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Short review

Marine invertebrates' proteins: A recent update on functional property

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ABSTRACT

The marine invertebrates are vast species in the animal kingdom which consists abundant source of novel functional biopolymers like proteins, lipid and polysaccharides that possess numerous biological activities. These biopolymers had been used for multiple application and served as a functional food for health perspective. In recent times, marine organisms were effectively investigated for potential pharmaceuticals and natural drugs. Besides, marine invertebrate proteins including peptides served as a traditional food and effective alternative medicine for infectious disease. This review focuses on antioxidant, anticancer, antimicrobial activities of peptides and protein including collage and gelatin, were critically analysed with global market status of protein and peptides from marine invertebrates. Hence, this would give more insight on functional property of marine invertebrate, and their applications in biomedical and food industrial application.

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1. Introduction

The marine environment serves as a significant reservoir of biodiversity with the richest source of primary and secondary metabolites. Marine invertebrates are found to be a diverse group widely distributed in the intertidal zone to deep ocean ecosystem. These are classified into different taxonomic groups such as Porifera (sponges), Cnidaria (corals, jellyfish), Annelida (marine worms), molluscs (oysters, squids, mussels, prawns and crayfish), and echinoderms (starfish, sea cucumbers and sea urchin). There is a long history of dietary habits and medicinal practices of using marine invertebrates among the coastal communities (Sudhakar and Nazeer, 2015). Therefore, this raising the aquaculture production in last few decades which had annual growth rate of 5.8% during the period of 2000–2016 (FAO, 2018). The growth of aquaculture contribution about 73.4 million tonnes which are almost 44% of total food fish production and from the marine and brackish environment (mariculture) it contributes 27.6 million tonnes (37.6%). About 60% of mariculture income from the molluscs and crustaceans farms. The economic important species are salmon, seabass, seaweeds, seabream, barramundi and bivalve molluscs (e.g., clams, mussels, oysters, and scallops) (Ahmed and Thompson, 2019). Mariculture production is dominated by algae (46.2%) followed by bivalve 42.9% and marine fishes (3.7%) and crustaceans (1.8%) (FAO, 2018). Further, awareness of functional foods and therapeutic properties on marine natural products have been growing in recent times. According to the latest report, marine aquaculture products reach the global market at $226.2 billion by 2022 (Newswire, 2019a). These type of foods are mainly utilized for pharmacological and medicinal properties and extraction of metabolites such as fatty acids, protein, peptides and other carotenoid derivatives.

Therefore, this review focuses on wide variety of marine invertebrate proteins and peptides aiming for food application in future. In addition, different fraction of proteins and peptides from marine invertebrates with a detailed comparison of molecular weight for upscaling their uses for human wellness were discussed and evaluated with recent literature.

2. Protein fractions and its functional property

2.1. Biological action of protein sequence based on molecular weight

Bioactive peptides are discharged during enzymatic dehydration or solvent extraction; their biological activity might affect the type of protein fractions, hydrolytic compounds, catalyst substrate proportion, temperature and time of response (Xu et al., 2013). These conditions would influence the sub-atomic weight and peptides fractions and, this influence the functional property of proteins. As per recent report jellyfish had highest amount of bioactive peptides due to high protein content, mainly collagen from 40 to 60% of DW. Besides, the peptides PIIVYWK (Pro-Iso-Iso-Val-Tyr-Try-Lys) (1004.57 Da), and FSVVPSPK (Phe-Ser-Val-Val-Pro-Ser-Pro-Lys) (860.09 Da) from m*ytilus edulis* exhibit hepatoprotective activity through upregulation of heme oxygenase-1 (HO-1) on hepatocytes against H_2O_2-induced hepatic damage (Park et al., 2016). The hydrolysis of ark shell Scapharca subcrenata by pepsin yielded two peptides MCLDSCLL(P1)(Met-Cys-Leu-Asp-Ser-Cys-Leu-Leu) and HPLDSLCL(P2) (His-Pro-Leu-Asp-Ser-Leu-Cys-Leu) with MW of 897.5 Da showed potent free radical scavenging activity to (2,2-diphenyl-1-picrylhydrazyl) DPPH, ABTS (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) and (oxygen radical absorbance capacity) ORAC (Jin et al., 2018). However, ark shell protein hydrolysate with less than 1 kDa fractions stimulate the production of bone morphogenetic protein-2 (BMP-2), p-Smad1/5, Runx2, Dlx5, osterix, and mitogen-activated protein kinase (MAPKs) in mouse mesenchymal stem cells (MSC) and also up-regulated alkaline phosphatase (ALP) activity, mineralization, type I collagen and osteocalcin seen in MSC (Hyung et al., 2017). Similarly, Hyung et al. (2018) reported that blue mussel M. edulis protein hydrolysates with less than 1 kDa stimulate the osteoblast differentiation in mouse MSC through enhance the ALP initiation, osteocalcin and type I collagen activity along with calcium deposition. In addition, the peptic hydrolysate of ark shell with the average MW of 235.17–897.52 Da showed inhibition of adipogenesis through down-regulating adipocyte-specific protein expression together with peroxisome proliferator-activated receptor γ, CCAAT/enhancer-binding protein α, with sterol regulatory element-binding protein 1c, but this action down-regulated fatty acid synthase expression and lipoprotein lipase (Hyung et al. 2017). This confirms that based on the amino acid sequences, peptides derived from different marine invertebrates had varied biological property (Fig. 1).

