Saudi Journal of Biological Sciences 28 (2021) 224–231

Contents lists available at ScienceDirect

Saudi Journal of Biological Sciences

journal homepage: www.sciencedirect.com

Review

Marine microorganisms as an untapped source of bioactive compounds

Fuad Ameen [a,*], Saleh AlNadhari [b], Ali A. Al-Homaidan [a]

[a] Department of Botany & Microbiology, College of Science, King Saud University, Riyadh 11451, Saudi Arabia
[b] Department of Plant Protection, College of Agriculture, King Saud University, Riyadh, Saudi Arabia

ARTICLE INFO

Article history:
Received 2 August 2020
Revised 11 September 2020
Accepted 27 September 2020
Available online 9 October 2020

Keywords:
Ocean
Marine microorganism
Bioactive compounds
Extreme environments
Metabolites

ABSTRACT

The search for novel biologically active molecules has extended to the screening of organisms associated with less explored environments. In this sense, Oceans, which cover nearly the 67% of the globe, are interesting ecosystems characterized by a high biodiversity that is worth being explored. As such, marine microorganisms are highly interesting as promising sources of new bioactive compounds of potential value to humans. Some of these microorganisms are able to survive in extreme marine environments and, as a result, they produce complex molecules with unique biological interesting properties for a wide variety of industrial and biotechnological applications. Thus, different marine microorganisms (fungi, myxomycetes, bacteria, and microalgae) producing compounds with antioxidant, antibacterial, apoptotic, antitumoral and antiviral activities have been already isolated. This review compiles and discusses the discovery of bioactive molecules from marine microorganisms reported from 2018 onwards. Moreover, it highlights the huge potential of marine microorganisms for obtaining highly valuable bioactive compounds.

Contents

1. Introduction

Most bioactive compounds are derived from terrestrial microorganisms and, although the terrestrial environment is a bountiful source of bioactive producers, the discovery of novel metabolites is diminishing (Jensen and Fenical, 2000). Hence, new sources of bioactive substances need to be explored. In this sense, the enormous biodiversity present in marine ecosystems offers a promising resource to find new compounds with numerous worthwhile biological activities. According to the Global Biodiversity Assessment by the United Nations Environment Programme, there are 178,000 marine species belonging to 34 phyla (Mitra and Zaman, 2016). Thus, ocean's biodiversity represents 50% of the whole globe's biodiversity, making marine microorganisms a promising sustainable source of novel biologically active compounds (Jimeno et al., 2004; Vignesh et al., 2011).

* Corresponding author.
E-mail address: fuadameen@ksu.edu.sa (F. Ameen).

Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

https://doi.org/10.1016/j.sjbs.2020.09.052
1319-562X/

Oceans contain many different specific habitats characterized by a wide range of temperatures, hydrostatic pressures and levels of salinity. To survive in such unique ecosystems, marine microorganisms have developed different adaptation mechanisms, including the production of specific biomolecules. Consequently, marine microorganisms would seem to hold a considerable potential of producing bioactive compounds not found in terrestrial environments (Xie et al., 2018). In particular, extreme marine habitats are unique ecological niches in which extremophile microorganisms develop specific biochemical pathways and characteristics.

Although the first cephalosporin C antibiotic was obtained from a marine fungus in 1949, the discovery rate of biologically active metabolites from marine microorganisms remained very slow until the 1980 s. Thus, since 1985, more than 15,000 new metabolites have been identified from marine organisms, many of which have displayed interesting bioactivities (Blunt et al., 2009; Al-Dhabi et al., 2019). Thus, marine microorganisms are able to produce active biomolecules with diverse pharmacological activities (e.g. anticancer, anti-inflammatory, antidiabetic and antibiotic) (Rateb and Ebel, 2011). In addition, marine microorganisms are renewable and more easily cultured than marine macroorganisms (Blunt et al., 2015). Also, their use would avoid excessive exploitation of marine resources and adverse collection practices (Romano et al., 2017).

Excellent reviews on natural marine products that covered the available literature published in 2016 (Blunt et al., 2018) and 2017 (Carroll et al., 2019) have been published. In addition, another review by (Barzkar et al., 2019) highlighted the pharmaceutical potential of natural compounds isolated from marine microalgae. Also, Corinaldesi et al. (2017) outlined different bioactive compounds with cosmeceutical and cosmetic applications isolated from marine bacteria and marine fungi. Consequently, the present review compiles the most recent published research on the isolation of different novel biologically active metabolites from marine microorganisms.

2. Marine microorganisms

The main species of bacteria found in seawater belong to the genera *Pseudomonas* sp., *Vibrio* sp., *Achromobacter* sp., *Flavobacterium* sp. and *Micrococcus* sp. (Baharum et al., 2010). However, the genus *Streptomyces* has been the main provider of new molecules so far (Blunt et al., 2018). Marine bacteria are supposed to possess physiological, biochemical and molecular properties that are different from their terrestrial equivalents and, accordingly, they may produce different compounds (Siddharth and Vittal, 2018). As such, marine bacteria are likely the most promising microorganisms for the detection of novel molecules with antibacterial properties, especially since the majority of natural antibacterial drugs come from one group of terrestrial bacteria, the actinomycetes (Butler et al., 2013).

Several myxomycetes were recovered from freshwater environments (Shearer and Crane, 1986; Lindley et al., 2007; Winsett and Stephenson, 2013), where they appear to be relatively common. Dyková et al. (2007) reported that they identified a possible myxomycete living as an endocommensal of a sea urchin in the Adriatic Sea. Studies of myxomycetes in aquatic freshwater habitats are few in number and we are not aware of any study that has been directed towards surveying myxomycetes in marine habitats. It seems likely that any species of myxomycetes isolated from marine habitats would include unusual taxa, possibly including those new to scientists.

Numerous novel secondary metabolites were isolated from myxomycetes (Dembitsky et al., 2005; Huynh et al., 2017; Nguyen et al., 2017). However, the comprehension of their biological properties is still rather limited. Biologically active molecules from myxomycetes were highly researched from the 1950′s to the 1970′s and then they were stopped until the beginning of the twenty-first century (Tran and Adamatzky, 2017). Overall, nearly all bioactive compounds isolated from myxomycetes exhibited the highest inhibition effects on Gram positive bacteria (e.g. *Bacillus subtilis*) followed by fungi (e.g. *Candida albicans*) and low or no inhibition effects on Gram negative bacteria (Sawada et al., 2000). Nonetheless, their effect on other microbial cells has not been investigated yet.

Marine fungi constitute the main degraders of lignocellulosic and aromatic materials in marine habitats (Ameen et al., 2016; 2015a; 2015b; 2015c; 2014;; Hyde et al., 1998). According to their capability to grow in marine habitats, they are classified as obligate or facultative marine fungi (Borse et al., 2012). The former grow rapidly and sporulate only in a marine or estuarine environment, whereas the latter usually come from the terrestrial environment and are adapted to the marine one. Marine fungi are linked to algae, corals and detritus of marine macrophytes. About 1500 species of marine fungi, from which 530 correspond to obligate marine fungi, are established. Occasionally, it is hard to distinguish the obligate or facultative character of the marine fungi and hence, the more extensive term "marine-derived fungi" is utilized (Bugni and Ireland, 2004). Most marine fungi belong to the phylum Ascomycota (Jones et al., 2015), whereas the phylum Basidiomycota is under-represented (Jones and Pang, 2012; Jones et al., 2015; Raghukumar, 2017). Very recently, an online database devoted to marine fungi has been developed (Jones et al., 2019).

