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Natural Bioactive Cyclopeptides from Microbes as Promising Anticancer Drug Leads: A Mini-review

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ABSTRACT

Natural products from microbes are a rich source of bioactive molecules to serve as drug leads, predominantly in cancer therapy. Peptides are among the essential nature-derived biomolecules. Owing to their great diversity and favorable characteristics, cyclic peptides (cyclopeptides) from natural sources have become a propitious lead candidate for developing therapeutic agents, including drugs for cancer treatment. This mini-review highlights cyclopeptides from microbial-derived natural products that have demonstrated significant cytotoxicity or anticancer activities. A literature search for the potent anticancer cyclopeptides isolated in the recent decade from fungi and bacteria from both terrestrial and marine origins was carried out. A total of eighty-three papers from 2000-2020 were summarized. The primary information from the literature was elicited, and the recently selected examples of anticancer cyclopeptides (2010-2020) are discussed herein. Moreover, this mini-review also provides a look into the mode of action of anticancer cyclopeptides. Naturally occurring cyclopeptides with canonical and non-canonical amino acids isolated from fungi, myxobacteria, actinomycetes, marine cyanobacteria, and microbes associated with marine organisms and their anticancer activity are featured herein.

Keywords: bioactive anticancer, cyclopeptides, natural products, microbes

INTRODUCTION

Heretofore, cancer is a leading cause of a high mortality rate globally, both in developed and developing countries (Siegel *et al*., 2020). Conservative cancer treatments, such as chemotherapy and radiation, have failed to gain therapeutic functions due to a lack of tumor or cancer selectivity towards drug resistance. Therefore, there is still an imperative unfulfilled need for novel therapeutic approaches or anticancer drugs research and development (Holohan *et al*., 2013; Xie *et al*., 2020). Being an essential source of bioactive molecules, natural products (NPs) remain to take into account for drug discovery and development. A significant number of microbially produced NPs have generated excellent drugs, including anticancer drugs. As one of the essential biomolecules in nature, peptides show high specificity against cancer cells compared with traditional cancer treatments (Henninot *et al.*, 2018; Holohan *et al*., 2013; Thundimadathil, 2012; Tyagi *et al*., 2015;).

Cyclic peptides, also called cyclopeptides, are defined by closed peptides comprised of a head-to-tail cyclization structure or disulfide bridges that assemble cysteine knots. These low-molecular-weight peptides have favorable characteristics as drug or therapeutic candidates, including good binding affinity, low toxicity, as well as target selectivity (Horton *et al.*, 2000; Hoskin & Ramamoorthy, 2008; Zorzi *et al*., 2017). Due to their conformational flexibility, cyclopeptides are more stable and possess greater cell permeability and biological properties than their counterpart (linear peptides). Moreover, they demonstrate *in vivo* resistance towards exoproteases due to the absence of both N or amino and C or carboxyl termini (Aina *et al*., 2002; Horton *et al*., 2000). Thus, the bioavailability of cyclopeptides bestows fascinating properties to be applied in therapeutics. In nature, cyclopeptides have been isolated from plants (Hu *et al*., 2015; Tan and Zhou, 2006), microorganisms (Abdalla, 2016, 2017; Abdalla and Matasyoh, 2014; Liu *et al*., 2016;

