Chinese Journal of Natural Medicines

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Citation: Xiangyu Cheng, Ziqi Tang, Zhongqi Li, Shuaijie Hu, Kehan Qin, Yindi Zhao, Baoming Hao, Qinghua Hu, Marine-derived products as pharmaceutical treasure troves: a focus on recent research techniques and potential bioactive activities of marine peptides, Chinese Journal of Natural Medicines, 2026, 24(5), 543-558. doi: 10.1016/S1875-5364(26)61178-8.

View online: https://doi.org/10.1016/S1875-5364(26)61178-8

Chinese Journal of Natural Medicines 24 (2026) 543-558

Contents lists available at ScienceDirect

Chinese Journal of Natural Medicines

journal homepage: www.cjnmcpu.com/

Review

Marine-derived products as pharmaceutical treasure troves: a focus on recent research techniques and potential bioactive activities of marine peptides

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ARTICLE INFO

Article history:
Received 21 October 2025
Revised 11 December 2025
Accepted 24 December 2025
Available online 20 May 2026

Keywords:
Marine peptides
Extraction technology
Separation and purification
Biological activities
Bioinformatics

ABSTRACT

With the intensified exploration of marine resources, marine bioactive peptides have become one of the research focuses in biomedicine, food science, and materials science because of their structural diversity, unique biological activities, and broad application potential. At present, the extraction of marine peptides has expanded beyond conventional chemical extraction and enzymatic hydrolysis, with microbial fermentation and gastrointestinal simulation technologies further broadening peptide diversity. In addition, the integration of multiple chromatographic techniques with advanced detectors has significantly improved the efficiency of marine peptide identification. Owing to their diverse biological activities, including immunoregulatory, antioxidant, antibacterial, antitumor, hypotensive, and hypoglycemic effects, marine peptides not only enrich the pool of candidates for marine drug development but also provide new perspectives for addressing numerous health challenges. Importantly, substantial progress has been made in the screening, identification, and mechanistic elucidation of marine bioactive peptides, driven by advances in high-throughput technologies and the bioinformatics. However, marine peptide research still faces several challenges, including complex sourcing, difficulties in large-scale acquisition, and insufficient exploration of biological activities. Therefore, this article concisely reviews recent progress in the extraction, purification, and identification of marine bioactive peptides, summarizes current research on their biological activities, and highlights the application of bioinformatics in marine peptide studies.

1. Introduction

Marine biodiversity represents a rich and underexplored reservoir of bioactive peptides. Living in environments characterized by extreme variability and numerous survival challenges, including exposure to a wide range of pathogens, marine organisms experience intense competition and antagonism. As a result, they have evolved a diverse array of host-defense peptides during growth and metabolic processes [1]. These peptides possess unique compositions, sequences, and structures that differ markedly from those of terrestrial organisms, thereby exhibiting distinctive biological activities and considerable medicinal potential. Marine bioactive peptides are generally defined as peptides consisting of 2–20 amino acid residues derived from marine organisms. They include natural peptides, bio-derived peptides, synthetic analogs, and recombinant derivatives, and their activities are fundamentally determined by their amino acid composition [2]. Common extraction methods include ultrasonic extraction [3], solvent extraction [4], enzymatic hydrolysis [5], microbial degradation [6], gastrointestinal digestion [7], recombinant DNA technology [8], and chemical synthesis [9]. However, chemical synthesis is often time-consuming, costly, and environmentally unfriendly, and it also requires prior knowledge of the peptide sequence. In the classical screening process for marine polypeptides, activity-guided fractionation is commonly used to isolate and purify individual peptides step by step, employing techniques such as membrane filtration [10], gel chromatography [11], size-exclusion chromatography [12], ion-exchange chromatography [13], and reverse-phase high-performance liquid chromatography [14]. Each purification method has its own limitations, and in most cases, multiple techniques must be combined. Consequently, low efficiency and high cost remain major constraints. Therefore, improving separation and purification technologies while maintaining high selectivity and accuracy is essential.

In recent years, rapid advances in mass spectrometry-based peptidomics and proteomics have facilitated the identification of active peptide structures and significantly shortened the structural characterization cycle. Representative techniques include MALDI-TOF MS, CE-TOF MS, and UPLC-Q/TOF MS [15, 16]. With the accumulation of large amounts of peptide data, various peptide databases have been established. Among them, BIOPEP, one of the most comprehensive databases of bioactive peptides, currently contains more than 3600 entries [17]. Bioinformatics now plays a crucial role in analyzing structure–function relationships, enabling computer-aided peptide design, prediction of peptide bioactivities, sequence searching and multiple sequence alignment, simulation of proteolysis, identification of potential precursor proteins, and molecular docking between peptides and

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https://doi.org/10.1016/S1875-5364(26)61178-8

target proteins [18]. These bioinformatics approaches help clarify the relationship between peptide structure and activity and enable rapid, high-throughput screening of bioactive peptides.

Clarifying the pharmacological activities and mechanisms of marine polypeptides is of great significance for the development of new marine-derived drugs. Research on marine bioactive peptides can be traced back to 1970, when pioneering studies on cone snail venom led to the discovery of conotoxins. These peptides, characterized by disulfide bond-rich structures, have shown enormous promise for neuroscience-related drug development [19]. Marine polypeptides with unique structures have been reported to exhibit a broad range of biological activities, including antioxidant [20], antibacterial [21], antitumor [22], antithrombotic [23], and opioid agonistic effects [24]. With the increasing discovery of bioactive peptides, therapeutic peptides have come to play an important role in the chemical and pharmaceutical industries. For example, marine peptide drugs such as plitidepsin and Prialt were approved in 2004 for the treatment of diseases such as multiple myeloma and severe pain, respectively [25, 26]. In summary, this article reviews recent advances in the production of marine bioactive peptides, their pharmacological activities, and the application of bioinformatics in bioactive peptide research.

2. Production of marine peptides

In recent years, with the development and utilization of marine biological resources, increasing attention has been paid to methods for extracting and purifying bioactive peptides from marine organisms, particularly in terms of peptide separation, identification, synthesis, and functionality [27]. To obtain peptide products with high purity and strong bioactivity, researchers have developed a series of extraction, purification, and separation methods based on the different physicochemical properties of marine organisms (Fig. 1).

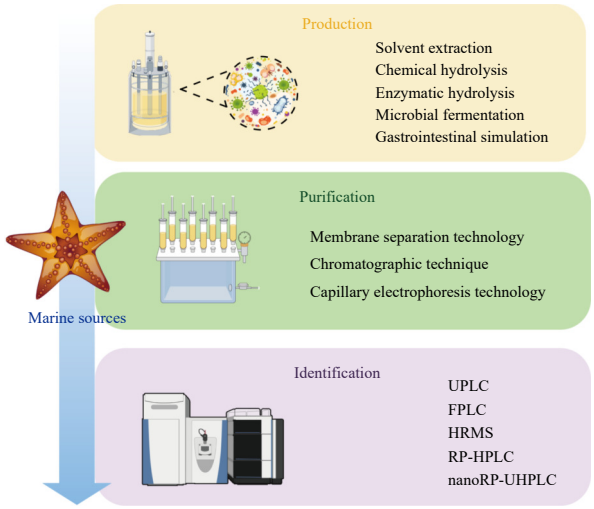

Fig. 1 Advanced production technologies for marine peptides.

2.1. Peptide preparation methods–solvent extraction

The extraction of active peptides utilizes various solvents depending on their polarity and solubility [28]. Methanol is effective for extracting antibacterial peptides from mussels [29], while a sequential extraction procedure using hexane, dichloromethane, and methanol can be applied to compounds such as milnamide A [30]. Green solvents, such as deep eutectic solvents (DESs), are emerging as non-toxic, biodegradable, and efficient alternatives [31], and have demonstrated considerable potential in the extraction of bioactive peptides [32]. For example, one specific DES extracted more protein from sardine residues (162.2 $mg \cdot g^{-1}$) than water (145.7 $mg \cdot g^{-1}$) [33], while another DES improved both the extraction efficiency (96%) and yield (100%) of collagen peptides from cod skin [34].

To further improve extraction efficiency, methods such as enzyme-assisted extraction (EAE), ultrasound-assisted extraction (UAE), and high-pressure-assisted extraction have also been employed [35, 36]. The combination of green solvents with these physically assisted technologies has enhanced both extraction efficiency and environmental sustainability. However, the core of this process still depends on chemical hydrolysis for the degradation of marine collagen.

2.2. Peptide preparation methods–chemical hydrolysis

Chemical hydrolysis extracts proteins by cleaving peptide bonds using acids or bases. Alkaline hydrolysis, which commonly uses strong alkalis such as sodium hydroxide, can be enhanced by increasing the temperature and extending the reaction time. One traditional method extracted algal proteins with a recovery rate of 35.1% by lysing algae in ultrapure water using ultrasound, followed by ammonium sulfate precipitation and dialysis through a 3.5 kDa MWCO membrane [36]. High-pH conditions can also improve the functional properties of cod myosin and fibrin and enhance the activity of cod-derived peptides [37]. However, alkaline hydrolysis may damage amino acids such as serine and threonine, thereby reducing product functionality, and may also generate carcinogenic chloropropanols [38]. Acid hydrolysis, which is more commonly used than alkaline hydrolysis, involves reagents such as sulfuric, nitric, hydrochloric, and phosphoric acids [39]. Its advantages include relatively milder and more controllable reaction conditions. For example, gelatin extracted from cod and flatfish skin using 0.05 $mol \cdot L^{-1}$ acetic acid (1 : 10 *W/V*), followed by treatment with Flavourzyme at 70 °C, yielded polypeptides with DPP-IV inhibitory activity and GLP-1 secretion-promoting activity [40]. However, acid hydrolysis often requires high temperatures, and the neutralization process may result in high sodium content and destruction of tryptophan [41]. Furthermore, chemical hydrolysis can result in collagen dissolution [42].

