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Review

Structural diversity of marine cyclic peptides and their molecular mechanisms for anticancer, antibacterial, antifungal, and other clinical applications

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ABSTRACT

Many cyclic peptides and analogues derived from marine sources are known to possess biological properties, including anticancer, antitumor, antibacterial, antifungal, antiparasitic, anti-inflammation, anti-proliferative, anti-hypertensive, cytotoxic, and antibiotic properties. These compounds demonstrate different activities and modes of action according to their structure such as cyclic oligopeptide, cyclic lipopeptide, cyclic glycopeptide and cyclic depsipeptide. The recent advances in application of the above-mentioned cyclic peptides were reported in dolastatins, soblidotin, didemnin B, aplidine, salinosporamide A, kahalalide F and bryostatin 1 and they are currently in clinical trials. These cyclic peptides are possible novel drugs discovered and developed from marine origin. Literature data concerning the potential properties of marine cyclic peptides were reviewed here, and the structural diversity and biological activities of marine cyclic peptides are discussed in relation to the molecular mechanisms of these marine cyclic peptides.

1. Introduction

The marine environment has an extraordinary supply of bioactive natural products, many of which demonstrate different structural or chemical characteristics from those found on land. Marine organisms are a rich source of bioactive compounds [1]. In recent years, increasing marine pharmacology studies have suggested that the secondary metabolites from marine organisms are likely to yield potential therapeutics with antibiotic, antiviral, antiparasitic, analgesic, and anticancer activities [2]. Recently, various new metabolites with potent biological properties have been discovered from marine organisms. These discoveries might lead to the development of new pharmaceutical agents from marine metabolites [3]. Cyclic peptides are one of the underexplored classes of bioactive peptides with a marine origin that have great promise in pharmaceutical areas. These compounds have garnered increased interest because of their significant bioactivities. Cyclic peptides originating from marine organisms have increased our understanding of potent new anticancer, antibacterial, ion channel-specific blockers, and antifungal properties of novel chemical structures related to the mechanisms of pharmacological activity [4]. This information demonstrates that marine cyclic peptides are a novel alternative for biological and biomedical research. In this review, the chemical structures, bioactivities, and clinical research of marine cyclic peptides are described to provide updated information regarding this area of study.

2. Bioactive cyclic peptides from marine sources

Marine species account for approximately 50 percent of total global biodiversity [4]. A wide range of marine organisms from microorganisms to sponges, algae, mollusks, and fish offer a tremendous resource for novel compounds. Among those compounds, cyclic peptides have introduced new options for pharmaceutical development since they possess many potential biologically active components [4].

Various anticancer cyclic peptides have been reported from marine sources (Table 1) including jaspamide isolated from sponges of the genus *Jaspis johnstoni* [5], didemnin produced by Caribbean tunicate *Tridemnum solidum* and other species of the same genus [6], aplidine obtained from the tunicate *Aplidium albicans* [7], dolastatins isolated from the marine mollusk *Dolabella auricularia* [8], kahalalides, a family of cyclic peptide found in the mollusk *Elysia rufescens* [9], lyngbyabellin A obtained from *Lyngbya majuscula*, the marine cyanobacterium [10], antillatoxin produced from *Lyngbya majuscula*, the marine cyanobacterium [11], bryostatins researched from the marine bryozoan

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Table 1
List of bioactive marine cyclic peptides.

