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Natural Products Mediating Ecological Interactions in Antarctic Benthic Communities: A Mini-Review of the Known Molecules

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Out of the many bioactive compounds described from the oceans, only a small fraction has been studied for its ecological significance. Similarly, most chemically mediated interactions are not well understood, because the molecules involved remain unrevealed. In Antarctica, this gap in knowledge is even more acute in comparison to tropical or temperate regions, even if polar organisms are also prolific producers of chemical defenses, and pharmacologically relevant products are being reported from the Southern Ocean. The extreme and unique marine environments surrounding Antarctica along with the numerous unusual interactions taking place in benthic communities are expected to select for novel functional secondary metabolites. There is an urgent need to comprehend the evolutionary role of marine derived substances in general, and particularly in the Poles, since molecules of keystone significance are vital in species survival, and therefore, in structuring the communities. Here we provide a mini-review on the identified marine natural products proven to have an ecological function in Antarctic ecosystems. This report recapitulates some of the bibliography from original Antarctic revisions, and updates the new literature in the field since 2009 to our days.

1. Introduction

The sea is a rich source of bioactive molecules with great potentialities, including a range of applications from the development of drugs to fight cancer or inflammatory diseases, cosmetics, to ecologically friendly antifouling paints for boats and underwater machinery (see [1] and previous reviews of the series). Such products, however, did not originate in nature to serve humans in the first place. These substances most likely appeared as products of secondary metabolic pathways and assisted organisms under ecological constrains, regulating biology, co-existence and co-evolution, and enhancing survival. Subsequently the particular natural compounds have been maintained during evolution to mediate ecological interactions (allelopathy).[2–5] Fruit of the collaboration of chemists and biologists, aiming to examine the ecological functions of natural products obtained from marine organisms, marine chemical ecology became known as a multidisciplinary scientific branch, somewhat younger than its terrestrial counterpart. Methodologies have been refined, and with that the validity of the experiments attempting to explain the original bioactivities of natural products in the ecosystem. For all intents and purposes, full understanding about the functionality of most metabolites in the communities is still far from being disentangled. The research effort to comprehend chemical ecology is also notably asymmetric, and much more work has been published from tropical and temperate waters than from the Poles.[3,6–8] To date, less than 3% of the ~24 000 marine reported compounds originates from higher latitudes, despite the fact that a huge portion of global shallow-water habitat is found around the Antarctic Continent. The reasons for this asymmetry are probably related to the difficult accessibility, harsh climate, and the prevailing theory that Polar systems should be less biochemically productive.[9,10]

Benthic organisms are under constant demand for space, light and food, and have developed a wide range of defensive mechanisms. Early geographical comparisons proposed a latitudinal hypothesis with an inverse gradient between latitude and defensive chemistry in marine ecosystems, suggesting highest production of bioactive products near the Equator and lowest in the Poles. These studies focused on fish predation, which is intense in the Tropics and diminishes with latitude.[11] Soon this theory was refuted, after observing that in Polar zones fishes had been replaced by invertebrate predators (e.g., sea stars and nemertine worms) exerting equivalent ecological pressures, and that the incidence of chemically defended species was also extremely elevated.[12,13,4,14] Other than predation, fouling, competition for space/resources, or ultraviolet radiation also promote challenges to Antarctic biota. Diatom blooms in high latitudes during the Austral summer promote produce intense fouling events in exposed organisms. This is different from any other places, where prokaryotic microbes are normally the initiators of epibiosis all year around.[15] Despite the slow growth characterizing much of Southern Ocean's biota, there are also certain opportunistic species able to rapidly colonize space and overgrow displacing others.[13] In addition to all these competing interactions, the Southern Pole is the most affected area by ozone (O_3) depletion due to the Polar vortex, which consequently increases surface UV-B levels, and leads to biological damage.[16] Therefore, shallow water inhabitants here require some sort of chemical photoprotection.[17] Antarctic benthic ecosystems are antique, long evolved and diverse. They are dominated by sessile filter-feeding assemblages composed of sponges, cnidarian hydroids, gorgonians and soft corals, ascidians and bryozoans, accompanied by macroalgae and other motile invertebrate groups like echinoderms, molluscs, nemertines and polychaetes.[18,19,12,20–22] Below the zone influenced by ice dynamics, physical environment is fairly stable, and communities are exposed to marked seasonal nutrient fluctuations (winter limitation *vs* summer primary production explosion due to the ice melting and phytoplankton liberation), and intense ecological interactions. Bioactive compounds are, under these circumstances, of major relevance for species survival, and in mediating avoidance of opportunistic predators, fouling and competing organisms.[12,3] The interest in Southern Ocean regions, regarding ecological interactions involving chemistry, is growing, as is reflected by the increased publication rate, and the number of characteristic natural products discovered in the past years, some with ecological functions (current review and [9,4,1,14]).

