



# Exploring Fish Processing By-Products as an Alternative Source of Bioactive Peptides: A Review on Extraction and Food Applications

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## Abstract

**Purpose of Review** This review explores non-thermal-based extraction techniques for obtaining bioactive peptides from fish processing by-products. It emphasizes the potential of these peptides as alternatives in the development of functional foods. With a focus on preserving bioactivity, the review aims to explore the utilization of fish peptides in food applications.

**Recent Findings** Recent research highlights the potential of bioactive peptides in the food, pharmaceutical, and cosmetic industries. Fish processing by-products are valuable sources of these peptides. Non-thermal technologies preserve their bioactivity, while encapsulation techniques further enhance peptide protection and efficacy in industrial applications.

**Summary** This review highlights fish processing by-products as a source of bioactive peptides, with non-thermal extraction techniques preserving their bioactivity. It emphasizes their promising bioactivities for industrial use and the importance of encapsulation techniques in maintaining bioactivity. It provides comprehensive insights into their extraction, bioavailability, safety considerations, and food applications.

**Keywords** Fish processing by-products · Bioactive peptides · Extraction · Peptide's bioavailability · Safety · Food applications

## Introduction

The fish processing industry generates significant by-products, accounting for approximately 55% to 65% of the total weight of the catch per year. These by-products include fillet remains (15% to 20%), viscera (12% to 18%), bones (9% to 15%), heads (9% to 12%), scales (5%), and skin

and fins (1% to 3%) [1]. Various types of wastewaters are also generated during processing operations like washing, thawing, cooking, and fishmeal production [2]. Although these by-products may have limited direct commercialization potential, there are opportunities for developing high-value-added products.

Fish by-products contain proteins (8% to 35% crude content) that can be extracted as an environmentally friendly solution [3, 4]. However, optimal extraction techniques and high-quality raw materials are crucial for producing high-quality fish bioactive peptides [4]. Conventional extraction methods like chemical hydrolysis and fermentation pose challenges due to protein sensitivity to degradation factors like oxidation and excessive heat [3]. Therefore, there is a growing focus on developing non-thermal-based technologies that minimize energy consumption and operate at lower temperatures. Methods such as pulsed electric field (PEF), high hydrostatic pressure (HHP), membrane techniques, ultrasound treatment, and enzyme-assisted extraction are employed to enhance the extraction efficiency, bioactivity, yield, and other properties of bioactive peptides from fish by-products [5–9]. These methods offer advantages like low solvent consumption, non-toxicity, rapid processing, and

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high extraction yields, significantly improving the utilization of bioactive peptides from fish by-products [10].

The significance of bioactive peptides, particularly those derived from fish proteins and peptides, lies in their ability to provide diverse health and functional benefits beyond their basic nutritional value. Fish-derived proteins/peptides exhibit a wide range of physiological activities, making them valuable in various industries, including the food industry and pharmaceutical and cosmetic industries. In the food industry, bioactive peptides can act as natural antioxidants, antimicrobials, and have anti-hypertensive and gut health-promoting effects [11]. Recognizing their health-promoting potential, popular functional food brands like Amizate®, Stabilium® 200, and Nutripeptin® utilize these fish-derived proteins/peptides as bioactive ingredients, highlighting their positive impacts on human health and nutrition [12]. In the pharmaceutical industry, they have therapeutic potential and can be used for drug delivery applications [13]. In the cosmetic industry, they have demonstrated skin rejuvenation and anti-inflammatory properties [14]. The utilization of fish processing waste as a source of bioactive peptides is significant from an environmental perspective. The fish processing sector produces a significant amount of by-products and waste, which can lead to adverse environmental consequences if not handled and utilized appropriately. By extracting valuable bioactive compounds from this waste, the industry can adopt more sustainable waste management practices, reducing the environmental burden and promoting a circular economy. The development of innovative technologies to recover and purify bioactive peptides from fish by-products not only provides health and functional benefits but also contributes to more sustainable and eco-friendly practices in the seafood industry. This review offers an overview of recent research on bioactive peptides, highlighting the significant environmental benefits and sustainable waste management practices associated with their extraction from fish processing by-products. Adopting a novel and comprehensive perspective, the review emphasizes the valorization of fish industry by-products, which can contribute to a more sustainable and environmentally conscious future for the sector. This work addresses the challenges of waste management and highlights innovative non-thermal extraction technologies, providing valuable insights into the development and food applications of these valuable compounds, positioning it as a crucial resource for researchers and industry stakeholders alike.

## Fish Processing by-Products as a Rich Source of Bioactive Peptides

Fisheries pose significant challenges in effectively managing fish by-products, leading to economic losses and environmental concerns. Improper disposal of these by-products

results in the release of organic matter into the environment, contributing to greenhouse gas emissions and environmental degradation [15]. Approximately 45% of total fish production accounts for fish by-products, which are often discarded [16].

