

32 sequencing has revealed that many of these strains are a rich source of biomedically relevant
33 secondary metabolites ^{1,2}. In recent years, next generation sequencing has provided evidence of
34 sponge specific bacterial communities, suggesting the possibility that bacteria could be (at least
35 partly) responsible for some of the bioactive compounds found within their hosts ^{3,4}. The biomedical
36 potential of marine drugs from sponge-derived endosymbionts has been illustrated by many examples
37 from temperate and tropical waters, including the antibacterial compound quinomycin G which was
38 produced by a *Streptomyces* strain isolated from the sponge *Gelliodes carnosa* ⁵, or eight low-toxicity
39 diindol-3-ylmethanes with significant antifouling properties ⁶.

40 Horizontal gene transfer plays a crucial role in bacterial evolution and ecosystem adaptation, which in
41 turn can alter the biosynthetic ability of the microorganism and therefore the metabolites they produce
42 ^{7,8}. Horizontal gene transfer has been recognised as a mechanism employed by bacteria to form
43 resistances against antibiotic compounds, as bacteria can utilise horizontal gene transfer to acquire
44 antibiotic resistant genes from bacteria belonging to surrounding communities. This increases
45 biosynthetic diversity, as strains have to continuously adapt to new traits of competitors within the
46 community ^{9,10} and improve their adaptations to extreme and fast changing environmental conditions
47 ¹¹. Antarctica is one of the least accessible and most hostile parts of the world, which is partly why
48 this region remains understudied. Extreme seasonality and temperatures can contribute to high
49 selective pressures on microorganisms. Antarctic conditions also affect the microbial community
50 structure associated with sponges as demonstrated by Marconi et al. when they showed sponges
51 exhibit Antarctic signatures in terms of their microbial community composition ¹². However, cold-
52 water bacterial symbionts, in particular Antarctic bacteria, have been studied in significantly less
53 detail. Studies collated in this review demonstrate that these cold-water bacterial symbionts have been
54 shown to yield a huge potential for the production of novel bioactive secondary metabolites with
55 bioactivity against medically relevant bacterial strains. For example, Antarctic sponge associated
56 *Psychrobacter*, *Pseudoalteromonas* and *Arthrobacter* strains have exhibited growth inhibition
57 towards *Burkholderia cepacia* complex (Bcc), a consortia of 18 Gram-negative bacterial species
58 which are pathogenic towards humans and resistant to most common antibiotics ^{13,14}. Fungal strains
59 associated with sponges have also been proven to be a promising source of novel compounds with
60 high biomedical potential, for example multiple fungal *Lindgomycetaceae sp.* strains produced two
61 polyketides (**1,2**) with significant antibiotic activity against methicillin resistant *Staphylococcus*
62 *aureus* (**Figure 1**) ¹⁵.

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

65

82 formation because of increased exposure to UVB radiation in the subsequent spring²⁰. Furthermore,
83 formation of sea-ice also leads to brine rejection which has been shown to alter the salinity from 35 ‰
84 to up to 150 ‰²¹. These sea-ice dynamics also enhance mixing of surface waters, providing a
85 constant nutrient-flux for immobile species²² and the melting of sea-ice, glaciers or terrestrial run-off
86 contribute to extreme fluctuations in salinity and nutrient content, which can result in osmotic stress
87 for microorganisms²³.