Although chemical hydrolysis efficiently cleaves peptide bonds and releases bioactive peptides, it has several major drawbacks. These include reduced product functionality and safety, the strong corrosiveness of the reagents, and ionic residues generated during neutralization, all of which may pose environmental and health risks. Therefore, enzymatic hydrolysis, which relies on specific biological catalytic mechanisms, has become a major research focus for overcoming these limitations.

2.3. Peptide preparation methods–enzymatic hydrolysis

Proteases from different sources can modify marine-derived proteins through enzymatic reactions by cleaving specific peptide bonds [43]. These enzymes include alkaline proteases, neutral proteases, and flavor proteases of bacterial origin, as well as trypsin, pepsin, papain, bromelain, and subtilisin from animal and plant sources [2]. Using animal proteases, supramolecular self-assembled peptide materials derived from marine oysters have been shown to exhibit procoagulant effects, radical-scavenging activity, anti-inflammatory properties, and the ability to promote fibroblast proliferation and angiogenesis, thereby accelerating epithelialization and demonstrating high efficacy in skin wound healing [44]. Alkaline protease hydrolysis of the red alga *Gracilaria lemaneiformis* led to the identification of three novel antioxidant peptides, LSPGEL, VYFDR, and PGPTY, which protected HepG2 cells against H_2O_2-induced damage [45]. Proteases also play a crucial role in the valorization of marine fish by-products. Through mixed fermentation with seven lactic acid bacteria, three novel

bioactive peptides, SAQ, PW, and VGGT, were identified in the enzymatic hydrolysate of seabass by-products and were found to inhibit cholesterol-related activity [46]. In addition, five novel ACE-inhibitory peptides with IC_{50} values ranging from 0.012 to 1.680 mmol·L^{-1} were obtained from stonefish protein hydrolyzed with bromelain [47]. Eight antioxidant peptides were also identified from *Trichiurus japonicus* protein hydrolyzed using proteases such as papain and alkaline protease, exhibiting reducing power and inhibitory capacity against lipid peroxidation in a linoleic acid model system [48].

The specific catalytic activity of proteases provides an efficient technical route for the targeted production of marine bioactive peptides, and the resulting products show unique advantages in the development of antioxidant, anti-inflammatory, and functional materials. However, conventional enzymatic hydrolysis still faces several bottlenecks, including the high cost of exogenous enzyme preparations, limited substrate adaptability, and sensitivity to reaction conditions, making it difficult to meet the large-scale development demands of complex marine protein resources. In contrast, microbial fermentation offers greater advantages for large-scale green production.

2.4. Peptide preparation methods–microbial fermentation

Microbial fermentation is a technique that uses enzymes produced by microorganisms during growth to degrade proteins and generate bioactive peptides. Because of its GRAS status and numerous health-related advantages, microbial fermentation has been widely applied in the industrial production of marine bioactive peptides [29]. Recent studies have shown that a heptapeptide, FEDPEFE, obtained by fermenting scallop skirt with Bacillus sp. 3*1-3 at high altitudes, exhibits enhanced stability in gastrointestinal fluids after chelation with ferrous ions. In addition, the fermentation process can reduce costs by up to 50% [49]. In fisheries and aquaculture, a large number of by-products are discarded as waste; however, further processing through microbial fermentation can provide abundant bioactive molecules [50]. For instance, fermentation of salmon by-products with *Pseudoalteromonas* produces hydrolysates with strong antioxidant activity, making them promising materials for antioxidant peptide preparation [51]. Co-incubation of *Bacillus subtilis* A26 and *Bacillus amyloliquefaciens* with stingray skin has also enabled the production of ACE-inhibitory and antioxidant peptides [52]. Another study found that fermentation of *Chlamys farreri* with *Bacillus natto* yielded five ACE-inhibitory peptides that improved vascular remodeling, inhibited myocardial fibrosis, and restored intestinal microbial balance [53]. In studies of the flavor of fermented aquatic products, microbial fermentation has also played an important role, as flavor peptides generated during decomposition enhance taste while providing additional health benefits [54]. Umami peptides produced through microbial metabolism contribute substantially to the characteristic umami taste of Chouguiyu and are also rich in ACE-inhibitory peptides that may help alleviate hypertension [55]. Furthermore, metagenomic analysis combined with molecular docking identified and characterized seven core ACE-inhibitory peptides and confirmed that the genus *Lactobacillus* was the microbial genus responsible for their production [56].

Microbial fermentation produces marine bioactive peptides through the synergistic action of microbial enzymes and offers clear advantages in cost reduction, efficiency improvement, product diversity, and flavor modulation. However, the gastrointestinal stability, absorption efficiency, and maintenance of structure–activity relationships of bioactive peptides prepared *in vitro* remain unclear. Therefore, extending static preparation methods to dynamic digestion simulation and constructing gastrointestinal biomimetic systems may further optimize peptide molecular design and delivery strategies.

2.5. Peptide preparation methods–gastrointestinal simulation

Digestion, as a crucial step in metabolism and nutrient absorption, converts large food molecules into small molecules that can be absorbed by the body and functions through specific metabolic sites. By simulating gastrointestinal digestion *in vitro* to degrade marine organisms, we can mimic the degradative capacity under physiological conditions to a certain extent and obtain a large number of marine-derived active peptides. Research has found that when simulating gastrointestinal digestion of the heart of *Katsuwonus pelamis in vitro* using pepsin as the main enzyme, 11 antioxidant peptides can be obtained from the hydrolysates, among which PKK, YEGGD, and GPGLM exhibit stronger antioxidant activity and stability [57]. Another study investigated the degradation of sea cucumber (*Stichopus japonicus*) using simulated intestinal fluid combined with pepsin and found that low-molecular-weight peptides identified from the resulting protein hydrolysates inhibited dipeptidyl peptidase IV (DPP-IV), demonstrating favorable antidiabetic potential [58]. ACE-inhibitory peptides such as TAA, ATT, ITT, and TL have also been identified from hydrolysates of ocean cobia skin obtained through gastrointestinal simulation, and these novel peptides showed significant antihypertensive activity in rats [59]. Simulated gastrointestinal digestion of the marine bivalve mollusk *Tergillarca granosa*led to the identification of antioxidant peptides MDLFTE and WPPD from the protein hydrolysates. However, because of their relatively low stability, these peptides may be more suitable as isolated nutritional or health supplement candidates [60]. In addition, the novel peptide AEYLCEAC, derived from oyster hydrolysis, exhibited potent ACE-inhibitory activity (IC_{50} 4.287 mmol·L^{-1}) and reduced both systolic and diastolic blood pressure in rats [61].

Overall, *in vitro* simulated gastrointestinal digestion can mimic the *in vivo* digestion and absorption process and thereby generate various bioactive peptides. However, current gastrointestinal simulation techniques still cannot fully reproduce physiological conditions, and the subsequent separation and purification processes remain relatively complex, which limits industrial application. At present, studies on the development of marine products using gastrointestinal simulation remain limited, and continuous optimization is needed to improve the accuracy and reliability of these models.

2.6. Peptide purification methods–membrane separation technology

After marine proteins have been converted into bioactive peptides through a series of preparation methods, further purification still requires careful separation and extraction techniques. Membrane separation technology is an effective approach for purifying marine bioactive peptides. It achieves selective separation through micropores of different sizes under driving forces such as pressure, electric fields, or concentration gradients [62]. Pressure-driven membrane filtration includes ultrafiltration and nanofiltration [63]. Among these, ultrafiltration membranes are the most commonly used in membrane separation technology. They can screen peptide fractions with high bioactivity according to molecular mass and are therefore widely used in the separation and extraction of bioactive peptides. However, they cannot finely distinguish peptides with similar molecular sizes and are prone to membrane fouling under high pressure [62]. Introducing an electric field as an additional driving force can effectively improve the migration efficiency and selectivity of pressure-driven membranes. Shyam Suwal and colleagues developed a two-step electro-driven membrane fractionation (EMF) method and evaluated the feasibility of a sequential electrokinetic flow fractionation membrane (EDFM) process for separating cationic (CP) and anionic (AP) peptides from rainbow trout bone protein hydrolys-

ates. Their study demonstrated that EDFM is an effective technique for recovering antioxidant peptides from enzymatic hydrolysates of fish protein by-products [62]. Electrodialysis with ultrafiltration membranes (EDUF) has also been applied to selectively separate and enrich peptides from protein hydrolysates, and its low energy consumption makes it more economical for industrial applications [64]. In addition, ceramic ultrafiltration technology offers advantages such as high temperature resistance, chemical corrosion resistance, high mechanical strength, and long service life in the separation of bioactive peptides. Supitchaya Pinrattananon and colleagues used 1 kDa ceramic membranes for the preliminary separation of enzymatic hydrolysates from skipjack tuna (*Katsuwonus pelamis*) under different pressures (2.85, 3.85, and 4.85 bar), and demonstrated that membrane performance is affected by the pH of the hydrolysates [65].

Overall, membrane separation technology demonstrates both efficiency and economic advantages in the preliminary separation and component enrichment of marine bioactive peptides through the combined driving forces of pressure and electric fields. However, because its screening mechanism is mainly based on differences in molecular weight, it is difficult to achieve precise discrimination among structurally similar peptide fragments. Therefore, separation strategies based on finer characteristics, such as molecular hydrophobicity, charge distribution, and spatial conformation, as exemplified by chromatographic techniques, can provide important technical support for the targeted capture and functional validation of high-purity bioactive peptides.