Solid by-products generated during fish processing include heads, trimmings, skin, liver, gut, bones, and scales, which are typically discarded [17, 18]. These by-products constitute a significant portion of the fish body, with approximately 30–50% of the fish meat being left unused during filleting [17]. However, suitable treatment processes offer an opportunity to recover bioactive peptides from these solid by-products, creating value-added products that provide both economic and environmental benefits [18]. The isolation of a novel bioactive peptide (CP) from a *Chromis notata* by-product hydrolysate with potent antioxidant, antimicrobial, and anti-atopic dermatitis effects showcases its potential applications in functional food, cosmetic, and pharmaceutical products. Additionally, a highly potent ACE inhibitory peptide, VGLFPSRSF (1009.17 Da), was obtained from steam-exploded tilapia skin hydrolysates [19]. ACE inhibitory peptides are known for their antihypertensive properties, making this discovery from tilapia skin particularly valuable for the development of cardiovascular health-promoting ingredients [20].

Fish processing wastewater is generated during various operations in fish processing plants, such as freezing, cleaning, filleting, drying, canning, and smoking [21]. On average, around 11 m<sup>3</sup> of water is consumed per tonne of prepared fish, with a significant portion being discharged as wastewater [22]. This wastewater, including blood water, fish canning cooking wastewater, and stickwater, contains various pollutants such as salts, organic molecules, and particles. These wastewaters have high levels of chemical oxygen demand (COD) due to the presence of biodegradable substances like proteins and lipids [17, 18]. Blood water contains valuable compounds such as proteins, peptides, amino acids, vitamins, trace elements, and salt, which can be recovered and utilized [23, 24]. Fish canning cooking wastewater, characterized by high concentrations of organic materials and fats, is produced during the canning process, and contains water-soluble proteins and essential amino acids [9, 18]. Stickwater, generated in the production of fishmeal, is a significant wastewater stream containing proteins and other components [25]. Efforts have been made to recover valuable compounds from fish processing by-products, including proteins, peptides, amino acids, and other nutrients. These compounds can be utilized in various sectors, offering opportunities for sustainable resource utilization [23, 24].

## Innovative Non-Thermal-Based Technology for Extracting Bioactive Peptides from Fish Processing by-Products

Non-thermal-based technologies have significantly enhanced the utilization of fish processing by-products, such as proteins and peptides, which were previously considered waste. These innovative methods provide efficient and sustainable extraction of valuable compounds. They offer high extraction efficiency, capturing a broad range of bioactive compounds while being environmentally friendly and non-toxic. Compared to traditional approaches, non-thermal-based methods require less time, lower temperatures, and preserve the integrity of heat-sensitive compounds, resulting in cost savings. These techniques also exhibit solvent selectivity, enabling targeted extraction of specific compounds based on their properties, leading to improved efficiency and purity. Furthermore, non-thermal-based methods are energy-efficient, reducing their environmental impact and promoting sustainability [26].

### Membrane Technology

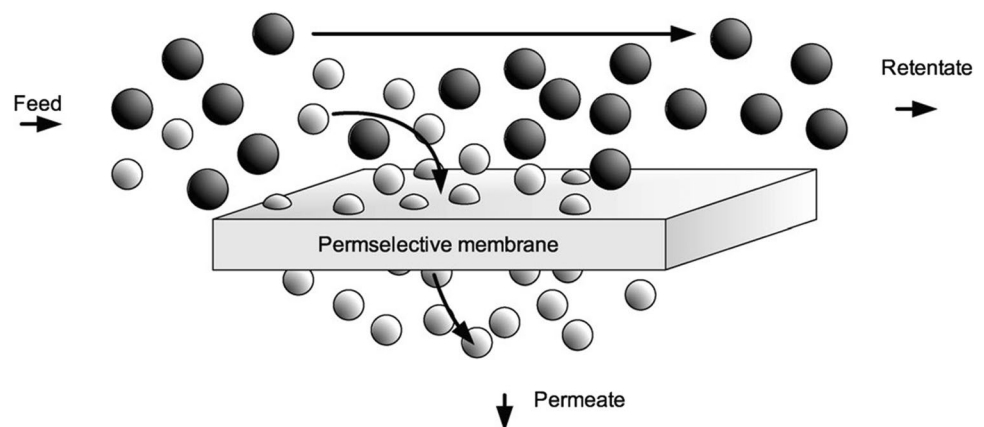
Membrane filtration is a separation technique that exploits the selective permeability of specific components in a liquid solution through a semi-permeable membrane, based on factors such as size, charge, and shape [27]. The separation process can be driven by pressure, electrical fields, or concentration gradients. In the context of bioactive peptide enrichment, pressure-driven membranes are commonly used for size-based separations of biological molecules. These membranes have pores with a defined size, allowing smaller compounds to pass through while rejecting larger compounds and biomolecules [28]. Membrane technologies provide significant advantages in concentrating or fractionating valuable molecules from wastewater in the seafood processing industry. They selectively allow

certain molecules, like proteins, to pass through while preserving their integrity and bioactivity. However, there is a risk of denaturation and precipitation when processing larger proteins through pressure-driven membranes, particularly hydrophobic ones. Processing peptides is comparatively easier, but the use of hydrophilic membranes is still crucial to maintaining desired separation and preserving peptide bioactivity. This process improves the efficiency and sustainability of the seafood processing industry by extracting and purifying valuable molecules from wastewater while minimizing protein denaturation [29]. Figure 1 depicts a schematic representation of membrane filtration process.

