Food Science of Animal Products

Review Article

Research progress on active peptides in marine fish

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Abstract: With the deepening research on marine resources, active peptides from marine fish have gradually become a hot spot. This review based on the background of the important value and broad application prospect of active peptides in marine fish. Various preparation methods for active peptides from marine fish, such as enzymolysis, extraction, microbial fermentation, and enzymatic hydrolysis, are described in detail. The antioxidant, antibacterial, anti-blood pressure, immunomodulatory, anti-skin photoaging, and anti-fatigue functions and the corresponding mechanisms of action of the active peptides of marine fishes are discussed in depth. The active peptides of marine fish are further proposed to strengthen the in-depth investigation of the mechanism of action and optimise the preparation process in future research, as well as the application in functional food. It is hoped that more ideas can be provided for the safe, effective and compliant application of marine fish active peptides in promoting human health food.

Keywords: marine fish; active peptides; preparation; functions and mechanisms

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1 Introduction

Bioactive peptides are specific peptide sequences found in dietary proteins, which provide important support for the body health and work as molecular polymers between amino acids and proteins, generally consisting of 2–50 amino acids, with a molecular weight of less than 6 000 Da[1], and oligopeptides with a molecular weight of less than 1 000 Da have been widely used in functional foods. Most of the active peptides are present in an inactive state in dietary proteins and are released when hydrolyzed by appropriate enzymes, thus exerting different physiological regulatory functions[2]. Numerous studies have demonstrated the significant and abundant nutritional value and health functions of active peptides derived from animal sources, particularly the various active peptides extracted from marine organisms that are known as anti-fatigue peptides, immune-active peptides, and anti-skin photoaging active peptides, which play a vital role in supporting the health effects[3].

This paper focuses on a review of marine fish active peptides, i.e., peptides with specific biological activities extracted from marine fish or prepared by specific methods. The wide range of physiological effects of marine fish active peptides is specifically characterized by their significant antioxidant effects, which can effectively scavenge free radicals in the body and reduce the damage to cells and tissues caused by oxidative stress, which is of great significance for the maintenance of normal physiological functions of the organism and the slowing down of aging[4]. Besides, antimicrobial activity is also one of outstanding features of marine fish active peptides, some of them can inhibit the growth and reproduction of a variety of pathogenic bacteria, providing new ideas and ways to fight bacterial infections[5]. Additionally, the active peptide of marine fish also has the function of immunomodulation, which can stimulate the response of the immune system, enhance the activity and function of immune cells, improve the resistance of the body, and have the potential value for the prevention and treatment of immune-related diseases[6]. At the same time, the active peptides also play a positive role in cardiovascular health, such as lowering blood pressure, regulating blood lipids, and other functions, which helps to prevent the occurrence of cardiovascular disease[7]. Research on anti-fatigue and anti-skin photoaging has also made some progress.

The oceans cover more than 70% of the Earth's surface area, and marine fish are a major component of it[8]. It is of great value for the comprehensive investigation of active peptides in marine fishes. The perspective of scientific research provides an important opportunity to have a deeply understand of the structure-function relationship of bioactive substances. The discovery of how the distinct chemical structure of marine fish active peptides confers on them particular biological activities serves as a catalyst for the advancement of biochemistry, molecular biology, and related sciences. In the food field, marine fish active peptides can be used as an important component of functional foods to develop foods with health care functions to meet the demand of consumers for healthy diets. In the pharmaceutical field, its potential therapeutic effects provide new directions and possibilities for the development of new drugs and are expected to bring innovative breakthroughs in the treatment of many diseases. In the realm of cosmetics, products with anti-aging and skin care effects can be developed to improve people's lives by leveraging its antioxidant and other qualities. Therefore, this paper summarizes the research progress of marine fish active peptides in detail, including the source and preparation method of marine fish active peptides, the physiological activity and

mechanism of action of marine fish active peptides are reviewed in detail. It is also proposed that the active peptides of marine fish should strengthen the in-depth investigation of the mechanism of action and optimize the preparation process in the future research, as well as the application in the field of functional foods. It is hoped that more ideas can be provided for the safe, effective, and compliant application of marine fish active peptides in the promotion of human health food.

2 Preparation of active peptides from marine fish sources

Marine fish sources have a wide variety of active peptides, including antioxidant peptides, antimicrobial peptides, inhibitory peptides, and anticancer peptides[4]. The preparation methods for these active peptides mainly involve extraction, isolation, and purification steps[9]. At present, the extraction methods of active peptides from marine fish include physical extraction, microbial fermentation, and enzymatic hydrolysis, among which enzymatic hydrolysis is the most commonly used, and physical extraction methods mainly include solvent extraction, ultrasound-assisted extraction and supercritical fluid extraction. Commonly used separation techniques are mainly based on membrane separation, including microfiltration, ultrafiltration, nanofiltration and affinity membrane filtration, and active peptide separation can be carried out by electrophoresis. The purification of the active peptides is mainly carried out by high-performance liquid chromatography (HPLC), ion-exchange column chromatography, gel column chromatography, reversed-phase (RP)-HPLC, and high-speed counter-current chromatography. Table 1 summarizes the preparation methods of active peptides from marine fish.

3 Biological activity and mechanism of action of active peptides from marine fishes

The physiological activities of marine fish bioactive peptides are mainly related to several physiological functions such as antioxidant, antibacterial, antihypertensive, immunomodulation, anti-skin photoaging, anti-fatigue, and so on. The application and mechanism of action of marine fish active peptides in these types of functions are discussed in detail below. Figure 1 shows the main physiological activities and mechanisms of action of marine fish active peptides.

3.1 Antioxidant peptides

Reactive oxygen is one of the main products of the body's metabolism, of which free radicals account for the main part, which includes hydroxyl radicals (·OH), superoxide anion (O_2^-·) and alkyl peroxyl radicals (ROO·) and other substances[11]. Currently, the generation and scavenging of free radicals is a hotspot of research, which plays an important role in physiological and biochemical reactions, and can be used as cell growth factors and regulators, but it is very unstable *in vivo*, and can also cause some damage to cells and tissues under specific conditions[14]. Normally, free radicals reach a relative balance with antioxidants in the body, and they interact with each other to maintain healthy life[16]. However, when subjected to internal and external environmental stresses such as ultraviolet light, ionizing radiation, high concentrations of glucose, excess free radicals, and antioxidant deprivation, can make the body's antioxidant defenses insufficient to resist such changes, leading to a disruption of the homeostasis of the body and inducing oxidative stress, which in turn may lead to lipid oxidation and many health disorders such as neurological dysfunction, hypertension, cardiovascular disease, diabetes mellitus, cancer, and autoimmune diseases[18]. Therefore, supplementing a certain dose of antioxidants can prevent and timely scavenge excessive free radicals, which plays an important role in maintaining the health of the organism.

