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Antarctic Sponge Associated Microbial Chemistry with Biomedical Relevance– the Need for Ecologically Driven Studies

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Abstract

Sponges are known to be a rich source of structurally diverse bioactive natural products, accounting for approximately one third of the 25,000 novel marine natural products discovered to date. The advancement of molecular techniques, especially next generation sequencing, has revealed a highly diverse and complex microbial consortia associated with sponges. Currently, research is on-going to investigate the role of these microorganisms in symbiosis and in the production of these sponge-associated secondary metabolites. It is hypothesised that adaptations to extreme temperatures and oxygen levels in the Antarctic may result in novel microbial strains with unprecedented bioactive metabolites. Although ecological and environmental factors are believed to play a crucial role in the expression of microbial bioactive secondary metabolites, underpinning the ecological function of microorganism-sponge interactions within Antarctica is poorly understood, despite mounting evidence that these metabolites play an important role in chemical defence and microbial community structure. The importance of the Antarctic ecosystem as a research resource will be underpinned by future global change; therefore it will be vital for ecological approaches to be addressed in addition to these biomedical functions. This review collates studies that assess the biomedical activity of secondary metabolites produced by Antarctic sponge associated microorganisms, which may stimulate the ecological function to be addressed by the community.

Keywords Biomedical Applications, Secondary Metabolites, Antarctic Sponges, Symbiotic Bacteria, Antagonism

Introduction

Technological advances over the last decade, in particular next generation sequencing, have revealed taxonomically diverse microbial consortia associated with sponges, furthermore whole genome sequencing has revealed that many of these strains are a rich source of biomedically relevant secondary metabolites [1,2]. In recent years, next generation sequencing has provided evidence of sponge specific bacterial communities, suggesting the possibility that bacteria could be (at least partly) responsible for some of the bioactive compounds found within their hosts [3,4]. The biomedical potential of marine drugs from sponge-derived endosymbionts has been illustrated by many examples from temperate and tropical waters, including the antibacterial compound quinomycin G which was produced by a *Streptomyces* strain isolated from the sponge *Gelliodes carnosa* [5], or eight low-toxicity diindol-3-ylmethanes with significant antifouling properties [6].

Horizontal gene transfer plays a crucial role in bacterial evolution and ecosystem adaptation, which in turn can alter the biosynthetic ability of the microorganism and therefore the metabolites they produce [7,8]. Horizontal gene transfer has been recognised as a mechanism employed by bacterial to form resistances against antibiotic compounds, as bacteria can utilise horizontal gene transfer to acquire antibiotic resistant genes from bacteria belonging to surrounding communities. This increases biosynthetic diversity, as strains have to continuously adapt to new traits of competitors within the community [9,10] and improve their adaptations to extreme and fast changing environmental conditions [11]. Antarctica is one of the least accessible and most hostile parts of the world, which is partly why this region remains understudied. Extreme seasonality and temperatures can contribute to high selective pressures on microorganisms. Antarctic conditions also affect the microbial community structure associated with sponges as demonstrated by Marconi et al. when they showed sponges exhibit Antarctic signatures in terms of their microbial community composition [12]. However, cold-water bacterial symbionts, in particular Antarctic bacteria, have been studied in significantly less detail. Studies collated in this review demonstrate that these cold-water bacterial symbionts have been shown to yield a huge potential for the production of novel bioactive secondary metabolites with bioactivity against medically relevant bacterial strains. For example, Antarctic sponge associated *Psychrobacter*, *Pseudoalteromonas* and *Arthrobacter* strains have exhibited growth inhibition towards *Burkholderia cepacia* complex (Bcc), a consortia of 18 Gram-negative bacterial species which are pathogenic towards humans and resistant to most common antibiotics [13,14]. Fungal strains associated with sponges have also been proven to be a promising source of novel compounds with high biomedical potential, for example multiple fungal *Lindgomycetaceae sp*. strains produced two polyketides (**1**,**2**) with significant antibiotic activity against methicillin resistant *Staphylococcus aureus* (**Figure 1)** [15].

This review will focus on the biomedical applications of secondary metabolites from microorganisms associated with Antarctic sponges, highlighting activity against medically relevant strains.

