16 Biotechnology of Marine Fungi: New Workhorses and Applications

ANNEMARIE KRAMER[1], ANTJE LABES[1]

CONTENTS

I. Introduction

The diversity in the fungal tree of live and their manifold ecological functionalities are not yet reflected in the applied variety of taxonomic groups and the diversity of products on the market. Recently, new ecological niches and habitats including the oceans came into focus to increase the diversity of fungi available for biotechnology (Manohar and Raghukumar 2013). Marine fungi have been neglected for a long time and therefore the knowledge of them is still quite rare. But early screening campaigns revealed that marine fungi are an excellent source for new natural products, indicating their **potential for biotechnological application**. Especially fungi from unique and extreme marine environments, such as the deep sea, are potentially a promising source for rare and unusual compounds (Fenical and Jensen 1993; Vignesh et al. 2011).

The latest large review on marine fungi and their biotechnological potential was published in 2015 (Bonugli-Santos et al. 2015), reflecting on the findings from basic research. This knowledge is rarely transferred into the scientific and bioengineering community working with terrestrial fungi and their biotechnological application.

Here, we aim to illustrate the marine fungal diversity and its potential for biotechnology, describe the current stage of technological realization, and highlight special challenges in working with marine fungi. We hope to provide access to this amazing source to the fungal biotech and scientific community.

II. Marine Fungi: A Disputed Group with High Diversity

A. Taxonomic and Phylogenetic Considerations

Within the marine microorganisms, fungi are still a poorly investigated group. For many years, the presence of fungi in marine habitats was negated, mainly as a consequence of their

---

[1] Flensburg University of Applied Sciences, Flensburg, Germany; e-mail: antje.labes@hs-flensburg.de

Genetics and Biotechnology, 3rd Edition
The Mycota II
J.P. Benz, K. Schipper (Eds.)

cell biology and feeding strategies and partly because of the **bias of research** (Richards et al. 2012). However, the number of isolated fungal strains from the marine environment illustrates the presence of marine fungi. They have been found in association with algae (Raghukumar 2006), sponges (Wiese et al. 2011), and corals (Golubic et al. 2005), as well as in deep-sea mud (Takami et al. 1997, Nagahama 2003) and sediments (Damare et al. 2006), even in anoxic (Stoeck et al. 2003) and methane hydrate-bearing deep-sea sediments (Lai et al. 2007). Living fungi were isolated from marine sediments with an estimated age from 0.18 to 0.43 million years (Gupta 2002, Raghukumar et al. 2004b). In 1979, Kohlmeyer and Kohlmeyer distinguished between two groups of marine fungi, i.e., the obligate and the facultative marine fungi (Kohlmeyer and Kohlmeyer 1979). Due to the fact that many taxa isolated from marine habitats are already known from terrestrial habitats, Hyde et al. stated marine fungi to be rather a **physiological and ecological** group, but certainly not a systematical and taxonomical one (Hyde et al. 2000).

Recent molecular studies on marine mycology revealed the formation of **environmental clusters** within the major fungal phyla and showed that marine fungi occupy a central position in a large number of marine habitats (Manohar and Raghukumar 2013). The rising acceptance of the significance of marine fungi is reflected by the increasing number of publications over the last 60 years. To enhance the currently incomplete understanding of fungal evolutionary diversity (Hawksworth 2001; Jones 2011; Jones et al. 2011), the investigation of the fungal evolution in marine habitats, especially in the deep sea, is essential. These habitats are considered to be hot spots of early evolution (Manohar and Raghukumar 2013).

In the past, the identification of novel strains from marine habitats was impeded by fungal taxonomy based on the morphological description of cultivable strains from terrestrial origin (Richards et al. 2012). Nowadays, the use of additional molecular identification techniques has led to a renewal within the fungal tree of life. Holomorphic relationships were disclosed, as for the genus *Aspergillus* and eight related teleomorph genera (Pitt and Samson 2007), illustrating the obscurity of the nomenclature of fungi.

In 2011, the eighteenth International Botanical Congress in Melbourne, Australia, released the International Code of Nomenclature for algae, fungi and plants, the so-called Melbourne Code (Hawksworth 2011). The code favors the **one-fungus-one-name-rule**, with respect to the teleomorph forms. Besides the deficient nomenclature within the group of fungi, the reconstruction of the tree of life refuted the formerly assumed close relationship of fungi and plants. Fungi are an independent group equal to plants and animals, to the latter of which they are more closely related (Hedges et al. 2004) as both groups belonging to the *Opisthokonta* (Adl et al. 2012). The last common ancestor was a unicellular organism living in the ocean, equipped with a flagellum (Buckley 2008). Molecular data revealed that fungi colonized the land up to 1 billion years ago (Parfrey et al. 2011).

Metagenomics approaches identified a diverse collection of marine fungi, including sequences branching close to chytrids (flagellated protozoa related to fungi), filamentous hypha-forming fungi, and multicellular fungi. The majority of the sequences branched with ascomycete and basidiomycete yeasts (Richards et al. 2012).

With respect to the cultivated diversity, the availability of novel marine genera is still limited. From a total of approximately 30 studies on secondary metabolites from fungi of the deep sea, one-third of the production strains were identified as belonging to *Penicillium* and one-third to *Aspergillus*, and the remainder was distributed to different other genera (Wang et al. 2015). The high proportion of members of the genera *Penicillium* and *Aspergillus* may reflect the high abundance of representatives of these two genera in the samples. Alternatively, the commonly used isolation media favor the growth of these fast-growing groups, reducing the probability to isolate fungi present in low abundance and with other nutrient requirements.

B. Fungal Role in the Marine Environment

Fungi are widely distributed in marine environments from the deep sea to polar ice covers. They occur in sediments and are found in all kinds of living and dead organic matter (Hyde et al. 2000; Jones 2011). Their numbers in the water column of the oceans are low compared to bacteria, and most of the studies on marine fungi have been made with those associated with marine sediments, specific substrates like driftwood or with living macroorganisms such as algae, corals, and sponges (Imhoff 2016).

Cultivation-based data and molecular functional studies demonstrated that fungi in the ocean cover a variety of ecological roles. As known for the terrestrial habitats, many marine fungi act as **saprophytes**, especially degrading macromolecular material as the starter for the microbial food chain (Scheu 2002). Fungi, besides directly serving as nutrient source, also help in removing hardly digestible compounds present in plant parts (Raghukumar et al. 2004b). The fibrous lignocellulose tissues may be softened by the lignocellulose-degrading enzymes of the saprophytic fungi. Fungi might also supply essential nutrients to detritivores. Thereby, fungi play a crucial role in the chemical cycling of carbon and nitrogen in the sea sediments (Karthikeyan et al. 2014). Especially deep-sea fungi were postulated to significantly contribute to aggregate formation and carbon contribution (Raghukumar et al. 2004b).

