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REVIEW

Can be marine bioactive peptides (MBAs) lead the future of foodomics for human health?

Abdur Rauf^a, Anees Ahmed Khalil^b, Muneeb Khan^c, Sirajudheen Anwar^d, Abdulwahab Alamri^d, Abdulmalik M. Alqarni^e, Adel Alghamdi^f, Farhan Alshammari^g, Kannan R. R. Rengasamy^h , and Chunpeng Wanⁱ

^aDepartment of Chemistry, University of Swabi, Anbar, Khyber Pakhtunkhwa, Pakistan; ^bUniversity Institute of Diet and Nutritional Sciences, Faculty of Allied Health Sciences, The University of Lahore, Lahore, Pakistan; ^cDepartment of Human Nutrition and Dietetics, Riphah College of Rehabilitation and Allied Health Sciences, Riphah International University, Lahore, Pakistan; ^dDepartment of Pharmacology and Toxicology, University of Hail, Hail, Saudi Arabia; ^eDepartment of Pharmaceutical Chemistry, College of Clinical Pharmacy, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia; ^fPharmaceutical Chemistry Department, Faculty of Clinical Pharmacy, Al Bahia University, Al Bahia, Saudi Arabia; ^gDepartment Of Pharmaceutics, College of Pharmacy, University of Hail, Hail, Saudi Arabia; ^hGreen Biotechnologies Research Centre of Excellence, University of Limpopo, Polokwane, Sovenga, South Africa; ⁱJiangxi Key Laboratory for Postharvest Technology and Nondestructive Testing of Fruits & Vegetables, College of Agronomy, Jiangxi Agricultural University, Nanchang, People's Republic of China

ABSTRACT

Marine organisms are considered a cache of biologically active metabolites with pharmaceutical, functional, and nutraceutical properties. Among these, marine bioactive peptides (MBAs) present in diverse marine species (fish, sponges, cyanobacteria, fungi, ascidians, seaweeds, & mollusks) have acquired attention owing to their broad-spectrum health-promoting benefits. Nowadays, scientists are keener exploring marine bioactive peptides precisely due to their unique structural and biological properties. These MBAs have reported ameliorating potential against different diseases like hypertension, diabetes, obesity, HIV, cancer, oxidation, and inflammation. Furthermore, MBAs isolated from various marine organisms may also have a beneficial role in the cosmetic, nutraceutical, and food industries. Few marine peptides and their derivative are approved for commercial use, while many MBAs are in various pre-clinical and clinical trials. This review mainly focuses on the diversity of marine bioactive peptides in marine organisms and their production procedures, such as chemical and enzymatic hydrolysis. Moreover, MBAs' therapeutic and biological potential has also been critically discussed herein, along with their status in drug discovery, pre-clinical and clinical trials.

KEYWORDS

clinical data; marine drugs; molecular pharmacology; structure-activity relationship; synthetic approaches

Introduction

Nearly 70% of the world's surface comprises oceans, which encompasses the vast potential of biologically active natural products with therapeutic and nutraceutical characteristics. Since the last few decades, extensive research has been carried out on novel and unique bioactive compounds present in organisms living in marine habitat (Ngo et al. 2012). Marine organisms, including sponges, fish, mollusks, ascidians, seaweeds, marine fungi, marine bacteria, etc., are known to be caches of undiscovered bioactive components having medicinal perspectives. Therefore, the vast natural class of bioactive compounds present in marine organisms possesses a significant opportunity in drug discovery and development. The uniqueness of metabolites (vitamins, minerals, polyunsaturated fatty acids, antioxidants, polysaccharides & bioactive peptides) in marine organisms may be subject to their exposure to the extreme environment like temperature and salinity, and pressure (Wang et al. 2017).

Notably, marine peptides have gained more attention among all these metabolites due to their potent health-promoting and disease reducing characteristics (Lee, Phat, and Hong 2017).

Generally, bioactive peptides constitute 3 to 20 amino acid residues, and their mechanism of action depends on the sequential arrangement and composition of amino acids. Low molecular weight bioactive peptides pass rapidly via the intestinal wall and therefore possess more functional and biological properties. In recent times, bioactive peptides' importance has attained scientists' attention due to their novel structural and compositional properties (Jo et al. 2017). Nevertheless, marine bioactive peptides (MBAs) have been identified in different organisms like fish, lobsters, crabs, shrimps, clams, squid, oysters, mollusks, sponges, ascidians, and other marine microorganisms (bacteria & fungi). Their unique structure and amino acid sequence are responsible for associated disease-preventing properties against oxidation, hypertension, cancer, diabetes,

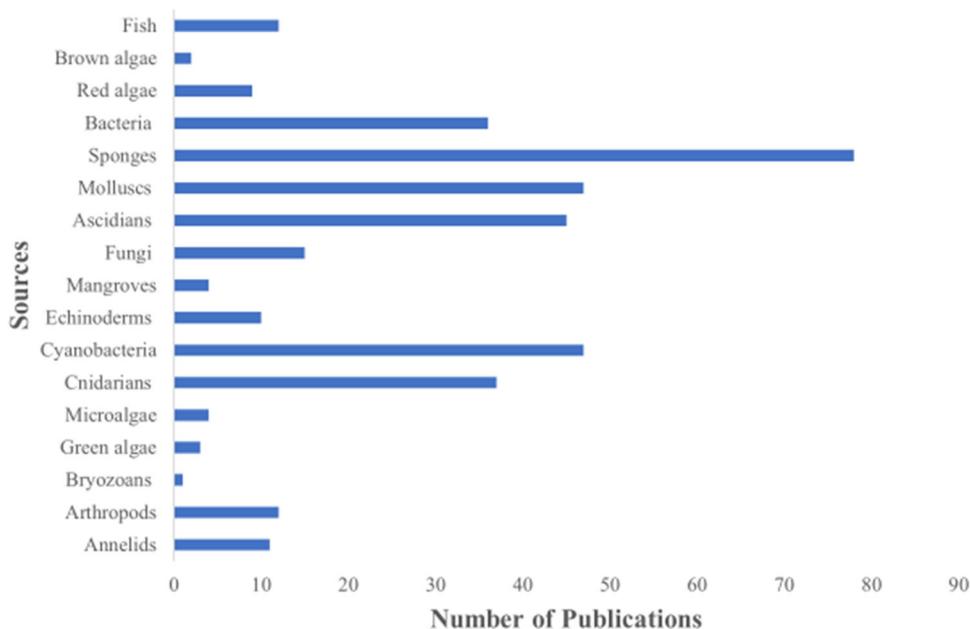


Figure 1. The sources of marine bioactive peptides in terms of publications used in this review.

hypercholesterolemia and thrombosis (Najafian and Babji 2012; Ngo et al. 2012). Despite their pharmaceutical potential, they have shown a beneficial role in cosmetic (anti-aging & antioxidative properties) and food (foaming & emulsifying properties) industries (Ucak et al. 2021; Wang et al. 2021). Furthermore, marine-derived bioactive peptides isolated from seaweed have also been utilized as nutraceuticals and prebiotics (Charoensiddhi et al. 2017).

Scientists consider marine bioactive peptides a potent candidate in drug discovery due to their significant bio-regulatory role and unique mode of action (See Figure 1 for the number of papers published on marine peptides in each source).

In recent times, after discovering cyclic and linear marine bioactive peptides, the horizon of innovative drug discovery has changed completely (Aneiros and Garateix 2004; Jo et al. 2017). Moreover, MBAs are an opportunity in pharmaceuticals and nutraceutical as consumer preferences are shifting toward functional food. Therefore, it is necessary to identify, characterize and develop natural product-based drugs (Erdmann, Cheung, and Schröder 2008; Siro et al. 2008). In this context, this review provides insight on the diversity of MBAs in marine organisms, their preparation and purification, along with their potent pharmacological perspectives evidently from pre-clinical, clinical and drug discovery pipeline.

Diversity of MBA's in marine organisms

Fish

Peptides have been derived from different marine fish (tuna, yellowfin sole, scad, Hoki, Pacific hake, yellow stripe trevally, conger eel, etc.) and fish body parts (fish bones, muscles, skin, intestines, etc.). Fish derived peptides have shown to possess antihypertensive and antioxidative properties (Giri and Ohshima 2012). Fish peptides isolated from seafood

industrial processing byproducts are enzymatically hydrolyzed for enhancing the recovery of proteins. These protein hydrolysates derived from fish and fish by-products demonstrates functional & nutritional properties, and hence scientists are keener in exploring possible bioactive peptides (Senevirathne and Kim 2012).

Potent bioactive peptides have been isolated from shark meat, skipjack tuna muscle, and sardine muscle (Bougatet et al. 2008; Wu et al. 2008). Specific antimicrobial peptides that are abundantly present in the mucous layer have also been derived from Atlantic halibut, winter flounder, and American plaice (Douglas et al. 2003; Senevirathne and Kim 2012). Fish peptides have shown to scavenge free radicals (Ranathunga, Rajapakse, and Kim 2006) inhibit ACE activity (Je et al. 2005a), and suppress intrinsic coagulation pathways (Rajapakse et al. 2005a). Table 1 demonstrates an amino acid sequence of bioactive peptides derived from fish sources.

Sponges

Sponges are marine organisms belonging to the phylum Porifera predominantly present on shores and in deep waters of oceans. Diverse species of sponges are considered sources of novel bioactive components such as alkaloids, terpenoids, bioactive peptides, and nucleoside derivatives (Anand et al. 2012). Various studies have recently shown significant biological activities of unique bioactive peptides isolated from sponges compared with peptides from other sources. Marine sponges abundantly comprise unique bioactive peptides, including cyclic, linear, and depsipeptides having 2 to 48 amino acid residues. Marine peptides obtained from sponges are novel structurally and biologically owing to the presence of cyclic or linear peptides and a unique amino acid sequence, respectively (Jo et al. 2017; Matsunaga and Fusetani 2003).

Table 1. Marine bioactive peptides isolated from a fish source.

Source	Body part	Amino acid sequence	References
Croaker	Skin	GNRGFACRHA	Kumar, Nazeer, and Jaiganesh (2011)
Big eye tuna	Muscle	LNLPTAVYMT WPEAAELMEVDP	Je et al. (2008) Qian, Je, and Kim (2007)
Tuna	Backbone	VKAGFAWTANEELS	Je et al. (2007)
Conger eel	Muscle	LG LNGDDVN	Ranathunga, Rajapakse, and Kim (2006)
Horse mackerel	Skin	NHRYDR	Kumar, Nazeer, and Jaiganesh (2011)
Big eye tuna	Frame	GDLGKTTTWSNWSPPKYKDTP	Lee, Qian, and Kim (2010)
Hoki fish	Skin	HGPLGPL	Mendis, Rajapakse, and Kim (2005b)
Alaska pollock	Skin	GPL GPM	Byun and Kim (2001)
Sea bream	Scales	VIY	Fahmi et al. (2004)
Alaska pollock	Backbone	VLSGGTTMAMYTLV	Jung et al. (2006a)
Yellowfin Sole	Frame	RDPDFPLEPPY MIFPGAGGPEL	Jun et al. (2004) Jung et al. (2006b)
Seaweed pipefish	Muscle	TFHGP HWTTQR	Wijesekara et al. (2011)

First bioactive peptide isolated from *Discodermiu kiiensis* (marine sponge) having antimicrobial and cell growth inhibitory properties were structurally elucidated as discodermins (B, C, & D) (Matsunaga, Fusetani, and Konosu 1985). Discodermins (A-H) are cytotoxic peptides comprising of both standard and unique chain of amino acids in addition to a macrocyclic ring (Matsunaga, Fusetani, and Konosu 1984; Ryu, Matsunaga, and Fusetani 1994a, b). A tetrapeptide naming Kasumigamide possessing N-terminal α -hydroxy acid has been derived from a bowl-shaped sponge (*Discodermia calyx*) (Nakashima et al. 2016). Marine sponges of various species (*Geodia*, *Pseudaxinyssa*, & *Cymbastela*) are known to possess the unique class of cyclodepsipeptides (Geodiamolides A-R) that are reported to be responsible for various biological activities (Chan et al. 1987; Coleman, Van Soest, and Andersen 1999; de Silva, Andersen, and Allen 1990; Rangel et al. 2006; Tinto et al. 1998). Likewise, proline-rich unique cycloheptapeptides (Phakellistatins 1-19) have been isolated from *Phakellia* sp. and are found to inhibit cellular growth against leukemia, lung carcinoma, epidermoid carcinoma, and ovarian cancer cell lines, respectively (Li et al. 2003; Mechnich and Kessler 1997; Pelay-Gimeno et al. 2013; Pettit et al. 1993; Pettit, Rhodes, and Tan 1999; Pettit and Tan 2003, 2005; Pettit et al. 1994a; Pettit et al. 1995a; Pettit et al. 1995b; Pettit et al. 1994b; Pettit et al. 1994c; Pettit et al. 1995c; Shaheen et al. 2016; Zhang et al. 2010) (Table 2).

Milnamides (A-G) are other marine bioactive peptides that have been identified in different sponges like *Pipestella candelabra* and *Hemiasterella minor* (Talpir et al. 1994; Tran et al. 2014). Similarly, Scleritodermin A, Mirabamide C, Mirabamide G, and Mirabamide H are present in *Scleritoderma nodosum*, *Siliquariaspongia mirabilis*, and *Stelletta clavosa*, respectively (Liu, Cui, and Nan 2008a; Schmidt et al. 2004). Celebesides (A-C) are unique cyclic depsipeptides derived from *S. mirabilis*. Celebesides (A-C) comprising a polyketide moiety and five other residues of amino acids, including 3-carbamoyl threonine and a phosphoserine residue (Plaza et al. 2009). Anti-HIV characteristics of Neamphamides (A-D), a cyclic depsipeptide isolated from *Neamphius huxleyi*, comprises 11-amino acid residues with an amide linked 3-hydroxy-2,4,6-trimethylheptanoic acid moiety (Oku et al. 2004; Oku et al. 2005; Tran et al.

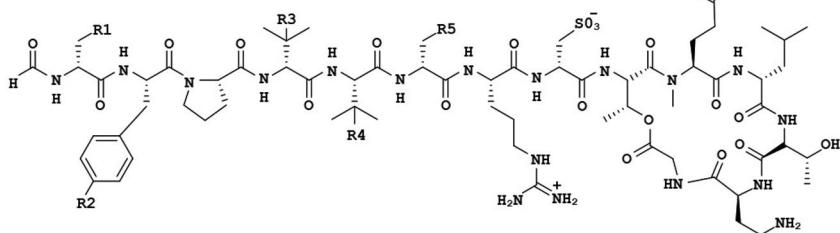
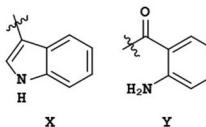
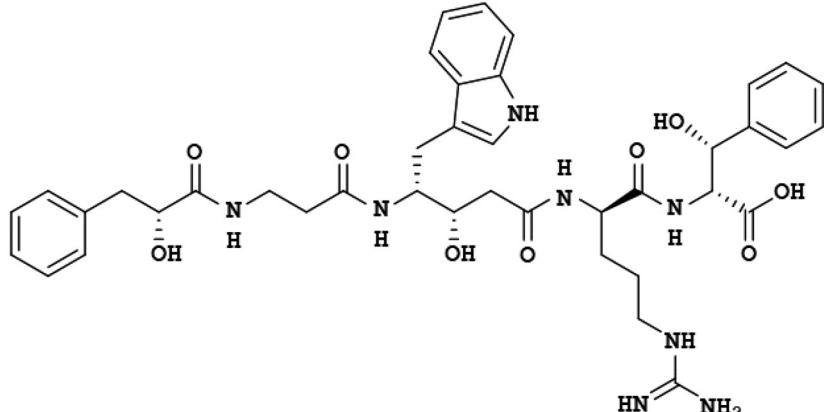
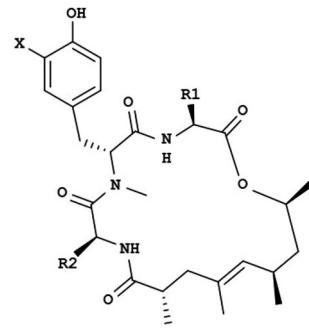
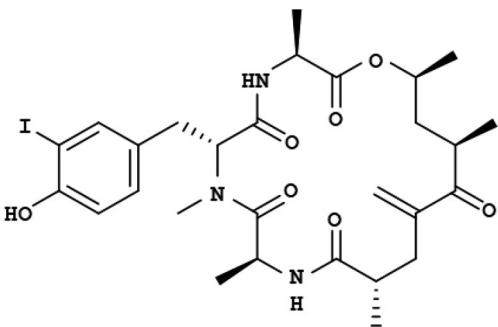
2012). Other than these, Carteritin A and Arenastatin A are cyclic heptapeptides and cyclic depsipeptide isolated from *Styliissa carteri* and *Dysidea arenaria*, respectively (Afifi et al. 2016; Kobayashi et al. 1994; Yadav et al. 2011) (Table 2).