Pressure-driven membrane operations classified by size selectivity include microfiltration (MF), ultrafiltration (UF), nanofiltration (NF), and reverse osmosis (RO) (Table 1). These processes differ in characteristics and applications. The molecular weight cut-off (MWCO) in Daltons (Da) defines a membrane's capability to reject molecules [28]. Considering the range of MWCO values for different membrane processes (Table 1), UF and NF are the preferred membrane technologies for the purification of bioactive peptides.

In summary, membrane filtration is a versatile separation technique that can be effectively employed for the enrichment and separation of bioactive peptides from fish processing wastewater. The selective permeability of membranes, driven by factors such as size, charge, and shape, enables the fractionation and concentration of valuable peptides while preserving their structural integrity and bioactivity. Among the different pressure-driven membrane processes, UF and NF are the preferred technologies for bioactive peptide recovery, as they can efficiently separate peptides based on their MW. The integration of membrane filtration into fish processing operations can enhance the sustainability of the industry by extracting and separating high-value compounds from waste streams.

**Fig. 1** Schematic depiction of the membrane filtration process [30]



**Table 1** Comparative characteristics of the membrane processes [31–33]

Membrane	MWCO (Da)	Pore size range ( $\mu\text{m}$ )	TMP (bar)	Permeate flow rate ( $\text{L}\cdot\text{h}^{-1}\cdot\text{m}^2$ )	Retentate compounds	Mechanism of separation	Application
MF	> 300,000	$\leq 0.1$	0.1–2	-	Resins/Fats Turbidity MO	Sieving	Food, Pharmaceutical industries, Water treatment
UF	1000–300,000	$\leq 0.01$	2–10	20–200	Macromolecule Proteins peptides	Sieving	Textile, Food, Pharmaceutical Industries, Dairy, Water treatment
NF	> 150	$\leq 0.001$	10–40	50–100	Ions low molecular-substances Peptides	Solution-diffusion	Brackish water desalination, Wastewater treatment
RO	< 350	$\leq 0.0001$	< 3	> 300	Ions Suspended- solids	Solution-diffusion	Brackish and seawater desalination, Concentration of juice and milk

TMP: Transmembrane pressure, MWCO: molecular weight cut-off, MO: microorganisms, MF: microfiltration, UF: ultrafiltration, NF: nanofiltration; RO: reverse osmosis

### Ultrafiltration

Ultrafiltration (UF) separates peptides based on molecular weight (MW) (1–300 kDa), recovering them from crude hydrolysates. It fractionates and isolates peptide fractions with different MWs and functional or biological activities using membranes with varying MWCOs. This selective separation and concentration produce peptides with the desired MW and functionalities [34]. UF membranes with different MWCOs were used to extract biopeptides from codfish blood and sardine cooking wastewater. The membranes selectively separated proteins and peptides by size, concentrating and enriching the desired peptides. For codfish blood, different MWCO membranes achieved selective peptide separation. For sardine cooking wastewater, transmembrane pressure (TMP) settings were optimized to recover biopeptides. The research demonstrated the effectiveness and versatility of UF in biopeptide extraction processes [24]. UF successfully recovers proteins and lipids from processed waters in industries like cuttlefish, shrimp, sardine, surimi, and fishmeal, with recovery rates up to 97% for proteins and 90% for lipids [35]. UF was effective in recovering proteins from surimi wash water [36] and Atlantic herring marination brine [37]. UF was also used to recover and identify ACE inhibitory peptides, such as by hydrolyzing a protein concentrate from cuttlefish softening wastewater using a 10 kDa MWCO membrane [38].

Polyethersulfone (PES) is commonly used for UF membranes due to its rigidity and thermal stability [39]. However, hydrophilic materials like regenerated cellulose [40], polyacrylonitrile [41], cellulose acetate [42], and polyamide [43] are preferred for proteins and peptides. Fouling is a significant challenge in industrial-scale UF for bioactive

peptide recovery, as retained peptides and proteins can accumulate on the membrane surface, affecting efficiency and selectivity and causing clogging. Fouling rate depends on feed, membrane, and operational factors [44].

Studies have examined the impact of feed, operational, and membrane factors on UF performance and selectivity in peptide fractionation. The origin, composition, and characteristics of peptides and membranes significantly affect outcomes. In a study among 4–9 kDa UF membranes, PES had lower permeating fluxes than modified polyethersulfone (m-PES) and polysulfone (PS) when recovering < 2 kDa antioxidant peptides from Saithe fish protein hydrolysate. The 4 kDa m-PES membrane was most efficient in terms of permeate flux and selectivity for the target < 2 kDa peptides [44]. The 4 kDa m-PES membrane, increased initial peptide content favored medium-sized peptides in the permeate, while higher pressure reduced their proportion, favoring low MW peptide recovery. Elevated pressure caused concentration polarization, hindering medium-sized peptide transfer and reducing the apparent MWCO. For separating a wide peptide size range, a high MWCO membrane offers higher flux and productivity. But to isolate specific or low-MW peptides, a low-MWCO membrane is preferred for better selectivity [45]. However, conventional hydrolysis followed by offline UF has limitations like high enzyme use, low peptide yield, and enzyme loss [46]. To address conventional limitations, the enzymatic membrane reactor (EMR) concept combines enzymatic hydrolysis and membrane separation to improve yield, optimize purification, and overcome drawbacks. In a study, UF and enzymatic hydrolysis were used to prepare a protein hydrolysate from shrimp cooking water, optimizing parameters like temperature (75 °C), pH (9.0), and enzyme-to-substrate (E/S) ratio (0.1%) [47].