2.7. Peptide purification methods–chromatographic techniques

Chromatography is a physical or physicochemical separation and analytical method that separates the components of a mixture by exploiting differences in properties such as distribution coefficient, adsorption capacity, ion-exchange capacity, and molecular size between the stationary phase and the mobile phase [66]. As a key technology for the separation of natural products, chromatography plays an important role in the purification of natural bioactive peptides. In recent studies, researchers purified a novel bioactive peptide from green clam trypsin hydrolysate using a two-step chromatographic strategy. First, fast protein liquid chromatography (FPLC), specifically an ÄKTA-FPLC system equipped with a Superose® 12 column, was used to separate fractions according to ACE-inhibitory activity. The most active fraction was then subjected to RP-HPLC using an Agilent HPLC ChemStation system and a ZORBAX SB-C_{18} column with a trifluoroacetic acid/acetonitrile gradient for further purification and purity assessment. This sequential approach successfully isolated the potent peptide [67]. During the purification process of a novel cyclic lipopeptide (CLP) derived from marine Bacillus lipolyticus SH-B74, researchers also performed careful purification using solid-phase extraction (SPE) and RP-HPLC. Subsequently, a series of spectroscopic and mass spectrometric techniques were applied for in-depth structural characterization of the novel CLP [68]. Gel filtration chromatography is a chromatographic technique that separates molecules according to size. It has been widely applied in the purification of bioactive peptides derived from abalone viscera [69], Pacific herring protein hydrolysates [70], and marine crustacean crab bioactive peptides [71]. The characterization of bioactive peptide amino acid sequences has also been greatly advanced by combining nano-reversed-phase ultra-high-performance liquid chromatography (nanoRP-UHPLC) with ultra-sensitive high-resolution mass spectrometry (HRMS). This powerful approach uses nanoRP-UHPLC for efficient peptide separation, followed by HRMS for accurate mass measurement and fragmentation analysis (MS/MS) to deduce peptide sequences. For example, peptides isolated from complex biological samples or obtained by chemical synthesis are first chromatographically separated and then analyzed by HRMS. The resulting MS data are subsequently processed using bioinformatics tools to enable reliable peptide identification and sequencing, which is crucial for functional characterization and quality control [72]. In addition, ultra-high-performance liquid chromatography (UPLC) can be used to determine peptide peak intensities in samples [71]. In most cases, multiple chromatographic techniques are integrated for the separation and identification of bioactive peptides.

Chromatographic techniques have established a central role in the separation and purification of complex marine peptide mixtures by enabling accurate discrimination of the multidimensional physicochemical properties of bioactive peptides. However, separation modes that rely on stationary-phase packing still face certain limitations, including reduced column efficiency, loss of trace samples, and long separation cycles. Studies have also shown that when peptides contain charged side chains, their retention behavior in ion-exchange chromatography may be affected [73]. Nevertheless, owing to their high-resolution separation capability, chromatographic techniques remain essential for the isolation and purification of bioactive peptides in both research and industrial applications.

2.8. Capillary electrophoresis technology

In view of the limitations of chromatographic techniques, capillary electrophoresis has emerged as another innovative tool for the high-throughput screening and trace-level analysis of marine bioactive peptides. Capillary electrophoresis is a technique that separates charged particles according to differences in their migration rates within a capillary under an electric field. Its basic principle is that, under specific pH conditions, ionized peptide molecules migrate directionally and in an orderly manner at different rates under the action of the electric field [74]. Capillary electrophoresis offers several advantages, including rapid analysis, high efficiency, low sample consumption, and diverse separation modes, making it widely used in peptide separation. As early as 2007, capillary electrophoresis was applied to rapidly determine the IC_{50} values of various hydrolysates for ACE-inhibitory activity [75]. Compared with HPLC, capillary electrophoresis provides faster operation, a higher degree of automation, and lower consumption of sample volume, solvents, and other auxiliary materials. Dominguez-Vega and colleagues developed a novel method for determining the composition of various deamidated peptides using capillary electrophoresis coupled with tandem mass spectrometry (CE-MS/MS) [76]. In another study, Wang et al. employed a curved capillary electrophoresis assay to determine antibody–peptide binding sites, monitor the formation of nanoscale antibody–antigen complexes, and elucidate biomolecular interactions [76]. Capillary electrophoresis has also been used to analyze protamine peptides in insulin preparations [77], thereby providing a scientific basis for extending the pharmacological effects of insulin formulations. In addition, capillary electrophoresis can be coupled with mass spectrometry to identify bioactive peptides in various nutritional products derived from protein hydrolysates [78].

In summary, capillary electrophoresis is an efficient and rapid technique for peptide separation. Its widespread application in environmental and food analysis also indicates its considerable potential in the detection and analysis of marine bioactive peptides. However, in practical applications, attention should still be paid to the selection and optimization of separation conditions, as well as to the limitations of instrumentation and equipment.

3. Biological activities of marine peptides

In recent years, marine-derived bioactive peptides have attracted considerable attention because of their diverse origins

and substantial benefits to human health. These peptides are generally considered highly safe and exhibit a broad range of biological activities, including anti-inflammatory, antimicrobial, antioxidant, antitumor, antihypertensive, and antidiabetic effects, demonstrating great therapeutic potential for various diseases such as cancer, cardiovascular diseases, and autoimmune disorders (Fig. 2) [79]. In this section, the biological activities and specific mechanisms of marine-derived bioactive peptides in these areas are discussed in detail (Table 1).

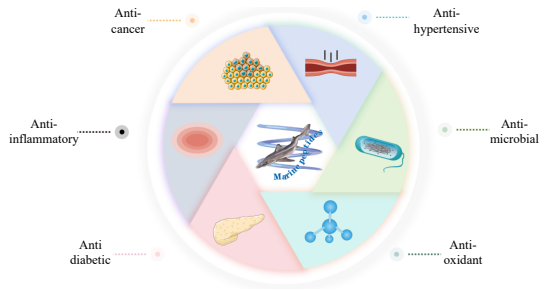

Fig. 2 Biological activities of marine-derived peptides.

3.1. Anti-inflammatory

Inflammation is a natural defense response of the innate and adaptive immune systems to harmful stimuli such as pathogen infection, damaged cells, and toxic chemicals, and it plays a crucial role in maintaining internal homeostasis. However, excessive inflammatory responses can lead to an imbalance between pro-inflammatory and anti-inflammatory mechanisms, triggering a "cytokine storm" that ultimately results in tissue damage and organ dysfunction [80]. Traditional anti-inflammatory drugs, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and immunosuppressants, are widely used in clinical practice. However, these drugs may cause intolerance or non-responsiveness in some patients, and prolonged use can result in significant side effects. Therefore, there is an urgent need to discover and develop novel anti-inflammatory drugs. Small peptides are increasingly valued in drug development because of their high safety, pronounced biological activity, and remarkable specificity. With the continuous exploration of marine biological resources, an increasing number of marine-derived bioactive peptides have been found to exhibit excellent anti-inflammatory activities both *in vitro* and *in vivo*. These peptides primarily alleviate inflammation by inhibiting the production of pro-inflammatory factors and suppressing the activation of inflammatory signaling pathways, indicating great potential for the treatment of inflammatory diseases [81].

Akshad et al. reported that the bioactive peptides PMpep and PVpep, extracted from pufferfish muscle and internal organs, effectively inhibited the expression of pro-inflammatory cytokines in LPS-stimulated RAW264.7 cells [82]. Furthermore, Ren et al. demonstrated that the bioactive peptide LPs, extracted from monkfish meat, reduced inflammatory cytokine levels, enhanced antioxidant activity, and regulated gut dysbiosis, thereby improving high-fat-diet-induced renal toxicity in mice [83]. These findings suggest that marine-derived bioactive peptides can regulate the release of pro-inflammatory factors to alleviate inflammation. Additionally, existing studies have shown that the anti-inflammatory mechanisms of marine-derived bioactive peptides are often associated with the regulation of inflammatory signaling pathways. FAGBOHUN et al. found that sea cucumber extracts suppressed inflammation and reduced LPS-induced acute lung injury through regulation of the NF-κB/MAPK/JNK signaling pathway [84]. Wu et al. identified a novel bioactive peptide, PCP3, derived from phycocyanin. Using intestinal organoids and a mouse model of intestinal inflammation, they found that PCP3 significantly restored the reduced cell viability and oxidative damage induced by LPS, reversed damage to the physiological morphology of the small intestine, and further revealed the critical roles of Akt and AMPK/autophagy signaling in PCP3-mediated protection against intestinal inflammation [85]. In another study, Pan et al. found that the *Sipunculus nudus*-derived tripeptide SRP ameliorated acute cadmium-induced kidney injury in mice by inhibiting activation of the MAPK signaling pathway, downregulating inflammatory cytokine expression, and reducing apoptosis [86]. Furthermore, Luo et al. revealed a key mechanism by which astaxanthin modulates ferroptosis and inflammatory responses through the Keap1-Nrf2/HO-1 signaling axis in LPS-induced acute lung injury [87]. High Fischer ratio oligopeptides (HFOPs) are composed of 3–9 amino acid residues, with a branched-chain amino acid to aromatic amino acid ratio greater than 20. Because of their unique amino acid composition, Sun et al. found that HFOPs-AK isolated from Antarctic krill could regulate enzyme systems related to alcohol metabolism, including alcohol dehydrogenase and aldehyde dehydrogenase. Mechanistically, HFOPs-AK activated the Nrf2 signaling pathway, thereby inhibiting liver inflammation by reducing the expression levels of TNF-α, IL-6, and IL-1β, and protecting mice from acute alcoholic liver injury [88]. At present, mechanistic studies on the pharmacological effects of marine-derived bioactive peptides mainly focus on anti-inflammatory and antioxidant effects and on signaling pathway localization at the phenotypic level. However, deficiencies remain in the exploration of refined regulatory mechanisms involving specific molecular targets and in understanding mechanistic heterogeneity across different disease models. Further systematic studies are therefore needed to identify the molecular targets and binding sites of marine-derived bioactive peptides. Such efforts will not only clarify their precise signaling cascades but also facilitate the rational design of tissue-specific or disease-adaptive therapeutics through structure–activity relationship optimization. The integration of molecular docking with *in vitro* activity validation has significantly accelerated the discovery of bioactive peptides and their molecular targets. Lin et al. demonstrated that the clam-derived anti-inflammatory peptides DQTF and GYTR significantly reduced the levels of pro-inflammatory cytokines and NO in serum and alleviated oxidative liver damage, revealing their potential to ameliorate acute inflammation [89]. Similarly, Maria et al. used computational simulation analysis to screen a variety of bioactive peptides with COX- and MAGL-inhibitory activities from mesopelagic fish protein hydrolysates. Among the tested peptides, QCPLHRPWAL showed potent inhibition of COX-1 (82.90%) and COX-2 (53.84%), with a selectivity index greater than 10 [90]. Although the anti-inflammatory activities of marine-derived peptides have been widely verified in diverse models, further investigation is still needed to elucidate their precise molecular mechanisms and to conduct more comprehensive *in vivo* pharmacokinetic studies to support the safety of their clinical application.

