Pharmrev Fast Forward. Published on 7 October 2024 as DOI 10.1124/pharmrev.124.001227 This article has not been copyedited and formatted. The final version may differ from this version.

Bioactives from Marine Resources as Natural Health Products: A review

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Financial support for the research: Natural Sciences and Engineering Research Council (NSERC) of Canada

Running title: Marine bioactives

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Text pages: 80

Tables: 7

Figures: 12

References: 281

Abstract: 200 words

List of Abbreviations:

DENV, dengue virus; EC_{50}, half maximal effective concentration; EU, European Union; EV7, enterovirus 71; FDA, Food and Drug Administration; HAdv, human adenovirus; Hc-CATH, sea snake cathelicidin; HIV, human immunodeficiency virus; HSV, herpes simplex viruses; IC_{50}, half maximal inhibitory concentration; MECs, minimal effective concentrations; MIC, minimum inhibitory concentration; MID, minimum infective dose; Rbpisc, Rock bream piscidin; SARS CoV-2, severe acute respiratory syndrome coronavirus 2; VpDef, *Venerupis philippinarum* defensin; WHO, World Health Organization

Abstract

The oceans are a rich source of a myriad of structurally different and unique natural products that are mainly found in invertebrates with potential applications in different disciplines. Microbial infection and cancer are the leading causes of death worldwide. Discovery of new sources of therapy for microbial infections is an urgent requirement due to the emergence of pathogenic microorganisms that are resistant to existing therapies. Marine bioactives have demonstrated to be promising sources for the discovery and development of novel antimicrobial and anticancer compounds. Several marine compounds are confirmed to have antibacterial effects and most marine-based antifungal compounds are cytotoxic. Numerous antitumor marine natural products, derived mainly from sponges or molluscs, and also bryozoans and cyanobacteria, exhibit potent antimitotic activity. In addition, marine biodiversity offers some possible leads or new drugs to treat human immunodeficiency virus (HIV). A majority of marine derived drugs are currently in clinical trials or under preclinical evaluation. Furthermore, marine-based drugs, approved by the US Food and Drug Administration (FDA) are available in the market. This review summarizes the sources, mechanisms of action and potential utilization of marine natural products such as peptides, alkaloids, polyketides, polyphenols, terpenoids and sterols as antifungal, antibacterial, antiviral, and anticancer compounds.

Significance Statement:

The utilization of bioactive compounds from marine resources as natural health products results in a crucial advancement in the field of healthcare and wellness. A valuable source of therapeutic potential has been discovered by harnessing the diverse and potent compounds from marine organisms. These bioactives offer a promising medicinal value for preventing various diseases, promoting overall wellbeing, and advancing pharmaceutical and nutraceutical industries. Their sustainable extraction and utilization not only benefit human health but also contribute to the conservation of marine ecosystems. Utilizing marine based bioactives implies a transformative approach towards enhancing health outcomes and sustainability in our modern world.

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I. Introduction

More than 70% of earth's surface is covered by oceans, and life on earth has its origin in the sea. Experts estimated that the biological diversity is higher in certain marine ecosystems, such as coral reefs and deep-sea floors, compared to tropical rain forests. Many marine organisms are soft bodied and have a sedentary lifestyle necessitating chemical means of defense. Marine ecosystem is an excellent source of both biological and chemical diversities. So far, more than 30,000 natural products have been reported from marine flora and fauna (Lindequist, 2016), and since 2008, over 1000 new natural products have been discovered each year as shown in Figure 1 (Carroll et al., 2024; Shahidi and Santhiravel, 2022). Over the past decades, a variety of natural compounds such as polyunsaturated fatty acids, proteins and peptides (e.g., collagen and gelatin), enzymes, polyphenols, polysaccharides, pigments, vitamins, and minerals possessing several biological activities have been discovered from the marine ecosystem (Barrow and Shahidi, 2007).

Marine invertebrates, fishes, seaweeds, and microorganisms are the major groups of marine organisms that produce bioactive compounds, and these compounds are commonly extracted from their muscles, skin, internal organs, and bones (Lobine et al., 2022). Depending on the species, temperature of the ocean, season, and geographical location, composition and diversity of bioactive molecules generated by marine species vary considerably. This diversity has been the source of unique chemical compounds with the potential for industrial applications as pharmaceuticals, nutraceuticals and other nutritional supplements, cosmetics, molecular probes, fine chemicals, and agrochemicals (Šimat et al., 2020; Shahidi and Ambigaipalan, 2015). The ongoing challenge is to sustainably produce an adequate quantity and quality of these products to avoid overexploitation of marine natural resources.

The development of new drug therapies has indeed played a crucial role in extending human life span and enhancing the overall well-being. In this regard, people have become more and more reliant on the safe and effective pharmaceutical products (Nascimento et al., 2023). Traditionally, new pharmaceuticals have originated from nature. Currently, more than half of the commercially available drugs are either derived from natural sources or synthesized by using natural products as templets or starting materials (Geigert, 2023). In recent years, pharmaceutical industries have intensified their efforts towards searching for marine organisms, including seaweeds, as a source for new drugs from natural products. These products are also being increasingly used in medical and biomedical research. Prior to the 1950s, the therapeutic application of marine sources, particularly seaweeds, were restricted to traditional and folk medicines (Lincoln et al., 1991). The actual development of marine drugs commenced in the 1950s when C-nucleosides, spongothymidine and spongouridine were identified from the Caribbean sponge *Tethya crypta* (Bergmann and Feeney, 1951). The discovery of antibiotic class of cephalosporins began with the isolation of Cephalosporin C from the fungus *Acremonium chrysogenum* derived from Mediterranean Sea water in the 1940s (Lindequist, 2016).

During the 1980s and 90s, molecules with therapeutic potential were identified from marine invertebrates, algae, and bacteria. Between 1977 and 1987, algae, sponges, and cnidarians contributed to around 35, 29, and 22% of the discovery of novel chemical compounds, respectively (Ireland et al., 1993). However, the identification of new natural products from seaweeds has decreased since 1995, and marine microorganisms have started gaining more attention (Kelecom, 2002). Studies have reported many pharmacologically active novel compounds that are probably used as protection mechanisms by marine organisms against their predators. Marine invertebrates that are sessile or slow moving and mostly lack morphological

defense structures, such as sponges, tunicates, and certain molluscs, and hence have provided the largest number of marine-derived secondary constituents, including some of the most interesting drug candidates (Romano et al., 2022; Liu et al., 2019a). Marine biodiversity also offers some possible leads or new drugs to treat the human immunodeficiency virus (HIV).

Till to date, marine species are screened for their antioxidant, antimicrobial, anticancer, neuroprotective, anti-inflammatory, anti-diabetic, anti-obesity, lipid-lowering, skin protective and sleep enhancing properties (Shahidi and Santhiravel, 2022). These properties are widely utilized in the new drug development across the world. Among these, certain marine-derived drugs are approved by Food and Drug Administration (FDA) and European Union (EU) and various drugs are in different phases of clinical trials, while a huge number of marine based molecules are in the pre-clinical testing pipelines (Malve, 2016).

Several recent comprehensive reviews have emphasized on the anti-diabetic (Agarwal et al., 2023), cardioprotective (Akram et al., 2023), anti-inflammatory (Khursheed et al., 2023), and neuroprotective (Pereira and Valado, 2023) effects of marine bioactives. However, there is a gap in comprehensive reviews addressing the antimicrobial properties of marine natural products. Moreover, cancer is the second leading cause of death globally (WHO, 2022) and microbial infectious diseases are the leading causes of death in low-income countries (WHO, 2020). This global burden of cancer and infectious diseases necessitates the development of novel anticancer and antimicrobial drugs from natural sources. In this context, marine bioactives have great potential for novel drug development since they have been proven to exhibit anticancer, antibacterial, antifungal, and anticancer activities (Wong et al., 2023; Das et al., 2023). Therefore, a comprehensive review on the antimicrobial and anticancer properties of marine natural products is needed for guiding the future research and clinical applications. This review

focusses mainly on antifungal, antibacterial, antiviral, and anticancer activities of proteins and peptides, alkaloids, polyketides, polyphenols, terpenoids, and sterols isolated from marine ecosystem during the period of last 30 years, with the emphasis on the challenges and future trends associated with the development of pharmaceutical products from the marine origin (Figure 2).

II. Mechanism of action of antifungal, antibacterial, antiviral, and anticancer activities exhibited by marine sources

A. Antifungal Activity

Fungi are a ubiquitous group of organisms that play a major role in different ecosystems, including decomposition of organic matter. Fungi are also utilized in the pharmaceutical industries for the purpose of obtaining certain drugs such as immunosuppressant, and antibiotics, among others. However, certain fungi can target different types of organs or tissues, namely lungs, neurons, and bones and threaten human health (Elabboubi et al., 2019). These fungal infections might be related to significant morbidity and mortality. The increase in the incidence of fungal infections is due to the emergence of resistant pathogens and their nosocomial dissemination, especially among immune-compromised or neutropenic patients. Scientific efforts to discover potential new antifungal drugs are principally leaned towards synthetic and natural products of plant origin. Fungi cells are eukaryotic, containing nucleus (DNA), endoplasmic reticulum, mitochondria, and Golgi apparatus. They differ from the mammalian cell membrane only by the type of sterol present in their cell membranes. Cholesterol is the major component of mammalian cell membrane, whereas fungal cell membranes mainly contain ergosterol (Lagrouh et al., 2017).

Several mechanisms of action have been proposed for the antifungal activity of secondary metabolites: (1) Disruption of cell wall integrity by inhibiting the fungal cell wall formation via prevention of the synthesis of β-glucans and chitins, the major cell wall components. Since bioactives can suppress β-glucan synthase and chitin synthase enzyme activities, involved in the synthesis of β-glucans and chitins, respectively (Walker and White, 2012); (2) Dysfunction of the mitochondria leading to a lower level of ATP generation and the following cell death. It is because natural products can inhibit the components (proteins) of electron transport chain such as complexes I, II, III, or IV and they can also depolarize the mitochondrial membranes (Agostini-Costa et al., 2012); (3) Suppression of RNA/ DNA or protein synthesis by influencing the transcription factors and enzymes involved in their synthesis such as RNA/DNA polymerase, topoisomerase, and tRNA synthetase. (Lagrouh et al., 2017); (4) Disruption of cell membrane when ergosterols are bound by antifungal agents or their synthesis is inhibited by ergosterol biosynthesis inhibitors which can suppress the activity of enzymes involved in ergosterol synthesis pathway such as squalene epoxidase (ERG1) and lanosterol synthase (ERG 7) (Walker and White, 2012); (5) Inhibition of efflux pumps by binding to active sites of efflux pumps like ATP-binding cassette transporters (Kang et al., 2010); or (6) Prevention of cell division via inhibition of the mitotic spindle formation by supressing the function of microtubule associated proteins and mitotic kinase (Lagrouh et al., 2017). Figure 3 illustrates the schematic diagram of the different mechanisms of action of antifungal activity of secondary metabolites.

Over the last few decades, marine environment has been recognized as a rich source of bioactive metabolites with varied biological and pharmacological activities. Among these natural products, numerous molecules with promising antifungal properties have been extracted from marine invertebrates, algae, and microorganisms. Sponges are identified as the major source of

antifungal metabolites, followed by bacteria and fungi (Cardoso et al., 2020). From 2000 to 2015, approximately 65% of the marine bioactive compounds exhibiting antifungal effects were identified from sponges and bacteria (El-Hossary et al., 2017). The remarkable chemical diversity of secondary metabolites produced by marine organisms contributes to the discovery and development of novel drugs for the prevention and treatment of several fungal infections (Alves et al., 2020).

B. Antibacterial Activity

Bacterial infection is one of the leading causes of death in both developed and developing countries, and resistance to antibiotics is a major health challenge and threat to public health globally [20]. The antibacterial resistance is either by intrinsic or acquired resistance (from other pathogenic bacteria) or their combination. Therefore, several strategies should be followed to overcome the bacterial resistance by employing novel antibacterial agents. Subsequently, the urge to find new compounds for treating bacterial infection has become a pressing global issue. Two mechanisms are mainly involved in the antibacterial activity of natural compounds by affecting the function or biosynthesis of essential components of bacteria and overcoming the antibacterial resistance (Yan et al., 2021).

These mechanisms include (Figure 4) (1) Inhibition of biosynthesis of bacterial cell-wall by affecting the enzymes involved in the synthesis pathway of peptidoglycans such as transpeptidase and transglycosylase (Galinier et al., 2023); (2) Affecting the synthesis of bacterial proteins by inhibiting the ribosomal function (binding to ribosomal subunits) and tRNA binding via suppressing aminoacyl-tRNA synthetase (Pang et al., 2021); (3) Prevention of DNA replication and repair by blocking the enzymes involved in DNA synthesis such as DNA polymerase, helicases, and primases, as well as influencing the nucleotide excision repair and

base excision repair mechanism (Barreiro and Ullán, 2016); (4) Destruction of bacterial cell membrane by binding to phospholipids and interacting with lipopolysaccharides in the outer membrane (Nowotarska et al., 2014); and (5) Inhibition of a metabolic pathway of amino acid, nucleotide, folate, coenzyme, fatty acid, and energy synthesis by interfering with enzymes involved in their synthetic pathways (Alamgir, 2018).

A large number of natural compounds with antibacterial activity has been isolated from different natural sources (Stan et al., 2021; Quinto et al., 2019). However, the efficacy of those compounds may differ due to the structural difference in the cell wall of Gram-positive and Gram-negative bacteria. Several marine-based compounds have demonstrated antibacterial effects. For instance, squalamine, isolated from dogfish shark *Squalus acanthias*, showed powerful antibacterial activity against both Gram-positive and Gram-negative bacteria (Moore et al., 1993).

C. Antiviral Activity

Viruses, a class of pathogenic microorganisms, threaten the health and safety of humans. Several epidemics have broken out over the past centuries killing thousands of people. Among all infections, viral pathogens cause more serious damage. However, the development of remedy to treat viral infection has been slow and only a few clinically approved antiviral drugs are available. For instance, the development of drugs to treat human adenovirus (HAdv) infections is still a great challenge for medicinal chemists (Pech-Puch et al., 2020). Moreover, fatal viral diseases such as hepatitis B, AIDS, influenza, and other diseases have not yet been completely eradicated. In addition, due to the increasing resistance of available drugs to viral infections, the need to develop new antiviral therapies has intensified. Exploration of marine resources for antiviral activity has yielded a remarkable number of bioactive natural products. Around 89

antiviral compounds, belonging to 8 structural classes, have been identified from marine microorganisms from 2015 to 2019 (Teng et al., 2020).

Numerous marine species, including tunicates, sponges, echinoderms, and microbes, exhibit considerable inhibitory activities against pathogenic viruses. Marine-derived compounds displaying antiviral activities are included in the chemical classes of terpenes, peptides, polyketides, polysaccharides, and nitrogen-containing compounds. Khan et al. (2021) investigated the potency of certain marine-based compounds against SARS CoV-2 main protease (PDB ID 6MO3) and reported that these compounds may be used as a potential inhibitor targeting SARS CoV-2 for better management of COVID-19.

Different phases of lifecycle of viruses have been the target for the discovery of novel antiviral compounds. Fundamental stages of the enveloped virus lifecycle of entry, synthesis, and assembly are interrupted by the natural antiviral products. Viral uncoating, viral penetration, viral particle or virion inhibition (virucidal effect), endosomal escape, viral genome replication, adsorption (cellular association), and viral assembly, packaging, and release are the major inhibition sites of antiviral compounds (Kausar et al., 2021; Vilas Boas et al., 2019; Magden et al., 2005).

D. Anticancer Activity

Cancer, an abnormal growth of cells and tissues, is still the leading cause of death globally. So far, over 277 different types of cancer have been diagnosed and the most prominent ones are lung, rectum, breast, prostate, urinary bladder, and bronchus cancers (Khalifa et al., 2019). According to WHO, nearly 18.1 million cancer cases were reported around the world and cancer accounts for approximately 10 million deaths in 2020 (WHO, 2022). The traditional therapeutic approaches include surgery, radiotherapy, chemotherapy, immunotherapy, and combination of

multiple therapies that may trigger irreversible injury to the important organs near to tumors. In addition, due to the increasing drug resistance, the discovery and development of novel active chemotherapeutic agents is highly desirable. Natural compounds are regarded as the most remarkable anticancer agents. Approximately 65% of the anticancer drugs commercially available in Europe and the USA are of natural origin, either microbially-derived or extracted from plant sources (Newman and Cragg, 2012).

