, and season (Guo et al., 2019; Nikoo et al., 2019; Nikoo et al., 2021b; Petrova et al., 2018; Vázquez et al., 2020). In contrast, enzymatic hydrolysis requires external enzymes to perform protein digestion, resulting in more specific functionality and desirable products (Petrova et al., 2018; Villamil et al., 2017). Moreover, both autolysis and enzymatic hydrolysis are considered to be environmentally friendly due to low energy expenditure to meet the working environment, effective, and less toxic chemical waste (Guo et al., 2019; Villamil et al., 2017).

Microorganisms can be used to obtain protein hydrolysate from fish by-products through microbial fermentation (Marti-Quijal et al., 2020a). During fermentation, lactic acid bacteria produce a proteolytic enzyme to digest protein molecules on the substrate into peptides (Kliche et al., 2017; Martí-Quijal et al., 2020b). Hydrolysis reaction improves over time with the accumulation of by-product fermentation, lactic acid, and reduction of pH environment. This condition gradually becomes more acidic and improves fermentation enzyme activity (Marti-Quijal et al., 2020a; Rajendran et al., 2018). Usually, this fermentation process is coupled with enzymatic hydrolysis during bioactive peptide extraction to improve the functionality of hydrolysate (Guo et al., 2019; Kang et al., 2020; Vázquez et al., 2020). Like enzymatic products, the fermentation products are more functional, and their process are more efficient, simple, and sustainable (Guo et al., 2019; Marti-Quijal et al., 2020a; Martí-Quijal et al., 2020b).

As illustrated in Fig. 1, subcritical water hydrolysis is one of the extraction techniques to obtain bioactive peptides. It is considered a green technology and safe for the environment, and yet still effective (Ahmed & Chun, 2018; Melgosa et al., 2020). This process employs superheated water or subcritical water, which is defined as water maintained in the liquid state at temperatures between the current boiling point of water (100℃) and the critical point of water (374℃) (Ahmed & Chun, 2018; Siahaan & Chun, 2020). Under this extreme condition, physicochemical water changes dramatically. The viscosity of water is declined, which improves water penetration and diffusion into the substrate (Melgosa et al., 2020). In addition, water forms hydronium ion (H_3O^+) and hydroxide ion (HO^-), which perform as acid and based catalyst agents for protein digestion (Ahmed & Chun, 2018; Melgosa et al., 2020). Also, these ion concentrations increase at increased working temperatures. Thus, this process does not require additional proteolytic enzymes due to the existence of those ions in the working environment (Choi et al., 2017; Melgosa et al., 2020). The increased temperature enhances protein digestion rate

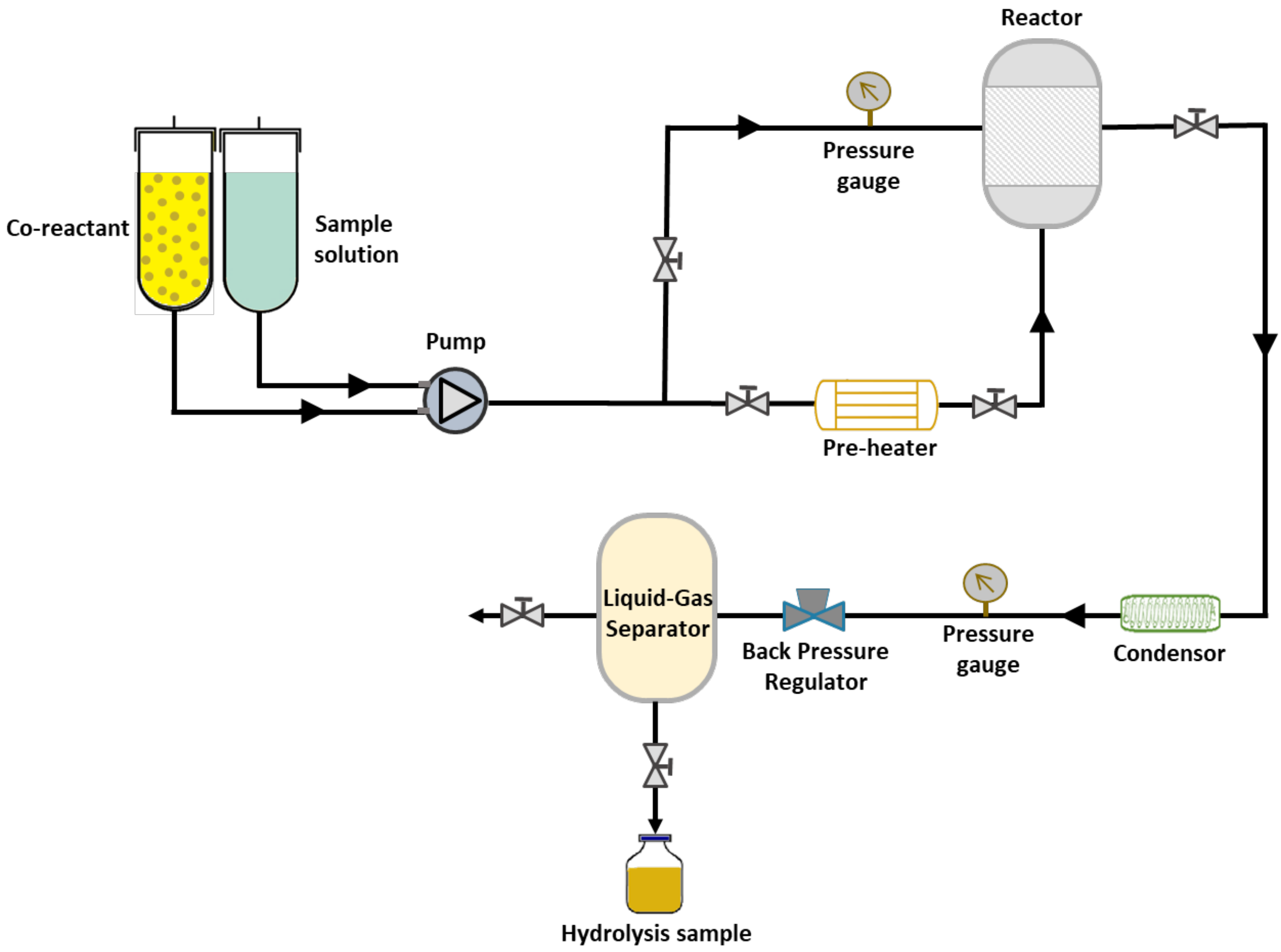

Fig. 1. Subcritical water hydrolysis extraction process.

and increases low molecular peptides (Ab Rahman et al., 2019; Ahmed & Chun, 2018; Lee et al., 2021). Moreover, the subcritical water hydrolysis might only demand up to 60 minutes during the hydrolysis process, faster than the enzymatic hydrolysis (Choi et al., 2017). However, these optimum working environments and periods are driven by objectives, targeted bioactive peptides products, body parts, and species. For example, the optimum condition to obtain the highest protein yield from gills and viscera of unspecified marine fish was at 180℃ for 5 minutes (Ab Rahman et al., 2019). In contrast, the strongest functional activities from tuna skin can be obtained after hydrolysis at 280℃ for 5 min (Ahmed & Chun, 2018). Meanwhile, the optimum condition for abalone viscera was at 170℃ for 1 h to obtain the strongest antioxidant activities of the hydrolysate (Hao et al., 2019). Another study displays that the optimum condition was between 170℃ to 230℃ for 15 minutes to obtain maximum protein extract and low molecular peptides (< 1 kDa) from comb pen shell (*Atrina pectinata*) viscera (Lee et al., 2021).

Health Benefit Effects of Bioactive Peptides Derived from Marine By-Products

Antioxidant peptide

Oxidation is a necessary metabolism in the vertebrate and the human body. However, it generates reactive oxygen species (ROS) and free radicals, which disrupt homeostasis that allows oxidative stress (Luan et al., 2020; Pisoschi et al., 2021; Rahman & Rahman, 2021). Oxidative stress can be excessively destructive for cells (Luan et al., 2020; Pisoschi et al., 2021; Rahman & Rahman, 2021), which can lead to several diseases over time, including heart disease (Cortassa et al., 2021; Vujic et al., 2021), stroke (He et al., 2020; Taira et al., 2020), arteriosclerosis (Carmona-Maurici et al., 2020; Lian et al., 2019; Varona et al., 2017), diabetes (Michurina et al., 2020; Pal et al., 2020) and cancer (Shrivastava et al., 2021; Zahra et al., 2020). Furthermore, the oxidation of lipids by ROS is of great concern to the food industry and consumers because it causes food deterioration and the production of toxic compounds (Wang et al., 2016; Wang et al., 2018; Wang et al., 2019b; Wang et al., 2021). Lipid peroxidation is a problem in the food industry and human health (Peña-Bautista et al., 2019; Vijayan et al., 2021).

Antioxidants can protect the human body against free radicals and ROS effects. They may inhibit the progress of many chronic diseases and lipid peroxidation occurring in the human body by interrupting the radical chain reaction of oxidation (Lu et al., 2020; Luo et al., 2021; Vijayan et al., 2021; Zahra et al., 2020). Moreover, antioxidants protect foodstuffs against deterioration by lipid peroxidation. They are usually used as preservatives in food products by directly adding as additives or indirectly through diffusion from packaging material (Feki et al., 2021; Kongkaoroptham et al., 2021; Mancini et al., 2017; Sellimi et al., 2017). Several synthetic antioxidants such as butylated hydroxytoluene (da Cruz et al., 2019; de Jesus et al., 2020; Zhou et al., 2019), tert-butylhydroquinone (de Jesus et al., 2020; Salmanzadeh et al., 2018; Ye et al., 2018), butylated hydroxyanisole (Caleja et al., 2017; da Cruz et al., 2019; de Jesus et al., 2020), and propyl gallate (Gálico et al., 2015; Salmanzadeh et al., 2018), are generally used in the food products to inhibit deterioration. However, there is a strict safety standard for synthetic antioxidants application in food products (Salmanzadeh et al., 2018; Xu et al., 2021; Ye et al., 2018). Hence, natural antioxidants have gained consumer preferences regarding their potential health benefits since they have little or no side effects (Salmanzadeh et al., 2018; Xu et al., 2021).

Several studies have shown that peptides derived from marine by-products possess potent antioxidant properties (Li et al., 2021; Nikoo et al., 2021a; Nikoo et al., 2021b; Zamorano-Apodaca et al., 2020) (Table 2). The antioxidant can prevent oxidation by donating a hydrogen atom or an electron to radicals formed from unsaturated lipids and can interrupt these radical chain reactions by removing initiators or radical intermediates from the medium through the inactivation of metal catalysts (Neha et al., 2019; Pisoschi et al., 2021; Siddeeg et al., 2021). All functional properties of the peptides are highly dependent on their molecular weight. Shorter size peptides are believed to have higher inhibition activities of scavenging and lipid peroxidation when compared to the long-chain peptides (Hajfathalian et al., 2018; Zamorano-Apodaca et al., 2020). Several antioxidant peptides derived from marine by-products such as frame, skin, and viscera are summarized in Table 3.