3.2. Antimicrobial

Because of the inappropriate use of traditional antibiotics, the emergence of multidrug-resistant pathogens has triggered a global health crisis and gradually weakened the effectiveness of existing treatment strategies and drugs. In response to this challenge, there is an urgent needed to identify new antimicrobial agents to combat multidrug-resistant pathogenic microorganisms [91]. Antimicrobial peptides (AMPs) are an indispensable component of host defense and are composed mainly of short cationic peptides with diverse structures and targets [92]. Owing to their potent antimicrobial activity and unique antibacterial mechanisms, AMPs are considered promising alternatives to conventional antimicrobial agents and show clear advantages over tradition-

Table 1 Recent studies on novel marine-derived peptides and their potential biological activities.

Source	Novel peptide	Indication	Findings	Reference
Osteichthyes Lophiiformes	Peptide mixture (LPs)	Inflammation	Regulates the release of pro-inflammatory factors	83
Apostichopus japonicus	Peptide Extracts	Inflammation	Regulates NF-κB/MAPK/JNK signaling pathway	84
Spirulina	PCP3	Inflammation	Participates in Akt and AMPK/autophagy signaling	85
Sipunculus nudus	SRP	Inflammation	Inhibits the activation of the MAPK signaling pathway, downregulates the expression of inflammatory cytokines	86
Crustacea	Astaxanthin	Inflammation	Regulates the Keap1-Nrf2/HO-1 signaling axis	87
Antarctic krill	AKP	Inflammation	Decreases pro-inflammatory factors and activates protein expression in the Nrf2/HO-1 single pathway	88
Ruditapes philippinarum	DQTF and GYTR	Inflammation	Reduces the concentration of pro-inflammatory factors and NO in the serum	89
Maurolicus muelleri and *Benthosema glaciale*	QCPLHRPWAL	Inflammation	Inhibits COX-1 and COX-2 activities	90
Chionodraco hamatus	LEAP2	Microbial infections	Penetrates bacterial cell membranes and binds to intracellular DNA targets	94
Sebastiscus marmoratus	Hepcidin-1, Piscidin, Moronecidin, NK-lysi and β-defensin	Microbial infections	Destruction of the biofilm system	95
Pinctada fucata martensii	SRSSRAGLQFPVGRIHRLLRK and RAGLQFPVGRLLLLRRLLRRLLR	Microbial infections	Destroy the biofilm system	96
Anabas testudineus	peptide mixture	Microbial infections and Immune regulation	Reduces levels of pro-inflammatory factors, serum aminotransferases, and creatinine	97
Paralichthys olivaceus	rPoHep2 and rPoNKL	Microbial infections and Immune regulation	Destroys cell membranes and also binds to bacterial gDNA	98
Tegillarca granosa	mTgHbP7	Microbial infections	Disrupts bacterial membranes through the formation of toroidal pores	125
Nerita versicolor	Nv-p1-3	Microbial infections	Destroys the bacterial cell membrane	126
Skipjack Tuna	QGD, PKK, GPQ, and GLN, GEQSN, GEEGD, YEGGD, GEGER, GEGQR, GPGLM, and GDRGD	Oxidative stress	Scavenges free radicals and protects plasmid DNA and HepG2 cells from oxidative stress	100
Acipenserbaerii	GPTGED, GEPGEQ, GPEGPAG, VPPQD, GLEDHA, GDRGAEG, PRGFRGPV, GEYGFE, GFIGFNG, PSVSLT, IELFPGLP, LRGEAGL and RGEPGL	Oxidative stress	Scavenges free radicals and regulates the activity of endogenous antioxidant enzymes	101
Carassius auratus	APLEEPSSPH	Oxidative stress	High Fe^{2+} chelating activity	102
Pinctada martensii	SPSSS, SGTAV, TGVAS, GGSIT, NSVAA, and GGSLT	Oxidative stress	Significantly improves HepG2 cell activity and binds to free radicals, antioxidant enzymes, and antioxidant channel proteins	103
Eucheuma cottonii	TA, MN, TSKT, YAVT, YLL, and FYKA	Oxidative stress	Scavenges free radicals	104
Chlorella vulgaris	AGWACLVG, YPLDL, and IDLAY	Oxidative stress	DPPH inhibition (competitive binding)	127
Pleuronectes americanus	GWGSFFKKAAHVGKH VGKAALTHYL, and GWGSFFKKAAHVGKHVGKAALTHYL-NH2	Cancer	Alter the morphology of cancer cells A549 and induce apoptosis	107
Enteromorpha prolifera	GPLGAGP	Cancer	Induces apoptosis	108
Osteichthyes	KLKSKLMVVCNKIGLLKSLARKFVKSH	Cancer	Promotes apoptosis	109
Clarias gariepinus	PACAP	Cancer	Affects the proliferation of cancer cells H460	110
Ulva lactuca	LAVISWKCQEWNSL WKKRKRKT	Cancer	Prevents non-small cell lung cancer cells from proliferating, promotes apoptosis, and inhibits cell migration	111
Thunnus albacares	Tuna trimmings protein hydrolysate (TPA)	Cancer and inflammation	the suppression rate of tumors and mitigate the damage of the mucosal and immune system induced by 5-FU in the intestines	112
Cololabis saira	VVLASLK, LTLK, LEPWR, ELPPK, and LPTEK	Hypertensive	Inhibits the activity of angiotensin-Iconverting enzyme	115
Takifugu flavidus	TLRFALHGME	Hypertensive	ACE inhibition (competitive binding)	116
Azumapecten pectinata viscera	*Azumapecten pectinata* viscera hydrolysate	Hypertensive and Oxidative stress	ACE inhibition and free radical scavenging capacity	117
Paralichthys olivaceus	IVDR, WYK, and VASVI	Hypertensive	Inhibits the activity of angiotensin -Iconverting enzyme	118
Stichopus japonicus	GPPGPQWPLDF, APDMAFPR, and GPGMMGP	Hypertensive	ACE inhibition (competitive binding)	128
Gracilariopsis chorda	IDHY and LVVER	Hypertensive	ACE inhibition (competitive binding)	129
Salmo salar	LTPFT and PLITT	Hypertensive	ACE inhibition (competitive binding)	130
Oreochromis mossambicus	Small peptides extracted from tilapia skin (TSP)	Diabete	Ameliorates mitochondrial dysfunction caused by diabetic nephropathy and activates the Bnip3/Nix pathway	120
Oreochromis mossambicus	Peptide mixture TY001	Diabete	Promotes wound healing, increases growth factor and collagen deposition in wounds	121
Capros aper	IPVDM	Diabete	Promotes the release of insulin	122
Trachinotus ovatus	FGNWR, MFK, SFGPR, NPPFK, CPPSPR, DFR, FNFSR, LFFSR, GFPSR, FFNSR, WPDAR, LSGFPR, QFLR, FLK, AFPYK, FFK, SFR, CPPTPR	Diabete	AAM and DPP-IV inhibition (competitive binding)	123
Thunnus albacares	APP, PPP, DPLL, EAVP, and EAIP	Diabete	Activates the PI3K/AKT and AMPK signaling pathways	124
Rhodophyta	APPVDID, GPPDSPY, PPSSPRP, and SPPPPPA	Diabete	AAM and DPP-IV inhibition (competitive binding)	131

al antibiotics in combating resistant bacterial infections. These peptides exert antibacterial effects mainly by regulating the host immune system and directly killing pathogenic microorganisms through interference with nucleic acid synthesis and disruption of the cytoplasmic membrane [93].

Francesco et al. reported chionodracine (Cnd), a peptide consisting of 22 amino acid residues derived from Antarctic icefish. Studies showed that the mutant peptide Cnd-M3A, derived from Cnd, could induce pore formation in the outer membranes of *Escherichia coli* and psychrophilic bacilli and bind to bacterial DNA, thereby effectively exerting antimicrobial activity [94]. Jun et al. analyzed the liver transcriptome of rockfish and identified six AMPs, among which the synthetic peptides LEAP-2 and moronecidin exhibited broad-spectrum antimicrobial activity against a variety of pathogens by directly disrupting microbial biofilms [95]. Importantly, no obvious hepatocellular toxicity was observed at effective concentrations ranging from 5 μmol·L^{-1} to 40 μmol·L^{-1}. Shen et al. found that two histone-derived AMPs extracted from *Pinctada fucata martensii*, were able to disrupt the bacterial cytoplasmic membrane and significantly inhibit the growth of both Gram-negative and Gram-positive bacteria [96]. These studies suggest that marine AMPs possess both targeting capability and broad-spectrum activity, enabling them to effectively penetrate microbial cell structures and making them a promising resource for the discovery of novel AMPs. With the continued exploration of marine bioactive peptides, increasing numbers of AMPs with both antibacterial and immunomodulatory activities have been identified, highlighting their potential as a source of new antibiotics. Al-rasheed et al. demonstrated that an AMP derived from the mucus secretion of climbing perch effectively reduced the bacterial burden in internal organs and blood samples and decreased the elevated serum aminotransferase (AST and ALT) and creatinine levels induced by multidrug-resistant *Pseudomonas aeruginosa* infection in mice, thereby significantly alleviating the symptoms of infection [97]. Li et al. obtained the recombinant proteins hepcidin 2 and NK-lysin (rPoHep2 and rPoNKL) from flounder (Paralichthys olivaceus) using a prokaryotic expression system. They found that rPoHep2 and rPoNKL could kill bacteria by disrupting cell membranes and could also bind bacterial genomic DNA *in vitro*, suggesting that they may inhibit bacterial growth through different bactericidal mechanisms. In addition to its direct antibacterial activity, rPoHep2 was also able to act on phagocytes to enhance phagocytosis, thereby exhibiting an immunomodulatory effect [98]. However, only a limited number of AMPs have been approved by the FDA because of inadequate thermal stability, susceptibility to protease degradation, and potential hemolytic activity. Therefore, it is imperative to further optimize the structural characteristics of natural AMPs to provide new solutions to the growing problem of antibiotic resistance.