Despite the rise of metagenome studies especially focusing on the marine environment, metagenome data specifically targeting fungi are missing. The use of NGS techniques opened a new era for marine fungal biodiversity research, tapping an unexpected fungal diversity and richness in the marine realm (e.g., Amend et al. 2012; Redou et al. 2014; Richards et al. 2012; Hassett and Gradinger 2016; Rämä et al. 2014). Generally, the fungal abundance in marine systems can vary greatly. The available studies suggest fungi to be represented in sediments and associated to macroorganisms with up to 30% of the obtained sequences but also show high abundances in the open water column. The fungal sequences found do illustrate the gap between molecular and cultural approaches; especially the deep lineages of fungi are not well represented in the cultural collections, and the overlap of the described diversity is still limited. However, the molecular studies underline the untapped potential of fungal diversity in the oceans.

Marine fungi can be repeatedly isolated from living organisms. Both plants and animals harbor a number of fungi, often with representatives of *Acremonium*, *Aspergillus*, *Fusarium*, *Penicillium*, *Phoma*, and *Trichoderma* (Wang 2006). Due to their accumulation within the animal or plant, usually a large number of fungal species can be isolated, which increases the probability to find representatives of less common taxa. For example, fungi belonging to the less common genera *Beauveria*, *Botryosphaeria*, *Epicoccum*, *Tritirachium*, and *Paraphaeosphaeria* have been obtained from marine sponges (Zhang et al. 2009). The fungi do occur on surfaces but also in specialized parts of macroorganisms. For instance, it was shown that the sponge *Tethia aurantia* harbors different fungal communities in its different tissue layers (Wiese et al. 2011; Thiel et al. 2007).

It is assumed that associations to macroorganisms are based on different ecological roles including mutual or even symbiotic beneficial interaction, saprophytic activity on injured parts of the host and pathogenicity (Richards et al. 2012; Yarden 2014). Aspergillosis in marine animals is a well-studied example of fungal pathogenicity. *Aspergillus sydowii* is a pathogen, e.g., of the Caribbean sea fan (*Gorgonia* spp.) as well as other gorgonian corals. The impact of disease ranges from local mass impact to partial tissue loss and eventual recovery. *A. sydowii* is known as a common terrestrial soil fungus but was shown to prosper in both terrestrial and marine environments. Although *A. sydowii* is common and cosmopolitan, it had not previously been recognized causing disease in terrestrial plants or animals. It was concluded that isolates taken from diseased corals have acquired specific pathogenic potential not seen in isolates from other sources, because non-marine strains of *A. sydowii* did not cause disease in sea fans (Kim and Rypien 2015).

A wide number of fungi were described in association with marine plants, including mangroves. On the one hand, endophytic lifestyle seems to be quite common (Rashmi et al. 2019). On the other hand, pathogenic, e.g., oomycetes and chytrids frequently occurred and induced prevalence of disease in algal aquacultures. These infections can destroy the populations of host plants to a great extent (Li et al. 2010), mainly known from Asian countries cultivating a number of algal species since long time. Frequent re-isolation of fungi and specific occurrence of fungal species in association with specific macroorganisms point toward a number of host-microbe interactions beyond pathogenicity and opportunistic commensalism. Cultured fungi isolated from sessile marine animals and algae have been demonstrated to be capable of producing novel chemicals, which have the potential to affect the marine hosts and their microbiome (as reviewed in Imhoff et al. 2011; Rateb and Ebel 2011; Raghukumar 2008). Also, the determination of abundant bioactive compounds of fungal origin in the **holobiont** indicates their roles in host-fungal and fungal-microbe interactions.

In any case, a thorough understanding of the roles marine fungi do have in the ecosystem will help to prospect for novel genes and products and facilitate realization of biotechnological application of marine fungi, their enzymes, and metabolites.

III. Biotechnology of Marine Fungi: Challenges and Opportunities

A. Cultivation of Marine Fungi: Same But Different?

Any biotechnological production depends on the fungal physiology, as well as on culture medium composition. **Carbon and nitrogen sources** play an important role in biotechnological production. This is well established for numerous fungi from terrestrial environments and was confirmed for marine fungi. Complex substrates, such as starch, casein, pectin, malt extract, wheat bran, olive oil, xylan, and sugarcane bagasse, were used for the cultivation of marine fungi from a variety of marine sources. The optimum temperature and pH of most of these fungi (and subsequently their enzymes) ranges from 20 to 70 °C and from 3 to 9, respectively (Kjer et al. 2010; Golubic et al. 2005; Imhoff 2016).

Marine fungal strains of genera also described from terrestrial habitats have approximately the same optimum conditions for growth and use the same primary pathways for energy and biomass production. However, the **demand of salt** during cultivation can be crucial as a consequence of adaptation to ocean salinity (e.g., D'Souza-Ticlo et al. 2009; Chen et al. 2011 for enzymes from marine fungi). Salt demand means not only presence of sodium chloride in the appropriate concentration. **Sulfate**, one of the major constituents of sea water but also minor elements including heavy metals, is equally important for proper growth media composition of many, especially the obligate marine fungi. Accordingly, many researchers use "**artificial sea water**" for cultivation of these strains (Kjer et al. 2010; Jones and Jennings 1964).

The diversity of marine fungi is not adequately represented in the cultured diversity. Many studies have focused on just a few genera, mainly *Penicillium*, *Aspergillus*, *Fusarium*, and *Cladosporium*. This might be due to the relatively easiness of isolation of these groups, which also dominate isolation campaigns from terrestrial habitats. But still, even when comparing marine strains of these groups to terrestrial relatives, different secondary metabolite biosynthesis pathways can be found (Imhoff 2016). The high diversity seen at the genus level extends further to the subgenus level. For example, representatives of *Penicillium* are among the most studied fungi and represent important drug producers. Nevertheless, many new secondary metabolites are continuously found within strains of marine origin of this genus as shown in reviews by Rateb and Ebel (2011) and Blunt et al. (2015). However, many of the novel and unknown environmental fungal taxa identified in molecular studies are likely to be difficult to propagate in culture, either because they are outcompeted by spores of (terrestrial) fungi also contained in the environmental samples, or alternatively their life cycle is dependent on a symbiotic interaction (Del Campo et al. 2014).