At present, there is a growing interest for potential anticancer agents derived from the marine ecosystem. Improvements in the technology of deep-sea collection and culture and the increasing understanding of marine biodiversity have raised the interest of exploring the ocean as a potential source of new anti-cancer candidates. Several antitumor marine natural products, derived mainly from marine sponges or molluscs, but also bryozoans and cyanobacteria, exhibit potent antimitotic activities. The marine pharmacology literature highlights the fact that the discovery of novel marine antitumor agents continued to increase between 1998 and 2022 (Dyshlovoy and Honecker, 2022; Mayer and Lehmann, 2001). Examples of antitumor compounds isolated from marine organisms include didemin B from a marine tunicate, bryostatin 1 from marine bryozoa, dolastatin 10 from sea hare, as well as halichondrin B, calyculin A and mycalamides A and B from sponges (Khalifa et al., 2019).

Several mechanisms of action are involved in the anticancer activities of natural compounds. These compounds have created exciting new means for, (1) Disrupting tumor-specific cell signalling mainly by blocking ligand binding to receptor tyrosine kinases and inhibiting their activity (Ghosh et al., 2020); (2) Preventing cell division by targeting the cell division regulators such as cyclin-dependent kinases (CDKs) (Santo et al., 2015); (3) Suppressing energy metabolism by the inhibition of enzymes involved in glycolysis, TCA cycle, amino acid and fatty

acid metabolism, among others (Muniraj et al., 2019); (4) Modifying gene expression mainly by epigenetic modification and inhibition of transcription factor binding (Huang et al., 2018); (5) Inducing apoptosis and necrosis through intrinsic (mitochondrial) and extrinsic (death receptor) pathways (Lossi, 2022); (6) Blocking proliferation by the cell cycle arrest by the inhibition of CDKs and DNA damage; (7) Inhibiting invasion and metastasis through the suppression of epithelial-mesenchymal transition and matrix metalloproteinases (Ge et al., 2022); and (8) Inhibiting angiogenesis via blocking vascular endothelial growth factor (VEGF) signalling by targeting tyrosine kinase activity of VEGF receptors (Cerezo et al., 2019); and preventing tumor promoting inflammation by inhibiting pro-inflammatory cytokines (TNF-α, IL-6 and IL-1β), modulating nuclear factor kappa B (NF-κB) pathways, and suppressing cyclooxygenase-2 and lipoxygenase enzymes (Al-Khayri et al., 2022) as shown in Figure 5. Marine-based bioactive compounds exhibiting anticancer activities include peptides, phenols, alkaloids, sterols, and terpenoids, among others.

III. Marine resources for pharmaceutical and medical products

Research into pharmacological properties of marine natural products has led to the discovery of many potent active agents considered worthy of clinical application. The marine environment is an exceptional reservoir of bioactive natural products, many of which exhibit structural and chemical features not found in terrestrial natural products (Khalifa et al., 2019). As mentioned above, the first marine-based bioactive compounds, C-nucleosides, spongothymidine and spongouridine, were discovered from Caribbean sponge *Cryptothecaa crypt* by Bergmann and Feeney in 1951 (Bergmann and Feeney. 1951). Later in mid 1960s, these compounds were proven to possess anticancer and antiviral activities (Cragg et al., 1997). In 1970s, research on marine products accelerated and began to appeal to different disciplines, including biochemistry,

biology, ecology, organic chemistry, and pharmacology. Since the 1970s, more than 15,000 structurally diverse natural products with different bioactivities have been discovered from marine microbes, algae, and invertebrates (Mohamed et al., 2021). A majority of marine natural products have been obtained from sessile soft-bodied invertebrates, such as sponges and cnidaria. Most of the marine-based bioactive compounds, which have the application as natural health products, are categorized into groups of proteins and peptides, alkaloids, polyketides, and polyphenols.

A. Protein and Peptides

Ocean is an important biological ecosystem with an excellent source of novel functional proteins and peptides. Peptides are made up of an amino acid sequence, mostly in the range of 2 to 20 amino acid residues. Bioactive peptides, protein fragments, exhibit biological activities when released from the parent protein. Marine derived peptides possess numerous functionalities including antiviral, anticancer, antimicrobial, and cardioprotective effects, among others. Antimicrobial peptides are generally classified based on their prevalence of cationic and hydrophobic amino acid residues (Cunha and Pintado, 2022).

1. Antifungal

Caspofungin is a well-known antifungal peptide with the MIC_{50} values typically in the range of 0.03-0.1 μg/mL against *Candida albicans* (Pfaller et al., 2006) and around 0.5-1 μg/mL against *Aspergillus fumigatus* (Espinel-Ingroff, 2003). Numerous studies have shown that marine-based peptides are potent antifungal agents. Recently, Karim et al. (2021) isolated two bicyclic peptides, namely nyuzenamides A and B, from deep sea water *Streptomyces* collected from Sea of Japan. Nyuzenamide A exhibited potent antifungal activity against human and plant pathogen, *Trichophyton rubrum* NBRC5467 and *Glomerella cingulata* NBRC5907 with the minimum

inhibitory concentration (MIC) values of 6.3 and 3.1 μg/mL, respectively, while nyuzenamide B was weakly active against these two fungi with the MIC value of 25 μg/mL. Maribasins C-E and maribasins A-B, cyclic lipopeptides isolated from marine gorgonian-associated fungus *Aspergillus* sp. SCSIO 41501 (Trichocomaceae), exhibited antifungal activity against five fungal strains such as *Fusarium oxysporum, Curvularia australiensis, Pyricularia oryzae, Alternaria solani, and Colletotrichum gloeosporioiles* with the MIC values of 3.12–50 μg/disc (Yao et al., 2021).

Moreover, a bicyclic glycopeptide theonellamide G extracted from Red Sea sponge *Theonella swinhoei* inhibited the activity of wild and amphotericin-B-resistant strains of *C. albicans*, with an IC_{50} of 4.49 and 2.0 μM, respectively (Youssef et al., 2014). Gageopeptides A-D, discovered from the marine based bacterium *Bacillus subtilis*, showed antifungal effects towards pathogenic fungi *P. capsica*, *C. acutatum*, *R. solani*, and *B. cinerea* with MIC values of 0.02-0.06 μM (Tareq et al., 2014a). In addition, mohangamide A, a dilactone-tethered pseudodimeric peptide, was identified from a marine-derived *Streptomyces* sp. Mohangamide A was active against *C. albicans* isocitrate lyase with an IC_{50} value of 4.14 mg/mL (Bae et al., 2015).

2. Antibacterial

Living organisms use antibacterial peptides as an important tool to combat bacterial infections. Daptomycin and vancomycin are the well-established antibacterial peptide. MIC values of daptomycin is typically ≤1 μg/mL against all MRSA isolates (Moses et al., 2020) and MIC value of vancomycin against vancomycin-sensitive *S. aureus* is ≤2 μg/mL (Wang et al., 2006). Marine environment is a rich source of antibacterial peptides with new discoveries. These peptides can act against a broad spectrum of bacteria including both Gram-positive and Gram-negative bacteria. For instance, Oreoch-1, isolated from Teleost fish, tilapia gills *Oreochromis niloticus,*

was active against Gram-positive bacteria, namely *B. subtilis* (MIC = 3 μM) and *S. aureus* (MIC = 5 μM), and Gram-negative bacteria such as *E. coli* (MIC = 6.7 μM) and *P. aeruginosa* (MIC = 35 μM) (Acosta et al., 2013). Further, SpHyastatin, obtained from Crab *Scylla paramamosain*, had potential effect towards Gram-positive bacteria (*S. aureus*, *Micrococcus luteus*, *Micrococcusluteus*, and *Corynebacterium glutamicum*), and Gram-negative bacteria (*Pseudomonas stutzeri*, *Aeromonashydrophila*, and *P. fluorescens*) with MIC values in the range of 0.63-2.5 μM (Shan et al., 2016).

Chemical investigation of Antarctic Fish *Parachaenichthys charcoti* yielded a moronecidin-like peptide called MoroPC-NH_2, which exhibited antibacterial activity against Gram-positive *S. aureus*, *L. monocytogenes*, and *Streptococcus pyogenes* with MICs < 5 μM and Gram-negative *Psychrobacter* sp., *E. coli* DH5α, and *Shigella sonnei* with MICs < 5 μM (Shin et al., 2017). *Venerupis philippinarum* defensin (VpDef), obtained from a clam *Venerupis philippinarum*, displayed potent antibacterial properties against *Micrococcus luteus* (MIC = 6.25-12.5 μM) and *Enterobacter aerogenes* (MIC = 12.5-25 μM) (Zhang et al., 2015a). In addition, Qin et al. (2014) extracted Mytichitin-CB, an antimicrobial peptide with 55 amino acid residues, from Hemolymph of *Mytilud coruscus.* This peptide was effective against different species of bacteria, including *S. luteus*, *B. subtilis*, *B. megaterium*, and *S. aureus* with MIC values < 5 μM. SA-hepcidin2, a cysteine rich antibacterial peptide isolated from spotted scat fish *Scatophagus argus*, exhibited activity against *S. aureus*, *Vibrio anguillarum*, and *V. alginolyticus* with MIC values of 50 μM (Gui et al., 2016). Antibacterial activities of marine derive peptides discovered after 2010 are explained in Table 1.

3. Antiviral

Antiviral peptides are short-chain peptides with 12-50 amino acid residues. Among all the general characteristics of antimicrobial peptides, hydrophobicity is the key feature for antiviral peptides to act against enveloped viruses (Wang et al., 2017), particularly hydrophobic cysteine residues that are abundant in antiviral peptides (Mishra et al., 2012). The mechanism of action of antiviral peptides includes direct inhibition of viral pathogenesis or host cell infection by directly binding to the viral target and indirect inhibition by attaching to the target site on the host surface, inhibiting viral enzymes associated with intracellular replication and transcription, and suppressing viral gene expression (Kausar et al., 2021; Gao et al., 2021). Enfuviride is a common antiviral peptide drug and its IC_{50} value is in the range of 0.01 to 0.1 μM against HIV-1.

Ford et al. (1999) found that cyclic depsipeptides papuamides A and B, derived from sponges *Theonella mirabilis* and *Theonella swinhoei*, inhibit the infection of HIV in T-lymphoblastic cells. Marine sources are regarded as potential therapeutics to treat HIV and have gained much attention as natural anti-HIV compounds due to the several side effects, resistance, and toxicity of commercially available anti-HIV drugs (Singh and Bodiwala, 2010). Examples of compounds exhibiting anti-HIV activities include mollamide F, stellettapeptines A and B, malformin C, mirabamides E-H, and divamide A (Sukmarini, 2022). Certain peptides have also proven to exhibit potent antiviral activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), an epidemic associated with high rates of mortality. Plitidepsin, a cyclic depsipeptide originally identified from tunicate *Aplidium albicans*, has been shown to possess antiviral activity against SARS-CoV-2 with 90% inhibitory concentration of 0.88 nM (White et al., 2021). Table 2 summarizes some antiviral peptides derived from marine sources.

4. Anticancer

Numerous anticancer peptides have been isolated from different marine sources, such as sponges, fungi, ascidians, cyanobacteria, fish, and mollusks. For example, nearly 2500 new peptides with anti-cancer activities have been discovered from marine flora from 2002 to 2012 (Malaker and Ahmad, 2013). Currently, various novel marine-derived anti-tumor peptides and their derivatives have been largely used in clinical research (Dyshlovoy and Honecker, 2020). Anticancer potential of bioactive peptides is mainly dependent on the structural properties of peptides attributed to their varying unusual amino acid residues (Cheung et al., 2015).

Mechanism of anti-cancer activity of peptides include induction of apoptosis, inhibition of cell migration, prevention of cell cycle arrest, and disorganization of tubulin structure (Srinivasan et al., 2020). Cancer cell apoptosis caused by peptides is mainly through the collapse of cellular membrane. Overall charge of the outer surface of the of cancer cells is negative due to their higher concentration of anionic phosphatidylserine. Therefore, cationic anticancer peptides can bind to the surface of the cell membrane and cause their breakdown and prompt cell apoptosis (Yang et al., 2013). Bortezomib (Velcade®), peptide-based proteasome inhibitor, is a well-known anticancer drug with the IC_{50} of 1.9 to 10.2 nM against multiple myeloma cell lines (Shabaneh et al., 2013). However, IC_{50} values vary depending on the specific target cell lines.

Cyanobacteria are considered as a remarkable source of bioactive peptides exhibiting anticancer activities. Different types of anticancer peptides derived from cyanobacteria include apratoxins A-D, coibamide A, bisebromoamide, aurilide B and C, cryptophycin, hectochlorin, grassypeptolide A-E, desmethoxymajusculamide C, coibamide A, desmethoxymajusculamide C, hantupeptin A, itralamide A and B, hormothamnin A, largazole, lagunamide A-C, symplocamide A, laxaphycin A and B, and tasiamide B, among others. Apratoxin A, a cyclic

depsipeptide isolated from cyanobacterium *Lyngbya majuscule*, exhibited anticancer activity in human tumor cell lines such as epidermal KB carcinoma cancer cells and LoVo colon carcinoma cancer cells, with IC_{50} values of 0.52 and 0.36 nM, respectively (Luesch et al., 2002). Apratoxin D showed *in vitro* cytotoxicity against H-460 lung cancer cells with IC_{50} value of 2.6 nM (Gutiérrez et al., 2008).

Anti-proliferative peptides derived from marine fungi include azonazine, sansalvamide A, and scopularides A and B and tunicates include aplidin and didemnin B. Chemical analysis of *Fusarium* sp. derived from marine plant *Halodule wrightii* yielded a cyclic depsipeptide, sansalvamide A exhibiting cytotoxic activity towards several cell lines, namely colon, pancreatic, prostrate, breast sarcoma, and melanoma cancer cell lines (Vasko et al., 2010), while azonazine, obtained from *Aspergillus insulicola* (collected from Hawaiian marine sediments), displayed cytotoxic activity in HCT-116 cell line with IC_{50} value < 15 ng/mL (Wu et al., 2010). Didemnin B, discovered from marine tunicate *Tridemnum solidum*, exhibited potent anti-tumor activity towards human prostatic cancer cell line with IC_{50} value of 2 ng/mL in L1210 leukemia cells and antiproliferative properties on B16 melanoma and P388 leukemia cells (Kotoku et al., 2006).

Sponge-derived peptides, mainly cyclodepsipeptides, display a wide range of anticancer activities. Examples of these peptides are arenastatin A, geodiamolide H, homophymine A-E, discodermin A-H, hemiasterlin A and C, orbiculamide A, koshikamide B, jaspamide, microcionamide A and B, scleritodermin A, papuamide A-F, and rolloamide A. Exploration of marine sponge *Scleritoderma nodosum* resulted in the isolation of a cyclic peptide Scleritodermin A, which exhibited *in vitro* anticancer activities towards different human cancer cell lines such as A2780 ovarian carcinoma, HCT116 colon carcinoma, and SKBR3 breast carcinoma with IC_{50} values of 0.94, 1.92, and 0.97 μM, respectively (Liu et al., 2008; Schmidt et

al., 2004). Some other examples of marine peptides possessing anticancer activities are presented in Table 3.

B. Alkaloids

Alkaloids are a broadly distributed and a vastly diverse group of compounds. Depending on their chemical structure, biosynthetic pathway, biological activity, and heterocyclic and non-heterocyclic composition, alkaloids can be classified in several subclasses such as indole alkaloids, guadinine alkaloids, sterol alkaloids, pyridoacrine alkaloids, isoquinoline alkaloids, aminoimidazole alkaloids, and pyrrole alkaloids. A variety of biologically active metabolites containing an indole ring have been identified from marine sponges. They include tryptophan/tryptamine derivatives, clionamide, topsentin A, jaspamide, and fascaplysin, among others (Roll et al., 1988; Andersen et al., 1979). Marine-based alkaloids, a large and structurally diverse group of natural products, are used in the development of several antibacterial drugs.

1. Antifungal

Berberine is a well-known antifungal supplement extracted from natural sources, exhibiting antifungal properties against *Candida* species. It exhibits varying MIC against different *Candida* species between 16 μg/mL against *C. krusei* and >128 μg/mL against *C. haemulonii* (Freile et al., 2003). Studies on Australian marine sponge *Xestospongia exigua* yielded dimeric 2,9-disubstituted 1-oxaquinolizidine alkaloids xestospongin A, C, and D (Moon et al., 2002; Nakagawa et al., 1984). Demethylxestospongin C and xestospongin A, C, and D (Figure 6) exhibited moderate inhibitory effect towards a fluconazole-resistant *C. albicans* ATCC 14503 strain with the MIC value of 100 μg/mL (Moon et al., 2002).