3.3. Antioxidant

The body's antioxidant defense system plays an important role in eliminating reactive oxygen species (ROS) and preventing cellular damage. However, excessive ROS production can cause oxidative damage to biomolecules such as DNA, RNA, and membrane lipids, thereby contributing to premature aging, cancer, atherosclerosis, diabetes, and cardiovascular diseases [99]. Therefore, sufficient intake of antioxidants is necessary to support the body's antioxidant defense processes. At present, chemically synthesized antioxidants widely used on the market are restricted in the food and cosmetics industries because of food safety concerns. As a result, increasing attention has been directed toward the search for safe and effective natural antioxidants, such as marine-derived antioxidant peptides.

Studies have shown that antioxidant peptides can neutralize oxidative damage caused by free radicals and ROS through hydrogen atom donation or electron transfer. At present, most studies have focused on the scavenging of hydroxyl, peroxyl, DPPH, and ABTS radicals by peptides. For example, Cai et al. optimized the conditions for pepsin hydrolysis of the arterial bulb of tuna heart, from which 11 bioactive peptides were isolated. Among them, three novel peptides, PKK, GPGLM, and YEGGD, exhibited excellent free radical-scavenging activity and provided substantial protection against oxidative damage in plasmid DNA and HepG2 cells [100]. Lipid peroxidation is a major destructive process in oxidative stress that leads to cell membrane damage and dysfunction, and it is widely regarded as an important indicator for evaluating the antioxidant activity of natural peptides. Sheng et al. isolated 13 antioxidant peptides from collagen hydrolysate extracted from Siberian sturgeon cartilage. Among them, GEYGFE, PSVSLT, and IELFPGLP exhibited significant protective effects against the peroxidation of unsaturated fatty acids. Importantly, these peptides also reduced malondialdehyde (MDA) levels and alleviated H_2O_2-induced lipid peroxidation of the cell membrane [101]. Furthermore, peptide chelation with metal ions can prevent free radical formation by altering the chemical reactivity of metals, forming insoluble metal complexes, or sterically hindering metal–lipid interactions. Zhang et al. used two different antioxidant assays, DPPH radical-scavenging activity and Fe^{2+}-chelating activity, to evaluate four novel peptides isolated from crucian carp. Among these peptides, APLEEPSSPH showed strong Fe^{2+}-chelating activity (IC_{50} 0.09 mmol·L^{-1}) and exhibited superior antioxidant activity during gastrointestinal digestion [102]. In addition to the mechanisms described above, marine peptides can also reduce oxidative damage by regulating the levels of endogenous antioxidant enzymes. For example, Huang et al. isolated six novel antioxidant peptides from pearl shell meat. These peptides significantly enhanced the viability of HepG2 cells in an AAPH-induced oxidative damage model and showed strong binding affinity to free radicals (DPPH and ABTS), antioxidant enzymes (catalase and superoxide dismutase), and the antioxidant regulatory protein Keap1, thereby exhibiting multiple antioxidant activities [103]. In addition, Sun et al. found that two bioactive peptides, EP4 and EP5, extracted from red algae, displayed excellent free radical-scavenging activity by regulating antioxidant enzyme systems, including superoxide dismutase and glutathione peroxidase, thereby reducing ROS and MDA levels [104]. Considering the stepwise synergistic relationship between inflammation and oxidative stress, marine-derived antioxidant peptides often share common signaling pathways with anti-inflammatory peptides and therefore exhibit diverse biological activities. This hierarchical regulatory characteristic indicates that the activity of marine-derived peptides is not isolated but rather functions as a signaling hub that coordinates a broad range of physiological and pathological networks. In conclusion, marine-derived antioxidant peptides exert their biological activities through free radical scavenging, chelation of pro-oxidative metal ions, inhibition of lipid peroxidation, and regulation of intracellular antioxidant enzyme systems. However, antioxidant capacity measured *in vitro* cannot accurately reflect the actual utilization value of antioxidant peptides, and their digestion, absorption, metabolism, and bioavailability still require further investigation.

3.4. Anticancer

Cancer is one of the leading causes of death worldwide and is characterized by abnormal proliferation of normal cells [105]. Conventional treatment approaches mainly involve chemotherapeutic agents that bind to or disrupt microtubules, thereby interfering with the cell cycle and mitosis of cancer cells. However, this strategy often shows limited efficacy and causes toxicity to normal tissues. Other small-molecule drugs can block active sites and specific enzyme-binding pockets, mainly in kinases that are fre-

quently dysregulated in cancer. Nevertheless, these compounds usually exhibit limited specificity and selectivity, resulting in numerous off-target effects. In contrast, anticancer peptides (ACPs), which are typically cationic and amphipathic, can selectively bind to and eliminate cancer cells while sparing normal cells through direct or indirect mechanisms of action [106]. At present, peptide-based anticancer therapies mainly involve the induction of apoptosis, the disruption of cell cycle progression, damage to cell membrane integrity, and the inhibition of tumor angiogenesis.

Xu et al. identified two bioactive peptides, Ple and PL-A, from winter sole, which showed broad-spectrum cytotoxicity against multiple cancer cell lines, with IC_{50} values ranging from 11 to 340 μmol·L^{-1}. Further investigation revealed that PL-A suppressed autophagy while inducing apoptosis in A549 cells after 48 h of exposure [107]. HTDT-6-2-3-2, a heptapeptide derived from *Enteromorpha prolifera*, also demonstrated broad antiproliferative activity and induced apoptosis in a dose-dependent manner across multiple human cancer cell lines. Molecular docking analysis suggested that HTDT-6-2-3-2 might interact with XIAP to inhibit the activation of caspase-9 [108]. In another study, Buonocore et al. designed and synthesized a cysteine-mutant peptide, NKL-MUT, based on the NKL-WT peptide isolated from Antarctic bony fish. It was shown that NKL-MUT selectively induced apoptosis in the melanoma cell line B16F10 while exhibiting low cytotoxicity toward normal mammalian cells [109]. Marine-derived bioactive peptides have also shown remarkable potential in the treatment of non-small cell lung cancer (NSCLC). Juana et al. investigated pituitary adenylate cyclase-activating polypeptide (PACAP) derived from the North African catfish and found that PACAP acted as a regulatory neuropeptide capable of influencing the proliferation of the human NSCLC cell line H460 in a dose-dependent manner [110]. Heabin et al. synthesized a 22-amino-acid peptide, MP06, from green algae and demonstrated that MP06 significantly induced apoptosis and exerted antiproliferative effects in NSCLC cells compared with non-cancerous cells. Further study indicated that MP06 inhibited cell migration and invasion while suppressing the expression of epithelial-mesenchymal transition (EMT) markers such as N-cadherin and vimentin [111]. Zhao et al. found that the combination of tuna trimmings (*Thunnus albacares*) protein hydrolysate (TPA) and 5-FU enhanced tumor suppression and mitigated 5-FU-induced damage to the intestinal mucosa and immune system. The anticancer and anti-inflammatory activities of TPA may be related to its unique peptide sequence composition, among which 55.96% of the peptide sequences were hydrophobic. CSM-PEPTIDES analysis predicted the biological activities of TPA peptide sequences and identified 68 of 109 peptides (62.4%) with potential antitumor activity and 77 peptides (70.6%) with anti-inflammatory properties [112]. Consequently, bioactive peptides are regarded as promising candidates for antitumor therapy because of their high biocompatibility and potent anticancer activity, and they may also serve as innovative adjuvants to reduce the side effects of chemotherapy or enhance the efficacy of anticancer drugs. However, low membrane permeability remains a major barrier to the effective targeting of intracellular components by these agents. This limited intracellular delivery efficiency may be related to violations of Lipinski's Rule of Five. Encouragingly, recent discoveries of amino acid sequences capable of crossing cellular membranes have opened new possibilities for intracellular delivery of such therapeutic agents. At present, multiple research groups and companies are actively developing anticancer peptides with cell-penetrating capabilities.

3.5. Antihypertensive

Hypertension is a disease characterized by persistently elevated blood pressure and is a major risk factor for cardiovascular and renal diseases [113]. A common strategy for the management of hypertension is the inhibition of angiotensin-converting enzyme (ACE), thereby preventing the conversion of angiotensin I into angiotensin II, a potent vasoconstrictor that causes constriction of arterial walls and arterioles. However, traditional ACE inhibitors are associated with adverse reactions, which negatively affect patient compliance and therapeutic outcomes. In view of these limitations, increasing attention has been paid to the development of natural ACE inhibitors as an alternative therapeutic strategy for hypertension. Clinical studies have shown that regular consumption of fish and seafood may reduce the risk of cardiovascular events [114]. As rich sources of high-quality proteins and bioactive peptides, marine organisms deserve further investigation for their potential antihypertensive activity.

