

Review

Marine Fungi: Biotechnological Perspectives from Deep-Hypersaline Anoxic Basins

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Abstract: Deep-sea hypersaline anoxic basins (DHABs) are one of the most hostile environments on Earth. Even though DHABs have hypersaline conditions, anoxia and high hydrostatic pressure, they host incredible microbial biodiversity. Among eukaryotes inhabiting these systems, recent studies demonstrated that fungi are a quantitatively relevant component. Here, fungi can benefit from the accumulation of large amounts of organic material. Marine fungi are also known to produce bioactive molecules. In particular, halophilic and halotolerant fungi are a reservoir of enzymes and secondary metabolites with valuable applications in industrial, pharmaceutical, and environmental biotechnology. Here we report that among the fungal taxa identified from the Mediterranean and Red Sea DHABs, halotolerant halophilic species belonging to the genera *Aspergillus* and *Penicillium* can be used or screened for enzymes and bioactive molecules. Fungi living in DHABs can extend our knowledge about the limits of life, and the discovery of new species and molecules from these environments can have high biotechnological potential.

Keywords: marine fungi; deep hypersaline anoxic basins; blue biotechnologies; deep sea

1. Introduction

Deep-sea ecosystems represent the last frontier of scientific research in marine ecosystems [1]. Compared to terrestrial and coastal ecosystems, the deep sea (beyond 200 m below sea level) hosts some of the most extreme habitats, characterised by complete darkness, wide temperature ranges from below 0 °C to 450 °C or more, and high hydrostatic pressure of average 400 atm [2,3]. The deep sea also includes the deep-sea hypersaline anoxic basins (DHABs), which are depressions of the seafloor found at more than 2 km below the sea level. Since DHABs were first discovered in the Red Sea [4,5], more than 36 hypersaline basins have been observed in regions all over of the world (Figure 1), from the Mediterranean Sea to the Gulf of Mexico and also in the Black Sea [6]. Although DHAB geological features can change considerably from case to case, most DHABs originated from the re-dissolution of evaporitic deposits buried under layers of sediments and exposed to seawater because of tectonic activity [7]. Therefore, chemical and physical characteristics are specific to each DHAB ([6] and references therein). Overall, salinity can vary from 240 to 500 PSU [7,8] with variable concentrations of halite (NaCl-mineral) [9,10], kieserite (MgSO₄-mineral) [9–11], sulphate [9,10] and other minerals, as well as toxic compounds, such as hydrogen sulphide, ammonium, and manganese [6]. The dissolution of the anciently buried evaporites creates a thick layer of brines, which are separated by a halocline from the overlying oxygenated deep-seawater column [9]. Thus, microbial degradation of organic

matter within the basin eventually consumes the oxygen available in the water, and since this cannot mix with the overlying oxygenated water, the basin becomes ultimately anoxic. Anoxia and sulfidic conditions combined with the high salinity and hydrostatic pressure and the absence of light, make these deep, hypersaline, anoxic basins some of the most hostile environments on our planet.

Although life has been thought to be absent in such conditions, DHABs provided relevant insights into the extent of life for all three domains, including the possible presence of living metazoans [8,10,12–20]. Other studies on molecular diversity, metabolic activities and microscopy analyses have revealed diverse and abundant prokaryotic assemblages [18,21–25]. At the same time, investigations on eukaryotic life obtained by ribosomal DNA analyses and microscopic images showed the presence of unexpected micro-eukaryotic communities thriving in DHABs where fungi accounted for a high number of reads or operational taxonomic units (OTUs)/phylotypes to the entire assemblage [12,26,27].

Fungi are essential decomposers of organic matter and play a key role in carbon cycling and food web dynamics in terrestrial and marine ecosystems, also including mutualistic, parasitic and pathogenic taxa [28,29]. In particular, saprotrophic fungi are known to produce a vast array of organic compounds and enzymes able to decompose even the most recalcitrant fraction of natural and human-made organic materials [30]. In the Tethis basin, the relative abundance of the rRNA reads of fungi was high, especially in the lower halocline where the conditions of salinity and oxygen are more challenging [31,32]. Since organic material accumulates at the halocline, fungi have been suggested to be active remineralisers in such extreme conditions [31,32].

Fungi, among marine organisms, produce a large and diverse array of bioactive compounds exploitable for several biotechnological purposes [33]. However, quantitative relevance, diversity, ecological role and adaptations of fungi to the extreme conditions of DHABs are still largely unexplored. Consequently, the bioactive compounds they produce remain still unexploited also. The present review provides an overview of the fungal ecology and diversity in DHAB systems highlighting their potential in producing enzymes and bioactive molecules for industrial, pharmaceutical and environmental applications.

2. Fungi in DHABs

Advances in “omics” analyses, including next-generation sequencing, genome mining, and bioinformatic tools revealed that fungi are an important eukaryotic group in several DHABs. Although the information is still limited, Ascomycota and Basidiomycota fungi were identified in many DHABs from the Mediterranean and Red Seas, mostly through high-throughput sequencing analyses (Table 1). For example, fungi were found in the upper and lower halocline of L’Atalante basin [12,26] and in the Thetis basin [27]. In the brine pool adjacent to Thuwal cold seep as well as in the Discovery and L’Atalante basins, fungal reads contributed to 68 to 99% of the eukaryotic reads [26,34].