B. Availability of Strain Collections

For the optimal and sustainable use of the marine fungal sources, it is essential to store the microbial cultures. Culture collections keep strains available for further investigations and production processes. Conservation of living cells while reducing metabolism, e.g., by **cryoconservation,** is crucial in order to prevent genetic and phenotypic changes induced by repeated passaging of the cultures. Culture collections thus play a vital role in the conservation and sustainable use of microbial resources including fungi (Daniel and Prasad 2010). They also provide the authentic biological material needed for research in the form of **reference strains** (Fig. 16.1). Until now, only a limited number of marine fungi are deposited in **culture collections with public access.** As a consequence, only a few voucher sequences are available although they are a prerequisite for an accurate sequence-based identification of marine fungi. Bearing in mind the huge number of so far undescribed taxa and strains, there is a strong need for further extension of culture collections with marine fungal specimen and adopted software to store the different kinds of data related to a cultured taxon (Pena and Malm 2012). Nevertheless, some small specific collections of marine fungi exist (Table 16.1).

C. Genetic Background as a Prerequisite for Biotechnological Application

The overall potential of marine fungi for biotechnological application can only be estimated. A better description of the **phylogenetic diversity** of marine fungi, the **biosynthetic potential** of strains, and the **phylogeny of natural products biosynthesis** are needed. Therefore, much emphasis has to be given to determine the phylogenetic position of the fungal strains in order to enable correlation of the phylogenetic relationship to the desired product or, alternatively, to the genetic potential. Accordingly, an increasing number of genome sequences of fungi are currently completed demonstrating an overall tremendous biosynthetic capacity of fungi. High numbers of biosynthetic gene clusters are coding for secondary metabolites in a single genome (e.g., Kumar et al. 2018). For the majority of these

Fig. 16.1 Examples of unclassified strains from a marine fungal strain collection at Flensburg University of Applied Sciences, Flensburg, Germany, illustrating the morphological diversity of marine fungi

Table 16.1 Strain collections comprising a significant number of marine fungal strains

Collection	Focus organisms	Web contact[a]	Description
American type culture collection (ATCC)	Filamentous fungi and yeasts, representing over 7600 fungal species	www.lgcstandards-atcc.org/en/Products/Cells_and_Microorganisms/Fungi_and_Yeast.aspx	Offers storage and management of biomaterials
Biological Resource Center, NITE (NBRC)	Filamentous fungi and yeasts	www.nite.go.jp/en/nbrc/	General deposit possible
Canadian Collection of Fungal Cultures (CCFC)	Over 350,000 fungal and fungal plant disease specimens	https://www5.agr.gc.ca/eng/scientific-collaboration-and-research-in-agriculture/agriculture-and-agri-food-research-centres-and-collections/canadian-collection-of-fungal-cultures-daomc/?id=1503505359059	Small subset of national culture collection comprises marine isolates
mFSC Flensburg strain collection of marine fungi	Unclassified marine fungal isolates	https://hs-flensburg.de/forschung/fue/forschungsinstitute/zait	Collection from different marine habitats, in preparation for storage in public collection
Kiel collection of marine microbes	Marine fungi	www.geomar.de	Collection of marine fungi at Helmholtz Centre for Ocean Research, GEOMAR, not public
Marbank	Marine organisms from Norwegian waters	https://en.uit.no/forskning/forskningsgrupper/gruppe?p_document_id=405720	Offers storage of samples, marine products and customized sampling
National Center for Genetic Engineering and Biotechnology (BIOTEC)	2486 fungal species[b]	www.thai2bio.net	Small subset of marine isolates
United Kingdom National Culture Collection	Central access point for a variety of collections: fungi, yeast, pathogenic fungi	www.ukncc.co.uk	Small subset of national culture collection comprising also marine isolates
Westerdijk Fungal Biodiversity Institute	More than 50,000 fungal strains	www.westerdijkinstitute.nl/	Small subset of national culture collection comprising also marine isolates

Adapted from Reich and Labes (2017)
[a] Accessed 12th February 2020
[b] Number obtained 12th February 2020

gene clusters, the corresponding natural products remain to be identified, but the ever-improving analytical tools will certainly help to elucidate new compounds. Combination of molecular methods and genomic approaches will also contribute to solve the problems related to taxonomy and species identification of marine fungi (Reich and Labes 2017; Kramer et al. 2016).

IV. Biotechnological Products and Processes: From Potential to Application

A. Bioactive Natural Products: Secondary Metabolites

Communication with the host and within associated microbial communities was demonstrated to be mediated by secondary metabolites. Therefore, associations of fungi and macroorganisms are of special interest with respect to the discovery of bioactive natural products (Rashmi et al. 2019). Accordingly, many screening campaigns led to the discovery and subsequent identification of new compounds with interesting bioactivities, including **antibiotic**, **antiviral**, **antitumoral**, etc. Marine fungi produce **structurally unique bioactive natural products** that are not found in terrestrial counterparts. Kong et al. showed that large portions of marine scaffolds are novel (Kong et al. 2010). Auranomides A and B, quinazolin-4-ones substituted with a pyrrolidin-2-iminium moiety from the marine-derived fungus *Penicillium aurantiogriseum*, or aspergillols A and B with a C–C fusion of an anthraquinone and orcinol unit from a deep-sea *Aspergillus versicolor* represent new scaffolds from marine habitats (Song et al. 2012; Wu et al. 2016). Probably, these compounds constitute only a small portion of the possible repertoire, as drug discovery efforts often involve a specific focus, either on disease target, taxonomic groups or on habitats, but do not aim to describe the full **genetic biosynthetic potential**.

Today, only a few compounds made their way to the pharmaceutical market. Marine fungal compounds do face the same challenges in drug discovery and drug development as any other fungal compounds. However, in the 1950s, **cephalosporin C**, a **β-lactam type natural antibiotic**, was discovered from a *Cephalosporium* (later reclassified as *Acremonium*) strain obtained at the Sardinian coast (Newton and Abraham 1955; Abraham et al. 1953). Gliotoxin was identified as a new type of the **antibiotic diketopiperazine** produced by a marine deep-sea sediment *Aspergillus* sp. strain (Okutani 1977).

Marine fungi did also prove to be effective producers of natural products with antitumoral activity (Pejin and Karaman 2017). However, halamid, an anticancer compound of marine fungal origin (trade name plinabulin) is the only one already being in clinical testing phase 2 and 3 for different indications (for review see Pereira et al. 2019). Nevertheless, the current chemotherapeutic clinical pipeline will be fed with marine-derived fungal agents, which are in preclinical stage at the moment.