Antioxidants are mainly categorized into natural antioxidants and organic synthetic antioxidants. Synthetic antioxidants show good antioxidant function but have certain potential toxicity, so more attention and research have been paid to safe and effective natural antioxidants. More and more antioxidant peptides have been unearthed in marine fish, which are generally composed of 2–20 amino acid residues, and these amino acid residues can effectively play an antioxidant role by utilizing their structure[23]. Studies have shown that active peptides from marine fishes exert antioxidant effects mainly through scavenging free radicals and chelating pro-oxidative transition metals[24]. On the one hand, the amino acid residues carried can provide hydrogen, using their

Table 1 Preparation of active peptides from marine fishes.

Raw materials	Peptide type	Extraction methods and parameters	Separation methods and parameters	Purification methods and parameters	Reference
Sturgeon	Anti-inflammatory peptide	10% Substrate: pepsin = 1:100 (*m*/*m*), pH 2.0, 37 °C water bath for 6 h	Ultrafiltration: 3 kDa cut-off membrane	Ion exchange chromatography: SP-650M cation exchange column, buffer A (20 mmol/L sodium acetate buffer, pH 4.8), buffer B (0.5 mol/L NaCl in Buffer A); Gel column chromatography: SP-120-50-ODS column, elution A (0.05% (*V*/*V*) TFA solution), elution B (acetonitrile with 0.05% (*V*/*V*) TFA)	[10]
Pseudosciaena crocea	Antioxidant peptide	Papain/substrate 1%, 50 °C, pH 7.0, 4 h Alkaline enzyme/substrate 2%, 50 °C, pH 9.5, 4 h	Ultrafiltration: 3 and 10 kDa membranes	Ion exchange chromatography: DEAE-52 cellulose column, mobile phase: NaCl solution; Gel column chromatography: Sephadex G-15 column, mobile phase: ultrapure water; HPLC: C_{18} column, eluent: acetonitrile (0.05% (*V*/*V*) TFA)	[11]
Indian major carps, *Catla catlaJohnius* sp. nov.	Inhibitory peptide	Protease (10.5; 60 °C), South Asian pangolin protease (8.5; 60 °C), enzyme/substrate was 10 U/mg for 30 min	Ultrafiltration: 5–10 kDa membrane	Ultra-high performance liquid chromatography system	[12]

Table 1 (*Continued*)

Raw materials	Peptide type	Extraction methods and parameters	Separation methods and parameters	Purification methods and parameters	Reference
Skipjack tuna roes	Inhibitory peptide	Alkaline enzyme (55 °C, pH 8.5), neutral enzyme (55 °C, pH 7.0), flavour enzyme (50 °C, pH 7.0), papain (55 °C, pH 7.0), pepsin (37.5 °C, pH 2.0), and trypsin (37.5 °C, pH 7.8), at enzyme dosage rates of 2% (*m*/*m*), were administered for 90, 120, 150, 180, 210, 240, or 270 min	Ultrafiltration: 1.0–5.0 kDa cut-off membrane	Ion exchange chromatography: DEAE-52 cellulose column, mobile phase: NaCl solution; Sephadex G-25 column, mobile phase: ultrapure water; Zorbax 300SB-C_{18} column; eluent: acetonitrile (10%–50%)	[13]
Miiuy croaker (*M. miiuy*)	Antioxidant peptide	1% Enzyme dose: pepsin 2 h, pH 7.0 trypsin 2 h	Ultrafiltration: 1, 5, 10 kDa ultrafiltration membranes	Gel chromatography: Sephadex G-25 column; Ion exchange chromatography: Zorbax 300SB-C_{18} column, 25%–50% acetonitrile, 50%–100% acetic acid	[14]
Piaractus brachypomus	Antioxidant peptide	Biofermentation: *Bacillus* medium (30% RBPFM and 2% sucrose)	Ultrafiltration: 3 kDa MWCO membrane 0.25 mmol/L	Gel chromatography: Sephadex G-25 gel filtration column; HPLC: C_{18} column, eluent: 0.1% (*V*/*V*) acetonitrile solution	[15]
Thunnus albacares	Antioxidant peptide	Enzymatic: papain, E/S 0.98%, 240 min, pH 6.5	Centrifugal filters: 3–100 kDa	HPLC: C_{18} column, mobile phase is phosphate and borate buffer (pH 8.2)	[16]
Engraulis japonicus	Antimicrobial peptide	Enzymatic: papain, substrate concentration 5%, 5 h	Microfiltration: 0.22 μm membrane filter; Ultrafiltration: 10 kDa	Solid phase extraction chromatography: SPE column, buffer A is methanol, buffer B is 0.1% (*V*/*V*) TFA solution, buffer C is an 80% (*V*/*V*) acetonitrile solution of 0.1% (*V*/*V*) TFA solution	[17]
Lophius litulon	Antioxidant peptide	Enzymatic method: papain production 65 °C, pH 7.5, enzyme dosage 2.5%, time 5 h	Membrane separation technology: cut-off membrane fractionation of MSBH with 1, 3.5 and 10 kDa, respectively	Gel chromatography: Sephadex G-15 column, mobile phase: ultrapure water; HPLC system: Zorbax SB C_{18} column, elution solution: 0.1% (*V*/*V*) acetonitrile solution	[18]
Katsuwonus pelamis	Inhibitory peptide	Enzymatic method: neutral enzyme, 50 °C, enzyme dose 1.6%, pH 6.7	Membrane separation technology: MWCO membranes (10, 5 and 3.5 kDa)	Gel permeation chromatography: Sephadex G-25 column, mobile phase: ultrapure water; RP-HPLC: Zorbax 300SB-C_{18} column, eluent: 0.06% (*V*/*V*) TFA and acetonitrile solution	[19]
Clarias gariepinus, Burchell, 1822	Antimicrobial peptide	Extraction: 10% (*V*/*V*) acetic acid, 95 °C, water bath for 5 min	Ultrafiltration: 5 kDa MWCO membrane	Solid phase extraction chromatography: SPE C_{18} column, 30%–70% (*V*/*V*) acetonitrile solution	[20]
Clarias batrachus	Antimicrobial peptide	Extraction method: Tris buffer (pH 7.2), 16 000 r/min for 40 min	Membrane technology: 0.22 μm filter	RP-HPLC: C_{18} column, elution solution: 0.1% (*V*/*V*) TFA solution, acetonitrile solution	[21]
Scomber scombrus	Immol/lunomodulatory peptide	Enzymatic: Protamex® (Novozymes, Bagsvaerd, Denmark), enzyme: substrate ratio 1:1 000 (120 min, 45 °C), pH 8	Membrane separation technologies: microfiltration (0.3 μm), ultrafiltration spiral wound (10 000 Da) and nanofiltration (200 Da) membranes	Chromatographic solid phase extraction techniques: 0.07% (*V*/*V*) TFA solution, 10%–70% (*V*/*V*) acetonitrile solution	[22]
Salmon	Antioxidant peptide	Enzymatic method: trypsin from porcine pancreas, pH 8.5, 50 °C, 5 h	/	HPLC: Sephadex G-35 column, Macro-prep high Q column, eluent: 3% (*V*/*V*) acetonitrile solution, NaCl (0–0.35 mol/L) solution	[23]
Dasyatis akajei	Antioxidant peptide	Enzymatic: trypsin, pH 8.0, 40 °C, total enzyme dose of 2.5% for 4 h	Ultrafiltration: 3 and 10 kDa ultrafiltration membranes	Anion exchange chromatography: DEAE-52 cellulose column, mobile phase: NaCl solution; Gel filtration chromatography: Sephadex G-15 column, elution solution: DW solution; HPLC: Thermo C_{18} column, elution solution: 0%–40% acetonitrile solution	[24]
Tetrapturus angustirostris Kajikia audax	/	Enzyme mixture of collagenase and protease (7.2:2.8, *m*/*m*) Enzyme dose 6%, 32 °C, 6 h	Ultrafiltration (30 kDa)	RP-HPLC system: TSKgel ODS-80TM column, eluent: 70% (*V*/*V*) acetonitrile; Milli-Q aqueous mobile phase A with 0.1% (*V*/*V*) TFA; mobile phase B with acetonitrile containing 0.1% (*V*/*V*) TFA; Electrophoresis: sodium dodecyl sulfate-polyacrylamide gel electrophoresis	[25]