A study on the antioxidant activity of protein hydrolysate (Table 4) from abalone viscera revealed that the hydrolysis process using pepsin, papain, trypsin, and neutral protease had similar strength for scavenging activity (half maximal inhibitory concentration [IC_{50}] 500 µg/mL) of 2,2-diphenyl-1-picrylhydrazyl (DPPH) (Zhou et al., 2012). Meanwhile, the antioxidant activity of protein hydrolysate was higher when squid pen was hydrolyzed with bacterial endopeptidase high-throughput (40%–45%) and trypsin (40%–45%) rather than pepsin (35%–40%) (Shavandi et al., 2017). Protein hydrolysate of tuna had higher antioxidant activity after its dark muscle was hydrolyzed with protease XXIII (41.0%) rather than orientase (31.5%) (Hsu, 2010). Lastly, protein hydrolysate of stripped weakfish by-product obtained with alcalase had higher DPPH activity (60%–70%) rather than with protamex (50%–60%) (Lima et al., 2019).

Antihypertensive peptides

Cardiovascular disease (CVD) is one of four noncommunicable diseases that took the biggest number of casualties around the globe. There were 17.9 million people that sadly passed away due to this disease in 2016. The major risk factor for CVD is blood pressure elevation or hypertension (World Health Organization, 2020). Renin and angiotensin-converting enzyme (ACE) are the two key enzymes associated with the renin-angiotensin system, the important endocrine system which regulates blood pressure (Te Riet et al., 2015). ACE plays an important role in raising blood pressure since it regulates the inactivation of bradykinin. ACE can raise blood pressure by converting angiotensin I released from angiotensin by renin into biologically active angiotensin II (Abdelhedi & Nasri, 2019; Pujiastuti et al., 2019; Te Riet et al., 2015). Therefore, inhibiting ACE and renin may positively contribute to hypertension treatment (Abachi et al., 2019; Pujiastuti et al., 2019). Many synthetic inhibitors of ACE and renin such as aliskiren, captopril, enalapril, lisinopril, and alcacepril have been widely used. However, the natural antihypertensive is more desirable for future prevention and hypertension treatment due to its low adverse side effects (Abachi et al., 2019; Abdelhedi & Nasri, 2019).

In addition, the whole body of *Oratosquilla woodmasoni* from the by-product of marine captured fisheries had antioxi-

Table 2. Biological activity of peptide from by-product fisheries and aquaculture

By product source	Bioactive peptide extraction	Benefits	References
Skate cartilage	Papain and thermal hydrolysis	Improve free radical scavenging activity	Li et al., 2021
Pacific white shrimp mix by-products (cephalothorax, shells, and pleopods)	Trypsin autolytic hydrolysis	Inhibit oxidative reactions by scavenging hydroxyl radicals	Nikoo et al., 2021b
Various marine fish by-products (skin, heads, and skeletons)	Collagen hydrolysis	Potential antioxidant ingredients for functional foods and pharmaceuticals industry	Zamorano-Apodaca et al., 2020
Abalone viscera	Enzymatic hydrolysis (papain, trypsin, neutral protease, alkali protease, pepsin)	Potential source of antioxidant	Zhou et al., 2012
Squid pen	Trypsin hydrolysis	Enhance antioxidant activity	Shavandi et al., 2017
Tuna dark muscle	Orientase and protease XXIII hydrolysis	Generate strong DPPH radical-scavenging activity and antioxidative activity	Hsu, 2010
	n-Hexane/ethanol extraction	Inhibit the growth of obesity related diseases through the suppression of hepatic triacylglycerol and cholesterol accumulation	Maeda et al., 2017
Stripped weakfish by-products (skin and bone)	Alcalase and protamex hydrolysis	Potential natural antimicrobial and antioxidant preservatives in food	Lima et al., 2019
Bycatch shrimp *Oratosquilla woodmasoni* waste	Thermolysin hydrolysis	Produce ACE-I inhibition peptide that could be utilized as anti-hypertentsive and free radicals prevention	Joshi et al., 2020
Pearl oyster shell	Orientase hydrolysis	Potent ACE inhibitory activity	Sasaki et al., 2019
Squid skin	Pepsin hydrolysis	Good source of ACE inhibition peptide	Lin et al., 2012
Tuna blood	Enzymatic hydrolysis (alcalase, neutrase, flavourzyme)	Exhibit strong antioxidant and ACE inhibitory activity	Mongkonkamthorn et al., 2020
Shrimp shell	Protease hydrolysis	Demonstrate higher ACE inhibitory activity compared to hypertension drug (captopril)	Mechri et al., 2020
Marine catfish skin	Chemical extraction	Possess anticancer activity against human colon cancer line	Raja et al., 2020
Octopus ink	Dichloromethane extraction	Potential immunomodulatory and anti-proliferative against colorectal and breast cancer	Hernández-Zazueta et al., 2021
Cuttlefish posterior salivary gland toxin	SDS-PAGE extraction	Exhibit great cytotoxicity against breast cancer and inhibit penetration of metastatic cells	Karthik et al., 2017
Rainbow trout skin	Flavourzyme and alcalase hydrolysis	Possess antioxidant and anticancer activities	Yaghoubzadeh et al., 2020
Flathead by-products (head, back-bone, skeleton)	AFP hydrolysis	Potent antioxidant and cancer cells cytotoxic agents	Nurdiani et al., 2017
Blue mussel by-product	Protamex hydrolysis	Exhibit inhibitory activity against cancer cells	Beaulieu et al., 2013
Sardine by-products (viscera, heads, skins, and edges)	Isoelectric precipitation	Improve LCAT activity and reduce complications related to obesity	Affane et al., 2018
Skate skin	Collagen extraction	Demonstrate anti-obesity impact	Woo et al., 2018
Squid by-products (viscera and ink sacs)	Protease hydrolysis	Suppress the activity of gram-negative and gram-positive bacteria	Jiang et al., 2018
Salmon by-products (bones, fins, and tails)	Protease hydrolysis	Enhance copper-binding capacity	Vo & Pham, 2020
Giant croaker skin	Neutral protease hydrolysis	Potential immunomodulatory agent	Yu et al., 2020

DPPH, 2,2-diphenyl-1-picrylhydrazyl; ACE, angiotensin-converting enzyme; SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; AFP, acid fungal protease; LCAT, lecithin-cholesterol acyltransferase.

Table 3. The antioxidant peptides derived from marine by-product

Organism	Body part	Antioxidant peptides	Reference
Sardinella aurita	• Head • Viscera	• Gly-Gly-Glu (263.08 Da) • Leu-His-Tyr (431.2 Da) • Gly-Ala-Trp-Ala (403.1 Da) • Leu-Ala-Arg-Leu (471.3 Da) • Gly-Ala-Leu-Ala-Ala-His (538.2 Da)	Bougatef et al., 2010
Thunnus tonggol	Dark muscle	• Pro–Met–Asp–Tyr–Met–Val–Thr (756 Da) • Leu–Pro–Thr–Ser–Glu–Ala–Ala–Lys–Tyr (978 Da)	Hsu, 2010
Cynoscion guatucupa	• Skin • Bone	• IELIEKPMGIF (1,288.71 Da) • RADLSRELEEISERL (1,814.95 Da)	Lima et al., 2019
Raja kenojei	Skin	• Pro–Gly–Pro–Leu–Gly–Leu–Thr–Gly–Pro (975.38 Da) • Gln–Leu–Gly–Phe–Leu–Gly–Pro–Arg (874.45 Da)	Lee et al., 2011
Gadus macrocephalus	Skin	• Thr-Cys-Ser-Pro (388 Da) • Thr-Gly-Gly-Gly-Asn-Val (485.5 Da)	Ngo et al., 2011
Haliotis discus hannai	Whole body	ATPGDEG (752 Da)	Qian et al., 2018
*Oratosquilla woodmason***i**	Muscle	Asn-Gly-Val-Ala-Ala (431 Da)	Joshi et al., 2020
Pinctada fucata	Shell	Gly-Val-Gly-Ser-Pro-Tyr (578.7 Da)	Sasaki et al., 2019
Dosidicus gigas	Skin	DPVAPGGPQP	Alemán et al., 2013

dant activities that give nutraceutical industries more benefits (Joshi et al., 2020). A study on pearl oyster (*Pinctada fucata*) revealed hexapeptide that has ACE inhibitory properties (82.4%) from its shell (Sasaki et al., 2019). Another study also showed that blood from tuna and squid skin from *Dosidicus eschrichitii* have similar ACE inhibitory properties as well (IC_{50} 0.28 mg/mL and 0.33 mg/mL, respectively) (Lin et al., 2012; Mongkonkamthorn et al., 2020). Moreover, protein hydrolysate from shrimp captured by-product, *Metapenaeus monoceros*, had strong ACE inhibitory activities (IC_{50} 71.52%) than the hypertension drug, captopril (IC_{50} 85.33%) (Mechri et al., 2020).

Anticancer peptides

Cancer is the second largest non-communicable diseases worldwide that had caused 9 million deaths in 2016 (World Health Organization, 2020). Cancer is complex because it is several diseases caused by uncontrolled growth of cells. Genetic mutation in normal cell alters cell function and growth that turns into a cancer cell, and thus it is considered a genetic disease or cellular disease. Moreover, this cellular alteration also causes disruption and even deterioration to an adjacent cell, tissue, and organ in the body (Miller, 2018; Papaccio et al., 2017; Wellenstein & de Visser, 2018). Recently, there have been four treatments for cancer such as mechanical treatment (surgery), physical treatment (radiotherapy), chemical treatment (chemotherapy), and biological treatment (immunotherapy) (Link, 2019). A natural product can be used for cancer treatments (Link, 2019). Previous studies show that protein extract from marine by-products, such as skin and even visceral organs, had anticancer activities. For example, protein-rich extract from *Tachysurus dussumieri* skin revealed anticancer properties against the proliferation of colon cancer cells. Moreover, it also induced cell cycle arrest and even apoptosis of the cells (Raja et al., 2020). Anticancer properties were also observed from *Octopus vulgaris* ink extract that constrained colorectal cancer cell proliferation by inducing apoptosis (Hernández-Zazueta et al., 2021).

The marine natural product has a wide range of molecular size and chemical diversity that could not be chemically synthesized and could give more benefits for treatments due to the complex physiological process of cancer (Link, 2019; Lu et al., 2021; Patra et al., 2020). For instance, hemocyanin from marine gastropods shows antitumor and immunogenic properties (Mora Román et al., 2019; Nigam et al., 2019). This immunomodulatory activity is important for biological treatment because the tumor microenvironment greatly alters non-tumor adjacent cells and matrix phenotypes that hinder the natural body immune system (Kumar, 2020). In the other case, protein extract from salivary gland of cuttlefish *Sepia pharaonis* inhibited cell proliferation and induced apoptosis, and suppressed cancer cell infiltration to adjacent cells. Thus, the salivary extract becomes an anti-metastasis agent (Karthik et al., 2017).