A steadily increasing number of new, active fungal natural products have been identified from the marine environment, proving them to be a prolific source for bioactive compounds: Blunt et al. listed over 200 natural products from marine-sourced fungi (excluding those from mangroves) in the year 2013 (Blunt et al. 2015). **Cosmetic and cosmeceutical applications** might also be taken into account for marine fungal secondary metabolites (Agrawal et al. 2018). Here, biotechnological approaches can help to close the developmental gap between discovery and production in order to solve compound availability issues in drug development (as reviewed for antibiotics in Silber et al. 2016).

B. Enzymes

Marine fungi can be used for the biotechnological production of **salt- and osmostable enzyme variants** but do also provide new enzymatic activities. Fungi foster, e.g., the detrital processes by production of extracellular degradative enzymes (Sikes et al. 2009). These fungal enzymes from marine origin can be used in biotechnological applications. Extracellular degradative enzymes such as cellulases, xylanases, and ligninases of several terrestrial fungi already have found biotechnological applications in paper and pulp industries, food production, and clothing industry. Fungi isolated from living and decaying marine plant material are capable of degrading "classical" plant macromolecules, like cellulose, cellobiose, lipids, pectin, starch, xylan, and tannic acid (Gessner 1980). In addition, marine fungi can degrade the special carbohydrates found in marine plants, such as alginates, sulfated polysaccharides, laminarin, fucoidan, etc. (as early described as in Schaumann and Weide 1990). These enzymes can be applied in transforming these sugars for energetic use of algal remaining's (e.g., for biogas production) especially from aquacultures. Also, fungal polygalacturonases are useful enzymes for clarification of fruit juices in the food industry (Sandri et al. 2011).

The removal of color residues is a major challenge in paper and textile industries. Effluents from such plants can possess alkaline pH and high salt content. Marine fungi may be ideally suited for the bioremediation of such effluents (Verma et al. 2010): White-rot fungi containing laccase and other enzymes capable of decolorization were isolated from mangroves. Laccase production was shown in several marine fungi in the presence of sea water (D'Souza-Ticlo et al. 2009). However, salt-tolerant lignin-degrading enzymes have not been sufficiently explored for their biotechnological applications.

Marine fungi have also been discussed as source for enzymes or for whole cell application in the **degradation of polycyclic aromatic hydrocarbons** (PAHs). PAHs are widely distributed in the environment and may persist for extended periods of time with toxic, mutagenic, and carcinogenic effects (for review see Bonugli-Santos et al. 2015). The ligninolytic and the monooxygenase system of cytochrome P-450 may be involved in PAH degradation by filamentous fungi (Haritash and Kaushik 2009). The use of marine-derived fungi for the **bioremediation of polluted saline environments** will be facilitated by their tolerance to saline conditions.

Additionally, deep-sea fungi growing under extreme conditions are a good source for industrially useful enzymes with novel properties (Synnes 2007). Proteases constitute one group of the several extracellular enzymes being produced by these fungi; elevated pressure resistance, high pH stability and activity in the presence of several commercial detergents and high salt content were shown for fungal proteases from deep-sea sediments. These features are desirable for commercial application, e.g., as detergents additive for cold wash (Raghukumar 2008).

C. Compatible Solutes

All organisms in marine environments have to adapt to the high salinity of seawater causing significant osmotic pressure. Seawater organisms therefore need to maintain water potentials lower than that of their environment in their cells to enable water uptake. Cells developed a number of strategies to deal with salts: effective efflux machineries, antiporter proteins, and the production of compatible solutes (Forsyth et al. 1971; Ahmadi et al. 2016). The latter strategy is frequently observed in marine fungi. They accumulate osmolytes such as **glycerol, mannitol, polyol, and trehalose** (Blomberg and Adler 1992). These compounds are of technological interest due to their **stabilizing effects, stress-protective and therapeutic activities** in cosmeceuticals and pharmaceuticals but also as **cryoprotectants** (Jadhav et al. 2018).

D. "Detox" Activities

Deep-sea hot vent systems are often characterized by high heavy metal concentration. Fungi thriving in these habitats need to cope with these conditions by producing detoxification compounds, often extracellular sugars such as chitosan-like molecules. These can be applied in cosmetic industry (Brown et al. 2016). Also, enzymes from these fungi show high resistance against heavy-metal intoxication. For instance, deep sea *Cryptococcus* strain was tolerant to $CuSO_4$ up to a concentration of 50 mM and showed high activity of superoxide dismutase, an enzyme responsible for scavenging superoxide radicals (Miura et al. 2002).

V. How to Design Biotechnological Processes for True Marine Fungi

Bonugli-Santos et al. (2015) reviewed the biotechnological production of marine enzymes including bioprocess strategies adopted for the cultivation of marine organisms for enzyme production. Large-scale production (e.g., in bioreactors) of glucoamylase, superoxide dismutase, lignin peroxidase, chitinase, protease, and glutaminase by marine fungal strains including, e.g., *Aureobasidium pullulans*, *Penicillium janthinellum*, and others, has been reported in the literature (Sarkar et al. 2010). These enzymes are produced in bioreactors largely through submerged-state fermentation, and the conditions related to bioreactor production are quite comparable to processes using terrestrial strains. Specific studies for establishing strategies of marine enzyme purification are scarce; the same holds true for processes of secondary metabolite production.

The approach to bring marine fungi into biotechnological application is similar to other microbial processes: After the optimum culture conditions are defined on a small scale (in general, Erlenmeyer flasks in shaking conditions are used), the cultivation has to be transferred to bioreactor-based systems and subsequent scale-up must be performed. Substrate consumption, product formation, and cellular biomass are important factors, which should be considered, and quantified, for appropriate scale-up studies. Special attention in fungal production processes has to be given to **pellet formation** (Krull et al. 2013).