88 *Sponges as Microbial Hosts*

89 Nutrition for sponge communities (which can cover up to 50% of the benthos) can be provided by the
90 upwelling of Antarctic nutrient rich circumpolar currents²⁴. These currents can include
91 taxonomically diverse and chemically rich bacterial species, many of which are indigenous to the
92 Antarctic environment²⁵. Out of the 436 described Antarctic sponge species reported in an overview
93 of the ecology of Antarctic marine sponges, 81% belong to the class Demospongiae (352
94 Demospongiae, 49 Calcarea, 35 Hexactinellida)²⁶. Bacteria find in their host a biotope rich in organic
95 material including sources of carbon and nitrogen and physical protection. Sponges are therefore a
96 habitat more favourable than the surrounding seawater but with limited space²⁷. Thus endosymbiotic
97 microorganisms have to adapt to a high level of competition from both pelagic microorganisms
98 invading the host and other endosymbionts, which is driving adaptations on a molecular level as well,
99 leading to the production of various novel secondary metabolites²⁸. Webster et al compared the
100 bacterial community composition of the Antarctic sponges *Kirkpatrickia varialosa*, *Latrunculia*
101 *apicalis*, *Homaxinella balfourensis*, *Mycale acerta* and *Spaerotylus antarcticus* as well as seawater
102 samples using DGGE analysis. They found multiple undescribed archaeal sequences as well as a
103 broad variety of bacteria, diatoms and dinoflagellates species in communities that were more
104 consistent with particular host species rather than sampling sites¹. The abundance of sponge-
105 associated bacteria has been reported in several studies, and it has been found to vary greatly
106 depending on sponge species and environmental conditions. In Mediterranean sponges, it was found
107 that bacteria can account for 40% to 70% of the sponges total volume²⁹⁻³¹. Antarctic sponges also
108 host a wide and highly diverse range of microorganisms^{1,12,32}. However, the Antarctic microbial
109 community changes significantly during an annual cycle due to the extreme seasonality and sea-ice
110 coverage²⁰. A significant number of microbial populations have also been found to be host specific,
111 for example, Taylor et al. estimated that approximately 30% of the microbial community within the
112 Australian sponge *Cymbastela concentrica* were host-specific³³, although not many studies address
113 sponge-specificity. Observations show that the epibiotic microbial consortium composition of a
114 particular Antarctic sponge species remained the same regardless of location, whereas microbial
115 communities from different sponge species in the same location varied substantially³⁴. Hence sponges
116 are thought to be a microbial ecosystem in their self with complex interactions between microbes and
117 host³⁵.

118 *Microbial Adaptations*

119 Low temperature, high oxygen concentration and high UVB exposure can favour the creation of
120 reactive oxygen species (ROS), which can damage cells and increase oxidative stress^{36,37}. As a
121 response, Antarctic bacteria such as *Pseudoalteromonas haloplanktis* have developed specialised 2-
122 on-2 haemoglobins used for resistance against oxidative and nitrosative stress³⁸. In order to withstand
123 the low temperatures and high oxygen concentration, Antarctic microorganisms have been shown to
124 produce haemoglobins with enhanced conformational flexibility³⁹. For example, *P. haloplanktis* has
125 been shown to increase levels of antioxidant secondary metabolites, oxygen-scavenging enzymes and
126 alter metabolic pathways, to minimise ROS side products⁴⁰. In addition, psychrophilic
127 microorganisms have to cope with extreme temperature-related issues, such as maintenance of protein
128 function, prevention of cell-freezing and intracellular ice-crystal formation^{7,8}. Bacteria and also fungi,
129 like *Geomyces pannorum*, produce high levels of trehalose-sugars, carotenoids, polyols, unsaturated
130 and polyunsaturated fatty acids to maintain favourable membrane fluidity and permeability⁴¹⁻⁴⁴.
131 Studies have also revealed exopolysaccharide production in bacteria promotes growth at low
132 temperatures and high salinity as well as acting as a ligand for micronutrient trace-metals such as iron
133⁴⁵. Psychrophilic proteins and cold-active enzymes (psychrozymes) are similar in conformation and
134 3D structure compared to mesophilic homologues, however, psychrozymes often show higher
135 flexibility especially at active sites due to the reduction of weak intra-cellular bonds⁴⁶. This enables
136 higher enzyme efficiency of psychrophiles, compared to temperate-water counterparts, providing
137 efficient chemical defences in cold environments⁴⁶. The cold-adapted bacterium *Colwellia*
138 *psychrerythraea* changes its protein homology to enhance enzyme efficiency at low temperatures⁴⁷.
139 The concentration of produced metabolites also varies with changing conditions. In a long-term
140 experiment 16 specimens of the sponge *Aplysina aerophoba* were analysed *in vitro* for their
141 secondary metabolite production. At the beginning and the end of the experiment, they showed
142 increased concentrations of the major aerophobin compounds, possibly due to cultivation stress⁴⁸.
143 The psychrotolerant bacterium *Listeria monocytogenes* grown at 8 °C and 37 °C also has increased
144 concentrations of metabolites at low temperature⁴⁹.