As previously mentioned, anticancer activities from protein

Table 4. Antioxidant activity of peptide from by-product fisheries and aquaculture

By product source	Protease / peptide extraction	Scavenging activity (Activity value or IC$_{50}$ at certain condition i.e. sample concentration or certain degree hydrolysis)	
		DPPH	Hydroxyl radical
Abalone *Haliotis discus hannai* viscera (Zhou et al., 2012)	Alkali protease	IC$_{50}$; 7 mg/mL	IC$_{50}$; 10 mg/mL
	Neutral protease	IC$_{50}$; 4 mg/mL	IC$_{50}$; 11 mg/mL
	Papain	IC$_{50}$; 4 mg/mL	IC$_{50}$; 17 mg/mL
	Pepsin	IC$_{50}$; 4 mg/mL	IC$_{50}$; 5 mg/mL
	Trypsin	IC$_{50}$; 4 mg/mL	IC$_{50}$; 23 mg/mL
Arrow squid *Nototodarus sloanii* pen (Shavandi et al., 2017)	Bacterial endopeptidase (HT)	40%–45%; 4 mg/mL	NA
	Trypsin	40%–45%; 4 mg/mL	NA
	Pepsin	35%–40%; 4 mg/mL	NA
Squid *Ommastrephes bartrami* (Song et al., 2016)	Endogenous protease	IC$_{50}$; 0.231 mg/mL	IC$_{50}$; 0.74 mg/mL
Salmon *Salmo salar* skin (Zhang et al., 2022)	Alcalase	NA	70%–80%; 4 mg/mL
	Neutrase	NA	50%–60%; 4 mg/mL
	Flavourzyme	NA	30%–40%; 4 mg/mL
	Protamex	NA	40%–50%; 4 mg/mL
Rainbow trout *Oncorhynchus mykiss* skin (Yaghoubzadeh et al., 2020)	Alcalase	40%–45%; 0.8 mg/mL	NA
	Flavourzyme	45%–50%; 0.8 mg/mL	NA
Tuna dark muscle (Saidi et al., 2018)	Prolyve BS	30%–35%; 2 mg/mL	35%–40%; 2 mg/mL
Tuna *Thunnus tonggol* dark muscle (Hsu, 2010)	Orientase	31.5%; 3 mg/mL	NA
	Protease XXIII	41.0%; 3 mg/mL	NA
Striped weakfish *Cynoscion guatucupa* skin and bones (Lima et al., 2019)	Alcalase	50%–60%; hydrolysis at 10% DH	70%–80%; hydrolysis at 10% DH
		60%–70%; hydrolysis at 15% DH	40%–50%; hydrolysis at 15% DH
	Protamex	50%–60%; hydrolysis at 10% DH	30%–40%; hydrolysis at 10% DH
		50%–60%; hydrolysis at 15% DH	40%–50%; hydrolysis at 15% DH

IC$_{50}$, half maximal inhibitory concentration; DPPH, 2,2-diphenyl-1-picrylhydrazyl; HT, protein/protease prepared from bacteria using high-throughput preparation; NA, not available; BS, Prolyve BS. A neutral enzyme composed of metalloprotease produced by fermentation using a selected strain of *Bacillus subtilis*.; DH, degree of hydrolysis.

hydrolysate of marine by-products disregard the molecular size of protein extract. However, it shows that small molecular size tends to have stronger bioactivities. For instance, low molecular weight peptide (< 3kDa) retained from protein hydrolysate of rainbow trout (*Oncorhynchus mykiss*) skin has stronger cytotoxicity (IC$_{50}$ 0.249 mg/mL) on colon cancer cells than higher molecular weight (> 3 kDa) (IC$_{50}$ 2.738 mg/mL) that hindered cell proliferation (Yaghoubzadeh et al., 2020). A similar result shows that small molecular size peptides (< 3 kDa) isolated from Flathead by-products were reported to inhibit the growth of HT-29 colon cancer cells up to 91.04% (Nurdiani et al., 2017). On the other hand, 50 kDa fraction from protein hydrolysate of *Mytilus edulis* by-product had been reported to have anticancer activities on 85% of colon cancer cells (Beaulieu et al., 2013).

Antiobesity peptides

Obesity is a significant threat to human health worldwide, and its global prevalence has increased up to 1.5 times since 2000 (World Health Organization, 2020). This epidemic poses a risk for several diet-related chronic diseases, including type II diabetes mellitus, CVD, hypertension and stroke, and certain forms of cancer. The health consequences of obesity range from increased risk of premature death to severe chronic conditions that reduce the overall quality of life (Blüher, 2019; Chooi et al., 2019; World Health Organization, 2020). The proposed mechanisms to prevent and treat overweight and obesity such as increased satiety and thermogenesis, accretion of fat-free mass, and lowering food intake (World Health Organization, 2010).

Relating to dietary intake, natural product from marine based by-product that has benefits to ameliorate overweight and obesity is shown in Table 5. Protein hydrolysate from *Sardina pilchardus* by-products (viscera, head, skin, and fins) has been reported to reduce food intake and body weight gain (Affane et al., 2018). The essential amino acids in fish protein hydrolysate alter adipogenesis by suppressing the genetic expression of key genes for preadipocytes differentiation and lipid accumulation in adipose tissue (from 3.14% reduced to 2.58%) (Lee et al., 2017). Moreover, a previous study shows that protein hydrolysate from dark muscle tuna increased fatty acid oxidation in mitochondria, promoted lipid excretion, limited lipid absorption by the intestine wall, and suppressed lipid deposition in adipocytes tissue (from ~0.35 mg/g decreased to ~0.25 mg/g) (Maeda et al., 2017). Similarly, a peptide from skate (*Raja kenojei*) skin shows anti-obesity activities by restraining lipogenesis and adipocyte differentiation and allowing more fatty acid oxidation. Adipose tissue size reduced from 3% (control) to 1.5% (skin) (Woo et al., 2018).

Other biological activities

Protein hydrolysate obtained from marine by-products has a wide range of biological activities due to various compounds and metabolites of marine organisms. Antibacterial activity is another biological activity from protein hydrolysate that can inhibit bacterial growth (Kang et al., 2019a). A previous study shows that protein extract from squid by-products (viscera and ink sac) has bioactivities to inhibit gram-negative and gram-positive bacteria (Jiang et al., 2018). White shrimp (*Litopenaeus vannamei*) carapaces has antibacterial activities after the conjugation with glucosamine (Djellouli et al., 2020). Furthermore, the application of protein hydrolysate from shrimp by-products in food processing has been studied in the bakery to underline improved shelf-life period, palatability, and bread quality. It is suggested that glutamic acid in protein hydrolysate is responsible for the better taste and low molecular weight peptide for the growth of fermentative bacteria (Karimi et al., 2020). Meanwhile, protein hydrolysate obtained from yellowfin tuna (*Thunnus albacores*) by-products (viscera) has similar biological activity against bacterial growth. Moreover, its bioactivities are inversely related to molecular weight. It is suggested that the low molecular weight of peptides has better interaction and penetration to disrupt bacterial cell wall structure (Pezeshk et al., 2019).

Protein hydrolysate also possesses anti-inflammation and immunomodulatory activities. For instance, protein hydrolysate from sardine (*S. pilchardus*) by-products of the canning industry has anti-inflammation properties. Its low molecular weight fraction (< 10 kDa) hinders inflammation regulation in endothelial cells (Vieira et al., 2018). Meanwhile, protein hydrolysate from giant croaker (*Nibea japonica*) skin promotes the immune system through cell-mediated immunity, such as increased splenocyte proliferation, and humoral immunity, such as elevated immunoglobin level (Yu et al., 2020). Together with antibacterial properties, marine organisms are potential sources for pharmaceutical industries (Kang et al., 2019a).

As indicated previously, marine by-products have a wide range of biological activities. Its protein hydrolysate also has a metal chelating ability due to the aromatic ring of specific amino acids in its chain (Lima et al., 2021). For instance, protein hydrolysate from salmon by-products has a copper-binding capacity which is essential to delivering copper into the hu-

Table 5. Anti-obesity activity of peptide from by-product fisheries and aquaculture

Protein source		BW gain or final BW	Food intake	Adipose tissue	Total cholesterol	Fecal total lipid
Sardines *Sardina pilchardus* (Affane et al., 2018)	Viscera, heads, skins and edges	0.17 g/day/rat	16.13 g/day/rat	2.58	1.51 mmol/L	76.8 mg/day/rat
	Fillet	0.64 g/day/rat	20.49 g/day/rat	2.87	1.60 mmol/L	68.5 mg/day/rat
	Control (Casein)	1.10 g/day/rat	25.27 g/day/rat	3.14	2.20 mmol/L	56.9 mg/day/rat
Tuna *Thunnus orientalis* (Maeda et al., 2017)	Dark muscle	0.50 g/day	129 g	4.19	~0.25 mg/g	NA
	Control (Casein)	0.45 g/day	124 g	3.95	~0.35 mg/g	NA
Tuna (Lee et al., 2017)	Skin	0.216 g/day/rat	33.24 g/day/rat	Smaller cell size	1,670 mg/L	NA
	Control (high fat diet)	0.365 g/day/rat	35.30 g/day/rat	Bigger cell size	2,245 mg/L	NA
Skate *Raja kenojei* (Woo et al., 2018)	Skin	33.3 g	1.5–2 g/day	1.5%–2%	~400 mg/L	NA
	Control (high fat diet)	36.6 g	2–2.5 g/day	2.5%–3%	~400 mg/L	NA

BW, body weight; NA, not available.

man body (Vo & Pham, 2020). It is crucial to attenuate copper deficiency which will cause anemia, fetal death, and Menkes disease (Chen et al., 2020a). Moreover, iron and calcium are essential minerals for respiration, cellular communication, and body movement. Overload or deficiency of these metals results in dire conditions. Thus, a metal-chelating peptide is crucial to ameliorate the effects by transporting the metal into the body or absorbing metal ions to remove the excess metal in the body (Walters et al., 2018). In this regard, calcium-binding peptides have been extracted from Pacific cod (*Gadus macrocephalus*) by-product (bone) (Zhang et al., 2019a), and iron-binding peptides as well from cod skin (Wu et al., 2017).

Potential Applications of Bioactive Peptides Derived from Fish By-Products

A significant number of research on producing functionally active peptides from marine waste have been carried out. To date, antioxidant, antihypertensive, anticancer, antimicrobial, and mineral binding peptides from marine by-products have been most identified for their beneficial health effects. A successfully finding of bioactive peptides from marine waste suggests that they can potentially be used as valuable ingredients for a comprehensive array of products, especially in biomedicine. Fishbone peptides from *Johnius belengerii* has been studied for their bioactive potential in the biomedical application of osteoporosis treatment. Its peptides promote osteogenesis through increased genetic expression for osteoblastic differentiation and mineral accumulation (Heo et al., 2018). Meanwhile, collagen and gelatine are essential compounds in connective tissue and extracellular matrix (He et al., 2019; Nurilmala et al., 2020). Collagen has numerous applications in the biomedical and pharmaceutical industries such as for wound healing and skin regeneration (Jang et al., 2018; Sghayyar et al., 2020; Wei et al., 2019), a drug delivery (Kang et al., 2019b; Song et al., 2018), orthopedics (Gao et al., 2020; Han et al., 2021), angiogenesis (Chen et al., 2020b; Kook et al., 2018), the medical implant (Knopf-Marques et al., 2019; Liu et al., 2020; Versteegden et al., 2018). Fish gelatine from hydrolytic degradation of collagen can be obtained from marine by-products such as skin, scales, and bones of bigeye snapper (*Priacanthus hamrur*) (Radhika Rajasree et al., 2020), tuna (*Thunnus albacares*) (Nurilmala et al., 2020), skipjack tuna (*Katsuwonus pelamis*) (Yang et al., 2019), salmon (Dave et al., 2019), barred mackerel (*Scomberomorus commerson*) (Mirzapour-Kouhdasht et al., 2020) and pacific cod (*Gadus macrocephalus*) (Wu et al., 2017). The utilization of fish skin collagen and gelatin has gained a greater preference from industries, especially for medical uses, since the marine product does not contradict any religious issues (Nurilmala et al., 2020; Yuswan et al., 2021).