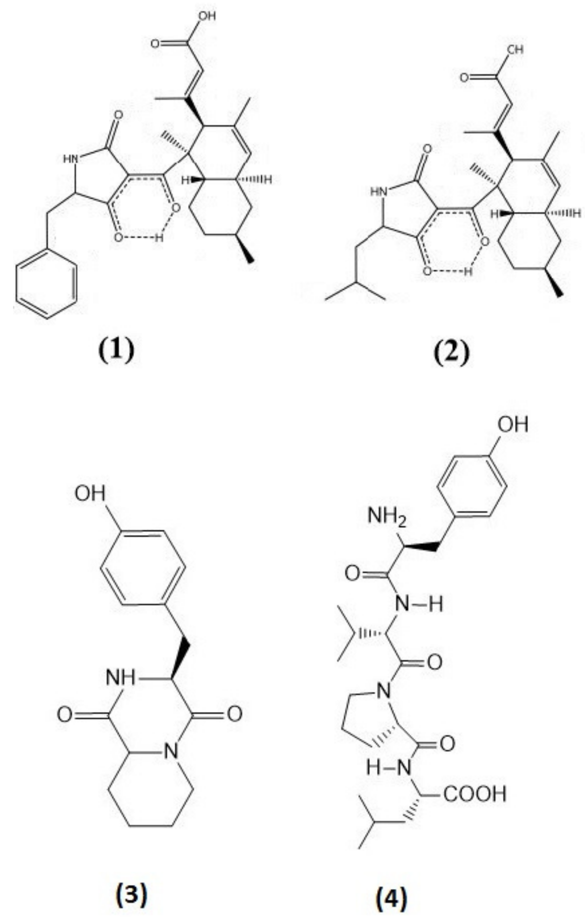

Figure 1. Chemical structures, with isolation source in brackets, of bioactive compounds, including lingomycin (**1**) (*Lindgomycetaceae sp.*), ascosetin (**2**) (*Lindgomycetaceae sp.*) and two diketopiperazines, cyclo-(L-prolyl-L-tyrosine) (**3**) and L-tyrosyl-L-valyl-L-prolyl-L-leucine (**4**) (both *Pseudoalteromonas haloplanktis*) [15,16].

The Antarctic Ocean Environment

Marine cold-water environments are considered extreme environments, defined as areas exposed to temperatures below an average of 15 °C [17]. Oceans cover approximately 71% of our planet, with 14% covered by polar-regions[18]. The major fraction is that of cold-water deep-sea, contributing 90% of the total ocean volume. Hence, by volume, nearly 85% of Earth's biosphere has to be considered a cold-water environment [8]. The Antarctic Ocean is a high-nutrient low-chlorophyll (HNLC) region which is constantly exposed to temperatures between +5 °C and -2 °C. It often remains close to the freezing point, with average temperatures of −1.9 °C throughout the year. The Antarctic Ocean is also characterised by high oxygen concentrations, which are approximately twofold higher with respect to water temperatures of 20 °C [19]. Due to sea-ice formation, the Ultraviolet B (UVB) radiation exposure changes greatly over a year. Microbial abundance is reduced after low levels of winter sea-ice formation because of increased exposure to UVB radiation in the subsequent spring [20]. Furthermore, formation of sea-ice also leads to brine rejection which has been shown to alter the salinity from 35 ‰ to up to 150 ‰ [21]. These sea-ice dynamics also enhance mixing of surface waters, providing a constant nutrient-flux for immobile species [22] and the melting of sea-ice, glaciers or terrestrial run-off contribute to extreme fluctuations in salinity and nutrient content, which can result in osmotic stress for microorganisms [23].