Marine cyanobacteria

Cyanobacteria widely distributed in aquatic and terrestrial environments, but those present in marine habitat are marine cyanobacteria. These cyanobacteria are considered the required course of novel bioactive metabolites (Uzair et al. 2012). Marine bioactive peptides from these marine bacteria are discussed herein. Tutnagainolides A-B is C-3 epimeric cyclic peptides isolated from *Bacillus* species that are found to be inositol 5-phosphate SHIP1 stimulators having anti-inflammatory and anti-cancer properties. Other cyclic peptides (Solonamides A-B) have been isolated from *Photobacterium halotolerans* associated with tropical Pacific Ocean mussels to control viral gene expression. Lafunamide C is a cyclodepsipeptide, which has been isolated from *Lyngbya majuscule* possesses cytotoxic and antimalarial properties. Similarly, Wewakamide A and Guineamides E-F are cyclic depsipeptides with biological activity derived from *Lyngbya semiplena* and *Lyngbya majuscula*, respectively (Table 3) (Blunt et al. 2013; Han et al. 2011).

On the other hand, Wewakazole, a cyclic dodecapeptide isolated from *L. majuscula*, revealed cytotoxic (IC_{50} : 10 μ M) potential against H460-human lung cancer cell line (Nogle, Marquez, and Gerwick 2003). Norbisebromoamide, a dimethyl analogue of bisebromoamide derived from *Lyngbya* sp. significantly inhibited the proliferation (Gao et al. 2010; Nogle, Marquez, and Gerwick 2003; Sasaki et al. 2011; Teruya et al. 2009). Marine-derived modified linear peptides having anti-leishmanial potential (IC_{50} : 5.9 μ M) such as Herbamide B have been isolated and identified from *L. majuscula* (Balunas et al. 2010). Structurally cyclodepsipeptides (apratoxins A-C & D) isolated from *L. majuscula* contain the same macrocycle while apratoxin D also comprises unique polyketide moiety (3,7-dihydroxy-2,5,8,10,10-pentamethylundecanoic acid). However, Apratoxin E is isolated from *L. bouillonii* and have cytotoxic characteristics (Gutiérrez et al. 2008; Liu and Rein 2010). A lipopeptide

Table 2. Name, source, and structures of some bioactive peptides isolated from diverse marine sponges.

Bioactive peptide	Source	Structure	References
Discodermins A-H	<i>Discodermia kiiensis</i>	 <p style="text-align: center;"> Discodermins { A: R1=R2=H; R3=R4=Me; R5=X B: R1=R2=R3=H; R4=Me; R5=X C: R1=R2=R4=H; R3=Me; R5=X D: R1=R2=R3=R4=H; R5=X E: R1=R2=H; R3=R4=Me; R5=Y F: R1=R2=H; R3=Me; R4=Et; R5=X G: R1=R3=R4=Me; R2=H; R5=X H: R1=H; R2=OH; R3=R4=Me; R5=X </p> 	Matsunaga, Fusetani, and Konosu (1984, 1985); Ryu, Matsunaga, and Fusetani (1994a, 1994b)
Kasumigamide	<i>Discodermia calyx</i>		Nakashima et al. (2016)
Geodiamolides A-F	<i>Pseudaxinysa</i> sp.	 <p style="text-align: center;"> Geodiamolides { A: R1=Me; R2=Me; X=I B: R1=Me; R2=Me; X=Br C: R1=Me; R2=Me; X=Cl D: R1=Me; R2=H; X=I E: R1=Me; R2=H; X=Br F: R1=Me; R2=H; X=Cl </p>	Chan et al. (1987); Coleman, Van Soest, and Andersen (1999); de Silva, Andersen, and Allen (1990); Rangel et al. (2006); Tinto et al. (1998)
Geodiamide G	<i>Geodia</i> sp.		Chan et al. (1987); Coleman, Van Soest, and Andersen (1999); de Silva, Andersen, and Allen (1990); Rangel et al. (2006); Tinto et al. (1998)

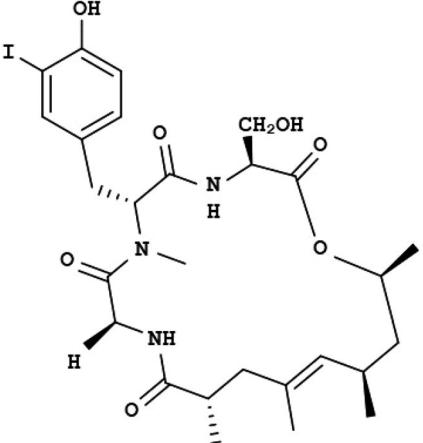
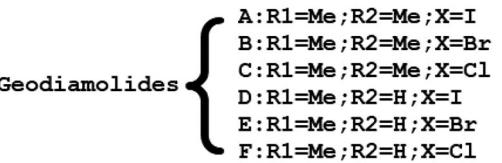
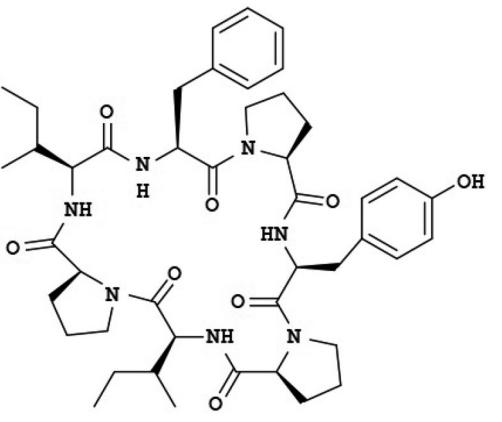
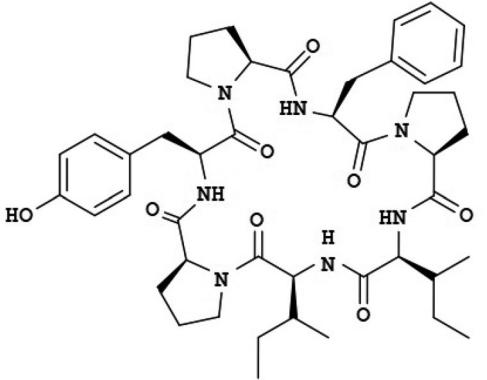
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Table 2. Continued.

Bioactive peptide	Source	Structure	References
Geodiamolides H, I			Tinto et al. (1998)
Geodiamolides J, K	<i>Cymbastela</i> sp.		Chan et al. (1987); Coleman, Van Soest, and Andersen (1999); de Silva, Andersen, and Allen (1990); Rangel et al. (2006); Tinto et al. (1998)
Geodiamolides L-Q			Chan et al. (1987); Coleman, Van Soest, and Andersen (1999); de Silva, Andersen, and Allen (1990); Rangel et al. (2006); Tinto et al. (1998)

(continued)

Table 2. Continued.

Bioactive peptide	Source	Structure	References
Geodiamolide R			Chan et al. (1987); Coleman, Van Soest, and Andersen (1999); de Silva, Andersen, and Allen (1990); Rangel et al. (2006); Tinto et al. (1998)
Geodiamolides			A : R1=Me ; R2=Me ; X=I B : R1=Me ; R2=Me ; X=Br C : R1=Me ; R2=Me ; X=Cl D : R1=Me ; R2=H ; X=I E : R1=Me ; R2=H ; X=Br F : R1=Me ; R2=H ; X=Cl
Phakellistatin 1	<i>Phakellia sp.</i>		Li et al. (2003); Mechnich and Kessler (1997); Pelay-Gimeno et al. (2013); Pettit et al. (1993); Pettit, Rhodes, and Tan (1999); Pettit and Tan (2003, 2005); Pettit et al. (1994a); Pettit et al. (1995a); Pettit et al. (1995b); Pettit et al. (1994b); Pettit et al. (1994c); Pettit et al. (1995c); Shaheen et al. (2016); Zhang et al. (2010)
Phakellistatin 2			

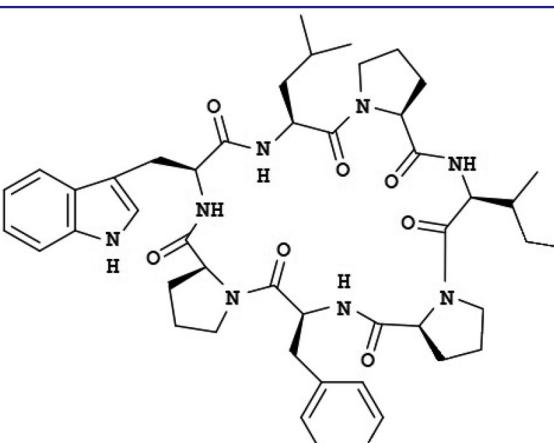
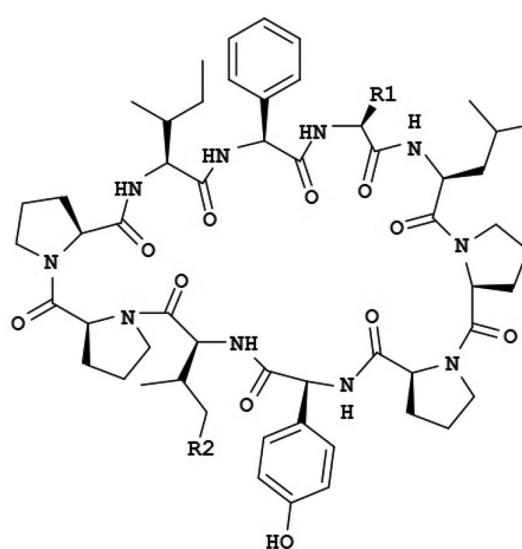
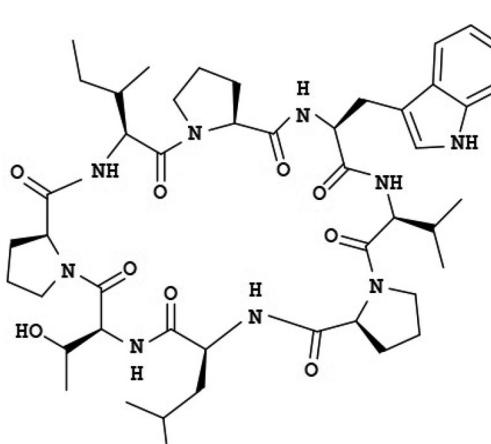
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Table 2. Continued.

Bioactive peptide	Source	Structure	References
Phakellistatin 3		<p>Phakellistatin 3:44R,52S Isophakellistatin 3:44S,52R</p>	
Phakellistatin 4			
Phakellistatin 5			

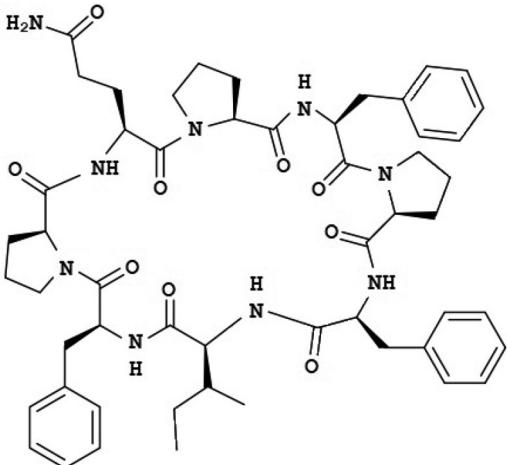
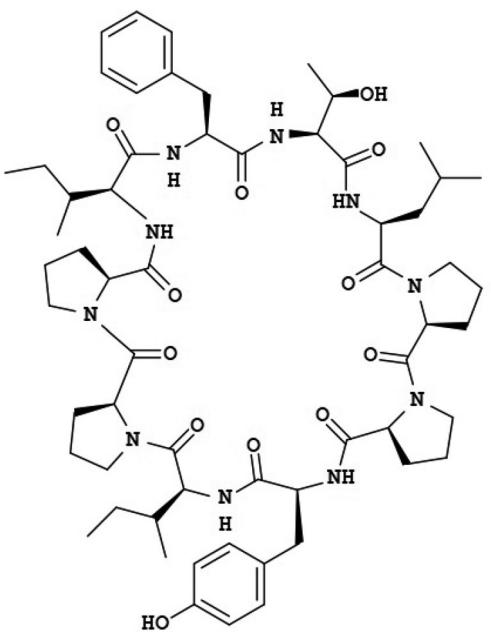
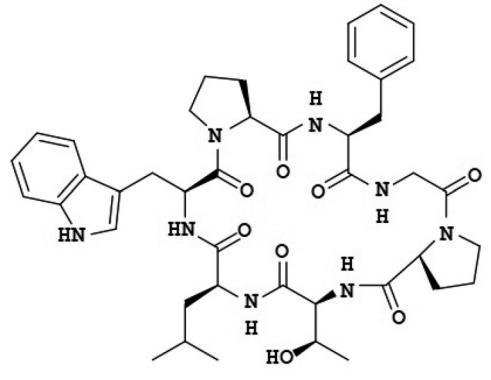
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Table 2. Continued.