Note: / Represents not mentioned; MWCO, molecular weight cut-off; TFA, trifluoroacetic acid; MSBH, protein hydrolysate of monkfish swim bladders; RBPFM, red-bellied pacu fish meat.

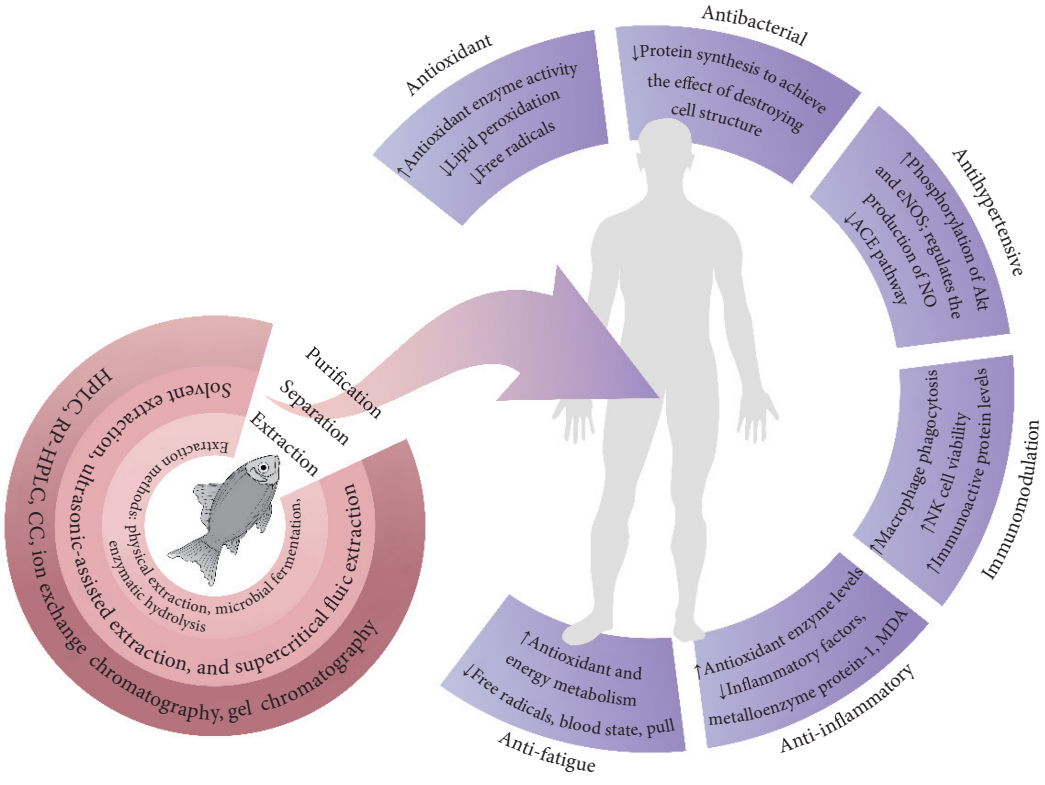

Figure 1 Main physiological activities and mechanisms of action of active peptides from marine fishes. CC, countercurrent chromatography; Akt, protein kinase B; eNOS, endothelial nitric oxide synthase; ACE, angiotensin converting enzyme; NK, natural killer; MDA, malondialdehyde.

unpaired electrons to form a stable molecular structure with free radicals to achieve the effect of scavenging free radicals. On the other hand, it can activate the antioxidant enzymes in the cell, and ultimately reduce oxidative stress, maintain the balance of the body's oxidative system and the antioxidant defense system, and play a good antioxidant activity[25]. In addition, these amino acid residues can form a cyclic stabilizing structure with pro-oxidant transition metals, such as Fe^{2+}, through coordination, to retard lipid peroxidation[26]. The current research on the antioxidant mechanism of active peptides in marine fish is mainly evaluated by the scavenging ability of free radicals and the chelating ability of Fe^{2+}, in which the scavenging ability of free radicals is mainly determined by free radical scavenging experiments, such as ·OH and O_2^-·.