The optimal exploitation of marine bioactive peptides from by-products for human consumption may bring an exciting scientific and technological challenge while at the same time offering the potential for successful commercialization. Many scientific, technological, and regulatory aspects must be resolved before these marine by-product peptides can be optimally utilized. Firstly, it is necessary to treat the by-products as a valuable raw material. Best handling and sorting of the by-product are essential to reduce enzymatic degradation and microbial spoilage. Secondly, since the production of bioactive peptides from marine by-products may be scaled up to an industrial level, there is a need to develop an industrial-friendly technology. Methodologies for pilot-scale extraction and the purification of the bioactive peptides are critical for the commercial exploitation of peptides. Furthermore, to isolate the desired molecular weight and functional properties of the peptides, suitable extraction, and purification methods are needed. Thirdly, a clinical test of the marine by-product peptides on the human body is a critical aspect. Up to now, most of the biological effects of the peptides have been tested in animal models. In addition, the safety and quality standards of the peptide product should be assessed before the peptide product can be handed to the market.

Potential Resources of Marine By-Product Bioactive Peptides from Indonesia

Indonesia is one of the central fish-producing countries globally. The total production volumes of capture and aquaculture fisheries in 2017 were 7,071,453 tons and 16,114,991 tons, respectively (Ministry of Marine Affairs and Fisheries, 2017). Fisheries by-products that have been produced by fisheries industries, including capture, aquaculture, and processing activities in Indonesia, have not been used optimally (Irianto et al., 2014). A marine by-product from the fisheries industry is raw materials that can be used to generate value-added products such as marine bioactive peptides. Those raw materials are underutilized fish parts such as cut-offs, fishbone, skin, viscera, and blood (Hayes & Flower, 2013).

Indonesia, consisting of 18,110 islands, has high species richness and endemicity of marine biodiversity, and it is part of the coral reef triangle (Asaad et al., 2018; Hutomo & Moosa, 2005).

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This high marine biodiversity has become essential for various marine bioactive natural products, including protein and peptides (Chasanah, 2008; Fawzya & Irianto, 2020; Putra & Murniasih, 2016). Nine major marine fish obtained from one of the main fishing ports in Indonesia contained up to 86.56% total protein (Priatni et al., 2018). Moreover, its marine by-products, such as fish skin obtained from red snapper, contained easily digested collagen peptides (Wibawa et al., 2015). Similarly, collagen peptides obtained from tuna skin waste from the processing industry have antioxidant properties (IC_{50} 251.23 ppm) and antiglycation (4.36%) (Nurilmala et al., 2019; Nurilmala et al., 2020).

Several studies revealed that some marine fisheries by-products from Indonesia were utilized to retrieve their bioactive peptides, components, and activity (Table 6). Dolphin

Table 6. Biological activity from Indonesian marine by-product and its component

By product source	Biological activity and value	Protein, bioactive peptides, amino acids or nitrogen content of hydrolysate
Milkfish skin (collagen extraction) (Wibawa et al., 2015)	NA	Protein (0.407 mg/mL)
Dolphin fish *Coryphaena hippurus* (Thenu et al., 2017)	NA	Protein (19.16%), proline (3.32%), arginine (3.01%), serine (2.85%), phenylalanine (2.65%). Cystine, histidine, valine and methionine (< 2%)
Mackerel *Scomber japonicus* heads (Setijawati et al., 2019)	Alternative peptone for bacterial growth medium. Improve biomass of *Escherichia coli* (from control 61.04% to 76.85%), *Staphylococcus aureus* (from control 48.24% to 56.08%), *Salmonella thypi* (from control 59.46% to 71.04%), and *Aeromonas hydrophila* (from control 49.83% to 54.15%)	Nitrogen (11.53%)
Grouper *Epinephelus fuscoguttatus* head (Jaziri et al., 2020)	Alternative peptone for bacterial growth medium. Improve biomass of *E. coli* (from control 42.81% to 64.63%) and *S. aureus* (from control 35.74% to 59.38%)	Peptone yield (4.61%–5.70%), protein (85.08%–86.43%), glycine (21.48%), glutamic acid (10.67%), alanine (10.26%), proline (8.99%), arginine (8.16%) and aspartic acid (7.60%). Tyrosine, and histidine were less than 3%
Parrotfish *Scarus javanicus* head (Jaziri et al., 2020)	Alternative peptone for bacterial growth medium. Improve biomass of *E. coli* (from control 25.87% to 50.33%) and *S. aureus* (from control 33.20% to 55.63%)	Peptone yield (3.27%–3.45%), protein (83.80%–86.67%), glycine (21.34%), glutamic acid (10.12%), alanine (8.97%), proline (8.94%), aspartic acid (7.76%), and phenylalanine (6.73%). Tyrosine and histidine were less than 3%
Parrotfish *Chlorurus sordidus* head (Prihanto et al., 2019)	Antioxidant (DPPH 58.2%)	Protein (69.15%), glutamic acid (14.43%), aspartic acid (11.06%), leucine (8.48%), lysine (8.3%), glycine (7.63%) and alanine (7.41%). Serine and histidine were less than 3%
Milkfish *Chanos chanos* skin (Kusumaningtyas et al., 2019)	Antioxidant (ABTS 80%–90%) and antifungal (*Candida albicans* ~5 Log CFU/mL)	NA
Grouper *E. fuscoguttatus* swim bladder (collagen hydrolysate) (Trilaksani et al., 2020)	Collagen extract suitable for cosmetic material	Protein (75.20%), glycine (102.04%), proline (48.20%), alanine (41.11%), glutamic acid (35.68%), aspartic acid (19.98%), serine (18.02%)
Bigeye tuna *Thunnus obesus* skin (collagen) (Devita et al., 2021)	Antioxidant (DPPH 0.18–0.46 mg AAE/g)	Protein (6.58%–16.37%)
Yellowfin tuna *Thunnus albacares* skin (collagen hydrolysate) (Nurilmala et al., 2019)	Antioxidant (IC_{50} 251.23 ppm), antiglycation (4.36%)	Glycine (175.75 mg/g), proline (70.44 mg/g), arginine (64.10 mg/g), glutamic acid (58.37 mg/g), alanine (54.72 mg/g), aspartic acid (27.66 mg/g)
Mackerel by-product (Setijawati et al., 2020)	Alternative peptone for bacterial growth medium	Soluble protein (0.98–2.10 g/L), lysine (16.73%), glutamic acid (12.74%), alanine (9.32%), aspartic acid (8.74%), proline (8.73%), arginine (6.91%)
Mackerel *S. japonicus* head (Nurdiani et al., 2022)	Antioxidant (DPPH 15.64%–36.95%)	Serine (21.16%), glycine (13.27%), histidine (7.99%), aspartic acid (6.82%), alanine (6.74%), glutamic acid (6.17%)
Blue swimming crab *Portunus pelagicus* hepatopancreas (Fadilah et al., 2020)	NA	Protein (49.21%), glutamic acid (3.75%), leucine (2.41%), arginine (2.13%), aspartic acid (1.96%), valine (1.84%), glycine (1.65%)

NA, not available; DPPH, 2,2-diphenyl-1-picrylhydrazyl; ABTS, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid; AAE, ascorbic acid equivalent; IC_{50}, half maximal inhibitory concentration.

fish (*Coryphaena hippurus*) roe is another by-product of the fishing industry in Indonesia that consists of 19.16% of protein. Seventeen amino acids have been discovered, such as proline (3.32%), arginine (3.01%), and serine (2.85%) (Thenu et al., 2017). Protein hydrolysate from fish by-products could be utilized as peptone, a component of bacterial growth medium. For instance, the by-product of the mackerel fishing industry has improved the bacterial growth of *Escherichia coli* to 76.85% in the positive control (Setijawati et al., 2019). Meanwhile, grouper and parrotfish heads have been documented to improve the bacterial growth of *E. coli* from control of 42.81% to 64.63% in grouper heads and 25.87% to 50.33% in parrotfish heads (Jaziri et al., 2020). Other parrotfish heads showed high antioxidant activity around 58.2% of its protein hydrolysate that contained 69.15% of protein (Prihanto et al., 2019). Milkfish skin hydrolysate has not only antioxidant activity (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid [ABTS] 80%–90%) but also antifungal activity of *Candida albicans* (5 Log CFU/mL) (Kusumaningtyas et al., 2019). Moreover, fermented shrimp from shrimp by-products has been reported to have bioactive peptides and improved taste (Hajeb & Jinap, 2012).

Conclusion

The increasing of marine by-products rich in protein gives concern to obtaining bioactive peptides to minimize waste and increase economic value in marine industries. Bioactive peptides recovery from marine by-products can be performed through several types of protein hydrolysis that will break protein molecules apart into the small molecular size of peptides. Subcritical water hydrolysis is more superior hydrolysis process by having a fast hydrolysis process and no additional digestion enzymes. Recovered peptides from marine by-products show a wide range of biological activities favorable for biomedicine application, for instance, in cancer treatment. Thus, valorization of marine by-products through obtaining bioactive peptides gives benefits to the environment and human health as well. However, scale-up applications should be considered and prepared together with stakeholders to optimize this marine bioactive peptide exploitation from marine by-products.

Competing interests

No potential conflict of interest relevant to this article was reported.

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Availability of data and materials

Upon reasonable request, the datasets of this study can be available from the corresponding author.

Ethics approval and consent to participate

This article does not require IRB/IACUC approval because there are no human and animal participants.

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References

Ab Rahman WNS, Nordin MFM, Syariff AHM. Extraction of local fish waste by subcritical water. Mal J Fund Appl Sci. 2019;15:716-9.

Abachi S, Bazinet L, Beaulieu L. Antihypertensive and angiotensin-I-converting enzyme (ACE)-inhibitory peptides from fish as potential cardioprotective compounds. Mar Drugs. 2019;17:613.

Abdelhedi O, Nasri M. Basic and recent advances in marine antihypertensive peptides: production, structure-activity relationship and bioavailability. Trends Food Sci Technol. 2019;88:543-57.

Abdollahi M, Undeland I. Physicochemical and gel-forming properties of protein isolated from salmon, cod and herring by-products using the pH-shift method. LWT-Food Sci Technol. 2019;101:678-84.

Abhari K, Khaneghah AM. Alternative extraction techniques to obtain, isolate and purify proteins and bioactive from aquaculture and by-products. Adv Food Nutr Res. 2020;92:35-52.

Affane F, Louala S, El Imane Harrat N, Bensalah F, Chekkal H,

https://doi.org/10.47853/FAS.2022.e33

Allaoui A, et al. Hypolipidemic, antioxidant and antiatherogenic property of sardine by-products proteins in high-fat diet induced obese rats. Life Sci. 2018;199:16-22.

Ahmed R, Chun BS. Subcritical water hydrolysis for the production of bioactive peptides from tuna skin collagen. J Supercrit Fluids. 2018;141:88-96.

Al Khawli F, Martí-Quijal FJ, Ferrer E, Ruiz MJ, Berrada H, Gavahian M, et al. Aquaculture and its by-products as a source of nutrients and bioactive compounds. Adv Food Nutr Res. 2020;92:1-33.