Research proceeds at a rapid pace, with significant progress made in almost every area of marine chemical ecology: predator–prey and seaweed–herbivore interactions, defenses against fouling organisms and infection by microorganisms, competitive interactions, and settlement cues. Most advances however, refer to non Polar regions, since ecological and field experimentation is very difficult in isolated areas like Antarctica. Several comprehensive reviews have been published that relate to the discovery of new natural products with bioactivities in applied fields like pharmacology or industry (e.g., [1] and previous revisions of the series), or to global marine chemical ecology (see [5], and previous reviews from Paul and co-authors [7,6,23]). Among these last ones, most of the bibliography refers majorly to Tropical and Temperate systems. A few more specific surveys have focused on high latitude habitats. In 2007 Lebar et al.[9] reviewed the literature up to the end of 2005 on cold-water marine natural products. In this very complete revision though, the ecological significance of the metabolites was not a major scope. Also, some years ago McClintock and co-authors (2010)[14] in a delightful re-evaluation addressed some relevant aspects on the chemical ecology of benthic invertebrates along the Western Antarctic Peninsula. Neither of these reviews embraces most of the compounds and/or activities here exposed. Furthermore, since our comprehensive review on 2008 covering the state-of-the-art on Antarctic chemical ecology and marine metabolites,[4] several novel molecules and new bioactivities have been revealed in Southern Ocean organisms. For this compilation we have added up from the previous reviews the new published data since 2009, keeping out those compounds and bioactivities that are not related to direct roles in the natural ecosystem; for instance, clinical or industrial functions. Properties related to experimentation using non-sympatric (allopatric) organismal models, alluding to organisms geographically not sharing the same habitat as the source of the metabolites tested, have been as well excluded. Our current report compiles the literature published up to date about the ecological significance of identified Antarctic marine natural products, intending to disseminate a quite unknown information from this isolated geographic area.

2. Methods

The information in this mini-review was selected from the literature available on this specific area up to September 2014. The results are summarized throughout the text and in Table 1. MarinLit,[10] as well as other databases were used to complete the information. Molecular formulae were drawn with MarvinSketch software (ChemDraw format). Taxonomy databases have been used to check current names for all the species (e.g., WoRMS, Encyclopedia of Life (EOL), World Porifera, Algae Base), and species which name had changed since the original description have been corrected, maintaining the previous name in brackets. This review is organized by the type of ecological activity of natural products, with two introductory sub-sections; the first exposing several energy saving theories to counteract the expenses of defense, and the second explaining some of the experimental limitations when dealing with isolated marine compounds. A last miscellaneous sub-section addresses additional relevant insights of Antarctic chemical ecology.

3. Results and discussion

Among the types of molecules found from Antarctic organisms are terpenoids, alkaloids, peptides, steroids, polyketides, organic acids, and many derivatives. Some of these compounds have proved to possess functions as antipredatory deterrents, competition mediators, antifouling, antibiotic, toxic, photoprotective agents and reproduction promoters/inhibitors. Similar to other zones, the most studied taxa are sponges and algae, followed by molluscs, cnidarians, ascidians and echinoderms, whereas other important groups are notably overlooked in what regards chemical ecology and natural product characterization.