It has been shown that antioxidant-active peptides extracted and identified from marine fishes have more significant antioxidant activities[23–24]. Two *Piaractus brachypomus* peptides exhibited significant antioxidant activity by free radical scavenging related experiments[16]. The antioxidant activities of 18 active peptides in *Lophius litulon* were determined by ultrafiltration and chromatographic techniques, and the results showed that all 18 active peptides possessed certain antioxidant activities, and it was found that YDYD, QDYD, GRW, ARW, DDGGK, and YPAGP among them possessed higher antioxidant activities[18]. Studies on the antioxidant activity of active peptides in *Katsuwonus pelamis* revealed that the antioxidant active peptides in *K. pelamis* have significant antioxidant effects, which can delay lipid peroxidation and scavenge excessive free radicals[26].

In summary, the active peptides from marine fish sources mainly exert antioxidant effects by scavenging free radicals and activating the activity of antioxidant enzymes, and the peptides can delay lipid peroxidation and enhance the chelating ability of metal ions. Different antioxidant active peptides maintain the balance between the oxidative system and antioxidant defense system of the body through direct or indirect effects. The current research on the various mechanisms of action of different antioxidant peptides in marine fishes is listed in Table 2.

3.2 Antibacterial peptides

In the last decades, many antimicrobial peptides have been identified in organisms, among which a variety of antimicrobial peptides expressed and secreted by fish have strong antimicrobial activity. This class of active peptides has a maximum amino acid number of only 50 amino acid residues, which are non-toxic to the host, can target pathogen structures, play a role in molecular host defence, exhibit their significant antimicrobial activity, and have a low risk of developing drug resistancex[27]. Many studies have been conducted on the mechanism of action of antimicrobial peptides, which are mainly categorized into specific and non-specific mechanisms of action[28]. The specificity is mainly reflected in the fact that antimicrobial peptides can be translocated in the cytoplasm of the cell by utilizing their secondary structure and charge, and inhibit the protein synthesis process by targeting the cell wall and the cell membrane, leading to cell death[28]. Non-specificity is mainly reflected in the fact that antimicrobial peptides not only have a single mode of action, but also maintain the internal homeostasis of the body by responding to the external environment within cells[28–29].

Bacteria, as one of the most numerous groups of organisms, are mainly categorized into Gram-negative and Gram-positive bacteria, some of which can cause adverse effects on the human body, and most of the current research investigates the antimicrobial mechanism of antimicrobial peptides by testing the inhibitory effect

Table 2 Mechanisms of antioxidant action of active peptides from marine fishes.

Subject source	Acquisition method	Model	Dosage	Time	Antioxidant mechanism	Reference
Croceine croaker	Enzymatic digestion + ultrafiltration and chromatography	*In vitro*: lipid peroxidation inhibition assay and DPPH/hydroxyl/superoxide/ABTS cation radical scavenging assays	5.0 mg/mL	7 d	Peptide PC-1 showed higher DPPH radical scavenging activity and exhibited more effective inhibition of linoleic acid peroxidation	[2]
Piaractus brachypomus	Enzymatic digestion + ultrafiltration and chromatography	*In vitro*: DPPH radical, ABTS cation radical, ferric-reducing antioxidant power, Fe^{2+}-chelating activity	/	4.5 h	These 2 peptides (m_w < 3 kDa) showed significantly higher antioxidant activities	[6]
Lophius litulon	Enzymatic digestion + ultrafiltration and chromatography	*In vitro*: DPPH radical, ·OH, O_2^-·, ASBTS cation radical-lipid peroxidation inhibition assay	/	18 h	YDYD, QDYD, and YPAGP exhibited strong scavenging of ABTS cation radicals. YDYD, ARW, and DDGGK exhibited significant lipid peroxidation inhibition and ferric oxide reduction antioxidant properties. YDYD, QDYD, GRW, ARW, DDGGK, and YPAGP were highly antioxidant	[9]
Salmon protamine	Enzymatic digestion + ultrafiltration and chromatography	*In vitro*: DPPH radical, ·OH, O_2^-·	1 mg/mL	2 h	The peptide has strong antioxidant activity against hydroxyl, DPPH and superoxide anion radicals	[14]
Dasyatis akajei	Enzymatic digestion + ultrafiltration and chromatography	*In vitro*: DPPH radical, ·OH, O_2^-·, ABTS cation radical-lipid peroxidation inhibition assay	/	/	IEPH had the strongest reducing power and lipid peroxidation inhibitory activity, whereas LEEEE had the strongest Fe^{2+}-chelating ability	[15]
Katsuwonus pelamis	Hydrolysis + ultrafiltration and chromatography	*In vitro*: DPPH radical, ·OH, O_2^-· lipid peroxidation inhibition assay	/	/	MDLFTE, WPPD, and EMGPA exhibited high free radical scavenging, reducing power, and lipid peroxidation inhibition	[17]

Note: / Represents not mentioned; m_w, molecular weight; ABTS, 2,2′-azinobis-(3-ethylbenzthiazoline-6-sulphonate); DPPH, 1,1-diphenyl-2-picryl-hydrazyl.

on these bacteria[30]. Li et al.[27] extracted a novel antimicrobial peptide from the muscle of catfish bridle by extraction and chromatographic techniques and found that it had a strong antibacterial impact. Bridle et al.[31] studied the activity of antimicrobial peptides from trout and found a significant inhibition against *Escherichia coli*, *Photobacterium*, and *Vibrio anguillarum*, including 6 Gram-negative and Gram-positive bacteria showed significant bacteriostatic effects. The antimicrobial peptide from *Thunnini* was studied and found to have a more significant antimicrobial effect against Gram-positive bacteria, especially *Staphylococcus aureus*[30]. In addition, it was found that 2 antimicrobial peptides from salmonids, although they did not show significant antimicrobial activity against *Vibrio vulnificus*, were found to have very significant bacteriostatic effects against *Salmonella typhimurium* and *S. aureus*[32].