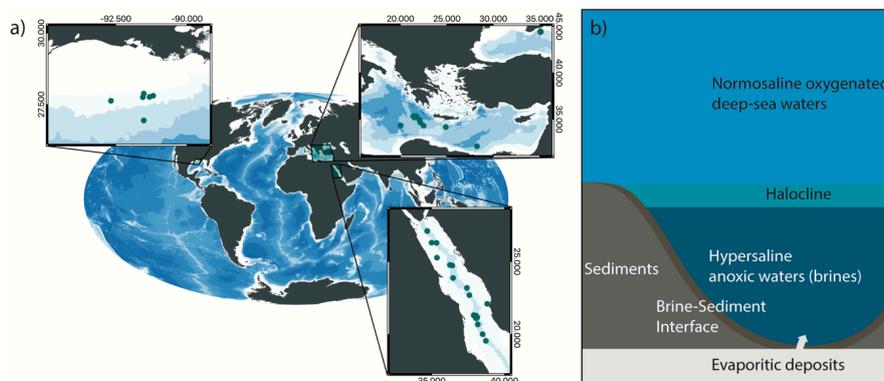


Figure 1. Locations of the DHABs identified in the Gulf of Mexico, Mediterranean Sea, Black Sea and the Red Sea (a) (for detailed elucidation on the environmental features and coordinates see [6]). Schematic vertical section of a generic DHAB showing the normo-saline oxygenated deep water, halocline and anoxic brines, brine-sediment interface and sediments (b).

Table 1. List of fungal taxa identified in deep-sea hypersaline anoxic basins. Taxa are expressed as Sub-Division (SD), Order (O), Class (C) and Family (F).

Fungal Taxon/Closest Relative	DHAB	Site	Depth	Area	Coordinates	Reference
Malasseziales (O)	Bannock	Halocline	3330	Mediterranean	34°17.488' N 20°00.692' E	[20]
Malasseziomycetes (C), Microbotryomycetes (C) and Dothideomycetes (C)	Discovery	Upper halocline	3582	Mediterranean	35°17.150' N 21°42.308' E	[26]
<i>Aspergillus</i> and <i>Penicillium</i>	Discovery	Upper halocline	3583	Mediterranean	35°17.150' N 21°42.308' E	[35]
<i>Aspergillus</i> and <i>Penicillium</i>	Discovery	Lower halocline	3586	Mediterranean	35°17.150' N 21°42.308' E	[35]
<i>Aspergillus</i> , <i>Penicillium</i> , <i>Sordaria</i> , <i>Rhodotorula glutinis</i> , <i>R. mucillaginosa</i>	L'Atalante	Upper halocline	3499	Mediterranean	35°18.865' N 21°24.338' E	[12]
Ustilaginomycetes (C)	L'Atalante	Lower halocline	3501	Mediterranean	35°18.865' N 21°24.338' E	[12]
Ustilaginomycetes (C)	L'Atalante	Upper halocline	3430	Mediterranean	35°18.865' N 21°24.338' E	[26]
Malasseziomycetes (C), Microbotryomycetes (C) and Dothideomycetes (C)	L'Atalante	Lower halocline	3430	Mediterranean	35°18.865' N 21°24.338' E	[26]
Malasseziomycetes (C), Microbotryomycetes (C) and Dothideomycetes (C)	L'Atalante	Lower halocline	3501	Mediterranean	35°18.865' N 21°24.338' E	[35]
<i>Aspergillus</i> and several Ascomycota and Basidiomycota strains	L'Atalante	Lower halocline	3501	Mediterranean	35°18.865' N 21°24.338' E	[35]
Fungi	Thetis	Lower halocline	3258	Mediterranean	34°40.158' N 22°08.703' E	[31]
<i>Rhodotorula mucillaginosa</i> , Malasseziales (O) and Atheliaceae (F)	Thetis	Halocline	3258	Mediterranean	34°40.189' N 22°8.728' E	[27]
<i>Rhodotorula mucillaginosa</i> , <i>Rhodosporidium</i> , <i>Cladosporium</i> , <i>Aspergillus</i> , <i>Candida</i> , Pucciniomycotina (SD) and Atheliaceae (F)	Thetis	Brine	3415	Mediterranean	34°40.189' N 22°8.728' E	[27]
<i>Acremonium</i>	Thuwal brine pool sediments	Brine sediments	850	Red sea	22°16' N 38°53' E	[34]
Malasseziomycetes (C), Microbotryomycetes (C) and Dothideomycetes (C)	Urania	Halocline	3468	Mediterranean	35°13.784' N 21°42.308' E	[26]
<i>Aspergillus</i> and <i>Penicillium</i>	Urania	Middle halocline	3470	Mediterranean	35°13.784' N 21°42.308' E	[35]

Some of the fungal taxa found in DHABs were closely related to described species, widely distributed in the deep sea, such as the genera *Rhodotorula*, *Cladosporium* and *Aspergillus*. However, most of the observed fungal taxa were only distantly related to described species, which could represent novel taxa even at high taxonomic levels [36]. In addition, the hypoxic/suboxic brine layer near the Thuwal cold seeps in the Red Sea was characterised by abundant fungal taxa mostly affiliating with the *Acremonium* genus, which includes several saprophytic species [34]. While Thetis and Thuwal DHABs were characterised by abundant fungal genera belonging to Ascomycota [27,34], 18S rRNA analyses of some Mediterranean DHABs (i.e., Discovery, Urania, L'Atalante) showed a large number of reads affiliating to Basidiomycota, of which malasseziomycetes accounted for the largest majority [26]. *Malassezia* reads detected by [26] contributed to a significant proportion to the OTUs identified in the lower haloclines of both Discovery and L'Atalante. These sequences were also related to phylotypes reported from the anoxic lower halocline of the Thetis basin [27], the anoxic Cariaco Basin, the anoxic fjord Saanich Inlet [37] and deep sub-surface marine sediments of Peru Margin [38]. This cosmopolitan genus is probably of great importance in extreme deep-sea environments [26]. The diversity of habitats in which malasseziomycetes were found suggests that this group may have a variety of trophic strategies ranging from saprotrophy to biotrophy [39].