The severe physical and chemical conditions existing in the marine environment are responsible for the development of particular metabolic routes in marine fungi not found in their terrestrial counterparts (LiBerra and Lindequist, 1995; Abdel-Lateff, 2008). During the past few decades, a large array of novel natural metabolites with a diverse range of pharmacological activities was obtained from marine fungi (Rateb and Ebel, 2011). However, few drugs from marine fungi are at present commercially available (Kiuru et al., 2014).

Marine microalgae are tiny unicellular plants which form what is known as phytoplankton. They play a crucial role in oceans as primary producers of biomass and organic compounds, thanks to their photosynthetic process (Camacho et al., 2007; Sieg et al., 2011; Kiuru et al., 2014). In addition, marine microalgae produce about 50% of atmospheric oxygen (Singh et al., 2011). Marine microalgae can be classified into three groups: blue-green algae (Cyanobacteria), diatoms (Bacillariophyta) and dinoflagellates (Dinophyceae). It is thought that there are about 50,000 species of microalgae, however few of them have been characterized (Lee et al., 2013). The considerable biochemical differences found among marine microalgae make them an untapped source for the biosynthesis of a huge diversity of bioactive molecules (Abida et al., 2013; Coêlho et al., 2019). Microalgae can be applied for biomass production, primary metabolite production (e.g. carotenoids, proteins and lipids), as biosorbent for heavy metals (Al-Homaidan et al., 2018) and secondary metabolite production (generally compounds with pharmaceutical applications) (Barra et al., 2014) (Fig. 1) (Khan et al., 2018). In Fig. 2, the cultivation of microalgae in the laboratory is illustrated (Malibari et al., 2018).

3. Bioactive compounds from marine microorganisms

In Table 1 a list of the different biologically active molecules from marine microorganisms reported recently are presented.

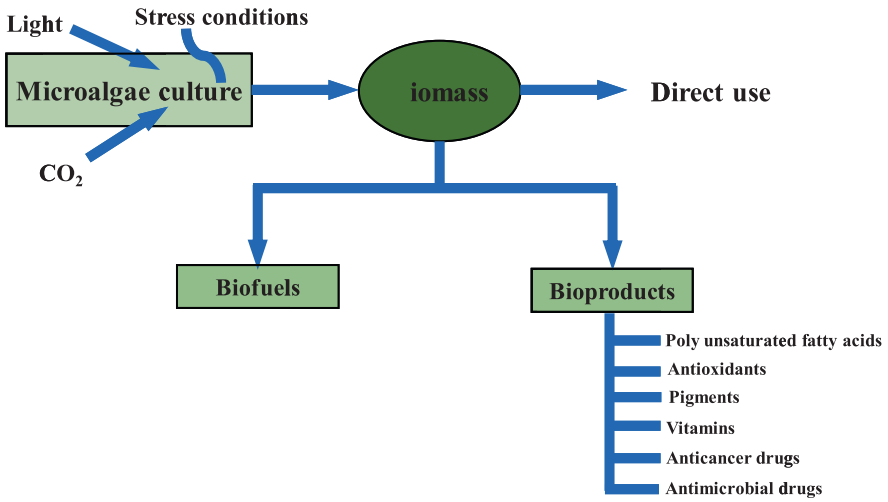

Fig. 1. Microalgae convert atmospheric CO_2 to a variety of valuable bioproducts by using light (after Khan et al., 2018).

Fig. 2. Marine microalgae cultured in the laboratory (Reprinted from *Journal of Cleaner Production* 198, Malibari, R., Sayegh, F., Elazzazy, A.M., Baeshen, M.N., Dourou, M., Aggelis F, G., Reuse of shrimp farm wastewater as growth medium for marine microalgae isolated from Red Sea-Jeddah, 160–169, Copyright (2018), with permission from Elsevier Ltd., UK).

3.1. Bioactive compounds from marine bacteria

Galaviz-Silva et al. (2018) reported acute antimicrobial activity against the food borne poisoning strains *Staphylococcus aureus* and *Vibrio parahaemolyticus* by the bacteria *Bacillus aerius*, *B. oryzicola*, *B. safensis*, *B. boroniphilus*, *B. altitudinis* and *Virgibacillus senegalensis* isolated from marine habitats in Mexico. It would seem that these marine bacteria could serve as a potential alternative against other clinically important bacteria for the elaboration of new antimicrobials.

A new discovered metabolite named dentigerumycin E by co-cultivation of the marine strains *Streptomyces* sp. and *Bacillus* sp., obtained from the shore of a muddy wetland, showing antiproliferative and antimetastatic activities against human carcinoma. This indicated that co-cultivation of marine microorganisms could be a promising approach to find new bioactive microbial metabolites (Shin et al. (2018).

Shivale et al. (2018) isolated two novel antioxidant-producing bacteria from marine soil samples, which were identified as *Janibacter melonis* and *Pseudomonas stutzeri*. Nevertheless, more research is required to identify the antioxidant compounds produced and their possible industrial utilisation.

A marine actinobacterium *Streptomyces* sp.S2A, was identified and isolated from sea sediment samples. This organism produced an extract that exhibited antimicrobial activity against pathogen bacteria and fungi, inhibitory activity against α-glucosidase and α-amylase enzymes and antioxidant and cytotoxic activities against different cell lines. They identified the principal constituent of the extract (80%) as pyrrolo[1–a] pyrazine-1,4-dione, hexahydro-3-(2-methylpropyl), corresponding to a peptide derived from diketopiperazine (Siddharth and Vittal 2018).

Wang et al. (2018a) isolated and purified an exopolysaccharide from the marine bacterium *Aerococcus uriaeequi* that exhibited antioxidant activities which, according to its safety assessment on mice, was safe for both topical and oral application. Therefore, it could have potential applications in medicine.

Zhang et al. (2018) identified five bagremycin analogues, including two new ones, from a marine actinobacterium, isolated from a marine mud sample and identified as *Streptomyces* sp. ZZ745. The two novel bagremycins exhibited antibacterial activity against *E. coli*.

Al-Dhabi et al. (2019) demonstrated significant antimicrobial activity of extracts from the Saudi Arabian marine-derived actinomycete *Streptomyces* sp. Al-Dabhi 90 against drug resistant pathogens such as *S. aureus*, *Klebsiella pneumoniae*, *E. coli*, *Pseudomonas aeruginosa, Proteus mirabilis* and *Enterococcus faecium*. Furthermore, they found that the main components of the *Streptomyces* extracts were 3-methylpyridazine, n-hexadecanoic acid, indazol-4-one, octadecanoic acid and 3a-methyl-6-((4-methylphenyl) sul. Therefore, *Streptomyces* sp. Al-Dhabi-90 is a promising source for the production of new antibiotics to fight against multidrug resistant clinical pathogens.