Haga et al. (2013) isolated four novel 4-hydroxy-2-pyridone alkaloids, didymellamides A-D, from the marine-based fungus *Stagonosporopsis cucurbitacearum*. They found that didymellamide A displayed antifungal effect against azole-resistant and -susceptible *C. albicans*, *C. glabrata*, and *Cryptococcus neoformans* (MIC = 1.6 or 3.1 μg/mL) and didymellamide B acted against *C. neoformans* (MIC = 6.3 μg/mL), whereas didymellamides C and D exhibited no effect against fungi. Therefore, it was proposed that hydroxamic acid moiety has an influence on the antifungal property of alkaloids. Moreover, caerulomycin A (Figure 7), isolated from the marine actinomycete *Actinoalloateichus cyanogriseus*, inhibited two fluconazole-resistant *C. krusei* GO3 and *C. glabrata* HO5 (MICs in the range of 0.39–1.56 μg/mL) (Ambavane et al., 2014).

Evaluation of antifungal activity of an alkaloid 5-bromo-8-methoxy-1-methyl-β-carboline (Figure 7), purified from New Zealand bryozoan *Pterocella vesiculosa*, proved its inhibitory effect against *C. albicans* and *Trichophyton mentagrophytes* (MID = 4-5 μg/mL) (Till and Prinsep, 2009). Takahashi et al. (2012) isolated nakijinamines A, B, F-I, and 6-bromoconicamin from an Okinawan marine sponge *Suberites* sp. and evaluated their antimicrobial properties. It was found that nakijinamine A (Figure 7) exhibited antifungal action towards *C. albicans* (IC_{50} = 0.25 μg/mL), *Trichophyton mentagrophytes* (IC_{50} = 0.25 μg/mL), and *C. neoformans* (IC_{50} = 0.5 μg/mL), whereas nakijinamines B and C (Figure 7) inhibited the growth of *C. albicans* (IC_{50} = 8 μg/mL).

Investigation of Okinawan marine sponges *Hyrtios* spp. led to the discovery of novel indole alkaloids, hyrtimomines A-C (Momose et al., 2013), hyrtimomines D and E (Tanaka et al., 2013a), and hyrtimomines F-K (Tanaka et al., 2014). Hyrtimomine A showed inhibitory activity against *A. niger* (IC_{50} = 4.0 μg/mL), while hyrtimomines A and B (Figure 8) were active against

C. neoformans (IC_{50} = 2.0 and 4.0 μg/mL, respectively) and *C. albicans* (IC_{50} = 1.0 μg/mL each). Hyrtimomines F, G, and I (Figure 8) showed antifungal effect towards *Aspergillus niger* (IC_{50} = 8.0 μg/mL each) and hyrtimomine I inhibited *C. neoformans* (IC_{50} = 4.0 μg/mL) (Tanaka et al., 2014). Recently, two novel quinazoline indole alkaloids, fumigatosides E and F (Figure 8), were discovered from the deep-sea fungus *Aspergillus fumigatus* SCSIO in the Indian Ocean. Fumigatosides E exhibited strong antifungal activity against *Fussarium oxysporum* sp. *momordicae* and moderate inhibitory effect towards *F. oxysporum* sp. *cucumerinu* (Limbadri et al., 2018).

Hyrtinadines C and D, new bisindole alkaloids, were extracted from a marine sponge *Hyrtios* sp. (Okinawa, Japan). Hyrtinadine C exhibited inhibitory activity against *A. niger* with IC_{50} value of 32 µg/mL (Kubota et al., 2016). Kubota et al. (2015) identified two novel bromotyrosine alkaloids, tyrokeradines G and H, from a marine sponge of the order Verongida (Okinawa, Japan). Both compounds displayed antifungal effect towards *A. niger* with IC_{50} value of 32 µg/mL for each, whereas tyrokeradine G was active against *Cryptococcus neoformans* (IC_{50} = 16 µg/mL). Bromopyrrole alkaloids namely, longamides D-F, 2-oxethyl-3-[1-(4,5-dibromopyrrole-2-yl)-formamido]-methyl propionate, and 3-oxethyl-4-[1-(4,5-dibromopyrrole-2-yl)-formamido]-butanoic acid methyl ester , isolated from the South China Sea sponge *Agelas* sp., showed antifungal activity versus *C. albicans* in a *Caenorhabditis elegans* candidiasis model (Zhu et al., 2016).

South China Sea sponge *Agelas nakamurai* derived diterpene alkaloids, such as isoagelasine C, agelasine B, agelasine J, nemoechine G, isoagelasidine B, and (-)-agelasidine C, exhibited potential antifungal effect towards *C. albicans* (MICs ranging from 0.59 to 4.69 µg/mL) (Chu et al., 2017). Chemical investigation of an Okinawan marine sponge *Amphimedon* sp. yielded a

new manzamine alkaloid zamamidine D, which was active against *Cryptococcus neoformans* IFM62681and *Trichophyton mentagrophytes* IFM62679 with IC_{50} values of 2 and 8 μg/mL, respectively (Kubota et al., 2017). Recently, Shaala et al. (2021) discovered two dimeric alkaloids fusaripyridines A and B from the organic extract of the fungus *Fusarium* sp. LY019 associated with Red Sea sponge *Suberea mollis*. Both compounds exhibited antifungal activity versus *C. albicans* with MIC value of 8.0 μM.

In a recent study, the analysis of South China Sea fungus *Talaromyces mangshanicus* BTBU20211089 resulted in the discovery of seven new compounds such as talaromydene, talaromylectone, talaromanloid A, ditalaromylectones A and B, 10-hydroxy-8-demethyltalaromydine, and 11-hydroxy-8-demethyltalaromydine, along with seven known natural products. Among these compounds, ditalaromylectones A and B exhibited antifungal activity towards *C. albicans* with an MIC value of 200 μg/mL (Zhang et al., 2022). Indolepyrazines A and B, obtained from marine based *Acinetobacter* sp. ZZ1275, exhibited antifungal activity against *C. albicans* with MIC value of 12-14 μg/mL (Anjum et al., 2019). Furthermore, two diketopiperazine alkaloids cyclo(L-Phe-cis-4-OH-D-Pro) and cyclo(L-Phe-trans-4-OH-L-Pro) were isolated from a sponge *Callyspongia siphonella* derived actinomycete strain *Streptomyces coelicolor* LY001. Both compounds were more active against *C. albicans* with MIC of 32 μg/mL (Shaala et al., 2020). Eutypellenoid B, isolated from Arctic fungi *Eutypella* sp. D-1, displayed inhibitory effect towards *C. albicans, C. parapsilosis, C. tropicalis*, and *C. glabrata* with MIC values of 8, 8, 32, and 16 μg/mL, respectively (Yu et al., 2018a). Some examples of marine based alkaloids exhibiting antifungal activities are presented in Table 4.

2. Antibacterial

Alkaloids groups such as pyrrolidines, pyrrolizidines, indoles, quinazolines, quinolines, diketopiperazines, and purines exhibit antibacterial activities. Mechanism of action of antibacterial activity of most alkaloids is the inhibition of efflux pump (Cushnie et al., 2014). Recently, Wang et al. (2022a) identified six novel phenethylamine-containing alkaloids, dispyridine, discolins A and B, dispyrrole, and dispyrrolopyridine A and B, from predatory bacterium *Tenacibaculum discolor* sv11. Among these compounds, dispyrrole exhibited moderate inhibitory activity towards Gram-positive bacteria. Dispyrrolopyridine A and B displayed strong activity against *B. subtilis* DSM10, *Mycobacterium smegmatis* ATCC607, *S. aureus* ATCC25923, and *L. monocytogenes* DSM20600 with MIC values ranging from 0.5 to 4 μg/mL, whereas dispyrrolopyridine A showed potent activity against efflux pump deficient *E. coli* ATCC25922 (MIC = 8 μg/mL) and *Caenorhabditis elegans* N_2 (MIC = 32 μg/mL).

Exploration of deep-sea sediment-derived fungus *Aspergillus fumigatus* SCSIO41012 yielded two new alkaloids fumigatosides E and F (Figure 9) along with five known compounds. Among these compounds, fumigatosides F exhibited antibacterial activity against *Acinetobacter baumannii* ATCC 19606 with a MIC value of 6.25 μg/mL (Limbadri et al., 2018). Pyrrospirone C–F and I (Figure 9), obtained from Fungus *Penicillium* sp. ZZ380, derived from a wild crab (*Pachygrapsus crassipes*), inhibited the growth of Gram-negative *E. coli* and Gram-positive *S. aureus* with MIC values of 3.0 μg/mL and 1.7 μg/mL, respectively (Song et al., 2019). A list of alkaloid compounds with the potential antibacterial activities is presented in Table 5.

3. Antiviral

Sun et al. (2015) isolated several tetramic acid derivatives containing a decalin ring, such as trichobotrysins A, B and D, from the culture of fungal stain *Trichobotrys effuse*, collected from

deep sea sediment of South China Sea. These natural products exhibited potential activity towards HSV-1 with IC_{50} values of 3.08, 9.37 and 3.12 μM, respectively. Recently, El-Demerdash and coworkers explored the antiviral potential of fourteen structurally diverse brominated tyrosine alkaloids against five SARS-CoV-2 proteins. Among all tested compounds, the polybrominated alkaloid, fistularin-3, exhibited antiviral properties against protease, spike glycoprotein, nucleocapsid phosphoprotein, membrane glycoprotein and non-structural protein of SARS-CoV-2 (El-Demerdash et al., 2021).

Chemical investigation of marine-derived fungus *Penicillium raistrickii* yielded Raistrickindole A and raistrickin, exhibiting *in vitro* antiviral activity against Hepatitis C virus with E_{50} values of 5.7 and 7.0 μM, respectively (Li et al., 2019a). Neosartoryadins A and B, having pyrido [2,1-b]-quinazoline framework and a tetrahydrofuran ring, were purified from the endophytic fungus *Neosartorya udagawae*. Both Neosartoryadins A and B inhibited the activity of H1N1 with IC_{50} values of 66 and 58 μM, respectively (Yu et al., 2016). Trypilepyrazinol, extracted from marine-derived fungus *Penicillium* sp., displayed antiviral properties towards human immunodeficiency virus (HIV) and hepatitis C virus with IC_{50} values of 4.6 and 7.7 μM, respectively (Li et al., 2019b). Polycitone A, an aromatic alkaloid isolated from *Polycitor* sp. (ascidian), inhibited the reverse transcriptase and DNA polymerases of HIV and retroviruses (Loya et al., 1999).

4. Anticancer

A large number of cyclic nitrogen and amine-containing alkaloids derived from marine sources displayed potent anticancer activities. Vincristine is an example of established anticancer alkaloid drug, which can induce apoptosis in tumor cells with IC_{50} values of 0.1 μM (Donoso et al., 1977). Several scientists have investigated the anticancer properties of marine alkaloids. In a recent study, Wang et al. (2020) identified that ascomylactam A, an alkaloid isolated from

mangrove endophytic fungus *Ascomycota* sp., suppressed the growth of A549 and NCI-H460 tumor cells (6 mg/kg/day) in male BALB/c-nu mice. Moreover, (−)-Agelamide D (1), isolated from marine sponge *Agelas* sp., aided the cancer treatment in xenograft Hep3B cells by increasing the radiation therapy efficiency (Choi et al., 2020). Recently, Dyshlovoy et al. (2020) reported that monanchoxymycalin C, isolated from marine sponge *Monanchora pulchra*, possess cytotoxic activity towards human prostate cancer by JNK1/2 activation and non-apoptotic cell death. Antiviral activities of some marine derived alkaloids are given in Table 6.

In another study, 4-chlorofascaplysin, found in marine sponges, exhibited antiangiogenic activity in mice with human breast cancer MDAMB- 231 via decreasing VEGFs levels (Sharma et al., 2017). Medellin et al. (2016) reported that C2-substituted 7-deazahypoxanthine showed inhibitory effect of tumor growth in animals xenografted with colon cancer SW620. Moreover, reduction of tumor growth in epidermoid-nasopharyngeal and colon cell lines was observed in nude mice supplemented with neoamphimedine, extracted from marine sponge *Xestospongia* sp. (Marshall et al., 2003).

C. Polyketides

Polyketides are a large group of biologically active secondary metabolites with varying chemical structures and functionalities. Polyketides contain various β-hydroxyaldehyde and β-hydroxyketone functional groups and are highly oxygenated. Examples of polyketides include macrolides, polyols, polyethers, and aromatic compounds.

1. Antifungal

Marine-derived antifungal polyketides include aurantosides, forazoline, hippolachnin, and woodylide. Aurantosides are a group of compounds produced by sponge genera *Theonella*,

Siliquariaspongia, and *Homophymia*. They contain a N-glycosidic part of one to three monosaccharides and a tetramate ring with a mono- or dichlorinated long conjugated polyene chain (Kumar et al., 2012; Angawi et al., 2011). Aurantosides were originally obtained as antifungal and cytotoxic constituents and later found to inhibit binding of interleukin-6 to its receptors (Beutler et al., 1988; Schabacher and Zeeck, 1973). Aurantosides A and B are polyketide metabolites isolated from the marine sponge *Theonella swinhoei* (Matsunaga et al., 1991). Wolf et al. (1999) isolated aurantoside C from the Philippine sponge *Homophymia conferta* (Theonellidae).

Later, Sata et al. (1999) isolated aurantosides D, E, and F, new polyene tetramic acids comprising an N-trisaccharide units, from the marine sponge *Siliquariaspongia japonica*. Their structures were determined by spectral and chemical methods, and the NMR data of the previously discovered aurantosides A and B were reinvestigated. It was found that aurantosides A, B, D, and E exhibited potential antifungal effect towards *Aspergillus fumigatus* and *Candida albicans*. Angawi et al. (2011) isolated a new aurantoside J along with three known aurantosides G-I from an Indonesian sponge *Theonella swinhoei*. The antifungal activity of these four compounds were tested against four *Candida* and one *Fusarium* fungal strains, which cause fungal infections in immune-compromised patients. Only aurantosides G and I exhibited detectable antifungal effect. Aurantoside I showed strong antifungal activity against all the tested strains, particularly towards *C. albicans*, *C. tropicalis*, and *C. glabrata*, while aurantoside G exhibited only moderate to poor effect towards all the tested strains with the MIC_{90} of 4-16 μg/mL. The C18 polyene chain and three sugar chains linked to the tetramate ring by the nitrogen atom of the compound Aurantoside I are responsible for the inhibition of the growth of five fungal strains. Aurantoside K, a novel tetramic acid glycoside, was discovered from a marine sponge *Melophlus* sp. This compound

displayed antifungal effect towards wild type *C. albicans* and amphotericin-resistant *C. albicans* with the MIC values of 1.95 and 31.25 µg/mL, respectively. In addition, it showed potent inhibitory activity against pathogenic *Penicillium* sp., *Sordaria* sp., *Aspergillus niger*, *Cryptococcus neoformans*, and *Rhizopus sporangia* (Kumar et al., 2012). Figure 10 depicts the chemical structures of Aurantoside A-I.

Wyche et al. (2014) isolated forazoline A (Figure 11), a novel polyketide, from a marine invertebrate-associated bacteria *Actinomadura* sp. Forazoline A exhibited *in vivo* antifungal activity against *C. albicans* in a mouse model by affecting their cell membranes via dysregulating the phospholipid homeostasis. Chemical investigation of South China Sea sponge *Hippospongia lachne* resulted in the discovery of Hippolachnin A (Figure 11), a polyketide with a four-membered ring and an unprecedented carbon skeleton. This compound exhibited potential inhibitory activity at MIC value of 0.41 µM against pathogenic fungi *Trichophyton rubrum*, *Cryptococcus neoformans*, and *Microsporum gypseum* (Piao et al., 2013). Yu et al. (2012) identified three novel polyketides woodylides A-C (Figure 11) from Southern China Sea sponge *Plakortis simplex*, collected from Xisha islands. Woodylides A and C displayed moderate antifungal effect towards fungi *Cryptococcus neoformans* with IC_{50} values of 3.67 and 10.85 µg/mL, respectively.

2. Antibacterial

Erythromycin, belongs to macrolide class, is an established antibiotic drug for various infections with MIC values in the range of 0.25 to 2 µg/mL against *S. aureus* (Champney, 2003). Difficidins, a class of polyketides, were derived from a heterotrophic *Bacillus amyloliquefaciens* MTCC12713 associated with the red macroalga *Kappaphycus alvarezii*. Difficidin analogues displayed antibacterial effect towards methicillin-resistant *Staphylococcus aureus*, vancomycin-

resistant *Enterococcus faecalis*, and other drug-resistant strains, namely *Pseudomonas aeruginosa* and *Klebsiella pneumonia* with the MIC values in the range of 2-9 x 10^{-3} μM (Chakraborty et al., 2021). The compound 5-methoxydihydrosterigmatocystin, extracted from *Aspergillus versicolor* MF359 associated with a marine sponge *Hymeniacidon perleve*, exhibited antibacterial effect against *B. subtilis* and *S. aureus* with MIC values of 3.125 and 12.5 μg/mL, respectively (Song et al., 2014b). A polyketide compound, produced by the filamentous actinomycete SCA-7 (Alkhobar marine region), exhibited bactericidal activity against Gram-positive *Enterococcus* sp. (Almalki, 2020). The compound α,2,5-trihydroxyacetophenone, an aromatic polyketide extracted from marine based fungus *Pseudopithomyces maydicus* PSU-AMF350, exhibited bactericidal activity against *Acinetobacter baumannii*, *S. aureus*, and *A. baumannii* (MIC = 200 μg/mL) and methicillin-resistant *S. aureus* (MIC = 128 μg/mL) (Ningsih et al., 2022).

