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Characterization, therapeutic applications, structures, and futures aspects of marine bioactive peptides

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Abstract— *Bioactive peptides from marine species have gained attention due to their promising biological features, and the disciplines of pharmaceutical, cosmeceutical, nutraceutical, and biomedical product development have increased recently. Their molecular mass, immunity, and natural abilities that they evolved are essential for host defense mechanisms. Marine bioactive peptides have extremely complex and diverse structures that vary greatly depending on the sources from which they are obtained. They frequently have secondary structures and can be cyclic in the form of depsi-peptides. Bioactive peptide purification from marine sources can be achieved via chromatography techniques, including reverse-phase high-performance liquid chromatography, gel filtration chromatography, and ion exchange chromatography, which is a current technique to extract biologically active peptides. Studies of marine plants, microbes, and animals over the last several eras have revealed a huge variety of structurally varied and bioactive secondary metabolites. With a particular focus on the conversion of nutraceutical and pharmaceutical research into commercially available products, this review summarizes current findings in marine peptide research as well as emerging patterns, and its promising directions are briefly reviewed. The use of active peptides derived from the sources mentioned earlier their health advantages and bioactivities are also focused. Along with safety concerns, their possible usages in the processed food industry, wound healing, feed, cosmetic, and pharmaceutical industries, for the growth of efficient goods, are highlighted.*

Keywords— ***Bioactive peptide, functional food, pharmaceutical, sources, therapeutic applications***

I. INTRODUCTION

Protein fragments known as bioactive peptides are beneficial to various bodily functions and general human health. Most bioactive peptides have molecular masses between 0.4 and 2 kDa and contain two (dipeptides) to twenty amino acid residues (Zaky et al, 2022). There have also been a few components of longer peptides being reported. One peptide with anti-cancer and hypocholesterolemic effects is called lunatic, which is made of 43 amino acids and is obtained from soy (Ulug, et al., 2021). From marine microorganisms, algae, fungi, mollusks, crustaceans, and marine byproducts like inferior muscles, viscera, skins, trimmings, and shell, bioactive peptides with antihypertensive, antioxidant, antidiabetic, anti-cancer, and anti-allergic effects were identified (Wang, et al,. 2017). Despite the fact that marine peptides have just recently received the attention that is well-deserved (particularly when compared to peptides from

other plant/animal sources) and they have the potential to produce classes of peptides with intriguing features, such as antituberculosis, antiaging,anticoagulant, and antidiabetic and making them prospective agents not just in medicine and pharmacy. (Mayer et al., 2013; Rangel et al., 2017),as well as in the cosmetics sector (Corinaldesi et al., 2017; Kim & Wijesekara, 2010). Additionally, efforts have also been made to use biopolymers and nutraceuticals synthesized from microalgae (Charoensiddhi et al., 2017). The widespread usage of peptides generated from marine sources still faces several challenges that have not yet been resolved: this needs to identify ideal conditions for peptide isolation and consistent production from specific sources.; correlating structural and bioavailability; indicating the peptide's consistency and efficiency in vivo; and, in most situations, enhancing their availability and production rates. For example, microalgae is a common source of marine bioactive peptides. However, there are many challenges associated with both the availability of the source material and the effectiveness of peptide extraction. Seaweed cell walls contain polymers that limit peptide extraction (Admassu et al., 2018). However, these differences between the structures and functions of marine peptides are significantly more evident due to the vast biodiversity of the five basic classes of aquatic creatures that are used as food, including fishes, microalgae, bivalves, crustaceans, and cephalopods, which span four kingdoms of biological organisms (Phyo et al., 2018; Shinnar et al., 2003) Nutraceuticals can originate from a variety of marine creatures, including sponges, marine plants, and microbes. Each of these sources has distinctive biomolecules that help them to thrive and survive in aquatic surroundings. Seaweed is being investigated as a superior source of antioxidants due to its high amount of bioactive peptides (Shahidi & Ambigaipalan, 2015). The development of novel glucosidase inhibitors by marine microorganisms may provide an alternative to traditionally used diabetes treatments (Trang et al., 2021). Dieticians and food technologists have recently become interested in the vast range of purposes that marine and freshwater mollusks might serve as food and nutraceutical resources due to their tremendous biodiversity and abundance. The phyla of mollusks with the most bioactive properties and nutraceutical applications were Cephalopoda, Bivalvia, and Gastropodia (Chakraborty and Joy, 2020). Aquatic food intake has increased globally in recent years due to greater knowledge of their health benefits and a good attitude toward seafood. Due to the variety of their environments, marine creatures have evolved distinctive traits and bioactive substances compared to terrestrial sources. Functional food ingredients have long been recognized for their value in promoting health and lowering illness risk (Shahidi and Ambigaipalan, 2015). Seaweed is a potential crop because of its anticancer, anti-inflammatory, anti-bacterial, antioxidant, anti-obesity, and anti-coagulant effects. The discovery of more sensitive and the development of new bioactive substances has been enhanced by omics technologies, including nuclear magnetic resonance, liquid chromatography-mass spectrometry (NMR-LC/MS), and next-generation high-throughput sequencing. (Rosic, 2021). Several aquatic invertebrate species can be located everywhere in the atmosphere, which include the deep ocean and the intertidal zone. Some taxonomic families include Cnidaria (corals, jellyfish), Porifera (sponges), Annelida (marine worms), and echinoderms (sea cucumbers, sea urchins, and starfish) and mollusks (oysters, crayfish, and prawns). Marine invertebrates have long been used in coastal community's diets and for therapeutic purposes (Ganesan et al., 2020). This article aims to provide a comprehensive overview of the origins, applications, and relevance of bioactive compounds derived from different marine animal species. Using marine bioactive compounds in the pharmaceutical and food industries. Multiple reviews on marine bioactive chemicals have been conducted in the past few years. In marine bioactive peptides domain several reviews explain bioactivities like as antioxidant, antimicrobial, antihypertensive. Additionally, most of the reviews concentrate on a specific source of bioactive peptide such as algae, fish, or mussels. This study gathers current and comprehensive knowledge about bioactive peptides from marine sources, concentrating on their biological activities, functional properties, and industrial uses that are already exploited.

II. MARINE BIOACTIVE PEPTIDES SOURCES

Crabs, mollusks, and echinodermata are examples of edible marine invertebrates that can be exploited as organically derived biopolymers for a range of applications. Humans have used these biopolymers, which are comprised of protein, as food and supplement ingredients for decades to cure a variety of illnesses. Microalgal biomass are used in animal feed and have anti-bacterial, wound-healing, anti-inflammatory, anti-cancer, and antimicrobial properties **Fig. 1** (Ganesan et al., 2020).