A marine actinomycete isolated from the mollusc *Drupa granulata* that showed antagonistic activity against prochloraz-resistant strains of *Penicillium digitatum*, which cause green mould in post-harvested citrus. The isolated actinomycete was identified as *Streptomyces chumphonensis* (Hu et al. (2019).

Kim et al. (2019) isolated four 2-alkyl-4-hydroxyquinoline compounds from semi-solid rice cultures of the marine-derived actinobacterium *Streptomyces* sp. MBTG13. Among them, one compound highly inhibited the hyphal growth of *Candida albicans*.

The antioxidant properties of the methanolic extract from the marine Gram-negative bacterium *Novosphingobium* sp. PP1Y, was reported and obtained from a contaminated zone in the seaport of Pozzuoli (Naples, Italy) (Petruk et al. (2019).

Sran et al. (2019) isolated a marine actinobacterium from Rasthakaadu Beach (Tamil Nadu, India), identified as *Microbacterium aurantiacum* FSW25 according to polyphasic taxonomy. The cultivation of this bacterium produced a large amount of an exopolysaccharide with interesting rheological and antioxidant features to be used as a viscous antioxidant in various industries.

Table 1
Bioactive compounds from marine microorganisms reported since 2018.

Microorganism	Compound	Activity	Reference
Bacteria			
Bacillus aerius, *Bacillus oryzicola*, *Bacillus safensis*, *Bacillus boroniphilus*, *Bacillus altitudinis* and *Virgibacillus senegalensis*	Not identified	Antimicrobial	Galaviz-Silva et al. (2018)
Streptomyces sp and *Bacillus sp*	Dentigerumycin	Antitumoral	Shin et al. (2018)
Janibacter melonis Pseudomonas stutzeri	Not identified	Antioxidant	Shivale et al. (2018)
Streptomyces sp.S2A	Pyrrolo[1–a]pyrazine-1,4-dione,hexahydro-3-(2-methylpropyl)	Antimicrobial, enzyme inhibitory, antioxidant and cytotoxic	Siddharth and Vittal (2018)
Aerococcus uriaeequi HZ	Exopolysaccharides	Antioxidant	Wang et al. (2018a)
Streptomyces sp. ZZ745	Bagremycins	Antimicrobial	Zhang et al. (2018)
Streptomyces sp. Al Dhabi-90	3-methylpyridazine, n-hexadecanoic acid, indazol-4-one, octadecanoic acid and 3a-methyl-6-((4-methylphenyl) sul	Antibacterial	Al-Dhabi et al. (2019)
Streptomyces chumphonensis	Not identified	Antimicrobial	Hu et al. (2019)
Streptomyces sp.	2-Alkyl-4-hydroxyquinolines	Antifungal	Kim et al. (2019)
Novosphingobium sp. PP1Y	Not determined	Antioxidant	Petruk et al. (2019)
Microbacterium aurantiacum FSW-25	Exopolysaccharide	Antioxidant	Sran et al. (2019)
Penicillium sp. ZZ380	Abyssomicin	Antiviral	Zhang et al. (2020)
Fungi			
Simplicillium lamellicola, *Leptosphaerulina* sp., *Penicillium citrinum*, *Penicillium chrysogenum*, *Aspergillus sydowii*	Not identified	Antibacterial	Agrawal et al. (2018)
Hansfordia sinuosae	Polysaccharide	Antitumoral	Li et al. (2018a)
Penicillium sp. ZZ901	(+)-Scleroderolide	Antiglioma and antibacterial	Li et al. (2018b)
Fusarium sp. 152	Equisetin	Anti-MRSA*	Luo et al. (2018a)
Diaporthe sp. SCSIO 41,011	Polyketides	Antiviral	Luo et al. (2018b)
Trichoderma sp. SCSIO41004	5-acetyl-2-methoxy-1,4,6-trihydroxy-anthraquinone	Antiviral	Pang et al. (2018)
Penicillium sp. ZZ380	Pyrrospirone alkaloids	Antiglioma	
Antimicrobial	Song et al. (2018)		
Aspergillus niger AKV-MKBU	L-asparaginase	Anticancer	Vala et al. (2018)
Chaetomium sp. NA-S01-R1	Chaephilone, chaetovirides	Antimicrobial, Anti-tumoral	Wang et al. (2018b)
Aspergillus alabamensis EN-547	4-epi-seco-shornephine A carboxylic	Antimicrobial	Yang et al. (2018)
	4-epi-seco-shornephine A methyl ester		
	28-acetoxy-12b,15a,25-trihydroxyergosta-4,6,8 (14),22-tetraen-3-one		
	Shornephine A		
Truncatella angustata	Isoprenylated cyclohexanols	Antiviral	Zhao et al. (2018a)
Fusarium equiseti	(11S)-1,3,6-trihydroxi-7-(1-hydroxyethyl)-anthracene-9,10-dione	Cytotoxic	Zhao et al. (2018b)
Alternaria sp.	7-acetyl-1,3,6-trihydroxyanthracene-9,10-dione	Antifungal	
	Stemphyperylenol		
	Alterperylenol	Antibacterial	
Curvularia sp. IFB-Z10	Spirocurvulaide	Cytotoxic	An et al. (2019)
Penicillium chrysogenum	Tyrosol	Anti-quorum sensing	Chang et al. (2019)
Penicillium sp.	2-[(5-methyl-1,4-dioxan-2-yl)methoxy]ethanol	Antimicrobial	Le et al. (2019)
	2-[(2R-Hydroxypropanoyl)amino]benzamide, 4-hydroxybenzandehyde	Antimicrobial	
	2′,3′-Dihydrosorbicillin	Anti-α-glucosidase/	
Penicillium sp. IMB17-046	Trypilepyrazinol	Antiviral, antibacterial	Li et al. (2019)
	(+)-Neocitreoviridin	Antibacterial	
	3β-Hydroxyergosta-8,14,24(28)-trien-7-one	Antiviral	

(*continued on next page*)

Table 1 (*continued*)

Microorganism	Compound	Activity	Reference
Penicillium sclerotiorin	Azaphilone derivative	Anti-inflammatory	Liu et al. (2019)
	Isochromophilone IX Sclerketide C		
Penicillium citrinum HDN-152–088	Dicitrones	Antioxidant	Wang et al. (2019)
Aspergillus sp.	Asperphenin A	Antitumoral	Bae et al. (2020)
Penicillium minioluteum ZZ1657	N-acetyl-L-valine conjugated drimarane sesquiterpenoids	Antimicrobial	Ma et al. (2020)
	Drimane sesquiterpenoids	Antiglioma	
Aspergillus sp. LS116	Aspergillsteroid A	Antibacterial	Xu et al. (2020)
Microalgae			
Prorocentrum hoffmannianum, Prorocentrum arenarium, Prorocentrum reticulatum, Alexandrium tamarensis, Gambierdiscus australes	Not identified	Apoptotic	de Vera et al. (2018)
Navicula sp.	Sulfated polysaccharides	Antioxidant	Fimbres-Olivarria et al. (2018)
Skeletonema costatum Chaetoceros pseudocurvisetus	Not identified	Antibacterial	Lauritano et al. (2018)
Amphidinium carterae	Amphidinol 22	Cytotoxicity, antimicrobial	Martinez et al. (2019)

* MRSA: anti methicillin-resistant *Saphylococcus aureus*.