Microscopic analyses from three DHABs of the Mediterranean Sea (Discovery, Urania and L'Atalante) revealed the presence of several filamentous hyphae, which were hypothesised as belonging to fungi adapting to hypersaline environments [26,40]. In particular, several Ascomycota and Basidiomycota fungi are known to tolerate high salinity [41–43]. Fungi, as osmotolerant organisms, can balance the osmotic pressure of the surroundings by accumulating small organic molecules (i.e., glycerol, sugars, mannitol, arabitol) and thus maintaining low ion intracellular concentrations (such as Na^+ , Mg^{2+} , Ca^{2+}) [44,45]. Particularly, halotolerant and halophilic fungi employ a strategy through which the response to stress due to increasing concentrations of organic osmolytes or salt is under the control of the high osmolarity glycerol (HOG) signalling pathway [44]. Consistently, microscopic observations also provided evidence of the presence of both yeast and filamentous fungi on bottom sediments of the oxycline and deep anoxic zones of the Black Sea [40]. Furthermore, the isolation of specimens related to *Sarocladium strictum* and *Acremonium* sp. from the brine pool adjacent to the Thual cold seep indicate that fungi might be active components of DHAB microbial assemblages [34].

So far, very little information is available on the specific eukaryotic metabolic activities in DHABs [31], even though existing methods have been proven to be reliable for the identification of eukaryotic-only transcripts (e.g., enrichment in eukaryotic transcripts in metatranscriptome data to capture a higher fraction of eukaryotic sequences). Recently, the metatranscriptomic approach has begun to blossom as a powerful method for the functional characterisation of complex microbial communities [46] and has been carried out in different ecosystems, including non-marine subsurface systems [47,48], marine deep-sea sediments [49,50]. The metatranscriptomic approach has several advantages over DNA-based amplicon sequencing: It is less susceptible to amplification biases, it captures only living organisms, and provides a larger set of genes, which can be exploited for taxonomic identification [51]. In addition, the use of RNA-sequencing can reveal not only the taxonomic composition but also the active biochemical functions of microbial assemblages living in extreme environments [52]. The most critical step in such an approach is represented by the assignment of putative assembled transcripts to specific functions, as many uncultured organisms can be characterised by genomic novelties with no (or weak) similarity to genes and enzymes available in public databases [53]. The lack of fungal reference genomes and specific pipelines make analysis and interpretation of these datasets very challenging [35,54,55]. Therefore, the improvement and advancement of scientific technologies for deciphering fungal activity and identity in DHABs, also through the combination of multiple approaches (e.g., molecular-based and microscopic-based technologies and fungal-specific stains), are needed [56].

Eukaryotic metatranscriptome analyses performed on DHABs indicated that fungi are not only present but also metabolically active [26,27,31,35]. In particular, the middle and lower haloclines of the Urania and Discovery basins, respectively, were characterised by high metabolic potential, amenable to *Malasseziomycetes*, *Dothideomycetes* and *Microbotryomycetes* as well as to *Aspergillus* and *Penicillium* genera and various yeasts [26,31,35]. On the other hand, in the Discovery and Urania basins, a relevant number of transcripts indicates their saprophytic habits [35]. For example, the high expression level of a clathrin coat-binding protein of *Aspergillus* involved in clathrin-mediated endocytosis suggests that saprophytic fungi are active at the middle halocline of the Urania basin [35]. Up-regulation of genes related to antibiotic production, including fusaric acid production by the fungal genus *Fusarium*, has been reported in the upper and lower halocline of the Discovery basin and in the middle halocline of the Urania basin, suggesting that fungi in DHABs could compete with microorganisms [35]. Consistently, abundant mRNA sequences associated with the polyketide synthase enzymes, which play a key role in the production of antibiotics and participate in other secondary metabolite syntheses, were observed [35,57]. These results are also consistent with the high number of transcripts related to mechanisms involved in anti-microbial resistance, including drug resistance transporters, efflux pumps and multidrug resistance proteins [35,58]. Overall, these results indicate that fungi are active components of microbial assemblages even in DHAB extreme environmental conditions.

In anoxic conditions, fungi might act as a biological source of hydrogen, thus supporting the growth of hydrogen-consuming prokaryotes [59,60]. Moreover, in such conditions, fungi and chemoautotrophic prokaryotes might establish symbiotic relationships [59,61], enhancing the fitness of microbial communities in challenging environments, such as the DHABs.

Overall, the available literature suggests that fungi can take advantage of the high concentration of organic material in DHABs [31,32,62]. Thus they could play a role in carbon and nutrient cycling even under such extreme ecosystems [29]. In addition, since previous studies reported that competition could occur among different members of the microbial community (i.e., prokaryotes and fungi [35]), it is possible that fungi in the different matrices of DHABs (i.e., upper water column, brines and sediments) and at their interfaces can also be involved in ecological interactions with other microbes [35].

3. Biotechnological Potential of Fungi Inhabiting DHABs

Marine fungi are a potentially relevant source of bioactive molecules [33,63–65]. Since extremophiles show unique capabilities and adaptations, which allow them to thrive in systems characterised by harsh environmental conditions [66], halophilic and halotolerant fungi holding alternative metabolic pathways and adaptive mechanisms have important applications in industrial, pharmaceutical and environmental fields [67–69].