Bioactive peptide	Source	Structure	References
Phakellistatin 6			
Phakellistatin 7-9			
		Phakellistatins { 7 : R1=R2=CH ₃ 8 : R1=CH(CH ₃) ₂ ; R2=CH ₃ 9 : R1=CH(CH ₃) ₂ ; R2=H}	
Phakellistatin 10			

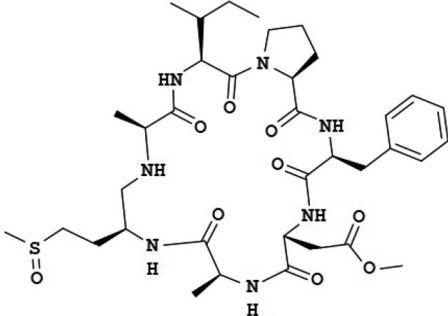
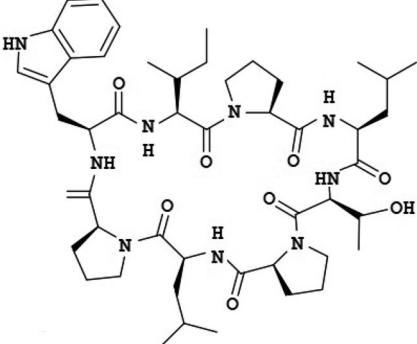
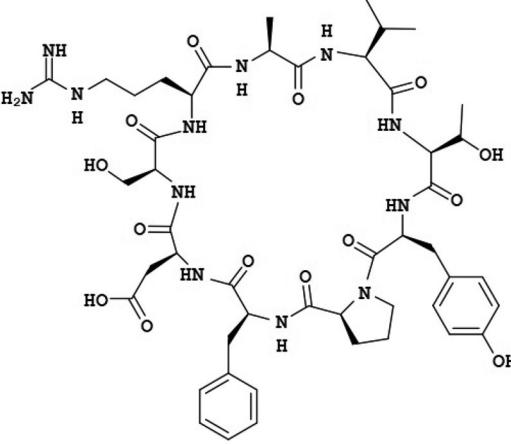
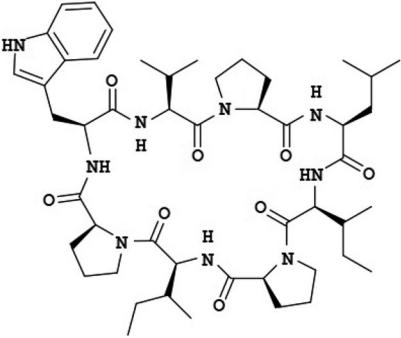
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Bioactive peptide	Source	Structure	References
Phakellistatin 11			
Phakellistatin 12			
Phakellistatin 13			

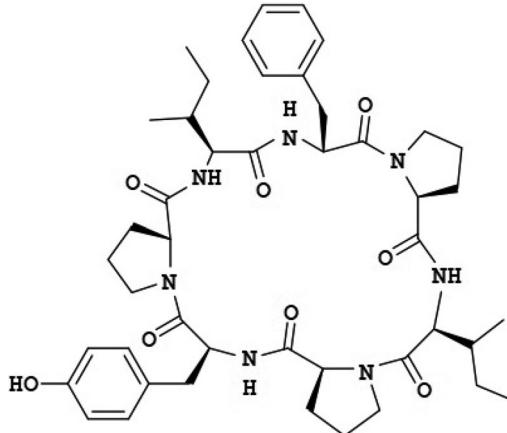
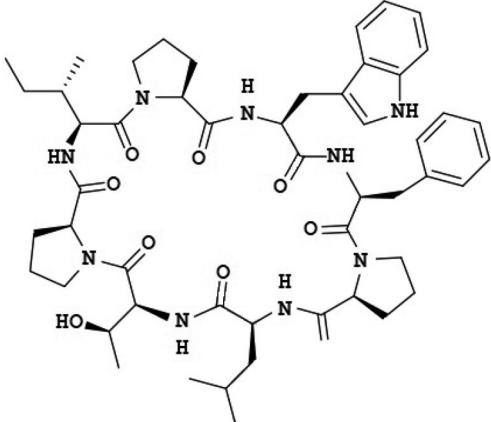
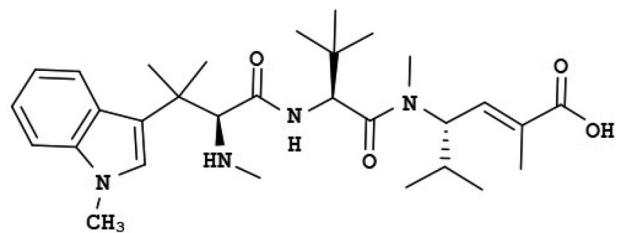
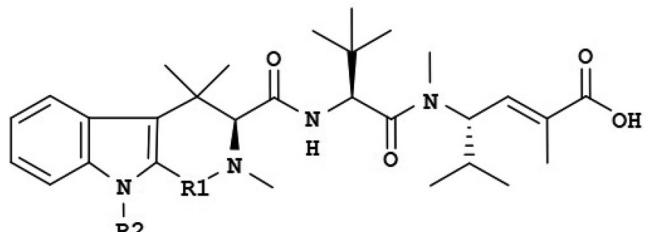
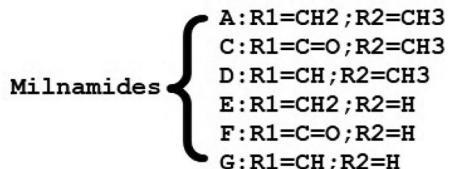
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Table 2. Continued.

Bioactive peptide	Source	Structure	References
Phakellistatin 14			
Phakellistatin 15			
Phakellistatin 16			
Phakellistatin 17			

(continued)

Table 2. Continued.

Bioactive peptide	Source	Structure	References
Phakellistatin 18			
Phakellistatin 19			
Milnamide B	<i>Hemiasperella minor</i>		Talpir et al. (1994)
Milnamide A, C-G	<i>P. candelabra</i>		Tran et al. (2014)
Milnamides		 <p>A : R1=CH₂; R2=CH₃ C : R1=C=O; R2=CH₃ D : R1=CH; R2=CH₃ E : R1=CH₂; R2=H F : R1=C=O; R2=H G : R1=CH; R2=H</p>	

(continued)

Table 2. Continued.

Bioactive peptide	Source	Structure	References
Scleritodermin A	<i>Scleritoderma nodosum</i>		Liu, Cui, and Nan (2008a); Schmidt et al. (2004)
Mirabamide C	<i>Siliquariaspongia mirabilis</i>		Liu, Cui, and Nan (2008a); Schmidt et al. (2004)
Mirabamide G-H	<i>Stelletta clavosa</i>		Liu, Cui, and Nan (2008a); Schmidt et al. (2004)

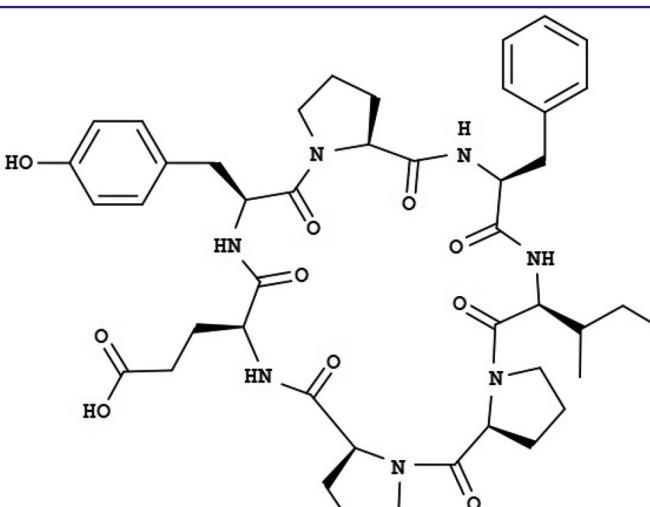
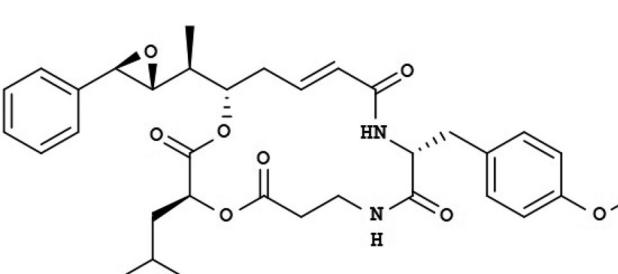
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Table 2. Continued.

Bioactive peptide	Source	Structure	References
Celebesides (A-C)	<i>S. mirabilis</i>		Plaza et al. (2009)
Neamphamide A	<i>Neamphius huxleyi</i>		Oku et al. (2004); Oku et al. (2005); Tran et al. (2012)
Neamphamide B-D			

(continued)

Table 2. Continued.

Bioactive peptide	Source	Structure	References
Carteritin A	<i>Styliessa carteri</i>		Afifi et al. (2016)
Arenastatin A	<i>Dysidea arenaria</i>		Kobayashi et al. (1994); Yadav et al. (2011)

isolated from *Lyngbya majuscula/Schizothrix* sp. have been identified as Somocystinamide A-induced apoptosis in different tumor cell lines (Wrasiidlo et al. 2008; Zheng et al. 2011). Similarly, Lobocyclamides B-C is two lipopeptides comprising of an uncommon amino acid (4-hydroxythreonine) together with long-chain β -amino acids (3-aminoctanoic acid and 3-aminodecanoic acid), correspondingly that were isolated from *L. confervoides* (MacMillan et al. 2002). Another cyclic depsipeptide (Hoiamide A) isolated from *L. majuscula* contains a 15-carbon sub-unit between C-30 to C-44 that is suggested to be derived from the polyketide pathway. A macrocyclic depsipeptide, i.e. Grassypeptolide isolated from *L. confervoides* contains a β -amino acid and rare high content of D-amino acid along with two thiazoline moieties (Liu and Rein 2010). Obynamide is another cyclic depsipeptide derived from *L. confervoides* having cytotoxic potential against KB cell lines (Williams et al. 2002).

Marine fungi

Sansalvamide A (cyclic depsipeptide) isolated from genus *Fusarium* present on the surface of *Halodule wrightii* (seagrass) is found to possess anti-cancer properties as it induced cell cycle arrest (G-phase) in CD18 of the examined human pancreatic cell line (AsPC-1) (Belofsky, Jensen, and Fenical 1999). A rare hexacyclic dipeptide (Azonazine) isolated from marine sediment derived fungus (*Aspergillus*

insulicola) demonstrated anti-inflammatory (IC_{50} : 8.37 μM) properties (Wu et al. 2010). An unidentified sponge derived fungus present in saltwater was cultured for the isolation guangomides A-B (cyclic depsipeptides). These peptides showed weak antibacterial potential against *S. epidermidis* and *E. durans* (Amagata et al. 2006). *Simplicillium obclavatum* is a deep-sea fungus from which a group of linear tetrapeptides (Simplicillumtides A-H) have been isolated (Table 4). Among these Simplicillumtides, A & B tetrapeptides' linear structure contains a 2-aminobenzoic acid residue; however, C-H is acetylated di/tripeptides (Liang et al. 2016).

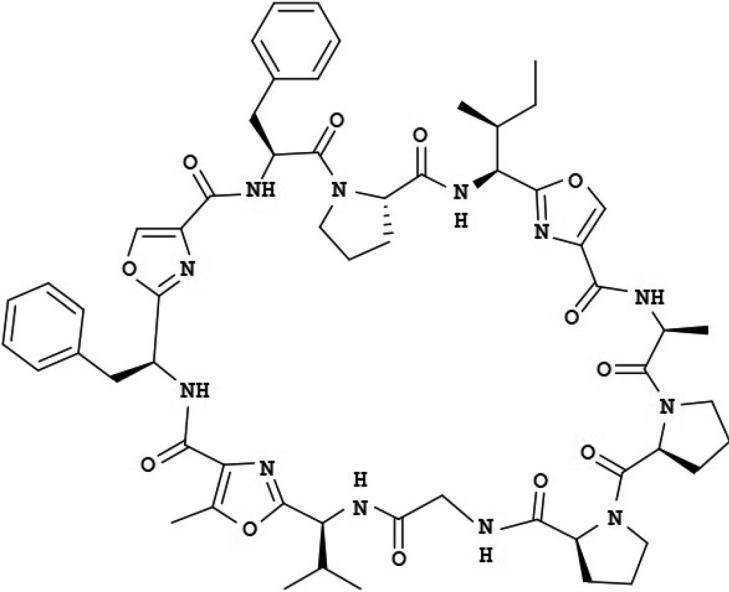
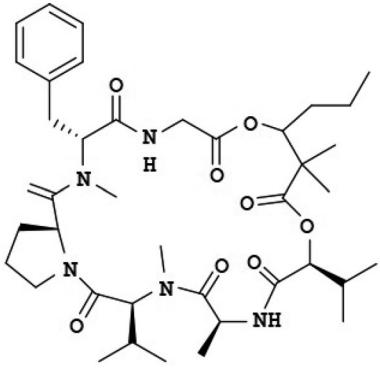
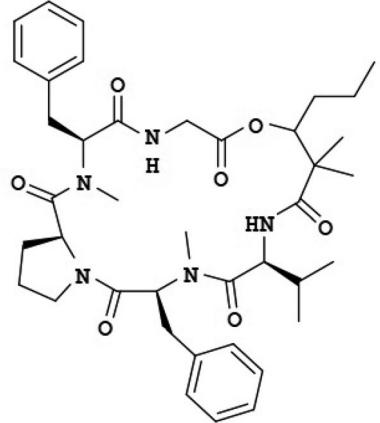
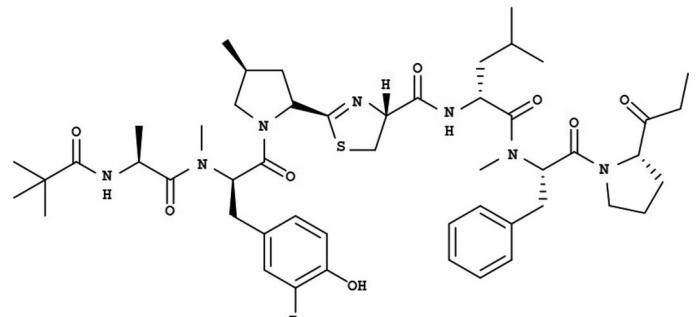
Cordyheptapeptides A and B comprise N-methyl-L-tyrosine and N-methyl-L-phenylalanine moieties, respectively isolated from *Cordyceps*, have elucidated cytotoxic (IC_{50} : 0.18 & 3.1 μM) properties against NCI-H187 cells (Isaka et al. 2007). In comparison, Cordyheptapeptides C-E is cycloheptapeptides derived from a marine fungus, i.e. *Acremonium persicum* (Chen et al. 2012). A marine sponge-associated *Acremonium* sp. were cultured for isolation of N-methylated linear octapeptide (Efrapeptin G) (Boot et al. 2006). Culture of *Nigrospora oryzae* PF18 (marine fungus) from a marine sponge (*Phakellia fusca*) revealed isolation of cyclohexadepsipeptides (Oryzamides A-B) (Ding et al. 2016). Halolitoralin A (cyclic hexapeptides) and Halolitoralins B-C (cyclic tetrapeptides) were isolated from marine sediment-derived *Halobacillus litoralis* together with three cyclic dipeptides i.e. cyclo (Ile-Val, Pro-Leu, & Pro-Val) (Yang

Table 3. Name, source, and structures of some bioactive peptides isolated from diverse marine cyanobacteria.