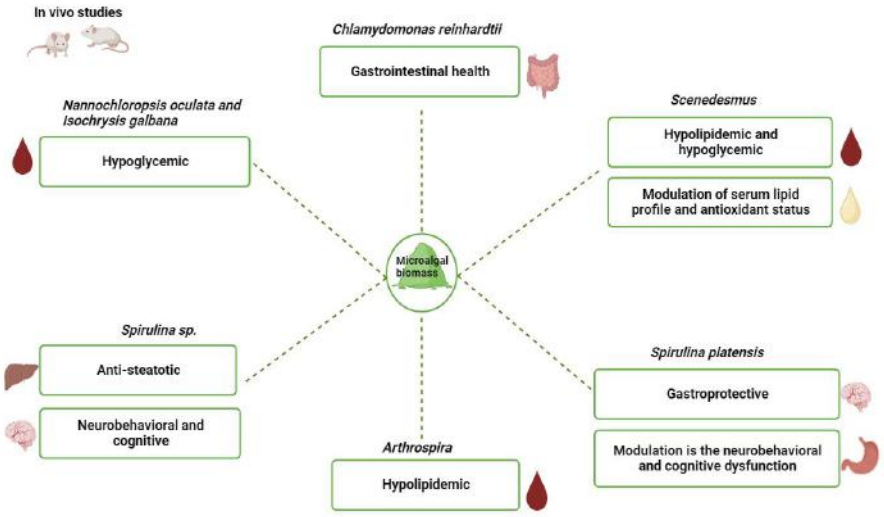

Fig. 1: Applications of microalgal biomass

It is well-acknowledged that sponges contain a lot of bioactive substances that have antimicrobial effects. Bioactive compounds have also been extracted from bryozoans. A marine *Polychaete* (*phylum Annelida*) has proven to be efficient in treating many pathophysiological conditions, such as bone cancer osteoporosis, and arthritis, among others. The marine annelid arenicola marina was used to separate bioactive substances. Several bioactive chemicals have also been produced by marine arthropods. The most well-known bioactive compound derived from marine arthropods is tachypleus, amoebocyte, and amoebocyte lysate from limulus lysate. (John et al., 2018). The bioactive substance pisulosine has antileukemic properties and is obtained from the hawaiian mollusk elysia rufescens. The synthetic equivalents of synthadotin dolstatin, and Soblidotin, which were derived from the mollusk species D. auricularia and are presently being studied for their potential as medicines, are synthadotin soblidotin. It has been discovered that the mollusk dolabella auricularia produces several aolastatins, which are cytotoxic and anticancer substances (Papon et al., 2022). The most prevalent bioactive substances that can be found in echinoderm metabolites are saponins. Among other things, sea urchins, sea cucumbers and starfish contain these sterol compounds are called asterosaponin's, but it has been declared that sea cucumber saponins are derived from terpenoids (Datta et al., 2015). From the marine snail neptunea arthritica cumingii, two newly multifunctional peptides were discovered. Both peptides had anti-inflammatory, ACE-inhibitory, and anti-diabetic properties (Li, et al,. 2019). Each conus species venom contains a unique variety of neurophysiologically active peptides (Neves et al,. 2019). The sea cucumber protein hydrolysates were used to isolate ACE-inhibitory peptides using a plastein reaction (Ovchinnikova, 2019). Two new effective ACE-inhibitory peptides were isolated and discovered from Acaudina molpadioidea (sea cucumber). These compounds may be used to create hypertension medications (Li, et al,. 2018). Gram-positive bacteria called actinomycetes are widely known for producing a wide range of antibiotics. Although most actinomycetes in nature are free-living organisms, some of them can be dangerous. With many different plants and animals, they develop symbiotic connections. Moreover, actinomycetes are symbiotic with a range of marine macrofauna, such as ecologically significant fora-like insects, cone snails, marine sponges, and invertebrates (Haliclona, Axinella polypoides etc.) are included. (Mahapatra et al., 2020). The main biologically active components used as functional foods come from marine sources such as peptides. Fish oils and microalgae are highly poly-saturated fatty acids that can help to enhance the nutritional profile of diets (Prabha et al., 2019).

2.1 Bioactive peptides from chelicerata and crustacea

Antimicrobial peptides have many physiological components that are active in the hemolymph of marine invertebrate chelicerate and crustacea. These substances typically produce pores in membranes and have modest molecular weights (less than 10 kDa) (Tincu & Taylor, 2004). The amphipathic nature of these peptides makes it easier for them to cling to, disrupt, and/or permeate the cytoplasmic membrane of bacteria. The horseshoe crab lymulus polyphemus is the source of the 2-18 residue peptides known as polyphemusins I and II, which inhibit the development of both Gram-negative and Gram-positive bacteria. Peptides with antibacterial activity are also

present in the hemolymph of Charybdis lucifera and thalamita crenata (Rameshkumar et al., 2009; Rameshkumar et al., 2009). A 37-amino-acid antimicrobial peptide that are rich in proline and arginine was identified from the spider, Hyas Araneus,' crab, hemocytes. Arasin 1 is a peptide with two disulfide bonds at its C-terminus and a proline and arginine-rich N-terminal region. (Stensvg et al., 2008).

2.2 Fishes

There has not been much research done on marine vertebrates as a source of proteins and peptides with living activity. Fish have a defense mechanism that prevents dangerous microorganisms from penetrating their skin barrier. Pleuronectes americanus the winter flounder produces a peptide antibacterial in the skin mucus (Haefner 2003; Lazcano et al., 2012). Antifreeze polypeptides are produced by a variety of marine species e.g fish as a defense against freezing in chill saltwater environment. Longhorn sculpin (*Myoxocephalus octodecemspinosus*) skin has been used to isolate type I and type IV anti-freezing proteins (Low et al., 2001). From the epidermal tissues of the cunner Tautogolabrus adspersus and the Atlantic snailfish (Liparis atlanticus) have been discovered and partially characterized more anti-freezing proteins. (Evans & Fletcher 2004). The red sea bream's Chrysophrys gills contain a novel, C-terminally amidated peptide with three distinct isoforms (Iijima et al. 2003). Peptides with 20–25 amino acids make up Chrysophsin-1, Chrysophsin-2, and Chrysophsin-3. They are extremely cationic and have an odd Arg-Arg-Arg-His order at the C-terminus. The secondary structures of the chrysophsin peptides were used to predict their -helical topologies, which were then verified by CD spectroscopy. Fish proteins that have experienced hydrolysis-induced modification are target of bioactivity identification. The peptides produced during hydrolysis are highly dependent on the specialty of the proteolytic enzymes, the hydrolysis depends on temperature, the pH, and the enzyme/substrate ratio (Otte et al., 2007). Many hydrolysates are the product of successive hydrolysis with an endopeptidase (a peptidase that does not break peptides into single amino acids) followed by an exopeptidase (a peptidase that will break the peptides into small amino acid residues from the end of peptide chains) (Hamada 2000).

2.3 Seaweed derived peptides

2.3.1 Glycoproteins

A diverse group of algae species have different protein and sugar ratios in their GPs; for example, GPs-rich fractions in Ulva species demonstrated a protein content of high to 33.4 percent (Wijesekara, et al., 2017), GPs with MWs of 48 kDa are present in Codium decorticated, where the protein content is 60% (Thangam, et a,l. 2014). Mannose appears to be the main constituent of the prosthetic portion in seaweed GPs (Yoshiie, et al,. 2012).Various oligosaccharide chains are covalently bonded to these glycoproteins and make them substances called glycans. O-glycosylated and N-glycosylated chains are the two main forms of sugar chains found in GPs (Charoensiddh et al., 2017). The two functions of GPs are intercellular contacts and recognition, which can be found either free, after secretion, on the cell surface, or on the cell wall (Yoshiie et al., 2012).

2.3.2 Lectins proteins

Lectins are GPs with extraordinary traits in their binding to specific mono or oligosaccharides. Red seaweed is an excellent source of high and low-MW lectins (Barre, et al.,. 2019). Lectins serve a variety of purposes, including gamete identification, reproductive cell fusion, and pathogen protection (Barre, et al. 2019; Frenkel, et al, 2014). The four major categories of lectins are chitin-binding lectins, legume lectins, lectins, type-2 ribosome-inactivating proteins, and mannose-binding (Van Damme, et al,. 2007). Many of these proteins bind mannose because mannose-binding glycans make up the majority of the glycans in seaweed. (Yoshiie et al. 2012). Relevant seaweed lectins exhibit a strong affinity for these residues similar to pertinent mannose-specific lectins. (Ambrosio et al., 2003). Like bacterial, viral, or eukaryotic cell surface GPs, they can "agglutinate" particles that contain these residues because of this characteristic (Wu et al. 2016). For instance, griffithsin, which is derived from red Griffithsia sp. seaweeds and possesses a variety of biological features has been described (Gunaydn, et al,. 2019). Due to pharmacological characteristics, research in molecular biology, biochemistry, and medicine is concentrated on characterizing and isolating these compounds. Although seaweed lectins have been chemically characterized more carefully, more data is still required to fully comprehend their binding affinities, molecular structures, and potential biochemical activities for future implementations (Fontenelle, et al,. 2018).

2.4 Macroalgae and seaweeds

Seaweed, commonly referred to as macroalgae, is a diverse group comprising around 10,000 species (Makkar et al., 2016). Green algae (*Chlorophyceae*), Brown algae (*Phaeophyceae*), and Red algae (*Rhodophyceae*), are the three major phyla of algae (*Chlorophyceae*). Fresh sea algae have a high water content, which can make up to 94% of the biomass (Holdt and Kraan, 2011). Microalgae have been cited in the literature as being excellent sources of bioactive peptides for usage in functional meals due to the characteristics of the aquatic environment and other

conditions which is salt content, temperature, and lighting conditions. (Gallego et al., 2019).