3.1. DHABs as Reservoirs of Fungal Amylases, Lipases and Esterases

Recent literature information reports that the extremophiles, such as fungi in DHABs, might produce native proteins, homologous or heterologous recombinant enzymes for several industrial applications, such as for “White Biotechnology” [70]. White Biotechnology, also defined as industrial biotechnology, exploits living cells and enzymes to synthesise bio-based products, which are readily biodegradable, thus requiring less energy and producing less waste [71]. Generally, enzymes as industrial biocatalysts offer various advantages over traditional chemical processes concerning sustainability and process efficiency [72] and are rapidly replacing chemicals counterparts [73–76].

Extremophilic marine organisms, including marine fungi, are important sources of stable and valuable enzymes [77]. Such molecules, defined “extremozymes”, can carry out the same enzymatic functions as their non-extreme homologues, but they can catalyse such reactions in conditions which inhibit or denature the non-extreme forms [78,79]. Some of these enzymes, in the form of isolated molecules or directly produced by extremophilic fungi including those inhabiting DHABs, can display polyextremophilicity, i.e., stability and activity in more than one extreme condition, including

high salinity (2~5 M NaCl), acid or basic pH, high temperatures (55~113 °C) [80]. Several marine extremozymes have been exploited for biotechnological research, whereas others for pharmaceutical, biofuel, and textile industry [81]. Despite the important results obtained in the field of research on extremophiles, the advantages of extremozymes over those of normal enzymes, the increasing demand of biotechnological industries for novel biocatalysts only a few extremozymes are currently being produced and used at the industrial level. Therefore, further scientific challenges need to be overcome before it will be possible to fully realise the potential of extremozymes [82].

Typically, high salinity tends to inactivate the enzymes by altering protein structures [83]. Therefore, the peculiar characteristics of fungal strains living in hypersaline conditions could represent a new source for exploitable enzymes able to operate at extreme pH and high salt concentrations (Table S1; [84]). Salt-tolerant enzymes are usually isolated from the marine environment, and halotolerant fungi show extraordinary biotechnological potential compared to enzymes isolated from their terrestrial counterparts [84]. These molecules have applications in all branches of biotechnology with significant benefits for many kinds of industries (Table 2). In particular, they are employed in the Red Biotechnology applied to pharmaceutical and medical fields (e.g., amylases, chitinase, cellulases, proteases, lipases, tannase, inulinase, esterase, methioninase, asparaginase), Grey or environmental biotechnologies (e.g., cellulase, chitinase, hydrolase, β -glucosidase, laccase, peroxidase, lipase, protease, hydrolase, β -glucanase, feruloyl esterase), and in the Blue Biotechnology applied to aquatic organisms (e.g., lipase).

As an example of biotechnological application of enzymes, α -amylases (i.e., enzymes that catalyse the hydrolysis the α -1,4 glycosidic linkages in amylose to release maltose and glucose, [85]) have been first produced industrially from the fungus *Aspergillus oryzae*, whose genus has been identified in the L'Atalante Upper halocline, Thetis brine and Urania Middle halocline, to be used as a digestive aid ([86], Table 2). Nowadays, microbial amylases commercially available have replaced chemical hydrolysis of starch in the processing industry [87]. Consistently, amylases are the most important among the enzymes of industrial interest, accounting for approximately 30% of the world enzyme market [86]. Polyextremophilic characteristics of α -amylases from marine fungi can be exploited for biotechnological processes, being used, among others, in aquaculture, biofuel, textile, food, bakery, anti-staling, fermentation, paper-making, pharmaceutical, detergent industries [88,89]. α -amylases can hydrolyse starch, which has attracted industrial attention for the uses as additives in food or as a natural ingredient but also for the production of renewable biofuels [79]. Although piezophilic and halophilic enzymes have a great potential for industrial applications, little information on enzymes from extreme environments is available [79]. For instance, the obligate halophilic *Aspergillus penicillioides* TISTR 3639, isolated from an extreme hypersaline environment is able to produce an α -amylase, which can exhibit high catalytic activity even at extreme salt concentrations (300–400 g mL⁻¹ NaCl), much higher than amylase activities reported from extreme halophilic marine prokaryotes as well as other halophilic organisms [90]. The potential use of extremophilic α -amylase in the food industry was proposed by Abe and Horikoshi demonstrating that α -amylase produces trisaccharide in place of maltobiose and tetrasaccharide, with maltooligosaccharide as substrate, at great pressure and little energy, offering great industrial and biotechnological possible applications [91].

Table 2. Examples of enzymes produced by fungi genera found in DHABs, and their industrial applications. Stars indicate enzymes exploited as extremozymes.