Zhang et al. (2020) identified a new abyssomicin and six known abyssomicin and proximicin analogs from extracts of the cultures of a marine bacterium isolated from sea sediments and identified as *Verrucosispo*ra sp. MS100137. The new compound and two of the known ones exhibited considerable antiviral effects against the IAV.

3.2. Bioactive compounds from marine fungi

Agrawal et al. (2018) isolated new marine fungal species identified as *Simplicillium lamellicola*, *Leptosphaerulina* sp., *Penicillium citrinum*, *Penicillium chrysogenum* and *Aspergillus sydowii* with high antimicrobial activity against the acne-inducing bacteria *Cutibacterium acnes* and *Staphylococcus epidermidis* with minimum inhibitory concentrations (MIC) ranging from 0.8 to 1.0 mg/mL. Hence, the extracts of these fungi could represent an interesting option for obtaining antibiotics for *acne vulgaris* cure. Nevertheless, the specific bioactive molecules conferring the antimicrobial activity were not determined.

Li et al. (2018a) demonstrated the antitumoral effect on cervical cancer (HeLa cells) and breast cancer (MCF-7) human cells of a polysaccharide, containing mainly mannose, produced by cultivation of the marine fungus *Hansfordia sinuosae*.

Li et al. (2018b) obtained six novel peniciphenalenins and the already identified metabolites (+)-sclerodin, (+)-scleroderolide, (+)-sclerodione and physcion from cultured extracts of the marine-derived fungus *Penicillium* sp. ZZ901. They found that the known (+)-scleroderolide compound inhibited the growth of glioma cells and also presented antibacterial activity against the pathogenic bacteria *S. aureus* (MIC 7.0 μg/mL) and *Echerichia coli* (MIC 9.0 μg/mL).

Luo et al. (2018a) found a novel anti methicillin-resistant *S. aureus* (MRSA) compound from the deep marine fungus *Fusarium* sp. 152. Subsequently, that compound was identified as equisetin and showed a MIC value of 1 μg/mL against MRSA.

Luo et al. (2018b) isolated twenty-eight aromatic polyketides from the mangrove-associated fungus *Diaporthe* sp. SCSIO 41011, four of which showed high antiviral activities against three varieties of the influenza A virus (IAV). These compounds were identified as 2 pestalotiopsone, 3,8-dihydroxy-6-methyl-9- oxo-9H-xanthene-1-carboxylate and 5-chloroisorotiorin.

Pang et al. (2018) obtained three new and six known molecules from the rice cultivation extract of the sponge-derived fungus *Trichoderma* sp. SCSIO41004. From the isolated compounds only one (the already known compound 5-acetyl-2-methoxy-1,4,6-trihy droxy-anthraquinone) exhibited significant antiviral activity against the human Enterovirus 71 (EV71).

Song et al. (2018) found that the fungus *Penicillium* sp. ZZ380, collected from a wild crab, produced new seven pyrrospyrone alkaloids, one of which exhibited high anti-glioma activity and the other three presented antimicrobial activity against MRSA and *E. coli* with MIC values of 2.0–5.0 μg/mL.

Vala et al. (2018) produced an L-asparaginase enzyme with anticancer activities by the marine-derived fungi *Aspergillus niger*. In addition, a cost-effective production at laboratory bioreactor scale (5 L) utilizing groundnut oil cake as an inexpensive substrate was achieved.

Various bacteria from marine sponges, collected from the Red Sea coast of Saudi Arabia were isolated and cultivated for the production of the anticancer enzyme L-asparaginase. Among them, a bacterium identified as *Bacillus subtilis* produced L-asparaginase with no glutaminase activity which is very important from a medical point of view (Ameen et al., 2020).

Wang et al. (2018b) identified four new chlorinated compounds, named chaephilone C and chaetovirides A, B and C, and four known ones derived from azaphilone, designed as chaetoviridin A, chaetoviridine E, chaetomugilin D and cochliodone A, from the deep sea derived fungus *Chaetomium* sp. NA-S01-R1. Chaetoviride A and chateoviride B presented antibacterial activities against *Vibrio rotiferianus* and *Vibrio vulnificus* and chaephilone C, chaetoviride B and chaetoviride C showed anti-MRSA activities. In addition, chaetoviride A exhibited cytotoxic activity against Hep G2 cells and chephilone C and chateoviride B towards HeLa cells.

Yang et al. (2018) obtained three new and four known natural derivatives from the extracts of the marine-derived fungus *Aspergillus alabamensis* EN-547, obtained from the marine red alga *Ceramium japonicum*. The new molecules were identified as 4-epi-seco-shornephine A methyl ester, 4-epi-seco-shornephine A carboxylic

acid and 28-acetoxy-12*b*,15*a*,25-trihydroxyergosta-4,6,8(14),22-tetraen-3-one and the known compounds as shornephine A, 25-hydroxyergosta-4,6,8(14),22-tetraen-3-one, 25,28-dihydroxyergosta-4,6,8(14),22-tetraen-3-one and 12*b*,15*a*,25,28-tetrahydroxyergosta-4,6,8(14),22-tetraen-3-one. The three new compounds and shornephine A presented inhibition against the human pathogens *E. coli* and *Micrococcus luteus* and the aquatic bacteria *Edwardsiella ictaluri* and *Vibrio alginolyticus* with MIC values varying from16 to 64 μg/mL.

Zhao et al. (2018a) isolated eight novel isoprenylated cyclohexanols and fourteen known analogous compounds from solid cultures of the sponge-associated fungus *Truncatella angustata*. From the eight-novel isolated isoprenylated cyclohexanols, one of them displayed considerable levels of inhibition towards both human immunodeficiency virus 1 (HIV-1) and swine-origin influenza A virus (H1N1) virus and another one against the HIV-1 virus.

Zhao et al. (2018b) identified two promising fungi with bioactive activities among different 141 fungal strains isolated from marine plants. These two fungi were identified as *Fusarium equiseti* and *Alternaria* sp. The former produced two compounds, identified as (11S)-1,3,6-trihydroxi-7-(1-hydroxyethyl)-anthracene-9,10-dione and 7-acetyl-1,3,6-trihydroxyanthracene-9,10-dione with cytotoxicity against lung (A-549), cervical (HeLa) and hepatic (HepG2) carcinoma human cell lines. *Alternaria* sp. produced one compound (stemphyperylenol) with strong antifungal activity against Pestallozzia theae and Alternaria brassicicola and another one (alterperylenol) with antibacterial activity against Clavibacter michiganensis (MIC 1.95 μg/mL).

The compound spirocurvulaide, a new bicyclic polyketide with a unique spiro[furan-2,2′-naphthalene] ring system, produced by the symbiotic fungus *Curvularia* sp. IFB-Z10, isolated from the gut of an *Argyrosomus argentatus* gathered in the Yellow Sea. Spirocurvulaide showed moderate cytotoxic activity against model cells of hepatomas (An et al. (2019).