As previously indicated, many factors affect the protein content of seaweed. Furthermore, it is difficult to compare the protein content of algae due to different methodologies, particularly when extracting proteins, and the vast variety of species identified (Lourenço et al., 2002). Although the protein content of brown seaweed is typically lower than that of green or red seaweed, Pereira, Barbarino, Lourenço, De-Paula, and Marquez. (Schiener et al., 2015) found that the protein content of the species *Padina gymnospora*, *Dictyota menstrualis*, Chnoospora minima, and *Sargassum vulgare* was relatively high, ranging between 10 and 15 percent. *Fucus vesiculosus*, *Ascophyllum nodosum*, *Laminaria digitata*, and *Himanthalia elongata* are examples of common brown seaweed. *Laminaria digitata* has an average protein content of 6.8%, with the lowest and highest protein levels occurring in the first and third quarters of the year, accordingly (Schiener et al., 2015). This result was comparable to that of Peinado, Girón, Koutsidis, and Ames (2014), who estimated Laminaria digitata's protein concentration to be 5.8%. As previously mentioned, algae are known to contain significant amounts of high-quality vitamins, minerals, polysaccharides, and bioactive substances such as proteins, lipids, and various polyphenols (Holdt and Kraan, 2011). There are very few structurally and functionally effective peptides produced from seaweed. Currently, a variety of functional foods, primarily in Japan, are being promoted that contain peptides produced from seaweed. Foods for Specified Health Uses (FOSHU) are foods with specific health purposes that have been authorized by the law of the Japanese Ministry of Health and Welfare (Arai, 2000). Nori peptides (Shirako Co., Ltd., Tokyo, Japan) and Wakame peptide jelly (Riken Vitamin Co., Ltd., Tokyo, Japan) are two products containing seaweed-derived peptides with FOSHU-approved claims for lowering blood pressure (Fukami, 2010).

III. CHARACTERIZATION OF MARINE BIOACTIVE PEPTIDES

3.1 Preparation and purification

The bioactive peptides significantly differed on the basis of species, amino acid compositions and sequences, and they could be created by using various techniques. The bioactivities of peptides are also impacted by specific techniques (Agyei et al., 2016).

3.2 Organic synthesis

The use of organic synthesis in marine natural products rise with the advancement of technology and structural elucidation methods (Pindur & Lemster, 2001). Marine biological compounds have produced many therapeutic applications due to their unique bioactivities. The target peptides are typically obtained through batch synthesis in organic production techniques utilizing a variety of solvents in the solid phase. In order to batch synthesize target peptides as a result of low production, organic synthesis is always used, starting from cyclic peptides to simple peptides (Zhou, 2014). Mass spectrometry is used to detect the final result to check the consistency of ultimate molecular mass. Its confirmed bioactivity would also be continued. The target peptides might be produced in large quantities because of organic synthesis. Nevertheless, the organic synthesis method is costly, time-consuming, and unsustainable. Targeting peptides with a distinct sequence is also required for this method. As researchers may need to determine the peptides compositions therefore better extraction procedures are recommended. Utilizing a variety of purification and isolation technologies (Wang et al., 2017).

3.3 Chemical hydrolysis

Proteins can be hydrolyzed chemically by cleavage peptide bonds either with alkali or acid. This technology has been extensively utilized by the industry due to its low cost and simplicity. However, this method has significant limitations, including a difficult-to-control procedure and a tendency to produce mutated amino acids (Vijaykrishnaraj & Prabhasankar, 2015) and manufacturing products with varying functional and chemical qualities. Acidic hydrolysis is a substantial chemical transformation that can strongly alter the functional and structural characteristics of peptides (Lee & Jeffries, 2011). Because of its simplicity and efficiency, acid hydrolysis is favored over alternative pretreatments (Loow et al., 2016). Sulfuric acid (H2SO4) is the most prevalent kind of utilized diluted acid. However, research has also been done on hydrochloric acid (HCl), nitric acid (HNO3), phosphoric acid (H3PO4), and other acids (Xu & Huang, 2014). Maleic and oxalic acids hydrolyzed biomass better than H2SO4 (Lee & Jeffries, 2014). Scales of bluefish, mackerel, salmon, and scup were assimilated by adding 25% to 0.4 M HCl (Richard et al., 2011). Acidic hydrolysate demands high temperatures and produces salty hydrolysates. Moreover, desalination in the subsequent experiment is complicated. Furthermore, acid hydrolysis can degrade tryptophan, an important amino acid. However, some study has been done on alkali hydrolysis using samples from Cod. Nevertheless, alkali hydrolysis

frequently leads to poor functioning and low nutrient content (Wang et al., 2017). Alkali treatment also results in increased solubility of collagen (Huang et al., 2016; Cho et al., 2004; Da Trindade Alfaro et al., 2009). In other words, whereas acidic hydrolysis might lead to the simple degradation of peptide bonds and yield a high output of peptides, it is unsecured and environment unfriendly. Hence, it is primarily utilized for industrial manufacturing.

3.4 Enzymatic hydrolysis

Recent investigations have demonstrated that enzymatic hydrolysis release the majority of peptide sequences encoded in dietary proteins and gives bioactive characteristics (Qilong et al., 2013). Proteins are often modified in the food industry through enzymatic cleavage of certain peptide couplings with proteolytic enzyme preparation. Although many other methods exist for increasing the value of the target peptides, animal sources and proteolytic enzymes from plants have been explored broadly or documented by multiple researchers over the last 60 years (Wang et al., 2017). Commercially available enzymes derived from bacteria, such as neutrase (Je et al., 2009; Foh et al., 2010), alcalase (Je et al., 2007; Sila et al., 2014), and flavour enzyme (Klompong et al., 2007; Liu et al., 2015), including from plants and animals, such as pepsin (Ko et al., 2012; Moreda-Piñeiro et al., 2011), trypsin (Alemán et al., 2011; Wu et al., 2015), subtilisin (Mbatia et al., 2010; Salampessy et al., 2015), papain (Liu et al., 2010; tripoteau et al., 2015), and bromelain (García-Moreno et al., 2016; Wang, Yu, Xing, & Li, 2017), are favored. Moreover, the usage of external enzymes may improve the control and reproducibility of the hydrolytic process. Enzymatic hydrolysis involves five distinct factors, each of which affects the process differently: extraction temperature, enzyme concentration, extraction time, water/material ratio, and pH (Wang, Yu, Xing, Chen, et al., 2017). For instance, (Bhaskar et al., 2008) employed an alcalase enzyme hydrolyze the intestinal excess catla proteins of (Catla catla) and produced a greater hydrolysate under optimal conditions, with an enzyme-to-substrate concentration 1.5 percent and a total hydrolysis time 135 minutes, the degree of hydrolysis approaches 50%. To get hydrolysis with the maximum amount of peptide, another study employed protamex to hydrolyze blue shake skin at the ideal pH of 7.1, a substrate-to-enzyme ratio of 4% is required, and a temperature of 51 C (Wang, Yu, Xing, & Li, 2017). Pepsin hydrolysis was also investigated by (Song et al., 2012), Who employed an 1100 U/g enzyme-to-substrate ratio, a pH of 2.0, at 2.4-hour average reaction time, and a 4:1 (v/w) water-to-substrate ratio. In a broad sense, many scientists have emphasized the hydrolysis of enzymes because of how conveniently it can be replicated and manipulated (Wang, Yu, Xing, & Li, 2017). Additionally, enzymatic processes do not involve any unwanted byproducts and do not compromise the proteins nutritional content. Inorganic mass, such as salt, may be added when the pH is adjusted with acid or alkali, which may be difficult and expensive to remove afterward.

IV. PURIFICATION OF MARINE BIOLOGICALLY ACTIVE PEPTIDES

The bioactivities of the peptides are reliant on their amino acid sequences and structures, which typically range from 3 to 20 residues. According to recent research, 95% of peptide sequences that are contained in dietary proteins offer bioactive characteristics after being released by hydrolysis of enzymes (Agyei & Danquah, 2011). Then, it is essential to determine the peptide structures, that is why there are several researchers who have studied peptide decontamination. An average approach for the identification of aquatic bioactive peptides is produced by isolating peptides from aquatic species, screening them for certain bioactivities, separating them using MTT assay fractionation techniques, and then purifying each individual bioactive peptide. To design an effective purification procedure, it is also required to conduct extensive research on techniques such as membrane filtering systems, gel filtration chromatography, ion exchange chromatography, and reverse-phase high-performance liquid chromatography (HPLC). Before purifying peptides, the researcher must carefully analyze the advantages and downsides of each purification technique.