Producing Fungus	Enzyme	Industrial Applications	References
<i>Aspergillus gracilis</i> , <i>A. penicillioides</i> and <i>A. oryzae</i>	Amylase *	Foods, detergents, pharmaceuticals, and paper and textile	[90,92,93]
<i>Aspergillus niger</i> , <i>A. sydowii</i> and <i>A. terreus</i>	Cellulase *	Biofuel production, food and feed industry, brewing, pulp and paper, textile, laundry and agriculture	[94–96]
<i>Aspergillus terreus</i> and <i>Penicillium sp.</i>	Chitinase *	Pharmaceutical and food	[97,98]
<i>Aspergillus aculeatus</i> , <i>A. fumigatus</i> , <i>A. niger</i> , <i>A. terreus</i> and <i>Penicillium canescens</i>	β -Glucosidase *	Biofuel production, pharmaceutical and food industry	[99–103]
<i>Aspergillus sclerotiorum</i> , <i>Cladosporium cladosporioides</i> and several strains	Laccase, Li/Mn-peroxidase	Bioremediation, pulp biobleaching, pollutant degradation, biosensors, textiles, production of bioethanol and animal feed	[104,105]
<i>Candida intermedia</i> , <i>C. parapsilosis</i> , <i>C. quercitrusa</i> , <i>Rhodotorula mucilaginosa</i> , <i>Aspergillus pullulans</i> , <i>A. awamori</i> and several strains from Antarctica	Lipase *	Food, beverages, detergents, biofuel productions, animal feed, textiles, leather, paper processing and cosmetics	[106–108]
<i>Aspergillus ustus</i> , <i>Penicillium chrysogenum</i> , <i>Rhodotorula mucilaginosa</i> and several strains from Antarctica	Protease *	Bioremediation, laundry detergents, degumming of silk and leather	[106,109–111]
<i>Aspergillus awamori</i> , <i>A. candidus</i> , <i>A. fumigatus</i> and several strains from <i>Posidonia oceanica</i>	Tannase	Food, feed, pharmaceutical, beverage, brewing and chemical	[105,112–115]
<i>Aspergillus niger</i> , <i>A. fumigatus</i> , <i>A. ochraceus</i> , <i>A. niveus</i> and several strains from Antarctica	Xylanase *	Paper and pulp and the feed and food	[106,116,117]
<i>Penicillium notatum</i>	Tannin acyl hydrolase	Bioremediation, leather, food and beverage	[118]
<i>Aspergillus aculeatus</i> , <i>A. niger</i> and <i>Penicillium decumbens</i>	α -rhamnosidase	Food and pharmaceutical	[119–121]
<i>Aspergillus fumigatus</i> and <i>A. terreus</i>	β -glucanase	Textile industry, paper recycling, detergents, beverage, animal feed additives and renewable energy	[122–125]
Several strains of <i>Aspergillus</i> and <i>Penicillium</i> , <i>Candida membranifaciens</i> and <i>Cladosporium sp.</i>	Inulinase	Food and pharmaceutical	[126–128]
<i>Aspergillus terreus</i>	Feruloyl esterase	Food, pharmaceutical, pulp and paper, and biofuel	[112,129]
Several strains	l-asparaginase	Food and pharmaceutical	[130]
Several strains of <i>Aspergillus</i>	l-methioninase	Food and pharmaceutical	[131]

Lipase is a relevant enzyme with various industrial applications, which can be produced by some fungal genera found in DHABs (i.e., *Aspergillus*, *Candida*, *Rhodotorula*) [106–108,132]. Lipases catalyse the hydrolysis of lipids and remove fatty stains and are important compounds in the production of polyunsaturated fatty acids, food, and biodiesel [133]. In 1935, for the first time, the fungal lipase was extracted from *Penicillium oxalicum* and *Aspergillus flavus* [134]. Several genera belonging to *Aspergillus* and *Penicillium*, as well as *Candida* and *Rhodotorula*, have been encountered in many DHABs (see Table 1) [108,135], and can actively hydrolyse different oils, gaining a substantial interest due to their end-use market potential for numerous products, such as animal feeds, detergents, biosensors, diagnostic tools, oleochemicals and bioremediation agents [136,137].

In the Urania basin (Eastern Mediterranean Sea), extreme pressure, pH and salts can rapidly inactivate most of the known enzymes, but here, tolerant esterases were identified [138]. Esterases catalyse the hydrolysis of ester bonds in fatty acid esters with short-chain acyl groups which are harnessed in the pharmaceutical, cosmetic and food industries [139]. In particular, in the Urania basin, O.16 esterase, through mining metagenomic libraries, maintained remarkable properties as in the original environment (i.e., 180× enhanced activity at 2 to 4M NaCl and functioning at 40 MPa; [138]).

3.2. Fungi in DHABs as Potential Producers of Biomolecules for Pharmaceutical and Clinical Applications

Within the area of Red Biotechnology, some investigations highlighted the potential of marine fungi to produce compounds of clinical interest with a wide array of antibacterial, anticancer, antiviral, and antioxidant applications [140–144]. In the last few decades, new antibiotics have failed due to increasing antibiotic resistance [145], and the ever-increasing demand for new natural bioactive compounds to provide benefits in all the aspects of human life has stimulated the exploration of other different Earth environments for improving the safeness and effectiveness of these molecules [146]. Compared to their terrestrial counterparts, marine fungi are understudied although they can produce a complex and diverse set of metabolites, whose functions remain largely undescribed [147].