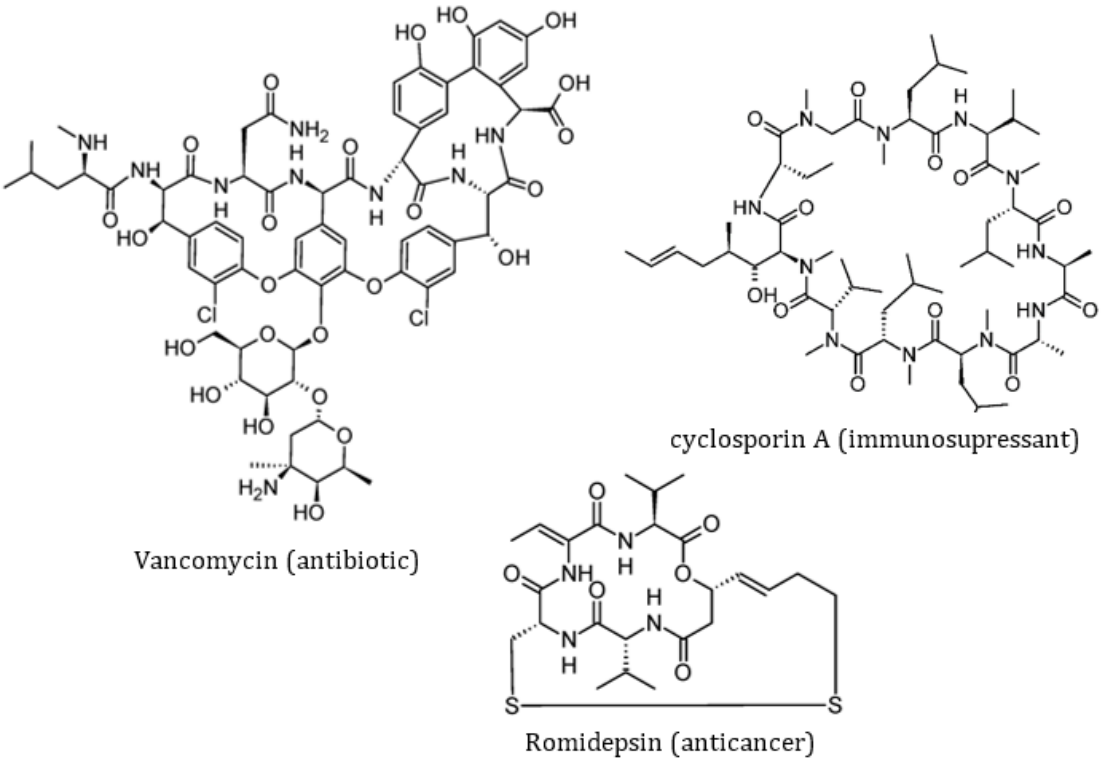


Figure 1. Cyclopeptide-derived microbial NPs as therapeutic agents

Taevernier *et al*., 2016), mammals (Brogden *et al*., 2003; Falanga *et al*., 2017), as well as marine entities (Andavan & Lemmens-Gruber, 2010; Blunt *et al*., 2016; Carroll *et al*., 2020; Lee *et al*., 2017; Sainis *et al*., 2010; Sarasan *et al*., 2017; Zhang *et al*., 2016). They contain canonical (proteinogenic) and non-canonical amino acids (including D-amino acids, *N*-methylated amino acids, hydroxy acids, and fatty acids), which are biosynthesized by ribosomal or multimodular non-ribosomal mechanisms (Bajaj, 2019; Simmons *et al*., 2008; Xu, Li, Du, & Tan, 2011).

To date, over 40 cyclopeptide-based drugs are now in clinical use. Moreover, in the vicinity of one new cyclopeptide passes into the market nearly every year. Many clinically developed cyclopeptides as therapeutic agents are microbial NPs, including peptide antibiotics. Most of these peptides are inherently antimicrobial agents (Zorzi *et al*., 2017). Several widely applied semi-synthetic or synthetic cyclopeptide drugs have entered clinical approval based on their structure-activity relationship studies (the rational design), such as the antibiotic vancomycin, the immunosuppressant cyclosporin A, and the recent anticancer drug romidepsin (Istodax®) (Figure 1).

Reviews on cyclopeptides and their medicinal significance or therapeutic functions (Abdalla, 2016; Abdalla & Mcgaw, 2018; Zorzi *et al*., 2017), as well as anticancer peptides (Chiangjong *et al*., 2020; Hilchie *et al*., 2019; Xie *et al*., 2020), have been published extensively. However, the reviews on microbial anticancer cyclopeptide and their mechanism of action are still limited. This present mini-review focuses on naturally occurring cyclopeptides from microorganisms with remarkable cytotoxicity and anticancer activity. The emphasis is on the structure (with canonical and non-canonical amino acids) and the anticancer activity of the pharmacologically active cyclopeptides. The mechanism of action of anticancer cyclopeptides will also be described. Therefore, this mini-review aims to identify bioactive cyclopeptides from microbial natural products that have demonstrated considerable antitumor activities. Recently isolated natural bioactive anticancer cyclopeptides during 2010-2020 are documented and discussed herein.

MODES OF ACTION OF ANTICANCER CYCLOPEPTIDES

As mentioned earlier, peptides have shown high specificity against cancer cells; hence they are potential molecular models in search of anticancer drugs and drug leads. Several studies have shown that anticancer activity was also described for some of the antimicrobial peptides, namely anticancer peptides. Besides inhibiting the growth of pathogenic microbes (bacteria and fungi), these peptides could also kill tumor or cancer cells as well as participate in immune system regulation. It is believed that the primary aspect of the selectivity of these peptides for killing cancer cells is the electrostatic interactions between cationic charged anticancer peptides and anionic charged cancer cell membrane components (Cunha *et al*., 2017; Felício *et al*., 2017; Hoskin & Ramamoorthy, 2008; Tornesello *et al*., 2020; Xie *et al*., 2020). Most anticancer peptides often act via the cell membrane destruction, apoptosis, angiogenesis inhibition, or immune regulation. Currently, cyclopeptides account for most anticancer peptides in clinical studies (Pan, Xu, & Jia, 2020; Xie et al., 2020). It has been reported that they induce cancer cell death mainly through apoptosis induction and angiogenesis inhibition (Figure 2) (Zheng *et al*., 2011; Felicio *et al*., 2017)