Sponges as Microbial Hosts

Nutrition for sponge communities (which can cover up to 50% of the benthos) can be provided by the upwelling of Antarctic nutrient rich circumpolar currents [24]. These currents can include taxonomically diverse and chemically rich bacterial species, many of which are indigenous to the Antarctic environment [25]. Out of the 436 described Antarctic sponge species reported in an overview of the ecology of Antarctic marine sponges, 81% belong to the class Demospongiae (352 Demospongiae, 49 Calcarea, 35 Hexactinellida) [26]. Bacteria find in their host a biotope rich in organic material including sources of carbon and nitrogen and physical protection. Sponges are therefore a habitat more favourable than the surrounding seawater but with limited space [27]. Thus endosymbiotic microorganisms have to adapt to a high level of competition from both pelagic microorganisms invading the host and other endosymbionts, which is driving adaptations on a molecular level as well, leading to the production of various novel secondary metabolites [28]. Webster et al compared the bacterial community composition of the Antarctic sponges *Kirkpatrickia varialosa, Latrunculia apicalis, Homaxinella balfourensis, Mycale acerta* and *Spaerotylus antarcticus* as well as seawater samples using DGGE analysis. They found multiple undescribed archaeal sequences as well as a broad variety of bacteria, diatoms and dinoflagellates species in communities that were more consistent with particular host species rather than sampling sites [1]. The abundance of sponge-associated bacteria has been reported in several studies, and it has been found to vary greatly depending on sponge species and environmental conditions. In Mediterranean sponges, it was found that bacteria can account for 40% to 70% of the sponges total volume [29–31]. Antarctic sponges also host a wide and highly diverse range of microorganisms [1,12,32]. However, the Antarctic microbial community changes significantly during an annual cycle due to the extreme seasonality and sea-ice coverage [20]. A significant number of microbial populations have also been found to be host specific, for example, Taylor et al. estimated that approximately 30% of the microbial community within the Australian sponge *Cymbastela concentrica* were host-specific [33], although not many studies address sponge-specificity. Observations show that the epibiotic microbial consortium composition of a particular Antarctic sponge species remained the same regardless of location, whereas microbial communities from different sponge species in the same location varied substantially [34]. Hence sponges are thought to be a microbial ecosystem in their self with complex interactions between microbes and host [35].

Microbial Adaptations

Low temperature, high oxygen concentration and high UVB exposure can favour the creation of reactive oxygen species (ROS), which can damage cells and increase oxidative stress [36,37]. As a response, Antarctic bacteria such as *Pseudoalteromonas haloplanktis* have developed specialised 2-on-2 haemoglobins used for resistance against oxidative and nitrosative stress [38]. In order to withstand the low temperatures and high oxygen concentration, Antarctic microorganisms have been shown to produce haemoglobins with enhanced conformational flexibility [39]. For example, *P. haloplanktis* has been shown to increase levels of antioxidant secondary metabolites, oxygen-scavenging enzymes and alter metabolic pathways, to minimise ROS side products [40]. In addition, psychrophilic microorganisms have to cope with extreme temperature-related issues, such as maintenance of protein function, prevention of cell-freezing and intracellular ice-crystal formation [7,8]. Bacteria and also fungi, like *Geomyces pannorum*, produce high levels of trehalose-sugars, carotenoids, polyols, unsaturated and polyunsaturated fatty acids to maintain favourable membrane fluidity and permeability [41–44]. Studies have also revealed exopolysaccharide production in bacteria promotes growth at low temperatures and high salinity as well as acting as a ligand for micronutrient trace-metals such as iron [45]. Psychrophilic proteins and cold-active enzymes (psychrozymes) are similar in conformation and 3D structure compared to mesophilic homologues, however, psychrozymes often show higher flexibility especially at active sites due to the reduction of weak intra-cellular bonds [46]. This enables higher enzyme efficiency of psychrophiles, compared to temperate-water counterparts, providing efficient chemical defences in cold environments [46]. The cold-adapted bacterium *Colwellia psychrerythraea* changes its protein homology to enhance enzyme efficiency at low temperatures [47]. The concentration of produced metabolites also varies with changing conditions. In a long-term experiment 16 specimens of the sponge *Aplysina aerophoba* were analysed *in vitro* for their secondary metabolite production. At the beginning and the end of the experiment, they showed increased concentrations of the major aerophobin compounds, possibly due to cultivation stress [48]. The psychrotolerant bacterium *Listeria monocytogenes* grown at 8 °C and 37 °C also has increased concentrations of metabolites at low temperature [49].