Over the last years, marine fungi have offered new incentives for research on marine natural products for Red Biotechnology, becoming a storehouse of bioactive metabolites [65,148–151]. Since the discovery of penicillin, fungi have been established as good producers of antibiotics, which are low-molecular-weight organic natural products with antibiotic activity, which exert their effect at low concentration against other microbial organisms [152]. Fungi are considered as not only sources of antibiotics but also producers of anti-inflammatory inhibitors, anticancer drugs, and hypercholesterolemia treatment agents (Table 3). Some of the most promising molecules derived from marine fungi, particularly from deep-sea sediments, also have anti-tumoural activities. For example, a new tetranorlabdane diterpenoid, asperolide E was isolated from the deep-sea sediment-derived fungus *Aspergillus wentii* SD-310, showing cytotoxicity against cervical, breast, and lung cancer cell lines [153]. This fungal genus identified in the Discovery, L'Atalante and Urania basins, also produces Asperethers A-E, five new 20-nor-isopimarane diterpenoids, which displayed cytotoxicity toward human pulmonary adenocarcinoma cell line [153]. *Aspergillus westerdijkiae* SCSIO 05233 cultures isolated from deep-sea sediments in the South of China, can produce Circumdatin G, which owns antiproliferative activity against myelogenous and promyelocytic leukemia cell lines with IC50 values ranging between 25.8 and 44.9 μ M [154]. Similarly, *Penicillium commune* SD-118, whose genus was identified in DHABs (Discovery, L'Atalante and Urania), produces Xanthocillin X, chrysogine, and meleagrins which show antiproliferative and cytotoxic activities. Xanthocillin X resulted in the most promising secondary metabolites extracted from this fungus for displaying an antiproliferative activity against liver, prostate, and breast cancer cell lines. Similar effects were observed with meleagrins on the prostate cancer cell line [155,156]. In addition, *Aspergillus dimorphicus* SD317, isolated from deep-sea sediments of South China Sea, whose genus identified in DHABs (i.e., L'Atalante, Thetis and Urania), produced anti-tumour agent Wentilactone A and B [157]. While Wentilactone A induced apoptosis inhibiting G2/M cell cycle through the stabilisation of the p53-p21 dimer within human lung carcinoma cells [158], Wentilactone B blocked proliferation and migration of human hepatoma

cells [159]. Finally, one of the most important anti-cancer compounds employed for the production of drugs with an estimated value of millions of dollars is Taxol[®] (generic name Paclitaxel) [160]. Since its discovery in 1993 by Stierle et al. [161], many fungi showed the ability to synthesise this molecule, improving the synthesis at an industrial scale [161–163]. Interestingly, it was recently reported that *Aspergillus aculeatinus* Tax-6, whose genus was also found in Discovery, L'Atalante and Urania basins could increase taxol production [164].

Table 3. Examples of bioactive molecules for therapeutic use isolated from marine fungi belonging to the genera found in DHABs.

Fungi	Product	Bioactivity	Source	Reference
<i>Aspergillus terreus</i> , <i>Penicillium citrinum</i> and <i>P. purpurogenum</i>	Lovastatin	Cholesterol-lowering agent	Marine sediments	[165,166]
<i>Aspergillus</i> sp. 16-5C	Asperlones A and B	Anti-tuberculosis drugs	Mangrove	[167]
<i>Aspergillus versicolor</i> , <i>A. ochraceus</i> , <i>A. ostianus</i> , <i>Cladosporium herbarum</i> and <i>Penicillium</i> sp.	Various	Antibacterial	Marine sponges, coastal water	[148]
Several strains	Various	Antibiotic	Deep seafloor fungal	[168]
<i>Penicillium sclerotiorum</i>	Penicilazaphilone C	Antibiotic, cytotoxic, anti-inflammatory and antioxidant	Rotted leaves in coastal water	[169,170]
<i>Acremonium</i> sp. LL-Cyan416 and <i>Penicillium</i> sp. LL-WF159	Anthraquinones and flavomannin	Antibiotic	n.a.	[171]
<i>Aspergillus</i> , <i>Cladosporium</i> and <i>Penicillium</i> species	Taxol (paclitaxel)	Antitumoural	Plants	[162,172]
<i>Aspergillus fumigatus</i> , <i>A. ustus</i> and <i>Penicillium citrinum</i>	Tryprostatins A and B, phenylahistin	Antitumoural and anti-inflammatory inhibitor	<i>Stichopus japonicus</i> (Sea cucumber) salt water	[173]
<i>Aspergillus quadricinctus</i> , and <i>Rhodotorula pilimanae</i>	Siderophores	Anticancer and antimicrobial	n.a.	[174]
<i>Aspergillus ungui</i> NHK-007	7-Chlorofolipastatin	Anticholesterolemic	Deep-sea sediments	[175]
Several strains	n.a.	Antimicrobial and antifungal	Deep-sea sediments	[176]
<i>Penicillium chrysogenum</i>	PgAFP	Antifungal	<i>Tedania anhelans</i> (marine sponge)	[177,178]
<i>Aspergillus nidulans</i>	Anidulafungin	Antifungal	n.a.	[179]
<i>Penicillium</i> sp.	Cycloexpansamines A and B	Anti-inflammatory	Bryozoa	[180]
<i>Penicillium chrysogenum</i>	Sorbicillactone A	Antileukemic and antiviral	<i>Ircinia fasciculata</i> (marine sponge)	[181,182]
<i>Penicillium</i> sp.	Penicyrones A and B	Antifungal	Marine	[183]
<i>Aspergillus versicolor</i>	phenolic compounds	Antioxidant	Marine sediments	[144]
<i>Aspergillus versicolor</i>	Anthraquinone	Antioxidant	Deep-sea sediments	[184]
<i>Penicillium citrinum</i>	Sorbicillinoid derivative	Antioxidant	Marine sponge	[185]
<i>Aspergillus westerdijkiae</i>	Circumdatin G	Antiproliferative	Deep sea	[154]
<i>Aspergillus</i> sp.	Avrainvillamide	Antitumoural	n. a.	[186]
<i>Aspergillus ustus</i>	Phenylahistin	Antitumoural	Mangrove	[187]
<i>Aspergillus wentii</i>	20-Nor-isopimarane diterpenoids	Antitumoural	Deep-sea sediments	[153]
<i>Penicillium</i> sp.	Breviones I	Antitumoural	Deep-sea sediments	[188]
<i>Aspergillus versicolor</i> ZBY-3	various	Antitumoural	Deep-sea sediments	[189]
<i>Aspergillus</i> sp.	Dihydroxy-fumitremorgin C	Antitumoural	Coastal sediments	[190]
<i>Penicillium paneum</i>	Penipacids A and Penipacids E	Antitumoural	Deep-sea sediments	[191]
<i>Aspergillus sulphureus</i> KMM 4640	Decumbenone C	Antitumoural	Marine sediments	[192]
<i>Aspergillus</i> sp.	Furanocoumarin	Antitumoural	Mangrove	[193]
<i>Penicillium oxalicum</i>	Oxalicumone A	Antitumoural	Marine	[194]
<i>Aspergillus wentii</i> SD-310	Asperolides A-E	Antitumoural	Marine derived endophyte	[158]
<i>Penicillium commune</i> SD-118	Xanthocillin X, Meleagrins	Antitumoural	Deep-sea sediments	[155]
<i>Penicillium</i> sp. PR19N-1	Sesquiterpene, Eremofortine C	Antitumoural	Antarctic deep-sea	[195]
<i>Aspergillus nidulans</i>	Asperfuranone	Antitumoural	Marine	[196]
<i>Aspergillus</i> sp.	Terrequinone A	Antitumoural	n.a.	[197]
<i>Penicillium</i> sp.	Chromanone A	Antitumoural and antioxidant	n.a.	[198,199]
<i>Penicillium</i> and <i>Aspergillus</i> sp.	Ergot alkaloids	Precursors of drugs	Marine	[200]
<i>Penicillium chrysogenum</i>	Hexadentate siderophores	Protective agents of LDL oxidation and anti-atherosclerotic metabolites	<i>Tedania anhelans</i> (marine sponge)	[201]
<i>Aspergillus nidulans</i> and <i>Penicillium chrysogenum</i>	Penicillin	Antibiotic	Marine	[202,203]