Chang et al. (2019) described the anti-quorum sensing (anti-QS) activity against *Chromobacterium violaceum* and *P. aeruginosa* by ethyl acetate extracts of the marine fungus *Penicillium chrysogenum* DXY-1, isolated from sea sediments. One of the compounds showing anti-QS activity was identified as tyrosol. They observed that for the same concentration the anti-QS activity of the identified compound (i.e. tyrosol) was not higher than that of the whole extract. So, they concluded that other active compounds may exist in the crude fungal extracts.

Le et al. (2019) found that the extracts of *Penicillium* sp., isolated from marine sediments, contained ten secondary metabolites such as sporogen AO-1, 3-indolecarbaldehyde, 2-[(5-methyl-1,4-dioxan-2-yl)methoxy]ethanol, 2-[(2R-hydroxypropanoyl)amino]benzamide, 4-hydroxybenzandehyde, chrysogine, 3-acetyl-4-hydroxycinnoline, acid1H-indole-3-acetic, cyclo (Tyr-Trp) and 2′,3′-dihydrosorbicillin. Among them, 2-[(5-methyl-1,4-dioxan-2-yl) methoxy] ethanol exhibited high inhibitory properties against *Enterococcus faecalis* (MIC 32 μg/mL), both 2-[(2R-hydroxypropanoyl) amino] benzamide and 4-hydroxybenzandehyde selectively inhibited *E. coli* (MIC 16 and 8 μg/mL, respectively) and 2′,3′-dihydrosorbicillin inhibited α-glucosidase activity. Therefore, marine *Penicillium* sp. appears to be a valuable resource to produce drugs to fight against pathogens and diabetes.

Li et al. (2019) obtained three new compounds identified as trypilepyrazinol, (+)-neocitreoviridin and 3β-hydroxyergosta-8,14,24(28)-trien-7-one by the mangrove-derived *Penicillium* sp. IMB17-046. Trypilepyrazinol and 3β-hydroxyergosta-8,14,24(28)-trien-7-one exhibited antiviral activities against various classes of virus, such as HIV-1, hepatitis C virus (HCV) and IAV while (+)-neocitreoviridin exhibited considerable antibacterial activity against *Helicobacter pylori* (MIC 1–4 μg/mL) and antiviral activity against IAV.

Liu et al. (2019) isolated four new and nine known polyketides from the coral-derived fungus *Penicillium sclerotiorin*, three of which (identified as an azaphilone derivative, isochromophilone IX and sclerketide C) exhibited anti-inflammatory activity. This pointed out the capacity of marine fungal polyketides as anti-inflammatory compounds.

Wang et al. (2019) obtained two novel citrinin dimers (i.e. dicitrones) and a common citrinin monomer from the marine-derived fungus *Penicillium citrinum* HDN-152–088. Interestingly, one of the new citrinin dimers showed antioxidant activity.

The antitumoral activity of the compound asperphenin A, was described and isolated from the marine-derived fungus *Aspergillus* sp., against human colon cancer cells. Therefore, it could have potential as a new chemotherapeutic agent (Bae et al. (2020).

Ma et al. (2020) isolated three new purpuride compounds, a new isocoumarin peniisocoumarin compound and 15 known metabolites from the marine-derived fungus *Penicillium minioluteum* ZZ1657. Two of the purpurides, which resulted to be N-acetyl-L-valine conjugated drimarane sesquiterpenoids, exhibited antimicrobial activities against MRSA, *E. coli* and *C. albicans* (MIC values of 6–12 and 3–6 μg/mL, respectively), whereas the another purpuride, identified as a new drimane sesquiterpenoid, presented high antiproliferative activities against human glioma cells.

Xu et al. (2020) firstly isolated two cyclocitribol analogs, designed as aspergillsteroid A and neocyclocitrinol B, from a marine sponge-associated *Aspergillus* fungus. Aspergillsteroid A showed considerable antibacterial activity against the aquatic pathogen *Vibrio harveyi* (MIC 16 μg/mL).

3.3. Bioactive compounds from marine microalgae

De Vera et al. (2018) studied the bioactive potential of the extracts of thirty-three marine microalgae. They found that the dinoflagellates *Prorocentrum hoffmannianum*, *P. arenarium*, *P. reticulatum*, *Alexandrium tamarensis* and *Gambierdiscus australes* showed promising apoptotic activities.

Fimbres-Olivarria et al. (2018) extracted sulphated polysaccharides from the marine diatom *Navicula* sp. grown at three wavelengths (i.e. white light, red light and blue light). The recovered polysaccharides exhibited antioxidant activity, especially the ones grown under white and blue light. Consequently, these sulphated polysaccharides can have potential applications in biotechnology as antioxidants.

Lauritano et al. (2018) reported anti-tuberculosis activity in diatoms for the first time. They found that the organic extracts of the diatoms *Skeletonema costatum* and *Chaetoceros pseudocurvisetus* presented activity against tuberculosis when cultured under control (i.e., with no stress) and phosphate starvation conditions.

The production of bioactive compounds by the marine microalga *Amphidinium carterae* was investigated. They identified a new substance linked to the amphidinol family, given the name amphidinol 22, with potent cytotoxicity activity and moderate antimicrobial activity against *C. albicans* (Martinez et al. 2019).

4. Conclusions

The biodiversity of the oceans represents a potentially abundant source of new chemically diverse compounds with potential industrial applications. Thus, bioprospecting of marine ecosystems has resulted in the identification of new microorganisms able to produce bioactive compounds with interesting pharmacological activities (i.e. antibacterial, antitumoral and antiviral). In addition,

marine microorganisms are a renewable and environmentally friendly alternative for drug discovery. Results reported up to now are very encouraging. Hence, compounds obtained from marine microorganisms could be the solution in the ongoing struggle against antibiotic-resistant bacteria and many awful diseases such as the acquired immune deficiency syndrome (AIDS), cancer and even the current major global pandemic Covid-19 provoked by the virus SARS-CoV-2.

Acknowledgements

This project was funded by the National Plan for Science, Technology and Innovation (MAARIFAH), King Abdulaziz City for Science and Technology, Kingdom of Saudi Arabia, Award Number (13-BIO2290-02).