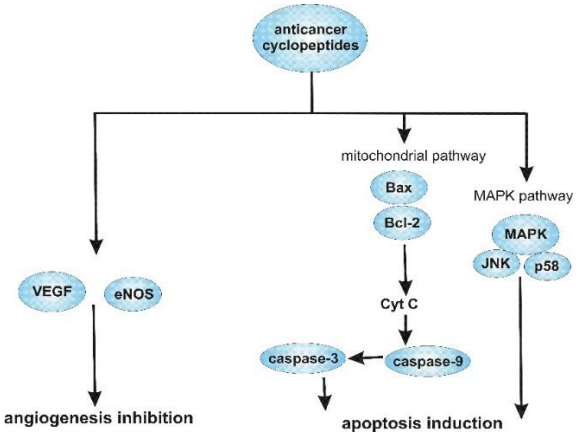


Figure 2. Molecular mechanisms of anticancer cyclopeptides.

Apoptosis becomes one of the leading cell death mechanisms (programmed cell death). This mechanism is preferable during cancer treatments since it does not commonly induce an immune response or inflammatory (Wong, 2011). Anticancer cyclopeptides with cytotoxicity, especially from marine origin, have been shown to lead to cytochrome c (Cyto-c) release and trigger apoptosis by breaking down the mitochondria membrane of cancer cells. Stimulation of the intrinsic mitochondrial pathway was shown by the increased expression level of Cyto-c and Bax and Bad (pro-apoptotic genes), together with the decreased expression level of Bcl-2 (pro-survival gene) (Ercolano *et al*., 2019; Zhao *et al.*, 2018). This mechanism has been observed in the marine sponge-derived cyclodepsipeptide jaspamide (jasplakinolide) that showed considerable *in vitro* cytotoxicity towards the human Jurkat leukemic T-cell. The jasplakinolide-induced apoptosis is correlated with the activation of caspase-3, the downregulated expression of Bcl-2 protein, and the upregulated expression of Bax (Odaka *et al*., 2000).

Moreover, a marine tunicate-derived anticancer plitidepsin can activate the release of mitochondrial Cyto-c by activating p-38 mitogen-activated MAPK protein kinases pathways and the JNK Jun *N*-terminal kinase. These pathways activation could induce the release of Cyt-c and switch on the cascape cascades subsequently. Apparently, the capcase mechanism and protein kinase C delta mediate the cytotoxicity activity of plitidepsin. This anticancer cyclodepsipeptide has demonstrated apoptosis in the breast cancer cells (MDA-MB-231), leading to continuing switching on of the Ser/Thr kinases JNK, p38 MAPK, the epidermal growth factor (EGFR), and the non-receptor protein kinase Src (Lee *et al*., 2017). Approved recently as an anticancer drug by the Australian Regulatory Agency, the synthetic plitidepsin (under the trade name Aplidin®) can be used to treat multiple myeloma (Delgado-Calle *et al.*, 2019; Sukmarini, 2021).

In addition to apoptotic-induced jasplakinolide and plitidepsin, some cyclopeptides that act as natural histone deacetylase (HDACis) inhibitors exhibited strong anticancer efficacy and have shown considerable antimetastatic as well as antiangiogenic activities. Their angiogenesis inhibition effects were mediated by decreased vascular endothelial growth factor (VEGF) and endothelial nitric oxide synthase (eNOS) expression levels. Through this mechanism, cancer cells are not directly killed, but neovascularization is inhibited; hence, cyclopeptides exert the least side effects on normal cells. Therefore, these peptides are beneficial as promising cancer therapeutics. Thus far, an example of the U.S FDA-approved HDCis as the anticancer drug is cyclodepsipeptide romidepsin (FK-228 or FR-901228, marketed as Istodax®) for the cutaneous T-cell lymphoma therapy (Tiffon *et al.*, 2011).

FUNGAL CYCLOPEPTIDES

Fungi, as well as macroscopic fungi (mushrooms), have also been known as an ample source of chemically diverse anticancer lead structures. Most of the naturally occurring peptides are (myco)fungal origins, such as recently isolated cyclopeptides malformin E, gymnopeptides, and pseudoxylallemycins that display significant anticancer activities.

Malformin E (Figure 3), a cyclopentapeptide disulfide cyclo-(Leu-Val-Ile-Cys-Cys), was obtained along with 13 known cyclodipeptides from the fermentation broth of the endophyte *Aspergillus tamarii* of the plant *Ficus carica.* Besides its antimicrobial property, this peptide had potent cytotoxicity against the human MCF-7 and A549 cancer cells with IC_{50} values of 0.65 and 2.42 μM, respectively (Ma *et al*., 2016).