Bioactive peptide	Source	Structure	References
Turnagainolide A-B	<i>Bacillus</i> sp.		Blunt et al. (2013)
Solonamides A-B	<i>Photobacterium halotolerans</i>		Blunt et al. (2013)
Lagunamide C	<i>L. majuscula</i>		Blunt et al. (2013)
Wewakamide A	<i>Lyngbya semiplena</i>		Blunt et al. (2013); Han et al. (2011)

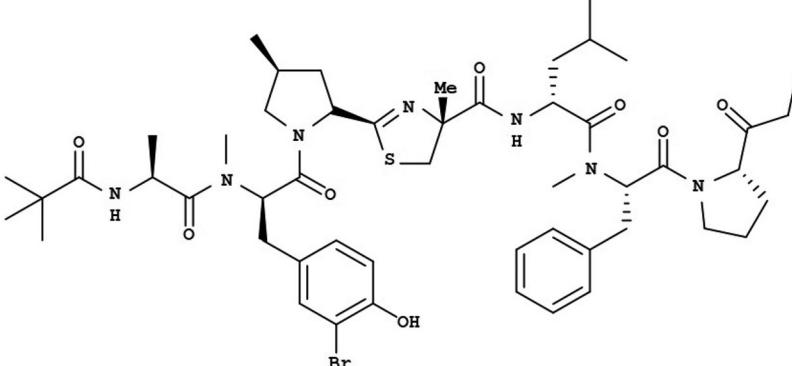
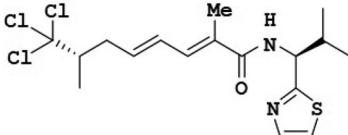
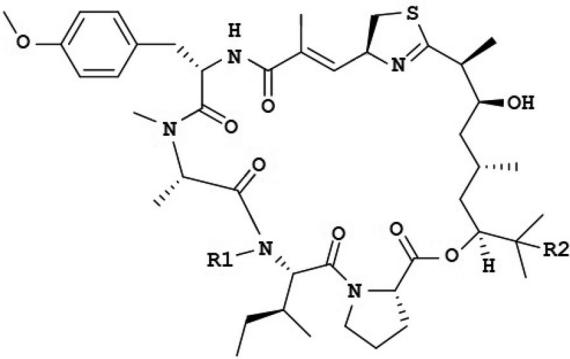
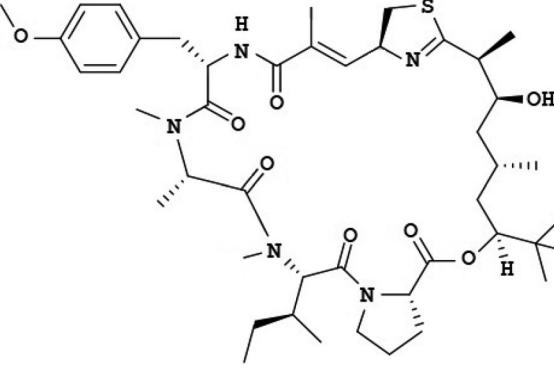
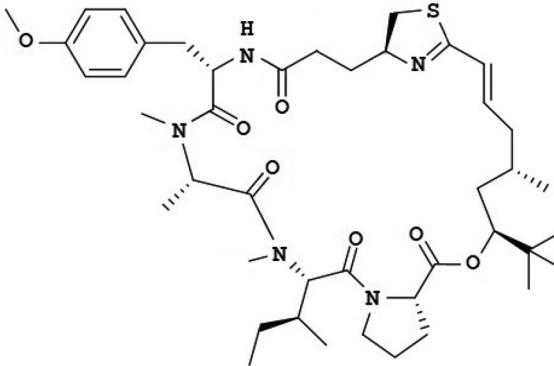
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Table 3. Continued.

Bioactive peptide	Source	Structure	References
Wewakazole	<i>L. majuscula</i>		Nogle, Marquez, and Gerwick (2003)
Guineamide E	<i>Lyngbya semiplena</i>		Blunt et al. (2013); Han et al. (2011)
Guineamide F	<i>Lyngbya majuscula</i>		Blunt et al. (2013); Han et al. (2011)
Norbisebromoamide	<i>Lyngbya</i> sp.		Sasaki et al. (2011)

(continued)

Table 3. Continued.

Bioactive peptide	Source	Structure	References
Bisebromoamide	<i>Lyngbya</i> sp.		Gao et al. (2010); Sasaki et al. (2011); Teruya et al. (2009)
Herbamide B	<i>L. majuscula</i>		Balunas et al. (2010)
Apratoxin A-C	<i>L. majuscula</i>	 Apratoxins A: R1=R2=CH ₃ B: R1=H; R2=CH ₃ C: R1=CH ₃ ; R2=H	Liu and Rein (2010)
Apratoxin D	<i>L. majuscula</i>		Gutiérrez et al. (2008); Liu and Rein (2010)
Apratoxin E	<i>L. bouillonii</i>		Liu and Rein (2010)

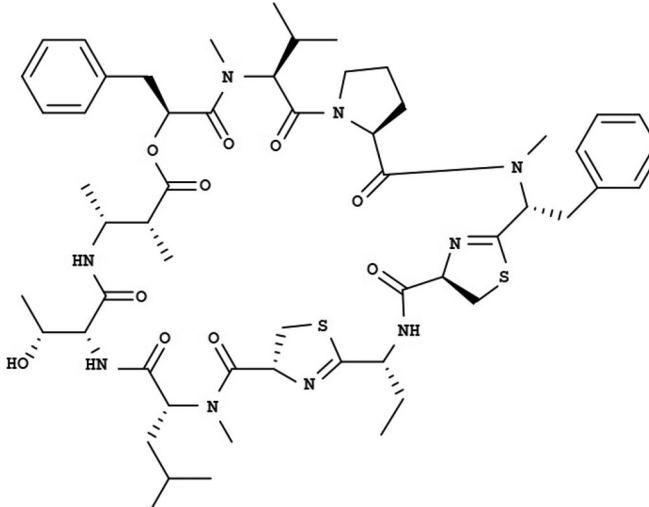
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Table 3. Continued.

Bioactive peptide	Source	Structure	References
Somocystinamide A	<i>Lyngbya majuscula/ Schizothrix sp</i>		Wrasidlo et al. (2008)
Hoiamide A	<i>L. majuscula</i>		Liu and Rein (2010)
Lobocyclamides B-C	<i>L. confervoides</i>		MacMillan et al. (2002)
Obyanamide	<i>L. confervoides</i>		Williams et al. (2002)

(continued)

Table 3. Continued.

Bioactive peptide	Source	Structure	References
Grassypeptolide	<i>L. confervoides</i>		Liu and Rein (2010)

et al. 2002). Endolides A-B are isolated from a marine sponge-derived fungus (*Stachyliidium* sp.) (El Maddah et al. 2016).

2000; Rudi et al. 2003; Swersey et al. 1994; Toske and Fenical 1995).

Marine ascidians

Bioactive peptides isolated from ascidians have demonstrated potent bioactivities and are linear, cyclic, and acyclic in structure. Marine bioactive peptides isolated from marine ascidians have shown potent human promoting benefits discussed in the pharmacological and health properties section. The novel chemical structure of bioactive peptides present in marine ascidians has made them a potential candidate in drug discovery and design. Marine ascidians-derived peptides have displayed various therapeutic properties against different diseases like cancer, diabetes, inflammation and hypertension (Arumugam et al. 2018). *Polysyncraton lithostrotum* and *Didemnum cuculiferum* are two marine ascidians from which a bicyclic 13-amino acid residue have been isolated; they inhibited tubulin polymerization (IC₅₀: 2.0 μM) & lymphocytic leukemia and stabilized colchicine binding to tubulin (Edler et al. 2002). Bistratamide C is a unique oxazoline-based cyclic hexapeptide derived from marine ascidian *Lissoclinum bistratum* (Bertram and Pattenden 2007; Foster et al. 1992; Wipf et al. 1998). Marine peptide Didemnin N comprises N-methylamino acids and is isolated from *Trididemnum solidum*. They possess cytotoxic (IC₅₀: 50 ng/mL) potential against the P388 cell-line (Sakai et al. 1995). Similarly, the cytotoxic potential of Cyclohexazoline (cyclic hexapeptide) against MRC5CV-1 and T24 cell lines that was isolated from *Lissoclinum bistratum* have also been reported by Hambley et al. (1992). Furthermore, Patellamide A-C, Eusynstyelamide, cyclodidemnamide, didmolamides A-B, and virenamides A-C are bioactive peptides isolated various marine ascidians, i.e. *Lissoclinum patella*, *Eusynstyela misakiensis*, *Didemnum molle*, and *Diplosoma virens*, respectively (Table 5) (Carroll et al. 1996; Fu, Su, and Zeng

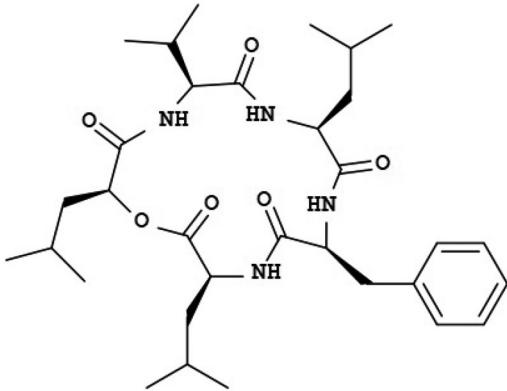
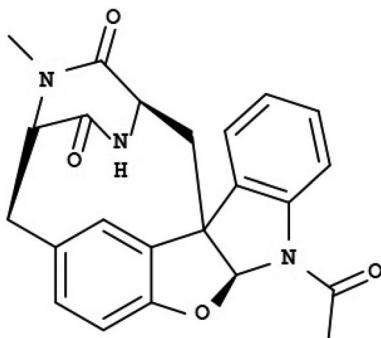
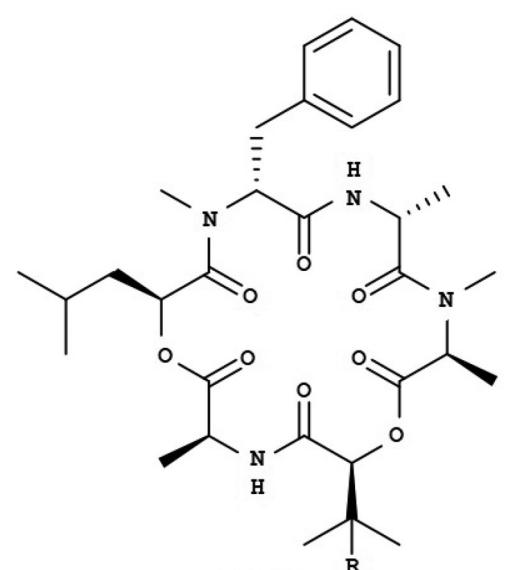
Seaweeds

Seaweeds are known to be an abundant source of marine bioactive peptides. Bioactive peptides isolated from seaweeds are unique in their functionality and structural attributes (Garg 1994). Results of animal modeling have revealed that Phycobiliproteins and lectins isolated from seaweeds possess varied biological characteristics. Lectins are characterized as a diverse group of carbohydrate-binding proteins having structures contributing to vital biological processes like cancer metastasis, cellular communication, and apoptosis (Hori, Matsubara, and Miyazawa 2000; Ziolkowska and Wlodawer 2006). Intravenous administrated *Eucheuma serra* agglutinin-2 (ESA-2)-a lectin isolated from *Eucheuma serra* (marine red alga)-have shown suppression of Colon26 tumors in experimented mice (Fukuda et al. 2006). Furthermore, a study has reported that ESA induced apoptotic conditions in Colo201 (colon) and HeLa (cervix) cancer cells (Sugahara et al. 2001). Similarly, isoafflutinin glycoproteins (solnins A-C) derived from the extract of *Soleria robusta* (marine red alga) have an inhibitory action on the growth of L1210 (leukemia) and FM3A tumor cells (Hori et al. 1988). Literature has shown that lectins from marine macroalgae possess anti-inflammatory, anti-HIV, anti-nociceptive and anti-platelet properties. Phycobiliproteins are water-soluble proteins that inhibit tumor, viral replication, inflammation, and neurodegeneration (Harnedy and FitzGerald 2011; Sekar and Chandramohan 2008).

Marine mollusks

Generally, mollusks are invertebrates belonging to phylum Mollusca and include oysters, snails, chitons, squids, octopuses, scallops, etc. clams. These species are diversified

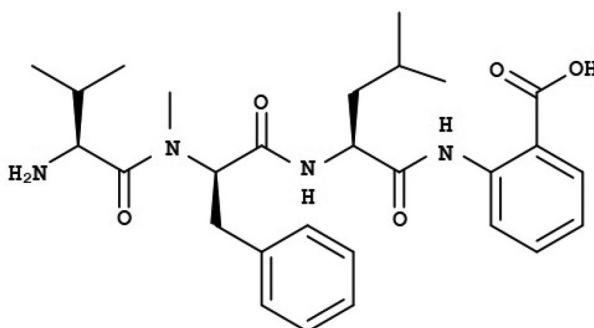
Table 4. Name, source, and structures of some bioactive peptides isolated from diverse marine Fungi.

Bioactive peptide	Source	Structure	References
Sansalvamide A	<i>Fusarium</i> present of <i>Halodule wrightii</i>		Belofsky, Jensen, and Fenical (1999)
Azonazine	<i>Aspergillus insulicola</i>		Wu et al. (2010)
Guangomides A-B	Unidentifiable fungus	 Guangomides { A : R=OH B : R=H	

Simplicilliumtide A

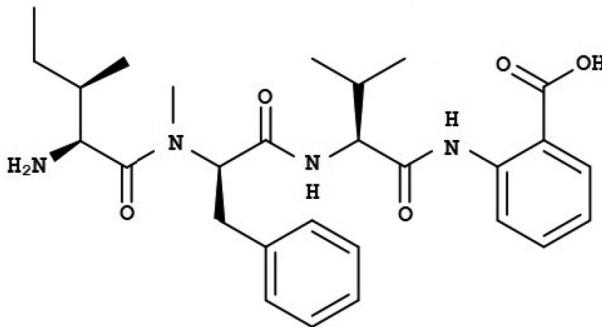
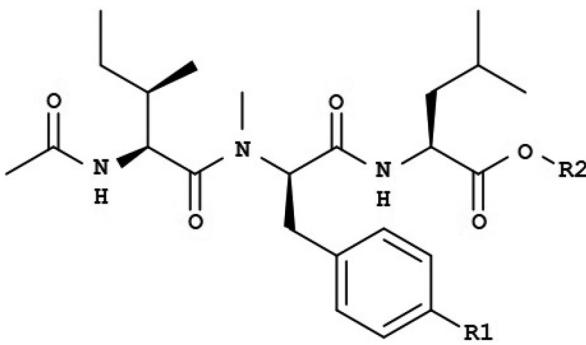
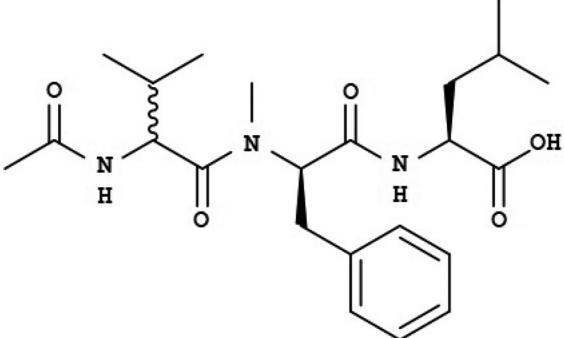
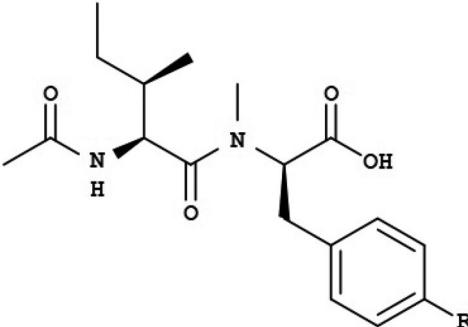
S. obclavatum

[84]



(continued)

Table 4. Continued.

Bioactive peptide	Source	Structure	References
Simplicilliumtide B	<i>S. obclavatum</i>		Liang et al. (2016)
Simplicilliumtides C-E	<i>S. obclavatum</i>		Liang et al. (2016)
		Simplicilliumtides { C: R1=R2=H D: R1=OH; R2=H E: R1=OH; R2=CH ₃	
Simplicilliumtide F	<i>S. obclavatum</i>		Liang et al. (2016)
Simplicilliumtides G-H	<i>S. obclavatum</i>		Liang et al. (2016)
		Simplicilliumtides { G: R=OH H: R=H	

(continued)

Table 4. Continued.