Generally, the unique features of marine environment do have relevance to marine fungal biotechnology. A consideration of the unique properties of the marine environment is important for marine biotechnology: Biotechnological production processes are influenced by the special adaptations of organisms to their environment. The physical factors relevant for cultivation that influence the growth of marine fungi most are **salinity** (including low water potential, high concentrations of sodium ions and high osmotic pressure), **slightly alkaline pH**, partly **oligotrophic nutrient conditions** (especially in the water column), and **high hydrostatic pressure** in combination with **low temperature**, especially in the deep-sea environments (Richards et al. 2012; Bonugli-Santos et al. 2015). Sea water in average has a salinity of 33–35 ppt. Freshwater in comparison contains less than 0.5 ppt salts. Sea waters in estuaries and brackish areas, like in the Baltic Sea or in river deltas, can show wide salinity gradients, requiring special adaptation of the inhabiting organisms. Also, hypersaline waters occur, e.g., in the Dead Sea with salinities of 50–100 ppt. The presence of high levels of salt in seawater are challenging with respect to classical performance of biotechnological processes in stainless steel vessels, as corrosion becomes a severe issue. Even more, early experiments demonstrated that salinity optima for growth in some marine fungi show upward shifts with increasing incubation temperature (Damare and Raghukumar 2008). This interaction of salinity and temperature is termed ***Phoma* pattern** since it was first described in the marine species of *Phoma* (Lorenz and Molitoris 1990). Interestingly, only few reports have investigated the impact of varying salt concentrations on production of marine fungal metabolites. Initial findings show that some marine fungal species exhibit increased growth with increasing seawater concentration in the medium (Masuma et al. 2001). In addition to the osmotic effects on the cell, secondary metabolite production might be sensitive to the seawater composition, i.e., concentration of specific salts, which could have implications for tank reactor cultivation of marine fungi.

In contrast to terrestrial fungi, which generally grow best at pH 4.5–6.0, marine fungi were demonstrated to grow and produce various extracellular enzymes at pH 7–8 (Damare et al. 2006; Raghukumar et al. 2004a). Accordingly, the pH-control in biotechnological processes will need adaptations, when marine strains of a well-known terrestrial species are cultivated. Pressurized conditions are of importance for the cultivation of deep-sea fungi. Low temperature optima in combination with high pressures are of interest, as the catalytic properties of enzymes may be altered (Eisenmenger and Reyes-De-Corcuera 2009).

Bioprocess engineering in marine biotechnology follows the path from **discovery to commercialization** with a variety of possible starting points, but a full value chain remains mainly theoretical, as quantitative biotechnological engineering studies on marine fungi are virtually non-existing in the literature. Silber et al. (2016) reviewed the biotechnological realization of marine fungal antibiotics and demonstrated that biotechnology has a vast potential for sustainable production of antibiotics. Biotechnology, as studied and developed with terrestrial representatives, may help to expand and understand the chemical space in a targeted manner, provide classical full fermentative and semi-synthetic processes, and may include metabolic engineering manipulating the genetic background as a basis for generation of "biological" derivatives (Silber et al. 2016). For terrestrial fungi, the technical and economic feasibility of large-scale processes has been proven many times. Successful transfer into stirred-tank-reactor-system for antibiotic production from marine fungi has been demonstrated, e.g., for the biosynthesis of the tetramic acid compounds ascosetin and lindgomycin by an Arctic marine fungus of the Lindgomycetaceae family (Wu et al. 2015) exhibiting a novel chemical composition.

Sarkar et al. (2010) provided bioprocess data for fermentations of marine fungi for enzyme production. Based on their analysis, there is a demand for further adaptations of scale and inclusion of knowledge on the biology of the fungi into the design of the production processes (e.g., salinity adaptations or pressure for deep-sea organisms). Development of full fermentative processes is required (Sarkar et al. 2010). The increasing knowledge gained on all regulatory levels by means of "omics" techniques will provide the necessary insights. Knowledge on the regulatory genes can be applied in genetic approaches to activate natural product production. Due to the lack of model organisms upon marine fungi, genetic tools for heterologous expression and for homologous manipulation of marine fungi are still in their infancy. The recently successful overexpression of genes leading to synthesis of enniatins, cyclodepsipeptides originally isolated from *Halosarpheia* sp., in *Aspergillus niger* demonstrated reprogramming and transplanting of biosynthetic pathways into established models as a further tool for such approaches (Zobel et al. 2016).

Inclusion of new methods into process development will significantly contribute to further improvements. The use of immobilized cells in a repeated batch tower reactor led to a significant increase of yield in the production of cephalosporin (Ozcengiz and Demain 2013). Niche-mimic bioreactors might be one opportunity to enhance productivity as well as the development of specialized reactors in industrial scale.

VI. Conclusions

A majority of culture-dependent and culture-independent fungi recovered from marine resources show homology to terrestrial species, which obfuscated the ecological role of marine fungi. The presence of novel fungal sequences with less than 97% similarity to previously identified fungal sequences in public databases and culture studies demonstrating obligate marine culture conditions has proven the multiphyletic ecological group of marine fungi.

These fungi show unique cultivation properties and features. In nature, they fulfill a number of ecological functions, comparable to terrestrial fungi. Their unique features may be applied in biotechnology for new products but also for redesign of existing biotechnological processes with more robust culture conditions, as marine fungi did adapt to harsh conditions including high pressure, high osmolarity, cold, toxic heavy metal concentrations, etc.

Only few examples of industrial processes using marine fungi as production organisms are available, but the number of studies highlighting the potential is impressive for enzymes, secondary metabolites, and other possible products. Industrial-scale biotechnological processes should be feasible from scientific, technical, and economic perspectives. This viability needs to be demonstrated through the development of process concepts based on fermentation including metabolic engineering, purification, molecular design, and synthesis data. Some obstacles remain, which need to be solved. Especially, the reduction of the salinity in culture media is a technological challenge.

To realize the potential, we suggest to:

1. Apply products of marine fungi but also establish new and robust workhorses in biotechnology. The biodiversity of filamentous fungi from marine sources is mostly untapped for these applications.
2. Bring together the different scientific communities working on marine and terrestrial fungi and learn from existing processes. Interdisciplinarity between technologists, ecologists, and marine scientist will help

to close gaps in the knowledge of marine fungi relevant for biotechnological productions.

In summary, marine fungal biotechnology can deliver new production strains, enzymes, and products for a sustainable use of marine resources and deeper insights into technological and ecological questions.

Conflicts of Interest The author declares no conflict of interest.