The evaluation of antihypertensive potential typically involves *in vitro* enzymatic assays targeting key regulators of blood pressure, particularly ACE activity. In ACE inhibition studies, researchers use various synthetic substrates in the reaction system and apply different analytical methods to quantify enzyme activity either through direct product measurement or through substrate-product separation. For example, using gel filtration chromatography, reverse-phase high-performance liquid chromatography (RP-HPLC), and molecular docking, Wang et al. identified a novel group of antihypertensive peptides from chub mackerel. Among them, LEPWR exhibited the strongest ACE-inhibitory activity (IC_{50} = 99.5 μmol·L^{-1}). *In vitro* bioavailability studies further showed that the apparent permeability coefficient (Papp) of LEPWR was approximately 3.56 × 10^{-6} cm/s, indicating that it could be readily absorbed by the human body. The study also found that paracellular transport through tight junctions was the main transport pathway for LEPWR, allowing the peptide to remain intact during transport [115]. Su et al. identified a novel bioactive peptide, TLRFALHGME, derived from yellowtail pufferfish, which exhibited excellent ACE-inhibitory activity (IC_{50} 93.5 μmol·L^{-1}) [116]. In addition, Lee et al. found that hydrolysates obtained from *A. pectinata* viscera by subcritical water hydrolysis contained abundant amino acids and confirmed their significant antihypertensive and antioxidant activities through evaluation of ACE inhibition and free radical-scavenging capacity [117]. Jae-Young et al. isolated three novel peptides from *Paralichthys olivaceus* that showed strong ACE-inhibitory activity. In a spontaneously hypertensive rat model, oral administration of peptides derived from fish surimi reduced blood pressure through the Akt/eNOS pathway, thereby demonstrating antihypertensive activity [118]. These studies indicate that marine organisms, as abundant biological resources, are excellent sources for the preparation of ACE-inhibitory peptides. As technologies related to nutrigenomics and nutrigenetics continue to advance, the biological functions of these bioactive peptides may be further optimized. The development of natural ACE inhibitors as functional foods and nutritional supplements, therefore, holds considerable promise as an alternative approach for the management of hypertension.

3.6. Antidiabetic

Diabetes is a chronic metabolic disorder characterized by persistently elevated blood glucose levels and is associated with complications such as cardiovascular disease, retinopathy, nephropathy, and neuropathy [119]. Although several pharmacological interventions are currently available, including sulfonylureas, biguanides, α-glucosidase inhibitors, PPARγ agonists, dipeptidyl peptidase-IV (DPP-IV) inhibitors, and SGLT2 inhibitors, their long-term use may lead to serious adverse effects. Recent findings from extensive clinical trials and observational studies have highlighted the critical role of diet and specific food components in the management and prevention of diabetes. Among these, naturally derived marine peptides have attracted increasing attention because of their low toxicity and high specificity.

Lin et al. identified a mixture of small peptides extracted from tilapia skin, termed TSP. Their study demonstrated that TSP treatment improved mitochondrial morphology and reversed the excessive generation of mitochondrial superoxide and intracellular reactive oxygen species by activating the Bnip3/Nix signaling pathway, thereby alleviating mitochondrial dysfunction caused by diabetic nephropathy [120]. In addition, Xiong et al. found that a mixture of tilapia collagen peptides, designated TY001, effectively improved delayed wound healing associated with diabetes. The underlying mechanism may involve increased growth factor expression and collagen deposition at the wound site, which alleviates chronic inflammation caused by diabetes, enhances tissue antioxidant capacity, and provides essential nutritional support [121]. Maintaining normal blood glucose levels is one of the most effective strategies for the treatment of type 2 diabetes. Extensive studies have identified α-amylase (AAM) and dipeptidyl peptidase-IV (DPP-IV) as key enzymes that can be targeted to improve glycemic control by enhancing the incretin effect and reducing glucose absorption, thereby establishing them as validated therapeutic targets for type 2 diabetes management. Rothwell et al. identified 22 novel DPP-IV-inhibitory peptides and 15 new insulinotropic peptides. Among them, IPVDM exhibited the strongest antidiabetic activity, showing significant DPP-IV inhibition in both *in vitro* and cellular assays and enhancing insulin secretion in cultured BRIN-BD11 pancreatic cells [122]. Wan et al. investigated the antidiabetic properties of *Trachinotus ovatus* protein hydrolysates (TOH) in streptozotocin-induced diabetic mice and identified a total of 22 potentially active peptide sequences with AAM- and DPP-IV-inhibitory activities [123]. Furthermore, Meng et al. used artificial neural network methods to screen five DPP-IV-inhibitory peptides, APP, PPP, DPLL, EAVP, and EAIP, from skipjack tuna dark muscle protein hydrolysates. These peptides played important roles in improving insulin resistance in human HepG2 cells, partly through activation of the PI3K/AKT and AMPK signaling pathways [124]. The consistency observed in DPP-IV inhibition between *in vitro* and cellular assays suggests that certain antidiabetic peptides may be able to cross the human epithelial cell membrane in intact form and may therefore exert multiple biological effects through different mechanisms. In the future, systematic *in vivo* and *in vitro* studies will be needed to comprehensively evaluate the multiple biological activities of marine-derived bioactive peptides and to clarify their mechanisms of action and clinical potential in the prevention and treatment of diabetes. Such studies will not only contribute to the development of novel antidiabetic drugs but may also provide new strategies for the prevention and management of diabetes-related complications.

Overall, these studies indicate that marine-derived bioactive peptides have considerable potential as sources of antidiabetic agents. However, the discovery of novel peptides from marine organisms still faces several important challenges, including the need for optimal methods to separate and purify individual peptides from complex mixtures, the relatively low bioactivity of some peptides, potential toxicity to human health, and the difficulty of selecting the most appropriate cell and animal models for antidiabetic activity studies.

4. Bioinformatics approaches for marine bioactive peptides research

The diversity of precursor proteins and the structural complexity of peptide mixtures in hydrolysates pose significant challenges to the production of bioactive peptides with clear origins, high abundance, and well-defined structures. Moreover, the uncertain bioactivities of hydrolysis products require extensive experimental screening, validation, and mechanistic investigation. This process is both costly and time-consuming, making the rapid and efficient acquisition of bioactive peptides a major bottleneck in current peptide research [132]. In view of the limitations of traditional methods for bioactive peptide discovery, bioinformatics has rapidly emerged as a crucial tool for the identification and evaluation of potential bioactive peptides from protein sources. Based on a variety of algorithms and peptide databases, peptide activities and structures can be theoretically predicted and simulated, including protein hydrolysis, three-dimensional conformation or folding patterns, and biological effects (Fig. 3) [133].

4.1. Virtual proteolysis

Protein hydrolysis is typically the first step in the discovery of bioactive peptides. Hydrolysis parameters, including the specificity and concentration of hydrolytic enzymes, processing conditions, and degree of hydrolysis, all influence the biological properties of enzymatic hydrolysates and the resulting peptides [134]. Common methods for determining hydrolysis parameters include response surface methodology and single-factor experiments, but these approaches often require substantial experimental effort and resources and may fail to comprehensively explore all parameter combinations [135]. In recent years, virtual proteolysis has become a popular strategy for the discovery of bioactive hydrolysates. Combined with existing bioactive peptide databases, virtual proteolysis can simulate the hydrolysis of different proteins under the action of various enzymes, thereby enabling the rapid acquisition of information on protein-specific hydrolytic enzymes and the corresponding bioactive peptides. Several platforms, including BIOPEP, PeptideCutter, and EnzymePredictor, have been used to predict potential enzyme-specific cleavage sites and hydrolysis products [134]. For example, Tharindu et al.

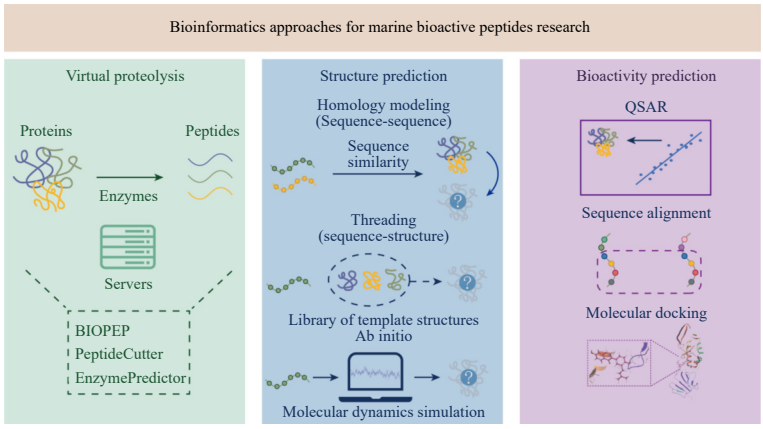

Fig. 3 Bioinformatics approaches for marine bioactive peptides research.

used the BIOPEP "Enzyme(s) Action" program to simulate gastrointestinal digestion by enzymes such as pepsin, trypsin, and chymotrypsin. Their results showed that three peptides, GPPGPQWPLDF, APDMAFPR, and GPGMMGP, isolated from sea cucumber by-products, could release active ACE-inhibitory fragments from their original sequences and were rich in proline and phenylalanine residues, which are frequently found in ACE-inhibitory peptides [128]. By combining *in silico* enzymatic hydrolysis using ExPASy PeptideCutter with PeptideRanker bioactivity prediction, Wang et al. screened 23 umami peptides from Atlantic cod myosin, of which 12 synthetic peptides showed synergistic umami effects with monosodium glutamate [136]. Based on a complex protein database containing 5 412 039 proteins from the salivary apparatus of 14 cephalopod species, Anrunes et al. generated more than 9 million nonredundant peptides using five proteases and effectively screened them using a series of prediction and sequence comparison tools. Through multiple analytical strategies, including machine learning, deep learning, multi-query similarity models, and complex network analysis, 808 representative nonhemolytic and non-toxic AMPs were identified [137]. To explore potential anticoagulant peptides, Zhang et al. constructed a deep-sea peptide database by simulating *in silico* proteolysis of protein sequences from animals inhabiting deep-sea hydrothermal vents and cold seeps. Using molecular docking and binding free energy calculations against coagulation factor FXIa, they identified two novel peptides, PRNIF (IC_{50} 0.67 mmol·L^{-1}) and GNDRCL (IC_{50} 1.52 mmol·L^{-1}), as promising anticoagulant candidates [138]. In physiological and pathological processes, proteases exhibit unique expression patterns and functional characteristics in different tissues and cellular environments. Therefore, in addition to nonspecific proteolysis strategies, targeting proteases specifically expressed *in vivo* for the screening and discovery of bioactive peptides represents an important strategic approach for the exploration of natural bioactive molecules. To systematically map the proteolytically regulated factors and therapeutic targets potentially cleaved by PCSK1 in the human genome, Coassolo et al. developed Peptide Predictor, a systematic computational-functional platform based on prohormone convertase PCSK processing analysis. Using this approach, they identified a broad group of evolutionarily conserved peptides and characterized BRP, a 12-mer peptide, as a potent anorexigenic agent [139]. Taken together, virtual proteolysis significantly enhances understanding of the relationship between peptide amino acid composition and gastrointestinal digestibility, thereby improving the efficiency of bioactive peptide discovery and screening. However, although computer-simulated hydrolysis is an efficient and low-cost method for generating theoretical hydrolysis products, *in vitro* and *in vivo* experiments are still required to validate the predicted results.