Peptide name	Source	Class/Type	Biological activity (targeted/tested pathogens)	References
Discodermin A-H	*Discodermia* sp.	Cyclic oligopeptide	Antimicrobial (fungi, gram-positive bacteria, gram-negative bacteria)	[4,35,36,70]
Discobahamins	*Discodermia* sp.	Cyclic depsipeptide	Antifungal (*Candida albicans*)	[25]
Jaspamide (Jasplakinolide)	*Jaspis* and *Hemiastrella*	Cyclic depsipeptide	Anticancer (apoptosis in Jurkat T cells)	[5,45,46,64,65]
Halicylindramides (A–C)	*Halichondria cylindrata*	Cyclic oligopeptide	Antifungal (*Mortierella ramanniana*)	[26,77]
Theonellamide G	*Theonella swinhoei*	Cyclic glycopeptide	Antifungal (*Candida albicans*)	[27]
Microsclerodermins	*Microscleroderma herdmani*	Cyclic oligopeptide	Antifungal (*Aspergillus fumigatus, Candida albicans, Cryptococcus neoformans*)	[28,76]
Hymenamides A and B	*hymeniacidon* sp.	Cyclic oligopeptide	Antifungal (*Candida albicans, Cryptococcus neoformans*)	[29,87]
Didemnin B	*Tridid*emnum sp.	Cyclic depsipeptide	Anticancer (lymphatic, colorectal, prostate cancer)	[6,8,48,49,60,81]
Aplidine	*Aplidium albicans*	Cyclic depsipeptide	Anticancer (breast cancer, non-small cell lung cancer, melanoma)	[7,49,45,52,61,62,63,81]
Dolastatins	*Dolabella auricularia*	Cyclic and linear lipopeptide	Anticancer (melanoma, sarcoma, colorectal cancer, and ovarian cancer cells, leukemia)	[8,38,39,56–58,78]
Kahalalide F	*Elysia rufescens*	Cyclic depsipeptide	Anticancer (NSCLC, breast cancer, hepaticcancer cell lines)	[8,9,47,82–84,85]
Sansalvamide A	*Fusarium* sp.	Cyclic depsipeptide	Anticancer (pancreatic, colon, prostate, melanoma, breastcancer)	[5,16,50,67]
N-methylsansalvamide	*Fusarium* sp.	Cyclic depsipeptide	Anticancer (human Colon adenocarcinoma (HCT-116))	[17,51]
Fijimycin A-C	*Streptomyces* sp.	Cyclic depsipeptide	Antibacterial (*Staphylococcus aureus* (MRSA))	[21,44]
Lyngbyabellin A	*Lyngbya majuscula*	Cyclic lipopeptide	Anticancer (lung cancer cell line NCIH460)	[10,68]
Antillatoxin	*Lyngbya majuscula*	Cyclic lipopeptide	Anticancer (Chinese hamster lung cells, (CHL1610), neuro-2a mouse neuroblastoma cells)	[11,42]
Vancomycin	*Streptomyces fradiae* BW2-7	Cyclic glycopeptide	Antimicrobial (*Aspergillus niger, Staphylococcus aureus, Salmonella typhi, Penicillium aeruginosa, Trichophyton rubrum*)	[22,43,71,88]
Bryostatins	*Bugula neritina*	Cyclic depsipeptide	Anticancer (ovarian and breast)	[12,52,53,69,86]
Salinosporamide A	*Salinispora tropica*	Cyclic depsipeptide	Anticancer (myeloma cells) Antiparasitic (*Plasmodium falciparum, Plasmodium yoelii*)	[13,33,54,55]
Lobocyclamides A-C	*Lyngbya* sp.	Cyclic lipopeptide	Antifungal (*Candida* albicans, *Candida glabrata*)	[30]
Guineamides	*Lyngbya majuscula*	Cyclic lipopeptide	Anticancer (mouse neuroblastoma cell line)	[14,37]
Arenamides A-C	*Salinispora arenicola*	Cyclic depsipeptide	Anticancer (human colon carcinoma cell line (HCT-116), blocking TNF induced activation of 293/NFkappa B-Luc human embryonic kidney cells)	[15,45]
Largamides	*Oscillatoria* sp.	Cyclic lipopeptide	Protease-inhibition (chymotrypsin)	[37,40,41]
Papuamides A-B	*Theonella swinhoei Theonella mirabilis*	Cyclic depsipeptide	Antiviral (HIV)	[23,74,75]
Microspinosamide	*Sidonops microspinosa*	Cyclic depsipeptide	Antiviral (HIV-1)	[24]
Cyclomarin A	*Streptomyces* sp.	Cyclic heptapeptide	Antibacterial (*Mycobacterium tuberculosis*)	[19,20,72]
Salinamide A,B	*Streptomyces* sp.	Cyclic depsipeptide	Antibacterial (*Enterobacter cloacae*, *Haemophilus influenza*)	[19,20,73]
Valinomycin	*Streptomyces* sp.	Cyclic depsipeptide	Antiparasitic (*Leishmania major,Trypanosoma brucei*)	[31]
Avermectin	*Streptomyces avermitilis.*	Cyclic depsipeptide	Antiparasitic (*Nematospiroides dubius*)	[32]