In summary, the purified antimicrobial peptides extracted from marine fishes mainly inhibit protein synthesis to achieve the effect of destroying the cell structure, thus exerting their antimicrobial effects. The types of organisms and mechanisms targeted by different antimicrobial peptides are significantly different, and in general, they mainly work through specific and non-specific mechanisms. Table 3 summarizes the antibacterial mechanisms of antimicrobial peptides from different marine fish.

3.3 Antihypertensive peptides

Blood pressure is the force that pushes against the walls of blood vessels (arteries) produced by the heart when it pumps blood; the higher the pressure, the harder the heart pumps. Hypertension, which is high blood vessel pressure (140/90 mm Hg or higher), is a serious disease and the leading cause of premature death worldwide, accounting for 20% of deaths worldwide[33]. It is estimated that 31.1% of adults (1.39 billion people) worldwide had hypertension in 2010, and the prevalence of adult hypertension was higher in low- and middle-income countries (31.5%, 1.04 billion people) than in high-income countries (28.5%, 349 million people)[34]. The pathogenesis of hypertension is complex, and existing studies suggest that it is mainly related to inflammatory responses, oxidative stress, impaired endothelial function, vascular remodelling, renin-angiotensinogen-aldosterone system (RAAS), sympathetic nervous system, immune system[35], especially RAAS, which is the main direction of the research on blood pressure-lowering active peptides nowadays.

RAAS is a network system in the body that regulates cardiovascular and renal function, in which renin is secreted from paraglomerular cells in the kidney, and angiotensinogen secreted by the liver under the action of renin generates inactive angiotensin I (AngI), which is catalyzed by angiotensin-converting enzyme (ACE) further to generate AngII[36], and binds to the type 1 receptor (AT1 receptor) receptor of the angiotensin receptor in a short period to induce an increase in blood pressure, which acts directly on the glomerular arterioles of the kidneys, leading to a decrease in urinary excretion and a consequent increase in plasma water and increasing blood pressure[37]. It also binds to the angiotensin type 2 receptor, which indirectly binds to aldosterone in the adrenal glands, leading to the reabsorption of sodium and water, at which point elevated plasma water induces an increase in blood pressure[38–39]. Therefore, ACE-inhibiting prilosec or sartans acting on AngII receptors are the main recommended drugs for blood pressure lowering. Similarly, 2 ACE inhibitory peptides, C111 and C112, were identified in bonito intestinal autolysate peptides, which were further found to significantly lower blood pressure in hypertensive rats after gavage of bonito intestinal autolysate peptides to spontaneously hypertensive rats, and to significantly inhibited the blood pressure-raising effect of intravenous AngI[40]. Similarly, an active peptide obtained from Atlantic mackerel (*Scomber scombrus*) using solid-phase extraction showed significant anti-ACE activity, and the hypotensive activity of this active peptide may be attributed to the role of its leucine at the terminal end (C- or N-terminal) and/or leucine-rich motifs depositing[41]. Three peptides obtained from olive flounder (*Paralichthys olivaceus*) surimi showed high ACE inhibitory activity, significantly increased phosphorylation of protein kinase B (Akt) and endothelial nitric oxide synthase (eNOS), and significantly promoted production of NO in human umbilical vein endothelial cells. The peptides significantly increased the Akt and eNOS, and significantly promoted the production of NO in human umbilical vein

Table 3 Antibacterial mechanisms studies of active peptides from marine fishes.

Subject source	Acquisition method	Model	Dosage	Time	Antimicrobial mechanism	Reference
The epidermal mucus of catfish	SPT + RP-HPLC	Agar diffusion method: *S. putrefaciens* and *S. aureus* MIC: CF-14 against *S. putrefaciens* was determined using the microdilution method	1 mg/mL	/	The bacteriostatic properties of the test drug or material are determined based on the size of the inhibitory circle; the peptide has significant bacteriostatic activity	[27]
Rockfish (*Sebastiscus marmoratus*)	HPLC	*In vitro:* antimicrobial activity and rapid time-killing kinetic	/	/	Significant inhibitory effects were observed against most of the tested microorganisms. In particular, the synthetic peptides of liver-expressed antimicrobial peptide 2 and moronecidin exerted broad-spectrum antimicrobial activity against important aquatic pathogens *in vitro* by directly disrupting microbial membranes	[28]
Yellowfin tuna (*Thunnus albacares*)	SPT	*In vitro:* antimicrobial activity (*Escherichia coli* (ATCC 25 922) and *S. aureus* (NCTC 6 571))	7.0 mg/mL	4 h	The peptide showed high antimicrobial efficacy and low MIC against a wide range of Gram-positive bacteria, i.e., higher antimicrobial activity against *S. aureus*	[30]
Antarctic fish		*In vitro:* 3 Gram-negative strains *(E. coli*, *S. typhimurium* and *V. cholerae*) and 3 Gram-positive strains (*S. aureus*, *Bacillus subtilis* and *Enterococcus faecalis*)	1×10^5 CFU/mL	36–42 h	LEAP with 4 cysteines shows potent antimicrobial activity against Gram-positive and Gram-negative bacteria	[31]
Red drum	HPLC	*In vitro*: macrophage bactericidal activity	/	/	Active against Gram-positive bacteria *Micrococcus luteus* and *S. aureus*	[32]

Note: / Represents not mentioned; SPT, solid-phase technique; MIC, minimal inhibitory concentration.

endothelial cells. With the help of animal experiments, it was determined that the peptides were able to lower the blood pressure of spontaneously hypertensive rats and that the mechanism of the blood pressure lowering may be through the Akt/eNOS pathway[42]. In addition, elastin peptides obtained from skipjack tuna have been found to promote phenylephrine action in hypertensive rats to levels close to normal blood pressure, and the main mechanism may be that skipjack tuna elastin peptides prevent hypertension-associated vascular dysfunction through the eNOS signalling pathway, and this beneficial effect most likely relies on the proline in skipjack tuna elastin[43].

In summary, in the study of blood pressure lowering by active peptides from marine fish, it was found that these active peptides can mainly inhibit the ACE pathway, increase the phosphorylation of Akt and eNOS, and regulate the production of NO to play the efficacy of blood pressure lowering. Table 4 shows the mechanism of action of marine fish active peptides in lowering blood pressure.