3.1 The Cost of Defense

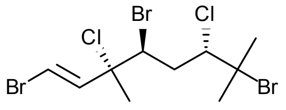
Defended organisms divert part of their energy, otherwise assigned to growth or reproduction, for defensive purposes, which compensate the investment by providing greater survival potential. Operating with defensive metabolites entails costs derived from the biosynthesis of the product *per se*, as well as from possible detoxification mechanisms required both, to store the active chemical forms in the protected organism, and in the 'enemies' to which the allelochemicals are addressed to, to handle the effect of bioactive compounds.[24] Several theories intend to explain how organisms should manage chemical protection in order to optimize the energy budget. The Optimal Defense Theory (ODT) claims that secondary metabolites for defense should be allocated preferentially in most exposed and/or valuable structures, considering the most influencing types of enemies and threats, and in coordination with other defensive traits.[25] The Optimality Theory (OT) in lieu, proposes that the same defensive traits should protect for a wide variety of enemies to save energy.[26] Another way to save energy is the usage of products with a primary metabolic role as chemical defenses,[27,28] or the accumulation of inorganic acids (in some sea slugs, nemertines, ascidians) and/or rare metals (ascidians' tunics) which serve as defensive agents.[4,29,30] Some defenses are constitutive, and keep species in a constant status of protection. Instead, inducible chemical defense, which is also extended among marine organisms, represents an energy conservation tactic, by maintaining basal levels of bioactive secondary metabolites that are increased in response to attacks. In some species precursor products are accumulated, and the final bioactive forms are converted induced by a signal of aggression. Defense induction processes, are thought to be more common in organisms with clonal growth (e.g., corals, sponges, algae, colonial invertebrates), since they are able to survive and react (increasing secondary metabolism and defense production) after episodes of grazing.[31–35] Indeed, chemical defense induction is seen in many cases as an explanation for defense variability in conspecifics from the same location.[8] In Antarctic organisms, there is a suspicion that induced protection must operate nonetheless, this has not been fully proven for the moment.[4,14]

3.2 Natural concentration estimations

Defining the real "natural" concentration of an isolated product is hampered by a variety of limitations. Generally, isolated metabolites for ecological experiments are prepared at concentrations referred per unit of wet or dry weight, or volume, intending to approximate those in the living organisms. However, intrinsic considerations make it impossible to know what compounds' concentration would be the actual effective used in nature. For instance, defensive metabolites may be stored in the outermost layers of an organism,[25] or be sequestered in specialized structures or glands,[29] as is predicted by the ODT.[25] Natural products are thus likely to be concentrated at levels many-fold higher within those localized areas than the laboratory estimates, based on calculations of the entire organism or of portions much larger than the cumulative defensive structures. Moreover, due to chemical defense inductive processes, variable quantities of the bioactive molecules may be found within the same specimen at different time points, depending on whether protection is being activated or not. Therefore, in a number of studies the activities recorded are somewhat conservative, and many of the compounds revealed as innocuous, could actually be efficient defenses at their optimal concentrations.[4,8] Technological advances in methods of chemical purification and dissection, as well as an increased knowledge on species life histories, will allow us to obtain more accurate results to explain the mechanisms behind allelochemical interactions in marine environments.