Marine fungi identified in DHABs can also produce other types of biomolecules of interest for Red Biotechnology. For instance, the isolated deep-sea fungus *Aspergillus versicolor*, which was also found in the Thetis basin, has shown high antifungal efficacy against human pathogens for the

secretion of PeAfpA protein, becoming a promising candidate for its application in medicine [204]. The *Aspergillus versicolor* is also able to produce antioxidant compounds with potential therapeutic use or preventive agents for ROS-associated pathologies, such as neurodegenerative diseases (Alzheimer's and Parkinson's diseases) [144,184,205]. Other metabolites extracted from *Aspergillus nidulans* has shown the ability to inhibit the aggregation of tau filaments within neurons, which is the primary cause of Alzheimer's disease or other related dementias. Moreover, some intermediates produced by *Candida antarctica* are used for the synthesis of anti-Alzheimer's drugs [206]. (±) Asperlone A-B and (−)-mitorubrin, extracted from *Aspergillus* sp. 16-5C exhibited potent inhibitory activity against *Mycobacterium tuberculosis* protein tyrosine phosphatase B, which is encouraging for the elaboration of new anti-tuberculosis drugs [167]. Other investigations revealed that cholesterol-lowering agents extracted from fungi could inhibit the activity of HMG-CoA reductase, a key enzyme in the biosynthesis of cholesterol in the human liver, whose high levels in plasma are major risk factors for the onset of heart diseases [207,208]. For example, lovastatin, isolated from *Aspergillus terreus* was the first agent to be approved by the Food and Drug Administration (FDA, Silver Spring, MD, USA) in 1987, when it became available as a hypercholesterolemia lowering drug in the market [166,209]. Molecules with such properties were also isolated by other fungal strains belonging to *Penicillium* identified in the Atalante, Urania and Discovery DHABs ([165] and references therein).

Overall, evidence suggests that DHABs fungi may produce bioactive molecules, which can be employed as new drugs or pharmaceuticals with upgraded features (safer, more effective and with broader spectrum). The expanding number of extremophilic genomes and metagenomes from DHABs samples can provide important information for the identification of novel fungal enzymes and molecules applicable for biotechnologies.

As the biosynthesis of fungal metabolites depends on even small alterations in environmental factors, and ecological and biological interactions [210], it can be expected that DHABs differing in physical and chemical conditions and characterised by different microbial assemblages may host fungi with different biotechnological potential. This suggests that investigating the diversity and functioning of fungal assemblages in a wider array of DHABs locations and environmental settings may lead to a more complete understanding of the biotechnological potential of DHABs fungi.

3.3. Can DHABs Fungi Be Exploited for the Bioremediation of Polluted Environments?

Grey biotechnology is dedicated to environmental applications and focuses on recycling, treatment of waste or bioremediation purposes. Chemical and solid waste management have become an important topic of debate since the environment is being overloaded with a variety of contaminants and toxic compounds, such as polyaromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs) and heavy metals. However, many established methods of treatment or removal of pollutants are not conceivable for applications on a large spatial scale [211,212]. In recent years bioremediation has emerged as an environmental-friendly and cost-effectively strategy for transforming pollutants into non-dangerous products by applying natural biological processes, especially in contaminated land and water [213]. This method can be applied in polluted hypersaline environments by adding appropriate microorganisms, such as haloalkaliphilic fungi, which perform specific physical and chemical reactions as a part of their metabolism, thus degrading, removing and/or reducing the toxicity of pollutants [214,215].