3.4 Immunizing peptides

Immunity is a physiological function in which the body recognizes and excludes antigenic foreign bodies to maintain its physiological balance and the stability of the internal environment[44]. The immune system consists of immune organs, immune cells, and immune molecules that work in concert to defend against pathogens and prevent the development of disease[45–46]. The immune response is mainly divided into intrinsic immunity (the body's innate rapid defense mechanism), and adaptive immunity (a more targeted immune response generated through specific antigen recognition)[47–48].

Macrophages are the body's "scavengers" and important innate immune cells, which are capable of engulfing and killing germs[49]. The study showed that peptides HIAEEADRK and AEQAESDKK from the trypsin hydrolysate of tuna proteins exhibited significant immunomodulatory effects on RAW264.7 (mouse monocyte macrophage leukemia cells), which were able to significantly increase its phagocytosis capacity, promote the release of NO and the secretion of cytokines interleukin 1β (IL-1β), IL-6 and tumor necrosis factor α (TNF-α) secretion, and the mechanism of its immune-enhancing effect may be through the activation of the nuclear factor κB (NF-κB) signaling pathway, while promoting the immune response of RAW264.7 cells[50]. Natural killer (NK) cells are a type of white blood cell and the core cells of the immune cells, capable of destroying cells that have been infected by viruses[51]. Monkfish protein hydrolysate (MPH) prepared using papain (enzyme concentration 829.51 U/g), pH 7.37, enzyme digestion time 5.86 h, enzyme digestion temperature 47.09 °C, liquid-solid ratio 5.79:1 (*m*/*V*) significantly enhanced the proliferation of mouse splenic lymphocytes and the activity of NK cells[52]. Further, the low molecular peptide extracted from monkfish (*Lophius litulon*) roe also showed good immunomodulatory effects on cyclophosphamide-induced immunosuppressed mice and its mechanism of action was mainly related to the enhancement of immune organ indices of mice, the increase of serum levels of IL-6, IL-1β, TNF-α, immunoglobulins (Ig) A, IgM and IgG levels in serum, increasing antioxidant activity in immunocompromised mice, and activating NF-κB and mitogen-activated protein kinase (MAPK) pathways in splenic tissues[53].

Table 4 Antihypertensive pressure mechanisms studies with active peptides from marine fishes.

Subject source	Acquisition method	Model	Dosage	Time	Mechanisms for lowering blood pressure	Reference
Bonito bowels	Ultrafiltration + reversed-phase chromatography and vacuum concentration and purification	*In vivo*: SHR	1–3 g/kg	30–180 min	Identification showed that it was an ACE inhibitory peptide, which significantly inhibited AngI	[40]
Atlantic mackerel	Enzymatic digestion + SPE	*In vitro*: ACE inhibition	/	/	The peptide has good ACE inhibitory activity	[41]
Olive flounder surimi	Enzymolysis	*In vitro*: ACE inhibition	/	/	This peptide significantly increased the phosphorylation of Akt and eNOS, significantly promoted NO production in human umbilical vein endothelial cells, and reduced blood pressure in SHR by a mechanism that may be exerted through the Akt/eNOS pathway	[42]
		In vivo: SHR	50 mg/kg	3–9 h		
Bulbus arteriosus of bonitos	Enzymolysis	*In vivo*: SHR/Izm	1 g/kg	5 weeks	Prevention of hypertension-associated vascular dysfunction through the eNOS signalling pathway	[43]

Note: / Represents not mentioned; SHR, spontaneously hypertensive rats; SPE, solid-phase extraction; Akt, protein kinase B; eNOS, endothelial nitric oxide synthase.

In summary, the immunity-enhancing effects of marine fish active peptides are mainly related to improving the phagocytosis of macrophages, promoting their release of cytokines such as IL-6, IL-1β, TNF-α, and other cytokines to play an indirect immunomodulatory role, and also related to improving the activity of NK cells and immune organs and increasing the level of immunoreactive proteins. Table 5 shows the mechanism of action of active peptide immunomodulation in marine fish.

3.5 Anti-skin photoaging peptides

Skin is the largest organ of the human body, exists on the surface of the body, protects the organism from the attack of harmful substances in the external environment. However, because it has been exposed to the external environment, it is easy to suffer from sunlight radiation, air pollution, germs, etc., skin photoaging is a skin ageing phenomenon caused by a certain dose of ultraviolet (UV) radiation, especially the UVA (320–400 nm) and UVB (290–320 nm) play an important role in the process of photoaging, which is mainly characterized by a decrease in skin elasticity, increase in wrinkles, pigmentation, laxity and sagging[54]. Studies have shown that UV light induces acute inflammation and oxidative stress in the skin, contributing to a significant up-regulation of inflammatory factors or peroxides such as transforming IL-1α, IL-1β, IL-6, transforming growth factor β1 (TGF-β1), malondialdehyde (MDA), cyclooxygenase 2 (COX-2) and a decrease in the levels of antioxidant enzymes, such as glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT)[55–59]. Destructive substance that induces elevated levels of matrix metalloproteinases (MMPs) in skin fibroblasts, leading to decreased skin elasticity and collagen synthesis, resulting in photo-aging of the skin[60–62]. Marine fish active peptides have been shown to have a significant effect in the fight against photoaging of the skin[62].

The bioavailability of orally administered collagen or hydrolysates is closely related to the molecular weight of collagen, and hydrolysates or collagen of marine origin usually have a low molecular weight, which is very favorable for absorption by the body[63–64].

Through animal experiments and combined with network pharmacology and other studies, it was found that 2 kinds of collagen hydrolysates (collagen hydrolysates with a higher content,

Table 5 Immunomodulation mechanisms studies with active peptides from marine fish.