2.2. Anticancer and antioxidant activity of protein and peptide of marine invertebrates

According to Hu et al. (2012) reported that polypeptide fraction from *Arca subcrenata* showed antitumor activity *in vitro* and *in vivo* HeLa and HT-29 (colon cancer cell line) cell lines (IC_{50} of 11.43 μg/mL for HeLa (cervical cancer cell line) and 13.00 μg/mL for HT-29, similarly the same species with purified polypeptide (H3) shows MW of 20,491.0 Da exhibited antioxidant action ranges from 56.8% and 47.5% against (DPPH). However, higher MW from protein-enriched fraction of *M. edulis* (50 kDa) displayed 90%, 89%, 85% and 81% mortality rate against PC3 (prostate cancer cell), A549 (type II pulmonary epithelial cell), HCT15 (colon carcinoma cell) and BT549 (breast carcinoma cell) cell lines, respectively at the concentration of 44 μg/mL (Beaulieu et al., 2013). The polypeptide fraction of *A. subcrenata* mediates anticancer activity through apoptosis which arrests the G2/M phase via ROS-Mediated MAPKs Pathways (Hu et al., 2015). The *M. edulis* α-chymotrypsin hydrolysate protect the human umbilical vein endothelial cells (HUVECs) against H_2O_2-Induced cytotoxicity and increased HUVEC viability up to 85.35% at the concentration of 0.5 mg/mL. The *M. edulis* α-chymotrypsin hydrolysate increased HUVEC cell viability of toxicity induced by H_2O_2 was mediated by inhibition of apoptotic pathway via downregulating apoptotic gene p53, caspase-3, and the bax and upregulating bcl-2. Besides, *M. edulis* α-chymotrypsin hydrolysate increase the intracellular antioxidant status, such as glutathione (GSH) , superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Oh et al., 2019).

The peptide obtained from pepsin hydrolysate of *Octopus aegina* exhibited DPPH scavenging activity of 44.39% at the concentration of 1.5 mg/mL and hydroxyl activity of 38.84% at a concentration of 0.25 mg/mL (Sudhakar and Nazeer, 2017). The different type of peptide was obtained by hydrolysis of *M. edulis* with eight different types of protease like alcalase, α-chymotrypsin, flavourzyme, neutrase, papain, pepsin, protamex, and trypsin. Amongst