References

Abraham EP, Newton GG, Crawford K, Burton HS, Hale CW (1953) Cephalosporin N: a new type of penicillin. Nature 171:343

Adl SM, Simpson AG, Lane CE, Lukes J, Bass D, Bowser SS, Brown MW, Burki F, Dunthorn M, Hampl V, Heiss A, Hoppenrath M, Lara E, Le Gall L, Lynn DH, McManus H, Mitchell EA, Mozley-Stanridge SE, Parfrey LW, Pawlowski J, Rueckert S, Shadwick RS, Schoch CL, Smirnov A, Spiegel FW (2012) The revised classification of eukaryotes. J Eukaryot Microbiol 59:429–493. https://doi.org/10.1111/j.1550-7408.2012.00644.x

Agrawal S, Adholeya A, Barrow CJ, Deshmukh SK (2018) Marine fungi: an untapped bioresource for future cosmeceuticals. Phytochem Lett 23:15–20. https://doi.org/10.1016/j.phytol.2017.11.003

Ahmadi N, Baroiller J, D'Cotta Carreras H, Morillon R (2016) Adaptation to salinity. In: Torquebiau E (ed) Climate change and agriculture worldwide. Springer, Dordrecht, pp 45–58

Amend AS, Barshis DJ, Oliver TA (2012) Coral-associated marine fungi form novel lineages and heterogeneous assemblages. ISME J 6:1291–1301

Blomberg A, Adler L (1992) Physiology of osmotolerance in fungi. In: Rose AH (ed) Advances in microbial physiology. Academic Press, London, pp 145–212

Blunt JW, Copp BR, Keyzers RA, Munro MH, Prinsep MR (2015) Marine natural products. Nat Prod Rep 32:116–211. https://doi.org/10.1039/c4np00144c

Bonugli-Santos RC, dos Santos Vasconcelos MR, Passarini MRZ, Vieira GAL, Lopes VCP, Mainardi PH, dos Santos JA, de Azevedo DL, Otero IVR, da Silva Yoshida AM, Feitosa VA, Pessoa A, Sette LD (2015) Marine-derived fungi: diversity of enzymes and biotechnological applications. Front Microbiol 6:269. https://doi.org/10.3389/fmicb.2015.00269

Brown D, Brunt K, Rehmann N (2016) Chitosan biopolymer from fungal fermentation for delivery of chemotherapeutic agents. Mater Matter 11:3

Buckley M (2008) The Fungal Kingdom - diverse and essential roles in earth's ecosystem. American Academy of Microbiology, Tucson, AZ

Chen HY, Xue DS, Feng XY, Yao SJ (2011) Screening and production of ligninolytic enzyme by a marine-derived fungal *Pestalotiopsis* sp. J63. Appl Biochem Biotechnol 165:1754–1769. https://doi.org/10.1007/s12010-011-9392-y

Damare S, Raghukumar C (2008) Fungi and macroaggregation in deep-sea sediments. Microb Ecol 56:168–177. https://doi.org/10.1007/s00248-007-9334-y

Damare S, Raghukumar C, Raghukumar S (2006) Fungi in deep-sea sediments of the Central Indian Basin. Deep Sea Res Pt I 53:14–27. https://doi.org/10.1016/j.dsr.2005.09.005

Daniel HM, Prasad GS (2010) The role of culture collections as an interface between providers and users: the example of yeasts. Res Microbiol 161:488–496

Del Campo J, Sieracki ME, Molestina R, Keeling P, Massana R, Ruiz-Trillo I (2014) The others: our biased perspective of eukaryotic genomes. Trends Ecol Evol 29:252–259. https://doi.org/10.1016/j.tree.2014.03.006

D'Souza-Ticlo D, Sharma D, Raghukumar C (2009) A thermostable metal-tolerant laccase with bioremediation potential from a marine-derived fungus. Mar Biotechnol 11:725–737. https://doi.org/10.1007/s10126-009-9187-0

Eisenmenger JM, Reyes-De-Corcuera J (2009) High pressure enhancement of enzymes: a review. Enzyme Microb Technol 45:331–347

Fenical W, Jensen PR (1993) Marine microorganisms: a new biomedical resource. In: Attaway DH, Zaborsky OR (eds) Pharmaceutical and bioactive natural products. Springer, New York, pp 419–457

Forsyth PM, Shindler BD, Gochnauer BM, Kushner JD (1971) Salt tolerance of intertidal marine bacteria. Can J Microbiol 17:825–828

Gessner RV (1980) Degradative enzyme production by salt-marsh fungi. Botanica Mar 23:133–139

Golubic S, Radke G, Le-Campion-Alsumard T (2005) Endolithic fungi in marine ecosystem. Trends Microbiol 13:229–235

Gupta SM (2002) Pyloniid stratigraphy – a new tool to date tropical radiolarian ooze from the central tropical Indian Ocean. Mar Geol 184:85–93. https://doi.org/10.1016/s0025-3227(01)00276-6

Haritash A, Kaushik C (2009) Biodegradation aspects of polycyclic aromatic hydrocarbons (PAHs): a review. J Hazard Mater 169:1–15

Hassett BT, Gradinger R (2016) Chytrids dominate arctic marine fungal communities. Environ Microbiol 18:2001–2009

Hawksworth DL (2001) The magnitude of fungal diversity: the 1.5 million species estimate revisited. Mycol Res 105:1422–1432

Hawksworth DL (2011) A new dawn for the naming of fungi: impacts of decisions made in Melbourne in

July 2011 on the future publication and regulation of fungal names. IMA Fungus 2:155–162. https://doi.org/10.5598/imafungus.2011.02.02.0610.3897/mycokeys.1.2062

Hedges SB, Blair JE, Venturi ML, Shoe JL (2004) A molecular timescale of eukaryote evolution and the rise of complex multicellular life. BMC Evol Biol 4:2. https://doi.org/10.1186/1471-2148-4-2

Hyde KD, Sarma VV, Jones EBG (2000) Morphology and taxonomy of higher marine fungi. In: Hyde KD, Pointing SB (eds) Marine mycology - a practical approach, 1st edn. Fungal Diversity Press, Hong Kong, pp 172–204

Imhoff JF (2016) Natural products from marine fungi - still an underrepresented resource. Mar Drugs 14:1–19. https://doi.org/10.3390/md14010019

Imhoff JF, Labes A, Wiese J (2011) Bio-mining the microbial treasures of the ocean: new natural products. Biotechnol Adv 29:468–482. https://doi.org/10.1016/j.biotechadv.2011.03.001

Jadhav K, Kushwah B, Jadhav I (2018) Insight into compatible solutes from halophiles: exploring significant applications in biotechnology. In: Singh J, Sharma D, Kumar G, Sharma NR (eds) Microbial bioprospecting for sustainable development. Springer, Singapore, pp 291–307

Jones EBG (2011) Are there more marine fungi to be described? Botanica Mar 54:343–354. https://doi.org/10.1515/bot.2011.043

Jones GEB, Jennings DH (1964) The effect of salinity on the growth of marine fungi in comparison with non-marine species. Trans Br Mycol Soc 47:619–625. https://doi.org/10.1016/S0007-1536(64)80041-3