References

Abdel-Lateff, A., 2008. Chaetominedione, a new tyrosine kinase inhibitor isolated from the algicolous marine fungus *Chaetomium* sp. Tetrahedron Lett. 49, 6398–6400.
Abida, H., Ruchaud, S., Rios, L., Humeau, A., Probert, I., De Vargas, C., Bach, S., Bowler, C., 2013. Bioprospecting marine plankton. Mar. Drugs 11, 4594–4611.
Agrawal, S., Adholeya, A., Barrow, C.J., Deshmukh, S.K., 2018. *In-vitro* evaluation of marine derived fungi against *Cutibacterium acnes*. Anaerobe 49, 5–13.
Al-Dhabi, N.A., Ghilan, A.-K.-M., Esmail, G.A., Arasu, M.V., Duraipandiyan, V., Ponmurugan, K., 2019. Bioactivity assessment of the Saudi Arabian Marine *Streptomyces* sp. Al-Dhabi-90, metabolic profiling and its *in vitro* inhibitory property against multidrug resistant and extended-spectrum beta-lactamase clinical bacterial pathogens. J. Infect. Public Health 12, 549–556.
Al-Homaidan, A.A., Al-Qahtani, H.S., Al-Ghanayem, A.A., Ameen, F., Ibraheem, I.B.M., 2018. Potential use of green algae as a biosorbent for hexavalent chromium removal from aqueous solutions. Saudi J. Biolog. Sci. 25, 1733–1738.
Ameen, F., Alshehri, W.A., Al-Enazi, N.M., Almansob, A., 2020. L-Asparaginase activity analysis, ansZ gene identification and anticancer activity of a new *Bacillus subtilis* isolated from sponges of the Red Sea. Biosci. Biotechnol. Biochem., 1–9
Ameen, F., Moslem, M., Hadi, S., Al-Sabri, A.E., 2016. Biodegradation of diesel fuel hydrocarbons by mangrove fungi from Red Sea Coast of Saudi Arabia. Saudi J. Biolog. Sci. 23, 211–218.
Ameen, F., Hadi, S., Moslem, M., Al-Sabri, A., Yassin, M.A., 2015a. Biodegradation of engine oil by fungi from mangrove habitat. J. General Appl. Microbiol. 61, 185–192.
Ameen, F., Moslem, M., Hadi, S., Al-Sabri, A.E., 2015b. Biodegradation of Low Density Polyethylene (LDPE) by Mangrove Fungi From the Red Sea Coast. Prog. Rubber Plast. Recycl. Technol. 31, 125.
Ameen, F., Moslem, M., Hadi, S., 2015c. Biodegradation of petroleum oil by mangrove fungi from Saudi Red Sea Coast. Research. J. Biotechnol. 10.
Ameen, F., Moslem, M.A., Hadi, S., Al-Sabri, A., 2014. Biodegradation of cellulosic materials by marine fungi isolated from South Corniche of Jeddah, Saudi Arabia. J. Pure Appl. Microbiol. 8, 3617–3626.
An, F.-L., Liu, W.-H., Zhang, Y., Tao, J., Lu, Y.-H., 2019. Spirocurvulaide, a novel spirobicyclic polyketide from a marine fungus *Curvularia* sp. IFB-Z10. Phytochem. Lett. 29, 12–16.
Bae, S.Y., Liao, L., Park, S.H., Kim, W.K., Shin, J., Lee, S.K., 2020. Antitumor Activity of Asperphenin A, a Lipopeptidyl Benzophenone from Marine-Derived *Aspergillus* sp. Fungus, by Inhibiting Tubulin Polymerization in Colon Cancer Cells. Mar. Drugs 18, 110.
Baharum, S.N., Beng, E.K., Mokhtar, M.A.A., 2010. Marine microorganisms: potential application and challenges. J. Biolog. Sci. 10, 555–564.
Barra, L., Chandrasekaran, R., Corato, F., Brunet, C., 2014. The challenge of ecophysiological biodiversity for biotechnological applications of marine microalgae. Mar. Drugs 12, 1641–1675.
Barzkar, N., Jahromi, S.T., Poorsaheli, H.B., Vianello, F., 2019. Metabolites from marine microorganisms, micro, and macroalgae: immense scope for pharmacology. Mar. Drugs 17, 464.
Blunt, J.W., Carroll, A.R., Copp, B.R., Davis, R.A., Keyzers, R.A., Prinsep, M.R., 2018. Marine natural products. Nat. Prod. Rep. 35, 8–53.
Blunt, J.W., Copp, B.R., Hu, W.-P., Munro, M.H.G., Northcote, P.T., Prinsep, M.R., 2009. Marine natural products. Nat. Prod. Rep. 26, 170–244.
Blunt, J.W., Copp, B.R., Keyzers, R.A., Munro, M.H.G., Prinsep, M.R., 2015. Marine natural products. Nat. Prod. Rep. 32, 116–211.
Borse, B.D., Bhat, D.J., Borse, K.N., Tuwar, N.S., Pawar, N.S., 2012. Marine Fungi of India (Monograph). Broadway Publishing House.
Bugni, T.S., Ireland, C.M., 2004. Marine-derived fungi: a chemically and biologically diverse group of microorganisms. Nat. Prod. Rep. 21, 143–163.
Butler, M.S., Blaskovich, M.A., Cooper, M.A., 2013. Antibiotics in the clinical pipeline in 2013. J. Antibiot. 66, 571–591.
Camacho, F.G., Rodriguez, J.G., Mirón, A.S., Garcia, M.C.C., Belarbi, E.H., Chisti, Y., Grima, E.M., 2007. Biotechnological significance of toxic marine dinoflagellates. Biotechnology advances 25, 176–194.
Carroll, A.R., Copp, B.R., Davis, R.A., Keyzers, R.A., Prinsep, M.R., 2019. Marine natural products. Nat. Prod. Rep. 36, 122–173.
Chang, A., Sun, S., Li, L., Dai, X., Li, H., He, Q., Zhu, H., 2019. Tyrosol from marine Fungi, a novel Quorum sensing inhibitor against *Chromobacterium violaceum* and *Pseudomonas aeruginosa*. Bioorg. Chem. 91, 103140.
Coêlho, D. de F., Tundisi, L.L., Cerqueira, K.S., Rodrigues, J.R. da S., Mazzola, P.G., Tambourgi, E.B., Souza, R.R. de, 2019. Microalgae: cultivation aspects and bioactive compounds. Brazilian Archives of Biology and Technology 62.
Corinaldesi, C., Barone, G., Marcellini, F., Dell'Anno, A., Danovaro, R., 2017. Marine microbial-derived molecules and their potential use in cosmeceutical and cosmetic products. Mar. Drugs 15, 118.
De Vera, C.R., Diaz Crespin, G., Hernández Daranas, A., Montalvão Looga, S., Lillsunde, K.-E., Tammela, P., Perälä, M., Hongisto, V., Virtanen, J., Rischer, H., et al., 2018. Marine microalgae: Promising source for new bioactive compounds. Mar. Drugs 16, 317.
Dembitsky, V.M., Rezanka, T., Spižek, J., Hanuš, L.O., 2005. Secondary metabolites of slime molds (myxomycetes). Phytochemistry 66, 747–769.
Dyková, I., Lom, J., Dvoráková, H., Pecková, H., Fiala, I., 2007. Didymium-like myxogastrids (class Mycetozoa) as endocommensals of sea urchins (*Sphaerechinus granularis*). Folia Parasitol. 54, 1.
Fimbres-Olivarria, D., Carvajal-Millan, E., Lopez-Elias, J.A., Martinez-Robinson, K.G., Miranda-Baeza, A., Martinez-Cordova, L.R., Enriquez-Ocaña, F., Valdez-Holguin, J.E., 2018. Chemical characterization and antioxidant activity of sulfated polysaccharides from *Navicula* sp. Food Hydrocolloids 75, 229–236.
Galaviz-Silva, L., Iracheta-Villarreal, J.M., Molina-Garza, Z.J., 2018. *Bacillus* and *Virgibacillus* strains isolated from three Mexican coasts antagonize *Staphylococcus aureus* and *Vibrio parahaemolyticus*. FEMS Microbiol. Lett. 365, fny202.
Huynh, T.T.M., Phung, T.V., Stephenson, S.L., Tran, H.T.M., 2017. Biological activities and chemical compositions of slime tracks and crude exopolysaccharides isolated from plasmodia of *Physarum polycephalum* and *Physarella oblonga*. BMC Biotech. 17, 76.
Hu, Z., Cheng, B., Du, D., Huang, Z., Pu, Z., Chen, G., Peng, A., Lu, L., 2019. Isolation and identification of a marine actinomycete strain and its control efficacy against citrus green and blue moulds. Biotechnol. Biotechnol. Equip. 33, 719–729.
Hyde, K.D., Jones, E.B.G., Leaño, E., Pointing, S.B., Poonyth, A.D., Vrijmoed, L.L.P., 1998. Role of fungi in marine ecosystems. Biodivers. Conserv. 7, 1147–1161.
Jensen, P.R., Fenical, W., 2000. Marine microorganisms and drug discovery: current status and future potential. Drugs from the Sea, 6–29.
Jimeno, J., Faircloth, G., Sousa-Faro, J.M., Scheuer, P., Rinehart, K., 2004. New marine derived anticancer therapeutics— a journey from the sea to clinical trials. Mar. Drugs 2, 14–29.
Jones, E.B.G., Pang, K.-L., 2012. Marine fungi: and fungal-like organisms. Walter de Gruyter.
Jones, E.B.G., Pang, K.-L., Abdel-Wahab, M.A., Scholz, B., Hyde, K.D., Boekhout, T., Ebel, R., Rateb, M.E., Henderson, L., Sakayaroj, J., et al., 2019. An online resource for marine fungi. Fungal Div. 96, 347–433.
Jones, E.B.G., Suetrong, S., Sakayaroj, J., Bahkali, A.H., Abdel-Wahab, M.A., Boekhout, T., Pang, K.-L., 2015. Classification of marine ascomycota, basidiomycota, blastocladiomycota and chytridiomycota. Fungal Div. 73, 1–72.
Khan, M.I., Shin, J.H., Kim, J.D., 2018. The promising future of microalgae: current status, challenges, and optimization of a sustainable and renewable industry for biofuels, feed, and other products. Microb. Cell Fact. 17, 36.
Kim, H., Hwang, J.-Y., Chung, B., Cho, E., Bae, S., Shin, J., Oh, K.-B., 2019. 2-Alkyl-4-hydroxyquinolines from a Marine-Derived *Streptomyces* sp. Inhibit Hyphal Growth Induction in *Candida albicans*. Mar. Drugs 17, 133.
Kiuru, P., D'Auria, M.V., Muller, C.D., Tammela, P., Vuorela, H., Yli-Kauhaluoma, J., 2014. Exploring marine resources for bioactive compounds. Planta medica 80, 1234–1246.
Lauritano, C., Martin, J., de la Cruz, M., Reyes, F., Romano, G., Ianora, A., 2018. First identification of marine diatoms with anti-tuberculosis activity. Sci. Rep. 8, 1–10.
Le, H.M.T., Do, Q.T., Doan, M.H.T., Vu, Q.T., Nguyen, M.A., Vu, T.H.T., Nguyen, H.D., Duong, N.T.T., Tran, M.H., Chau, V.M., et al., 2019. Chemical Composition and Biological Activities of Metabolites from the Marine Fungi Penicillium sp. Isolated from Sediments of Co To Island Vietnam. Molecules 24, 3830.
Lee, D.-S., Jang, J.-H., Ko, W., Kim, K.-S., Sohn, J.H., Kang, M.-S., Ahn, J.S., Kim, Y.-C., Oh, H., 2013. PTP1B inhibitory and anti-inflammatory effects of secondary metabolites isolated from the marine-derived fungus *Penicillium* sp. JF-55 Mar. Drugs 11, 1409–1426.
Li, H., Cao, K., Cong, P., Liu, Y., Cui, H., Xue, C., 2018. Structure characterization and antitumor activity of the extracellular polysaccharide from the marine fungus *Hansfordia sinuosae*. Carbohydr. Polym. 190, 87–94.
Li, J., Wang, Y., Hao, X., Li, S., Jia, J., Guan, Y., Peng, Z., Bi, H., Xiao, C., Cen, S., et al., 2019. Broad-Spectrum Antiviral Natural Products from the Marine-Derived *Penicillium* sp. IMB17-046. Molecules 24, 2821.
Li, Q., Zhu, R., Yi, W., Chai, W., Zhang, Z., Lian, X.-Y., 2018. Peniciphenalenins A- F from the culture of a marine-associated fungus *Penicillium* sp. ZZ901. Phytochemistry 152, 53–60.
LiBerra, K., Lindequist, U., 1995. Marine fungi: a prolific resource of biologically active natural products? Pharmazie 50, 583–588.
Lindley, L.A., Stephenson, S.L., Spiegel, F.W., 2007. Protostelids and myxomycetes isolated from aquatic habitats. Mycologia 99, 504–509.