Bioactive peptide	Source	Structure	References
Cordyheptapeptides A-B	<i>Cordyceps</i> sp.		Isaka et al. (2007)
Cordyheptapeptides C-E	<i>Acremonium persicum</i>		Chen et al. (2012)
Efrapeptin G	<i>Acremonium</i> sp.		Boot et al. (2006)

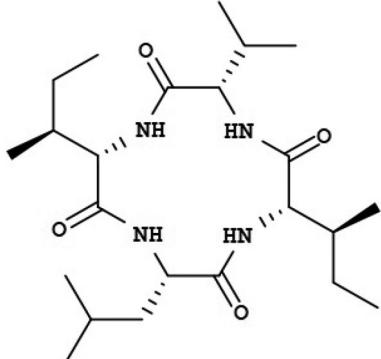
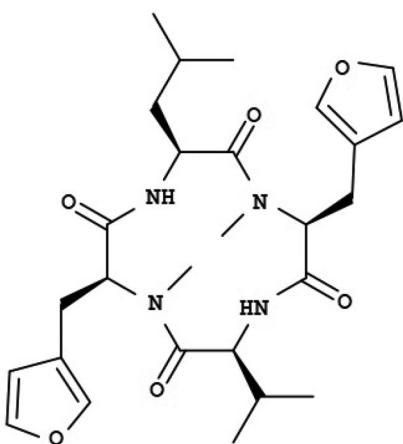
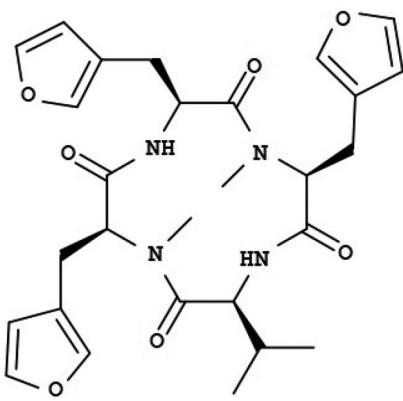
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Table 4. Continued.

Bioactive peptide	Source	Structure	References
Oryzamide A	<i>Nigrospora oryzae</i> PF18		Ding et al. (2016)
Oryzamide B	<i>Nigrospora oryzae</i> PF18		Ding et al. (2016)
Halolitoralin A	<i>Halobacillus litoralis</i> YS3106		Yang et al. (2002)
Halolitoralin B	<i>Halobacillus litoralis</i> YS3106		Yang et al. (2002)

(continued)

Table 4. Continued.

Bioactive peptide	Source	Structure	References
Halolitoralin C	<i>Halobacillus litoralis</i> YS3106		Yang et al. (2002)
Endolide A	<i>Stachyliidium</i> sp.		El Maddah et al. (2016)[90]
Endolide B	<i>Stachyliidium</i> sp.		El Maddah et al. (2016)

source of bioactive peptides having pharmacological properties (Khan and Liu 2019). Kahalalide A is a cyclic depsipeptide derived from *Elysia rufescens* (sacoglossan mollusk) having modest anti-malarial and anti-microbial properties (Gao and Hamann 2011; Hamann et al. 1996). Another unique cytotoxic bioactive peptide extracted from *Dolabella auricularia* (Japanese sea hare) was identified as Dolabellin (Table 6). This peptide contains unique dechlorinated β -hydroxy acid in addition to two thiazole hydroxy acids (Sone et al. 1995). Isolates from *Pleurobranchus forskalii* (notaspidean mollusk) contains two cyclic hexapeptides, namely Mollamide B & C. They comprise unusual prenylated ethers of serine and threonine amino acids in their structure (Donia et al. 2008). Dolastatin 3 (cyclic peptide),

Dolastatin 10 (linear pentapeptide), Dolastatin 13 (cyclic peptide) & Dolastatin D (depsipeptide) isolated from mollusk (*Dolabella auricularia*), which have shown various biological activities (Ciavatta et al. 2017). Nobilamide B and Keenamide A are novel bioactive peptides isolated from *Chicoreus nobilis* and *Pleurobranchus forskalii*, respectively (Lin et al. 2011; Wesson and Hamann 1996).

Preparation of marine bioactive peptides

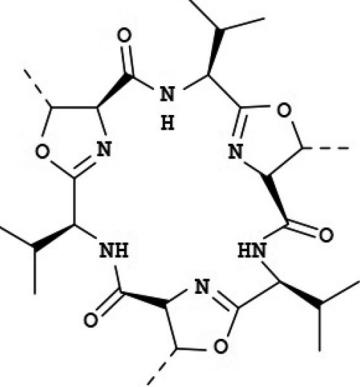
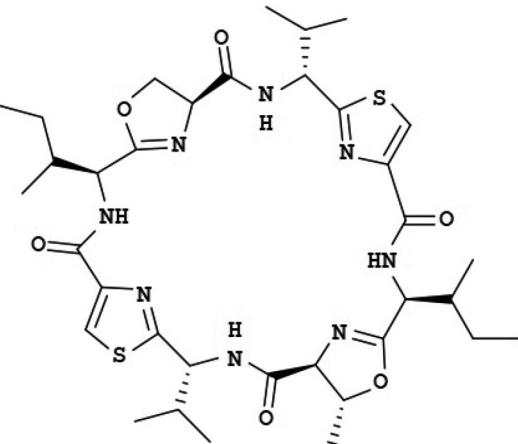
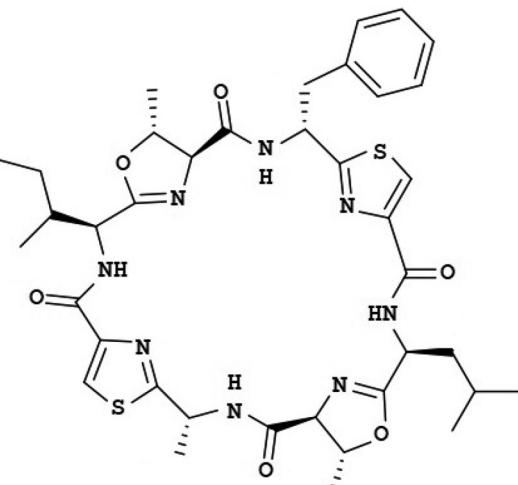
Bioactive peptides could be prepared using different methods. Some of these methods (chemical hydrolysis and enzymatic hydrolysis) are discussed in this section.

Table 5. Name, source, and structures of some bioactive peptides isolated from diverse marine *Ascidians*.

Bioactive peptide	Source	Structure	References
Vitilevuamide	<i>Didemnum cculiferum & Polysyncraton lithostrotum</i>		Edler et al. (2002)
Bistratamide C	<i>Lissoclinum sp.</i>		Bertram and Pattenden (2007); Foster et al. (1992); Wipf et al. (1998)
Westiellamide	<i>L. bistratum</i>		
Didemnin N	<i>T. solidum</i>		Sakai et al. (1995)

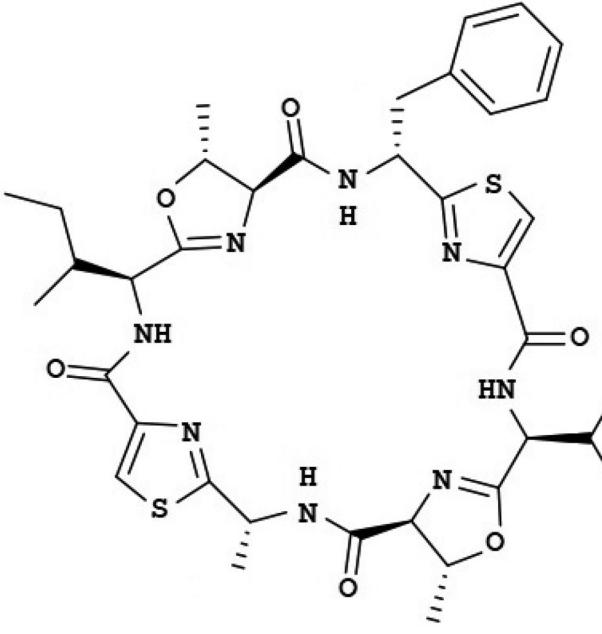
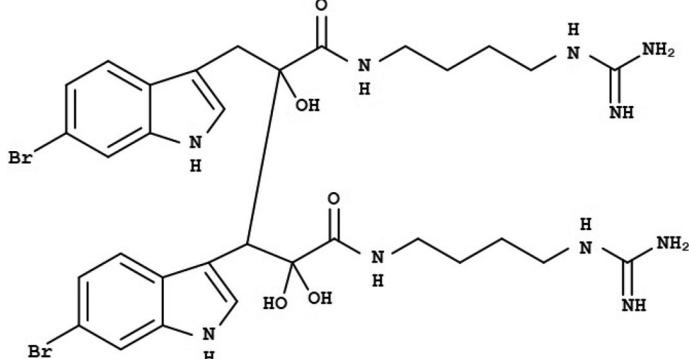
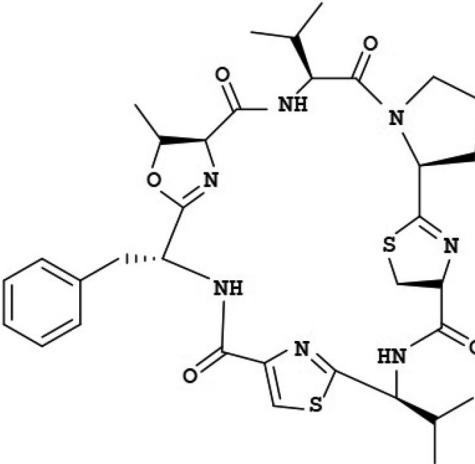
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Table 5. Continued.

Bioactive peptide	Source	Structure	References
Cyclohexazoline	<i>Lissoclinum bistratum</i>		Hambley et al. (1992)
Patellamide A	<i>Lissoclinum patella</i>		Fu, Su, and Zeng (2000)
Patellamide B	<i>Lissoclinum patella</i>		Fu, Su, and Zeng (2000)

(continued)

Table 5. Continued.

Bioactive peptide	Source	Structure	References
Patellamide C	<i>Lissoclinum patella</i>		Fu, Su, and Zeng (2000)
Eusynstyelamide	<i>Eusynstyela misakiensis</i>		Swersey et al. (1994)
Cyclodidemnamide	<i>Didemnum molle</i>		Carroll et al. (1996)

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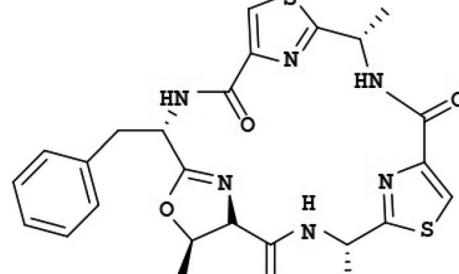
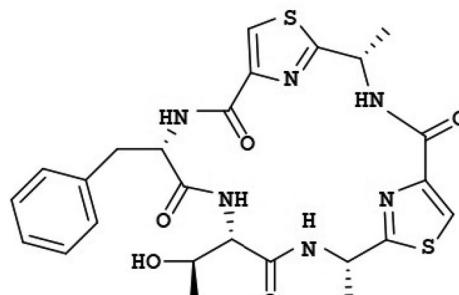
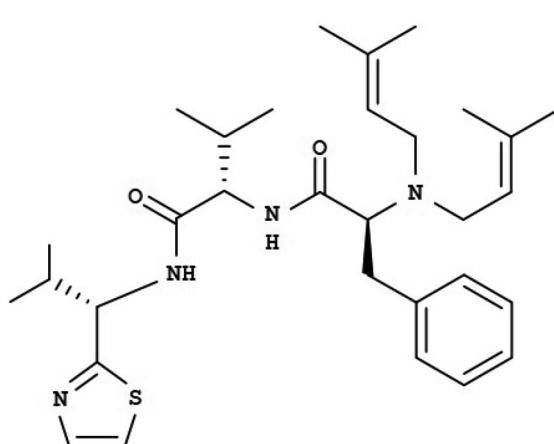
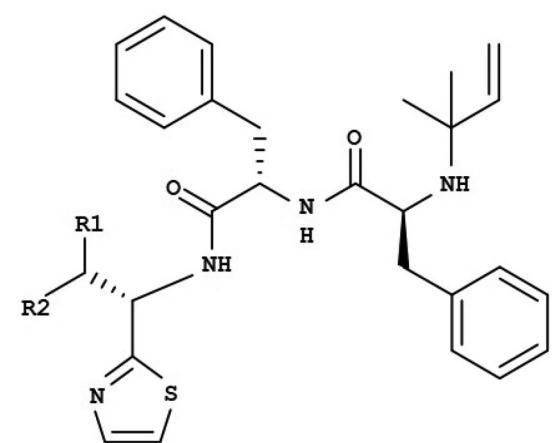
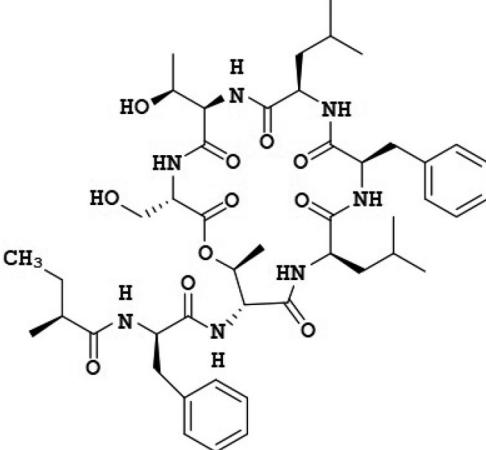
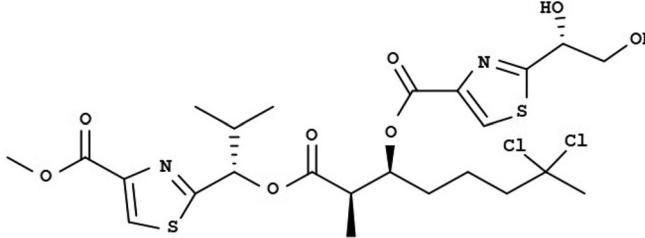
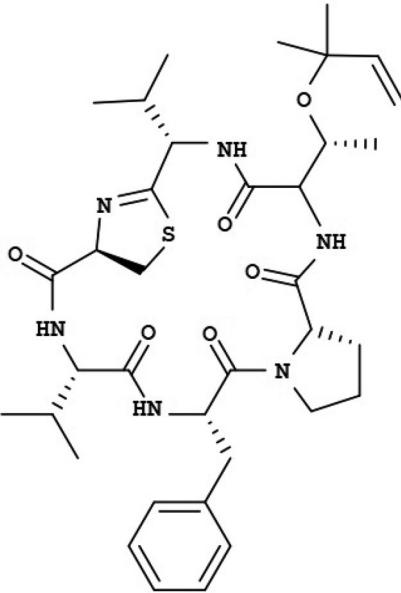
Bioactive peptide	Source	Structure	References
Didmolamide A	<i>Didemnum molle</i>		Toske and Fenical (1995)
Didmolamide B	<i>Didemnum molle</i>		Toske and Fenical (1995)
Virenamide A	<i>Diplosoma virens</i>		Rudi et al. (2003)
Virenamide B-C	<i>Diplosoma virens</i>		Rudi et al. (2003)
$\text{Virenamides} \left\{ \begin{array}{l} \text{B: R1=R2=Me} \\ \text{C: R1=H; R2=Ph} \end{array} \right.$			

Table 6. Name, source, and structures of some bioactive peptides isolated from diverse marine Mollusks.