145

146 **Utilising Ecological Function as a Source of Novel Biomedicines**

147 *Antioxidants*

148 Many psychrophilic microorganisms have evolved to produce compounds that inhibit oxidation of
149 molecules, thus preventing cell damage. To assess the antioxidant activity the 3-(4,5-
150 dimethylthiazole-2-yl)-2,5 diphenyltetrazolium bromide (MTT) method was applied to 101 fungal

151 strains of the genus *Geomyces* isolated from the Antarctic sponges *Dendrilla* sp., *Tedania* sp.,
152 *Hymeniacidon* sp. and *Poecilosclerida* spp.⁴³. A total of 97 strains (out of 101), showed antioxidant
153 activity, but only three strains exhibited greater than 60% antioxidant capacity compared with the
154 negative control. However, the chemical composition of antioxidants in Antarctic microorganisms is
155 generally unknown with only a few exceptions. Two exocellular diketopiperazines (**3**, **4**) were
156 extracted from *P. haloplanktis* (**Figure 1**) and showed free radical scavenging properties, which was
157 ascribed to the presence of a phenyl group, when tested in a DPPH free radical-scavenging assay¹⁶.
158 This demonstrates the potential function of diketopiperazines (**3**, **4**) as an antioxidant. Interestingly,
159 chemically synthesised cyclo-(L-prolyl-L-tyrosine) (**3**) has also been positively tested as a quorum
160 sensing molecule with bacterial *N*-acylhomoserine lactone (AHL) biosensors for *Pseudomonas putida*
161 strains⁵⁰. Considering that the diketopiperazines (**3**, **4**) produced by *P. haloplanktis* were isolated
162 from the extracellular supernatant of fermentation broths¹⁶, one could argue for the main function of
163 these compounds to be cell-to-cell communication rather than antioxidant purposes, implying a
164 double function as well. Another possible explanation could be that the exocellular antioxidants
165 reduce ROS at the cell surface, thus minimising extracellular ROS, which could otherwise potentially
166 diffuse through the bacterial cell wall or cause exterior damage to the cell. However, it is clear that
167 microorganisms are well equipped to withstand high levels of ROS in Antarctic waters and could well
168 be a prime source for the discovery of novel antioxidants.