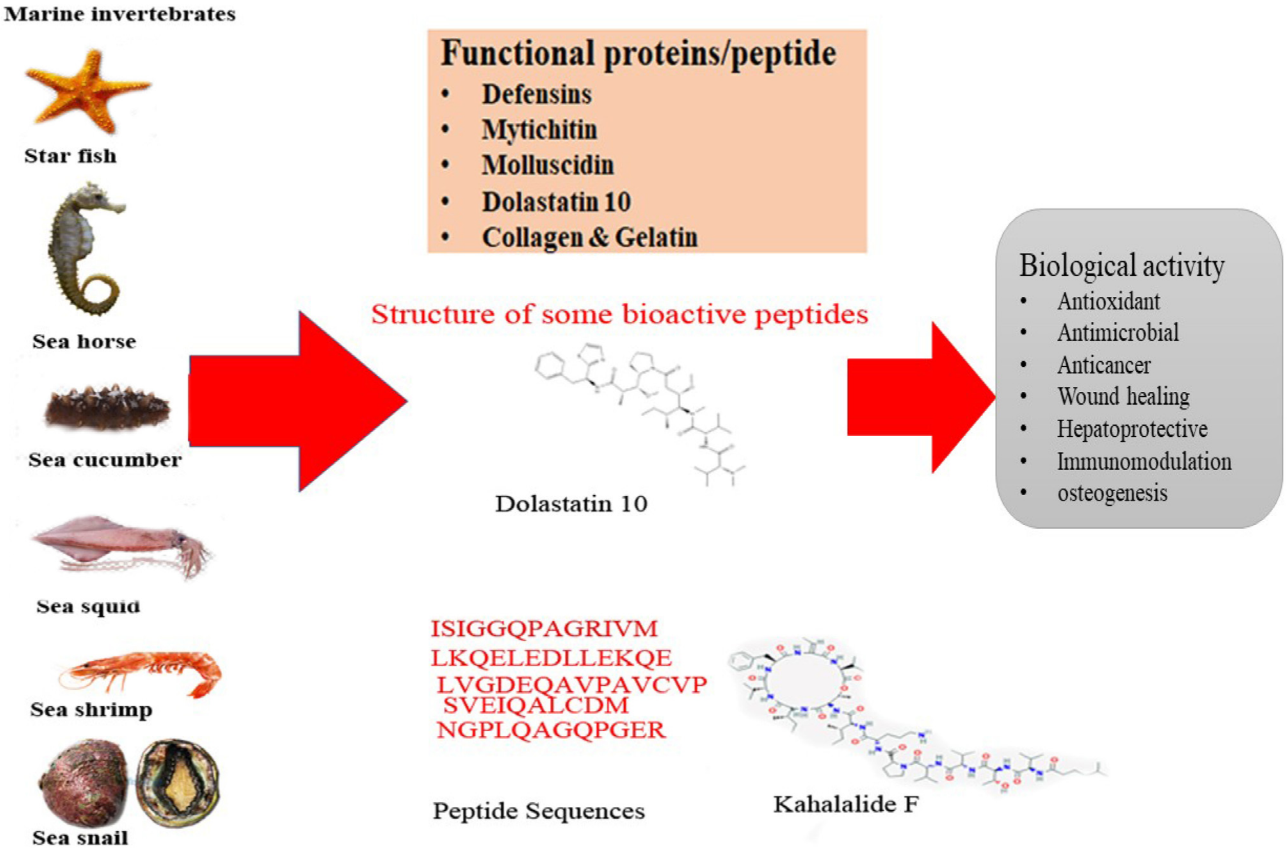

Fig. 1. Functional protein and peptides from marine invertebrate.