4.2. Prediction of peptide structures

The amino acid sequence and spatial conformation of peptides determine their physicochemical properties and biological functions. Accurate peptide structural information is essential for peptide design and optimization and facilitates deeper exploration of structure–activity relationships [133]. Advances in Edman degradation and mass spectrometry have enabled the elucidation of peptide primary structures. Although the primary sequence theoretically contains all the information necessary for folding into a functional conformation, the determination of stable folded conformations and their corresponding energy states remains challenging. Traditionally, physicochemical methods such as X-ray crystallography, nuclear magnetic resonance spectroscopy, and, more recently, cryo-electron microscopy have been used to observe the secondary and tertiary structures of peptides [140]. However, the complexity of sample preparation and high cost limit the broad application of these techniques. As a result, computer-based peptide structure prediction has become an important alternative for resolving complex peptide conformations. Molecular dynamics simulation (MDS) is a computational approach that calculates the motion and equilibrium of individual molecules and provides information about complex protein–ligand interactions at full atomic resolution and fine temporal scale [141]. At present, MDS-based peptide structure prediction methods can generally be divided into three categories: homology modeling, threading, and *ab initio* modeling. For instance, Armamdo et al. identified three antimicrobial peptides, Nv-p1-3, derived from *Nerita versicolor*. Given that Nv-p showed 100% sequence homology with the *N*-terminal region of *Tetrahymena* Gcn5 histone H4, the researchers predicted the tertiary structures of these Nv peptides by homology modeling and refined their conformations by molecular dynamics simulation, thereby providing a structural basis for the design and development of antibiotic alternatives against bacterial and fungal infections [126]. Bao et al. predicted and designed an artificially mutated AMP (mTgHbP7) from *T. granosa* hemoglobin. Utilizing the *ab initio* structure prediction platform I-TASSER, they predicted that mTgHbP7 formed an α-helical structure, which exhibited superior antimicrobial activity against *V. alginolyticus*, *V. parahaemolyticus*, and *E. coli* [125]. Kishimura isolated two novel peptides, IDHY and LVVER, from the water-soluble proteins of the red alga *Gracilariopsis chorda*, both of which showed significant ACE-inhibitory activity. The three-dimensional structures of the precursor proteins were then predicted using the SWISS-MODEL server, revealing that most ACE-inhibitory peptides were predominantly located in solvent-exposed α-helical regions [129]. Such studies support the analysis of peptide structure–activity relationships and the rational optimization of natural peptide derivatives. In addition, the rapid development of deep learning has greatly improved the accuracy of peptide structure prediction through the training of large-scale adjustable parameters. Current models such as AlphaFold2 [142], ESMFold [143], and RoseTTAFold [144] have shown outstanding performance in peptide structure prediction. Future progress will likely come from integrating traditional physics- and statistics-based algorithms with deep-learning approaches. Such integration may provide deeper insights into peptide folding mechanisms and further facilitate the study of structure–activity relationships in marine bioactive peptides.

4.3. Bioactivity prediction of peptides

Quantitative structure-activity relationship (QSAR) modeling is a robust computational method for analyzing chemical data. Its core concept is to establish relationships between the structural parameters of molecules and their biological activities and then use these mathematical models to predict or design target compounds with desired properties [145]. At present, QSAR modeling has been widely applied to the study of antimicrobial, antioxidant, ACE-inhibitory, and DPP-IV-inhibitory peptides. Zhu et al. constructed four QSAR models for antioxidant peptide screening, including two SVRG-DPPH and two SVEEVA-DPPH models. Combined with peptidomic analysis, this approach successfully identified three novel antioxidant peptides, AGWACLVG, YPLDL, and IDLAY, from the protein hydrolysate of *Chlorell* [127]. Based on a dataset of ACE-inhibitory peptides, Yang et al. developed prediction models for antihypertensive peptides, including tripeptides, hexapeptides, heptapeptides, and octapeptides, and screened six novel antihypertensive peptides. The *in vitro* evaluation results were highly consistent with the predicted values [146]. Wang et al. established a QSAR model based on the 5z-scale index and screened two novel potential ACE-inhibitory peptides, LTPFT and PLITT, from salmon muscle hydrolysates, demonstrating that this model is an effective strategy not only for the discovery of ACE-inhibitory pentapeptides but also for other beneficial bioactive

substances [130]. QSAR models predict peptide activity by clarifying structure-activity relationships, thereby enabling researchers to prioritize candidate molecules for further investigation. However, the predictive accuracy of current QSAR models is limited by the scope and quality of existing databases, particularly when applied to bioactive peptides with unique functions and complex chemical structures. Future discovery and characterization of novel bioactive peptides will contribute to database expansion and are expected to support the development of more accurate QSAR prediction models.

The amino acid sequence of a peptide, including the type, number, and position of amino acids, as well as the properties of key residues, such as charge, basicity, and hydrophilicity/hydrophobicity, greatly influences its biological activity. Therefore, establishing amino acid patterns based on residue preferences at specific positions in peptides with known functions can serve as a practical method for predicting peptides with similar activities [147]. For example, Xiao et al. analyzed the amino acid composition of peptides from fish swim bladders to evaluate their antioxidant activity. They then constructed a screening system for antioxidant peptides based on amino acid preferences, including: short peptides containing 2–15 amino acid residues, peptides containing aromatic amino acids, peptides containing specific residues such as proline, valine, leucine, and alanine, and peptides containing one or more hydrophobic amino acids. Using this strategy, they successfully predicted four new antioxidant peptides from fish swim bladders and verified their antioxidant activity *in vitro* [148]. Jiao et al. isolated and purified a series of potential ACE-inhibitory peptides from oysters. After sequence alignment, 13 peptides showed significant similarity to previously reported ACE-inhibitory peptides and shared several key active fragments, which were considered critical residues for ACE interaction [149]. In many cases, the biological activities of peptides can be attributed to the presence of specific key amino acids with characteristic properties, making this a simple and intuitive method for active peptide prediction. However, because bioactive peptides often possess complex tertiary conformations, accurate activity prediction still requires more advanced computational simulations combined with structural analysis.

Molecular docking is a bioinformatics-based simulation method used to explore the interactions between small peptide molecules and target proteins and to predict their binding modes and affinities [150]. It has been widely applied to the screening of bioactive peptides and the clarification of their molecular mechanisms. For example, Han et al. prepared several hypoglycemic peptides from red marine algae that enhanced insulin secretion and inhibited α-glucosidase activity. Molecular docking analysis showed that these peptides interacted strongly with α-glucosidase and DPP-IV, thereby exhibiting high inhibitory activity. Notably, proline residues were found to promote the binding of PBP peptides to the hydrophobic S1 pocket of DPP-IV [131]. In addition, Chen et al. discovered a neuropeptide Y-like peptide, ZoaNPY, from *Zoanthus sociatus* through transcriptomic analysis. Based on molecular docking and surface plasmon resonance experiments, they demonstrated that ZoaNPY directly and physically interacted with the NPY Y2 receptor [151]. Gao et al. used AlphaFold-driven molecular modeling combined with docking and molecular dynamics simulations to systematically elucidate the interaction mechanisms between Kv1.3 channels and ShK domain peptides from four sea anemone species in the South China Sea, highlighting their considerable potential for immune regulation and the treatment of metabolic disorders [138]. Despite its convenience for analyzing structure–activity relationships between proteins and bioactive peptides, molecular docking has certain limitations, including restricted sampling of ligand and receptor conformations and the use of approximate scoring functions that may generate results inconsistent with actual experimental binding affinities [152]. Therefore, molecular docking results still require experimental validation through methods such as cellular thermal shift assay (CETSA) [153], surface plasmon resonance (SPR) [154], and chemical pull-down assays [155] to confirm the interactions between peptides and target molecules.

5. Clinical applications of marine peptides

Marine peptide products have attracted increasing attention in a wide range of therapeutic fields because of their well-established biological activities and health benefits. In 2023, the global market for marine peptide products was valued at approximately USD 310 million, with a projected compound annual growth rate of 6.7%. This trend indicates that marine peptides are increasingly favored by both the market and consumers as bioactive ingredients with broad application potential. However, rigorous safety evaluation of marine-derived peptides remains essential for their commercialization. Although their biological activities have been widely confirmed, systematic assessment is still required because of their complex natural sources, potential toxicity risks, and interindividual variability.

As an important source of polypeptide raw materials, the pollution of the marine ecological environment directly threatens raw material safety. Pollutants, including heavy metals such as mercury and cadmium [156], microplastics [157], and algal toxins, such as ciguatoxin [158], can accumulate in marine organisms through bioaccumulation. These contaminants may then be transmitted through the food chain, causing acute poisoning in humans, such as respiratory failure after consumption of shellfish or seafood contaminated with algal toxins [159] or chronic health damage, such as DNA damage induced by heavy metals [160]. The characteristics of this contamination transfer chain make it necessary for polypeptide raw materials to undergo origin screening, pretreatment procedures such as ultrafiltration and ion exchange, and contaminant detection methods such as ICP-MS and ELISA to ensure safety.