Bioactive peptide	Source	Structure	References
Kahalalide A	<i>Elysia rufescens</i>		Gao and Hamann (2011); Hamann et al. (1996)
Dolabellin	<i>D. auricularia</i>		Sone et al. (1995)
Mollamide B	<i>Pleurobranchus forskalii</i>		Donia et al. (2008)

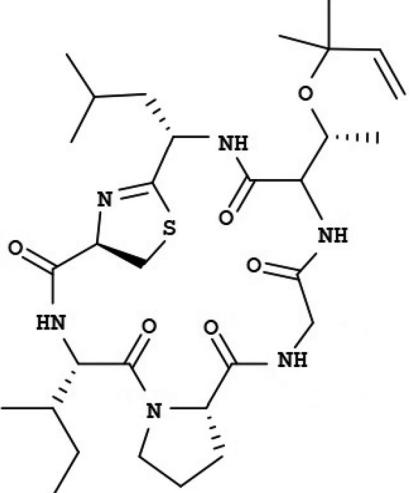
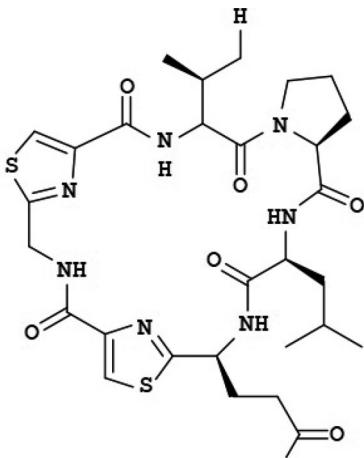
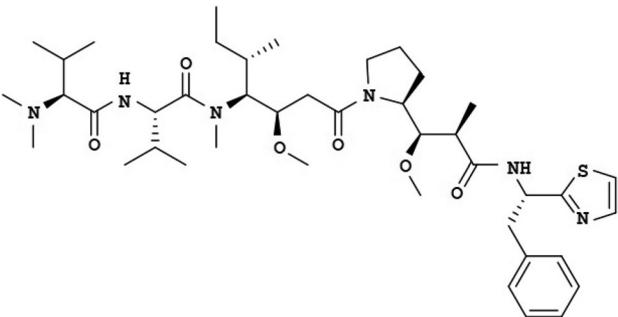
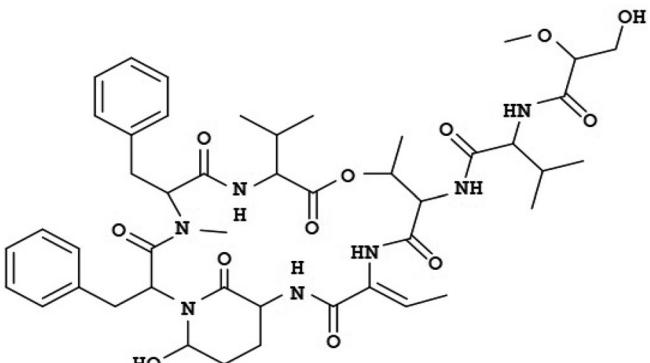
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Synthesis by chemical hydrolysis

In chemical synthesis, chemical reagents are used for the cleavage of peptide bonds. These chemical agents activate the RCOOH (carboxylic acid) group of the amino acid that donates the R-CO- (acyl) group for the formation of peptide linkages (Marcos et al. 2008). This method is inexpensive and straightforward; therefore, it has been extensively used by industries in recent times. Nevertheless, certain limitations are associated with this method, like difficult process control and production of modified amino acids (Vijaykrishnaraj and Prabhakar 2015). Acid hydrolysis is

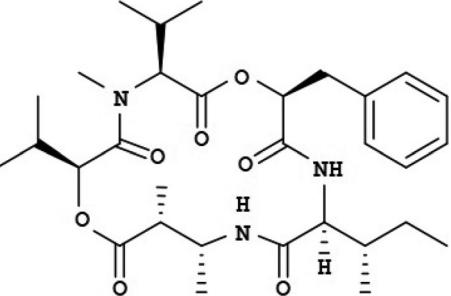
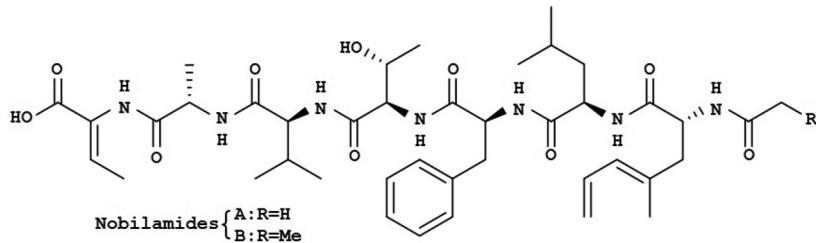
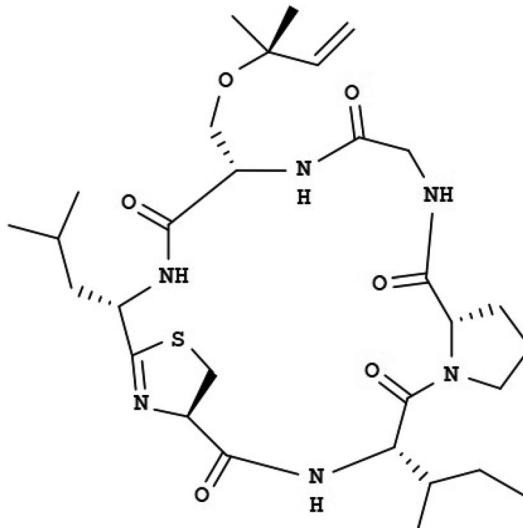
one of the most significant chemical modification methods as it effectively alters the structure and functionality of peptides. Preference is given to acid hydrolysis owing to its inexpensive and effective nature (Lee and Jeffries 2011; Loow et al. 2016). In this process, the most used acids are sulfuric, phosphoric, nitric, and hydrochloric acids. Hydrochloric acid has been used for hydrolysis of fish scales, Mackerel, salmon and scup (Richard et al. 2011; Wang, Zou, and Jiang 2015). Conversely, certain studies reveal the use of alkali hydrolysis on Channel Catfish, Cod, and Tilapia; however, alkali hydrolysis results in low functional properties

Table 6. Continued.

Bioactive peptide	Source	Structure	References
Mollamide C	<i>Pleurobranchus forskalii</i>		Donia et al. (2008)
Dolastatins 3	<i>D. auricularia</i>		Ciavatta et al. (2017)
Dolastatins 10	<i>D. auricularia</i>		Ciavatta et al. (2017)
Dolastatins 13	<i>D. auricularia</i>		Ciavatta et al. (2017)

(continued)

Table 6. Continued.

Bioactive peptide	Source	Structure	References
Dolastatin D	<i>D. auricularia</i>		Ciavatta et al. (2017)
Nobilamide A-B	<i>Chicoreus nobilis</i>		Lin et al. (2011)
Keenamide A	<i>Pleurobranchus forskalii</i>		Wesson and Hamann (1996)

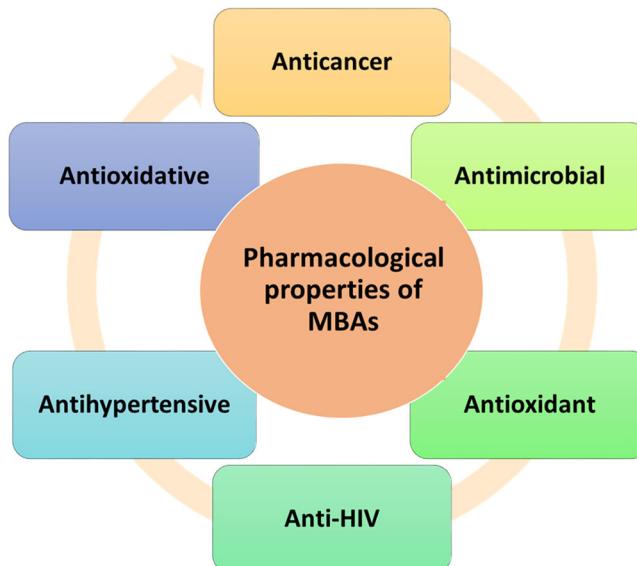
**Figure 2.** Pharmacological and health-promoting benefits of MBAs.

Table 7. Some marine bioactive peptides with anticancer activity.

Name of bioactive peptide	Source of bioactive peptide	Efficacy	Reference
Dolastatin	Sea hare	Induces proliferation	Madden et al. (2000)
Keenamide A	Sea slug	Inhibits cancer	Wesson and Hamann (1996)
PTAEGGVYMT	Tuna muscle	Induces proliferation	Hsu, Li-Chan, and Jao (2011)
LPHVLTPEAGAT	Tuna muscle	Induces proliferation	Hsu, Li-Chan, and Jao (2011)

(Kristinsson and Hultin 2003; Kristinsson and Ingadottir 2006; Kristinsson et al. 2006). This method effectively hydrolysis peptide bond and results in high peptide content; however, this technique is not environmental friendly.

Synthesis by enzymatic hydrolysis

Enzymatic hydrolysis is a method in which certain proteolytic enzymes are used to cleavage specific peptide bonds. Proteolytic enzymes used industrially or in the laboratory for the synthesis of peptides are trypsin, chymotrypsin, pepsin, papain, subtilisin etc. (Perez Espitia et al. 2012). Marine peptides have been extensively generated by hydrolysis of proteins extracted from marine organisms (Miguel et al. 2009). In vitro enzymatic hydrolysis is used for the production of bioactive peptides from various marine sources. In the food industry, proteolytic enzymes from marine organisms have been used to develop bioactive peptides through marine products' hydrolysis process of marine products. The reaction medium's temperature and pH must be optimized for an enzyme's effective activity (Ngo et al. 2012). Enzymatic hydrolysis depends on enzymes' physiochemical conditions in the raw material as these enzymes degrade marine proteins to peptides, which varies their bioactivity and functionality (Jo et al. 2017).

Purposely, Bhaskar et al. (2008) optimized the conditions (hydrolysis time: 2 hr 15 min, enzyme to substrate-level: 1.5%) for the use of Alcalase (enzyme) to hydrolyze Catla (fish) visceral waste proteins. Similarly, the enzyme Alcalase has also been used for enzymatic hydrolysis of dark muscle by-product of tuna to produce protein hydrolysate. In this study, the conditions for enzyme activity were optimized as temperature: 55 °C, pH: 8.5, enzyme concentration: 1%, and time: 1 hr (Saidi et al. 2016). Enzymatic hydrolysis resulted in bioactive peptides from various marine by-products like tuna head, fish bones, and shrimp wasted (Centenaro, Centenaro, and Hernandez 2011; Dey and Dora 2014; Ovissipour et al. 2009). Likewise, protein from viscera of horse mackerel was hydrolyzed using pepsin (1%, 37 °C & 120 min), α -chymotrypsin (1%, 37 °C & 150 min) and trypsin (1%, 37 °C & 150 min) for the production of antioxidative bioactive peptide (ACFL) (Kumar, Nazeer, and Jaiganesh 2011). Various studies have reported the production of bioactive peptides from enzymatic hydrolysis of gelatin or collagen. Enzymatic hydrolyzed tuna and squid skin gelatin resulted in antioxidant marine bioactive peptides (Mendis, Rajapakse, and Kim 2005b). Marine proteins hydrolyzed using proteolytic enzymes have shown to produce bioactive peptides with anti-bacterial properties. Song et al. (Song et al. 2012) optimized the conditions (pH: 2, Time: 135 min, & pepsin to substrate-level: 1100 U/g) for the

production of antibacterial peptides by using pepsin (Song et al. 2012). Moreover, the most vital factor in the production of peptides having bioactive properties is their molecular weight. Hence, sequential enzymatic digestion comprising three enzyme systems is preferred to produce bioactive peptides with desired functional properties (Doyen et al. 2011).

Pharmacological and health properties of marine bioactive peptides

The relationship between activity and chemical structure of peptides is currently not predicted. The peptide's chemical structure is responsible for its activity: the peptide chain length, the composition of amino acid, the type of C- and N-terminal amino acids, the hydrophilic or hydrophobic features of the amino acid chain, and others. For example, basic N-terminal or aromatic amino acids have more excellent angiotensin-converting enzyme inhibitory action. These peptides possess many positive and hydrophobic charged amino acids in C-terminal (Li and Yu 2015; Sánchez and Vázquez 2017). A peptide that displays a certain level of biological activity will be regarded as bioactive. Moreover, this bioactivity must helpfully influence health and not resulting in harmful impacts such as mutagenicity, allergenicity and toxicity (Möller et al. 2008). The pharmacological and health-promoting benefits of MBAs are shown in Figure 2.

Anticancer marine bioactive peptides

Bioactive peptides from marine have been shown to inhibit the development and formation of cancer. It has been evidenced that some bioactive peptides from marine induce anticancer action by decreasing proliferation in cells of human breast cancer (Picot et al. 2006). Table 7 shows some marine bioactive peptides with anticancer activities.

Apratoxin, a cyclic depsipeptide isolated from *Lyngbya majuscula*, showed cytotoxic action by inhibiting the cell cycle in Human HeLa cervical carcinoma cells (Ma et al. 2006). Another depsipeptide called Coibamide A extracted from *Leptolyngbya* species exhibited a similar action mode on the cell line of Human lung cancer (Medina et al. 2008). Another compound isolated from *L. majuscula* called Lyngbyabellin B showed cytotoxic action on human Burkitt lymphoma (Marquez et al. 2002). A linear pentapeptide called Symplostatin and Dolastatin 10 extracted from *Symploca* species displayed cytotoxic action on cell lines of Human breast carcinoma and Human lung cancer through phosphorylation and action of Bcl-1 and caspase-3, respectively (Kalemkerian et al. 1999; Mooberry et al. 2003). Nevertheless, several kinds of bioactive peptides with

Table 8. Some marine bioactive peptides with antioxidant activities.

The sequence of bioactive peptide	Marine organism	Antioxidant action	References
FDSGPGAVL	Jumbo squid (<i>Dosidicus gigas</i>)	Chelates iron (II) ions and scavenges hydroxyl radical	Mendis, Rajapakse, and Kim (2005b)
HGPLGPL	Hoki (<i>J. belengerii</i>)	Inhibits superoxide and DPPH radicals	Mendis, Rajapakse, and Kim (2005b)
LLGPGLYNHA	Rotifer (<i>Brachionus rotundiformis</i>)	Inhibits DPPH radicals	Byun et al. (2009)
IVGGFPHYL	Sand eel	Prevents oxidation of DNA	Lee et al. (2009)
FGHPY	Blue mussel (<i>Mytilus edulis</i>)	Inhibits hydroxyl radical	Jung et al. (2007)
LKQELEDLLEKQE	Oyster (<i>C. gigas</i>)	Inhibits hydroxyl and superoxide radicals	Qian et al. (2008)
GPEPTGPTGAPQWLR	Japanese sea cucumber (<i>Stichopus japonicus</i>)	Inhibits hydroxyl and superoxide radicals	Zhou, Wang, and Jiang (2012)

DPPH: 2,2-diphenyl-1-picrylhydrazyl, DNA: deoxyribonucleic acid.

anticancer actions are also extracted from *Nostoc* species and *Lyngbya* species on many cell lines by abrogating secretory cascade and disruption of microfilaments (Costa et al. 2012). Ascidia and tunicates found on the ocean floor were reported to produce multiplex molecules with anticancer actions (Malaker and Ahmad 2013). Among these complex molecules, didemnin extracted from *Trididemnum solidum* showed antiproliferative and antitumor action against human prostatic cancer cell lines. Among the isolated didemnin compounds, didemnin B was the most effective (Aneiros and Garateix 2004). The molecule was the first peptide from marine to be used for clinical trials. Didemnin B showed anticancer action via abrogation of protein synthesis (Vera and Joullié 2002). Aplidine, which was extracted from tunicate *Alpidium albicans*, possessed anticancer actions against several cell lines of human cancer, including lungs, breast and melanoma cancers (Faivre et al. 2005), and low concentration molecule was reported to be potent. Besides, the compound exhibited its action via induction of rapid cell cycle arrest at G1-G2, protein synthesis abrogation and induction of apoptosis of cancer cells, and antiangiogenic action (Broggini et al. 2003; García-Fernández et al. 2002). Vitilevuamide, a cyclic peptide extracted from *Didemnum cuculliferum*, induced cell cycle arrest of cancer cells at the G2/M stage and abrogated polymerization of tubulin (Edler et al. 2002; Newman and Cragg 2004).