Fungi represent a promising biotechnological alternative for achieving pollutants degradation or transformation into less toxic compounds with greater solubility in water, which, in turn, are degraded by the action of other microbial entities [216,217]. Absorption, degradation and accumulation are biological mechanisms employed by fungi for removing recalcitrant dyes from surrounding environments [212,213,218]. Moreover, halophilic fungi and their salt-tolerant enzymes (mainly lignin-degrading enzymes) seem to have great ability in bioremediation processes [219], and several fungi are well-known to degrade persistent pollutants, such as toxic dyes and PHAs [220]. As textile processes produce effluents characterised by extreme salinity and pH values, fungi from DHABs able to

thrive under such conditions could represent an important biological source for bioremediation of such effluents. Fungal taxa found in DHABs can carry out dye decolourisation through oxidative reactions, which, in turn, generate non-toxic derivatives [221]. In this regard, some isolated species belonging to *Aspergillus* and *Penicillium* genera identified in the Mediterranean DHABs (see Table 1) were tested in laboratory showing decolourisation activity against Congo red dye (used in clothing manufacture, histology and microscopy), which has been reported to jeopardise the environment and the presence of an azo-functional group [222,223]. A strain of *Rhodotorula mucilaginosa* isolated from the Pesqueria River in Nuevo León, Mexico, and also found in the Thetis DHAB, can aid the efficient removal of another widely used and highly toxic colourant, methylene blue. This fungus, when exposed to stressful conditions in the presence of high metal concentrations produces an exopolysaccharide, which in turn can absorb methylene blue [224].

The biodegradation of organic pollutants by fungi mainly occurs through the catalytic action of extracellular enzymes released by the fungi. Lignin peroxidase and manganese peroxidase enzymes are the main extracellular enzymes purified by fungi, which are believed to be responsible for the degradation of PAHs [104]. Moreover, the laccase enzyme secreted by fungi is generally used in environmental remediation processes [225]. Laccases are copper-containing oxidases, which can transform various compounds, such as some toxic chemical wastes (e.g., polycyclic aromatic hydrocarbons, chlorinated aromatic compounds, nitroaromatics, and pesticides) and dyes, into less harmful products [226]. Moreover, three additional enzyme families are produced by fungi for bio-remediation: Esterases, glutathione S-transferases (GSTs) and cytochrome P450 monooxygenase [227]. Accounting for this enormous set of enzymes, extremophilic marine fungi are suitable for the bioremediation of polluted saline environments due to their tolerance to high-salt conditions, thus becoming an essential resource in bioremediation of marine PAH-polluted environments [228,229].

Some marine fungal species found in the Mediterranean and Red Sea DHABs, belonging to *Aspergillus*, *Penicillium*, *Candida* and *Rhodotorula* genera, have been reported to degrade some hydrocarbon compounds [230,231]. In particular, *Rhodotorula glutinis* identified in the DHAB L'Atalante has been reported to actively reduce oil compounds in petroleum polluted soils [232]. The salt-tolerant fungus, *Aspergillus sclerotiorum* CBMAI 849, whose genus was found in Discovery, L'Atalante and Thetis basins, showed a great ability to degrade 99.7% of pyrene and 76.6% of benzo[a]pyrene after 8 and 16 days, respectively [219]. Furthermore, it has been demonstrated that *Aspergillus sclerotiorum* CBMAI 849 could metabolise pyrene to pyrenylsulfate and benzo[a]pyrene to benzo[a]pyrenylsulfate, suggesting a possible implication of this fungal cytochrome P-450 monooxygenase enzyme in the detoxification of polycyclic aromatic compounds [219]. *Aspergillus* sp. BAP14 isolated from coastal Chinese marine sediments, and also identified in the Atalante basin was able to degrade benzo[a]pyrene, removing approximately from 30% to 60% of Pyrene and benzo[a]pyrene ($10 \mu\text{g mL}^{-1}$) after 3 and 12 days, respectively [233].

Fungi inhabiting DHABs can also tolerate the presence of high concentrations of heavy metals. In particular, previous investigations revealed that species of *Aspergillus* and *Penicillium* genera showed good growth ability in the presence of arsenic, with particular regard to *Aspergillus sydowii*, which exhibited a remarkable tolerance toward trivalent as well as pentavalent arsenic at a concentration of 2 mg mL^{-1} [234]. This fungus is a good candidate for arsenic bioremediation for its ability to volatilise ca. 16% of supplied Arsenic (III) [212,235]. Other studies reported that *Aspergillus* is one of the most promising fungal genera found in DHABs for the bioremediation of heavy metals. In particular, *Aspergillus niger* is not only able to thrive in the presence of hexavalent chromium, but it can be employed as a biosorbent of this compound [234,236–238].

4. Conclusions and Future Directions

Marine fungi are a source of novel enzymes for different biotechnological applications, ranging from medicine to environmental fields. DHABs ecosystems are still largely underexplored for many

microbial components, and data on fungal diversity and ecology in deep-sea hypersaline anoxic basins are even scantier. Therefore, the knowledge of their biotechnological applications is still limited. However, the extreme and diverse environmental features of the DHABs make these habitats unique and able to select for highly specialised organisms, which display extreme morphological, physiological and molecular adaptations. The metabolic adaptations of fungi include the ability to break down a wide range of compounds with novel enzymes, as well as the production of antibiotics, antitumoural drugs and other metabolites which can be exploited for the development of new Blue Biotechnologies. The present review provides extensive information on the biotechnological potential of fungi in DHABs, highlighting that the genera *Aspergillus* and *Penicillium* are among the most promising taxa for biotechnological applications. At the same time, this review highlights that no specific tests have been made on DHAB fungi yet. Thus, specific investigations on fungal assemblages inhabiting these peculiar systems can lead to new and unpredictable discoveries of biotechnological interest. Further scientific studies should be carried out in this direction for promoting the development of DHAB Biotechnologies.

Supplementary Materials: The following are available online at <http://www.mdpi.com/1424-2818/11/7/113/s1>, Table S1: Enzymes potentially produced by DHABs fungi: bioactivity and environmental conditions

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