Yao et al. (2014) isolated engyodontiumones A-H and eight known polyketides from the deep-sea fungus *Engyodontium album* DFFSCS021. They found that engyodontiumones H, aspergillusone B, and AGI-B4 (Figure 12) inhibited the growth of *B. subtilis* and *E. coli*. Chemical investigation of deep-sea sediment derived fungus *Emericella* sp. SCSIO 05240 yielded four new prenylxanthones, emerixanthones A-D, along with six known analogues. Emerixanthones A and C (Figure 12) were weakly active against *Klebsiella pneumonia*, *Acineto bacterbaumannii*, *E. coli*, *S. aureus*, *Aeromonas hydrophila*, and *Enterococcus faecalis* (Fredimoses et al., 2014). An anthraquinone compound, isorhodoptilometrin-1-methyl ether (extracted from *A. versicolor*) was active against three Gram-positive bacterial strains *B. subtilis*, *B. cereus*, and *S. aureus* (Hawas et al., 2012). Trichodermaquinone and trichodermaxanthone, along with eleven known compounds were identified from the marine based fungus *Trichoderma*

aureoviride PSU-F95. Among these compounds, coniothranthraquinone 1 (Figure 12) and emodin showed potent inhibitory effect towards methicillin-resistant *S. aureus* with MIC values of 8 and 4 μg/mL, respectively (Khamthong et al., 2012).

3. Antiviral

Acyclovir, structurally resembling to polyketide, is a drug used to treat chickenpox and herpes virus infections with IC_{50} values between 0.12 and 10.8 μg/mL against varicella zoster virus (FDA, 2019). Truncateol M, an isoprenylated cyclohexanols, was isolated from a sponge (*Amphimedon* sp.) derived fungus *Truncatella angustata* from South China Sea. It suppressed influenza virus by inhibiting H1N1 virus with an IC_{50} value of 8.8 μM (Zhao et al., 2015). Asteltoxins E and F, isolated from marine-derived fungus *Aspergillus* sp., displayed inhibitory activity towards H3N2 with the IC_{50} values of 6.2 and 8.9 μM, respectively, whereas Asteltoxin E showed antiviral property towards H1N1 with an IC_{50} value of 3.5 μM (Tian et al., 2015). Huang et al. (2018) isolated neoabyssomicin D from marine derived *Streptomyces koyangensis* exhibiting mild antiviral activity towards herpes simplex virus at a concentration of 10 μM. Pestalotiolide A, obtained from a marine based fungus *Pestalotiopsis* sp., displayed considerable anti-EV71 activity *in vitro* with an IC_{50} value of 27.7 μM (Jia et al., 2015).

A weak *in vitro* antiviral activity was exhibited by coniochaetone J, extracted from a deep-sea derived sediment fungus *Penicillium* sp., against EV71 with an IC_{50} value of 81.6 μM (Liu et al., 2017a). Chemical investigation of deep-sea derived fungus *Spiromastix* sp. led to the discovery of several phenolic lactones such as spiromastilactones B, D-G, I-J and L. These compounds showed inhibitory activities against WSN influenza virus with IC_{50} values ranging from 6.0 to 74.9 μM (Niu et al., 2016). Wailupemycin J and R-Wailupemycin K, purified from the cultures

of *Streptomyces* sp. associated with the marine green algae, *Ulva prolifera* (formerly *Enteromorpha prolifera*), suppressed the activity of H1N1 virus (Liu et al., 2017b).

D. Polyphenols

Polyphenols are secondary metabolites containing multiple phenol rings. Phenolics produce by marine organism display a wide array of biological activities including anticancer activity. Based on their chemical structures, they are classified into different groups, including flavonoids, phenolic acids, lignans, and stilbenes.

1. Antibacterial

Song et al. (2018) isolated penicipyrrodiether A, a phenol A derivative, from a marine associated fungus *Penicillium* sp. ZZ380 and examined their antibacterial activities. It was found that penicipyrrodiether A exhibited inhibitory activity against methicillin-resistant *S. aureus* with a MIC values of 5.0 μg/mL.

2. Anticancer

Excellent antioxidant property (radical scavenging) of the phenolics is responsible for their anticancer activity since reactive oxygen species (ROS) initiate the growth and proliferation of cancer cells (Aggarwal et al., 2019). In addition, alteration of the proliferation signal pathways and reduction of the telomerase expression are also included in the mechanisms of anticancer property of phenolic compounds (Mateos and Pérez-Correa, 2020). Different types of phenolic metabolites such as flavonoids, pholorotannins, coumarins, bromophenols, quinones, hydroquinones, and terpenophenolics exhibit anticancer activities.

Investigation of fungus *Penicillium chrysogenum* cultured from a gorgonian *Carijoa* sp. (South China Sea) yielded a flavone, penimethavone A. This compound displayed anticancer activities

towards rhabdomyosarcoma and cervical cancer (HeLa) cell lines with IC_{50} values of 8.18 and 8.41 μM, respectively (Hou et al., 2016). Phloroglucinol (pholorotannins), isolated from brown seaweeds, enhanced the anticancer effects of 5-fluorouracil towards HT29 colorectal cancer cell lines (Lopes-Costa et al., 2017). Two coumarin compounds, alternariol and alternariol methyl ether, were extracted from the fungus *Alternaria alternata* collected from soft coral *Litophyton arboreum*, collected from the Egyptian Red Sea coast. Alternariol displayed antiproliferative activities verses leukemia cell lines such as L1210 and CCRF-CEM, while alternariol methyl ether showed antitumor activities towards the leukemia cell lines of H-125 and Colon-38 (Hawas et al., 2015).

Qu et al. (2019) isolated four angucycline glycosides (quinones and hydroquinones) from marine-derived *Streptomyces* sp. OC1610.4 and investigated their cytotoxic activities. Among which, moromycin B, saquayamycin B_1, and saquayamycin B exhibited potent antitumor activities towards breast cancer cells MCF-7, MDA-MB-231, and BT-474 with IC_{50} values in the range of 0.16–0.67 μM. Bis (2,3-dibromo-4,5-dihydroxy-phenyl)-methane, a bromophenol compound derived from marine algae, exhibited anticancer activity on different tumor cells such as RKO, HeLa, U87, Bel7402, and HCT116 with IC_{50} values of 11.37, 17.63, 23.69, 8.7, and 10.58 μg/mL, respectively (Wu et al., 2015b). Laurebiphenyl, a terpenophenolic compound isolated from red macroalga *Laurencia tristicha*, showed moderate antiproliferative activity against stomach cancer (BGC-823), lung adenocarcinoma (A549), colon cancer (HCT-8), hepatoma (Bel 7402), and HeLa cell lines with IC_{50} values of 1.22, 1.68, 1.77, 1.91, and 1.61 μg/mL, respectively (Sun et al., 2005). Anticancer activities of certain marine phenolics are depicted in Table 7.

Considering the *in vivo* studies, dieckols, isolated from seaweeds *Eisenia bicyclis*, *Ecklonia cava*, and *Ecklonia stolonifera*, were administered to ovarian carcinoma induced Bald/c athymic female nude mouse for four weeks. Results of the study showed that dieckols suppressed the tumor growth of ovarian cancer (Ahn et al., 2015). Similarly, Sadeeshkumar et al. (2017) showed that dieckols acted against N-nitrosodiethylamine-induced hepatocarcinogenesis in male albino Wistar rats through promotion of apoptosis and modulation of cell proliferation.

E. Terpenoids

Terpenoids (isoprenoid compounds), derived from five carbon isoprene units, are a large group of natural compounds present in nature. A wide range of terpenoid structures with varying structural properties are synthesized by marine organisms. Different classes of marine terpenoids include monoterpenes, sesquiterpenes, diterpenes, triterpenes, sesterterpenes, and meroterpenes (Gozari et al., 2021).

1. Antifungal

Asolkar and coworkers isolated marinocyanin A-F, bromo-phenazinone meroterpenoids, from the cultures of CNS-284 and CNY-960 strains of actinomycetes collected from the marine sediments of Solomon Islands. Among these compounds, marinocyanin A exhibited potent antifungal activity towards amphotericin resistant *C. albicans* with MIC value equal to 0.95 mM (Asolkar et al., 2017). Insuetolides A, a meroterpenoid extracted from cultures of fungi *Aspergillus insuetus* (OY-207) associated with Mediterranean sponge *Psammocinia* sp., showed moderate antifungal properties against *Neurospora crassa* with a MIC value of 140 mM (Cohen et al., 2011).

2. Antibacterial

Micromonohalimane B, isolated from actinomycete *Micromonospora* sp. associated with ascidian, *Symplegma brakenhielmi*, displayed moderate antibacterial effect on methicillin-resistant *S. aureus* with MIC value of 40 mg/mL (Zhang et al., 2016). Xiamycin B, indosespene, sespenine, and xiamycin A, extracted from *Streptomyces* sp. derived from mangrove, displayed antibacterial effect on methicillin-resistant *S. aureus* and vancomycin-resistant *Enterococcus faecalis* (Ding et al., 2010). Marine fungus *Cochliobolus lunatus* SCSIO41401yielded three new eremophilane sesquiterpenes dendryphiellins H-J. Among these compounds, dendryphiellin I exhibited potent antibacterial activity against *S. aureus*, *Pasteurella multocida*, and *Erysipelothrix rhusiopathiae* with MIC values of 1.5, 13, and 13 mg/mL, respectively (Fang et al., 2018).

3. Antiviral

Stachybonoid A, a meroterpenoid, was isolated from fungus *Stachybotrys chartarum*, derived from a crinoid (*Himerometra magnipinna*) from China. This compound inhibited the replication of dengue virus (DENV) (Zhang et al., 2017). Chrodrimanins K and N, meroterpenoids obtained from the cultures of *Penicillium* sp. associated with a marine worm, showed antiviral activity against H1N1 with IC_{50} values of 74 and 58 μM, respectively (Kong et al., 2017). Cao et al. (2019) discovered Talaromyolide D from a marine fungus *Talaromyces* sp. possessing inhibitory activity against pseudorabies virus. Xiamycin A, an indolosesquiterpene, isolated from mangrove-derived *Streptomyces* sp., exhibited selective anti-viral effect on HIV by blocking the R5 strain (Ding et al., 2010).

Moreover, Stachybogrisephenone B, isolated from the sponge associated fungus *Stachybotry* sp., exhibited antiviral effect against EV71 (enterovirus 71) with an IC_{50} value of 30.1 μM (Qin et

al., 2015). Recently, investigated the anti-SARS-CoV-2 potency of sixty-eight antiviral terpenoids isolated from marine sources using an advanced molecular docking study. Among all tested terpenoids, brevione F and stachyflin displayed inhibitory activity towards SARS−CoV−M^{pro}, while xiamycin, liouvilloside B, thyrsiferol, stachyflin, and liouvilloside A showed better docking scores towards SARS-CoV-2−RdRp (Sahoo et al., 2021).

4. Anticancer

Paclitaxel, a terpenoid compound, is a well-known chemotherapeutic agent marketed under the trade name Taxol, among others. The IC_{50} value of paclitaxel towards varying human tumor cell lines is in the range of 2.5 to 7.5 nm (Liebmann et al., 1993). This compound was also found in byproducts of hazelnuts (Hoffman and Shahidi, 2009). Cryptosphaerolide, a sesquiterpenoid derived from an ascidian-derived ascomycete strain, CNL-52, exhibited considerable cytotoxic effect towards HCT-116 cell line with IC_{50} values of 4.5 mM (Oh et al., 2010). Fermentation broth of a fungus *Paraconiothyrium* cf. *Sporulosum* isolated from sponge *Ectyplasia perox* (Lauro Club Reef, Dominica) yielded a meroterpenoid called Epoxyphomalins A-E. Epoxyphomalin D displayed cytotoxic effect on prostate PC3M and bladder BXF1218L cancer cell lines with IC_{50} values of 0.72 and 1.43 mM, respectively (Mohamed et al., 2010). Saccharoquinoline, a cytotoxic alkaloidal meroterpenoid, was extracted from the fermentation broth of marine-based bacteria *Saccharomonospora* sp. CNQ-490. This compound showed potent cytotoxic effect on HCT-116 cancerous cell line (Le et al., 2019).

Chemical investigation of fermentation extract of *Streptomyces* sp. yielded a meroterpenoid, guanahanolide A, which found to have moderate cytotoxicity against HCT-116, HTB-26, and MCF-7 human cancer cell lines with IC_{50} values of 11.9, 10.1, and 7.8 μM, respectively (Marchbank et al., 2020). Pestalachloride B and E and a mixture of pestalalactone atropisomers

were extracted from fungus *Pestalotiopsis heterocornis* derived from sponge *Phakellia fusca*. These compounds exhibited cytotoxic activity towards human cancer cell lines such as BGC-823, H460, PC-3, and SMMC-7721 with IC_{50} values in the range of 6.8–87.8 μM (Lei et al., 2017).

F. Steroids

Steroids and sterols (steroid alcohol), a subgroup of steroids, are important class of organic compounds naturally occurring in marine sources.

1. Antifungal

Wang et al. (2013) isolated seven novel polyoxygenated steroids, along with seven known analogues from *Sarcohyton* sp., a soft coral from South China sea. Result of this study stated that these compounds exhibited varying antifungal activities against *Microbotrym violcem* and *Septoria tritici* in *in vitro* bioassays. Moreover, it is reported that 11 α-acetoxy group might contribute towards the antifungal activity.

2. Antibacterial

Investigation of dendronephthya soft coral collected from Zhejing province, China, resulted in the discovery of four novel steroids, dendronecholones A-D, and two known analogues nanjiol A and 12 β ,16 β ,20-trihydroxycholesta-1,4-dien-3-one 16-acetate. The antibacterial activities of these compounds were tested against thirteen pathogenic Vibrios. It was found that dendronecholones C and nanjiol A exhibited antibacterial activity against *V. parahaemolyticus* with MIC values of 8 μg/mL. Meanwhile, dendronecholones A, B, and nanjiol A showed inhibitory activities towards *V. harveyi* with MIC values of 32, 8, and 8 μg/mL, respectively and all the compounds inhibited the growth of *V. scophthalmi* with MIC values between 8 and 32

μg/mL (Wang et al., 2022b). Moreover, polyoxygenated steroids isolated from soft coral *Sarcohyton* sp. exhibited antibacterial activities against *E. coli* and *B. megaerium* (Wang et al., 2013).

3. Antiviral

Comin et al. (1999) purified polyhydroxysteroids from the Brittle Star *Astrotoma agassizzi*. These compounds were shown to inhibit the growth of three human pathogenic viruses, namely junin virus, herpes simplex virus-2, and polio virus. Exploration of marine based fungus *Penicillium* sp. IMB17-046 resulted in the extraction of a new ergostane analogue, 3β-hydroxyergosta-8,14,24(28)-trien-7-one. This molecule exhibited a wide range of inhibitory activities targeting different types of viruses such as HIV and influenza-A virus with IC_{50} values of 3.5 μM and 0.5 μM, respectively (Li et al., 2019b).

Analysis of the extracts of *Cladosporium* sp., derived from marine sponge, yielded a highly oxygenated sterol Cladosporisteroid B, which displayed weak antiviral properties towards H3N2 with an IC_{50} value of 16.2 μM [240]. A pregnane 3α-hydroxy-7-ene-6,20-dione, isolated from fungus *Cladosporium* sp. derived from a gorgonian *Dichotella gemmacea* (South China Sea), exhibited inhibitory activity towards the respiratory syncytial virus with the IC_{50} value of 0.12 μM (Yu et al., 2018b).

4. Anticancer

Potential anticancer activity of seven steroids such as five 4α-methylated steroids and two 19-oxygenated steroids, identified from soft coral *Litophyton mollis*, has been reported (Eissa et al., 2023). Two isolated 19- oxygenated steroids showed strong cytotoxic effect towards MCF-7 tumor cell lines with IC_{50} values 8.6 and 8.4 μM, respectively, and exhibited moderate activities

in NCI-1299 cancer cell lines with IC_{50} values of 15.7 and 15.1 μM, respectively. In addition, two compounds included in the group of 4α-methylated steroids displayed weak cytotoxic effect against MCF-7, NCI-1299, and HepG2 cancer cell lines with IC_{50} values between 34.7 - 37.5 and 30.8 - 46.3 μM, respectively (Eissa et al., 2023).