Other isomers of depsipeptides called Tamandarins A and B, which were isolated from the Ascidian family of Didemnidae in seawater, showed anticancer actions against several human cancer cells. Another compound isolated from ascidian *Didemnum molle* called mollamide (cyclodepsipeptide) displayed cytotoxic action against several cell lines of human colon carcinoma and human lung cancer (Carroll et al. 1994; Hamada and Shioiri 2005; Vervoort, Fenical, and Epifanio 2000). Another cyclodepsipeptide known as Trunkamide, which has a structure similar to that of mollamide and isolated from *Lissoclinum*, showed anticancer action (Hamada and Shioiri 2005; Wipf et al. 1995). Fungi from marine are other sources of bioactive peptides with anticancer actions. Scopularide A and B are cyclodepsipeptides extracted from marine fungus *Scopulariopsis brevicaulis* (Yu et al. 2008). They exhibited their actions via abrogating the growth of cell lines of colon carcinoma and pancreatic carcinoma through an unknown mode of action. A cyclic depsipeptide compound (Sansalvamide) isolated from many

fungi from marine showed cytotoxicity against many types of cell lines such as colon, prostate, pancreatic and breast melanoma as well as sarcoma, indicating their potential as an anticancer agent (Vasko et al. 2010). These molecules' exact mechanistic action is still speculative, but a current work indicated an interaction between client cancer protein and heat shock protein in mammals' cell lines. Sansalvamide A forms a complex with the N-middle domain of heat shock protein and abrogates the formation of a protein complex required to propagate tumor growth (Vasko et al. 2010).

Similarly, many bioactive peptides have been extracted from marine sponges. The majority of these compounds are cyclodepsipeptides. Jaspamide (cyclic depsipeptide) extracted from *Hemiastralla* and *Jaspis* (sponges) was found to induce apoptosis in human brain tumor and promyelocytic leukemia cell line via activation of caspase-3 and reduction of expression of Bcl-2 protein (Braekman et al. 1987; Cioca and Kitano 2002; Odaka, Sanders, and Crews 2000). Another group of a molecule called Hemiasterlins (Hemiasterlins A and C) extracted from sponges of the genus Auletta, and Siphonochalina displayed cytotoxicity antitubulin action via inhibition of mitosis (Gamble et al. 1999; Loganzo et al. 2003). Reniochalistatin-E, a cyclic octapeptide derived from *Reniochalina stalagmitis* (marine sponge), have shown significant cytotoxic activities against various tumor cell lines, i.e. HeLa, HL-60, RPMI-8226, HepG2, and MGC-803 (Zhan et al. 2014). Similarly, amino-acid sequence of two anti-proliferative peptides (LPHVLTPPEAGAT and PTAEGGVYVMVT) derived from papain, and protease XXII hydrolysates of tuna darkened muscle by-product revealed concentration-dependent inhibitory activity (IC_{50} : 8.1 & 8.8 μ M) against MCF-7 cells (Hsu, Li-Chan, and Jao 2011). Numerous studies have highlighted marine bioactive peptides' role in the induction of cancer cell death through apoptosis and angiogenesis inhibition (Cheung, Ng, and Wong 2015; Zheng et al. 2011).

Antioxidative marine bioactive peptides

Shellfish is a source of antioxidant marine bioactive peptide produced in the gastrointestinal system. The digestion of oyster (*Crassostrea gigas*) in the gastrointestinal tract produced a bioactive peptide with 1.6 kDa weight and has an amino acid sequence of Leu-Lys-Gln-Glu-Leu-Glu-Asp-Leu-Leu-Glu-Lys-Gln-Glu. This bioactive peptide abrogated lipid

peroxidation and neutralized superoxide and hydroxyl radicals (Ngo and Kim 2013). Furthermore, a gastrointestinal digest of the protein (*Mytilus coruscus*) resulting in the formation of a bioactive peptide with the sequence formation e of Leu-Val-Gly-Asp-Glu-Gln-Ala-Val-Pro-Ala-Val-Cys-Val-Pro with a molecular weight of 1.59 kDa. The peptide displayed effective antioxidant action (Jung et al. 2007). The peptide displayed decisive inhibitory action against the peroxidation of lipid compared to α -tocopherol and ascorbic acid. Another bioactive peptide with a molecular weight of 1.8 kDa (16 residues of amino acids) isolated from Hoki peptic hydrolysate (*Johnius belengerii*) induced potent lipid peroxidation inhibition (Kim, Je, and Kim 2007). In another study, bivalve mollusks (*Mactra veneriformis*) hydrolysate produced a total of twenty-one bioactive peptides. These peptides induced antioxidant action by scavenging free radicals (Li and Yu 2015). Studies have shown that peptides with a molecular weight ranging from 500-1500 Da have potent biological activity than other peptides sequences (Sarmadi and Ismail 2010). Table 8 shows some sequences of bioactive peptides from marine with their antioxidant actions.

Antioxidants provide protective action on the body of organisms by binding to free radicals. Marine bioactive compounds also exhibit antioxidant action. They are found in organisms like shrimps, blue mussels, oysters and squid (Harada et al. 2010). Some studies found that marine bioactive peptides extracted from marine organisms displayed antioxidant actions. The molecules scavenge free radicals and inhibit oxidative damage induced by lipid peroxidation (Mendis et al. 2005a; Rajapakse et al. 2005b; Ranathunga, Rajapakse, and Kim 2006). In another study using a linoleic acid model system, marine bioactive peptides isolated from jumbo squid possessed antioxidant action comparable to butylated hydroxytoluene but more excellent than the action showed α -tocopherol (Mendis, Rajapakse, and Kim 2005b). The hydrophobicity and some aromatic amino acids are responsible for marine bioactive peptides' antioxidant actions. A bioactive peptide (Leu-Lys-Gln-Glu-Leu-GluAsp-Leu-Leu-Glu-Lys-Gln-Glu) extracted from oyster showed higher activity against polyunsaturated fatty acid peroxidation compared to α -tocopherol (Ranathunga, Rajapakse, and Kim 2006), and this was attributed to the quenching of reactive oxygen species and free radicals or the metal chelation. Consistently, gelatin bioactive peptides showed more significant emulsifying actions due to their hydrophobic amino acids and, therefore, displayed potent antioxidant actions than other peptides (Mendis, Rajapakse, and Kim 2005b). Due to all these antioxidant actions of marine bioactive peptides, they can be used as a substitute for synthetic antioxidants.

A study reported that protease N's action on mackerel muscle results in hydrolysates containing antioxidant peptides. These peptides inhibit free radicals through inhibition to ferric to ferrous ions (Wu, Chen, and Shiao 2003). Several potent bioactive peptides from marine crustacean and mollusks proteins have been reported (Je, Park, and Kim 2005b). Consistently, bioactive peptide (Leu-Lys-Gln-

Glu-Leu-Glu-Asp-Leu-Leu-Glu-Lys-Gln-Glu) with antioxidant derived from oyster (*C. gigas*) was revealed to exhibits potent inhibitory action against peroxidation of polyunsaturated fatty acid (Qian et al. 2008). The bioactive peptide antioxidant action could be responsible for specific radicals inhibition produced during metal-chelating processes and peroxidation. Many works have evidenced that marine bioactive peptides show remarkable antioxidant activities than reference antioxidant molecules such as α -tocopherol (Jun et al. 2004; Shukla 2016). Some works try to elucidate the antioxidant mechanistic actions of bioactive peptides from the marine. In this sense, histidine and some aromatic amino acids were indicated to play an essential impact in inhibiting free radicals by marine bioactive peptides. Also, gelatin peptides constituent several hydrophobic amino acids discovered to exhibit potent emulsifying action and are regarded as potent antioxidant peptides. Therefore, bioactive peptides isolated from marine with remarkable antioxidant effect could be used in pharmaceutical and nutraceutical industries to substitute synthetic antioxidants (Shukla 2016).

Antimicrobial marine bioactive peptides

Antimicrobial bioactive peptides are a diverse and abundant class of compounds synthesized by several cells and tissues in different types of animals, plants and invertebrates. Marine organisms can also be sources of bioactive peptides with antimicrobial actions. In this sense, it was reported that protein from oyster contains cysteine-rich bioactive peptides, which inhibited Gram-positive bacteria (Liu et al. 2008b). It was reported that marine bivalve mollusks (*Actinopyga lecanora*) contain bioactive peptides which induced antibacterial action against *Escherichia coli*, *Pseudomonas aeruginosa* and *Pseudomonas* sp (Ghanbari and Ebrahimpour 2018). Another report indicated that bioactive peptides isolated from half-fin anchovy possessed potent antibacterial action against *E. coli* (Song et al. 2012).

Antimicrobial bioactive peptides have been reported in the hemolymph of several marine invertebrates such as spider crab and green sea urchin (Liu et al. 2008b; Stensvåg et al. 2008). It was reported that the *Phaeobacter* sp. Y41 activity was linked to the formation of indigoidine, which abrogates *Vibrio fischeri* growth (Cude et al. 2012). The condensation of two glutamine units produces the compound through a biosynthetic cascade. In this biosynthetic pathway, indigoidine gene *igiC* codes for glutamic acid racemase, *igiB* for 6-phosphogluconic acid dehydrogenase, while *igiD* codes for indigoidine synthase. The gene known as *indC* has been discovered in a phylogenetically broad class of microorganisms such as γ -, β -, and α -proteobacteria (Battison, Summerfield, and Patrzykat 2008). More so, a bioactive peptide derived from *Homarus americanus* possessed potent bacteriostatic protozoacidal and protozoastatic actions against several types of pathogenic organisms such as *Anophryoides hemophilia*, *H. americanus* and *Mesanophrys chesapeakensis*. In another study, arasin 1, a bioactive peptide isolated from *Hyas araneus* induced inhibitory action against *Corynebacterium glutamicum* (Battison, Summerfield,

and Patrzykat 2008; Stensvåg et al. 2008). Furthermore, a marine peptide (CgPep33) derived from *C. gigas* exhibited potent antimicrobial action against *Bacillus subtilis*, *Penicillium expansum*, *E. coli*, *Botrytis cinerea* and *P. aeruginosa* (Liu et al. 2008b).

Antimicrobial marine bioactive peptides found extensively in the hemolymph of several invertebrates in the sea (Tincu and Taylor 2004). For instance, the blue crab's peptides displayed significant antibacterial action against Gram-negative bacteria (Achour et al. 1997). Many other studies have revealed the antimicrobial action of mud crab and seminal plasma (Lee and Maruyama 1998). Marine bioactive peptides isolated from American lobster showed actions against Gram-negative bacteria and other organisms (Battison, Summerfield, and Patrzykat 2008). A known peptide called arasin 1, with antimicrobial action derived from Hyas araneus crab, inhibited *Corynebacterium glutamicum* (DeFelice 1995). The peptide (CgPep33) extracted from *Crassostrea gigas* was reported to inhibit activities like *Pseudomonas aeruginosa*, *Escherichia coli*, and *Bacillus subtilis* and fungi such as *Botrytis cinerea* and *Penicillium expansum* (Achour et al. 1997). The peptides (Leu-Leu-Glu-Tyr-Ser-Ile and Leu-Leu-Glu-Tyr-Ser-Leu) derived from the thermolysin *Crassostrea gigas* hydrolysate reduces Human immunodeficiency virus-1 (Lee and Maruyama 1998) activities. Moreover, a marine bioactive peptide with a linear sequence of Arg-Arg-Trp-Trp-Cys-Arg-X (X: amino acid groups or amino acid) isolated from oyster was found to prevent the disease caused by the herpes virus (Zeng et al. 2008). The studies above showed that marine bioactive peptides are effective against microbes. Thus clinical studies could be carried out to validate their efficacy in humans.

Anti-hypertensive marine bioactive peptides

Many bioactive peptides from marine have been extracted from organisms such as sardine, bonito, and tuna (leucine-arginine-proline, leucine-lysine-proline and isoleucine-lysine-proline), *Styela clava* (alanine-histidine-isoleucine-isoleucine-isoleucine) and *Okamejei kenojei* (methionine-valine-glycine-serine-alanine-proline-glycine-valine-leucine). These bioactive peptides elevate the endothelial level of nitric oxide and vasodilation in experimental rats (Cheung, Ng, and Wong 2015). Marine bioactive peptides are evidenced to show cardioprotective action, and several of them are found in marine organisms such as yellow sole frame, krill, shrimp, tuna frame, and mussel. In this sense, the report revealed that *Theragra chalcogramma* contains proteins and peptides with the potential to inhibit angiotensin-converting enzyme (Byun and Kim 2001), a vital component that regulates blood pressure, thus, preventing the occurrence of hypertension. A study reported that hydrolysates isolated from sea bream scale collagen proteins of oyster showed anti-hypertensive action in spontaneously hypertensive rats (Fahmi et al. 2004; Wang et al. 2008). Another study revealed that protein hydrolysate yielded from salmon fish decreases cardiovascular disorders by reducing plasma concentration of cholesterol and inhibition of acyl-CoA: cholesterol

acyltransferase (ACAT) activity in vivo (Wergedahl et al. 2004). Hence, bioactive peptides with cardioprotective actions could be utilized in pharmaceuticals or nutraceuticals. More so, drugs with the potentials to inhibit hypertension or reduce it can be produced from these marine bioactive peptides. Besides, competitiveness against the angiotensin-converting enzyme activity of several peptides with anti-hypertensive activity has been estimated kinetically using Lineweaver-Burk plots marine the mechanistic action marine peptides differs from that of synthetic anti-hypertensive drugs (Ngo et al. 2012; Zhao et al. 2009). Peptides from marine source exhibit anti-hypertensive activity by competing with angiotensin-converting enzymes. This enzyme catalyzes the formation of angiotensin-II from angiotensin-I by removing a small peptide. Anti-hypertensive peptides react with the angiotensin-converting enzyme, preventing it from reacting with angiotensin-I (Ngo et al. 2012). Also, these peptides relax the walls of arteries and decrease fluid volume by abrogating angiotensin-II formatting. Hence, peptides with anti-hypertensive action improve the heart's function and elevate oxygen and blood flow to the kidneys, heart and hepatic cells (Ahhmed and Muguruma 2010). Several works have indicated that phenylalanine, tryptophan, proline or tyrosine at the C-terminal and N-terminal with branched-chain aliphatic amino acids promotes the binding of the peptide angiotensin to angiotensin-converting enzyme (Li et al. 2004). Consistently, a noncompetitive mode of action has been deduced for some bioactive peptides, which were proposed to react with an enzyme to form a dead-end complex. For instance, LIY and YLYEiar were discovered to react as noncompetitive inhibitors (Nakagomi et al. 1998; Nakagomi et al. 2000). The N-terminal hydrophobicity of bioactive peptides with angiotensin-converting enzyme inhibitory action may play a vital role in their anti-hypertensive properties (Rho et al. 2009). These peptides with angiotensin-converting enzyme inhibitory action are usually short sequence peptides and polar amino acid units like proline. The structure-activity relationship of different bioactive peptide inhibitors of the angiotensin-converting enzyme revealed that binding to the angiotensin-converting enzyme is significantly affected by the C-terminal tripeptide chain of the substrate, and it was proposed that bioactive peptides with hydrophobic amino acids at the C-terminal chain are potent inhibitors (Qian, Je, and Kim 2007).

A recent study revealed several bioactive peptides from organisms like a mussel, tuna frame, oyster, and shrimp inhibited angiotensin I-converting enzyme (Kannel and Higgins 1990). Some human studies revealed that bioactive peptides could reduce hypertension, linked to their angiotensin I-converting enzyme inhibition (Zhao et al. 2009). Thus, the inhibition of the angiotensin I-converting enzyme causes the arterial wall's relaxation and reduces fluid volume via abrogation of angiotensin II formation. This effect improves the heart's function and the supply of oxygen and blood to the kidney, heart and hepatocytes (Ahhmed and Muguruma 2010). In the bioactive peptides, reports indicated that N-terminal branched-chain amino acids and C-terminal proline, tyrosine, phenylalanine or tryptophan were

Table 9. Bioactive peptides from marine sources with anti-HIV activity.