Utilising Ecological Function as a Source of Novel Biomedicines

Antioxidants

Many psychrophilic microorganisms have evolved to produce compounds that inhibit oxidation of molecules, thus preventing cell damage. To assess the antioxidant activity the 3-(4,5-dimethylthiazole-2yl)-2,5 diphenyltetrazolium bromide (MTT) method was applied to 101 fungal strains of the genus *Geomyces* isolated from the Antarctic sponges *Dendrilla* sp., *Tedania* sp., *Hymeniacidon* sp. and *Poecilosclerida* spp. [43]. A total of 97 strains (out of 101), showed antioxidant activity, but only three strains exhibited greater than 60% antioxidant capacity compared with the negative control. However, the chemical composition of antioxidants in Antarctic microorganisms is generally unknown with only a few exceptions. Two exocellular diketopiperazines (**3**, **4**) were extracted from *P. haloplanktis* (**Figure 1**) and showed free radical scavenging properties, which was ascribed to the presence of a phenyl group, when tested in a DPPH free radical-scavenging assay [16]. This demonstrates the potential function of diketopiperazines (**3, 4**) as an antioxidant. Interestingly, chemically synthesised cyclo-(L-prolyl-L-tyrosine) (**3**) has also been positively tested as a quorum sensing molecule with bacterial *N*-acylhomoserine lactone (AHL) biosensors for *Pseudomonas putida* strains [50]. Considering that the diketopiperazines (**3, 4**) produced by *P. haloplanktis* were isolated from the extracellular supernatant of fermentation broths [16], one could argue for the main function of these compounds to be cell-to-cell communication rather than antioxidant purposes, implying a double function as well. Another possible explanation could be that the exocellular antioxidants reduce ROS at the cell surface, thus minimising extracellular ROS, which could otherwise potentially diffuse through the bacterial cell wall or cause exterior damage to the cell. However, it is clear that microorganisms are well equipped to withstand high levels of ROS in Antarctic waters and could well be a prime source for the discovery of novel antioxidants.

Potential adaption mechanisms

Extracts from the sponge *Anoxycalyx joubini* were found to contain ketosteroid 5α(H)-cholestan-3-one (**5**) (**Figure 2**) [51]. Several Antarctic sponges have been shown to produce ketosteroids, for example in the Antarctic sponge *Haliclona sp*. cholesterol and other sterols were surprisingly scarce or absent compared to the warm water sponge *Phyllospongia madagascarensis* (with cholesterol as the main sterol (85.3%)). Instead, several ketosteroid and Δ5-sterol ester derivatives were present such as cholesta-4,22-dien-3-one (**6**), cholest-4-en-3-one (**7**) and 24E-methylcholesta-4,22-dien-3-one (**8**) [52]. Suggesting the organisms are adapting to the extreme Antarctic conditions by promoting the production of ketosteroids over cholesterol. Chiang et al. found that dehydrogenases resembling 3-ketosteroid-Δ^1-dehydrogenases in *P. haloplanktis* can produce various derivatives of ketosteroid as a by-product of the metabolic pathway of cholesterol [53]. The original 3-ketosteroid-Δ^1-dehydrogenase in *P. haloplanktis* has since been used to synthesize sterol and ketosteroid catabolites in laboratory conditions [54]. *P. haloplanktis* has been associated with Antarctic sponges in other studies [55,56], therefore it is likely that *P. haloplanktis* in Antarctic sponges can also produce ketosteroids if environmental conditions trigger the expression of their encoding biosynthetic gene clusters. Ketosteroids and cholesterols have biomedical importance as demonstrated for example by Sun et al. who found promising antibacterial activity of Δ^1-3-ketosteroids isolated from warm water *Subergorgio rubra* against *Bacillus cereus* [57]. In another example Gelzo et al. found that bacterium *P.*

haloplanktis produces several catabolites of cholesterol and steroids, which could be potentially useful for biomedical applications [54].