4.1 Membrane filtration

A few years ago, several scientists used membrane filter as the first stage in the purifying process. For instance, (Cho et al., 2003), the galacturonic acid concentration in pectin raised from 68 to 72.2 percent using cross-flow membrane filtering. When Hoki (Johnius belengerii) protein hydrolysates were extracted by membrane filtering, it was shown that HPH-III, with a molar mass of 3-5 kDa, had the best anti-oxidant activity (Kim et al., 2007). In addition, with ultrafiltration membrane, the most efficient 1,1-diphenyl-2-picrylhydrazyl radical-scavenging peptide was identified with a molecular mass below 3 kDa (Wang et al., 2015). According to (Tonon et al., 2016), Shrimp ultrafiltration and hydrolysis were combined to produce protein hydrolysate, whereas filtration membranes (Roblet et al., 2016) used for the purification and electrodialysis of Atlantic salmon protein hydrolysate.

4.2 Cation-exchange chromatography IEX

In recent years IEX techniques has gained tremendous significance for the extraction, structural characterization, and detection of short sequences peptides. (Levison, 2003). IEX medium contain positive-charged hydroxyl functional-groups that bind electrostatically charged atoms. Bound molecules are dislocated and precipitated from the solvent by increasing concentrations of an identically polarized molecule. Proteins contain many hydroxyl groups with either positive or negative charges. Protein separation is achieved by adjusting the mobile phase's pH or ionic makeup. IEX is used for high-resolution separation to remove the heavy impurities from a high-volume solution, or to extract a specific protein as a preliminary filtration process or as a final purification step. Numerous researchers have utilized various IEX mediums to purify the target product based on the qualities described above to separate chitooligomers, for example, utilized C-25 Sephadex CM with (0-2 M)-HAc NaCl buffers eluted successively at 3 mL/min and a range of HAc-NaAc buffer (50 mM, pH = 4.8) (Li et al., 2012). The antioxidant peptide was isolated from hydrolysate blue mussel (Mytilus edulis) by using modified cation exchange C-25 SP-Sephadex, 50 mm acetate buffer (pH=4.0) (Park et al., 2016). Additionally, several studies use SP-Sephadex C-25 to isolate the desired peptide (Jun et al., 2004; S. Wang et al., 2014). Moreover, several media were used for marine organism purification, including Sepharose fast flow formulations, fast flow CM Sepharose (Hsieh et al., 2008; Song et al., 2015), fast flow DEAE Sepharose (Kumar et al., 2011; L. Wang et al., 2014; Ye et al., 2012), fast flow Q fepharose (Hui et al., 2004), fast flow SP Sepharose (Beaulieu et al., 2010; Wang, Yu, Xing, & Li, 2017), and others.

4.3 Gel filtration chromatography

Initially, the sample is subjected to gel filtration chromatography, then finally reversed phase C18 HPLC for further purification (Jai Ganesh et al., 2011; Zhang et al., 2012). For instance using DEAE Sepharose and Superdex 200 fast flow, increase and established with excellent resolution, high recovery, and low run times, as primary goals. (Huang et al., 2016). From the leaves of Clinacanthus nutans Lindau, an innovative peptide with a molar mass of 9.17 104 Da was identified (Qian et al., 2016). Similarly, Using Superdex 200 isolates an enzyme that breaks down fish scales was found to have a molar weight of 1.19 106 Da (Pan et al., 2010). Superdex prep grades, and Sephacryl are employed for high-throughput, separation with high recovery in the research laboratory or production areas (Wang, Yu, Xing, & Li, 2017; Shen et al., 2015; Wang, Yu, Xing, & Li, 2017). Yellowfin Tuna roe (Thunnus Albacores) trypsin inhibitor was isolated, initiated by column chromatography on, Sephacry S200, DEAE-cellulose, Sephadex G-50, and its apparent molecular weight was determined to be 7 104 Da (Wu et al., 2016). Moreover Sephadex is often used in the filtration of aquatic organisms and is suggested for fast group separations, such as exchange of buffers desalination (Bougatef et al., 2010; Hsu, 2010) (Vijaykrishnaraj et al., 2016). Internal organs of Parastromateus niger and the flavor of the mussel were separated in order to conform using Sephadex G-25 (Jai Ganesh et al., 2011). Sephadex G-7 marine yeast purification was also examined. Sephadex G-75 marine yeast purification was also examined (Ma et al., 2007).

4.4 High performance liquid chromatograph (HPLC)

The most well-known technique for identifying, classifying, and purifying biologically active substances is HPLC (Singh et al., 2014). The primary features of this technique are its simplicity of operating, sensitivity, and high resolution as well as the short time required to obtain elution spectra in comparison to the IEX and GFC which require twenty to twenty-five hours. Many scientists have utilized HPLC to purify marine organisms in recent years, including Thornback ray (Lassoued et al., 2015) cyanobacterium (Lopez et al., 2016), marine Snail (Dolashka et al., 2011), enteromorpha (Pan et al., 2016), abalone (Pan et al., 2016), sponge (Youssef et al., 2014), tuna (Seo et al., 2014), and others. Recently, HPLC has frequently been coupled with analytical tools like high performance liquid chromatography and mass spectrometry (MS), followed by (LC-MS/MS) tandem mass spectrometric detection, which has evolved the industrial level characterizing amino acid sequences (Vijaykrishnaraj & Prabhasankar, 2015), It has revolutionized protein and peptide structure elucidation but is expensive and time-consuming (Mann & Jensen, 200; Careri & Mangia, 2003). **Table 2** showed the different sequences of marine bioactive peptides.

Table 1: Sequence of Marine Bioactive peptides

Name	Biological activity	Sequence	References
Alaska Pollack	ACE inhibitory	FGASTRGA	(je, park, kwon, & kim, 2004)
Oyster	Anti-HIV	LLEYSL, LLEYSI	(Lee & Maruyama, 1998)
Marine Snail	Antifungal	SRSELIVHQR	Lopez-Abarrategui, Alba & silva, 2012)

Spirulina Maxima	Antiatherosclerotic	LDAVNR, MMLDF	(Voo & kim, 2013)
Yellow Catfish	Antimicrobial	GKLNLFLSRLE	(Su, 2011)
Jumbo Squid	Antioxidant	FDSGPAGVL, NGPLQAGQPGER	(Mendis, Rajapakse, Byun, & Kim 2005)
Sole	Antihypertensive	MIFPGAGGPEL	(jung, Mendis, & je 2006)
Hoki	Antioxidant	ESTVPERTHPA CPDFN	(Kim, Je, & Kim 2007)
Porphyra haitanesis	Anti-cancer	----------	(Marqus, et al,. 2017)
shellfish	Anti-cancer	Ala-Phe-Asn-Ile-His-AsnArg-Asn-Leu-Leu	(Kim, et al,. 2012)
koshikamides	Anti-HIV	----------	(Al-Khayri, et al,. 2022)
Prawn	Antioxidant	IKK, FKK, FIKK	(Zhou, et al,. 2012)
Sea cucumber	ACE inhibitors	MEGAQEAQGD	(Zhao, et al,. 2009)
Tuna	Anti-hypertensive	GDLGKTTTVS NWSPPKYKDTP	(Lee, et al,. 2010)
Yellow catfish	Anti-microbial	GKLNLFLSRLE ILKLFVGAL	(Su, 2011)

V. THERAPEUTIC APPLICATIONS

5.1 Antibacterial activity

Antibacterial peptides, which are typically 20–40 amino acids long, are used by a variety of organisms as a defense against infection. Most can quickly eradicate a variety of microorganisms. Large microbial peptides (>100 amino acids) usually serve as proteins that are lytic, nutrient-binding, or that specifically target bacterial cell membranes to fail or cease functioning as planned. Humans have been found many antibacterial proteins that are phagocytes, multicellular epithelial layer. Antimicrobial peptides (AMP) are endogenous antibiotics that also aid in wound healing, inflammation and the control of the defense mechanism (Da Costa, et al,. 2015; Kang, et al,. 2015). The scyphoid jellyfish's mesoglea is responsible for producing the AMP aurelin. *Auricula aurita* that is made up of 40 amino acid residues and aurelin was the name of the peptide which performed activity towards gram-positive bacteria and gram-negative bacteria. *Aurelin* reported to inhibit the growth of microorganisms under low salt conditions. The available therapies for various disorders, such as type-1 diabetes, Alzheimer's disease, other forms of arthritis and rheumatoid arthritis, cardiac disease, asthma allergies, Parkinson's disease, cancer, and irritable bowel syndrome many others are prohibited, and after a dosage, certain medications have major side effects on patients' health. Consequently, Numerous approaches for treating these persistent bacterial infections need further study. Natural remedies have long been considered a potential kind of treatment for illnesses and antimicrobial therapy (Suleria et al., 2016). The *Actinomadura sp*. TP-A0878 can produce a nomimicin spirotetrone complex from polyketide source with the value of MIC 6.3, 12.5, and 12.5 g/ml, nomimicin showed strong antibacterial activity against *Candida albicans*, *Micrococcus luteus*, and *Kluyveromyces fragilis* (Karthikeyan et al., 2022). *Zunyimycins* C and B extracted from Streptomyces sp. FJS31-2 displayed antibacterial activity with MICs between 3.7 and 8.14 g/ml and 0.94 g/ml against MRSA isolates (methicillin-resistant *S. aureus*) (Lü et al., 2017). Strains of *Tetracenediones Streptomyces formicae* KY5 can synthesize the polyketides formicamycins A–L, which are able to restrict the MRSA with a minimum inhibitory concentration (MIC) of 0.41 g/ml and vancomycin-resistant *Enterococcus faecium* (VRE) with a MIC of 0.80 g/ml (Qin et al., 2017). Epinecidin-1, an antibacterial peptide group of fish (*Epinephelus coioides*), showed bacterial medication efficacy against Vibrio vulnificus, Staphylococcus coagulase, pseudomonas aeruginosa, and staphylococcus coagulase. Electroporation was used to introduce plasmid DNA into decapsulated Artemia cysts that code for a