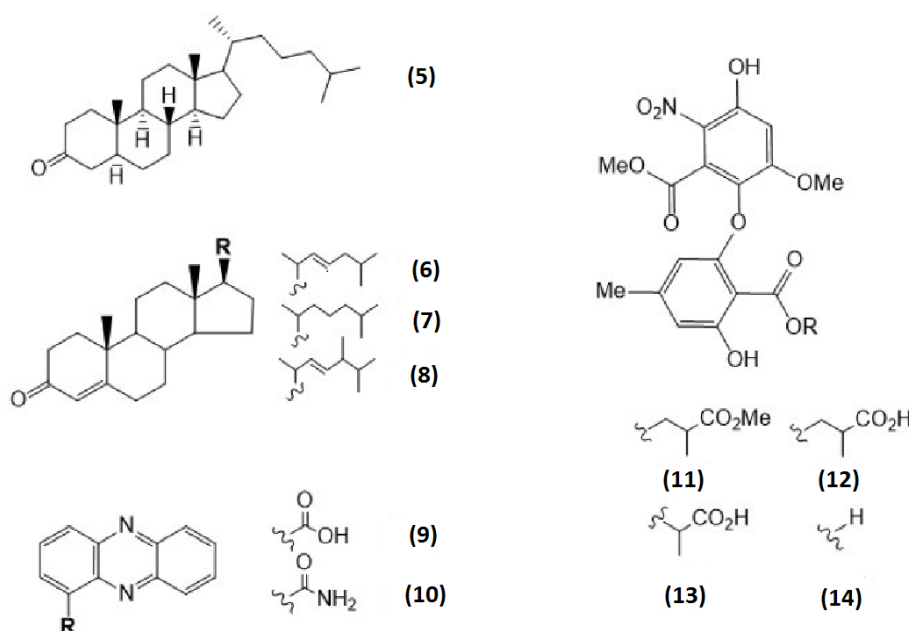
169 *Potential adaption mechanisms*

170 Extracts from the sponge *Anoxycalyx joubini* were found to contain ketosteroid 5 α (H)-cholestan-3-
171 one (**5**) (**Figure 2**)⁵¹. Several Antarctic sponges have been shown to produce ketosteroids, for
172 example in the Antarctic sponge *Haliclona* sp. cholesterol and other sterols were surprisingly scarce
173 or absent compared to the warm water sponge *Phyllospongia madagascarensis* (with cholesterol as
174 the main sterol (85.3%)). Instead, several ketosteroid and Δ^5 -sterol ester derivatives were present such
175 as cholesta-4,22-dien-3-one (**6**), cholest-4-en-3-one (**7**) and 24E-methylcholesta-4,22-dien-3-one (**8**)
176⁵². Suggesting the organisms are adapting to the extreme Antarctic conditions by promoting the
177 production of ketosteroids over cholesterol. Chiang et al. found that dehydrogenases resembling 3-
178 ketosteroid- Δ^1 -dehydrogenases in *P. haloplanktis* can produce various derivatives of ketosteroid as a
179 by-product of the metabolic pathway of cholesterol⁵³. The original 3-ketosteroid- Δ^1 -dehydrogenase in
180 *P. haloplanktis* has since been used to synthesize sterol and ketosteroid catabolites in laboratory
181 conditions⁵⁴. *P. haloplanktis* has been associated with Antarctic sponges in other studies^{55,56},
182 therefore it is likely that *P. haloplanktis* in Antarctic sponges can also produce ketosteroids if
183 environmental conditions trigger the expression of their encoding biosynthetic gene clusters.
184 Ketosteroids and cholesterol have biomedical importance as demonstrated for example by Sun et al.
185 who found promising antibacterial activity of Δ^1 -3-ketosteroids isolated from warm water
186 *Subergorgia rubra* against *Bacillus cereus*⁵⁷. In another example Gelzo et al. found that bacterium *P.*

187 *haloplanktis* produces several catabolites of cholesterol and steroids, which could be potentially useful
188 for biomedical applications⁵⁴.

189

190



191

192 **Figure 2.** The lipidic 5α(H)-cholestan-3-one (5) extracted from *A. joubini*; Δ4-3-ketosteroids
193 extracted from *Haliclona* sp.; cholesta-4,22-dien-3-one (6); Cholest-4-en-3-one (7); 24E-
194 Methylcholesta-4,22-dien-3-one (8)⁵¹. Antimicrobial metabolites isolated from an Antarctic sponge
195 associated *P. aeruginosa* (9) phenazine-1-carboxylic acid (10) and phenazine-1-carboxamide.⁵⁸; the
196 novel nitroasteric acids pseudogymnoascins A-C (11-14) and 3-nitroasterric acid (14) produced by the
197 marine fungal strain *Pseudogymnoascus* sp. F09-T18-1⁵⁹.