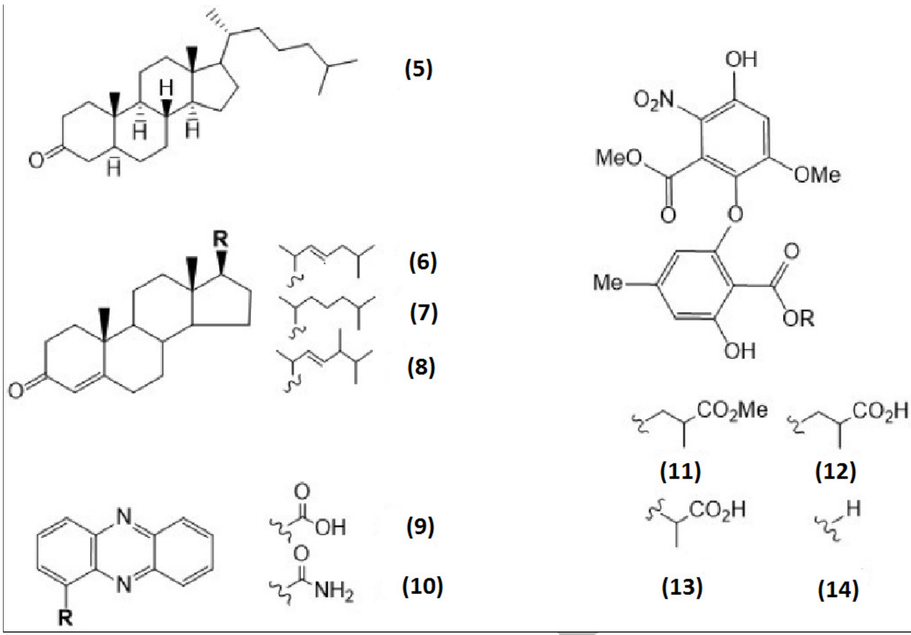

Figure 2. The lipidic 5α(H)-cholestan-3-one (**5**) extracted from *A. joubini*; Δ4-3-ketosteroids extracted from *Haliclona* sp.; cholesta-4,22-dien-3-one (**6**); Cholest-4-en-3-one (**7**); 24E-Methylcholesta-4,22-dien-3-one (**8**) [51]. Antimicrobial metabolites isolated from an Antarctic sponge associated *P. aeruginosa* (**9**) phenazine-1-carboxylic acid (**10**) and phenazine-1-carboxamide. [58]; the novel nitroasteric acids pseudogymnoascins A-C (**11-14**) and 3-nitroasterric acid (**14**) produced by the marine fungal strain *Pseudogymnoascus* sp. F09-T18-1 [59].

Antagonism among microorganisms

In order to gain an evolutionary advantage many microorganisms produce bioactive compounds to inhibit the growth of competitors. This can shape the diverse microbial communities in sponges and influence their highly dynamic interactions [12]. Many microorganisms, however, produce compounds to inhibit the growth of microbial competitors; the result is that microorganisms can also develop resistances against inhibiting compounds, with huge implications in a medical context, i.e. antibiotic resistant pathogens such as species of the *Burkholderia cepacia* complex (Bcc) in cystic fibrosis patients [60]. The bacterial species *P. haloplanktis* isolated from the Antarctic sponges *Haliclonissa verrucosa*, *A. joubini* and *Lissodendoryx nobilis* exhibited almost 100% inhibition against 21 Gram-negative Bcc species in a cross-streaking assay by producing the bioactive volatile organic compounds (VOCs) identified as benzenamine-N-ethyl and 3-buten-1-ol-3-methyl with the SPME-