IV. Evolution of marine derived drugs

There were several drugs derived from marine organisms that had been approved across various therapeutic areas or were in various stages of development. According to Malve (2016), marine pharmaceuticals undergoing clinical development include 13 compounds in various phases of clinical trials. Moreover, a substantial number of compounds and molecules derived from marine species are undergoing preclinical tastings. As of now, there are six distinct categories of approved therapeutic agents that can be regarded as derivatives of marine natural products. As mentioned in the introduction, two nucleosides, spongothymidine and spongouridine, were discovered from Caribbean sponge *Tethya crypta* in 1951. These compounds let to the synthesis of sugar modified nucleoside analog vidarabine and the related compound cytarabine, which were the first US FDA approved drugs derived from marine sources in the years of 1969 and 1976, respectively. Cytarabine remains in current usage, whereas vidarabine has been discontinued both in US and Europe (Abdelmohsen et al., 2017). Additionally, these compounds can serve as templets for the development of antiviral drugs that that are commercially available (Shahriari et al., 2022).

The first FDA-approved drug directly derived from a marine source is *ω*-conotoxin MVIIA ziconotide (Prialt), a peptide toxin isolated from cone snail venom, and it is used for pain control (Schroeder and Lewis, 2006). Similarly, ecteinascidin 743 (trabectedin, Yondelis), derived from the tunicate *Ecteinascidia turbinate*, was the first anticancer FDA approved drug directly isolated

from marine resources (Erba et al., 2001). Besides, examples of approved marine derived drugs include eribulin mesylate (a synthetic derivative of the polyketide halichondrin B), brentuximab vedotin, Lovaza (a mixture of two ethyl esters of fish-derived ω-3 polyunsaturated fatty acids), Vascepa (pure EPA ethyl ester ω-3 polyunsaturated fatty acid), and Epanova (mixture of three free ω-3 polyunsaturated fatty acids).

Furthermore, the global clinical pipeline for marine pharmaceuticals comprises 23 compounds currently undergoing Phase III, II, or I stages of drug development. Compounds in phase III include plitidepsin, plinabulin, tetrodotoxin, and soblidotin (TZT 1027), while in phase II include DMXBA (GTS-21), gelmbatumumab vedotin, ellsidepsin, PM 1004, tasidotin, synthadotin (ILX-651), and pseudopterpsins and phase I comprise of bryostatin 1, pinatuzumab vedotin (DCDT-2980S) and (DCDS-4501A), hemiasterlin (E7974), HuMax®-TF-ADC, and marizomib. In addition, a large number of marine based compounds are in the preclinical testing pipelines such as chrysophaentin A, phenethylamine, floridosides, pulicatin A, dysidine, capnellane, hymenidin, dysideamine, callyspongidiol and among others (Malve, 2016).

V. Challenges and future trends

Despite the vast potential of marine organisms for the discovery of novel therapeutic compounds, the development of marine-derived pharmaceutical faces several challenges. For instance, environmental conditions of the ocean play a major role in the types of metabolites produced by the same organism each time, which vary with the fluctuating environmental conditions (Martins et al., 2014). The harvesting of rare or slow-growing marine organisms for pharmaceutical research could lead to the overexploitation and ecosystem disruption. Therefore, sustainable harvesting practices need to be developed to ensure the conservation of marine biodiversity. In terms of pharmaceutical study, few grams of the primary compound are required for preclinical

drug development and safety studies, however quantities in kilograms are needed for clinical study in different phases. Thus, availability of primary compound can be an issue because low abundance of such compound makes it technically difficult to isolate from the marine species. In such case, research and development of several extremely potential marine based novel pharmaceutical compounds in clinical studies are held back due to the lack of sustainable supply of the candidate compound (Molinski et al., 2009).

To overcome this limitation, synthetic or hemisynthetic analogues of marine derivatives with desired pharmacological properties can be developed using biotechnological approaches, such as genetic engineering and synthetic biology. This can optimize and scale up the production of valuable pharmaceuticals from marine organisms (Papon et al., 2022). Furthermore, marine microorganisms are proven to be rich sources of marine derived natural products. Advances in metagenomics allow researchers to study the genetic material of entire microbial communities. Exploring the genetic material of microbiomes associated with marine organisms using advances in metagenomics could lead to the discovery of novel bioactive compounds with pharmaceutical potential (Dokania et al., 2023). Besides, marine organisms can be cultivated in controlled environments or through aquaculture to ensure a sustainable supply of key compounds with therapeutic potential, which can reduce the concern related to conservation of marine species.

VI. Conclusion

The marine environment is a rich source of both biological and chemical diversity. Over the past 50 years, approximately 30,000 natural products have been reported from marine flora and fauna. The majority of these natural products have been obtained from sessile soft bodied invertebrates, such as sponges and tunicates. This diversity has been the source of unique chemical compounds

with the potential for industrial development as functional foods, nutraceuticals, and pharmaceuticals. Major factors for the increasing rate of mortality globally include cancer and microbial infection. Therefore, discovery of novel therapies to treat cancer and microbial infection is a crucial requirement. Marine natural products, namely bioactive peptides, polyphenols, polyketides, terpenoids, alkaloids, and sterols, exhibit promising antifungal, antibacterial, antiviral, and anticancer activities. Marine natural products are responsible for the genesis of 60% of cancer drugs and 75% of infectious disease treatments. This review emphases the role of marine bioactive compounds such as peptides, alkaloids, polyketides and polyphenols against fungal, bacterial, and viral infections and cancers. At present, most of the studies related to the health effects of marine natural products are carried out using in vitro and in vivo mouse models. Although few compounds are under clinical trials and several compounds are in the preclinical pipeline, the number of approved marine based drugs are very low. Therefore, the current screening for promising natural products and their research and development in the pharmaceutical industry should be increased along with a large-scale rapid screening method and large number of compounds undergoing pre-clinical and clinical studies. Moreover, efficient technologies are need for higher extraction efficiency, screening of individual component for a target function and their preservation. These novel technologies should be used to target optimally for marine drug research, development, approval, and marketing in commercial levels.

Acknowledgement: We are grateful to NSERC for financial support.

Conflict of interest: No author has an actual or perceived conflict of interest with the contents of this article.

Data Availability: NA

Authorship Contribution:

Conceptualization, Fereidoon Shahidi; Writing of the original draft, Sarusha Senthiravel; Final review and editing, Fereidoon Shahidi and Deepika Dave.

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Figure captions:

Figure 1. Total number of new marine natural products discovered in each year from 2008 to 2021.

Figure 2. Certain biological activities exhibited by bioactive compounds derived from marine resources.

Figure 3. Schematic diagram of the different mechanisms of action of antifungal activity of secondary metabolites.

Figure 4. Mechanisms of antibacterial activities of marine derived bioactive compounds.

Figure 5. Mechanisms of anticancer activities of marine natural products.

Figure 6. Chemical structures of demethylxestospongin C and xestospongin A, C, and D.

Figure 7. Chemical structures of caerulomycin A, 5-bromo-8-methoxy-1-methyl-β -carboline, and nakijinamines A-C.

Figure 8. Chemical structures of hyrtimomines A, B, F, G, and I, and fumigatosides E and F.

Figure 9. Chemical structures of fumigatosides E and F and pyrrospirone C-F and I.

Figure 10. Chemical structures of aurantoside A-I.

Figure 11. Chemical structures of forazoline A, hippolachnin A, and woodylides A-C.

Figure 12. Chemical structures of engyodontiumones H, aspergillusone B, AGI-B4, emerixanthones A and C, and coniothranthraquinone 1.

Pharmrev Fast Forward. Published on 7 October 2024 as DOI 10.1124/pharmrev.124.001227 This article has not been copyedited and formatted. The final version may differ from this version.

Table 1. Antibacterial activities of marine derive peptides.

Peptide	Source	Antibacterial activity	Reference
Aurelin	Mesoglea of a scyphoid jellyfish *Aurelia aurita*	Activity towards *Bacillus megaterium*, strain B-392 (MIC = 10 μM) and *Micrococcus luteus*, strain Ac-2229 (MIC = 40 μM).	Shenkarev et al., 2012
Oreoch-1	Teleost fish, tilapia gills *Oreochromis niloticus*	Active against Gram-positive bacteria like *B. subtilis* (MIC = 3 μM) and *S. aureus* (MIC = 5 μM), Gram-negative bacteria like *E. coli* (MIC = 6.7 μM) and *P. aeruginosa* (MIC = 35 μM).	Acosta et al., 2013

Oreoch-2	Teleost fish, tilapia gills *Oreochromis niloticus*	Activity versus *B. subtilis* (MIC = 1.7 μM), *S. aureus* (MIC = 5 μM), *E. coli* (MIC = 5 μM), *P. aeruginosa* (MIC = 6.7 μM) and *E. tarda* (MIC = 20 μM).	Acosta et al., 2013
Myticusin-1	Hemolymph of *Mytilus coruscus* (Mussels)	Activity against *S. aureus* (MIC = 2.5-5 μM), *B. subtilis* (MIC = 1.2-2.5 μM), *E. coli* (MIC = 6.7-12.5 μM), and *Sarcina luteus* (MIC = 1.2-2.5 μM).	Liao et al., 2013
Venerupis philippinarum defensin (VpDef)	Clam *Venerupis philippinarum*	Activity against *Micrococcus luteus* (MIC = 6.25-12.5 μM) and *Enterobacter aerogenes* (MIC = 12.5-25 μM).	Zhang et al., 2015a
Gageostatins A-C	Marine bacterium *B. subtilis*	Effect towards *B. subtilis*, *S. aureus*, *P. aeruginosa*, and *S. typhi* with MIC ranging from 8 to 64 μg/mL.	Tareq et al., 2014b
Mytimacin-AF	Mollusks *Achatina fulica* snail	Active versus *S. aureus* with MIC value of 1.9 μg/mL.	Zhong et al., 2013
Cathelicidin (Hc-CATH)	Sea snake *Hydrophis cyanocinctus*	Potent towards *Shigella dysenteriae* (MIC = 0.16 μM) and *Klebsiella* 8 (MIC = 20.67 μM).	Wei et al., 2015
EC-hepcidin3	Marine fish *Epinephelus coioides* (Orange spotted	Active against *S. aureus* (MIC = 1.5-3 μM) and *Pseudomonas stutzeri* (MIC < 1.5 μM).	Qu et al., 2013

	grouper)		
β-defensins	Atlantic cod *Gadusmorhua*	Effect versus *P. citreus* NCIMB 1493 (MIC = 0.4-0.8 μM) and *M. lutes* ATCC 4698 (MIC = 25-50 μM).	Ruangsri et al., 2013
Mytichitin-CB	Hemolymph of *Mytilud coruscus*	Potent against *S. luteus, B. subtilis, B. megaterium,* and *S. aureus* (MIC < 5 μM).	Qin et al., 2014
Rock bream piscidin (Rbpisc)	Fish	Effect towards *Vibrio alginolyticus, V. harveyi, S. iniae* and *V. ordalii* with MIC values less than 0.9 μM and *V. vulnificus* (3.9-7.8 μM).	Bae et al., 2016
SpHyastatin	Crab *Scylla paramamosain*	Effect versus Gram-positive bacteria (*S. aureus, Micrococcus luteus, Micrococcusluteus*, and *Corynebacterium glutamicum*) and Gram-negative bacteria (*Pseudomonas stutzeri, Aeromonashydrophila*, and *P. fluorescens*) with MIC values of 0.63-2.5 μM.	Shan et al., 2016
TP3	Nile tilapia *Oreochromis niloticus*	Effective against Gram-positive bacteria (*S. agalactiae* 819, *S. agalactiae* BCRC 10787, and *E. faecalis* BCRC 10066) and Gram-negative (*V. alginolyticus* and *V.*	Peng et al., 2012

		vulnificus 204) with MIC of 0.6-20 μg/mL.	
TP4	Nile tilapia *Oreochromis niloticus*	Active towards Gram-positive (*S. agalactiae* 819, *S. agalactiae* BCRC 10787, and *E. faecalis* BCRC 10066) and Gram-negative (*V. alginolyticus*, *V. vulnificus* 204, *P. aeruginosa* ATCC 19660, and *A. hydrophila* BCRC 13018).	Peng et al., 2012
Sphistin	Crab *Scylla paramamosain*	Potent towards Gram-positive bacteria (*B. subtilis*, *S. aureus*, *Micrococcus luteus*, *C. glutamicum*, and *M. lysodeikticus*) and Gram-negative bacteria (*Pseudomonas stutzeri*, *Shigella flexneri*, and *P. fluorescens*) with MIC values less than 1.5 μM.	Chen et al., 2015
SMHEP1P	Turbot *Scophthalmus maximus*	Potent towards *S. aureus* (MIC = 2 μM) and *M. luteus* (MIC = 1 μM).	Zhang et al., 2014a
SEHEP2P	Turbot *Scophthalmus maximus*	Active against *E. tarda* (MIC = 1 μM) and *V. anguillarum* (MIC = 2 μM).	Zhang et al., 2014a
YFGPA	Yellowfin tuna *Thunnus albacares*	Activity versus Gram-positive bacteria such as *B. subtilis*, *Streptococcus iniae*, and *Micrococcus luteus* with minimal	Seo et al., 2012

		effective concentrations (MECs) of 1.2–17.0 μg/mL and Gram-negative bacteria like *Vibrio parahaemolyticus*, *Aeromonas hydrophila*, and *E. coli* D31 (MECs = 3.1–12.0 μg/mL).	
SA-hepcidin1	Spotted scat fish *Scatophagus argus*	Active against *S. aureus* (MIC = 50 μM), *Vibrio anguillarum* (MIC = 50 μM), *V. alginolyticus* (MIC = 50 μM), *V. fluvialis* (MIC = 25 μM) and *E. coli* (MIC = 50 μM).	Gui et al., 2016
SA-hepcidin2	Spotted scat fish *Scatophagus argus*	Active against *S. aureus* (MIC = 50 μM), *Vibrio anguillarum* (MIC = 50 μM) and *V. alginolyticus* (MIC = 50 μM).	Gui et al., 2016
ecPis-2, ecPis-3, & ecPis-4	Orange-spotted grouper *Epinephelu scoioides*	Activity against *S. aureus*, *E. coli*, and *V. parahaemolyticus.*	Zhuang et al., 2017
PaLEAP-2	Teleost fish *Plecoglossus altivelis*	Activity against *E. tarda* and *V. anguillarum* with MIC value of 6.25 μg/ml and against *E. coli* DH5α with MIC of 50 μg/ml. Also, active against *P. putida*, *V. vulnificus*, and *V. alginolyticus* (MIC = 100 μg/mL).	Li et al., 2015
Acipensins1	Russian sturgeon *Acipenser*	Effect towards *E. coli* ML35p (MIC = 0.7 μM), *L.*	Shamova et al., 2014

	gueldenstaedtii	*monocytogenes* EGD (MIC = 1.1 μM) and methicillin-resistant *S. aureus* ATCC 33591 (MIC = 0.9 μM).	
Acipensins2	Russian sturgeon *Acipenser gueldenstaedtii*	Active against *E. coli* ML35p (MIC = 0.3 μM), *L. monocytogenes* (MIC = 1 μM) and methicillin-resistant *S. aureus* ATCC 33591 (MIC = 0.6 μM).	Shamova et al., 2014
Acipensins6	Russian sturgeon *Acipenser gueldenstaedtii*	Activity against *E. coli* ML35p (MIC = 2.5 μM).	Shamova et al., 2014
MoroPC-NH_2	Antarctic Fish *Parachaenichthys charcoti*	Activity against Gram-positive *S. aureus*, *L. monocytogenes*, and *Streptococcus pyogenes* with MICs < 5 μM and Gram-negative *Psychrobacter* sp., *E. coli* DH5α, and *Shigella sonnei* with MICs < 5 μM.	Shin et al., 2017
Lc-NK-lysin	Yellow croaker *Larimichthys crocea*	Active against *V. harveyi*, *E. coli*, and *S. aureus* with the MIC values of 12-24 μM and against *B. subtilis* (MIC = 24-48 μM).	Zhou et al., 2016
WB Piscidin 5	White bass *Morone chrysops*	Effect towards *S. aureus* (MIC = 4.52 μM), *E. faecalis* (MIC = 4.52 μM), *E. coli* (MIC = 1.13 μM), and *Shigella flexneri* (MIC =	Salger et al., 2016

		1.13–2.26 μM).	
EeCentrocin 1	Sea urchin *Echinus esculentus*	Potent against Gram-positive bacteria *S. aureus* (MIC = 0.78 μM) and *C. glutamicum* (MIC = 0.78 μM) and against the Gram-negative bacteria *P. aeruginosa* (MIC = 0.78 μM) and *E. coli* (MIC = 0.1 μM).	Solstad et al., 2016
SJGAP	Skipjack tuna *Katsuwonus pelamis*	Effect towards Gram-positive bacteria, namely *M. luteus*, *B. subtilis*, *S. iniae*, and *S. aureus* with MECs in the range of 1.2-17.0 μg/mL, and Gram-negative bacteria, such as *E. coli* D31, *A. hydrophila*, and *V. parahaemolyticus* (MECs = 3.1-12.0 μg/mL).	Seo et al., 2014
Haliotisin	Mollusk *Haliotis tuberculate*	Active against *B. subtilis* (MIC = 0.3-1 μM) and *E. carotovor* (MIC = 1.6-2.6 μM).	Zhuang et al., 2015
PdBD-2	Chinese loach fish, *Paramisgurnus dabryanus*	Activity against Gram-positive *B. subtilis* and Gram-negative bacteria *A. hydrophila.*	Chen et al., 2013
Chionodracine	Icefish species *Chionodraco hamatus*	Inhibit the growth of Gram-positive *B. cereus* (MIC = 5 μM), Gram-negative *E. coli* (MIC = 5 μM) and Antarctic psychrophilic	Buonocore et al., 2012

		bacteria strains *Psychrobacter* sp. TAD1 (MIC = 10 μM) and *Psychrobacter* sp. TA144 (MIC = 15 μM).	
cgMolluscidin	Pacific oyster *Crassostrea giga*	Potent towards Gram-positive bacteria including *S. aureus, B. subtilis,* and *M. luteus* (MECs = 1.3-31.3 μg/mL), and Gram-negative bacteria including *S. enterica, E. coli,* and *V. parahaemolyticus* (MECs = 0.4-2.3 μg/mL).	Seo et al., 2013

Table 2. Antiviral activities of peptides derived from marine sources.