cytomegalovirus (CMV) promoter-driven expression of the EGFP-epinecidin-1 fusion protein. Zebrafish with better resistance to V. vulnificus and a greater mortality were Fed transgenic artemia generating CMV-gfp-epi in addition to commercial feed. The resultant protein, EGFP-epinecidin-1, decreased the proliferation of V. vulnificus. Immune-responsive gene expression and the immune-modulatory in reaction to V. vulnificus (204) infection were also impacted by feeding zebrafish transgenic artemia. These results imply that transgenic to have antimicrobial effects on fish larvae without introducing medication residues or creating bacterial drug resistance, artemia expressing CMVgfp-epi can be given (Jheng, et al,. 2015 ; Qin, et al,. 2014).

5.2 Anti-HIV activity

Marine sponges provide diverse habitats regarding a variety of marine organisms. They are filter feeding, soft-structured, aquatic invertebrate parazoans with a high concentration of bioactive components (Anjum, et al,. 2016). Sponges are made up of a variety of biomolecules with different chemical and structural properties and a range of bioactive properties (Vitali, 2018). This is demonstrated by the fact that four of the nine marine medications with FDA approval came from sponges (Wu, et al,. 2019). According to research studies, there are numerous bioactive substances that have been found from sponges and produce functional enzyme clusters. (Kang, et al,. 2015). According to reports, the koshikamides found in *Theonella sp*. sponges have anti-HIV properties. When evaluated infectivity of HIV-1 in a single round experiment with respect to a viral envelope that uses CCR5, comparing their linear equivalents to their cyclic counterparts, the IC50 values of the koshikamides F and H decreased HIV entrance to 2.3 and 5.5 M, respectively (Agrawal, et al,. 2016; Al-Khayri, et al,. 2022). Depsipeptides, also known as cyclodepsipeptides, are powerful compounds discovered from different marine sponge species that are particularly interesting for therapeutic development against HIV. Their structure comes from pre-loaded with peculiar non-proteinogenic amino acid combinations. (Wu, et al,. 2019). It has also been demonstrated that neamphamide A and callipeltin A, which are both derived from the plants *Callipelta sp*. and *Latrunculia sp*., inhibit the replication of HIV (Kang, et al,. 2018). For many years, sponges have been recognized for providing novel bioactive metabolites, including, polyethers, macrolides terpenoids, nucleoside derivatives, alkaloids, and many other chemical substances. An anticancer substance *Cytosine Arabinoside*, was subsequently create the synthetic analogues of the C-nucleosides pongouridine and pongothymidine that were discovered from a Caribbean sponge (Aneiros, and Garateix, 2004). Photosynthetic microorganisms called marine cyanobacteria are widely found in nature (Silipo, et al,. 2010). In addition to a wide range of toxins, they also contain several bioactive substances that may have properties including anticancer, antitumor, antifungal, antibacterial, protease inhibition and anti-inflammatory. An 11 kDa protein Cyanovirin-N (CV-N), obtained from the Nostoc ellipsosporum cyanobacterium, has undergone preclinical testing as an anti-HIV medication. (Fidor, et al,. 2019).

5.3 Anti-cancer activity

Cancers are the deadliest and feared diseases worldwide. Drugs to treat cancer and tumors are being developed quickly by pharmaceutical corporations. Additionally, oncology research has made significant advances and has helped us to understand tumors better over time (Noguchi, et al,. 2012). An effective starting point for the production of anticancer peptides is food protein hydrolysate. Protein hydrolysates from soy and rice have been shown to have anticancer properties in the past. Alcalase breaks down the proteins in rice bran to produce anticancer peptides in rice (Kannan, et al,. 2010). The shellfish proteins contained Ala-Phe-Asn-Ile-His-Asn-Arg-Asn-AsnLeu-Leu is a different anticancer peptide that was effective in killing prostate, breast, and lung cancer cells while sparing healthy liver cells (Kim, et al,. 2012). Peptides can pass through cell membranes because of their small size and chemical makeup; unlike proteins and antibodies, they do not accumulate to hazardous quantities. While having little interactions with other medicinal treatments, these molecules have demonstrated great affinity and specificity. While these substances often have limited oral bioavailability, which leads to quick clearance of the peptides, there are still issues with their utilization that must be resolved. These issues are primarily connected to the peptide delivery method (Marqus, et al,. 2017). Proteins from Porphyra haitanesis were hydrolyzed by trypsin to create peptides that have anti-proliferation properties. Five human cancer cell lines were used to test the peptides produced from this source: HepG2 for liver cancer, HT-29 for colon cancer, MCF-7 for breast cancer, A549 for lung cancer and SGC-7901 for gastric cancer. The fluorouracil (5-FU) an chemotherapeutic agent was used as a control (Marqus, et al,. 2017).

5.4 Antioxidant activity

A free radical is a chemical compound that has one or more orbital electrons that are unpaired and exist independently. It can form naturally in cells during normal cellular metabolism or because of external factors like radiation or pollution. The phenomenon of oxidative stress occurs when the body produces an excessive number of free radicals that cannot be effectively eliminated over

sometimes (Lafarga et al., 2020). Tumour formation and responses to anticancer therapy are both influenced by the level of oxidative stress present in the body (Gorrini et al., 2013). Antioxidants can be obtained endogenously or exogenously to reduce oxidative stress (via dietary means). Furthermore, as previously stated, seaweed has the potential to possess a significant amount of protein. These proteins derived from seaweed can be utilized in the production of antioxidant-hydrolyzed products and peptides. several enzymatic hydrolysates were obtained from Porphyra columbiana byproducts through the utilization of alcalase, trypsin, and a combination of both enzymes (Cian et al., 2012). Furthermore, the enzymatic hydrolysate of Palmaria palmata was produced by Harnedy, O'Keeffe, and FitzGerald (2017) utilizing the Corolase PP, a food-grade enzyme. SDITRPGNM displayed the maximum hydroxyl radical scavenging capacity (ORAC) and ferric lowering free radical scavenging power (FRAP) activity among the peptides produced, with measured values of 152.43 2.73 and 21.23 0.08 nmol TE/mol peptide, correspondingly. The hydrolysate that was produced underwent a series of fractionation techniques, including reversed-phase semi-preparative high-performance liquid chromatography (RP-HPLC) and solid-phase extraction. Antioxidant peptides availability has also been measured, after a simulated gastrointestinal digestion was performed the antioxidant activity of pyropia columbina peptides was found to increase (Cian et al., 2015).