Alemán A, Gómez-Guillén MC, Montero P. Identification of ace-inhibitory peptides from squid skin collagen after *in vitro* gastrointestinal digestion. Food Res Int. 2013;54:790-5.

Álvarez C, Lélu P, Lynch SA, Tiwari BK. Optimised protein recovery from mackerel whole fish by using sequential acid/alkaline isoelectric solubilization precipitation (ISP) extraction assisted by ultrasound. LWT-Food Sci Technol. 2018;88:210-16.

Asaad I, Lundquist CJ, Erdmann MV, Costello MJ. Delineating priority areas for marine biodiversity conservation in the Coral Triangle. Biol Conserv. 2018;222:198-211.

Ashraf SA, Adnan M, Patel M, Siddiqui AJ, Sachidanandan M, Snoussi M, et al. Fish-based bioactives as potent nutraceuticals: exploring the therapeutic perspective of sustainable food from the sea. Mar Drugs. 2020;18:265.

Atef M, Mahdi Ojagh S. Health benefits and food applications of bioactive compounds from fish byproducts: a review. J Funct Foods. 2017;35:673-81.

Azaza YB, Hamdi M, Charmette C, Jridi M, Li S, Nasri M, et al. Development and characterization of active packaging films based on chitosan and sardinella protein isolate: effects on the quality and the shelf life of shrimps. Food Packag Shelf Life. 2022;31:100796.

Beaulieu L, Thibodeau J, Bonnet C, Bryl P, Carbonneau ME. Evidence of anti-proliferative activities in blue mussel (*Mytilus edulis*) by-products. Mar Drugs. 2013;11:975-90.

Ben Slimane E, Sadok S. Collagen from cartilaginous fish by-products for a potential application in bioactive film composite. Mar Drugs. 2018;16:211.

Blüher M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol. 2019;15:288-98.

Bougatef A, Nedjar-Arroume N, Manni L, Ravallec R, Barkia A, Guillochon D, et al. Purification and identification of novel antioxidant peptides from enzymatic hydrolysates of sardinelle (*Sardinella aurita*) by-products proteins. Food Chem. 2010;118:559-65.

Bui XD, Vo CT, Bui VC, Pham TM, Bui TTH, Nguyen-Sy T, et al. Optimization of production parameters of fish protein hydrolysate from Sarda Orientalis black muscle (by-product) using protease enzyme. Clean Technol Environ Policy. 2021;23:31-40.

Caleja C, Barros L, Antonio AL, Oliveira MBPP, Ferreira ICFR. A comparative study between natural and synthetic antioxidants: evaluation of their performance after incorporation into biscuits. Food Chem. 2017;216:342-6.

Camargo TR, Ramos P, Monserrat JM, Prentice C, Fernandes CJC, Zambuzzi WF, et al. Biological activities of the protein hydrolysate obtained from two fishes common in the fisheries bycatch. Food Chem. 2021;342:128361.

Carmona-Maurici J, Cuello E, Ricart-Jané D, Miñarro A, Kissler JJO, Baena-Fustegueras JA, et al. Effect of bariatric surgery in the evolution of oxidative stress depending on the presence of atheroma in patients with morbid obesity. Surg Obes Relat Dis. 2020;16:1258-65.

Chakrabarti S, Guha S, Majumder K. Food-derived bioactive peptides in human health: challenges and opportunities. Nutrients. 2018;10:1738.

Chasanah E. Marine biodiscovery research in Indonesia: challenges and rewards. J Coast Zone Manag. 2008;12:1-12.

Chen J, Jiang Y, Shi H, Peng Y, Fan X, Li C, et al. The molecular mechanisms of copper metabolism and its roles in human diseases. Pflügers Archiv Eur J Physiol. 2020a;472:1415-29.

Chen M, Zhang Y, Zhang W, Li J. Polyhedral oligomeric silsesquioxane-incorporated gelatin hydrogel promotes angiogenesis during vascularized bone regeneration. ACS Appl Mater Interfaces. 2020b;12:22410-25.

Choi JS, Jang DB, Moon HE, Roh MK, Kim YD, Cho KK, et al. Physiological properties of *Engraulis japonicus* muscle protein hydrolysates prepared by subcritical water hydrolysis. J Environ Biol. 2017;38:283-9.

Chooi YC, Ding C, Magkos F. The epidemiology of obesity. Metabolism. 2019;92:6-10.

Choy BC, Cater RJ, Mancia F, Pryor EE Jr. A 10-year meta-analysis of membrane protein structural biology: detergents, membrane mimetics, and structure determination techniques. Biochim Biophys Acta Biomembr. 2021;1863:183533.

Coppola D, Lauritano C, Palma Esposito F, Riccio G, Rizzo C, de Pascale D. Fish waste: from problem to valuable resource. Mar Drugs. 2021;19:116.

Cortassa S, Juhaszova M, Aon MA, Zorov DB, Sollott SJ. Mitochondrial Ca^{2+}, redox environment and ROS emission in heart failure: two sides of the same coin? J Mol Cell Cardiol. 2021;151:113-25.

Costello MJ, Chaudhary C. Marine biodiversity, biogeography, deep-sea gradients, and conservation. Curr Biol. 2017;27:R511-27.

da Cruz RG, Beney L, Gervais P, de Lira SP, de Souza Vieira TMF, Dupont S, et al. Comparison of the antioxidant property of acerola extracts with synthetic antioxidants using an *in vivo* method with yeasts. Food Chem. 2019;277:698-705.

da Silva CP, Bezerra RS, dos Santos ACO, Messias JB, de Castro CROB, Junior LBC, et al. Biological value of shrimp protein hydrolysate by-product produced by autolysis. LWT-Food Sci Technol. 2017;80:456-61.

Daroit DJ, Brandelli A. *In vivo* bioactivities of food protein-derived peptides: a current review. Curr Opin Food Sci. 2021;39:120-9.

Dave D, Liu Y, Clark L, Dave N, Trenholm S, Westcott J, et al. Availability of marine collagen from Newfoundland fisheries and aquaculture waste resources. Bioresour Technol Rep. 2019;7:100271.

de Jesus JHF, Ferreira APG, Szilágyi IM, Cavalheiro ETG. Thermal behavior and polymorphism of the antioxidants: BHA, BHT and TBHQ. Fuel. 2020;278:118298.

de Silva MPKSK, Senaarachchi WARK. Efficiency of biotransformation of shellfish waste to carotenoprotein by autolysis and crab-shrimp endo-enzymes. J Aquat Food Prod Technol. 2021;30:526-34.

Devita L, Nurilmala M, Lioe HN, Suhartono MT. Chemical and antioxidant characteristics of skin-derived collagen obtained by acid-enzymatic hydrolysis of bigeye tuna (*Thunnus obesus*). Mar Drugs. 2021;19:222.

Djellouli M, López-Caballero ME, Arancibia MY, Karam N, Martínez-Alvarez O. Antioxidant and antimicrobial enhancement by reaction of protein hydrolysates derived from shrimp by-products with glucosamine. Waste Biomass Valor. 2020;11:2491-505.

Fadilah N, Dewi EN, Romadhon R, Purnamayati L. Characteristic of blue swim crab mustard (*Portunus pelagicus*) protein hydrolysate with different papain enzyme concentrations. Saintek Perikanan Indones J Fish Sci Technol. 2020;17.

Fawzya YN, Irianto HE. Fish protein hydrolysates in Indonesia: their nutritional values, health benefits, and potential applications. In: Nathani NM, Mootapally C, Gadhvi IR, Maitreya B, Joshi CG, editors. Marine niche: applications in pharmaceutical sciences. Singapore: Springer Singapore; 2020. p. 283-97.

Feki A, Sellem I, Hamzaoui A, Amar WB, Mellouli L, Zariat A, et al. Effect of the incorporation of polysaccharide from *Falkenbergia rufolanosa* on beef sausages for quality and shelf life improvement. LWT-Food Sci Technol. 2021;143:111139.

Foegeding EA, Plundrich N, Schneider M, Campbell C, Lila MA. Protein-polyphenol particles for delivering structural and health functionality. Food Hydrocoll. 2017;72:163-73.

Food and Agriculture Organization of the United Nations [FAO]. The state of world fisheries and aquaculture 2020: sustainability in action. Rome: FAO; 2020.

Gálico DA, Nova CV, Guerra RB, Bannach G. Thermal and spectroscopic studies of the antioxidant food additive propyl gallate. Food Chem. 2015;182:89-94.

Gao J, Zhang G, Xu K, Ma D, Ren L, Fan J, et al. Bone marrow mesenchymal stem cells improve bone erosion in collagen-induced arthritis by inhibiting osteoclasia-related factors and differentiating into chondrocytes. Stem Cell Res Ther. 2020;11:171.

Gham M, Um M, Kye S. Evaluation of dietary quality and nutritional status based on nutrition quotient and health functional food intake in the Korea elderly. J Korean Soc Food Cult. 2019;34:474-85.

Ghorbel-Bellaaj O, Maalej H, Nasri M, Jellouli K. Fermented shrimp waste hydrolysates: promising source of functional molecules with antioxidant properties. J Culin Sci Technol. 2018;16:357-77.

Guo N, Sun J, Zhang Z, Mao X. Recovery of chitin and protein from shrimp head waste by endogenous enzyme autolysis and fermentation. J Ocean Univ China. 2019;18:719-26.

Hajeb P, Jinap S. Fermented shrimp products as source of umami in Southeast Asia. J Nutr Food Sci. 2012;S10:006.

Hajfathalian M, Ghelichi S, García-Moreno PJ, Moltke Sørensen AD, Jacobsen C. Peptides: production, bioactivity, functionality, and applications. Crit Rev Food Sci Nutr. 2018;58:3097-129.

Han Y, Jia B, Lian M, Sun B, Wu Q, Sun B, et al. High-precision, gelatin-based, hybrid, bilayer scaffolds using melt electro-writing to repair cartilage injury. Bioact Mater. 2021;6:2173-86.

Hao G, Cao W, Li T, Chen J, Zhang J, Weng W, et al. Effect of temperature on chemical properties and antioxidant activities of abalone viscera subcritical water extract. J Supercrit Fluids. 2019;147:17-23.

Hayes M, Flower DJ. Bioactive peptides from marine processing byproducts. Bioact Compd Mar Foods Plant Anim Sources. 2013:57-71.

He D, Wu S, Yan L, Zuo J, Cheng Y, Wang H, et al. Antitumor bioactivity of porphyran extracted from *Pyropia yezoensis* Chonsoo2 on human cancer cell lines. J Sci Food Agric. 2019;99:6722-30.

He Y, Yang Q, Liu H, Jiang L, Liu Q, Lian W, et al. Effect of blood pressure on early neurological deterioration of acute ischemic stroke patients with intravenous rt-PA thrombolysis may be mediated through oxidative stress induced blood-brain barrier disruption and AQP4 upregulation. J Stroke Cerebrovasc Dis. 2020;29:104997.

Heo SY, Ko SC, Nam SY, Oh J, Kim YM, Kim JI, et al. Fish bone peptide promotes osteogenic differentiation of MC3T3-E1 pre-osteoblasts through upregulation of MAPKs and Smad pathways activated BMP-2 receptor. Cell Biochem Funct. 2018;36:137-46.