Subject source	Acquisition method	Model	Dosage	Time	Immunomodulatory mechanisms	Reference
Yellowfin tuna (*Thunnus albacares*)	Enzymatic digestion + ultrafiltration	*In vitro*: mouse macrophage cell line RAW264.7	0–200 μg/mL	24 h	T1 could enhance the phagocytosis of RAW264.7 cells, promote the secretion of NO, interleukin (IL)-1β, IL-6, and TNF-α; significantly accelerate the expression of TLR2 and TLR4, promote the phosphorylation of IKK and p65, further activate the NF-κB signaling pathway, and promote the immune response of RAW264.7 cells	[50]
Monkfish (*Lophius litulon*)	Enzymolysis	*In vivo*: Kunming mice	333, 667, 1 000 mg/kg bw	4 weeks	MPH significantly enhanced the proliferation of mouse splenic lymphocytes and NK cell activity	[52]
Monkfish (*Lophius litulon*) roe	Step-by-step enzymatic hydrolysis	*In vivo*: ICR mice	80, 100 mg/(kg bw·d)	20 days	MRP significantly increased body weight and immune organ index in mice, improved morphological changes in spleen and thymus; increased serum levels of IL-6, IL-1β, TNF-α, IgA, IgM, and IgG; and ameliorated cyclophosphamide-induced oxidative stress, and activated the NF-κB and MAPK pathways in splenic tissues	[53]

Note: / Represents not mentioned; MPH, monkfish protein hydrolysate; MRP, peptides from monkfish roe; TLR, toll-like receptors.

HCH; collagen hydrolysates with a lower content, LCH) and glycine-proline-hydroxyproline (Gly-Pro-Hyp) extracted from tilapia fish skin containing different Gly-Pro-Xaa tripeptide contents had better anti-skin photoaging effects, among which, both HCH and LCH increased the hyaluronic acid and collagen content, improve skin elasticity and epidermal thickness, reduce inflammation, and decrease MMP-1 and MMP-3 content, but the effect of HCH were more significant; meanwhile, the animals in the Gly-Pro-Hyp group showed comparable anti-photo-ageing activity to that of an equivalent amount of HCH, which suggested that Gly-Pro-Hyp might have strong anti-photo-aging activity. The network pharmacological analysis also suggested that *JUN*, *FOS*, IL-17, and TNF signaling pathways could be the potential targets and pathways of Gly-Pro-Hyp's anti-photoaging mechanism[65]. The anti-skin photoaging effects and differences between bigeye tuna (*Thunnus obesus*) skin collagen peptides (TSCP) and bone collagen peptides (TBCP) were further discussed in another study, whose cellular assay results showed that both TSCP and TBCP were effective in inhibiting reactive oxygen species after UVB-induced NIH/3T3 cell injury, reduce the mRNA and protein expression of MMP-1, and inhibit the decrease mRNA and protein expression of TGF-β1 and type I collagen; in the UVB-exposed ICR mouse model, both TSCP and TBCP effectively increased the levels of skin water content, Hyp content, and total antioxidant capacity, and ameliorated the skin photo-aging injury in mice. However, the mechanisms of action of TSCP and TBCP are not the same, in which TSCP shows better antioxidant activity and can inhibit the activation of p-p38 through the TGF-β1 signaling pathway and promote the expression of TGF-β to play the role of anti-skin photoaging, whereas the main mechanism of the anti-skin photoaging effect of TBCP is related to the down-regulation of the expression of phosphorylated-extracellular signal-regulated kinase (p-ERK), phosphorylated-c-Jun N-terminal kinases (p-JNK) and MMP-1 proteins. The main mechanism of TBCP's anti-photodamage effect is related to the down-regulation of p-ERK, p-JNK, and MMP-1[66]. In addition to *in vitro* and animal studies, marine fish active peptides have a successful application in clinical studies on anti-skin photoaging. Using a randomized double-blind method, 46 healthy women aged 45–59 years were divided into 2 groups, one of which consumed a placebo and the other consumed a commercially available hydrolyzed fish cartilage collagen peptide (which contains more than 65% collagen peptides, with ≥ 95% molecular weights below 3 000 Da, ≥ 25% chondroitin sulfate, and 9% minerals), the experiments lasted for a total of 90 days, and the final results found that the commercially available hydrolyzed fish cartilage collagen peptide contributed to micro-relief of the skin, improvement of dermal echogenicity and collagen structure, and significant reduction of wrinkles[67].

The aforementioned studies demonstrate the usefulness of marine fish active peptides in *ex vivo* and clinical experimental studies, where the use of marine fish skin is becoming increasingly prevalent. Marine fish active peptides primarily function to prevent photoaging of the skin by reducing the levels of inflammatory factors, metalloenzyme protein-1, MDA, and antioxidant enzymes. The mechanism of action of marine fish against skin photoaging is presented in Table 6.

3.6 Anti-fatigue peptides

In addition to antioxidant, antibacterial, anti-blood pressure, immunomodulatory, and anti-skin photoaging effects, active peptides from marine fish have also been found to have some research value in anti-fatigue.

The causes and symptoms of physical fatigue are complex and varied, and its pathogenesis involves multiple systems such as neurological, endocrine, and metabolic regulation. At present, the more popular mechanisms of fatigue theory: are energy exhaustion theory, blockage theory, free radicals theory, etc.[50,68]. The doctrine of energy depletion suggests that insufficient energy supply is one of the most important causes of reduced athletic performance and fatigue[69]; the blockage theory suggests that excessive metabolites such as blood lactate acid (BLA) and blood urea nitrogen (BUN)

Table 6 Anti-skin photoaging studies with marine fish active peptides.

Subject source	Acquisition method	Model	Dosage	Time	Anti-skin photoaging mechanism of action	Reference
Tilapia fish skin	Enzymolysis	*In vivo*: Kunming mice	31.36, 150 mg/kg bw	6 weeks	Both HCH and LCH increased hyaluronic acid and collagen content, improved skin elasticity and epidermal thickness, attenuated inflammation, and decreased matrix metalloproteinase-1 (MMP-1) and MMP-3 content in photodamaged skin of mice, but the effect of HCH was more pronounced. Animals in the Gly-Pro-Hyp group showed anti-photoaging activity comparable to that of equivalent amounts of HCH. Network pharmacological analyses further suggested that Gly-Pro-Hyp may interact with *JUN* and *FOS* to regulate IL-17 and TNF signaling pathways to exert anti-photoaging effects on the skin	[65]
Bigeye tuna (*Thunnus obesus*) skin and bone	Enzymatic digestion + ultrafiltration	*In vitro*: NIH/3T3 cells *In vivo*: ICR mice	Cellular assay: 0.1 mg/mL; animal assay: 200 mg/(kg·d)	Cell experiments: 24 h; animal experiments: 8 weeks	The main mechanism of TBCP's anti-skin photoaging effect is related to the strong down-regulation of p-ERK, p-JNK, and MMP-1 protein expression	[66]
Commercially available product	Enzymolysis	Healthy women aged 45–59 years	500 mg/d	90 days	Hydrolysed fish cartilage collagen peptides significantly reduced wrinkles and enhanced dermal echo enhancement; reflection confocal microscopy image analysis showed that hydrolysed fish cartilage collagen peptides improved skin collagen morphology and helped to inhibit elasticity reduction	[67]

Table 7 Other physiological function studies of active peptides in marine fishes.