5.5 Anti-inflammatory activity

In reaction to damage inflammation is an inherent component of the bodies defense mechanism, characterized by a self-regulating nature. However, some diseases in which the inflammatory response persists, can result in chronic inflammation. Chronic inflammation is a factor in the pathogenesis of numerous infections, including, rheumatoid arthritis, cardiovascular disorders, autoimmune diseases, diabetes, asthma, pulmonary diseases, Alzheimer's disease, and cancer atherosclerosis (Y. S. Kixxxm, Ahn, & Je, 2016). Macrophages play a crucial part in immunological responses since they are capable of secreting various mediators of inflammation, like nitric oxide (NO), prostaglandin E2 (PGE2), and cytokines including tumour necrosis factor (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6) interleukin-1 (IL-1), in response to stimuli (Ahn, Cho, & Je, 2015). Macrophages can be stimulated through various means, including the presence of pro-inflammatory cytokines, interferon-gamma (IFNγ) such as IL-1b, IL-6, and TNF-α and, as well as lipopolysaccharides of bacteria (LPS) derived by Gram-negative microorganism (Ahn et al., 2015). NO has been associated to both inflammation and the development of cancer, making its suppression is crucial for treatment (E. K. Kim, Kim, Hwang, Kang, et al., 2013). Numerous peptides from fish and mussels have been reported to have NO inhibiting action. A significant proportion of anti-inflammatory peptides was discovered in molluscs. Insufficient facts are available about the peptides that have already been isolated from fish, crustaceans, and algae. Peptides that reduce inflammation were recovered by flavour enzyme, alcalase, and protamex hydrolysis from the bivalves Crassostrea gigas, Ruditapes philippinarum and mytilus coruscu (E. K. Kim, Kim, Hwang, Kang, et al., 2013) (Lee et al., 2012), (Hwang et al., 2012). These three peptides exhibited in vitro inhibition of LPS-induced mouse macrophage (RAW264.7) cell line NO generation. Using pepsin hydrolysis, an anti-inflammatory peptide containing the amino acid order Pro-Ala-Tyr was derived from salmon pectoral fin. These peptides demonstrated numerous advantageous anti-inflammatories response in LPS-stimulated macrophage cells RAW264.7, including inhibition of NO and PGE2 synthesis (63.80 percent and 45.33 percent, respectively), cyclooxygenase-2 protein expression, suppression of inducible NO synthase and, and reduction of proinflammatory cytokine (IL-1b, TNF-, and IL-6,) synthesis (Ahn et al., 2015). The anti-inflammatory effects of aquatic lectins are attributed to their carbohydrate-binding domain (Cheung, Wong et al. 2015). To effectively create lectin, green seaweed caulerpa cupressoides are injected into the left temporomandibular joint zymosan before half an hour. For example, rats exhibit less zymosan-induced arthritis and mechanical hypernociception. In addition, there is a suppression of leukocyte accumulation in synovial fluid. However, the activity of the lectin decreased when it was treated with naloxone or ZnPP-IX an opioid receptor antagonist. However, lectin inhibited leukocyte infiltration and the expression of IL-1beta and TNF-alpha in the joint of temporomandibular, illustrating that lectin damaging the temporomandibular joint's hyper nociception and inflammation ultimately it bbased on the inhibition of TNF-alpha and IL-1beta (da Conceição Rivanor et al., 2014).

5.6 Antihypertensive activity

In the developed world, Cardiovascular-disease (CVD) is a leading cause of death. One of the main causes of CVDs is hypertension, which is sometimes Recognized as the "fatal disease." since this could take several years without showing any symptoms before causing a stroke or a heart attack (Sheih, Fang, & Wu, 2009). The system of renin-angiotensin (RAS) is crucial in the emergence of high blood pressure it regulates the body's water, electrolytes, and blood, (Fitzgerald et al., 2012). The enzyme angiotensin-converting-I (ACE-I) regulates

hypertension after stimulating Angiotensin II production, a potent vasopressor, bradykinin metabolism, and a vasodilator (Cao et al., 2017). Therefore, renin and ACE-I, two limiting enzymes involved in the RAS, can be inhibited or control excessive blood pressure (Fitzgerald et al., 2012). According to Riordan (2003), many anti-hypertensive medications with ACE inhibitory activity perform by increasing the bioavailability of bradykinin and lowering angiotensin II production (Samarakoon et al., 2013). However, they have a number of negative adverse reactions, including flavor loss, chronic cough, kidney disease, and angioneurotic edema (Cao et al., 2017). Finding natural compounds with antihypertensive effectiveness by suppression of ACE-I or enzymes for renin while avoiding unexpected effects became critical. Numerous ACE-inhibiting peptides have been investigated in various natural resources since the 1990s, including bovine whey, mushrooms, almonds, containing others(Cao et al., 2017). Peptides that lower blood pressure have been investigated in fish, mussels, and algae from marine sources (Samaranayaka et al., 2010, Neves et al., 2016; Cao et al., 2017; Chen et al., 2020). The algae Chlorella vulgaris obtained peptide VECYGPNRPQF (Sheih, Fang, & Wu, 2009), Gracilariopsis lemaneiformis derived peptides TGAPCR and FQIN [M(O)] CILR (Deng et al., 2018), the peptides derived from Undaria pinnatifida YH, KY, FY, I, YNKL, IY, and IW has shown the ACE inhibited activity in vitro with values of IC50 23.94, 5.1, 7.7, 3.7, 2.7,29.6, 9.64, 21.0, 6.1, and 1.5 M, respectively. The YH, KY, FY, and IY were derived using hot water and temperature, whereas the remaining peptides were all acquired through hydrolysis using trypsin or pepsin. Isolated peptides from Mytilus edulis and Crassostrea gigas fermented sauce showed IC50 values of in vitro 87.40 g/mL and 19.34 g/mL, respectively, suggesting that these two species may be potential sources of ACE inhibitory peptides (Sara Alexandra Cunha, Manuela Estevez Pintado2022).

5.7 Anti-allergic activity

As a defense mechanism against environmental chemicals, the immune system produces allergic reactions. It is common to see an overabundance of basophils, eosinophils, mast cells, and lymphocytes during an allergic reaction. In the pathophysiology of allergic disorders, mast cells are significant as they are triggered by IgE-mediated reactions to allergens (Ko et al. (2016). Several intracellular processes are triggered when mast cells become active, including the tyrosinase kinase activation ROS formation, which increases intracellular the production of cytokines calcium ion (Ca2+), degranulation, and the polymerization of microtubules, (Vo, Ngo, Kang, Park, & Kim, 2014) (Cunha and Pintado, 2021). One of the most crucial phases in allergic reactions is mast cell degranulation since it triggers the release of inflammatory cytokines, proteases, histamine, and mediators in lipids, that can be in charge of a number of typical allergic reaction events (mucous production, airway constriction, among others). Histamine is a key modulator of the acute inflammatory response and is linked to a number of adverse consequences, including vascular hyperpermeability, angioedema, vasodilation, mucus formation, bronchoconstriction, and hypothermia. As a result, mast cell degeneration and histamine production are inhibited by anti-allergic medications (Vo et al., 2014). The antiallergic activities of aquatic peptides produced from microalgae Spirulina already have been investigated in vitro. After antigen induction, the LDAVNR (P1) and MMLDF (P2) peptides that were produced by the enzymatic hydrolysis of *Spirulina maxima* demonstrated dose-dependent anti-allergic function they could decrease the release of histamine and increasing intracellular Ca2+ levels, thus preventing mast cell inflammatory reactions (verified by structural studies). While the P2 peptide blocked the activation of phospholipase C and the production of ROS, the peptide P1 functioned in the calcium and was dependent on microtube signaling pathways (Cheung, Ng, & Wong, 2015; Vo et al., 2014). The ability to derive a peptide with a MW of 1175.5 Da from the Haliotis discus hannai mussel to reduce the release of histamine and the production of pro-inflammatory cytokines, such as IL-1, TNF-, and IL-6 in human mast cells after antigen initiation demonstrated its potential as an in vitro antiallergic (Ko et al., 2016). Researchers are now devoting their attention to developing anti-allergic chemicals from aquatic sources to combat the issues of food-induced allergies. Many plants have been shown to be anti-food allergic in numerous papers, and these plants contain terpenes, flavonoids, and other anti-food allergic substances. Enhancing Th1 immune function, inhibiting the development of Th2, preventing basophil degranulation and mast cell, lowering cytokine production, and controlling intracellular calcium concentration are just a few of the mechanisms that active substances of aquatic-derived have been found to use to release aversions (Wang K. et al., 2020).