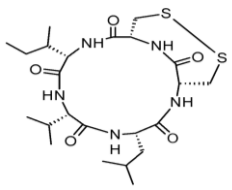


Figure 3. Structure of malformin E

A recent study on the identification of anticancer mycofungal NPs preceded the discovery of cyclic octapeptides, gymnopeptides A and B (Ványolós *et al*., 2016). These isolated compounds from the parasitic mushroom *Gymnopus fusipes* are unprecedented highly *N*-methylated cyclooctapeptides. They distinguished only in an amino acid residue in which a serine (Ser) found in gymnopeptide A was substituted by a threonine (Thr) in gymnopeptide B (Figure 4). Interestingly, both cyclopeptides showed strong cytotoxic activities in nM IC_{50} of several cancer cells, such as HeLa cervical, A431 skin epidermoid, and T47D, MCF7, and MDAMB-231 breast cells. However, gymnopeptide A is less potent than gymnopeptide B.

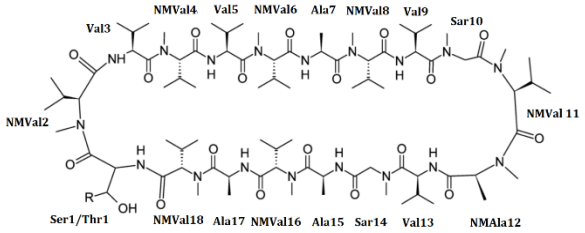


Figure 4. Structure of gymnopeptide A/B

Moreover, a *Microtermes*-associated fungus *Pseudoxylaria* sp. X802 has been recently known to produce six new cyclic tetrapeptides, namely pseudoxylallemycins A-F. These naturally occurring antimicrobial peptides, pseudoxylallemycins A and pseudoxylallemycins B-D (Figure 5) with rare allenyl moieties modification also showed antiproliferative activity towards human umbilical vein endothelial cells and K-562 cell lines. The GI_{50} values of pseudoxylallemycin C and D towards K-562 cells ranging from 4.2 μg-42.8 μg/mL. While, the pseudoxylallemycin C exihibited cytotoxic activity towards HeLa cells (CC_{50} = 10.3 μg/mL) (Guo *et al*., 2016).

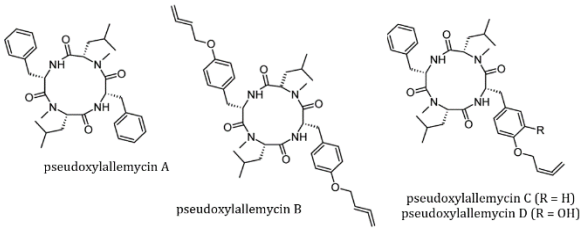


Figure 5. Structures of pseudoxylallemycins A-D

CYCLOPEPTIDES FROM ACTINOMYCETES AND MYXOBACTERIA

Actinomycetes, particularly genus *Streptomyces,* have long been a substantial reservoir for drug leads, as they have produced many novel bioactive compounds with anti-infective and anticancer properties. Approved anticancer drugs from streptomycetes include bleomycin (glycopeptide), dactinomycin (non-ribosomal peptide), mitomycin C (quinone), and doxorubicin (anthracycline) (Demain & Vaishnav, 2011; Katz & Baltz, 2016). With the advances in high-throughput next-generation sequencing, the genome mining approach is very useful for identifying the biosynthetic gene clusters (BGCs) with the potential for synthesizing new drugs. As a result of such an effort of genome mining method with *Streptomyces curacoi*, a new potent anticancer cyclopeptide was recently discovered, namely curacozole (Figure 6) (Albarano *et al*., 2020; Kaweewan *et al*., 2019; Lee *et al*., 2020; Ziemert *et al*., 2016).

Kodani and his co-workers (Kaweewan *et al*., 2019) have successfully identified BGCs of curacozole by comparing with that of the related cytotoxic compound YM-216391 from *S. nobilis* (Sohda *et al*., 2005a; Sohda *et al*., 2005b). Based on mass spectrometry (MS) and nuclear magnetic

resonance (NMR) analysis, curacozole was determined to be a cyclopeptide featuring oxazole/methyloxazole/thiazole moieties. This ribosomal cyclopeptide exhibited considerable cytotoxic activity towards colorectal (HCT116) and osteo (HOS) cancer cells (IC_{50} values = 8.6 and 10.5nM, respectively).