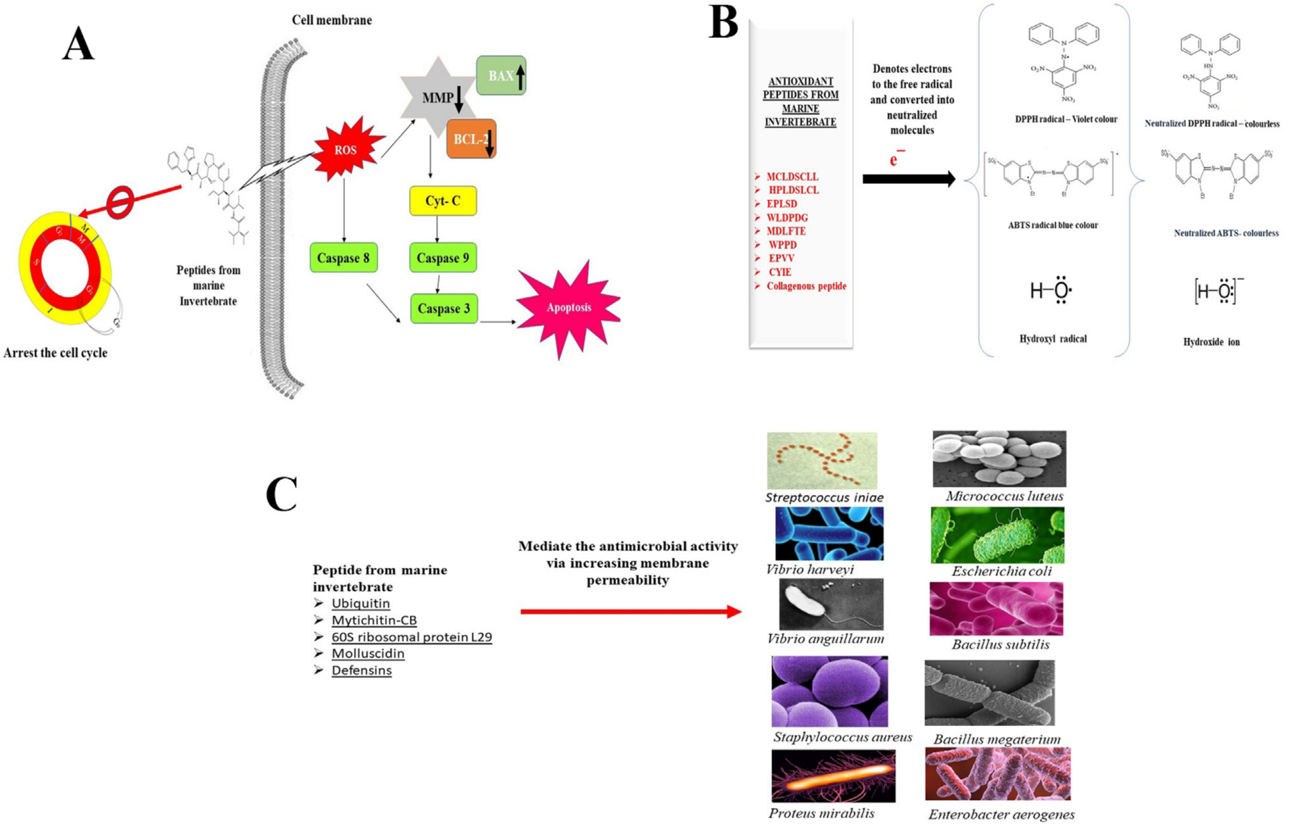

Fig. 2. Biological activity of peptides and proteins from marine invertebrate; A – Anticancer activity; B – Antioxidant activity; C – antimicrobial activity.

α-chymotrypsin mediated hydrolysate had highest ABTS$^+$ radical scavenging (117 μM TE/mg sample), ORAC (199.62 μM TE/mg sample) and DPPH radical scavenging activity (IC_{50} of 0.35 mg/mL). The report from Yang et al. (2019), purified six antioxidant peptides EPLSD (Glu-Pro-Leu-Ser-Asp), WLDPDG (Trp-Ile-Asp-Pro-Asp-Gly), MDLFTE (Met-Asp-Leu-Phe-Thr-Glu), WPPD (Trp-Pro-Pro-Asp), EPVV (Glu-Pro-Val-Val), and CYIE (Cys-Tyr-Ile-Glu) from marine bivalve mollusk *tergillarca granosa*. These peptides could be applied as functional food ingredients to enhance the nutraceutical value of regular diet (Fig. 2).

2.3. Antimicrobial activity of protein sequence from edible marine invertebrates

Seo et al. (2013) reported that polypeptide ubiquitin (74 amino acid residues) with MW of 8.47 kDa exhibited strong antimicrobial activity against gram-negative, positive bacteria including *Streptococcus iniae* and *Vibrio parahaemolyticus* with the minimal inhibitory concentrations (MIC) ranging from 7.8 and 9.8 (μg/mL) without hemolytic activity, respectively. The cysteine-rich polypeptide myricetin-CB from *M. coruscus* showed better antimicrobial activity against gram-positive strains like *Bacillus subtilis*, *Staphylococcus aureus, S. luteus* and *B. megaterium* with MIC of less than 5 μM and showed moderate antifungal active against *Candida albicans* and *Monilia albican* (MIC > 5 μM) (Qin et al., 2014). Similarly, pacific oyster *Crassostrea gigas* protein with MW 6.4 kDa consists of 60S ribosomal protein L29 displayed potent antimicrobial activity (Seo et al., 2017). Molluscidin, a polypeptide from *Haliotis discus* has MW of 4.76 kDa with 46 amino acids and showed broad and potent antimicrobial spectrum without hemolysis (Seo et al., 2016), besides, molluscidin (5.6 kDa) purified from *Atrina pectinata* had 59 amino acid residues with repeats of Lys-Lys and Lys-Gly dibasic amino acid reported antimicrobial activity against *B. subtilis* at MIC of 2.1 μg/mL and *Escherichia coli* of MIC = 0.5 μg/mL, without hemolytic activity (Hong et al., 2018). Antimicrobial activity of polypeptide defensins from *Venerupis phlippinarum* and reported that defensins increased the cell membrane permeability of bacteria (Yang et al., 2018), antiviral activity of proline-rich peptides from marine snail rapanavenosa and reported that its isoforms against Epstein-Barr virus (Dolashka et al., 2011; 2014). Further, defensins had broad spectrum of antimicrobial action against S. aureus, Micrococcus luteus, V. anguillarum, Enterobacter cloacae, V. harveyi, Proteus mirabilis, Enterobacter aerogenes, V. parahaemolyticus, V. splendidus and E. coli with the MIC ranging from 0.5 μM to 8 μM. The antimicrobial peptide defensin from *V. philippinarum* demonstrated potential inhibitory activity against *M. luteus* and destroyed this bacteria through membrane permeability (Zhang et al., 2015). The antimicrobial property of this peptide from marine invertebrate could act as a nutraceutical molecule with food preserving entity (Fig. 2).