## Nanofiltration

Nanofiltration (NF) is a membrane process between RO and UF, with MWCO > 150 Da. It operates at 150–500 psi, lower than RO. NF membranes have a negatively charged separation layer, allowing separation by both size and charge. Tight NF membranes with MWCO of 200–1000 Da are used for desalting or concentrating peptide solutions after UF, producing stable desalinated bioactive peptides for industrial applications [48, 49]. An integrated UF, NF, and RO process selectively separated, concentrated, and desalted peptides from sardine wastewater, enhancing their bioactive properties [9]. Cascading UF and NF membranes increased the purity of the 1–4 kDa fraction from 19% to 49.3% in tuna by-product hydrolysate [50]. Combining UF and NF with diafiltration effectively fractionated tuna by-product hydrolysate, isolating high-value peptide fractions [51].

Loose NF membranes up to 4 kDa MWCO are used for peptide separation. In NF, neutral peptides transmit by size rejection, while charged peptides depend on both size and charge repulsion. The Donnan effect in negatively charged NF membranes leads to the passage of positively charged peptides and the retention of negatively charged ones [52]. Novel NF membranes with large pores and strong charges are being developed to achieve charge-based separation of similar-MW amino acids or biopeptides. These membranes allow the permeation of neutral or anionic molecules while repelling charged peptides, facilitating selective separation [53].

A positively charged NF membrane with large pores was fabricated using a one-step random amphiphilic copolymer (RACP) nanoparticle method. This membrane selectively rejected basic peptides while allowing neutral or acidic peptides to permeate via size sieving and Donnan exclusion. This demonstrates the potential for designing NF membranes optimized for bioactive peptide separation [53].

## Enzyme Hydrolysis Extraction

Enzymatic hydrolysis (EH) is a sustainable technique for extracting biomolecules from food matrices, offering control and specificity over conventional methods [47, 54]. Key variables in EH include the E/S ratio, temperature, pH, incubation time, and the selected proteolytic enzyme. The enzyme's specificity is crucial as it affects the size and composition of the generated peptides, influencing the bioactive properties of the hydrolysates [54]. This approach uses enzyme solutions, either individually or in combination, to optimize the digestion process. The enzymes can come from different sources, with microbial enzymes being nonpathogenic. These enzymes and marine by-products are known for their high quality. Before further processing, the exogenous enzymes must be deactivated to extract

valuable compounds. The enzyme-assisted method has been effective in improving the recovery of oil and protein from marine by-products. The recovery (%) is an important factor in evaluating the efficiency of EH extraction. Studies have reported varying recovery rates for different marine by-products and target compounds. For example, the recovery of protein hydrolysates from seabream (*Sparus aurata*) and seabass (*Dicentrarchus labrax*) has been reported to range from 47.2–52.3% and 36.8–49.9% respectively [55], while the recovery of bioactive peptides from thread herring (*Ophistonema libertate*) stickwater was around 5–20% [56]. The lower recovery rates for wastewaters compared to solid by-products highlight the need for further optimization of hydrolysis conditions and downstream processing to improve the overall yield.

EH has gained attention for producing fish by-product protein hydrolysates, including tuna [51], tilapia [20], and salmon [57]. Protein hydrolysates are derived by enzymatically hydrolyzing protein-rich marine by-products like bones, heads, viscera, and skin, breaking them down into diverse bioactive peptides [58]. While solid by-products are well studied, research on using fishery wastewaters for hydrolysates is limited. Few studies have explored tuna [59, 60] and kilka [61] wastewaters as sources of valuable compounds. Further investigation in this area can contribute to the sustainable utilization of fishery wastewater and innovative extraction methods. EH is preferred for recovering industrial by-products due to the specificity of the enzymes used, ensuring efficient and selective hydrolysis [51]. Enzymes are eco-friendly and safe, enhancing sustainability. Compared to chemical methods, enzymes provide better control over parameters, improving efficiency and product quality. EH also generally requires less energy, reducing environmental impact and costs [62]. EH for bioactive peptides requires careful control of the E/S ratio, hydrolysis time, pH, and temperature to optimize peptide properties. Variation in these factors can impact peptide length, MW, and amino acid composition, affecting bioactivity. Enzyme choice also influences peptide bioactivity [63]. Pre-treating the substrate is often needed, but thermal treatments can denature proteins and damage certain amino acids like tryptophan, lysine, arginine, and cysteine [64]. EH can pose challenges at scale due to low yields, high costs, and the need to maintain enzyme activity, making it an expensive process [65].