5.8 Anti-microbial activity

In contrast to vertebrates, marine invertebrates lack adaptive immunity. Bivalves only exhibit the innate response to create defense mechanism against viruses and microorganisms, in order to adapt their frequently changing environment. Their susceptibility to infections is also enhanced by their filtering action (Nam et al., 2015). The sequence of antimicrobial peptides (AMPs) which range in length from 12 to 50 amino acids, is short, cationic, and amphipathic. They serve as the primary line of defense against diseases in both plants and animals (Cunha and

Pintado, 2021) (Semreen et al., 2018) (Costa et al., 2017). Antimicrobial peptides are often divided into four different classes based on the makeup of their amino acid sequence: (A) Linear basic peptides devoid of cysteine residues and with amphipathic -helices; (B) AMPs containing intramolecular disulfide linkages and cysteine residues; (C) AMPs with an excess of proline, arginine, glycine, or tryptophan, (D) antimicrobial Peptides generated by hydrolysate of huge amounts of inert protein (Cheng-Hua, Jian-Min, & Lin-Sheng, 2009). In this taxonomic arrangement, AMPs are typically defined in terms of hydrophobic and cationic amino acid groups (Silva, Sarmento, & Pintado, 2013). In contrast to other bivalves, such as clams and oysters, mussels are less susceptible to infectious and inflammatory parasites, suggesting that these organisms have stronger defenses. (Novoa et al., 2016). Numerous studies show the antimicrobial action of peptides found in mussels, and it has been found that mussels are the primary source of the majority of marine antimicrobial peptides. Seven groups of marine mussel AMPs have been identified: large defencin, myticusin, myticins, mytilins, and mytimycin (Qin et al., 2014). Antibacterial properties of myticalins were established against both Gram-negative and Gram-positive microbes (Leoni et al., 2017). It also include that the isolation of defensins from Crassostrea gigas and Haliotis discus (Cunha, S. A., & Pintado, M. E., 2022)(De Zoysa et al., 2010). The hemolymph and hemoglobin of mussels contain a number of antimicrobial peptides that have been identified. Myticin C peptides from the mediterranean mussel mytilus galloprovincialis have shown their antiviral attack against one ostreid herpesvirus (OsHV-1). A modified myticin-derived peptide that are nano encapsulated displayed in vitro antibacterial activity against HSV-1 and HSV-2 human herpes virus (Novoa et al., 2016). Both myticusin-1, and mytichitin-CB, are able to suppress the Gram-positive bacteria *Sarcina luteus*, *Staphylococcu*, *Bacillus subtilis*, and *megaterium Bacillus* with MICs less than 5 mm, these compounds were isolated from the mytilus coruscus (Liao et al., 2013) (Qin et al., 2014). These peptides did not have promising results against Gram-negative bacteria. Two types of yeast *candida albicans* and *monilia albicans* were also examined, and both showed potential at concentrations above 5 mm (Liao et al., 2013; Qin et al., 2014). According to a literature review, peptides extracted from mollusks show antibacterial efficacy against both Gram-negative and Gram-positive bacteria. Gram-positive bacteria had MECs ranging from 0.8 to 31.3 g/mL, whereas Gram-negative bacteria had MECs between 0.4 and 15.0 g/mL. Several other research found on algae AMPs demonstrated action against E. coli, S. aureus, and MRSA (Guzman'et al., 2019; Jiao et al., 2019; Sedighi, Jalili, Ranaei-Siadat, & Amrane, 2016). Despite recent research shown promising findings anti-*S. aureus*, anti-*E. coli*, and anti-MRSA, algal peptides are not frequently investigated for their antimicrobial capabilities (Guzman et al., 2019). This demonstrates that algae could also be a potential source of AMPs. Therefore, it would have been highly beneficial to investigate this characteristic in algae in order to determine and test new AMPs for possible industrial uses. *Euphausia superba*, a kind of crustacean, has an AMP that can prevent S. aureus with a MIC of 5 mg/mL (Zhao, Yin, Liu, & Cao, 2013).

Mechanism:

The capacity of AMPs to bind to lipopolysaccharides (LPS) can produce gaps in microbial membranes, which results in cell death. In contrast, AMPs may be unable to cross membranes, in this case, they can hinder essential cellular functions once they have passed the helix (Semreen et al., 2018). AMPs tend to act in the cell membrane, however they can sometimes act inside cells (for instance, DNA/RNA, protein targets, mitochondria, or protein synthesis,). The danger of genetic variations and resistance to bacteria must be considered when specific targets are presumed (Bechinger & Gorr, 2017).

5.9 Applications in pharmacology and nutraceuticals

The antihypertensive, antithrombotic, antimicrobial, and antioxidant characteristics of peptides may aid in the treatment or prevention of diseases. Many of the current studies are in vitro-based. However, several marine-derived peptides are increasingly being introduced into clinical practices. Therefore, in vivo testing is required to determine the efficacy of peptides before moving further with their use as nutraceuticals and medications. For instance, antihypertensive peptides are being extracted from a variety of marine sources, but additional in-vivo experiments and studies on pharmacokinetics are required to validate their effectiveness in lowering blood pressure (Chen et al., 2020). Due to their diverse bioactivities, several isolated peptides; one example is the BCP-A peptide (Trp-Pro-Pro, MW = 398.44 Da), which was extracted from the muscle of *Tegillarca granulosa*., may also be intriguing for a broader activity. BCP-A demonstrated DPPH, O2, OH, and ABTS+ show greater radical scavenging activity as well as the capacity to suppress lipid peroxidation. Due to its cytotoxicity in contradiction of the HeLa cell lines and DU-145, PC-3, H.1299, this peptide also shows a dose-dependent anticancer effect. These results suggest that this peptide may be significant for the pharmaceutical sector, both in terms of reducing excessive ROS and in terms of cancer

treatment (Chi, Hu, Wang, Li, & Ding, 2015). Since type II diabetes is a major concern worldwide, peptides with anti-diabetic action may have potential as nutraceuticals if it can be demonstrated that they sustain their function. However, several Peptides obtained from the marine are increasingly being examined in clinical studies (Ketnawa, Suwal, Huang, & Liceaga, 2019). Furthermore, very few of these peptides have been authorized by the FDA due to a lack of high-quality research (Rivero-Pino et al., 2020a). To introduce nutraceuticals with anti-diabetic qualities, more research is therefore required.

5.10 Cosmetic industry applications

Peptides with antioxidant properties might be very useful for cosmetics. Oxidative are one of the leading causes of skin age, thus they can be used to prevent cutaneous illnesses and age spots (Kammeyer & Luiten, 2015). Some wrinkles and hair care cosmetics, including shampoo, body lotion, hair coloring hair restorers, agents, cleansers, and others, may comprise polypeptides derived from specific microalgae (Ariede et al., 2017). Besides anti-aging experimental animals such caenorhabditis elegans and drosophila melanogaster, marine species' proteins, carbohydrates, pigments, flavonoids, fatty acids, and phenols were utilized to illustrate their mechanism and action. Amino acids like mycosporine were found in marine, microalgae, macroalgae, bacteria, and molds, where they could absorb ultraviolet light after being reformed by amino acids and cyclohexenone (Wang X. et al., 2021).

Fig 2. Explains the advantages of microalgae peptides from processing to chromatographic techniques and in silico analysis. It also shows how microalgae peptides can be useful for cosmetical applications as well as good for human health.

Fig 2: Applications of bioactive peptides

VI. FDA-APPROVED MBPs AND CLINICAL TRIALS

Many MBPs have obtained FDA approval due to their distinctive structural and multifunctional characteristics, which have already been described by a wide verity of bioactivities, including antimicrobial (antifungal and antibacterial), antiviral, antioxidant, anticancer, anticoagulant, antithrombotic, antihypertensive, cholesterol-lowering and immunomodulatory and activities. the products on the market. In order to create MBP-based products that are suitable for medical, nutraceutical, and pharmaceutical uses a special mix of pristine counterparts and compositional alternation was used. Diverse materials and

techniques have been used for extractions, modifications, and purifications for several BPs from marine resources. However, a very small percentage of these bioactive peptides have already been approved for experimental phase evaluation, and indeed fewer have made it access to market. FDA-approved marine bioactive peptides are summarized to avoid redundancy in the literature **(Table. 3)**. Many other biologically active substances and products with aquatic origins, such as *Hemiasterlin*, *Salinosporamide F*, *Pliditepsin*, *Spisulosine*, *Tetrodotoxin*, PM00104 *Plinabulin*, *Conotoxin G*, *A*, *Kahalalide*, *Bryostatin 1*, and, *Pseudopterosin A* are currently undergoing clinical trials (phases I–III) (Alves et al., 2018; Anjum et al., 2017; Ghareeb et al., 2020; Ucak et al., 2021; Zhang et al., 2021).

Table 2: Food and Drug Administration-approved MBPs.