198 *Antagonism among microorganisms*

199 In order to gain an evolutionary advantage many microorganisms produce bioactive compounds to
200 inhibit the growth of competitors. This can shape the diverse microbial communities in sponges and
201 influence their highly dynamic interactions¹². Many microorganisms, however, produce compounds
202 to inhibit the growth of microbial competitors; the result is that microorganisms can also develop
203 resistances against inhibiting compounds, with huge implications in a medical context, i.e. antibiotic
204 resistant pathogens such as species of the *Burkholderia cepacia* complex (Bcc) in cystic fibrosis
205 patients⁶⁰. The bacterial species *P. haloplanktis* isolated from the Antarctic sponges *Haliclona*
206 *verrucosa*, *A. joubini* and *Lissodendoryx nobilis* exhibited almost 100% inhibition against 21 Gram-
207 negative Bcc species in a cross-streaking assay by producing the bioactive volatile organic
208 compounds (VOCs) identified as benzenamine-N-ethyl and 3-buten-1-ol-3-methyl with the SPME-

209 GC-MS technique⁵⁵. Bacterial strains of the genera *Arthrobacter*, *Pseudoalteromonas*, *Psychrobacter*
210 and *Shewanella*, isolated from the Antarctic sponges *H. verrucosa*, *A. joubini* and *L. nobilis*, were in
211 another related study found to be the most predominant and abundant species within the associated
212 microbial consortia^{14,56}. This may be related to the fact that all of these species were shown to
213 produce the bioactive and growth inhibiting VOC 3-buten-1-ol-3-methyl^{14,56}. Interestingly, out of 15
214 bacterial genera, only the aforementioned four were consistently found within all sponges in this
215 particular study, supporting the hypothesis that VOCs such as 3-buten-1-ol-3-methyl may give the
216 producing organism an advantage over competitors. Further studies provide evidence for growth
217 inhibiting VOCs in *H. verrucosa* and *L. nobilis* produced by *Arthrobacter*^{61,62}, *Psychrobacter*⁶³ and
218 *Pseudoalteromonas sp.*⁶⁴; supporting the important role of VOCs as antibacterial secondary
219 metabolites in Antarctic sponge associated bacteria⁶⁵. In an ecological context, the production of
220 VOCs is an energetic expense, thus producing VOCs may give an evolutionary advantage, likely by
221 suppressing rival species. However, most of the aforementioned studies were using *in vitro* settings
222 with known human pathogens as target strains, i.e. Bcc species and has successfully demonstrated that
223 Antarctic sponge associated bacteria are a promising area for further bioprospecting efforts and
224 biomedical research on VOCs⁶⁶.

225 Research has demonstrated relatively low antagonistic activity in pelagic free-living bacteria for both
226 temperate waters and Antarctic waters^{67,68}. In one study, only 15% of isolates from Antarctic
227 seawater exhibited growth inhibition when screened for antagonistic interactions⁷⁰. In contrast,
228 Mangano et al. demonstrated that 90% of cultured Actinobacteria, Bacteroidetes and γ -Proteobacteria,
229 isolated from the Antarctic sponges *A. joubini* and *L. nobilis* (most dominant was the genus
230 *Pseudoalteromonas*) showed inhibitory activity towards each other in a cross-niche inhibition assay
231⁶⁹. However, *in vitro* communities live in much higher density compared to *in situ* conditions,
232 presumably resulting in higher competition, which would suggest an increase in the production of
233 antimicrobial products. It is well-supported that secondary metabolites produced by sponge associated
234 symbionts are important for antimicrobial activity³², as demonstrated for both warm water, i.e. α - and
235 γ -Proteobacteria isolated from Mediterranean sponges⁷⁰, and cold-water environments. The bacterium
236 *Pseudoalteromonas aeruginosa* isolated from the Antarctic sponge *Isodictya setifera* has been shown
237 to produce two phenazine alkaloids, phenazine-1-carboxylic acid (**9**) and phenazine-1-carboxamide
238 (**10**) (**Figure 2**)⁵⁸. Both compounds showed antimicrobial activity when tested against *Bacillus*
239 *subtilis*, *Staphylococcus aureus*, and *Micrococcus luteus*, three gram-positive bacterial species, the
240 latter two species are very common and potentially pathogenic in humans. Phenazine-1-carboxylic
241 acid (**9**) and 1-hydroxyphenazine produced by *P. aeruginosa* also inhibited growth of the fungus
242 *Fusarium oxysporum* (MIC 1 and 2 $\mu\text{g mL}^{-1}$, respectively), a common potential pathogenic species
243 towards plants in an agricultural setting⁷¹. These examples demonstrate that targeting sponge

244 associated symbiotic bacteria may result in a higher antibacterial metabolite discovery rate compared
245 to low-density open water species.