Hernández-Zazueta MS, Luzardo-Ocampo I, García-Romo JS, Noguera-Artiaga L, Carbonell-Barrachina ÁA, Taboada-Antelo P, et al. Bioactive compounds from *Octopus vulgaris* ink extracts exerted anti-proliferative and anti-inflammatory effects *in vitro*. Food Chem Toxicol. 2021;151:112119.

Hsu KC. Purification of antioxidative peptides prepared from enzymatic hydrolysates of tuna dark muscle by-product. Food Chem. 2010;122:42-8.

Hutomo M, Moosa MK. Indonesian marine and coastal biodiversity: present status. Indian J Mar Sci. 2005;34:88-97.

Irianto HE, Dewi AS, Giyatmi. Prospective utilization of fishery by-products in Indonesia. In: Kim SK, editor. Seafood processing by-products. New York, NY: Springer; 2014. p. 21-34.

Jackson A, Newton RW. Project to model the use of fisheries by-products in the production of marine ingredients with special reference to omega-3 fatty acids EPA and DHA [Internet]. Institute of Aquaculture, University of Stirling and Marine Ingredients Organisation. 2016 [cited 2021 Apr 2]. https://www.iffo.com/system/files/downloads/Report%20IoA%20IFFO%20project%20Final_0.pdf

Jang HJ, Kim Y, Yoo BY, Seo YK. Wound-healing effects of human dermal components with gelatin dressing. J Biomater Appl. 2018;32:716-24.

Jaziri AA, Setijawati D, Yufidasari HS, Pratomo MD, Wardani DW, Ersyah D, et al. Characteristics of peptones from grouper (*Epinephelus fuscoguttatus*) and parrotfish (*Scarus javanicus*) head by-products as bacterial culture media. J Biotech Res. 2020;11:1-12.

Jiang W, Liu Y, Yang X, Wang P, Hu S, Li J, et al. Recovery of proteins from squid by-products with enzymatic hydrolysis and increasing the hydrolysate's bioactivity by Maillard reaction. J Aquat Food Prod Technol. 2018;27:900-11.

Jo C, Khan FF, Khan MI, Iqbal J. Marine bioactive peptides: types, structures, and physiological functions. Food Rev Int. 2017;33:44-61.

Joshi I, Janagaraj K, Noorani KPM, Nazeer RA. Isolation and characterization of angiotensin I-converting enzyme (ACE-I) inhibition and antioxidant peptide from by-catch shrimp (*Oratosquilla woodmasoni*) waste. Biocatal Agric Biotechnol. 2020;29:101770.

Kang HK, Lee HH, Seo CH, Park Y. Antimicrobial and immunomodulatory properties and applications of marine-derived proteins and peptides. Mar Drugs. 2019a;17:350.

Kang MG, Lee MY, Cha JM, Lee JK, Lee SC, Kim J, et al. Nanogels derived from fish gelatin: application to drug delivery system. Mar Drugs. 2019b;17:246.

Kang NJ, Jin HS, Lee SE, Kim HJ, Koh H, Lee DW, et al. New approaches towards the discovery and evaluation of bioactive peptides from natural resources. Crit Rev Environ Sci Technol. 2020;50:72-103.

Karami Z, Akbari-Adergani B. Bioactive food derived peptides: a review on correlation between structure of bioactive peptides and their functional properties. J Food Sci Technol. 2019;56:535-47.

Karimi N, Nikoo M, Ahmadi Gavlighi H, Piri Gheshlaghi S, Regenstein JM, Xu X, et al. Effect of pacific white shrimp (*Litopenaeus vannamei*) protein hydrolysates (SPH) and (−)-epigallocatechin gallate (EGCG) on sourdough and bread quality. LWT-Food Sci Technol. 2020;131:109800.

Karthik R, Manigandan V, Ebenezar KK, Vijayashree R, Saravanan R. *In vitro* and *in vivo* anticancer activity of posterior salivary gland toxin from the cuttlefish *Sepia pharaonis*, Ehrenberg (1831). Chem Biol Interact. 2017;272:10-20.

Kliche T, Li B, Bockelmann W, Habermann D, Klempt M, de Vrese M, et al. Screening for proteolytically active lactic acid bacteria and bioactivity of peptide hydrolysates obtained with selected strains. Appl Microbiol Biotechnol. 2017;101:7621-33.

Knopf-Marques H, Barthes J, Lachaal S, Mutschler A, Muller C, Dufour F, et al. Multifunctional polymeric implant coatings based on gelatin, hyaluronic acid derivative and chain length-controlled poly (arginine). Mater Sci Eng C. 2019;104:109898.

Kongkaoroptham P, Piroonpan T, Pasanphan W. Chitosan nanoparticles based on their derivatives as antioxidant and antibacterial additives for active bioplastic packaging. Carbohydr Polym. 2021;257:117610.

Kook YM, Kim H, Kim S, Heo CY, Park MH, Lee K, et al. Promotion of vascular morphogenesis of endothelial cells co-cultured with human adipose-derived mesenchymal stem cells using polycaprolactone/gelatin nanofibrous scaffolds. Nanomaterials. 2018;8:117.

Kumar D. Cancer cell metabolism: a potential target for cancer therapy. Singapore: Springer Singapore; 2020.

Kumari R, Dhankhar P, Dalal V. Structure-based mimicking of hydroxylated biphenyl congeners (OHPCBs) for human transthyretin, an important enzyme of thyroid hormone system. J Mol Graph Model. 2021;105:107870.

Kusumaningtyas E, Nurilmala M, Sibarani D. Antioxidant and antifungal activities of collagen hydrolysates from skin of milkfish (*Chanos chanos*) hydrolyzed using various bacillus proteases. IOP Conf Ser Earth Environ Sci. 2019;278:012040.

Lapeña D, Vuoristo KS, Kosa G, Horn SJ, Eijsink VGH. Comparative assessment of enzymatic hydrolysis for valorization of different protein-rich industrial byproducts. J Agric Food Chem. 2018;66:9738-49.

Lee EJ, Hur J, Ham SA, Jo Y, Lee SY, Choi MJ, et al. Fish collagen peptide inhibits the adipogenic differentiation of preadipocytes and ameliorates obesity in high fat diet-fed mice. Int J Biol Macromol. 2017;104:281-6.

Lee HJ, Roy VC, Ho TC, Park JS, Jeong YR, Lee SC, et al. Amino acid profiles and biopotentiality of hydrolysates obtained from comb penshell (*Atrina pectinata*) viscera using subcritical water hydrolysis. Mar Drugs. 2021;19:137.

Lee JK, Jeon JK, Byun HG. Effect of angiotensin I converting enzyme inhibitory peptide purified from skate skin hydrolysate. Food Chem. 2011;125:495-9.

Li W, Kobayashi T, Meng DW, Miyamoto N, Tsutsumi N, Ura K, et al. Free radical scavenging activity of type II collagen peptides and chondroitin sulfate oligosaccharides from by-products of mottled skate processing. Food Biosci. 2021;41:100991.

Lian D, Yuan H, Yin X, Wu Y, He R, Huang Y, et al. Puerarin inhibits hyperglycemia-induced inter-endothelial junction through suppressing endothelial Nlrp3 inflammasome activation via ROS-dependent oxidative pathway. Phytomedicine. 2019;55:310-9.

Lima DAS, Santos MMF, Duvale RLF, Bezerra TKA, Araújo ÍBS, Madruga MS, et al. Technological properties of protein hydrolysate from the cutting byproduct of serra spanish mackerel (*Scomberomorus brasiliensis*). J Food Sci Technol. 2021;58:2952-62.

Lima KO, da Costa de Quadros C, da Rocha M, Jocelino Gomes de Lacerda JT, Juliano MA, Dias M, et al. Bioactivity and bioaccessibility of protein hydrolyzates from industrial byproducts of stripped weakfish (*Cynoscion guatucupa*). LWT-Food Sci Technol. 2019;111:408-13.

Lin L, Lv S, Li B. Angiotensin-I-converting enzyme (ACE)-inhibitory and antihypertensive properties of squid skin gelatin hydrolysates. Food Chem. 2012;131:225-30.

Link W. Principles of cancer treatment and anticancer drug development. Cham: Springer; 2019.

Liu C, Wang J, Gao C, Wang Z, Zhou X, Tang M, et al. Enhanced osteoinductivity and corrosion resistance of dopamine/gelatin/rhBMP-2–coated β-TCP/Mg-Zn orthopedic implants: an *in vitro* and *in vivo* study. PLOS ONE. 2020;15:e0228247.

Lu H, Hu H, Yang Y, Li S. The inhibition of reactive oxygen species (ROS) by antioxidants inhibits the release of an autophagy marker in ectopic endometrial cells. Taiwan J Obstet Gynecol. 2020;59:256-61.

Lu WY, Li HJ, Li QY, Wu YC. Application of marine natural products in drug research. Bioorg Med Chem. 2021;35:116058.

Luan X, Yan Y, Zheng Q, Wang M, Chen W, Yu J, et al. Excessive reactive oxygen species induce apoptosis via the APPL1-Nrf2/HO-1 antioxidant signalling pathway in trophoblasts with missed abortion. Life Sci. 2020;254:117781.

Luo J, le Cessie S, van Heemst D, Noordam R. Diet-derived circulating antioxidants and risk of coronary heart disease: a Mendelian randomization study. J Am Coll Cardiol. 2021;77:45-54.

Maeda H, Hosomi R, Fukuda M, Ikeda Y, Yoshida M, Fukunaga K, et al. Dietary tuna dark muscle protein attenuates hepatic steatosis and increases serum high-density lipoprotein cholesterol in obese type-2 diabetic/obese KK-Ay mice. J Food Sci. 2017;82:1231-8.

Mancini S, Preziuso G, Dal Bosco A, Roscini V, Parisi G, Paci G, et al. Modifications of fatty acids profile, lipid peroxidation and antioxidant capacity in raw and cooked rabbit burgers added with ginger. Meat Sci. 2017;133:151-8.

Marti-Quijal FJ, Remize F, Meca G, Ferrer E, Ruiz MJ, Barba FJ, et al. Fermentation in fish and by-products processing:

an overview of current research and future prospects. Curr Opin Food Sci. 2020a;31:9-16.

Martí-Quijal FJ, Tornos A, Príncep A, Luz C, Meca G, Tedeschi P, et al. Impact of fermentation on the recovery of antioxidant bioactive compounds from sea bass byproducts. Antioxidants. 2020b;9:239.

Mechri S, Sellem I, Bouacem K, Jabeur F, Laribi-Habchi H, Mellouli L, et al. A biological clean processing approach for the valorization of speckled shrimp *Metapenaeus monoceros* by-product as a source of bioactive compounds. Environ Sci Pollut Res Int. 2020;27:15842-55.

Melgosa R, Trigueros E, Sanz MT, Cardeira M, Rodrigues L, Fernández N, et al. Supercritical CO_2 and subcritical water technologies for the production of bioactive extracts from sardine (*Sardina pilchardus*) waste. J Supercrit Fluids. 2020;164:104943.

Michurina S, Stafeev I, Podkuychenko N, Sklyanik I, Shestakova E, Yah'yaev K, et al. Decreased UCP-1 expression in beige adipocytes from adipose-derived stem cells of type 2 diabetes patients associates with mitochondrial ROS accumulation during obesity. Diabetes Res Clin Pract. 2020;169:108410.

Miller ME. Cancer. New York, NY: Momentum Press; 2018.