Jones MD, Forn I, Gadelha C, Egan MJ, Bass D, Massana R, Richards TA (2011) Discovery of novel intermediate forms redefines the fungal tree of life. Nature 474:200–203. https://doi.org/10.1038/nature09984

Karthikeyan P, Kanimozhi K, Senthilkumar G, Panneerselvam A, Asho G (2014) Optimization of enzyme production in *Trichoderma viride* using carbon and nitrogen source. Int J Curr Microbiol App Sci 3:88–95

Kim K, Rypien K (2015) Aspergillosis of Caribbean sea fan corals, *Gorgonia* spp. In: Woodley CM, Downs CA, Bruckner AW, Porter JW, Galloway SB (eds) Diseases of coral. Wiley, Hoboken, NJ, pp 236–241

Kjer J, Debbab A, Aly AH, Proksch P (2010) Methods for isolation of marine-derived endophytic fungi and their bioactive secondary products. Nat Protoc 5:479–490. https://doi.org/10.1038/nprot.2009.233

Kohlmeyer J, Kohlmeyer E (1979) Marine mycology: the higher fungi. Academic Press, New York

Kong DX, Jiang Y-Y, Zhang H-Y (2010) Marine natural products as sources of novel scaffolds: achievement and concern. Drug Discov 15:884–886

Kramer A, Labes A, Imhoff JF (2016) Phylogenetic relationship and secondary metabolite production of marine fungi producing the cyclodepsipeptides scopularide A and B. Mar Biotechnol 18:466–474. https://doi.org/10.1007/s10126-016-9707-7

Krull R, Wucherpfennig T, Esfandabadi ME, Walisko R, Melzer G, Hempel DC, Kampen I, Kwade A, Wittmann C (2013) Characterization and control of fungal morphology for improved production performance in biotechnology. J Biotechnol 163:112–123. https://doi.org/10.1016/j.jbiotec.2012.06.024

Kumar A, Sorensen JL, Hansen FT, Arvas M, Syed MF, Hassan L, Benz JP, Record E, Henrissat B, Poggeler S, Kempken F (2018) Genome sequencing and analyses of two marine fungi from the North Sea unraveled a plethora of novel biosynthetic gene clusters. Sci Rep 8:10187. https://doi.org/10.1038/s41598-018-28473-z

Lai X, Cao L, Tan H, Fang S, Huang Y, Zhou S (2007) Fungal communities from methane hydrate-bearing deep-sea marine sediments in South China Sea. ISME J 1:756–762. https://doi.org/10.1038/ismej.2007.51

Li W, Zhang T, Tang X, Wang B (2010) Oomycetes and fungi: important parasites on marine algae. Acta Oceanol Sin 29:74–81

Lorenz R, Molitoris H-P (1990) Published. Phoma-pattern. Combined influence of salinity and temperature on growth of marine fungi. In: Reisinger A, Bresinsky A (eds) Fourth international mycological congress. IMC 4, Regensburg. 136/3

Manohar CS, Raghukumar C (2013) Fungal diversity from various marine habitats deduced through culture-independent studies. FEMS Microbiol Lett 341:69–78. https://doi.org/10.1111/1574-6968.12087

Masuma R, Yamaguchi Y, Noumi M, Omura S, Namikoshi M (2001) Effect of sea water concentration on hyphal growth and antimicrobial metabolite production in marine fungi. Mycoscience 42:455–459

Miura T, Abe F, Inoue A, Usami R, Horikoshi K (2002) Superoxide dismutase is involved in high tolerance to copper in the deep-sea yeast, *Cryptococcus* sp. N6. Biotechnol Lett 24:1069–1074. https://doi.org/10.1023/A:1016082530108

Nagahama T (2003) *Cryptococcus surugaensis* sp. nov., a novel yeast species from sediment collected on the deep-sea floor of Suruga Bay. Int J Syst Evol Microbiol 53:2095–2098. https://doi.org/10.1099/ijs.0.02712-0

Newton GGF, Abraham EP (1955) Cephalosporin C, a new antibiotic containing sulphur and D-aminoadipic acid. Nature 175:548–548

Okutani K (1977) Gliotoxin produced by a strain of *Aspergillus* isolated from marine mud. Bull Jap Soc Sci Fish 43:995–1000

Ozcengiz G, Demain AL (2013) Recent advances in the biosynthesis of penicillins, cephalosporins and clavams and its regulation. Biotechnol Adv 31:287–311. https://doi.org/10.1016/j.biotechadv.2012.12.001

Parfrey LW, Lahr DJ, Knoll AH, Katz LA (2011) Estimating the timing of early eukaryotic diversification with multigene molecular clocks. Proc Natl Acad Sci USA 108:13624–13629. https://doi.org/10.1073/pnas.1110633108

Pejin B, Karaman M (2017) Antitumor natural products of marine-derived fungi. In: Mérillon JM, Ramawat K (eds) Fungal metabolites. Reference series in phytochemistry. Springer, Cham, pp 1–28

Pena C, Malm T (2012) VoSeq: a voucher and DNA sequence web application. PLoS One 7:e39071. https://doi.org/10.1371/journal.pone.0039071

Pereira RB, Evdokimov NM, Lefranc F, Valentao P, Kornienko A, Pereira DM, Andrade PB, Gomes A (2019) Marine-derived anticancer agents: clinical benefits, innovative mechanisms, and new targets. Mar Drugs 17:1–21. https://doi.org/10.3390/md17060329

Pitt JI, Samson RA (2007) Nomenclatural considerations in naming species of *Aspergillus* and its teleomorphs. Stud Mycol 59:67–70. https://doi.org/10.3114/sim.2007.59.08

Raghukumar C (2006) Algal-fungal interactions in the marine ecosystem: symbiosis to parasitism. In: Tewari A (ed) Recent advances on applied aspects of Indian marine algae with reference to global scenario. CSMCRI, Bhavnagar, pp 366–385

Raghukumar C (2008) Marine fungal biotechnology: an ecological perspective. Fung Div 31:19–35

Raghukumar C, Muraleedharan U, Gaud VR, Mishra R (2004a) Xylanases of marine fungi of potential use for biobleaching of paper pulp. J Ind Microbiol Biotechnol 31:433–441. https://doi.org/10.1007/s10295-004-0165-2

Raghukumar C, Raghukumar S, Sheelu G, Gupta SM, Nath BN, Rao BR (2004b) Buried in time: culturable fungi in a deep-sea sediment core from the Chagos Trench, Indian Ocean. Deep Sea Res Part 1 Oceanogr Res Pap 51:1759–1768. https://doi.org/10.1016/j.dsr.2004.08.002