Bugula neritina [12], salinosporamide A produced by *Salinispora tropica*, an obligate marine actinomycete [13], guineamides reported from marine cyanobacterium *Lyngbya majuscula* [14], arenamides A-C isolated from *Salinispora arenicola* [15], and sansalvamide A and *N*-methylsansalvamide recently identified from the marine genus *Fusarium* [16,17]. Interestingly, neo*N*-methylsansalvamide, an analogue of *N*-methylsansalvamide was isolated from soil fungus of the genus *Fusarium* [18]. Neo*N*-methylsansalvamide possesses similar structure and biological activity to sansalvamide A and *N*-methylsansalvamide.

Marine cyclic peptides exhibit antibmicrobial activity, including discodermins A-H obtained from the genus *Discodermia* sp. [4], cyclomarine A and salinamide A and B produced by *Streptomyces* sp. [19,20], and fijimycin A–C isolated from *Streptomyces* sp. CNS-575 [21]. Vancomycin, a well-known antibiotic isolated from marine *Streptomyces fradiae* BW2-7, also has a cyclic peptide structure [22]. Marine cyclic peptides have also been reported to exhibit antiviral activity, such as papuamides A and B isolated from sponges of the genus *Theonella* [23] and microspinosamide isolated from the sponge *Sidonops microspinosa* [24].

Some marine cyclic peptides are reported to have antifungal activity, including discobahamins isolated from the marine sponge *Discodermia* sp. [25], halicylindramides (A–C) isolated from the marine sponge *Halichondria cylindrata* [26], theonellamide G obtained from the red sea marine sponge *Theonella swinhoei* [27], microsclerodermins isolated from the marine sponge *Microscleroderma herdmani* [28], hymenamides A and B isolated from the marine sponge *hymeniacidon* sp. [29], and lobocyclamides A–C obtained from the cyanobacteria *Lyngbya* sp. [30].

Furthermore, there are marine antiparasitic cyclic peptides, including valinomycin produced by marine *Streptomyces* sp. [31], avermectin isolated from marine *Streptomyces avermitilis* [32], and salinosporamide A produced by *Salinispora tropica*, an obligate marine actinomycete [13,33].

3. Cyclic peptides based on structure

3.1. Cyclic oligopeptides

Cyclic oligopeptides are cyclic peptides that consist of two to 20 amino acids and are produced by non-ribosomal peptide synthesis [34].

Antifungal cyclic oligopeptides, halicylindramides (A–C), were discovered from the marine sponge *Halichondria cylindrata* in the early 1990s. The chemical structures of halicylindramides demonstrate that a formyl group blocks the N terminus of tetradecapeptides, and that the C terminus is lactonized by the hydroxyl group of the threonine residue [26].

Discodermin A (Fig. 1), which exhibits antimicrobial activity, consists of 14 components with two *t*-Leu residues and several d-amino acids [35]. The structure of discodermin A was identified as CHO-D-Ala-l-Phe-D-Pro-D-*t*-Leu-l-*t*-Leu-D-Trp-l-Arg-D-Cys(O_3H)-l-Thr-l-MeCln-D-Leu-l-Asn-l-Thr-*S*ar by Matsunaga et al. [36].

3.2. Cyclic lipopeptides

Lipopeptides are linear or cyclic peptides acylated by a lipid, usually a fatty acid side chain. These compounds are produced only in bacteria