In summary, EH is a versatile and sustainable approach for extracting valuable biomolecules, including bioactive peptides, from marine by-products and wastewaters. While the recovery rates can vary depending on the substrate and processing conditions, EH offers advantages in terms of specificity, efficiency, and environmental sustainability compared to conventional extraction methods. Further research is needed to optimize the hydrolysis parameters

and downstream processing to improve the overall yield and cost-effectiveness of this technology for the recovery of high-value compounds from fishery waste streams.

### High Hydrostatic Pressure

High pressure processing, a non-thermal treatment technology, has demonstrated the capability to significantly lower microbial loads and deactivate enzymatic activity in seafood products [66]. It applies 100–1000 MPa pressure at 5–35 °C to improve the extractability of target compounds. The pressure deprotonates charged particles, breaks bonds, and increases cell permeability, enhancing extraction efficiency [67, 68]. HHP is highly efficient in yielding valuable compounds by applying high pressure to cells [69].

HHP was applied to tilapia fish by-products to obtain bioactive peptides from proteins through EH. High pressures promote enzymatic proteolysis by exposing more peptide bonds to fractionation and are vital in enhancing protein digestibility and improving enzyme functionality for forming antioxidant peptides in protein hydrolysates [70]. To optimize this process, the synergistic effect of pressure (38–462 MPa) and time (6–35 min) was investigated using HHP, finding the highest soluble protein content of 5.7 mg/mL and trichloroacetic acid-solubility index of 23% were obtained with 35 min extraction at 250 MPa. This demonstrates the significant potential of HHP for improving bioactive peptide extraction from tilapia by-products, with the high-pressure conditions enhancing enzymatic proteolysis and protein digestibility to achieve a 23% recovery rate, surpassing conventional methods. Even higher pressures up to 462 MPa further increased soluble protein, as the extreme pressures activated enzymes and unfolded protein structures, improving solubility and extraction efficiency [71]. The findings emphasize the versatility and effectiveness of HHP processing for the sustainable and high-value utilization of marine resources and their by-products.

HHP efficiently extracts bioactive compounds like astaxanthin, peptides, and polyunsaturated fatty acids (PUFAs) from marine by-products, surpassing conventional methods in yield. Pressure and holding time are crucial, depending on the sample properties. Industrial-scale HHP implementation requires further investigation to determine optimal conditions [72]. The benefits of efficient HHP processing can outweigh the high initial costs. HHP treatments up to 600 MPa have the potential to induce chemical alterations in target compounds [73].

### Pulsed Electric Field

Pulsed electric field (PEF) technology offers advantages like short processing times, low energy or temperature costs, quick response, and high extraction efficiency

compared to heat-based methods [74]. PEF uses high voltages and short electric pulses to disrupt cell membranes, enabling efficient extraction of intracellular contents through electroporation [75]. Factors like electric strength, pulse characteristics, cell properties, and equipment capabilities affect PEF application [74, 76]. Optimizing these factors is crucial for desired outcomes when using PEF in the marine industry.

PEF efficiently extracts antioxidants from marine by-products, offering advantages like reduced process time and improved yield. PEF extraction was demonstrated for antioxidants from sea bass and sea bream by-products using specific parameters, including 7000 V potential, 20 μs pulse width, 10 Hz frequency, and 100 pulses. The yield significantly increased compared to conventional solvent extraction. Further research is needed for the purification and identification of the extracted antioxidants, but the study highlights the potential of PEF as an effective and eco-friendly approach for extracting valuable compounds from marine by-products [77].

PEF has been used to efficiently extract collagen from bighead carp (*Aristichthys nobilis*) bones, with the maximum content achieved at 20 kV/cm and 8 pulses [78]. PEF was also used to extract fish bone protein hydrolysates with superior properties compared to enzymatic methods [79]. Accelerated solvent extraction as well as PEF (1–3 kV/cm, 123–300 kJ/kg, 15–24 h) processing were employed as the extraction technologies for fish by-products. The results showed that PEF processing significantly increased the protein extraction efficiency from the fish by-products, achieving yield improvements of up to 80% compared to conventional extraction methods. PEF processing was able to significantly increase the protein extraction efficiency from fish by-products by up to 80% compared to conventional extraction methods. This improvement in recovery rates is a truly remarkable result that highlights the immense potential of PEF technology for maximizing the valorization of marine processing by-products. The ability of PEF to so substantially boost extraction yields is a transformative advantage that could revolutionize the economics and sustainability of the marine industry. While further research is still needed to fully optimize PEF parameters and expand its applications, these results demonstrate that PEF can consistently deliver recovery rates in the 80% range or potentially even higher for a wide variety of target marine-derived compounds. This represents an extremely promising path forward for comprehensively extracting and capturing the maximum value from fish processing by-products [80].

PEF has advantages in processing marine by-products without detrimental effects, enhancing mass transfer, and being applicable to heat-sensitive foods without harmful solvents [81]. However, reliable industrial-level PEF equipment remains a challenge due to electrode issues [76]. Further

research is needed to explore broader industry applications of PEF for fish by-product valorization.