Name of Compound	Chemical Formula	Molecular Mass	CAS Number	Sources	Derivatives	Legal Presence	Availability	Half-life Elimination	Application
(intrathecal-ziconotide) Ziconotide	C102H172N36O32S7	2639.14 (g/mol)	107452-89-1	Spiral Snail	Organic Substance	Prescription only	50%	2.9 to 6.6 h	Analgesics
(Brentuximab vedotin) Adcetris	C6476H9930N1690O2030S40	149.2–151.8 (kg/mol)	914088-09-8	Dolabella auricularia	Derivative	Prescription only	50–80%	Approximately 4 to 6 days	Cancer therapy, specifically for those suffering from cutaneous T-cell lymphoma
Bacitracin (Baciim)	C66H103N17O16S	1422.71 (g/mol)	1405-87-4	A. subtilis (Bacillus)	Organic Substance	Only-Prescription for injection and OTC	unavailable	Not Available	Localized skin diseases, both acute and chronic
(Avodart) Dutasteride	C27H30F6N2O2	528.539 (g/mol)	164656-23-9		Synthetic	Only-Prescription	60%	5 Weeks	Hormone therapy for enlarged prostate and prostate cancer
A Curacin	C23H35NOS	373.60 (g/mol)	155233-30-0	A majuscule Lyngbya	Organic Substance	unavailable	unavailable	unavailable	treatment for Cancer
Eribulin (Halaven)	C40H59NO11	729.908 (g/mol)	253128-41-5	Sponge		Only-Prescription	unavailable	40 h	treatment for Cancer
(Yondelis) Trabectedin	C39H43N3O11S	761.84 (g/mol)	114899-77-3	Tunicate		Only-Prescription	unavailable	181 h	Chemotherapy drugs used to treat advanced cases of ovarian cancer and

									soft-tissue sarcoma
Dactinomycin	C62H86N12O16	1255.438 (g/mol)	50-76-0	parvulus	Derivative	Only-Prescription	unavailable	37 h	Treatment for several types of cancer, such as GTN, WT1, RMS, RMS, and Ewing's sarcoma,

6.1 Clinical trials phase II drugs derived from marine sources

Pseudopterosin H was found from aquatic coral Pseudoptero- gorgia elisabethae. The medicinal effciency of *pseudopterosin H* PC-3 cell line at varied proportions was evaluated in vitro utilizing the LDH, NBT and MTT tests, and also AO/EB fluorescence. As a result of causing apoptotic cell death and decreasing production of reactive oxygen species, *Pseudopterosin H* therapy decreases PC-3 cell proliferation, according to the outcomes. The PC-3 cells' chemosensitivity to *Pseudopterosin H* medication suggests that it may be used to treat and prevent metastatic castration-resistance the prostate cancer. PsH decreases PC-3 cell growth by inducing apoptosis and decreasing ROS levels. In order to reduce ROS, PsH may either simultaneously affect enzymes that promote oxidation or indirectly disrupt the pro-inflammatory mechanism, NF. Pharmacological features of PsH may effectively treat prostate cancer (Karthikeyan et al. 2022) (Bowers et al., 2021). Marine-derived bryostatin 1 exhibited procognitive and anti - depressive effects in animals and is being examined in humans for Alzheimer's disease (AD). Because of how well it improves retention of information, has been linked to the effects of bryostatin 1 on the structure and operation of hippocampal neurons. According to Calvin et al., bryostatin 1 encourages cortical synaptogenesis employing a variety of biochemical markers and pharmacologic antagonists and able to decrease dendritic spine density in a protein kinase C (PKC)-dependent approach. A unique pharmaceutical strategy for increasing memory by improving the signal-to-noise ratio in the nervous system may involve substances that improve synaptic density while also inducing the breakdown of immature dendritic spines brain (Ly et al., 2020). In both cell lines, calyculin-A boosted PP2A Y307 phosphorylation without reducing oral cancer cell growth. The available findings suggested that elevated p-PP2A expression caused by aberrant mechanisms may increase the proliferation of OSCC. The cell cycle, metabolism, migration, and viability are all directed by cell cycle regulation in which PP2A plays an important role. Calyculin-A therapy was known to increase GSK-3β (Ser9) and AKT (Ser 473) cancer cell phosphorylation, indicating PP2A inactivation. The results indicate that CLA reduced GSK-3β expression through disabling PP2A. (Velmurugan et al., 2018).

6.2 Phase III clinical trials drugs derived from marine sources

Cyclic depsipeptide plitidepsin is generated from the aquatic tunicate *albicans aplidium* that is chemically associated with didemnins, most of which possess antiviral properties. (Karthikeyan, A., Joseph, A., & Nair, B. G. (2022). In vitro models of SARSCoV-2 infection, plitidepsin performed better than other medicines, due to its strong antiviral efficacy and favorable therapeutic index such as remdesivir, in preclinical studies. Remarkably, plitidepsin has a significant in vitro antimicrobial activities effect on the SARS-CoV-2 B.1.1.7 diversity, which is known to contain several mutations that change the viral spike protein, which facilitates virus infection by associating in conjunction with the human ACE2 receptors (Reuschl et al., 2021).A neurotoxin called tetrodotoxin (TTX) is largely found in the puffer fish and other aquatic and the terrestrial animals. Voltage-gated Sodium channels that are obstructed by TTX (VGSCs). Many TTX-sensitive VGSCs are extremely expressed by major neuronal pathways and are important in the signaling of pain. Clinical trials are currently testing TTX for neuropathic pain brought on by radiotherapy and pain associated with cancer. The effectiveness and favorable safety profile of tetrodotoxin in treating pain brought on by neuropathies or cancer have been explored in both clinical and preclinical settings (González-Cano et al., 2021).

VII. FUTURE INDUSTRIAL APPLICATION

It is fascinating to learn about the research on marine peptides and the various important activities that have been discovered so far. It seems like there is still much untapped potential framework to be explored and

developed. Due to their abundance, efficiency of production, large biomass, protein content, and algae may be one of the most intriguing bioactive peptides from marine sources. Indeed, while considering the production range, it is comparatively simpler to acquire a greater quantity of proteins from microalgae in comparison to more prevalent crops like wheat and soybean. The identification of numerous advantageous peptides derived from algae serves to underscore their considerable opportunities for industrial exploitation. Beside this, a significant challenge in the synthesis of peptides from microalgae is reported fluctuations in protein contents, which are influenced by factors that include changes in the seasons, variations in temperature, and the specific site of algae growth. Therefore, the quantity of peptides that may be separated may vary if the protein content changes. A cyanobacterium known as spirulina has also been investigated as a source of marine bioactive organisms, with bioactivities including antibacterial, antihypertensive, and antiallergic, described. All essential amino acid is present in spirulina, which has a high protein concentration (53-62 percent of its dry weight). Compared to other species, this marine species' bioactive peptides have received fewer investigations than those of other species. Therefore, Spirulina could be a fascinating and potential marine source for bioactive peptide production. Marine seaweed is a promising and relatively unexplored novel compound for usage in functional products and nutraceuticals, such as carbohydrates and bioactive peptides. Because they are more readily available and have less side effects than chemical-based produced formulations, natural marine-derived bioactive compounds should be preferred. The use of marine organisms for the manufacture of biologically active peptides may promote significant contributions and could also represent economic benefits. The most significant future challenge will be integrating bioactive components into human health and nutrition, as the majority of research remains in vivo models because of time and expense constraints. In the coming years, study should be conducted on the enhancement of beneficial marine foods so that, their regular incorporation into the human diet may reduce the occurrence and severity of different diseases. Focus on ensuring the upcoming economic growth of marine natural organism's health and their specialty to innovative pharmaceutic agents, that can significantly contribute in order to the treatment of human pathological conditions, risk reduction of chronic disease, medical cost savings, new advancements, and effective connections between academic knowledge and manufacturing sectors will be required. For the development of new medications in the upcoming years, more details on bioactive peptides derived from marine origins is essential. A maximum degree of inventions in the area of seaweeds will lead to the development and successful innovation of marine nutraceuticals, providing us with the cause to expect that marine natural organisms will constitute a rising with the passage of time.

VIII. CONCLUSION

This review examined the potential of marine-derived bioactive peptides from various sources, highlighting their features and possible therapeutic applications in pharmaceutical, food, nutraceutical, and cosmetic industries. To further understand peptide uses, we also explored bioavailability and toxicity. Additionally, purifying methods have improved in recent years and numerous ways have been discovered and enhanced. As expenses continue to rise, they are still limited by their poor yield. The use of marine organisms for the creation of bioactive peptides may potentially lead to significant financial benefits because the marine ecology includes around half of the world's biodiversity, and there is a large amount of waste associated with marine exploration. There are significant resources of biologically active compounds that promotes drug discovery. The functionality of marine natural substances as pharmacological pathways is dependent on technological advancements such as sequencing techniques, nanotechnology, NMR for structural analysis, total medicinal chemistry, genetic modification, and biosynthesis.

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