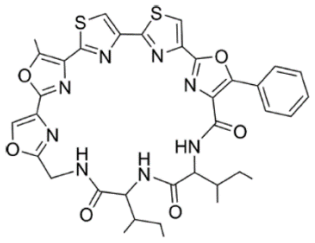


Figure 6. Structure of curacozole

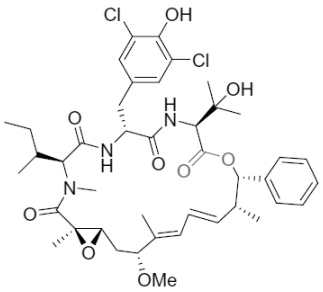


Figure 7. Structure of nannocystin A

Like fungi and streptomycetes mentioned above, myxobacteria are amongst the best-known natural product producers in recent years. Their secondary metabolites' diversity and rare structural properties are of great interest in drug discovery. A number of myxobacterial cytotoxic compounds have been screened and successfully isolated (Diez *et al*., 2012; Weissman & Müller, 2010). Interestingly, a novel anticancer cyclodepsipeptide nannocystin A was firstly discovered from a culture broth of the little-explored soil myxobacterial strain *Nannocyctis* sp. ST201196 (DSM18870) (Hoffmann *et al*., 2015), parallel with its finding in *Nannocyctis* sp. MB1016 (Krastel *et al*., 2015). Nannocystin A is a 21-mer macrocyclic scaffold of peptide-polyketide hybrid with non-canonical amino acid residues (such as 3,5-dichloro Tyr, 3-hydroxy Val, and *N*-methyl Leu) and epoxyamide moiety (Figure 7). This compound displayed a wide-range anticancer profile and highly active antiproliferative activity towards 14 cancer cell lines (at nM values) and significant inhibitory activity towards the drug-resistant MDA-A1 cell line with IC_{50} value of 12nM. Moreover, nannocystin A has been reported to be a strong inhibitor of cellular proliferation in HCT116 cancer cells through the induction of apoptosis at an early time-point of 24. Therefore, this compound becomes a promising anticancer drug lead due to its biological efficacy properties (Hoffmann *et al*., 2015).

CYCLOPEPTIDES FROM MARINE MICROBES

Besides terrestrial sources, marine life has been an enormous source of a variety of bioactive molecules. In modern-day drug research, marine metabolites or their synthetic analogs become important drug reservoirs, and many are employed in cancer treatments. Most of the marine compounds under clinical trials are also for application in cancer therapies, revealing the tremendous prospects of marine-derived anticancer drugs (Cragg & Pezzuto, 2016). Interestingly, based on the biosynthetic parallels and the distribution in taxonomically diverse organisms, the most promising of these compounds derive from microbial sources and also can be associated with marine macroorganisms (Rath *et al*., 2011; Simmons *et al*., 2008; Watters, 2018). Moreover, marine microorganisms include marine-sourced bacteria, cyanobacteria, and marine-sourced fungi (Carroll *et al*., 2020; Elrayess & El-Hak, 2019).

Marine-sourced bacteria

Carroll *et al*. (2020) reported that marine bacteria continue to be a prolific source of peptide compounds, including cyclopeptides, which account for approximately 10% of all new bacterial compounds (Carroll *et al*., 2020). It has been known that the genus *Bacillus* is one of the predominant sources of new chemistry. In the exploration of biologically active compounds from *B. amyloliquefaciens* GAS 00152 from the deep-sea sediment of the South China Sea (depth 2476m), two new cyclotetrapeptides have been successfully isolated (Gao *et al*., 2014). These cyclopeptides bearing canonical amino acid residues are cyclo-(Leu-Pro-Ile-Pro) and cyclo-(Tyr-Pro-Phe-Gly) (Figure 8). They showed cytotoxicity towards the human liver HepG2 and cervical HeLa cancer cells. Cyco-(Leu-Pro-Ile-Pro) had IC_{50} values of 26.6 and 34.7μM, respectively, while cyclo-(Tyr-Pro-Phe-Gly) exhibited cytotoxic activity with IC values of 38.2 and 46.1μM, respectively.

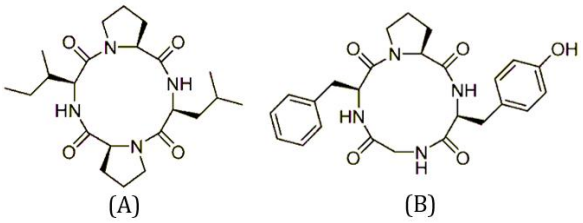


Figure 8. Structures of (A) cyclo-(Leu-Pro-Ile-Pro) and (B) cyclo-(Tyr-Pro-Phe-Gly)