246 *Fungal symbionts*

247 Although fungal associates of Antarctic sponges have been studied to a lesser degree than their
248 bacterial counterparts, they comprise an important component of the sponge holobionts, demonstrated
249 by highly diverse fungal communities that have been found. Out of 101 phenotypically different
250 fungal strains that were isolated from 11 sponges, 75.2% of isolates belonged to the fungal classes
251 Leotiomyces, 12.9% to Dothideomyces, 7.9% to Eurotiomyces and 4% to Sordiaromyces⁴³.
252 51% out of the 101 isolated strains had growth inhibiting effects on at least one bacterial assay strain,
253 42.6% showed >50% growth inhibition of which three *Geomyces sp.* isolates exhibited 100% growth
254 inhibition of crown gall tumours in a disc bioassay^{43,72}. This shows that there is a high potential for
255 the discovery of novel compounds for future anti-tumour drugs in sponge symbionts.

256 The genus *Geomyces* (class Leotiomyces) has been found to be the most common in Antarctic
257 soil, but interestingly also predominant in Antarctic sponges, with 32.7% of Leotiomyces strains
258 belonging to this genus. *Pseudogymnoascus sp.* isolated from the Antarctic sponge *Hymeniacidon sp.*
259 produced four novel nitroasteric acid derivatives (**11-14**, **Figure 2**), as well as the previously known
260 compounds, nitro-diketopiperazine pyriculamide and anthraquinone questin⁵⁹. However, the
261 nitroasteric acid derivatives (**11-14**) showed no significant antibacterial and antifungal activities (MIC
262 > 64 $\mu\text{g}\cdot\text{mL}^{-1}$). Nonetheless, nitrogen containing compounds with similar structure have been isolated
263 from the endophytic fungus *Coniothyrium sp.* and have been shown to exhibit antibacterial, antifungal
264 and antialgal activity (MIC 1 $\mu\text{g mL}^{-1}$) against *Escherichia coli*, *Microbotryum violaceum* and
265 *Chlorella fusca* respectively⁷³. The seawater isolated Antarctic fungi *Geomyces* has also been found
266 to produce asteric acid derivatives with *in vitro* antibacterial activity against Gram-positive and
267 Gram-negative bacteria (IC₅₀ > 50 μM)⁷⁴. However, many of these isolated compounds are assayed
268 against specific medically-relevant target species²⁵, thus, although nitroasteric acids (**11-14**) did not
269 show significant bioactivity against strains tested, potent bioactivity of nitroasteric acids (**11-14**) is
270 possible against ecologically relevant strains, and nitroasteric acids may serve similar ecological
271 functions for *Pseudogymnoascus sp.* as observed from other fungal species, however this has yet to be
272 confirmed^{59,73,74}.

273 *Biofilm formation*

274 Epibiosis describes the accumulation of non-pathogenic organisms on a biotic surface⁷⁵. The
275 antagonistic aspect of epibiosis is often termed biofouling. As reviewed by Wahl et al. the impact of
276 biofouling in an ecological context for sponges and other sessile filter feeders is mainly the
277 minimisation of the surface area, hence limiting water flux and nutrient supply³⁴. Microbial

278 biofouling is also referred to as biofilm formation, which in a medical context is often associated with
279 bacterial infections. Many secondary metabolites produced by microorganisms are found to have
280 antifouling properties ⁷⁶, and often play an ecological role for sponges from Antarctica hosting
281 microorganisms ⁷⁷.

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

297 **Conclusions and Future Direction**

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

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