GC-MS technique [55]. Bacterial strains of the genera *Arthrobacter*, *Pseudoalteromonas*, *Psychrobacter* and *Shewanella*, isolated from the Antarctic sponges *H. verrucosa*, *A. joubini* and *L. nobilis*, were in another related study found to be the most predominant and abundant species within the associated microbial consortia [14,56]. This may be related to the fact that all of these species were shown to produce the bioactive and growth inhibiting VOC 3-buten-1-ol-3-methyl [14,56]. Interestingly, out of 15 bacterial genera, only the aforementioned four were consistently found within all sponges in this particular study, supporting the hypothesis that VOCs such as 3-buten-1-ol-3-methyl may give the producing organism an advantage over competitors. Further studies provide evidence for growth inhibiting VOCs in *H. verrucos* and *L. nobilis* produced by *Arthrobacter* [61,62], *Psychrobacter* [63] and *Pseudoalteromonas sp.* [64]; supporting the important role of VOCs as antibacterial secondary metabolites in Antarctic sponge associated bacteria [65]. In an ecological context, the production of VOCs is an energetic expense, thus producing VOCs may give an evolutionary advantage, likely by suppressing rival species. However, most of the aforementioned studies were using *in vitro* settings with known human pathogens as target strains, i.e. Bcc species and has successfully demonstrated that Antarctic sponge associated bacteria are a promising area for further bioprospecting efforts and biomedical research on VOCs [66].

Research has demonstrated relatively low antagonistic activity in pelagic free-living bacteria for both temperate waters and Antarctic waters [67,68]. In one study, only 15% of isolates from Antarctic seawater exhibited growth inhibition when screened for antagonistic interactions [70] . In contrast, Mangano et al. demonstrated that 90% of cultured Actinobacteria, Bacteroidetes and γ-Proteobacteria, isolated from the Antarctic sponges *A. joubini* and *L. nobilis* (most dominant was the genus *Pseudoalteromonas*) showed inhibitory activity towards each other in a cross-niche inhibition assay [69]. However, *in vitro* communities live in much higher density compared to *in situ* conditions, presumably resulting in higher competition, which would suggest an increase in the production of antimicrobial products. It is well-supported that secondary metabolites produced by sponge associated symbionts are important for antimicrobial activity [32], as demonstrated for both warm water, i.e. α- and γ-Proteobacteria isolated from Mediterranean sponges [70], and cold-water environments. The bacterium *Pseudoalteromons aeruginosa* isolated from the Antarctic sponge *Isodictya setifera* has been shown to produce two phenazine alkaloids, phenazine-1-carboxylic acid (**9**) and phenazine-1-carboxamide (**10**) (**Figure 2**) [58]. Both compounds showed antimicrobial activity when tested against *Bacillus subtilis*, *Staphylococcus aureus*, and *Micrococcus luteus*, three gram-positive bacterial species, the latter two species are very common and potentially pathogenic in humans. Phenazine-1-carboxylic acid (**9**) and 1-hydroxyphenazine produced by *P. aeruginosa* also inhibited growth of the fungus *Fusarium oxysporum* (MIC 1 and 2 μg mL^{-1}, respectively) , a common potential pathogenic species towards plants in an agricultural setting [71]. These examples demonstrate that targeting sponge associated symbiotic bacteria may result in a higher antibacterial metabolite discovery rate compared to low-density open water species.

Fungal symbionts

Although fungal associates of Antarctic sponges have been studied to a lesser degree than their bacterial counterparts, they comprise an important component of the sponge holobionts, demonstrated by highly diverse fungal communities that have been found. Out of 101 phenotypically different fungal strains that were isolated from 11 sponges, 75.2% of isolates belonged to the fungal classes Leotiomycetes, 12.9% to Dothideomycetes, 7.9% to Eurotiomycetes and 4% to Sordiaromycetes [43]. 51% out of the 101 isolated strains had growth inhibiting effects on at least one bacterial assay strain, 42.6% showed >50% growth inhibition of which three *Geomyces sp*. isolates exhibited 100% growth inhibition of crown gall tumours in a disc bioassay [43,72]. This shows that there is a high potential for the discovery of novel compounds for future anti-tumour drugs in sponge symbionts.