Marine peptides are widely used in medicine and functional foods because of their structural diversity and high biological activity, but their potential toxicity remains an important limiting factor for industrialization [161]. Conotoxins are among the most extensively studied marine bioactive polypeptides. Although ziconotide, a conotoxin-derived drug, has been approved for the treatment of severe chronic pain, other modified conotoxins, such as Contulakin-G and χ-conotoxin MrIA, were discontinued during clinical development because of toxic side effects [162]. In addition, μ-conotoxin GIIIB can cause muscle paralysis by binding to voltage-gated sodium channels (Nav1.4), with a half-maximal inhibitory concentration as low as 1–10 nmol·mL^{-1}, which may induce respiratory failure [163]. Sea anemone peptides such as ShK target the Kv1.3 channel and inhibit T-cell activation, but excessive use may lead to immunosuppression [164]. Beyond toxicity caused by ion channel interference, marine peptides may also induce toxic side effects through irreversible inhibition of key proteases or disruption of cellular metabolism. For example, the cyanobacteria-derived peptide lyngbyatoxin-3 inhibits mitochondrial complex I activity (IC_{50} 30 nmol·mL^{-1}), leading to ATP depletion and oxidative stress in hepatocytes and ultimately causing liver necrosis [165]. Similarly, the sea anemone peptide APETx4 induces synchronous energy failure in cardiomyocytes and hepatocytes by inhibiting complex I (IC_{50} 50 nmol·mL^{-1}), thereby causing combined cardiohepatic toxicity [166]. Peptide therapeutics offer important advantages, including high target specificity, low molecular weight, and relatively limited off-target effects. However, their unique structural features may also contribute to dose-limiting toxicity, which remains a major obstacle to the development of marine-derived peptide drugs. At the same time, a deeper understanding of these toxicities may help accelerate pre-

cision drug design. By elucidating toxicity mechanisms through multi-omics analyses, applying artificial intelligence-driven structural optimization, and developing intelligent delivery platforms, it may be possible to promote the development of next-generation marine peptide drugs with controllable toxicity and enhanced therapeutic efficacy. Specifically, machine learning algorithms can be used to comprehensively analyze key peptide properties, such as antibacterial activity and hemolytic toxicity. In addition, random forest classifiers can integrate local and global molecular descriptors, including free energy conversion, solvation accessibility, and charge distribution, to improve the accuracy of prediction and screening [167].

Another major factor affecting the clinical development of marine peptides is pharmacokinetics. Their stability, bioavailability, and tissue distribution are all critical determinants of clinical success or failure. For example, the classic conotoxin peptide ziconotide cannot enter the central nervous system through systemic administration. In addition, it has a short half-life, ranging from 2.9 to 6.5 h after intrathecal injection, and therefore requires continuous intrathecal infusion to maintain efficacy. Clinically, intrathecal administration has only been approved for intractable pain, which limits the eligible patient population [168]. The marine fungal cyclic peptide plinabulin is rapidly metabolized after intravenous injection, with a plasma half-life of only 2–3 h. The failure of its phase III clinical trial in NSCLC in 2022 was associated with this short half-life [169]. Similarly, the sea anemone toxin peptide dalazatide shows poor subcutaneous absorption and a bioavailability of less than 10%, requiring high-dose administration (> 1 mg·kg^{-1}). In 2021, its development for psoriasis was terminated during phase II trials because of unstable efficacy [170]. Common pharmacokinetic challenges in the development of marine polypeptide drugs include low oral bioavailability, short half-life, poor blood–brain barrier penetration, and limited tissue distribution. Some established strategies have already been proposed to address these limitations. For example, cyclization or *D*-amino acid substitution can improve resistance to enzymatic hydrolysis and thereby enhance oral bioavailability [171]; PEGylation or albumin fusion can prolong circulation time and increase half-life [172]; and conjugation with cell-penetrating peptides can improve blood–brain barrier permeability [173]. In addition, integration of AI-based deep learning for the prediction of the ADME properties of marine peptides may accelerate the screening of lead compounds. Advanced predictive platforms such as OptADMET and ADMETlab 3.0 can be used to systematically improve ADMET assessment of bioactive peptides. Through data-driven chemical transformation rules, these platforms can optimize as many as 32 ADME-related properties [174].

Overall, the development of marine polypeptide drugs has made remarkable progress in recent years, with the market size continuously expanding and therapeutic potential being demonstrated across multiple disease areas. However, industrialization still faces two major challenges: potential toxicity and pharmacokinetic bottlenecks. As a result, many clinical studies have been terminated prematurely. Future development is likely to focus on AI-based prediction of toxicity and ADME properties, structural optimization, and intelligent delivery systems. By integrating multi-omics analysis of toxicity mechanisms with green production processes, the translation of marine polypeptide drugs from the laboratory to clinical practice may be substantially accelerated.

6. Conclusions and future perspectives

Marine peptide drugs have shown a positive development trend in both the market and clinical research because of their unique nutritional value and health benefits. Bioactive peptides or peptide analogs extracted from cone snails, sea hares, sea squirts, and mollusks have already been partially commercialized or have entered clinical trials. Compared with traditional small-molecule drugs, peptide therapeutics function as signaling molecules with high selectivity and activity, enabling them to bind specific cell-surface receptors through defined amino acid sequences or to penetrate cells and exert biological effects. In addition, compared with protein-based biopharmaceuticals, peptide therapies usually exhibit relatively low immunogenicity and are less likely to trigger severe immune reactions, which is especially important for long-term treatment. Owing to these attractive pharmacological characteristics and intrinsic properties, peptides represent excellent starting points for the development of new therapies. The isolation of peptides with novel structures, remarkable biological activities, and high safety from marine organisms of diverse origins has therefore become a major research focus. Traditional methods, combined with modern technologies and multi-technology integration, have substantially improved the efficiency of the separation, purification, and identification of marine bioactive peptides. On the one hand, in the field of metabolism, the gut microbiota contains a wide range of bacteria capable of efficiently degrading ingested protein fragments or signaling molecules. Therefore, the use of biomimetic systems that simulate the intestinal microbial environment, together with the colonization of bacteria capable of efficiently degrading natural products, may facilitate the identification of new bioactive peptides. On the other hand, bioinformatics has overcome many traditional limitations in bioactive peptide research by simulating proteolysis, providing conformational information, predicting potential biological activities, and elucidating molecular interaction mechanisms. To investigate the biological activities of marine peptides and analyze their structure-function relationships, accurate tertiary structural information is essential. Conventional structure prediction methods, including molecular docking and molecular dynamics simulation, are often time-consuming and have limited accuracy, which necessitates extensive experimental validation. The rapid development of deep learning has revolutionized structural biology. Recently, DeepMind introduced AlphaFold3, which can predict the tertiary structures and intermolecular interactions of biomolecules such as proteins and DNA with unprecedented accuracy, reportedly exceeding that of previous prediction methods by at least 50%. Such high-quality models have opened new opportunities for mechanistic studies and structural design of marine bioactive peptides. Accordingly, future research should focus on the development of more precise bioinformatics models incorporating flexible docking strategies and dynamic interaction prediction, so as to more accurately simulate peptide behavior in the cellular environment. Notably, multi-omics technologies integrate genomic, transcriptomic, proteomic, and metabolomic data to systematically elucidate the structure-function relationships of bioactive peptides. For example, transcriptome-based screening can identify coding sequences for degradation-prone peptide fragments, whereas metabolomic profiling can dynamically monitor degradation products, thereby guiding targeted optimization of side-chain modifications or backbone structures to improve peptide stability and bioactivity. At the same time, integrated analysis of transcriptomic and proteomic data enables comprehensive elucidation of the biosynthesis, regulation, molecular interactions, and downstream effector networks of bioactive peptides, thereby systematically revealing their precise mechanisms of action under both physiological and pathological conditions. This approach provides a solid theoretical foundation for their future clinical application. At present, marine bioactive peptides have been shown to offer multiple health benefits and have been incorporated into therapeutic studies and clinical investigations targeting cancer, cardiovascular diseases, autoimmune disorders, and other conditions. At the same time, some marine bioactive peptides have been used as major com-

ponents in dietary supplements, functional foods, and specialized medical formulae. However, the number of marketed marine-derived products remains limited, largely because of poor membrane permeability and insufficient metabolic stability. To overcome these barriers, chemical modification of peptide side-chain functional groups can improve the bioavailability and stability of peptide drugs. In particular, based on fixed molecular properties or responsiveness to external microenvironments, molecular and nanodrug delivery systems, including targeting peptides, cell-penetrating peptides, responsive peptides, and self-assembled peptides, are emerging as cutting-edge strategies in the pharmaceutical application of marine bioactive peptides. In addition, conjugation of peptides with small molecules, oligoribonucleotides, or antibodies may further expand the applicability of peptides as therapeutic agents. Overall, future studies should place greater emphasis on safety evaluation and quality control standards for marine bioactive peptides in order to promote their broader application in the food and pharmaceutical industries.

Funding

This work was supported by the National Key Research and Development Program of China (No. 2023YFC2812500).

Declaration of competing interests

These authors have no conflict of interest to declare.

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This cover illustration systematically delineates the multifaceted bioactivity mechanisms of marine-derived bioactive peptides. At the center, helical and linear peptide chains derived from diverse production pathways including marine organism extraction, enzymatic hydrolysis, microbial fermentation, and biosynthesis converge into a dynamic molecular network, visually representing the remarkable structural diversity of marine peptides. Radiating outward from this central network are six principal modules of bioactivity. Antidiabetic activity improves systemic glucose homeostasis via modulation of whole-body glycemic signaling networks; Anti-inflammatory activity maintains cellular integrity through immunomodulation; Antibacterial activity acts with precision upon structural targets in pathogenic microorganisms to maintain microecological equilibrium; Antioxidant capacity efficiently scavenges reactive oxygen species (ROS) throughout the body, thereby preserving the integrity of cellular macromolecules and membrane systems; Antihypertensive activity exerts cardiovascular protection through intervention in key pathways such as the renin-angiotensin system; Antitumor activity targets signaling transduction and apoptotic regulation nodes in aberrantly proliferating cells. Interwoven connection nodes and algorithmic graphical elements in the background symbolize the technical framework of artificial intelligence-driven structural prediction and virtual bioactivity screening. This visual metaphor highlights the enabling role of AI based learning in accelerating the translational trajectory of marine peptides, encompassing not only sequence discovery and structure-activity relationship elucidation but also the development of precision therapeutics and functional food ingredients.