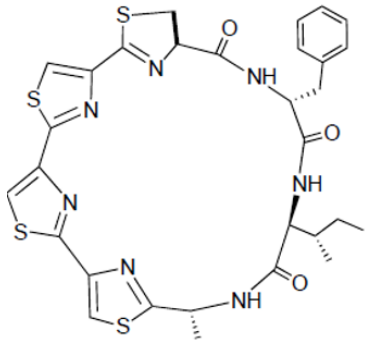


Figure 9. Structure of marthiapeptide A

As mentioned earlier, several potent cytotoxic compounds were derived from actinomycetes. A marine sediment-derived actinomycete from the South China Sea, *Marinactinospora thermotolerans* SCSIO 00652, was recently known to produce a cyclopeptide containing tristhiazole-thiazoline moieties, named marthiapeptide A (Figure 9). This finding was favoured by the genome mining technique that detected BGCs responsible for NRPs in the genome. Marthiapeptide A exhibited promising cytotoxic anticancer activity towards the human glioblastoma SF-268 (IC_{50}=0.38μM), the human breast MCF-7 (0.43 μM), the human lung NCl-H460 (0.47μM), and the human hepatocarcinoma HepG2 (0.52μM) cancer cells *(Zhou et al*., 2012).

Marine-sourced cyanobacteria

Another remarkable increase in the number of new bacterial NP-based compounds has also been reported from marine prokaryotic cyanobacteria, including cyclopeptides. The cytotoxicity activity of these cyanobacteria-derived peptides have extensively been investigated; mainly those belong to *Moorea* (formerly known as *Lyngbya*), *Symploca*, and *Oscillatoria* genera (Engene *et al*., 2012; Kang *et al*., 2018; Nunnery *et al*., 2010; Tan, 2010).

Filamentous marine cyanobacterium, *Moorea producens* (*L. majuscula*), has been reported to produce potent anticancer cyclopeptides wewakazole B (Lopez *et al*., 2016), tiahuramides B and C (Levert *et al*., 2018), and lagunamides A-C (Tripathi *et al*., 2011; Tripathi *et al*., 2010). Along with the known cytotoxic compound curacin D, wewakazole B (Figure 10) was isolated from a Red Sea (Saudia Arabia) *M. producens*. Structurally, this cyanobactin ribosomal peptide contains oxazoline and methyloxazoline moieties. Wewakazole B was found to be remarkably cytotoxic against the human lung H460 cancer cells (IC_{50}=1.0μM) and the human breast MCF7 cancer cells (IC_{50}=0.58μM) (Lopez *et al*., 2016).

Moreover, very recent new cyclohexa-peptides, tiahuramides A-C, have been isolated from the strain collected at Moorea Island, French Polynesia. These compounds are new members of the hybrid non-ribosomal peptide synthases (NRPS)-polyketides synthetases (PKS) bearing a fatty acid moiety within a cyclodepsipeptide framework. Tiahuramides B and C (Figure 11) showed cytotoxic activity with IC_{50} values of 14 and 6.0μM, respectively, against human SH-SY5Y neuroblastoma. It seemed that the cytotoxicity is produced by secondary necrosis, or late apoptotic cell mechanism (Levert *et al*., 2018).

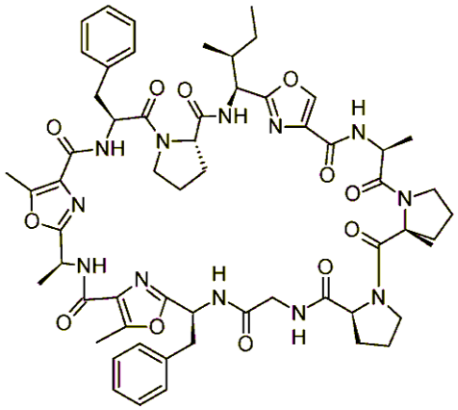


Figure 10. Structure of wewakazole B

Additionally, the two cyclic lipopeptides, lagunamides A and B (Figure 12) were cytotoxic towards murine leukemia P388 cancer cell lines (IC_{50} values of 6.24 and 20.5 nM, respectively) (Tripathi *et al*., 2010). While, the peptide lagunamide C (Figure 12) displayed vigorous cytotoxic activity towards several cancer cell lines such as P388 and A549 of lung cancer cells, PC3 and

HCT8 of human colon cancer cells, and ovarian SK-OV3 cancer cell with IC_{50} values of 2.1-24.4 nM (Tripathi *et al*., 2010).