Peptide	Source	Antiviral activity	Reference
Simplicilliumtides J	Deep-sea-derived fungal strain *Simplicillium obclavatum* EIODSF 020	Antiviral activity toward HSV-1 with IC_{50} values of 14.0 μM.	Liang et al., 2017
Verlamelins A & B	Deep-sea-derived fungal strain *Simplicillium obclavatum* EIODSF 020	Antiviral activity toward HSV-1 with IC_{50} values of 16.7 and 15.6 μM, respectively.	Liang et al., 2017
Divamide A	Tunicate *Didemnum molle* E11-036	Active against HIV-1 with IC_{50} value of 0.225 μM.	Smith et al., 2018

Stellettapeptins A & B	Sponge *Stelletta* sp., collected from northwestern Australia	Decrease infection of human T-lymphoblastoid cells by HIV-1 with EC_{50} values of 23 and 27 nM, respectively.	Shin et al., 2015
Myticin C	Mollusk *Mytilus galloprovincialis*	Antiviral activity against human herpes simplex viruses 1 (HSV-1) and 2 (HSV-2).	Novoa et al., 2016
Asperterrestide A	Endophytic fungus *Aspergillus terreus*	Inhibitory effects on influenza virus strains H1N1 and H3N2 with IC_{50} values of 20.2 and 0.41 μM, respectively.	He et al., 2013
Mirabamides E-H	Sponge *Stelletta clavosa*, collected from the Torres Strait	Potent inhibition of HIV-1 in a neutralization assay with IC_{50} values of 121, 62, 68, and 41 nM, respectively.	Lu et al., 2011
Malformin C	Endophytic fungus *Aspergillus niger* SCSIO Jcsw6F30	Strongest anti-HIV-1 activity with IC_{50} of 1.4 ± 0.06 μM.	Zhou et al., 2016
Molleurea F	Tunicate *Didemnum molle*	Anti-HIV activity in an HIV integrase inhibition assay and a cytoprotective cell-based assay with IC_{50} values of 39 and 78 μM, respectively.	Lu et al., 2012
Pa-MAP	Polar fish *Pleuronectes americanus*	Inhibition of the simplex virus 1 (HSV-1), and Aichi	Vilas Boas et

		virus with a selectivity index of 5 and 3.4, respectively.	al., 2017
Aspergillipeptides D & E	Marine gorgonian-derived fungus *Aspergillus* sp. SCSIO 41501	Antiviral activity towards herpes simplex virus type 1 (HSV-1) with IC_{50} values of 9.5 and 19.8 μM, respectively.	Ma et al., 2017
Acremonpeptides A & B	Marine fungus *Acremonium persicinum* SCSIO 115	Moderate antiviral activity against herpes simplex virus 1 with EC_{50} values of 16 and 8.7 μM, respectively.	Luo et al., 2019a
Al(III)–acremonpeptide D	Marine fungus *Acremonium persicinum* SCSIO 115	Moderate antiviral activity against herpes simplex virus 1 with EC_{50} value of 14 μM.	Luo et al., 2019a
Cyclo(L-Tyr-L-Pro) (diketopiperazine)	Endophytic fungus *Aspergillus versicolor*, isolated from Red Sea black sponge *Spongia officinalis*	Strong inhibitory activity towards Hepatitis C virus protease with IC_{50} value of 8.2 μg/mL.	Ahmed et al., 2017

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Table 3. Examples of marine peptides possessing anticancer activities.

Peptide	Source	Anticancer activity	Reference
Theopapuamides A−C	Marine sponge *Siliquariaspongia mirabilis*	Cytotoxicity against human colon carcinoma (HCT-116) cells with IC_{50} values between 2.1 and 4.0 μg/mL.	Plaza et al., 2009
Samoamide A	*Symploca* sp. collected in American Samoa	Potent cytotoxic activity versus H460 human non-small-cell lung cancer cells (IC_{50} = 1.1 μM).	Naman et al., 2017
Apratoxin D	Cyanobacterium *Lyngbya majuscule*	Cytotoxicity against H-460 lung cancer cells with IC_{50} value of 2.6 nM.	Gutiérrez et al., 2008
Sansalvamide A	*Fusarium* sp. derived	Cytotoxic activity	Vasko et

	from marine plant *Halodule wrightii*	towards several cell lines namely colon, pancreatic, prostrate, breast sarcoma, and melanoma cancer cell lines.	al., 2010
Azonazine	*Aspergillus insulicola,* collected from Hawaiian marine sediments	cytotoxic activity versus HCT-116 cell line with IC_{50} value < 15 ng/mL.	Wu et al., 2010
Didemnin B	Marine tunicate *Tridemnum solidum*	Anti-tumor activity towards human prostatic cancer cell line with IC_{50} value of 2 ng/mL in L1210 leukemia cell. Antiproliferative properties on B16 melanoma and P388 leukemia cells.	Kotoku et al., 2006
Scleritodermin A	Marine sponge *Scleritoderma nodosum*	*In vitro* anticancer activities towards different human cancer cell lines such as A2780 ovarian carcinoma, HCT116 colon carcinoma, and SKBR3 breast carcinoma with IC_{50} values of 0.94 µM, 1.92 µM, and 0.97 µM,	Liu et al., 2008; Schmidt et al., 2004

		respectively.	
Microsclerodermin A	Sponge genus Amphibleptul	Inhibit NFκB transcriptional activity. Cytotoxic activity against AsPC-1, BxPC-3, MIA PaCa-2 and PANC-1 pancreatic cancer cell lines.	Guzmán et al., 2015
Urukthapelstatin A	Thermoactinomycetaceae bacterium *Mechercharimyces asporophorigenens* YM11-542	Cytotoxic activity against A549 lung carcinoma epithelial cells with IC_{50} value of 12 nM.	Oberheide et al., 2019
Lagunamide A & D	Cyanobacterium *Lyngbya majuscule*	Antiproliferative activity against A549 human lung adenocarcinoma cells.	Luo et al., 2019b
Scopularides A & B	Fungus *Scopulariopsis brevicaulis*	Anticancer activities against the colon tumor cell line HT29 and pancreatic tumor cell lines Panc89 and Colo357.	Yu et al., 2008
Desmethoxymajusculamide C	Fijian cyanobacteria *Lyngbya majuscula*	Activity against HCT-116 human colon carcinoma cell line with	Simmons et al., 2009

		IC_{50} value of 20 nM.	
Rolloamides A & B	Dominican marine sponge *Eurypon laughlini*	Cytotoxic activities against SKBR3 and A2780 with IC_{50} values in the range of 0.4–5.8 µM.	Williams et al., 2009
Diazonamide A	Ascidian *Diazona angulata*	Activity towards CA46, MCF7, PC3, and A549 cancer cell lines with IC_{50} values of 2–5 nM.	Cruz-Monserrate et al., 2003; Lachia and Moody, 2008
Kulokekahilide-2	Cephalaspidean mollusk, *Philinopsis speciosa*	Cytotoxicity activity towards different cell lines such as P388, SK-OV-3, MDA-MB-435, and A-10 (IC_{50} values = 4.2 to 59.1 nM).	Nakao et al., 2004
Peptide YALRAH	Half-fin anchovy (*Setipinna taty*)	Antiproliferative activity against PC-3 cell line with an IC_{50} value of 11.1 µM.	Song et al., 2014a
Pardaxin	Red Sea Moses sole, *Pardachirus mamoratu*	Antiproliferative activity against HT1080 and induce apoptosis in HeLa cells.	Hsu et all., 2011

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Table 4. Examples of marine based alkaloids exhibiting antifungal activities.

Alkaloids	Source	Antifungal activity	Reference
Penicillatide B	Non-identified *Penicillium* strain associated with a Red Sea tunicate *Didemnum* sp.	Moderate activity against *C. albicans.*	Youssef et al., 2018
Lindgomycin	Two *Lindgomyces* strains (LF327 and KF970)	Activity against human pathogen *C. albicans* (Activity is four times less than by the control nystatin).	Wu et al., 2015a
Brocapyrrozin A 4-hydroxy-3-phenyl-1*H*-pyrrol-2(5*H*)-one	Fungus *P. brocae* MA-231 associated with marine mangrove plant *A. marina* (China)	Activities against *Fusarium oxysporum* with MIC values of 0.25 and 0.125 μgmL^{-1}, respectively.	Meng et al., 2017
Didymellamide A	Marine-derived fungus *Stagonosporopsis cucurbitacearum*	Activity versus azole-resistant *C. albicans.*	Haga et al., 2013
Varioxepine A	Fungus *Paecilomyces variotii*, from a marine	Activity versus *Fusarium graminearum.*	Zhang et al., 2014b

	red macroalga *Grateloupia turuturu* (Qingdao, China)		
Hyrtinadines C	Sponge *Hyrtios* sp. (Okinawa, Japan)	Inhibitory activity versus *A. niger* (IC_{50} = 32 μg/mL).	Kubota et al., 2016
Tyrokeradines G & H	Marine sponge of the order Verongida (Okinawa, Japan)	Effect towards *A. niger* (IC_{50} = 32 μg/mL for each). Tyrokeradine G was active against *Cryptococcus neoformans* (IC_{50} = 16 μg/mL).	Kubota et al., 2015
Isoagelasine C, agelasine B, agelasine J, nemoechine G, isoagelasidine B, (-)-agelasidine C	Sponge *Agelas nakamurai* (Xisha Islands, South China Sea)	Effect towards *C. albicans* (MICs ranging from 0.59 to 4.69 μg/ml).	Zhu et al., 2016
Nakamurin B	Sponge *Agelas nakamurai* (Xisha Islands, South China Sea)	Weak activity against *C. albicans* (MIC = 60 mg/mL).	Chu et al., 2017
Zamamidine D	Okinawan marine sponge *Amphimedon* sp.	Active against *Cryptococcus neoformans* IFM62681 and *Trichophyton mentagrophytes* IFM62679 (IC_{50} = 2 and 8 μg/mL, respectively).	Kubota et al., 2017

Fusaripyridines A & B	Fungus *Fusarium* sp. LY019 associated with Red Sea sponge *Suberea mollis*	Activity versus *C. albicans* with MIC value of 8.0 μM.	Shaala et al., 2021
Indolepyrazines A & B	Marine based *Acinetobacter* sp. ZZ1275	Activity against *C. albicans* with MIC value of 12–14 μg/mL.	Zhang et al., 2022
Eutypellenoid B	Arctic fungi *Eutypella* sp. D-1	Inhibitory effect towards *C. albicans, C. parapsilosis, C. tropicalis*, and *C. glabrata* with MIC values of 8, 8, 32, and 16 μg/mL, respectively.	Yu et al., 2018a
Ditalaromylectones A & B	Fungus *Talaromyces mangshanicus* BTBU20211089 (South China Sea)	Activity towards *C. albicans* with MIC value of 200 μg/mL.	Zhang et al., 2022
Hemimycalins C–E	Red Sea sponge *Hemimycale* sp.	Inhibitory activity against *C. albicans* with MIC value of 8 μM.	Shaala et al., 2021
Emethacin C	Marine-derived fungus *Aspergillus terreus* RA2905.	Activity against *C. albicans* (MIC = 32 μg/mL).	Wu et al., 2020
Demethylxestospongin C Xestospongin A, C, & D	Australian marine sponge *Xestospongia exigua*	Moderate inhibitory effect towards a fluconazole-resistant *C. albicans* ATCC 14503 (MIC = 100 μg/mL).	Moon et al., 2002

Didymellamide A	Marine based fungus *Stagonosporopsis cucurbitacearum*	Effect against azole-resistant and -susceptible *C. albicans*, *C. glabrata*, and *Cryptococcus neoformans* (MIC = 1.6 or 3.1 μg/mL).	Haga et al., 2013
Didymellamide B	Marine based fungus *Stagonosporopsis cucurbitacearum*	Acted against *C. neoformans* (MIC = 6.3 μg/mL).	Haga et al., 2013
Caerulomycin A	Marine actinomycete *Actinoalloateichus cyanogriseus*	Inhibited two fluconazole-resistant *C. krusei* GO3 and *C. glabrata* HO5 (MICs in the range of 0.39–1.56 μg/mL).	Ambavane et al., 2014
5-bromo-8-methoxy-1-methyl-β-carboline	New Zealand bryozoan *Pterocella vesiculosa*	Inhibitory effect against *C. albicans* and *Trichophyton mentagrophytes* (MID = 4-5 μg/mL).	Till and Prinsep, 2009
Nakijinamine A	Okinawan marine sponge *Suberites* sp.	Action towards *C. albicans* (IC_{50} 0.25 μg/mL), *Trichophyton mentagrophytes* (IC_{50} = 0.25 μg/mL), and *C. neoformans* (IC_{50} 0.5 μg/mL).	Takahashi et al., 2012
Nakijinamines B & C	Okinawan marine sponge *Suberites* sp.	Inhibited *C. albicans* (IC_{50} = 8 μg/mL).	Takahashi et al., 2012

Hyrtimomine A	Okinawan marine sponges *Hyrtios* spp.	Inhibitory activity against *A. niger* (IC_{50} = 4.0 μg/mL).	Momose et al., 2013; Tanaka et al., 2013a
Hyrtimomines A & B	Okinawan marine sponges *Hyrtios* spp.	Active against *C. neoformans* (IC_{50} = 2.0 and 4.0 μg/mL, respectively) and *C. albicans* (IC_{50} = 1.0 μg/mL each).	Momose et al., 2013; Tanaka et al., 2013a
Hyrtimomines F, G, & I	Okinawan marine sponges *Hyrtios* spp.	Effect towards *Aspergillus niger* (IC_{50} = 8.0 μg/mL each).	Tanaka et al., 2014
Hyrtimomine I	Okinawan marine sponges *Hyrtios* spp.	Inhibited *C. neoformans* (IC_{50} = 4.0 μg/mL).	Tanaka et al., 2014
Fumigatosides E	Deep-sea fungus *Aspergillus fumigatus* SCSIO (Indian Ocean)	Activity against *Fussarium oxysporum* sp. *momordicae* and moderate inhibitory effect towards *F. oxysporum* sp. *cucumerinu.*	Limbadri et al., 2018
Tyrokeradines G & H	Marine sponge of the order Verongida (Okinawa, Japan)	Effect towards *A. niger* with IC_{50} value of 32 µg/mL for each.	Kubota et al., 2015
Tyrokeradines G	Marine sponge of the order Verongida (Okinawa, Japan)	Active against *Cryptococcus neoformans* (IC_{50} = 16 µg/mL).	Kubota et al., 2015

(−)-ageloxime D Ageloxime B	Marine sponge *Agelas mauritiana*	Activity against *Cryptococcus neoformans* with MIC values of 10.00 μg/mL.	Yang et al., 2012
Nagelamide Z	Marine sponge *Agelas* sp.	Inhibitory activity against *Candida albicans* (IC_{50} = 0.25 μg/mL).	Tanaka et al., 2013b
Ceratinadins A & B	Okinawan marine sponge *Pseudoceratina* sp.	Effect against *Cryptococcus neoformans* (MIC = 4 and 8 μg/mL, respectively) and *Candida albicans* (MIC = 2 and 4 μg/mL, respectively).	Kon et al., 2010

Table 5. A list of alkaloid compounds with the potential antibacterial activities.