### Ultrasound-Assisted Extraction

Ultrasonic-assisted extraction (UAE) is an effective technique used in the food industry to extract natural compounds and enhance various properties like emulsification, solubility, and texture. UAE offers advantages such as short processing times, high yields, superior quality, reduced solvent and emulsifier use, and enhanced safety, making it a cost-effective and environmentally friendly processing method [82].

Ultrasound can be categorized into high-energy and low-energy frequencies. High-energy ultrasound disrupts food products, while low-energy ultrasound is used for non-destructive quality evaluation [83]. UAE utilizes sound waves to extract valuable components by inducing compression and extraction within cells, disrupting cell walls, and improving heat and mass transfer [84]. The efficiency of the UAE depends on factors like frequency, intensity, temperature, pressure, and time [85].

UAE was used for extracting valuable compounds from marine by-products, such as collagen from fish sources like skin and scales. UAE offers advantages over conventional techniques by reducing processing time and increasing yield. In one study, UAE used at 200 W and 60 °C for different durations (1, 3, and 5 h) to extract gelatin from bighead carp (*Hypophthalmichthys nobilis*) scales. UAE achieved significantly higher recoveries (30.94% to 46.67%) compared to water bath extraction (19.15% to 36.39%) at the same temperature and durations [86]. Longer UAE times provided more energy, disrupting bonds, promoting helix-to-coil transitions, and improving gelatin solubility and content. Acoustic cavitation generated in the UAE played a crucial role in releasing energy and accelerating gelatin release. However, as UAE time increased, gel strength and melting point decreased due to chain disruption and degradation. Interestingly, no significant differences were observed between UAE and water bath treatments with the same durations [87]. In a study, a strategy to obtain valuable compounds and minimize the presence of toxins from Sea bass side streams was presented, assisted by UAE. The UAE conditions were optimized using response surface methodology, with the dependent variables of time (0.5–30 min), pH (5.5–8.5), and temperature (20–50 °C). The results demonstrated a high recovery of proteins and antioxidant activity in the UAE extracts, particularly those derived from the viscera, when the extraction time and temperature were increased to 30 min and 50 °C, respectively [80]. A study was conducted to obtain protein concentrate from the flesh of snakehead fish (*Channa striata*) through consecutive ultrasound-assisted organic solvent extraction and vacuum

drying. The ultrasound-assisted extraction (UAE) method resulted in a higher protein content of 73.17%, compared to the conventional solvent extraction method, which only reached a maximum protein content of 65.77%. The best operating condition for the UAE method was using a mass ethanol volume to minced snakehead fish flesh ratio of 6:1 at 40 °C, employing 200 W ultrasound power for 25 min, and drying at 55 °C under reduced pressure (0.05 MPa), resulting in a highly efficient protein recovery process [88].

Scaling up UAE from a laboratory to an industrial scale can be challenging due to maintaining consistent ultrasound conditions, handling larger volumes, and ensuring uniform treatment across a larger system. UAE can also consume significant energy, especially with high-intensity ultrasound, leading to higher costs and environmental impacts. Addressing these challenges and optimizing the extraction process is crucial to achieving efficient and sustainable large-scale UAE operations [89].

### Food Application of Bioactive Peptides from Fish Processing by-Products

Proteins from seafood and fish by-products are valuable resources for extracting functional protein ingredients (FPIs) for use as supplements, nutraceuticals, or food ingredients to support weight management, muscle growth, and immune function [90].

Fish protein hydrolysates can enhance emulsification, foaming, and dispersion properties, making them valuable multi-functional food ingredients [91]. They can also act as antioxidants to extend shelf life, as demonstrated by tilapia hydrolysates inhibiting lipid oxidation in carp loach [92]. FPI from cape hake, with its high protein and low fat and ash content, has been successfully used in producing fish sausages resembling frankfurters with a lighter color than pork sausages [93]. Blending FPIs and surimi can enhance the texture of food products. Optimal equal proportions of FPIs and surimi resulted in improved hardness, cohesiveness, and whiteness, exhibiting a linear relationship in the development of fish-based products [94].

Restructuring is crucial in food technology to develop products resembling conventional items in appearance, texture, and flavor, meeting consumer expectations. Natural proteins and polysaccharides are commonly used to create restructured food products like sausages, fish balls, and composite fillets [95].

Marine protein supplements can be introduced into bakery and pasta products. Adding green mussel hydrolysate to gluten-free bread made with buckwheat, rice, and chickpea flour improves flavor and makes it suitable for gluten-sensitive individuals, with up to 20% inclusion showing promising results [96].

Bioactive peptides, such as collagen and gelatine, have promising applications as nutraceuticals [97]. Collagen peptides offer benefits for bone, joint, muscle, skin, and connective tissue health [98]. Seafood-derived antioxidant and antimicrobial peptides can be used as natural preservatives to prolong food shelf life [99]. Soluble, low-MW peptides can be used as fortifying ingredients, even in beverages [100]. Fish gelatines can be utilized for active packaging systems and as carriers for bioactive compounds, further extending food shelf life [101]. Table 2 provides a summary of potential food applications using fish processing by-products.