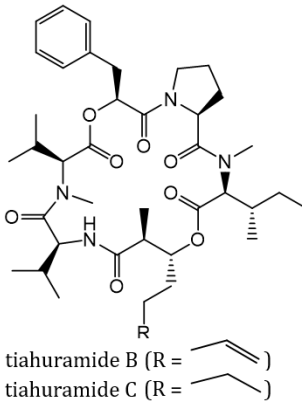


Figure 11. Structure of tiahuramides B-C

The cyclodepsipeptides veraguamides (Figure 13) were obtained from *Oscillatoria margaritifera* from Coiba National Park, Panama. Veraguamide A was severely toxic in human lung cancer cells (H-460) with LD_{50} value of 141 nM (Mevers et al., 2011). Moreover, veraguamides A-G have also been obtained from *Symploca* cf. *hydnoides* (collected from Ceti Bay, Gum), in which veraguamides D and E displayed high cytotoxicity towards the human HT29 colorectal (IC_{50} = 0.84 and 1.5 μM, respectively) and HeLa cervical cancer cells (IC_{50} = 0.54 and 0.83 μM, respectively). Veraguamides are distinguished by an invariable Pro residue, various *N*-methylated amino acid residues, α-hydroxy acid, and the fragment of PKS with terminus alkynyl bromide, vinyl group, or alkyne (Salvador *et al*., 2011).

Marine-souced fungi

Fungi have been found in nearly every possible marine habitat, such as deep-sea sediments and as a symbiont in marine plants (e.g., mangroves and algae) and marine invertebrates (e.g., corals). Marine-derived fungi have been acknowledged as an emerging reservoir for drug discovery, including anticancer agents, as studies of them continue to rise (Carroll *et al*., 2020; Youssef *et al*., 2019). Including recently isolated cytotoxic marine fungal cyclopeptides are cordyheptapeptides, psychrophilin E, asperterrestide A, and beauvericin.

Three new cycloheptapeptides cordyheptapeptides C-E (Figure 14) were isolated from the marine sediment fungus *Acremonium persicinum* SCSIO 115 collected from the South China Sea. Their cytotoxic activity towards human breast MCF-7 cancer, human glioblastoma SF-268, and human lung NCl-H460 cancer cell lines have been assessed. It has been shown that cordyheptapeptide E exhibited considerable IC_{50} values of 2.7, 3.2, and 4.5μM against MCF-7, SF-268, and NCl-H460 cell lines, respectively. Moreover, cordyheptapeptide C also significantly exhibited cytotoxicity towards those cancer cell lines (IC_{50}=3.7, 3.0, and 11.6μM, respectively), while a mild cytotoxic activity has been displayed by cordyheptapeptide D (Chen *et al*., 2012).

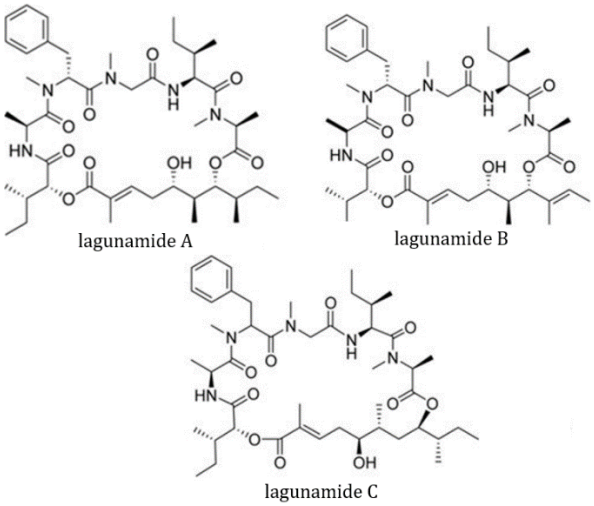
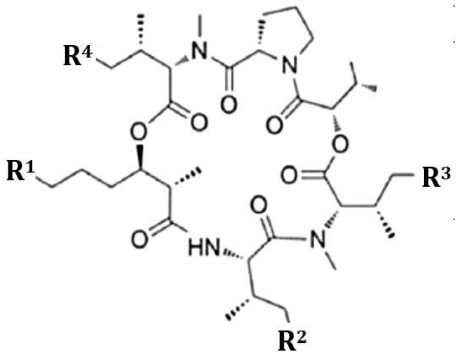


Figure 12. Structures of lagunamides A-C

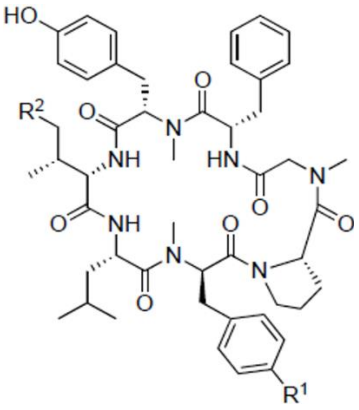


veraguamide	R1	R2	R3	R4
A	Br	H	H	H
D		H	H	CH_3
E		CH_3	CH_3	H

Figure 13. Structure of veraguamides

Interestingly, to identify novel chemical structures generated via different biosynthetic pathways, the co-fermentation of two or more marine fungal strains that simulate their natural

environment and/or promote other biosynthetic interactions has attracted significant interest (Pettit, 2009). Adopting this approach, a co-fermentation of two marine algae-sourced fungal strains of *Aspergillus* produced psychrophilin E (Figure 14). This cyclotripeptide bears side-chain cyclization at the indolic NH of the tryptophan within an acidic moiety of anthranilic acid (ABA). The antiproliferative activity was shown against the human colon HCT116 cancer cells (IC_{50}=28.5μM) (Ebada *et al*., 2014).