Bioactive peptide	Organism source	Efficacy	Reference
Callipeltin A	Sponge from marine	EC ₅₀ : 0.01 µg/ml	Zampella et al. (1996)
Celebeside A	Sponge from marine	IC ₅₀ : 1.9 µg.ml	Plaza et al. (2009)
Homophymine A	Sponge from marine	IC ₅₀ : 75 nM	Zampella et al. (2008)
Microspinosamide	Sponge from marine	EC ₅₀ : 0.2 µg/ml	Andjelic, Planelles, and Barrows (2008)
Mirabamide A	Sponge from marine	IC ₅₀ : 0.14 and 0.04 µM	Plaza et al. (2007)
Mirabamide C	Sponge from marine	IC ₅₀ : 1.3 and 0.14 µM	Plaza et al. (2007)
Mirabamide D	Sponge from marine	IC ₅₀ : 3.6 and 0.19 µM	Plaza et al. (2007)
Neamphamide A	Sponge from marine	EC ₅₀ : 28 nM	Oku et al. (2004)
Theopapuamide B	Sponge from marine	IC ₅₀ : 0.8 µG/ml	Plaza et al. (2009)
LLEYSI	Oyster (<i>C. gigas</i>)	20 nM	Lee and Maruyama (1998)
LLEYSL	Oyster (<i>C. gigas</i>)	IC ₅₀ : 15 nM	Lee and Maruyama (1998)

responsible for their inhibitory action (Li et al. 2004). In some in vivo model, marine bioactive peptides showed potent inhibitory action in spontaneously hypertensive rats (Zhao et al. 2007). In another clinical trial, it was revealed that oral administration of peptide (10 mg/kg body weight) induced a significant reduction in systolic blood pressure, which was comparable to a synthetic antihypertensive drug (captopril) (Lee, Qian, and Kim 2010). Therefore, taurine bioactive peptides' cardioprotective action could prompt their use in the production of safer and efficacious anti-hypertensive agents.

Marine bioactive peptides with anti-human immunodeficiency virus activity (HIV)

Several works have been shown that bioactive peptides from marine can serve as anti-HIV components in pharmaceuticals or functional foods as a result of their therapeutic effect in the prevention and management of diseases (Ngo et al. 2012). In this view, it was reported that two peptides (LLEYSL and LLEYSI) isolated from the hydrolysate protein of oyster (*C. gigas*) abrogated HIV-1 protease. The two peptides, LLEYSL and LLEYSI, showed intense inhibitory action with IC₅₀ value 15 and 20 nM, respectively. Besides, they exhibited a competitive inhibition for the HIV-protease (*Ki* value of 10 and 13 nM, respectively). N-, C-terminal hydrophobic amino acids and the length of amino acid sequence play a vital role in the inhibitory activity (Lee and Maruyama 1998).

Sponges are marine organism with broad pharmacological activities and novel structural characteristics, and they are used as a source of novel peptides in traditional settings (Ngo et al. 2012). Marine sponge called *Siliquariaspiongia mirabilis* was reported to contain bioactive peptides (mirabamides), which significantly abrogate the fusion of HIV-1. Also, mirabamide A was shown to potently abrogate HIV-1 in fusion and neutralization studies with IC₅₀ values of 140 and 40 nM, respectively, while mirabamide D and C displayed less activity with IC₅₀ values between 190 nM and 3.9 µM for mirabamide D and 140 nM and 1.3 µM for C. Moreover, it was proposed that mirabamides abrogate HIV-1 at the membrane fusion stage, presumably via interactions with glycoproteins of the HIV-1 envelope (Plaza et al. 2007). To further support marine peptides' anti-HIV activity, theopapuamide B (an undecapeptide consisting of amino acids, 4-amino-2,3-dihydroxy-5-methylhexanoic acid and 3-

acetamido-2-aminopropanoic acid) and celebesides A (a cyclic depsipeptide) derived from *S. mirabilis* displayed anti-HIV activity. Celebesides A inhibited entry of HIV-1 (IC₅₀ value of 1.9 µg.ml) while Theopapaumide B was potent in neutralization studies (IC₅₀ value of 0.8 µg/ml). More so, the anti-HIV action of celebesides A corresponds with phosphoserine unit presence. However, it is absent in the inactive theopapuamide (Plaza et al. 2009). However, this proposal was ruled out by Zampella et al. (Zampella et al. 2008). Homophymine A (a cyclodepsipeptide containing amide-linked 3-hydroxy-2,4,6-trimethyloctanoic acid group with 11 four unusual amino acid groups and 11 amino acid groups) isolated from marine sponge called Homophymia sp displayed anti-HIV property through cytoprotective action against the virus (IC₅₀ value of 75 nM). The bioactive peptide has an O-methyl threonine moiety instead of a β-methoxytyrosine group; hence, this ruled out the theory β-methoxytyrosine is vital for the anti-viral action (Ngo et al. 2012). Consistently, depsipeptides derived from several marine sponges have been discovered to be potent inhibitors of HIV. In this sense, Neamphamide A (a potent anti-HIV depsipeptide) isolated from sponge *Neamphius huxleye* displayed a remarkable cytoprotective action against HIV-1 with an effective concentration (EC₅₀) value of 28 nM (Oku et al. 2004). Another marine bioactive peptide called Callipeltin A (novel anti-fungal and anti-viral cyclodepsipeptide) yielded from *Callipelta* sp. inducted cytopathic actions on CEM4 cells of lymphocytes infected with HIV-1 and showed EC₅₀ value of 0.01 µg/ml (Zampella et al. 1996)[220]. Callipeltin A structure with C-terminus lactonised with a threonine unit and N-terminus blocked is similar to a class of efficacious anti-viral and anti-tumor (didemnins) which exhibits anti-HIV action (Ngo et al. 2012).

On another side, papuamides A and B (novel cyclic depsipeptides) derived from *Theonella swinhoei* and *Theonella mirabilis* constitute unusual amino acids (3,4-dimethylglutamine, β-methoxytyrosine, 2,3-diaminobutanoic acid or/and 2-amino-2-butenoic acid units). However, the peptides initially discovered were revealed to contain 3-hydroxyleucine and homoproline residues. Also, they contain 2,3-dihydroxy-2,6,8-trimethyldeca-(4Z,6E)-dienoic acid group N-linked to a glycine unit at the terminal point. They are shown to inhibit human T-lymphoblastoid cells infection by HIV-1 in an in vitro study with an EC₅₀ value of about 4 ng/ml. The peptide, papuamide A, inhibits the viral life cycle's initial phase, however, not the glycoprotein of the

Table 10. Marine bioactive peptides and their derivatives in drug discovery, clinical and pre-clinical trials.

Name	Source	Class	Targeted application (s)	Status
Ziconotide	<i>Conus magus</i>	Peptide	Relieves pain/ analgesic properties	FDA-Approved
Brentuximab vedotin	<i>Dolabella auricularia</i> associated <i>Symploca</i> sp.	the derivative of dolastatin 10 (monomethyl auristatin E)	Hodgkin lymphoma disorder	FDA-Approved
Glembatumumab vedotin	<i>Dolabella auricularia</i> associated <i>Symploca</i> sp.	the derivative of dolastatin 10 (monomethyl auristatin E)	Advanced or metastatic breast cancer	Phase-I/II trials
ILX-651 (Tasidotin)	<i>Dolabella auricularia</i>	A derivative of dolastatin 15	Non-small cell lung carcinoma, Melanoma	Phase-II trials
TZT-1027 (Soblidotin)	<i>Dolabella auricularia</i>	A derivative of dolastatin 15	Lung & Sarcoma cancer	Phase-II trials
HTI-286 (Taltobulin)	Marine sponge	A synthetic analog of hemiasterlin (tripeptide)	Human tumor xenografts	Pre-clinical trials
Elisidepsin	<i>Elysia rufescens</i>	A synthetic derivative of kahalalide F (cyclic peptide)	Advanced solid tumors	Phase-II trials
Plitidepsin	<i>Aplidium albicans</i>	cyclic depsipeptide	Advanced melanoma, Advanced thyroid carcinoma, non-Hodgkins lymphoma, and multiple myeloma	Phase-I/II trials
Xen-2174	<i>Conus marmoreus</i>	α -conopeptide	inhibitor of neuronal norepinephrine transporter	Phase-II trials

HIV-1 envelope (Andjelic, Planelles, and Barrows 2008; Ford et al. 1999; Pomponi 2001). On the other hand, papuamide B (710 nM) abrogates the virus's entry through interaction with phospholipid found on the viral membrane (Sagar, Kaur, and Minneman 2010). In another work, it was revealed that microspinosamide (a novel cyclic depsipeptide consisting of 13 amino acid units) derived from *Sidonops microspinosa* abrogated the cytopathic action of HIV-1 disease in an in vitro studies with an EC₅₀ value of about 0.2 µg/ml (Rashid et al. 2001). In this regards, bioactive peptides derived from sponges are shown as promising molecules for the synthesis of new potent inhibitors of viral infections (Ngo et al. 2012). The summary of the anti-HIV activity of some of the marine bioactive peptides is illustrated in Table 9.

Other health benefits of marine bioactive peptides

Marine bioactive peptides have other biological actions apart from the properties mentioned above. Peptides with calcium-binding actions derived *J. belengerii* frame can be introduced to oriental individuals with lactose intolerance (Jung and Kim 2007). Also, these bioactive peptides have the potential of decreasing the possibility of osteoporosis. In another study, Dolastatin yielded from *Dolabella auricularia* was reported to display antineoplastic action while Kahalalide F and isolated from a Marine mollusk called *Spisula polynyma* was reported to possessed antitubulin activity (Andavan and Lemmens-Gruber 2010; Pettit et al. 1989). Peptides from marine have been reported to exhibit anticoagulant actions. Organisms such as blue mussel, echiuroid worm are shown to contain these type of bioactive peptides, and the peptides derived from them are regarded as non-cytotoxic and could serve as a natural ingredient in pharmaceutical or nutraceutical industries (Jo, Jung, and Kim 2008; Shukla 2016).

Toxicological aspects of MBA's

Some of the bioactive peptides from marine showed some level of toxicity. For instance, Didemnin showed that

anticancer action was highly toxic and was discontinued for clinical trials (Newman and Cragg 2004). Aplidine was more active than didemnin B and showed no unwanted effects in preclinical studies (Faivre et al. 2005; García-Fernández et al. 2002; Raymond et al. 2000). However, more toxicity studies of marine bioactive peptides are required to ascertain their safety use.

Marine bioactive peptides: Drug discovery, pre-clinical and clinical trials

Bioactivities of different marine bioactive peptides have already been discussed in this review. Furthermore, marine bioactive peptides in their original and/or modified form are used by the marine pharmaceutical industry for their specific functional and nutraceutical uses. The vast range of marine bioactive peptides have been isolated and identified from diverse marine organisms, but only a few have entered clinical trials, and significantly fewer have attained FDA-approved status. Various other marine bioactive peptides having potent bioactivities entered the pre-clinical pipeline. Therefore, currently, the window of opportunities for scientists working on marine bioactive peptides in drug discovery and marine pharmaceuticals is brighter shortly (Mayer et al. 2010). This section highlights the update on drug discovery, clinical and pre-clinical trials of marine bioactive peptides and their derivatives (Table 10).

Ziconotide (25 amino acid peptide) isolated from toxin (ω -conotoxin) of cone snail (*Conus magus*) was the first marine-based drug that is being approved by the Food and Drug Administration (FDA). This cone snail uses conotoxin to immobilize its prey by targeting the neuro-muscular system (McIntosh et al. 1982; Olivera et al. 1985). Ziconotide (neuroactive peptide) is a synthetic derivative of ω -conotoxin that blocks NVSCCs (N-type voltage-sensitive calcium channels) and therefore inhibits the pain-related release of neurotransmitters (Lee, Orlikova, and Diederich 2015; Miljanich 2004). Likewise, similar to Ziconotide, Leconotide (27-amino acid peptide) is another ω -conotoxin comprising three internal CYS-CYS bonds in Phase-I clinical trials. It is also a blocker of

NVSCCs and is under trial to validate its ameliorative effect in cancer-related pains (Newman and Cragg 2014). Brentuximab vedotin (Adcetris®) is an immuno-conjugate drug originated from a synthetic structural derivative of dolastatin 10 (mono-methyl auristatin E) isolated from cyanobacteria (*Symploca* sp.). In 2011, it was approved by the FDA to treat patients with Hodgkin lymphoma, a CD30-positive lymphoproliferative disorder (Younes, Yasothan, and Kirkpatrick 2012). Phase-I/II trials of another drug (CDX011), also called glembatumumab vedotin (Celldex Therapeutics Inc.), has started against advanced or metastatic breast cancer (Bendell et al. 2014; Ott et al. 2014).

ILX-651 (tasidotin) and TZT-1027 (soblidotin) are synthetically derived analogs of marine peptides dolastatin 15 and dolastatin 10. Taltobulin (HTI-286)-a synthetic analog of hemi-asterlin (tripeptide)-have an inhibitory action on tubulin polymerization. In pre-clinical trials, HTI-286 have shown inhibitory action on human tumor xenografts in experimented mice (Lee, Orlíkova, and Diederich 2015; Loganzo et al. 2003). Elisidepsin (Irvalec®), a synthetic derivative of kahalalide F, is a cyclic peptide having potential against non-small cell lung cancer cell lines (Ling et al. 2009; Serova et al. 2013; Teixidó et al. 2012; Teixido et al. 2013). Results of a phase-I trial provide preliminary evidence of the anti-tumor potential of Elisidepsin in patients with advanced solid tumors (Salazar et al. 2012). In 1991, Plitidepsin (Aplidin®) was a cyclic depsipeptide derived from a marine tunicate (*Aplidium albicans*). It is also known as dehydrodidemnin B and is structurally closely related to didemnin B. Various clinical trials (Phase-I/II) have shown bioactivity of plitidepsin against patients suffering from advanced melanoma, advanced thyroid carcinoma, non-Hodgkins lymphoma, and multiple myeloma (Baudin et al. 2010; Dorr et al. 1988; Dumez et al. 2009; Kucuk et al. 2000; Mateos et al., 2010; Mittelman et al. 1999; Plummer et al. 2013; Ribrag et al. 2013; Taylor et al. 1998). Xen-2174 is a slightly modified form of natural γ -conotoxin, isolated from the venom of *Conus marmoreus*. Structurally, it is a modified 13-residue neuro-toxic peptide, which has shown noncompetitive inhibition of NET (neuronal norepinephrine transporter) and is in phase-II clinical trials (Brust et al. 2009; Nielsen et al. 2005). Table 10 mentions the details of clinical trials regarding marine bioactive peptides and their derivatives.

Conclusions and future trends

Marine bioactive peptides from diverse marine organisms and their pharmacological properties have been discussed in this review. Conclusively, marine bioactive peptides possess various biological activities like neuroprotective, antidiabetic, anticancer, antiviral, antioxidative, and immuno-modulating perspectives. Marine bioactive peptides provide an opportunity for marine pharmaceuticals to expand owing to their novel and unique structural and functional properties. The FDA has already approved some marine bioactive peptides, and various others are in different pre-clinical and clinical trials. Therefore, marine-derived bioactive peptides have immense potential in drug discovery against different diseases. Nevertheless, further clinical studies are required to

develop and produce safe, readily available, cost-effective marine bioactive peptides-based drugs.

ORCID

Kannan R. R. Rengasamy  <http://orcid.org/0000-0001-7205-7389>

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