Alkaloid	Source	Antibacterial activity	Reference
Pyranonigrin F	Fungus *Penicillium brocae* MA-231 associated with the marine mangrove-derived plant *Avicennia marina*	Activity against *S. aureus* (Gram-positive) and the Gram-negative aqua-bacteria *Vibrio harveyi* and *Vibrio parahemolyticus* with MIC values of 0.5 μg/mL.	Meng et al., 2015
Pyrrospirone C–F & I	Fungus *Penicillium* sp. ZZ380, derived from a wild crab (*Pachygrapsus crassipes*)	Inhibition against *E. coli* (Gram-negative) *and S. aureus* (Gram-positive) with MIC values of 3.0 μg/mL and 1.7 μg/mL, respectively.	Song et al., 2019
Brocapyrrozin A & B	Fungus *P. brocae* MA-231, derived from marine mangrove plant *A. marina*	Activity against *S. aureus* (MIC value of 0.125 μg mL^{-1} for Brocapyrrozin A).	Meng et al., 2017
Dispyrrolopyridine A & B	Predatory bacterium *Tenacibaculum discolor* sv11	Strong activity versus *B. subtilis* DSM10, *Mycobacterium smegmatis* ATCC607, *S. aureus* ATCC25923, and *L. monocytogenes* DSM20600 with MIC values ranging from 0.5 to 4 μg/mL.	Wang et al., 2022a

Dispyrrolopyridine A	Predatory bacterium *Tenacibaculum discolor* sv11	Potent activity against efflux pump deficient *E. coli* ATCC25922 (MIC = 8 μg/mL) and *Caenorhabditis elegans* N_2 (MIC = 32 μg/mL.	Wang et al., 2022a
Penijanthine C & D	*Penicillium janthinellum*, living in the sediments of the Bohai Sea, China	Inhibiting activities against *Vibrio alginolyticus*, *V. anguillarum*, and *V. parahemolyticus* with MIC values ranging from 3.1 to 50.0 μM.	Guo et al., 2019
19-Hydroxypenitrem A	Fungus *Aspergillus nidulans* EN-330, isolated from the marine red macroalga *Polysiphonia villum* (formerly *Polysiphonia scopulorum var. villum*)	Moderate antibacterial activity against human pathogens (*S. aureus* and *E. coli*) and aqua pathogens (*Edwardsiella tarda* and *Vibrio anguillarum*) with MIC values ranging from 16 to 64 μg/mL.	Zhang et al., 2015b
Fumigatoside F	Deep-sea sediment-derived fungus *Aspergillus fumigatus* SCSIO41012	Antibacterial activity against *Acinetobacter baumannii* ATCC 19606 with a MIC value of 6.25 μg/mL.	Limbadri et al., 2018
2-(4 hydroxybenzyl)-4-(3-acetyl) quinazolin-one	*Aspergillus sydowii* SW9 (China's seawater)	Activity against *S. epidermidis*, *S. aureus*, *E. coli*, and *Streptococcus pneumoniae* with MIC values in the range of 2.0 to 16 μg/mL.	Liu et al., 2019b

Penicillatide B	*Penicillium* strain associated with a Red Sea tunicate *Didemnum* sp.	Potent inhibitory effect on *V. anguillarum* and moderated effect on *S. aureus.*	Youssef et al., 2018
Spirobrocazine C	Fungus *P. brocae* MA-231 associated with mangrove plant (*A. marina*)	Antibacterial activity against *E. coli*, *V. harveyi*, and *Aeromonas hydrophila* with MIC value of 32.0 μg/mL.	Meng et al., 2016
Acremolin C	Antarctic-derived fungus *A. sydowii* SP-1	Activity against methicillin-resistant *S. aureus*, methicillin-resistant *S. epidermidis*, *S. aureus*, and *S. epidermidis.*	Li et al., 2018

Table 6. Anticancer activities of some marine derived alkaloids.

Alkaloid	Source	Anticancer activity	Reference
Discorhabdin and Discodermolide	Sponge *Latrunculia apicalis* and *L. biformis*	Cytotoxic activity towards HCT116 cell line.	Li et al., 2019c
Ascomylactam A	Mangrove endophytic fungus *Ascomycota* sp.	Suppressed A549 and NCI-H460 cancer cell lines (6 mg/kg/day).	Wang et al., 2020
(−)-Agelamide D	Marine sponge *Agelas* sp.	Improve the efficacy of radiation therapy in xenograft Hep3B cells.	Choi et al., 2020
Neoamphimedine	Marine sponge *Xestospongia* sp.	Reduce the growth of KB and HCT-116 tumors.	Marshall et al., 2003
Crambescidine-816	Marine sponge *Crambe crambe*	Reduce the tumor development in olorectal carcinoma (CRC) HTC-116 cells *in vivo in Zebrafish embryos.*	Roel et al., 2016
Isofistularin-3	Marine sponge *Aplysina aerophoba*	Supress the development of neuroblastoma (15–25 µM) and prostate (20 and 25 µM) cancers.	Florean et al., 2016
Monanchoxymycalin C	Marine sponge *Monanchor pulchra*	Cytotoxicity against human prostate cancer through JNK1/2 activation and non-apoptotic cell death.	Dyshlovoy et al., 2020

Table 7. Marine based phenolics displaying anticancer activities.

Phenolics	Source	Antifungal activity	Reference
Penimethavone A (flavone)	Fungus *Penicillium chrysogenum* cultured from a gorgonian *Carijoa* sp. (South China Sea)	Anticancer activities towards rhabdomyosarcoma and cervical cancer (HeLa) cell lines with IC_{50} values of 8.18 and 8.41 μM, respectively.	Hou et al., 2016
Phloroglucinol	Brown seaweeds	Enhanced the anticancer effects of 5-fluorouracil towards HT29 colorectal cancer cell lines.	Lopes-Costa et al., 2017
Alternariol and (coumarin)	Fungus *Alternaria alternata* collected from soft coral *Litophyton arboreum*	Antiproliferative activities verses leukemia cell lines such as L1210 and CCRF-CEM.	Hawas et al., 2015
Alternariol methyl ether	Fungus *Alternaria alternata* collected from soft coral *Litophyton arboreum*	antitumor activities towards the leukemia cell lines of H-125 and Colon-38.	Hawas et al., 2015
Moromycin B, saquayamycin B_1 and B	Marine derived *Streptomyces* sp. OC1610.4	Antitumor activities towards breast cancer cells MCF-7, MDA-MB-231, and BT-474 with IC_{50} values in the range of 0.16–0.67 μM.	Qu et al. 2019
Bis (2,3-dibromo-4,5-dihydroxy-phenyl)-methane	Marine algae	Anticancer activity on different tumor cells such as RKO, HeLa, U87, Bel7402,	Wu et al., 2015b

(Bromophenol)		and HCT116 with IC_{50} values of 11.37, 17.63, 23.69, 8.7, and 10.58 µg/mL, respectively.	
Laurebiphenyl (terpenophenolics)	Red macroalga *Laurencia tristicha*	Antiproliferative activity against stomach cancer (BGC-823), lung adenocarcinoma (A549), colon cancer (HCT-8), hepatoma (Bel 7402), and HeLa cell lines with IC_{50} values of 1.22, 1.68, 1.77, 1.91, and 1.61 µg/mL, respectively.	Sun et al., 2005
Fradimycin B	Marine *Streptomyces fradiae* strain PTZ0025	Activity against HCT-15, SW620 and C6 cancer cells with IC_{50} values of 0.13, 4.33 and 0.47 µM, respectively.	Xin et al., 2012
Fucodiphloroethol G	*Ecklonia cava* (Marine brown macroalgae)	Antitumor activity towards HeLa, A549, HT1080 and HT29 cancer cells (IC_{50} = 298.2, 226.5, 242.5 and 228.5 µM, respectively).	Li et al., 2011
Galvaquinone B and lupinacidin A (anthraquinones)	Sea anemone (*Gyractis sesere*) from Easter Island	Active against Calu-3 and H2887 cancer cells with IC_{50} values of 5.0 and 12.2 µM for Galvaquinone B and 8.8 and 3.1 µM for lupinacidin A.	Sottorff et al., 2019

Norhierridin B (hydroquinone)	Marine picocyanobacterium *Cyanobium* sp.	Antiproliferative activity against MDA-MB-231, SKBR3, MDA-MB-468, A375, Huh-7 and HCT116 cancer cells (IC_{50} = 0.61, 0.77, 0.68, 2.0, 0.61 and 3.2 µM, respectively).	Brandão et al., 2020
Diorcinol L	Marine sponge-derived fungus *Didymellaceae* sp. SCSIO F46	Anticancer activity towards Huh-7, DU145, HeLa and HL60 cancer cells (IC_{50} = 5.7, 9.1, 7.1 and 9.6 µM).	Tian et al., 2018
Plastoquinones	Brown macroalga, *Sargassum micracanthum*	Anticancer activity against murine colon 26-L5 adenocarcinoma cell line (IC_{50} = 1.51 and 1.69 µg/mL.	Mori et al., 2005
Phlorofucofuroeckol	Brown macroalga *Ecklonia cava*	Suppression of migration and invasion of breast cancer cells (MCF-7 and MDA-MB-231) by downregulation of Nf-κB and Toll-like receptor 4 (TLR-4).	Lee et al., 2020

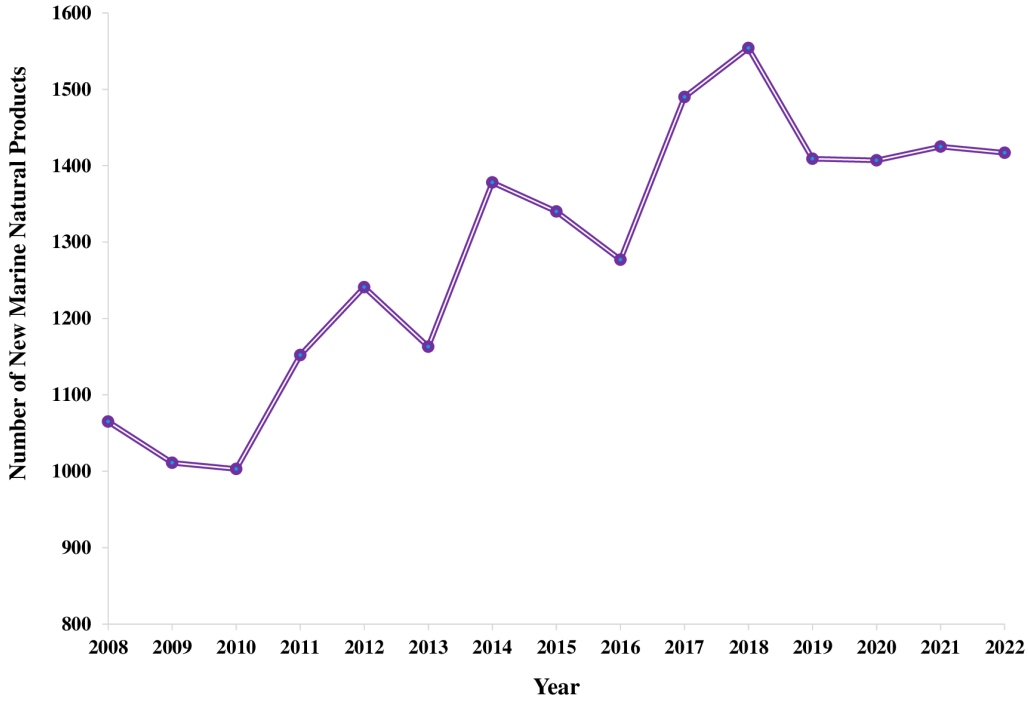


Figure 1

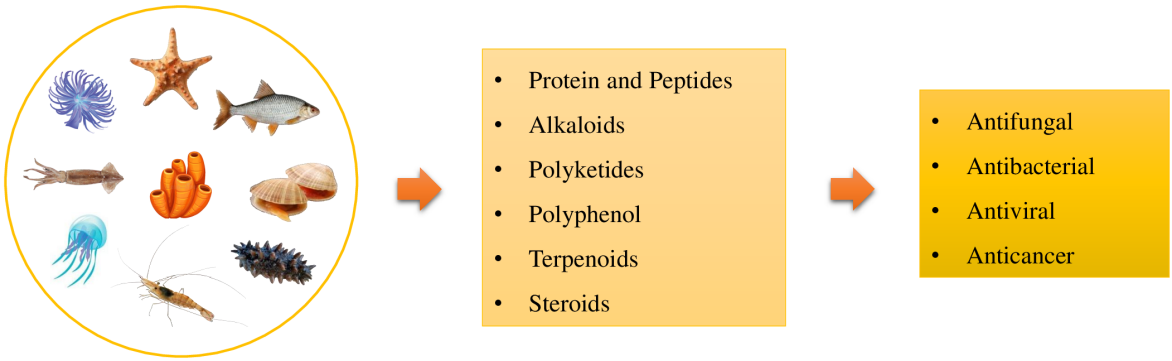
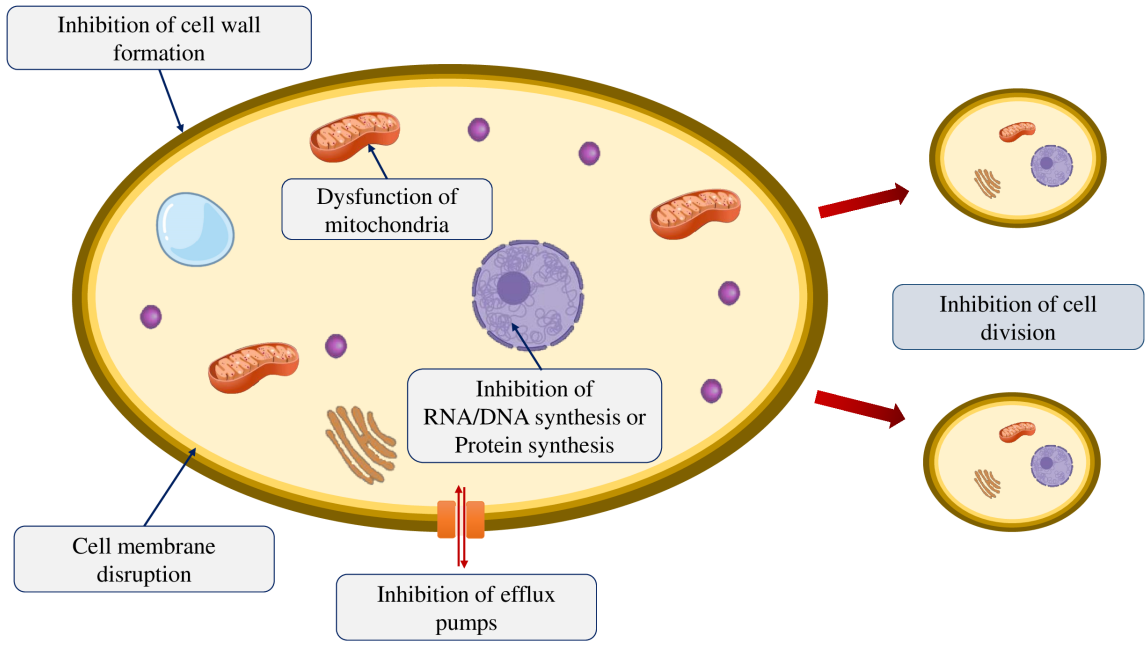