In conclusion, the utilization of proteins and bioactive peptides derived from fish processing by-products as functional food ingredients offers a sustainable approach to developing innovative, nutritious, and shelf-stable food products. Food products can enhance their functional properties, such as emulsification, foaming, and antioxidant capacity, by using seafood-derived proteins and peptides, which also offer health benefits related to weight management, muscle growth, and immune function. Incorporating these fish-based ingredients into a variety of food applications, including bakery, pasta, and restructured meat products, can help meet consumer expectations for texture, flavor, and appearance while also extending shelf life through natural preservation methods.

## Bioavailability of Bioactive Peptides

The biological efficacy of a peptide depends on maintaining its structural integrity during digestion and transport, as proteolysis can release previously inactive peptides and amino acids with unique benefits [112, 113]. While bioactive peptides demonstrate *in vitro* activity, their bioavailability *in vivo* may be limited. Orally administered peptides must through pass the intestinal epithelium intact to reach target sites [113]. However, they are susceptible to gastrointestinal proteolysis, which can degrade them into less active fragments. Only low-concentration peptides may successfully enter the systemic circulation [114]. Bioactive peptides are primarily composed of free amino acids and short-chain peptides, typically consisting of two to three amino acid residues. These short-chain peptides generally do not exceed 12 amino acid subunits. Dipeptides and tripeptides have improved bioavailability compared to equivalent amounts of free amino acids due to their lower hypertonic nature. This means that the absorption of short-chain peptides into cells is facilitated by a lower osmotic pressure difference. Additionally, some individual amino acids, such as glutamine, tyrosine, and cysteine, cannot be directly absorbed in their free form due to their limited chemical stability or water solubility [115]. The incorporation of these amino acids into

short-chain peptides can enhance their absorption and utilization by the body.

The bioaccessibility and bioavailability of protein hydrolysates derived from the industrial by-products of stripped weakfish (*Cynoscion guatucupa*) were evaluated. After simulated *in vitro* gastrointestinal digestion, the samples were found to be bioaccessible, meaning the proteins and peptides were available for absorption by the body. The high bioavailability of the protein hydrolysates was attributed to the presence of specific amino acids, such as phenylalanine (Phe), leucine (Leu), and tryptophan (Trp), within the peptide sequences. These amino acids are known to be more readily absorbed and utilized by the human body compared to some other amino acids [116].

The bioavailability of bioactive peptides is limited by factors like instability, size, sequence, charge, and hydrophobicity. Larger peptides are more susceptible to gastrointestinal protease degradation, and even resistant peptides have short half-lives due to plasma peptidases and clearance [117]. Micro- and nanoencapsulation techniques can enhance peptide resistance by providing a protective barrier while enabling controlled release. Investigated delivery systems include microemulsions, emulsions, nanoparticles, liposomes, and microgels [118, 119]. Fish peptides have limited practical use as antioxidants due to challenges like bitter taste, low bioaccessibility, and unfavorable food interactions. Encapsulating these peptides in liposomes can enhance their stability, protection from degradation, and bioavailability, mitigating these challenges and enabling wider practical applications [120, 121].

Hybrid liposome nanocarriers were developed to deliver fish-derived antioxidant peptides [122]. Encapsulation can protect peptides from degradation, enable controlled release, enhance stability, and reduce toxicity, demonstrating the potential of peptide delivery systems for nutraceutical and functional food applications [123]. Techniques to enhance bioactive peptide bioavailability can alter structural properties, which requires investigation to ensure retained bioactivity. The potential toxicity or allergic reactions of modified peptides also necessitate careful assessment. Comprehensive research is needed to understand the impact of these techniques on the structural properties, safety, and suitability of bioactive peptides for human use.

## Safety and Concerns of Bioactive Peptides Application

Concerns exist regarding the utilization of food-derived biopeptides due to potential negative biological effects, including disruption of the intestinal wall, toxicity, and cytotoxicity. Assessing the immunogenicity and potential toxicities of peptides is crucial before their use in food production or