3.3 Predation

Predation (described as the action of predators attacking other living beings for their eventual digestion) is a selective force that structures many ecosystems, and promotes evolution of physical, chemical, and/or behavioral protection in potential prey.[36] Most feeding deterrents reduce the attractiveness of prey items, and likely the probability of being consumed, but they do not completely impede predation. Still it is not clear how antifeedants operate. In most cases they do not seem to be highly toxic, being their action more related to eliciting bad taste to consumers. In this sense, generalist feeders obtain the profits of a varied diet, not only by compensating for low nutritious prey, but also by diluting possible negative effects derived from occasionally ingesting defensive metabolites.[37,38,24] Antarctic communities, adapted to unpredictable nutrient supply, harbor organisms with flexible foraging habits, and the biological composition is dominated by defended species with long life-spans subjected to intense generalist predation.[12,13] Here, benthic keystone predators are generalist invertebrates, such as giant nemertean worms of the species *Parborlasia corrutatus* and the sea star *Odontaster validus*.[12,39,40] Besides, populations of small-sized amphipods with diversified trophic habits congregate in high densities (up to 300.000 individuals m^{-2}) associated to their living/feeding substrata, exerting meaningful influences.[41] The most common experimental model Antarctic predators to test antipredatory chemical defenses in shallow samples have been for some time the sea star *Perknaster fucus* and amphipods like *Gondogeneia antarctica* (this last one though, has demonstrated bias caused by a phagostimulatory reaction to crude extracts within assay foods).[42–44] The usage of *P. fucus* was observed to be somewhat limited as well, due to its more specific diet preferences. Recently, the asteroid *O.validus* and the lyssianasid amphipod *Cheirimedon femoratus* have been used for shallow and deep potential prey,[4,45–48,28,49–51] for possessing both species broad circumpolar and eurybathic distributions, along with generalist/opportunistic habits.[12,40,41] Feeding repellence is quite extended among almost all dominant Antarctic taxa, as is shown in experiments with intact organisms, dissected tissues and crude extracts.[4,14] Over and above, several compounds have been identified as the promoters of such activity.



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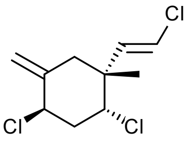

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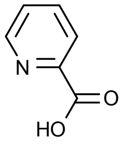
The red algae *Plocamium cartilagineum* contains anverene (**1**) and epi-plocamene-D (**2**), which defend against sympatric amphipods, e.g., *G. antarctica*.[52]



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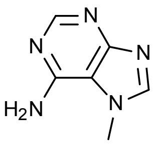

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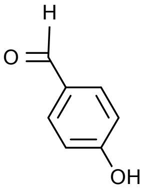

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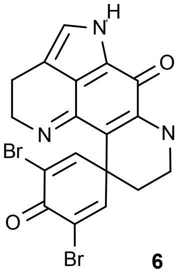
Among the Porifera, the picolinic acid (**3**) and 7-methyladenine (**4**) in *Dendrilla membranosa*,[53,54] p-hydroxybenzaldehyde (**5**) obtained from *Isodictya erinacea*,[55] an uncharacterized purple pigment from *Kirkpatrickia variolosa*,[56] discorhabdin C (**6**) and G (**7**) present in *Latrunculia apicalis*,[57–59] and suberitenones A (**8**) and B (**9**) found in *Suberites sp*.[60,61] contribute to protection from sea star predation by causing significant tube-foot retraction to the asteroid *Perknaster* *fuscus*.[62]



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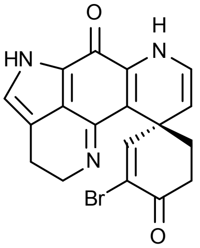

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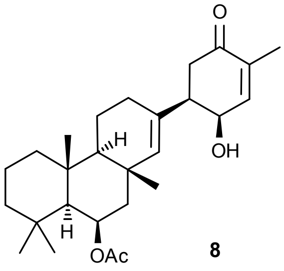

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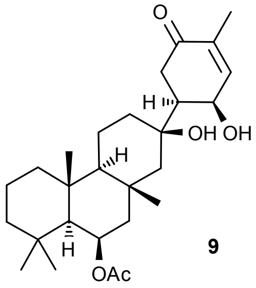