Liu, Z., Qiu, P., Liu, H., Li, J., Shao, C., Yan, T., Cao, W., She, Z., 2019. Identification of anti-inflammatory polyketides from the coral-derived fungus *Penicillium sclerotiorin*: *In vitro* approaches and molecular-modeling. Bioorg. Chem. 88, 102973.

Luo, M., Ming, Y., Wang, L., Li, Y., Li, B., Chen, J., Shi, S., 2018a. Local delivery of deep marine fungus-derived equisetin from polyvinylpyrrolidone (PVP) nanofibers for anti-MRSA activity. Chem. Eng. J. 350, 157–163.

Luo, X., Yang, J., Chen, F., Lin, X., Chen, C., Zhou, X., Liu, S., Liu, Y., 2018. Structurally diverse polyketides from the mangrove-derived fungus *diaporthe* sp. SCSIO 41011 with their anti-influenza A virus activities. Front. Chem. 6, 282.

Ma, M., Ge, H., Yi, W., Wu, B., Zhang, Z., 2020. Bioactive drimane sesquiterpenoids and isocoumarins from the marine-derived fungus *Penicillium minioluteum* ZZ1657. Tetrahedron Lett. 61, 151504.

Malibari, R., Sayegh, F., Elazzazy, A.M., Baeshen, M.N., Dourou, M., Aggelis, G., 2018. Reuse of shrimp farm wastewater as growth medium for marine microalgae isolated from Red Sea-Jeddah. J. Cleaner Prod. 198, 160–169.

Martinez, K.A., Lauritano, C., Druka, D., Romano, G., Grohmann, T., Jaspars, M., Martin, J., Diaz, C., Cautain, B., de la Cruz, M., others, 2019. Amphidinol 22, a New Cytotoxic and Antifungal Amphidinol from the Dinoflagellate *Amphidinium carterae*. Marine drugs 17, 385.

Mitra, A., Zaman, S., 2016. Basics of marine and estuarine ecology, Springer. Springer. https://doi.org/10.1007/978-81-322-2707-6

Nguyen, N.T.N., Huynh, T.T.M., Stephenson, S.L., Tran, H.T.M., 2017. Study of the biological activities of *Physarum polycephalum* and *Physarella oblonga* plasmodial extracts. MYCOSPHERE 8, 968–976.