Ministry of Marine Affairs and Fisheries. Marine and fishery production [Internet]. 2017 [cited 2022 Apr 6]. https://statistik.kkp.go.id/home.php?m=prod_ikan_prov&i=2#panel-footer

Mirzapour-Kouhdasht A, Moosavi-Nasab M, Krishnaswamy K, Khalesi M. Optimization of gelatin production from barred mackerel by-products: characterization and hydrolysis using native and commercial proteases. Food Hydrocoll. 2020;108:105970.

Mongkonkamthorn N, Malila Y, Yarnpakdee S, Makkhun S, Regenstein JM, Wangtueai S. Production of protein hydrolysate containing antioxidant and angiotensin-I-converting enzyme (ACE) inhibitory activities from tuna (*Katsuwonus pelamis*) blood. Processes. 2020;8:1518.

Mora Román JJ, Del Campo M, Villar J, Paolini F, Curzio G, Venuti A, et al. Immunotherapeutic potential of mollusk hemocyanins in combination with human vaccine adjuvants in murine models of oral cancer. J Immunol Res. 2019;2019:7076942.

Neha K, Haider MR, Pathak A, Yar MS. Medicinal prospects of antioxidants: a review. Eur J Med Chem. 2019;178:687-704.

Nghia ND. Seafood by-products: a new way from waste to high added value in pharmaceuticals and cosmetics. Encyclopedia Mar Biotechnol. 2020:2961-86.

Ngo DH, Ryu B, Vo TS, Himaya SWA, Wijesekara I, Kim SK, et al. Free radical scavenging and angiotensin-I converting enzyme inhibitory peptides from Pacific cod (*Gadus macrocephalus*) skin gelatin. Int J Biol Macromol. 2011;49:1110-6.

Nigam M, Suleria HAR, Farzaei MH, Mishra AP. Marine anticancer drugs and their relevant targets: a treasure from the ocean. DARU J Pharma Sci. 2019;27:491-515.

Nikoo M, Benjakul S, Gavlighi HA, Xu X, Regenstein JM. Hydrolysates from rainbow trout (*Oncorhynchus mykiss*) processing by-products: properties when added to fish mince with different freeze-thaw cycles. Food Biosci. 2019;30:100418.

Nikoo M, Regenstein JM, Noori F, Gheshlaghi SP. Autolysis of rainbow trout (*Oncorhynchus mykiss*) by-products: enzymatic activities, lipid and protein oxidation, and antioxidant activity of protein hydrolysates. LWT-Food Sci Techno. 2021a;140:110702.

Nikoo M, Xu X, Regenstein JM, Noori F. Autolysis of Pacific white shrimp (*Litopenaeus vannamei*) processing by-products: enzymatic activities, lipid and protein oxidation, and antioxidant activity of hydrolysates. Food Biosci. 2021b;39:100844.

Nisov A, Kakko T, Alakomi HL, Lantto R, Honkapää K. Comparison of enzymatic and pH shift methods to extract protein from whole Baltic herring (*Clupea harengus membras*) and roach (*Rutilus rutilus*). Food Chem. 2022;373:131524.

Nugroho G, Ekawati AW, Kartikaningsih H. Characteristics of tuna viscera (*Thunnus* sp.) hydrolysate protein fermented by *Bacillus licheniformis*. Res J Life Sci. 2020;7:101-7.

Nurdiani R, Ramadhan M, Prihanto AA, Firdaus M. Characteristics of fish protein hydrolysate from mackerel (*Scomber japonicus*) by-products. J Hunan Univ Nat Sci. 2022;49.

Nurdiani R, Vasiljevic T, Yeager T, Singh TK, Donkor ON. Bioactive peptides with radical scavenging and cancer cell cytotoxic activities derived from flathead (*Platycephalus fuscus*) by-products. Eur Food Res Technol. 2017;243:627-37.

Nurilmala M, Hizbullah HH, Karnia E, Kusumaningtyas E, Ochiai Y. Characterization and antioxidant activity of collagen, gelatin, and the derived peptides from yellowfin tuna (*Thunnus albacares*) skin. Mar Drugs. 2020;18:98.

Nurilmala M, Pertiwi RM, Nurhayati T, Fauzi S, Batubara I, Ochiai Y. Characterization of collagen and its hydrolysate from yellowfin tuna *Thunnus albacares* skin and their potencies as antioxidant and antiglycation agents. Fish Sci. 2019;85:591-9.

Pal S, Rao GN, Pal A. High glucose-induced ROS accumulation is a critical regulator of ERK1/2-Akt-tuberin-mTOR signalling in RGC-5 cells. Life Sci. 2020;256:117914.

Pangestuti R, Kim SK. Bioactive peptide of marine origin for the prevention and treatment of non-communicable diseases. Mar Drugs. 2017;15:67.

Papaccio F, Paino F, Regad T, Papaccio G, Desiderio V, Tirino V, et al. Concise review: cancer cells, cancer stem cells, and mesenchymal stem cells: influence in cancer development. Stem Cells Transl Med. 2017;6:2115-25.

Patra S, Praharaj PP, Panigrahi DP, Panda B, Bhol CS, Mahapatra KK, et al. Bioactive compounds from marine invertebrates as potent anticancer drugs: the possible pharmacophores modulating cell death pathways. Mol Biol Rep. 2020;47:7209-28.

Peña-Bautista C, López-Cuevas R, Cuevas A, Baquero M, Cháfer-Pericás C. Lipid peroxidation biomarkers correlation with medial temporal atrophy in early Alzheimer Disease. Neurochem Int. 2019;129:104519.

Petrova I, Tolstorebrov I, Eikevik TM. Production of fish protein hydrolysates step by step: technological aspects, equipment used, major energy costs and methods of their minimizing. Int Aquat Res. 2018;10:223-41.

Pezeshk S, Ojagh SM, Rezaei M, Shabanpour B. Fractionation of protein hydrolysates of fish waste using membrane ultrafiltration: investigation of antibacterial and antioxidant activities. Probiotics Antimicrob Proteins. 2019;11:1015-22.

Pisoschi AM, Pop A, Iordache F, Stanca L, Predoi G, Serban AI. Oxidative stress mitigation by antioxidants: an overview on their chemistry and influences on health status. Eur J Med Chem. 2021;209:112891.

Priatni S, Ratnaningrum D, Kosasih W, Sriendah E, Srikandace Y, Rosmalina T, et al. Protein and fatty acid profile of marine fishes from Java Sea, Indonesia. Biodivers J Biol Divers. 2018;19:1737-42.

Prihanto AA, Nurdiani R, Bagus AD. Production and characteristics of fish protein hydrolysate from parrotfish (*Chlorurus sordidus*) head. PeerJ. 2019;7:e8297.

Pujiastuti DY, Ghoyatul Amin MN, Alamsjah MA, Hsu JL. Marine organisms as potential sources of bioactive peptides that inhibit the activity of angiotensin I-converting enzyme: a review. Molecules. 2019;24:2541.

Putra MY, Murniasih T. Distribution and diversity of marine natural products from Indonesian marine organisms. J Coast Life Med. 2016;4:104-7.

Qian ZJ, Zhang YY, Oh GW, Heo SY, Park WS, Choi IW, et al. Antioxidant and angiotensin I converting enzyme inhibition effects and antihypertensive effect in spontaneously hyertensive rats of peptide isolated from boiled abalone by-products, *Hallotis discus hannai*. J Aquat Food Prod Technol. 2018;27:946-60.

Radhika Rajasree SR, Gobalakrishnan M, Aranganathan L, Karthih MG. Fabrication and characterization of chitosan based collagen/gelatin composite scaffolds from big eye snapper *Priacanthus hamrur* skin for antimicrobial and anti oxidant applications. Mater Sci Eng C. 2020;107:110270.

Rahman MS, Rahman MS. Effects of elevated temperature on prooxidant-antioxidant homeostasis and redox status in the American oyster: signaling pathways of cellular apoptosis during heat stress. Environ Res. 2021;196:110428.

Raja K, Martin LC, Bose L, Sahayanathan GJ, Padmanaban D, Chinnasamy A. Anti-proliferative and apoptotic effects of by-product (skin extract) from marine catfish *Tachysurus dussumieri*. Biocatal Agric Biotechnol. 2020;29:101816.

Rajendran SRCK, Mohan A, Khiari Z, Udenigwe CC, Mason B. Yield, physicochemical, and antioxidant properties of Atlantic salmon visceral hydrolysate: comparison of lactic acid bacterial fermentation with flavourzyme proteolysis and formic acid treatment. J Food Process Preserv. 2018;42:e13620.

Saidi S, Saoudi M, Ben Amar R. Valorisation of tuna processing waste biomass: isolation, purification and characterisation of four novel antioxidant peptides from tuna by-product hydrolysate. Environ Sci Pollut Res Int. 2018;25:17383-92.

Salmanzadeh R, Eskandani M, Mokhtarzadeh A, Vandghanooni S, Ilghami R, Maleki H, et al. Propyl gallate (PG) and tert-butylhydroquinone (TBHQ) may alter the potential anti-cancer behavior of probiotics. Food Biosci. 2018;24:37-45.

Sasaki C, Tamura S, Tohse R, Fujita S, Kikuchi M, Asada C, et al. Isolation and identification of an angiotensin I-converting enzyme inhibitory peptide from pearl oyster (*Pinctada fucata*) shell protein hydrolysate. Process Biochem. 2019;77:137-42.

Sellimi S, Ksouda G, Benslima A, Nasri R, Rinaudo M, Nasri M, et al. Enhancing colour and oxidative stabilities of reduced-nitrite turkey meat sausages during refrigerated storage using fucoxanthin purified from the Tunisian seaweed *Cystoseira barbata*. Food Chem Toxicol. 2017;107:620-9.

Setijawati D, Jaziri AA, Yufidasari HS, Pratomo MD, Wardani DW, Ersyah D, et al. Effect of incubation time and pH on the protein characterization of the aqueous soluble phase of acidified mackerel by-product. IOP Conf Ser: Earth Environ Sci. 2020;493:012030.

Setijawati D, Jaziri AA, Yufidasari HS, Wardani DW, Pratomo MD, Ersyah D, et al. Characteristics of peptone from the mackerel, *Scomber japonicus* head by-product as bacterial growth media. Biosci Biotechnol Res Commun. 2019;12:829-36.

Sghayyar HNM, Lim SS, Ahmed I, Lai JY, Cheong XY, Chong ZW, et al. Fish biowaste gelatin coated phosphate-glass fibres for wound-healing application. Eur Polym J. 2020;122:109386.

Shavandi A, Hu Z, Teh SS, Zhao J, Carne A, Bekhit A, et al. Antioxidant and functional properties of protein hydrolysates obtained from squid pen chitosan extraction effluent. Food Chem. 2017;227:194-201.

Shen K, Mu W, Xia S, Chen Y, Ren H, Xie X, et al. Preparation of protein powder from the liver of yellowfin tuna (*Thunnus albacores*): a comparison of acid- and alkali-aided pH-shifting. Food Sci Technol. 2021;42.

Shrivastava A, Mishra SP, Pradhan S, Choudhary S, Singla S, Zahra K, et al. An assessment of serum oxidative stress and antioxidant parameters in patients undergoing treatment for cervical cancer. Free Radic Biol Med. 2021;167:29-35.

Siahaan EA, Chun BS. Innovative alternative technology for fucoxanthin recovery. Encyclopedia Mar Biotechnol. 2020:3213-27.