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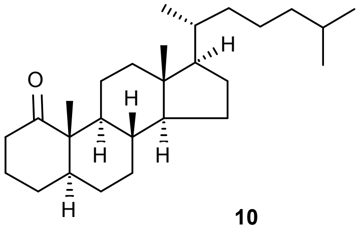
All the mentioned sponge species belong to the class Demospongia, which are considered to be chemically prolific and better defended as compared to Calcarea (calcarean sponges), or specially Hexactinellida (glass sponges), these last ones thought to lack secondary metabolites ([63] and revised in: e.g., [7,5,1] and previous reviews of the series). Against this backdrop, several species of the family Rossellidae: *Anoxicalyx (A.) ijimai, A. (Scolymastra) joubini, Rossella Antarctica, R. fibulata, R. nuda, R. racovitzae and R. villosa,* yielded a keto-steroid, 5α-cholestan-3β-one (**10**), with mild repellence against *C. femoratus* amphipods and the sea star *O. validus*, representing the first case of chemical defense reported from hexactinellid sponges.[45,51]



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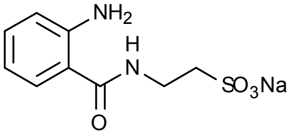

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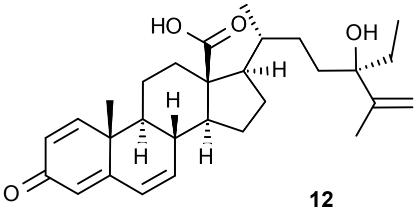
Recently, also a sample of *Anoxycalyx (S.) joubini* yielded a closely related taurine-like organic acid called glassponsine (**11**), never previously obtained from other conspecific glass sponges. Glassponsine (**11**) was found to cause deterrence in amphipods (*C. femoratus*) at concentrations higher than the reported as natural.[64,65] Similarly, norselic acid A (**12**) from the demosponge *Crella sp.* elicited repellence to *G. antarctica* when tested at three times its natural concentration.[66]



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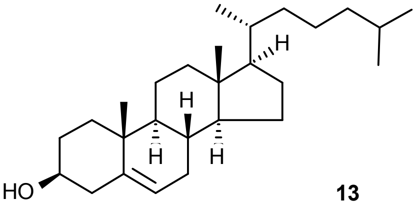
In both cases, the bioactive compounds might be playing a minor role in defense in cooperation with other repellents, but also these compounds in the living organism may be more concentrated within cellular structures, providing effective activities.

Cnidarians have stinging cnidocysts to keep enemies away, nonetheless, soft corals and gorgonians do not usually harbor effective stinging nematocysts, and the defense strategies in these groups largely rely on the chemistry. Typical allelochemicals of these anthozoan taxa include terpenoids and steroids.[2,67] A group of water-borne sterol compounds (cholesterol (**13**), 22-dehydrocholesterol (**14**) and 22-dehydro-7-hydroxy-cholesterol (**15**)) obtained from the soft coral *Alcyonium antarcticum (A. paessleri)* are involved in generalist antipredation by eliciting sea star tube-foot retraction (*O. validus*), and strong chemo-avoidance in Y-maze experiments in three Antarctic echinoderms (*O. validus, P. fuscus, Sterechinus neumayeri*) and the nemertean *Parborlasia corrugatus*.[27,68]



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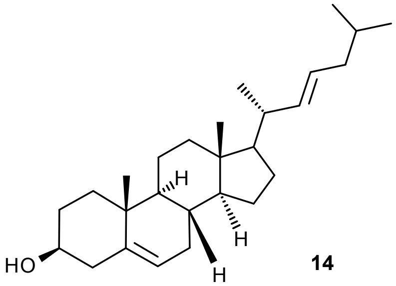

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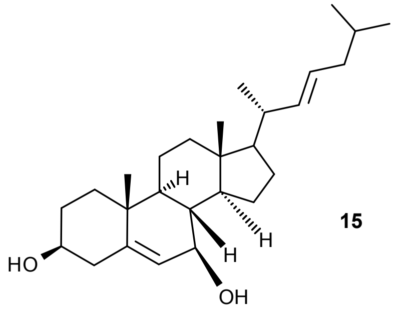