**Table 2** Bioactive peptides from fish processing by-products and their application in functional food

Fish species	Source of protein	Product	Findings	
Pangas fish ( <i>Pangasius Pangasius</i> ) [102]	Fillet frames	Fish sausage	Protein content improvement	11.57–15.79%
			Increase in emulsion stability	7.91–6.09%
			Cooking yield optimization	85.86–86.06%
			Insignificant effect on sensory characteristics	Overall acceptability 7.8–8.2
Sturgeon fish [103]	Skin Waste by-products	Fish sausage	Reduce lipid oxidation	~0.5 mg MAD/kg
Rohu ( <i>Labeo rohita</i> ) [104]	Heads Skin Bone frames Viscera	Pangasius ( <i>Pangasius pangasius</i> ) sausage	Protein content improvement	16.14%
			Whiteness enhancement	61.74
			Cooking yield optimization	93.67%
			Insignificant effect on sensory attributes	-
Pangas [105]	Processing waste	Semolina pasta	Reduce fluid content of paste	6.25%
			Protein digestibility improvement	78.80%
			Increase firmness	0.45 N
			Increase toughness	2.50 kg/s
			Reduce enthalpy of gelatinization	2.41 J/g
			No effect in the sensory attributes	-
Snakehead Fish ( <i>Channa striata</i> ) [106]	By-products	Cookies	Increase fat content	1.33%
			Increase protein content	11.40%
			Texture improvement (decreased hardness)	985 Nmm <sup>2</sup>
			Appearance enhancement	-
Tilapia [107]	Skin	Low-fat stirred yogurt	Good substitute: using fish gelatin substituted with xanthan gum yielded similar results	-
Beluga sturgeon ( <i>Huso huso, SG</i> ) [108]	Skin	Yogurt	Increase water holding capacity	66 g/g
			Increase Hardness	475 N
			Increase cohesiveness	0.62 N
			Enhancement of rheological properties	-
			Enhancement of texture	-
Catfish [109]	Bone	Banana ( <i>Musa paradisiaca</i> <i>fa. Corniculata</i> )-based ice cream	Enhancement of overrun value	52.67%
			Enhancement of melting time	20.33 min
			Characteristics (taste, fragrance, texture, and colour) improvement	-
Mackerel ( <i>Scomberomorus commerson</i> ) [110]	Bone	Ice cream	Enhancement of overrun value	88.5%
			Enhancement of melting power	83%
			Enhancement of viscosity	99.1%
			Softness improvement	-
Fish [111]	Scales	Coffee creamers	Increase lightness	60.22
			Increase lubrication and emulsion content	-

therapeutics [124]. Dietary proteins and peptides can have both positive and negative impacts on the gut microbiota, with non-digestible forms raising disease concerns. Evaluating allergenicity, digestibility, tolerability, and potential adverse effects is crucial before commercializing products with marine peptides, including the assessment of allergenic potential [125, 126].

Protein hydrolysates can have a bitter taste, presenting challenges for the food industry. Various strategies have been used to mitigate or eliminate the bitterness, such as selective extraction, adsorption, enzymatic debittering, the Maillard reaction, the "plastein reaction," and encapsulation techniques [127]. Furthermore, peptides can be blended with food additives, sweeteners, and flavors to create a more

pleasant taste for consumers. The food industry can overcome the bitterness of protein hydrolysates by employing strategies like selective extraction, enzymatic debittering, and blending with additives [127]. However, peptide bioactivities can be affected by food processing and interactions with other ingredients, as thermal and non-thermal treatments, storage, and separation techniques can induce changes that impact the peptides [128].

Food processing can alter the amino acid composition and produce compounds like D-amino acids and biogenic amines with potential health risks. Incorporating peptides into high-fiber food matrices shows promise for reducing chemical interactions and bitterness, but further research is needed to identify optimal methods or matrices that preserve peptide bioactivity while preventing undesirable effects [128]. The effectiveness of bioactive peptides is currently limited, highlighting the need to prioritize concerns in producing peptides for treating chronic diseases. Advancing the field requires expanding human trials, obtaining approvals for disease reduction claims, and conducting further research to facilitate the development and utilization of valuable bioactive peptides and unlock their potential health benefits [129].

## Conclusion

Extensive research has highlighted the immense potential of fish processing by-products as a valuable source of bioactive peptides. This review has explored the promising prospects offered by these peptides, which can be derived from various fish by-products and applied across diverse fields. The extraction and purification of these peptides can be achieved through different methods, making them suitable as active ingredients in food applications. Safety and bioavailability considerations have been addressed to enhance the understanding of their potential. Despite their significant potential, the application of fish bioactive peptides in final products remains limited. Further research is needed to better understand their behavior, untapped potential, and consumer acceptance.

Utilizing fish by-products to produce bioactive peptides presents promising opportunities for sustainable development and economic benefits. This approach promotes sustainable resource utilization, minimizes waste, and offers economic advantages. Continued research and innovation in this field will contribute to unlocking the full potential of fish-derived bioactive peptides and their integration into a wide range of products and applications.

**Abbreviations** PEF: Pulsed electric field; HHP: High hydrostatic pressure; COD: Chemical oxygen demand; UF: Ultrafiltration; MF: Microfiltration; UF: Ultrafiltration; NF: Nanofiltration; RO: Reverse osmosis; MWCO: Molecular weight cut-off; Da: Daltons; MW: Molecular weight; TMP: Transmembrane pressure; MO: Microorganism;

PES: Polyethersulfone; m-PES: Modified polyethersulfone; PS: Polysulfone; EMR: Enzymatic membrane reactor; RACP: Random amphiphilic copolymer; EH: Enzymatic hydrolysis; E/S: Enzyme-to-substrate; PUFAs: Polyunsaturated fatty acids; UAE: Ultrasonic-assisted extraction; FPI: Functional protein ingredients; Phe: Phenylalanine; Leu: Leucine; Trp: Tryptophan

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**Data Availability** The provision of data will be facilitated once a formal request is received.

## Declarations

**Competing Interests** The authors declare no competing interests.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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