Siddeeg A, AlKehayez NM, Abu-Hiamed HA, Al-Sanea EA, Al-Farga AM. Mode of action and determination of antioxidant activity in the dietary sources: an overview. Saudi J Biol Sci. 2021;28:1633-44.

Song R, Zhang K, Wei R. *In vitro* antioxidative activities of squid (*Ommastrephes bartrami*) viscera autolysates and identification of active peptides. Process Biochem. 2016;51:1674-82.

Song Y, Nagai N, Saijo S, Kaji H, Nishizawa M, Abe T. *In situ* formation of injectable chitosan-gelatin hydrogels through double crosslinking for sustained intraocular drug delivery. Mater Sci Eng C. 2018;88:1-12.

Stevens JR, Newton RW, Tlusty M, Little DC. The rise of aquaculture by-products: increasing food production, value, and sustainability through strategic utilisation. Mar Policy. 2018;90:115-24.

Surasani VKR. Acid and alkaline solubilization (pH shift) process: a better approach for the utilization of fish processing waste and by-products. Environ Sci Pollut Res Int. 2018;25:18345-63.

Taira Y, Yamashita T, Bian Y, Shang J, Matsumoto N, Sasaki R, et al. Antioxidative effects of a novel dietary supplement Neumentix in a mouse stroke model. J Stroke Cerebrovasc Dis. 2020;29:104818.

Te Riet L, van Esch JHM, Roks AJH, van den Meiracker AH, Danser AHJ. Hypertension: renin-angiotensin-aldosterone system alterations. Circ Res. 2015;116:960-75.

Thenu JL, Lokollo E, Wenno MR. Chemical compositions and amino acids of dolphin fish (*Coryphaena hippurus*) roes. In: Proceedings of the 3rd International Seminar of Basic Sciences; 2017; Ambon, Indonesia.

Trilaksani W, Adnyane IKM, Riyanto B, Safitri N. Nano collagen of the grouper swim bladder in compliance with quality standard of cosmetics materials. IOP Conf Ser: Earth Environ Sci. 2020;404:012050.

Ucak I, Afreen M, Montesano D, Carrillo C, Tomasevic I, Simal-Gandara J, et al. Functional and bioactive properties of peptides derived from marine side streams. Mar Drugs. 2021;19:71.

Valencia P, Valdivia S, Nuñez S, Ovissipour R, Pinto M, Ramirez C, et al. Assessing the enzymatic hydrolysis of salmon frame proteins through different by-product/water ratios and pH regimes. Foods. 2021;10:3045.

Varona S, García-Redondo AB, Martínez-González J, Salaices M, Briones AM, Rodríguez C. Vascular lysyl oxidase over-expression alters extracellular matrix structure and induces oxidative stress. Clín Investig Arterioscler. 2017;29:157-65.

Vázquez JA, Fraguas J, Mirón J, Valcárcel J, Pérez-Martín RI, Antelo LT. Valorisation of fish discards assisted by enzymatic hydrolysis and microbial bioconversion: lab and pilot plant studies and preliminary sustainability evaluation. J Clean Prod. 2020;246:119027.

Venkatesan J, Anil S, Kim SK, Shim MS. Marine fish proteins and peptides for cosmeceuticals: a review. Mar Drugs. 2017;15:143.

Versteegden LR, Ter Meer M, Lomme RMLM, van der Vliet JA, Schultze Kool LJ, van Kuppevelt TH, et al. Self-expandable tubular collagen implants. J Tissue Eng Regen Med. 2018;12:1494-8.

Vieira EF, Van Camp J, Ferreira IMPLVO, Grootaert C. Protein hydrolysate from canned sardine and brewing by-products improves TNF-α-induced inflammation in an intestinal-endothelial co-culture cell model. Eur J Nutr. 2018;57:2275-86.

Vijayan A, Chithra V, Sandhya C. The relationship of lipid peroxidation and antioxidant status to selected modifiable risk factors in coronary artery disease patients. Int J Cardiol Hypertens. 2021;8:100077.

Villamil O, Váquiro H, Solanilla JF. Fish viscera protein hydrolysates: production, potential applications and functional and bioactive properties. Food Chem. 2017;224:160-71.

Vo TDL, Pham KT. Copper-chelating peptide from salmon by-product proteolysate. Int J Food Eng. 2020;16.

Vujic A, Koo ANM, Prag HA, Krieg T. Mitochondrial redox and TCA cycle metabolite signaling in the heart. Free Radic Biol Med. 2021;166:287-96.

Walters ME, Esfandi R, Tsopmo A. Potential of food hydrolyzed proteins and peptides to chelate iron or calcium and enhance their absorption. Foods. 2018;7:172.

Wang CH, Doan CT, Nguyen VB, Nguyen AD, Wang SL, Wang SL. Reclamation of fishery processing waste: a mini-review. Molecules. 2019a;24:2234.

Wang K, Siddanakoppalu PN, Ahmed I, Pavase TR, Lin H, Li Z. Purification and identification of anti-allergic peptide from Atlantic salmon (*Salmo salar*) byproduct enzymatic hydrolysates. J Funct Foods. 2020;72:104084.

Wang LL, Yu QL, Han L, Ma XL, Song RD, Zhao SN, et al. Study on the effect of reactive oxygen species-mediated oxidative stress on the activation of mitochondrial apoptosis and the tenderness of yak meat. Food Chem. 2018;244:394-402.

Wang X, Yu H, Xing R, Li P. Characterization, preparation, and purification of marine bioactive peptides. BioMed Res Int. 2017;2017:9746720.

Wang YJ, Mäkelä N, Maina NH, Lampi AM, Sontag-Strohm T. Lipid oxidation induced oxidative degradation of cereal beta-glucan. Food Chem. 2016;197:1324-30.

Wang Z, He Z, Emara A, Gan X, Li H. Effects of malondialdehyde as a byproduct of lipid oxidation on protein oxidation in rabbit meat. Food Chem. 2019b;288:405-12.

Wang Z, Tu J, Zhou H, Lu A, Xu B. A comprehensive insight into the effects of microbial spoilage, myoglobin autoxidation, lipid oxidation, and protein oxidation on the discoloration of rabbit meat during retail display. Meat Sci. 2021;172:108359.

Wei LG, Chang HI, Wang Y, Hsu S, Dai LG, Fu KY, et al. A gelatin/collagen/polycaprolactone scaffold for skin regeneration. PeerJ. 2019;7:e6358.

Wellenstein MD, de Visser KE. Cancer-cell-intrinsic mechanisms shaping the tumor immune landscape. Immunity. 2018;48:399-416.

Wibawa SF, Retnoningrum DS, Suhartono MT. Acid soluble collagen from skin of common carp (*Cyprinus carpio* L), red snapper (*Lutjanus* sp.) and milkfish (*Chanos chanos*). World Appl Sci J. 2015;33:990-5.

Woo M, Song YO, Kang KH, Noh JS. Anti-obesity effects of collagen peptide derived from skate (*Raja kenojei*) skin through regulation of lipid metabolism. Mar Drugs. 2018;16:306.

World Health Organization. Global recommendations on physical activity for health. Geneva: World Health Organization; 2010. p. 1-60.

World Health Organization. World health statistics 2020: monitoring health for the SDGs, sustainable development goals. Geneva: World Health Organization; 2020. p. 77.

Wu W, Li B, Hou H, Zhang H, Zhao X. Identification of iron-chelating peptides from Pacific cod skin gelatin and the possible binding mode. J Funct Foods. 2017;35:418-27.

Xu X, Liu A, Hu S, Ares I, Martínez-Larrañaga MR, Wang X, et al. Synthetic phenolic antioxidants: metabolism, hazards and mechanism of action. Food Chem. 2021:129488.

Yaghoubzadeh Z, Peyravii Ghadikolaii F, Kaboosi H, Safari R, Fattahi E. Antioxidant activity and anticancer effect of bioactive peptides from rainbow trout (*Oncorhynchus mykiss*) skin hydrolysate. Int J Pept Res Ther. 2020;26:625-32.

Yang XR, Zhao YQ, Qiu YT, Chi CF, Wang B. Preparation and characterization of gelatin and antioxidant peptides from gelatin hydrolysate of skipjack tuna (*Katsuwonus pelamis*) bone stimulated by *in vitro* gastrointestinal digestion. Mar Drugs. 2019;17:78.

Ye Q, Meng X, Jiang L. Identification and assessment of residual levels of the main oxidation product of tert-butylhydroquinone in frying oils after heating and its cytotoxicity to RAW 264.7 cells. Food Chem. 2018;264:293-300.

Yu F, He K, Dong X, Zhang Z, Wang F, Tang Y, et al. Immunomodulatory activity of low molecular-weight peptides from *Nibea japonica* skin in cyclophosphamide-induced immunosuppressed mice. J Funct Foods. 2020;68:103888.

Yuswan MH, A Jalil NH, Mohamad H, Keso S, Mohamad NA, Tengku Md Yusoff TS, et al. Hydroxyproline determination for initial detection of halal-critical food ingredients (gelatin and collagen). Food Chem. 2021;337:127762.

Zahra K, Patel S, Dey T, Pandey U, Mishra SP. A study of oxidative stress in cervical cancer-an institutional study. Biochem Biophys Rep. 2020;25:100881.

Zamora-Sillero J, Gharsallaoui A, Prentice C. Peptides from fish by-product protein hydrolysates and its functional properties: an overview. Mar Biotechnol. 2018;20:118-30.

Zamorano-Apodaca JC, García-Sifuentes CO, Carvajal-Millán E, Vallejo-Galland B, Scheuren-Acevedo SM, Lugo-Sánchez ME. Biological and functional properties of peptide fractions obtained from collagen hydrolysate derived from mixed by-products of different fish species. Food Chem. 2020;331:127350.

Zeller D, Cashion T, Palomares M, Pauly D. Global marine fisheries discards: a synthesis of reconstructed data. Fish Fish. 2018;19:30-9.

Zhang K, Li J, Hou H, Zhang H, Li B. Purification and characterization of a novel calcium-binding decapeptide from Pacific cod (*Gadus Macrocephalus*) bone: molecular properties and calcium chelating modes. J Funct Foods. 2019a;52:670-9.

Zhang L, Zhao GX, Zhao YQ, Qiu YT, Chi CF, Wang B. Identification and active evaluation of antioxidant peptides from protein hydrolysates of skipjack tuna (*Katsuwonus pelamis*) head. Antioxidants. 2019b;8:318.

Zhang X, Dai Z, Zhang Y, Dong Y, Hu X. Structural characteristics and stability of salmon skin protein hydrolysates obtained with different proteases. LWT-Food Sci Technol. 2022;153:112460.

Zhou DY, Zhu BW, Qiao L, Wu HT, Li DM, Yang JF, et al. *In vitro* antioxidant activity of enzymatic hydrolysates prepared from abalone (*Haliotis discus hannai* Ino) viscera. Food Bioprod Process. 2012;90:148-54.

Zhou Y, Mao S, Zhou M. Effect of the flavonoid baicalein as a feed additive on the growth performance, immunity, and antioxidant capacity of broiler chickens. Poult Sci. 2019;98:2790-9.

Ziegler SJ, Mallinson SJB, St. John PC, Bomble YJ. Advances in integrative structural biology: towards understanding protein complexes in their cellular context. Comput Struct Biotechnol J. 2020;19:214-25.