2.4. Biological action of collagen and gelatin

Collagen and properase E hydrolysate from jellyfish had the ability to increase the moisture in skin of UV-induced mice and also restore the endogenous collagen and elastin fibers, through type I to III collagen (Fan et al., 2013). The collagenous peptide extracted from Chrysaora sp. by the action of enzyme trypsin displayed highest DPPH radical scavenging activities (94% at 2 mg/mL) which possess angiotensin-I-converting enzyme (ACE) inhibitory activity of 89% as compared to other protein hydrolysate extracted using enzymes alcalase and Protamex. The high biological activity of collagenous peptide from trypsin hydrolysate may due to high proposition of hydrophobic amino acids with unique amino acid arrangements (Barzideh et al., 2014). Similarly, jellyfish Nemopilema nomurai stimulate the immune system in mouse by activating bone marrow-derived dendritic cells and produces inflammatory cytokines tumor necrosis factor (TNF)-α, Interleukin 6 (IL-6), IL-1β and IL-12. This collagen peptide underwent macrophage J774.1 cells and stimulated cytokine production via activation of the (nuclear factor kappa-light-chain-enhancer of activated B cells) NF-κB and JNK (c-Jun N-terminal kinase) signalling cascades through TLR4 (Toll-like receptor 4) (Putra et al., 2015). The collagen from jellyfish Rhopilema esculentum acts like collagen type I which enhanced the hemostatic process. This mechanism of action was due to improved physical absorption of collagen on the system (Cheng et al., 2017) similar to other marine based biopolymer like carrageenan (Ganesan et al., 2018a, 2018b; Mohan et al., 2018). The collagen peptide fractions from *R. esculentum* with less than 25 kDa MW presented significant effects on scratch closure at a concentration of 6.25 μg/mL for 48 h and also showed that increased the production of β-fibroblast growth factor (β-FGF) and transforming growth factor-β_1 (TGF-β_1) expression (Felician et al., 2019). This confirms collagen found to be suitable candidate for wound dressing applications. Table 1 depicts the protein from the source of edible marine invertebrates and its biological action.

2.5. Collagen and gelatin prospective application

The commercially useful compounds from edible marine invertebrates are collagen and gelatin. Collagen is present in all animals in skins and bones around 30% of total content (Silva et al., 2014). Marine organism-based collagen is a promising candidate which replaces mammal-derived collagen and widely used for much biomedical application (Silva et al., 2014; Silvipriya et al., 2015). In food application, collagen is a primary raw material for the production of gelatin and acts as a functional protein for its gelling property. Further, the rheological properties of collagen found to be desirable such as improved elasticity, shear thinning and apparent viscosity which is directly used in food application as a texture enchancer (Ganesan et al., 2019). Gelatin is water soluble protein with MW of 80–250 k Da and it exhibits 88% protein, 10% moisture, and 1–2% salts. In gelatin and collagen, some of the amino acid derivatives are glycine, proline and hyroxyproline which play a role towards thermal stability and improve rheological properties. Moreover, using mammalian tissue causes serious health risk for human i.e hoof and mouth disease, bovine spongiform encephalopathy which is infectious disease spreading via food. Subsequently, marine source is the best alternative to prevent these kinds of disease widespread and also topped with functional properties (Silvipriya et al., 2015). Furthermore, the complex structure of gelatin is poly-ampholyte cross-linking and protein structure constituents biocompatible properties, because of this gelatin does not come under E-number which is classified as a food product (Ofokansi et al., 2010). In bioengineering, gelatin plays a crucial role as encapsulating material or coated gelatin shows efficient loading and drug release properties. There are many advantages of using gelatin in nanoencapsulation. This will improve the product deprivation, free from oxidation, and therefore extend core product shelf-life before its final (Nikkhah et al., 2016; Oh et al., 2019).