Pang, X., Lin, X., Tian, Y., Liang, R., Wang, J., Yang, B., Zhou, X., Kaliyaperumal, K., Luo, X., Tu, Z., et al., 2018. Three new polyketides from the marine sponge-derived fungus *Trichoderma* sp. SCSIO41004. Nat. Prod. Res. 32, 105–111.

Petruk, G., Roxo, M., De Lise, F., Mensitieri, F., Notomista, E., Wink, M., Izzo, V., Monti, D.M., 2019. The marine Gram-negative bacterium *Novosphingobium* sp. PP1Y as a potential source of novel metabolites with antioxidant activity. Biotechnol. Lett. 41, 273–281.

Raghukumar, S., 2017. Fungi in coastal and oceanic marine ecosystems. Springer.

Rateb, M.E., Ebel, R., 2011. Secondary metabolites of fungi from marine habitats. Nat. Prod. Rep. 28, 290–344.

Romano, G., Costantini, M., Sansone, C., Lauritano, C., Ruocco, N., Ianora, A., 2017. Marine microorganisms as a promising and sustainable source of bioactive molecules. Marine Environ. Res. 128, 58–69.

Sawada, T., Aono, M., Asakawa, S., Ito, A., Awano, K., 2000. Structure determination and total synthesis of a novel antibacterial substance, AB0022A, produced by a cellular slime mold. J. Antibiot. 53, 959–966.

Shearer, C.A., Crane, J.L., 1986. Illinois fungi. XII: fungi and myxomycetes from wood and leaves submerged in southern Illinois swamps. Mycotaxon 25, 527–538.

Shin, D., Byun, W.S., Moon, K., Kwon, Y., Bae, M., Um, S., Lee, S.K., Oh, D.-C., 2018. Coculture of marine *Streptomyces* sp. with *Bacillus* sp. produces a new piperazic acid-bearing cyclic peptide. Front. Chem. 6, 498.

Shivale, N., Marar, T., Samant, M., Harmalkar, M., 2018. Screening of Antioxidant Activity of marine bacteria isolated from marine soil obtained from North-West coastal region of India. Int. J. Biol. Pharm. Allied Sci. 7.

Siddharth, S., Vittal, R.R., 2018. Evaluation of antimicrobial, enzyme inhibitory, antioxidant and cytotoxic activities of partially purified volatile metabolites of marine *Streptomyces* sp. S2A. Microorganisms 6, 72.

Sieg, R.D., Poulson-Ellestad, K.L., Kubanek, J., 2011. Chemical ecology of the marine plankton. Nat. Prod. Rep. 28, 388–399.

Singh, A., Nigam, P.S., Murphy, J.D., 2011. Mechanism and challenges in commercialisation of algal biofuels. Bioresour. Technol. 102, 26–34.

Song, T., Chen, M., Chai, W., Zhang, Z., Lian, X.-Y., 2018. New bioactive pyrrospirones C- I from a marine-derived fungus *Penicillium* sp. ZZ380. Tetrahedron 74, 884–891.

Sran, K.S., Bisht, B., Mayilraj, S., Choudhury, A.R., 2019. Structural characterization and antioxidant potential of a novel anionic exopolysaccharide produced by marine *Microbacterium aurantiacum* FSW-25. Int. J. Biol. Macromol. 131, 343–352.

Tran, H.T.M., Adamatzky, A., 2017. Uses and Potential: Summary of the Biomedical and Engineering Applications of Myxomycetes in the 21st Century, in: Myxomycetes. Elsevier, 365–387.

Vala, A.K., Sachaniya, B., Dudhagara, D., Panseriya, H.Z., Gosai, H., Rawal, R., Dave, B. P., 2018. Characterization of L-asparaginase from marine-derived *Aspergillus niger* AKV-MKBU, its antiproliferative activity and bench scale production using industrial waste. Int. J. Biol. Macromol. 108, 41–46.

Vignesh, S., Raja, A., James, R.A., 2011. Marine drugs: Implication and future studies. Int. J. Pharmacol 7, 22–30.

Wang, C., Fan, Q., Zhang, X., Lu, X., Xu, Y., Zhu, W., Zhang, J., Hao, W., Hao, L., 2018. Isolation, characterization, and pharmaceutical applications of an exopolysaccharide from *Aerococcus Uriaeequi*. Mar. Drugs 16, 337.

Wang, L., Li, C., Yu, G., Sun, Z., Zhang, G., Gu, Q., Zhu, T., Che, Q., Guan, H., Li, D., 2019. Dicitrinones E and F, citrinin dimers from the marine derived fungus *Penicillium citrinum* HDN-152-088. Tetrahedron Lett. 60, 151182.

Wang, W., Liao, Y., Chen, R., Hou, Y., Ke, W., Zhang, B., Gao, M., Shao, Z., Chen, J., Li, F., 2018. Chlorinated azaphilone pigments with antimicrobial and cytotoxic activities isolated from the deep sea derived fungus *Chaetomium* sp. NA-S01-R1. Mar. Drugs 16, 61.

Winsett, K.E., Stephenson, S.L., 2013. Myxomycetes isolated from submerged plant material collected in the Big Thicket National Preserve, Texas. Mycosphere 4, 227–231.

Xie, C.-L., Xia, J.-M., Wang, J.-S., Lin, D.-H., Yang, X.-W., 2018. Metabolomic investigations on *Nesterenkonia flava* revealed significant differences between marine and terrestrial actinomycetes. Mar. Drugs 16, 356.

Xu, P., Ding, L., Wei, J., Li, Q., Gui, M., He, X., Su, D., He, S., Jin, H., 2020. A new aquatic pathogen inhibitor produced by the marine fungus *Aspergillus* sp. LS116. Aquaculture 520, 734670.

Yang, S.-Q., Li, X.-M., Li, X., Chi, L.-P., Wang, B.-G., 2018. Two new diketomorpholine derivatives and a new highly conjugated ergostane-type steroid from the marine algal-derived endophytic fungus *Aspergillus alabamensis* EN-547. Mar. Drugs 16, 114.

Zhang, D., Shu, C., Lian, X., Zhang, Z., 2018. New antibacterial bagremycins F and G from the marine-derived *Streptomyces* sp. ZZ745. Mar. Drugs 16, 330.

Zhang, J., Li, B., Qin, Y., Karthik, L., Zhu, G., Hou, C., Jiang, L., Liu, Miaomiao, Ye, X. others, 2020. A new abyssomicin polyketide with anti-influenza A virus activity from a marine-derived *Verrucosispora* sp. MS100137. Applied Microbiology and Biotechnology, 1–11.

Zhao, Y., Liu, D., Proksch, P., Zhou, D., Lin, W., 2018. Truncateols OV, further isoprenylated cyclohexanols from the sponge-associated fungus *Truncatella angustata* with antiviral activities. Phytochemistry 155, 61–68.

Zhao, D.-L., Wang, D., Tian, X.-Y., Cao, F., Li, Y.-Q., Zhang, C.-S., 2018a. Anti-phytopathogenic and cytotoxic activities of crude extracts and secondary metabolites of marine-derived fungi. Mar. Drugs 16, 36.