cordyheptapeptide D R1 = OH; R2 = H;
cordyheptapeptide E R1 = OH; R2 = CH3

Figure 14. Structure of psychorophilin E

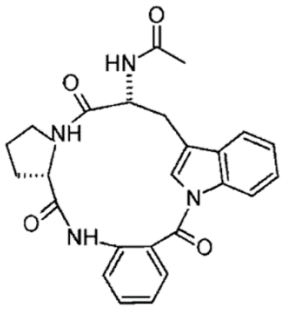


Figure 15. Structure of asperterrestide A

Furthermore, a cyclotetrapeptide, namely asperterrestide A, incorporating an ABA unit and β-hydroxy substituted *N*-methyl Phe residue (Figure 15). This peptide was isolated from the cultivation broth of the marine coral-associated *Aspergillus terreus* SCSGAF0162. The fungal strain was isolated from the tissue of the coral gorgonian *Echinogorgia aurantiaca* obtained from Hainan (China). Besides its antiviral activity, asperterrestide A has shown cytotoxicity towards the human leukemic U937 and MOLT4 cancer cells (He *et al*., 2012).

In addition to some new compounds, a previously well-known cyclohexadepsipeptide, beauvericin (Figure 16) (Gupta *et al*., 1991; Hamill *et al*., 1969), was also recently obtained from a mangrove-associated endophyte *Fusarium* sp. (No. DZ27), which was isolated from *Kandelia candle* in the South China Sea. The compound demonstrated cytotoxicity against the human epidermoid KB carcinoma (IC value of 5.76 μM) and KBv200 cancer cell lines (IC_{50} values of 5.34 μM). It has been reported that this cyclopeptide triggers apoptosis via the mitochondrial pathway; however, the regulation of Bcl-2 or Bax was not observed in this (Deshmukh *et al*., 2018a; Deshmukh *et al*., 2018b).

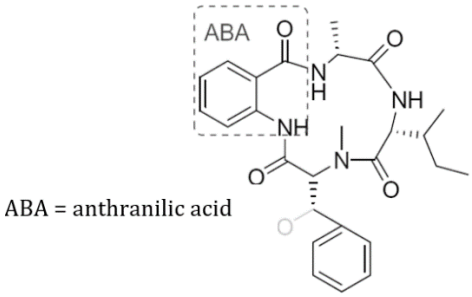


Figure 16. Structure of asperterrestide A

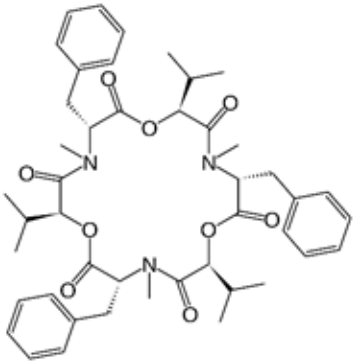


Figure 17. Structure of beauvericin

CONCLUSION AND PERSPECTIVES

To sum up, cyclopeptides are great of interest due to their diverse structures (containing canonical and non-canonical amino acids), biological significance (e.g., potent cytotoxic activity), and therapeutic properties (e.g., target selectivity). Microbial cyclopeptides have delivered chemical models for therapeutically potent anticancer lead molecules to the concern of the biopharmaceutical industry. Moreover, most of the recently bioactive cyclopeptides with significant

cytotoxic activity against several specific cancer cells that are identified in this present short review are from marine microbes.

Due to chemical redundancy, it is important to note that developing new methods is urgently needed to employ as traditional bioactivity-guided methods typically lead to previously known compounds. Successful approaches such as genome mining and co-culture approaches significantly impact discovering fascinating and valuable cyclopeptides as applied on actinomycetes and marine fungi. Natural product discovery is making significant progress in the genomic era and demonstrates vital signs of development. Since the investigation of genome sequences from microbes can dissect promising silent biosynthetic gene clusters, genome mining is an effective method to escort and accelerate the delivery of novel and intriguing cyclopeptides production. Moreover, a co-culture or a mixed-fermentation is an option to fully attain the metabolic potential of those cultivable microorganisms. In this approach, the chemical diversity can be increased as the neighboring microbes may also generate secondary metabolites.

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