3. Commercial value of protein from edible marine invertebrate's origin

The global market value of functional proteins expected to reach $7.98 billion by 2026 with an annual growth rate of 6.93% from 2019 to 2026 (Newswire, 2019a). Collagen is one of the important macromolecule from marine invertebrates. These molecules have vast application on food, pharmaceuticals and healthcare industry. Therefore, the demand for collagen and its hydrolyzed gelatin were

Table 1
Protein from edible marine invertebrates and its biological action.

Invertebrate type	Phylum	Species	Protein/peptide fraction	Biological activity	Molecular weight (MW)/ Extraction method/Techniques used for characterization	Reference
Squid	Mollusca	*Loligoduvauceli*	Hexapeptide Trp-Cys-Thr-Ser-Val-Ser,	Antioxidant activity (inhibited lipid peroxidation)	MW 682.5 Da/ion exchange chromatography and gel filtration chromatography using fast protein liquid chromatography (FPLC)	Sudhakar et al. (2015)
Squid	Mollusca	*Todarodespacificus*	Protein hydrolysate	anti-inflammatory tumour necrosis factor (TNF) and antioxidant (DPPH)	high hydrostatic pressure (HHP at 200, 400 and 600 MPa)	Zhang et al. (2016)
Sea snail	Mollusca	*Cumia reticulata*	Polypeptides, three vWFA1 domains and named vWFA48, vWFA59 and vWFA105	Anti-homeostatic compounds	Molecular docking	Modica et al. (2018)
Snail	Mollusca	*Helix lucorum*	RvH2-g hemocyanins	Anticancer activity (CAL-29 bladder cancer cell lines)	Gene expression	Antonova et al. (2015)
Sea snail	Mollusca	*Rapanavenosa*	RvH1 and RvH2 Hemocyanin	Antiviral action against (Epstein-Barr virus) *in vitro*	Pyridylethylation and Enzymatic Digestions	Dolashka et al. (2014)
–	Mollusca	*Mollusc species*	Hemocyanin, haliotisin peptides	Antimicrobial (B. subtilis and E. carotovara)	HPLC	Zhuang et al. (2015)
Sea snail	Mollusca	*Haliotis rubra*	Hemocyanin	antiviral activity (herpes simplex virus type-1)	700–800 kDa/Ultrafiltration	Zanjani et al. (2014)
Sea snail	Mollusca	*Haliotis rubra*	Hemocyanin	antiviral activity (vero cells vUL37-GFP HSV-1)	Gel filtration chromatography	Talaei Zanjani et al. (2016)
Clam	Mollusca	*Arcasubcrenata*	Polypeptide	Anticancer activity (HeLa (human cervical cancer cell) and RAW264.7 cells)	ion-exchange chromatography	Wu et al. (2014)
Snail	Mollusca	*Helix pomatia*	Hemocyanin	Immunomodulation action	anti-TT IgG (tetanus toxoid (TT)	Gesheva et al. (2015)
Oyster	Mollusca	*Crassostrea madrasensis*	Protein	Antibacterial activity (V. parahaemolyticus, Salmonella sp, Shigella sp, Streptococcus sp and Staphylococcus sp)	Dialysis	Muthezhilan et al. (2014)
Saltwater clam	Mollusca	*Venerupisphilippinarum*	Defensins (Protein)	Antimicrobial activity (Staphyloccocus aureus and M. luteus) and eight Gram-negative bacteria (V. anguillarum, Entherobacter cloacae, Pseudomonas putida, Proteus mirabilis, Enterobacter aerogenes, V. parahaemolyticus, V. splendidus and V. harveyi)	Recombinant expression	Zhang et al. (2015)
Sea snail	Mollusca	*Rapanavenosa*	Proline rich pepdite	Antiviral Activity (Staphylococcus aureus) and a Gram-negative (Klebsiella pneumoniae))	3000 and 9500Da/ ultrafiltration and reverse-phase high-performance liquid chromatography (RP-HPLC)	Dolashka et al. (2011)
Mussel	Mollusca	*Mytilus coruscus*	Pepdite (mytichitin-CB)	Antimicrobial activity (B. subtilis, S. aureus, S. luteus; and B. megaterium)	RP-HPLC	Qin et al. (2014)
Mussel	Mollusca	*Mytilus coruscus*	Cysteine-rich myticin, mytilin and mytimycin	Antimicrobial activity (Sarcina luteus and Escherichia coli)	11,269.37 Da/HPLC purification	Liao et al. (2013)
Mussel	Mollusca	*Mytilus coruscus*	Myticusin	Antimicrobial activity (gram-positive, gram-negative bacteria)	6202 Da/C18 reversed-phase high-performance liquid chromatography (HPLC)	Oh et al. (2018)
Sea snail	Mollusca	*Haliotis discus*	HdMolluscidin	Antimicrobial activity (Bacillus subtilis and Staphylococcus aureus (minimal effective concentrations [MECs]; 0.8–19.0 μg/mL) and Gram-negative bacteria including Aeromonas hydrophila, Escherichia coli, Pseudomonas aeruginosa, Salmonella enterica, Shigella flexneri, and Vibrio parahemolyticus)	4.7 kDa/C18 reversed-phase high-performance liquid chromatography (HPLC)	Seo et al. (2016)
Oyster	Mollusca	*Crassostrea gigas*	Ubiquitin with terminal Gly–Gly doublet	Antimicrobial activity (Streptococcus iniae and Vibrio parahemolyticus)	8471 Da/C18 reversed-phase HPLC	Seo et al. (2013a)
Oyster	Mollusca	*Crassostrea gigas*	60S ribosomal protein L29	Antimicrobial activity (B. subtilis and E. coli)	~6.4-kDa/C18 reversed-phase HPLC	Seo et al. (2017)
Oyster	Mollusca	*Crassostrea gigas*	cgMolluscidin	Antimicrobial activity (Bacillus subtilis, Micrococcus luteus, and Staphylococcus aureus)	5.5 kDa/C18 reversed-phase HPLC	Seo et al. (2013b)
Pen shell	Mollusca	*Atrinapectinata*	cgMolluscidin	Antimicrobial activity (Candida albicans, Bacillus subtilis)	5.6 kDa/cation exchange and C18 reversed-phase HPLC	Hong et al. (2018)