Rämä T, Norden J, Davey ML, Mathiassen GH, Spatafora JW, Kauserud H (2014) Fungi ahoy! Diversity on marine wooden substrata in the high North. Fungal Ecol 8:46–58

Rashmi M, Kushveer JS, Sarma VV (2019) Secondary metabolites produced by endophytic fungi from marine environments. In: Jha S (ed) Endophytes and secondary metabolites. Reference series in phytochemistry. Springer, Cham, pp 491–526

Rateb ME, Ebel R (2011) Secondary metabolites of fungi from marine habitats. Nat Prod Rep 28:290–344. https://doi.org/10.1039/c0np00061b

Redou V, Ciobanu MC, Pachiadaki MG, Edgcomb V, Alain K, Barbier G, Burgaud G (2014) In-depth analyses of deep subsurface sediments using 454-pyrosequencing reveals a reservoir of buried fungal communities at record-breaking depths. FEMS Microbiol Ecol 90:908–921

Reich M, Labes A (2017) How to boost marine fungal research: a first step towards a multidisciplinary approach by combining molecular fungal ecology and natural products chemistry. Mar Genomics 36:57–75. https://doi.org/10.1016/j.margen.2017.09.007

Richards TA, Jones MD, Leonard G, Bass D (2012) Marine fungi: their ecology and molecular diversity. Annu Rev Mar Sci 4:495–522. https://doi.org/10.1146/annurev-marine-120710-100802

Sandri IG, Fontana RC, Barfknecht DM, da Silveira MM (2011) Clarification of fruit juices by fungal pectinases. LWT Food Sci Technol 44:2217–2222. https://doi.org/10.1016/j.lwt.2011.02.008

Sarkar S, Pramanik A, Mitra A, Mukherjee J (2010) Bioprocessing data for the production of marine enzymes. Mar Drugs 8:1323–1372. https://doi.org/10.3390/md8041323

Schaumann K, Weide G (1990) Enzymatic degradation of alginate by marine fungi. Hydrobiologia 204 (205):589–596

Scheu S (2002) The soil food web: structure and perspectives. Eur J Soil Biol 38:11–20. https://doi.org/10.1016/S1164-5563(01)01117-7

Sikes EL, Uhle ME, Nodder SD, Howard ME (2009) Sources of organic matter in a coastal marine environment: evidence from n-alkanes and their δ13C distributions in the Hauraki Gulf, New Zealand. Mar Chem 113:149–163. https://doi.org/10.1016/j.marchem.2008.12.003

Silber J, Kramer A, Labes A, Tasdemir D (2016) From discovery to production: biotechnology of marine fungi for the production of new antibiotics. Mar Drugs 14:1–20. https://doi.org/10.3390/md14070137

Song F, Ren B, Yu K, Chen C, Guo H, Yang N, Gao H, Liu X, Liu M, Tong Y, Dai H, Bai H, Wang J, Zhang L (2012) Quinazolin-4-one coupled with pyrrolidin-2-iminium alkaloids from marine-derived fungus *Penicillium aurantiogriseum*. Mar Drugs 10:1297–1306. https://doi.org/10.3390/md10061297

Stoeck T, Taylor GT, Epstein S (2003) Novel eukaryotes from the permanently anoxic Cariaco Basin (Caribbean Sea). Appl Environ Microbiol 69:5656–5663

Synnes M (2007) Bioprospecting of organisms from the deep sea: scientific and environmental aspects. Clean Technol Environ Policy 9:53–59

Takami H, Inoue A, Fuji F, Horikoshi K (1997) Microbial flora in the deepest sea mud of the Mariana Trench. FEMS Microbiol Lett 152:279–285

Thiel V, Neulinger SC, Staufenberger T, Schmaljohann R, Imhoff JF (2007) Spatial distribution of sponge-associated bacteria in the Mediterranean sponge *Tethya aurantium*. FEMS Microbiol Ecol 59:47–63. https://doi.org/10.1111/j.1574-6941.2006.00217.x

Verma AK, Raghukumar C, Verma P, Shouche YS, Naik CG (2010) Four marine-derived fungi for bioremediation of raw textile mill effluents. Biodegradation 21:217–233. https://doi.org/10.1007/s10532-009-9295-6

Vignesh S, Raja A, James RA (2011) Marine drugs: implication and future studies. Int J Pharmacol 7:22–30. https://doi.org/10.3923/ijp.2011.22.30

Wang G (2006) Diversity and biotechnological potential of the sponge-associated microbial consortia. J Ind Microbiol Biotechnol 33:545–551. https://doi.org/10.1007/s10295-006-0123-2

Wang YT, Xue YR, Liu CH (2015) A brief review of bioactive metabolites derived from deep-sea fungi. Mar Drugs 13:4594–4616. https://doi.org/10.3390/md13084594

Wiese J, Ohlendorf B, Blumel M, Schmaljohann R, Imhoff JF (2011) Phylogenetic identification of fungi isolated from the marine sponge *Tethya aurantium* and identification of their secondary metabolites. Mar Drugs 9:561–585. https://doi.org/10.3390/md9040561

Wu B, Wiese J, Labes A, Kramer A, Schmaljohann R, Imhoff JF (2015) Lindgomycin, an unusual antibiotic polyketide from a marine fungus of the Lindgomycetaceae. Mar Drugs 13:4617–4632. https://doi.org/10.3390/md13084617

Wu Z, Wang Y, Liu D, Proksch P, Yu S, Lin WT (2016) Antioxidative phenolic compounds from a marine-derived fungus *Aspergillus versicolor*. Tetrahedron 72:50–57

Yarden O (2014) Fungal association with sessile marine invertebrates. Front Microbiol 5:228. https://doi.org/10.3389/fmicb.2014.00228

Zhang Y, Mu J, Feng Y, Kang Y, Zhang J, Gu PJ, Wang Y, Ma LF, Zhu YH (2009) Broad-spectrum antimicrobial epiphytic and endophytic fungi from marine organisms: isolation, bioassay and taxonomy. Mar Drugs 7:97–112. https://doi.org/10.3390/md7020097

Zobel S, Boecker S, Kulke D, Heimbach D, Meyer V, Süssmuth RD (2016) Reprogramming the biosynthesis of cyclodepsipeptide synthetases to obtain new enniatins and beauvericins. ChemBioChem 17:283–287. https://doi.org/10.1002/cbic.201500649