Subject source	Acquisition method	Model	Dosage	Time	Anti-skin photoaging mechanism of action	Reference
Monkfish (*Lophius litulon*)	Enzymolysis	*In vivo*: Kunming mice	333, 667, 1 000 mg/kg bw	4 weeks	MPH prolonged the swimming time of mice, increased HG levels and SOD, GSH-Px, and CAT activities, and decreased BUN, BLA, MDA levels, and LDH activity	[52]
Croceine croaker (*P. crocea*)	Enzymolysis	*In vivo*: ICR mice	50, 100, 200 mg/kg bw	/	Significantly prolonged the swimming time of ICR mice; elevated muscle glucose and liver glycogen levels; lowered BUN, BLA, and MDA levels; enhanced lactate dehydrogenase activity, cleared excess BLA, and slowed down the development of fatigue; increased the activities of SOD, CAT, and GSH-Px, and attenuated reactive oxygen species injury in mice	[71]

Note: BUN, blood urea nitrogen; BLA, blood lactic acid; MDA, malonaldehyde; LDH, lactate dehydrogenase.

accumulate during exercise, leading to exercise fatigue[70]; the free radical theory suggests that antioxidants in the body, such as SOD and CAT, and other antioxidant enzymes, help to scavenge peroxides during fatigue, maintain the balance of the body's internal environment, and play an anti-fatigue role[68]. Monkfish protein hydrolysate (MPH) was found to be able to prolong the swimming time of animals, increase the level of hepatic glycogen and the activities of SOD, glutathione peroxidation (GSH-Px), and CAT, and reduce the levels of BUN, BLA, MDA and the activity of *D*-lactic dehydrogenase, effectively exerting an anti-fatigue effect[52]. SBP-III-3 extracted from croceine croaker (*P. crocea*) using an enzymatic method prolonged the swimming time of ICR mice by 57.9%–107.5% compared with that of the blank control group; induced an increase in muscle glucose and hepatic gluconeogenesis levels by 9.4%–115.2% and 35.7%–157.3%, respectively; significantly decreased BUN, BLA and MDA levels; and enhance the activity of lactate dehydrogenase to remove excess BLA and slow down the development of fatigue; it can also increase the activity of SOD, CAT, and GSH-Px, and alleviate the reactive oxygen species damage in mice, which indicates that the active peptide of the marine fish has a significant anti-fatigue effect[71].

In summary, the anti-fatigue effects of marine fish active peptides are mainly related to the improvement of antioxidant and free radical scavenging activities, the reduction of the accumulation of BUN, BLA, and other substances, and the enhancement of energy metabolism and other pathways to play an anti-fatigue role. Table 7 shows the anti-fatigue mechanism of marine fish active peptides.

4 Conclusion

This review discusses the research progress of active peptides from marine fish. In terms of preparation methods, various feasible technical means are elaborated in detail. The main physiological activities of marine fish active peptides are also reviewed in detail, and their antioxidant function can effectively fight against free radicals, mainly through scavenging free radicals and activating antioxidant enzyme activity to play an antioxidant role, and this class of peptides can delay lipid peroxidation and enhance the chelating ability of metal ions. Different antioxidant active peptides maintain the balance of the body's oxidative system and antioxidant defense system through direct or indirect action, to achieve the slowing down of body aging and cellular damage; antimicrobial peptides play an important role in the inhibition of the growth of harmful bacteria, which provides ideas for the research and development of new antimicrobial drugs; antihypertensive peptides can help to control the level of blood pressure, mainly by inhibiting the ACE pathway, increasing the phosphorylation of Akt and eNOS, and regulating the production of NO to play a significant role in lowering blood pressure. Antihypertensive peptides help to control blood pressure, mainly by inhibiting the ACE pathway, increasing the phosphorylation of Akt and eNOS, and regulating the production of NO to play the efficacy of lowering blood pressure, which is of great significance to cardiovascular health; Immunoactive peptides help to maintain the balance and stability of the immune system, improve phagocytosis of macrophages, and promote the release of cytokines such as IL-6, IL-1β, TNF-α and other cytokines to play an indirect immunomodulatory role, and also increase the activity of NK cells, immune organs, and increase the level of immunoactive proteins to enhance the body's defense ability; anti-skin photoaging active peptides can protect the skin from UV damage. Anti-fatigue peptides can protect the skin from ultraviolet damage, marine fish active peptides mainly through the reduction of inflammatory factors, metalloenzyme protein-1, MDA, elevate the level of antioxidant enzymes to play the role of skin anti-photo-aging to maintain the health and vitality of the skin; anti-fatigue peptide can help to improve the antioxidant and scavenging free radicals, reduce the accumulation of BUN, BLA, and other substances, and improve energy metabolism and so on, to play an anti-fatigue role.

Although marine fish active peptides are relatively safe, their safety with long-term use, as well as the potential toxicity and side effects may exist, need to be studied in depth. In future research, it is necessary to further optimize the preparation process such as enzymatic hydrolysis to achieve efficient and large-scale production of marine fish active peptides and reduce costs to meet market demand. At the same time, to make better use of marine fish active peptides, research on improving their bioavailability can be increased, such as peptide microcapsule and nanocapsule technology, to improve the bioavailability of marine fish active peptides *in vivo* and make them more effective. In terms of physiological activity, it is necessary to explore its exact targets and signaling pathways more deeply to better exert its efficacy. In addition, the synergistic effect of marine fish active peptides with other bioactive substances or drugs can be studied to develop more effective combinations or treatment options. Long-term and comprehensive evaluation of the safety of the compounding is also required to ensure the reliability of the application. In conclusion, marine fish active peptides have broad research prospects and application potential, which are worthy of continuous in-depth exploration.

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Conflict of interest

The author declares no conflict of interests.

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