Figure 2



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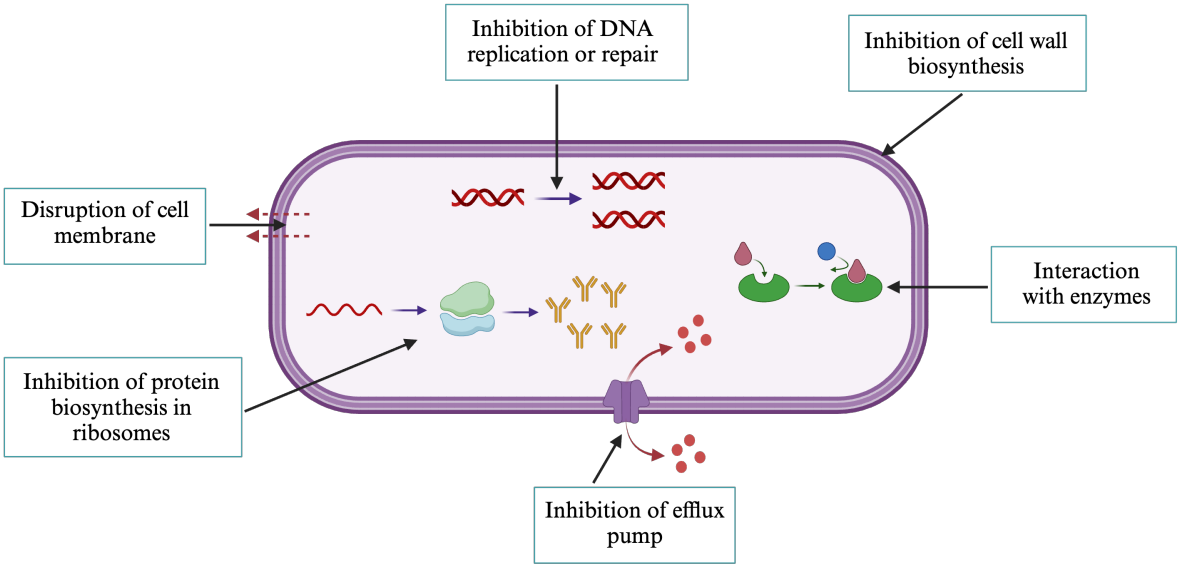

Figure 4

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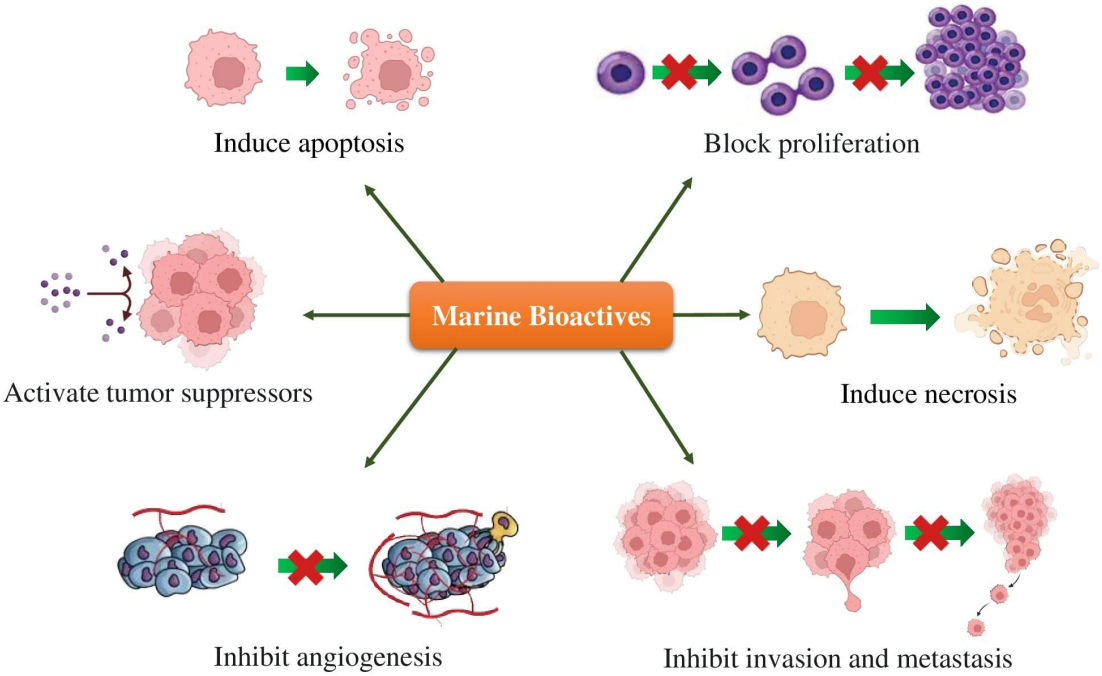

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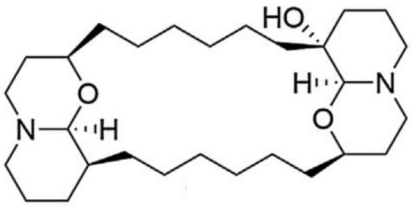
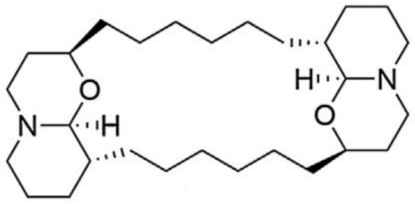
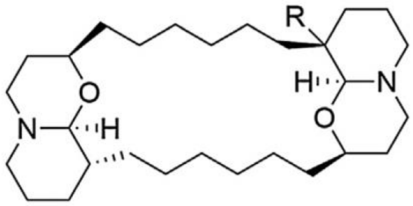


Demethylxestospongin

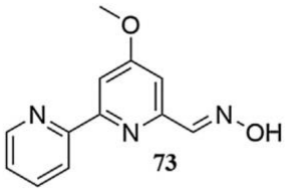


Xestospongin A

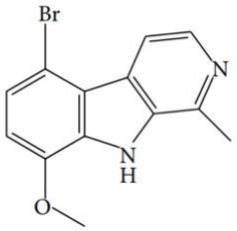


Xestospongin B: R = H
Xestospongin C: R = OH

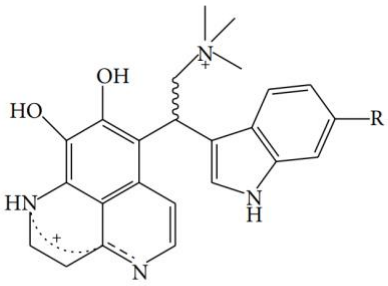
Figure 6



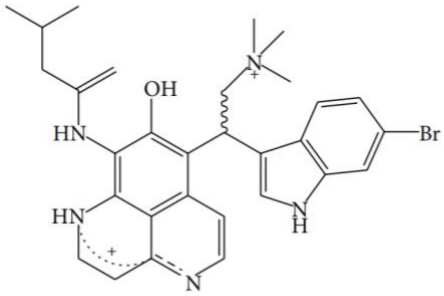
Caerulomycin A



5-bromo-8-methoxy-1-methyl-β-carboline



Nakijinamine A: R = Br
Nakijinamine B: R = H



Nakijinamine C

Figure 7

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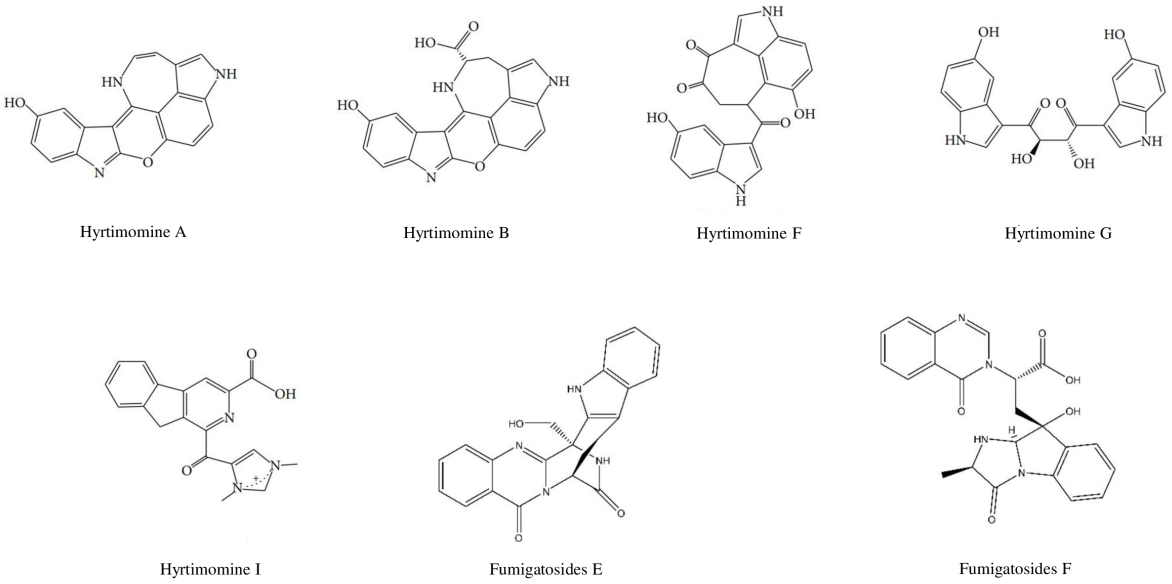
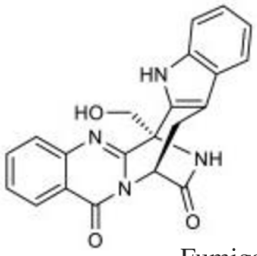
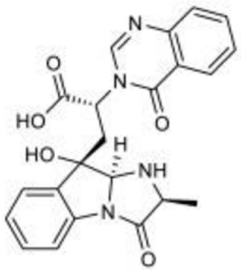


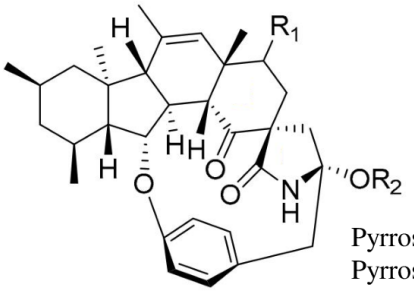
Figure 8



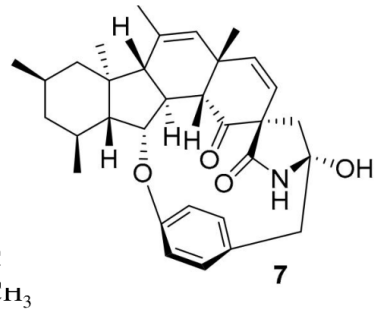
Fumigatosides E



Fumigatosides F



Pyrrospirone C: R_1 = αOH, R_2 = C
Pyrrospirone D: R_1 = βOH, R_2 = CH_3
Pyrrospirone E: R_1 = αOH, R_2 = H
Pyrrospirone F: R_1 = βOH, R_2 = H



Pyrrospirone I

Figure 9

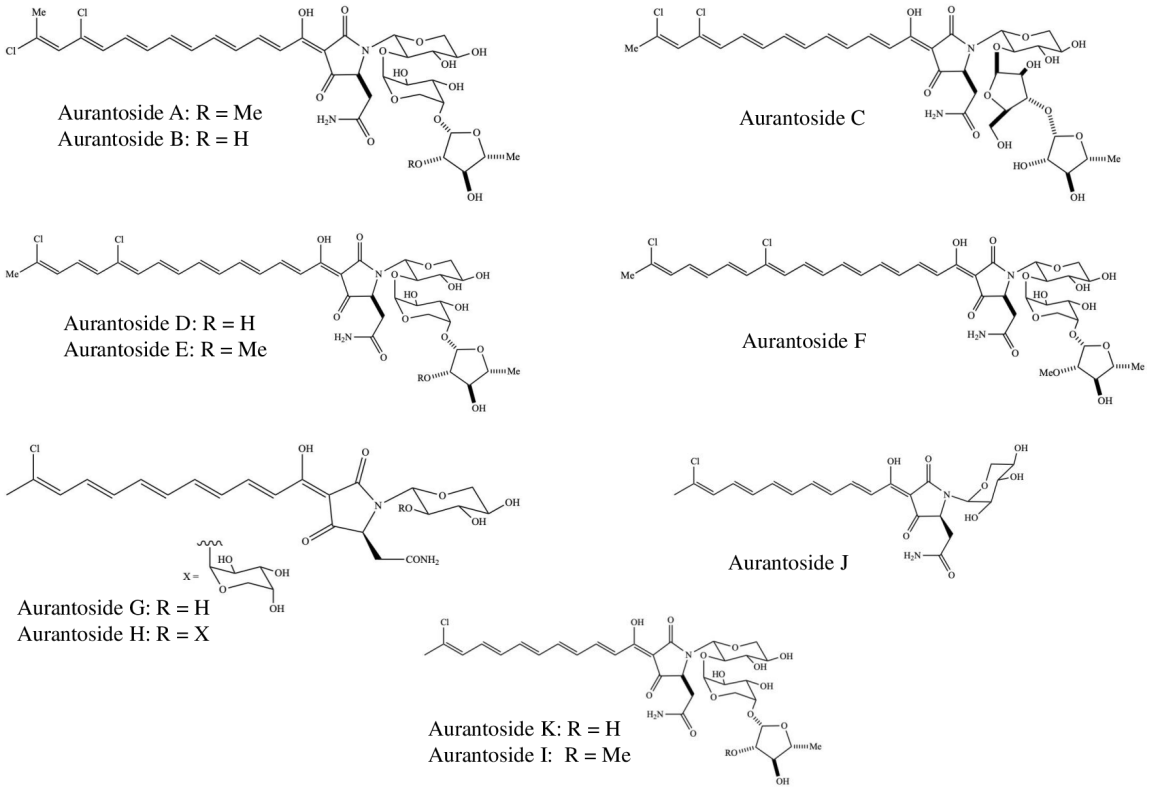
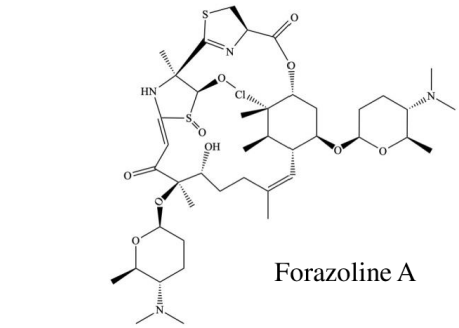
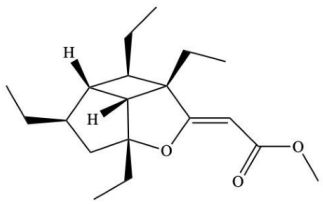


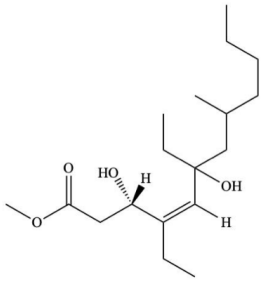
Figure 10



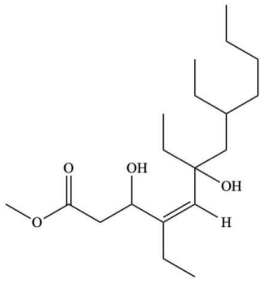
Forazoline A



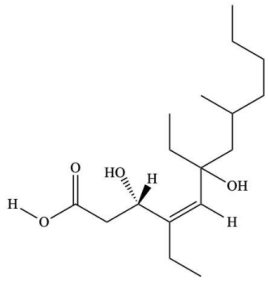
Hippolachnin A



Woodylide A

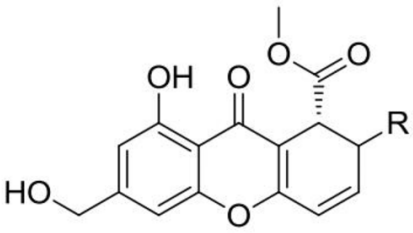


Woodylide B

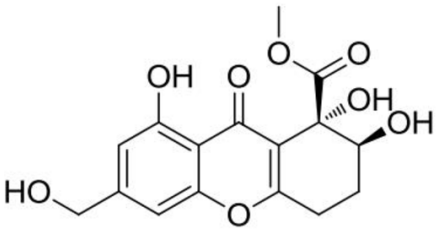


Woodylide C

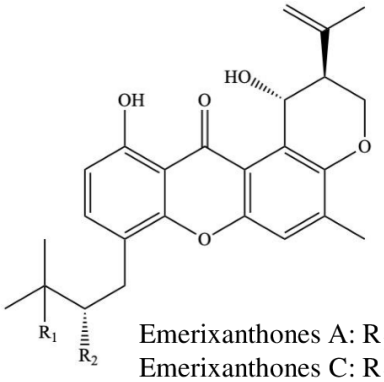
Figure 11



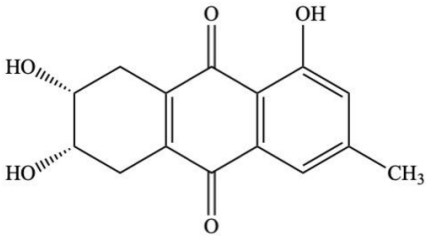
Engyodontiumones H: R = α-OH
AGI-B4: R = β-OH



Aspergillusone B



Emerixanthones A: R_1 = Cl, R_2 = OH
Emerixanthones C: R_1 = OCH_3, R_2 = OCH_3



Coniothranthraquinone 1

Figure 12