The genus *Geomycetes* (class Leotiomycetes) has been found to be the most common in Antarctic soil, but interestingly also predominant in Antarctic sponges, with 32.7% of Leotiomycetes strains belonging to this genus. *Pseudogymnoascus* sp. isolated from the Antarctic sponge *Hymeniacidon* sp. produced four novel nitroasteric acid derivatives (**11-14, Figure 2**)**,** as well as the previously known compounds, nitro-diketopiperazine pyriculamide and anthraquinone questin [59]. However, the nitroasteric acid derivatives (**11-14**) showed no significant antibacterial and antifungal activities (MIC > 64 $\mu g \cdot ml^{-1}$). Nonetheless, nitrogen containing compounds with similar structure have been isolated from the endophytic fungus *Coniothyrium* sp. and have been shown to exhibit antibacterial, antifungal and antialgal activity (MIC 1 $\mu g\ mL^{-1}$) against *Escherichia coli*, *Microbotryum violaceum* and *Chlorella fusca* respectively [73]. The seawater isolated Antarctic fungi *Geomyces* has also been found to produce asterric acid derivatives with *in vitro* antibacterial activity against Gram-positive and Gram-negative bacteria (IC50 > 50 μM) [74]. However, many of these isolated compounds are assayed against specific medically-relevant target species [25], thus, although nitroasteric acids (**11-14**) did not show significant bioactivity against strains tested, potent bioactivity of nitroasteric acids (**11-14**) is possible against ecologically relevant strains, and nitroasteric acids may serve similar ecological functions for *Pseudogymnoascus* sp. as observed from other fungal species, however this has yet to be confirmed [59,73,74].

Biofilm formation

Epibiosis describes the accumulation of non-pathogenic organisms on a biotic surface [75]. The antagonistic aspect of epibiosis is often termed biofouling. As reviewed by Wahl et al. the impact of biofouling in an ecological context for sponges and other sessile filter feeders is mainly the minimisation of the surface area, hence limiting water flux and nutrient supply [34]. Microbial biofouling is also referred to as biofilm formation, which in a medical context is often associated with bacterial infections. Many secondary metabolites produced by microorganisms are found to have antifouling properties [76], and often play an ecological role for sponges from Antarctica hosting microorganisms [77].

The bacterium *P. haloplanktis,* which has been found in Antarctic sponges as well as the pelagos, reduces biofilms composed of *Staphylococcus epidermidis* by 40% over 24 hours suggesting the presence of a compound with antifouling properties [78]. This is in line with findings of a similar experiment by Parilli et al. who also found evidence of anti-biofilm compounds from *P. haloplanktis*; after a 96 hour incubation period the collected supernatant of *P. haloplanktis* cultures reduced the biofilm formation of *S. epidermidis* by about 91% [79]. Diatoms have been shown to colonise the surface, pores and space in between sponge cells, which can lead to both epi-biofouling and endo-biofouling; therefore, antialgal compounds produced by bacteria, such as nitro-diketopiperazine, could provide an effective defence against diatoms [80,81]. Extracts from 25 Antarctic demosponge have been tested against the diatom *Syndroposis* sp. and were found to cause high diatom-mortality (60-96%) [82]. The same holds true for other sessile filter-feeding species, where the Antarctic sponge species *Alcyonium paessleri* and *Gersemia antarctica* both exhibited strong antifoulant activity against bacterial biofilm formation and diatom fouling [83].These results indicate a high level of anti-biofouling compounds in Antarctic sponges [78,79]. However, the identification of specific compounds and the true producer of the compounds remains a challenge for future researchers.

Conclusions and Future Direction

Despite logistical and financial challenges associated with studying marine invertebrates in Polar ecosystems, it is well known that sponges are keystone species in the Antarctic benthic ecosystem and are associated with highly diverse and abundant microbial communities. These diverse microbial consortia produce secondary metabolites under extreme Antarctic environmental conditions. This review has underpinned Antarctic sponge microorganisms as a source of biomedically relevant metabolites. For these metabolites, occasionally, ecological functions could be speculated. For example the production of structurally flexible psychrozymes and proteins, may be enforced to cope with water temperatures remaining close to the freezing point throughout the year, or the production of diketopiperazine antioxidants by psychrophylic microorganisms may protect against high oxidative stress due to increased levels of ROS in Antarctic waters. However a community effort is needed to research the ecological functions of these metabolites to provide further evidence of the microbiological and ecological importance of Antarctic sponge holobionts. By advancing our understanding and knowledge in this area, an informed bioprospecting approach would undoubtedly unveil further novel metabolites with biomedical applications from Antarctic sponge microorganisms.

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