Table 1 (*continued*)

Invertebrate type	Phylum	Species	Protein/peptide fraction	Biological activity	Molecular weight (MW)/ Extraction method/Techniques used for characterization	Reference
Sea horse	Chordata	*Hippocampus trimaculatus*	Peptide (Oligomeric Aβ42) Gly-Thr-Glu-Asp-Glu-Leu-Asp-Lys	neuroprotective effects against Aβ42-induced neuronal death in PC12 cells	906.4 Da/Enzymatic degradation	Pangestuti et al. (2013)
Clam	Mollusca	*Sinonovaculaconstricta*	Peptide	antihypertensive activity (ACE-inhibitory activity)	3 kDa/Ion exchange	Li et al. (2016)
Jellyfish	Cnidaria	*Rhopilema esculentum*	Peptide Ser-Tyr	Antioxidant (DPPH, super oxygen anion scavenging activities) and antihypertensive activity (ACE inhibitory activity)	268.1 Da/ultrafiltration, gel filtration chromatography, and RP-HPLC	Q. Zhang et al. (2018)

found increased utilization in tissue engineering, bone grafting, drug delivery system, wound healing and cosmetic surgeries. According to recent data, the growth rate of global collagen market increased by 9.4% over the period from 2015 to 2023 and collagen market value expected to attain a value of $9.37 billion by 2023 from a value of $4.13 billion in 2014 which mainly derived from marine sources. Gelatin has global market value of 7.14% annual growth rate between 2019 and 2024 (Newswire, 2019b,c). The commercial market value is expected to reach around $22 billion by 2016 with the annual growth rate of 20.2% over the estimated time frame from 2019 to 2026 (Newswire, 2019a).

4. Conclusion

Thus, marine peptides and proteins have vast biomedical applications like antioxidant, antimicrobial, anticancer, hepatoprotective, bone marrow regeneration and tissue regeneration properties. The market value of these proteins and peptides is increasing every year, and this shows the value in nutraceutical and biomedical industries. In future, these proteins and peptides from marine invertebrates could be a valuable ingredient in the food, feed and pharmaceutical industries.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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