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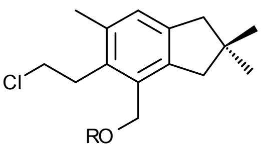
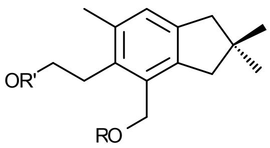
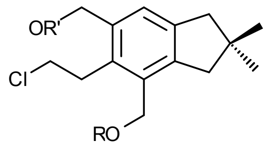
Alcyonium antarcticum (*A. paessleri*) has been analyzed several times providing different terpenoid compositions including: paesslerins,[69] alcyopterosins,[70] and a varied group of terpenes;[71] but still no ecologically relevant bioactivities have been attributed to any of these molecules. Actually, this species was proposed to possess an inconsistent secondary metabolite arsenal, which has probably prevented the identification of more functional products.[68,28] A closely related group of alcyopterosin sesquiterpenes as those found by Palermo and co-authors (2000)[70] in *A. antarcticum*, were discovered in *A. grandis,* the illudalanes 1-9 (**16-24**),[72] which demonstrated their role as potent antifeedants towards sea stars (*O. validus*).



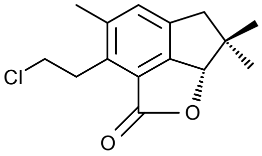
16: R= $COCH_3$
17: R= $COCH_2CH_2CH_3$



18: R= $COCH_2CH_2CH_3$; R'= $COCH_2CH_2CH_3$
19: R= $COCH_3$; R'= $COCH_3$
20: R= $COCH_3$; R'= $COCH_2CH_2CH_2CH_3$



21: R= $COCH_3$; R'= $COCH_3$
22: R= $COCH_3$; R'= $COCH_2CH_2CH_3$
23: R= H; R'= H



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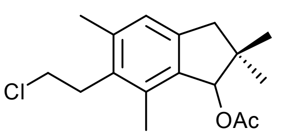
Similarly, *A. rosseum* also revealed the presence of two more illudalanes 10-11 (**25-26**) that were also proposed to be involved in protection against predation. It was observed that conspecific specimens lacking illudalanes 10-11 (**25-26**) were readily consumed, while samples harboring the terpenes were significantly rejected.[28]



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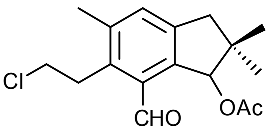

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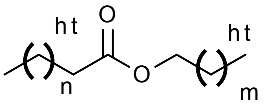
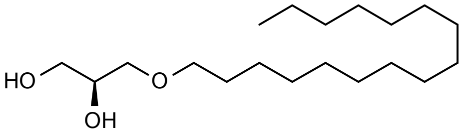
Additionally, five *Alcyonium* soft corals, comprising the above mentioned species (*A. antarcticum, A. grandis, A. rosseum*) plus *A. haddoni* and *A. paucilobulatum*, possess two commonly occurring marine wax esters (**27-28**), formed by a monosaturated 18:1 fatty acid and the unsaturated 16:0 and a 18:0 alcohols respectively.[73]



27: n = 15:1; m = 14
28: n = 15:1; m = 12

Waxes are indigestible by most predators,[74,75] and in fact waxes (**27-28**) were deterrent to Antarctic sea stars and amphipods at several concentrations, and as low as 2.5 mg g^{-1} in total dry weight. In corals, wax esters play a primary metabolic role as main lipid energetic reserves, thus their simultaneous use for defensive purposes could represent a mode of energy saving strategy. It is probable that waxes (**27-28**) cooperate with secondary metabolites (e.g., terpenes) to provide an effective defense tactic against generalist predation (and maybe other ecological functions), and that this 'chemical cocktail' is exuded within the coral mucus. Concretely, this has been proposed for the species *A. grandis* with the illudalanes 1-9 (**16-24**), and *A. rosseum* with the illudalanes 10-11 (**25-26**).[28] Another soft coral, *Clavularia frankliniana,* has been shown to contain, chimyl alcohol (**29**), and the gorgonian *Ainigmaptilon antarcticus* harbors the terpenoid ainigmaptilone A (**30**), both exhibiting strong deterrence to macropredators like *O. validus*.[76,77]



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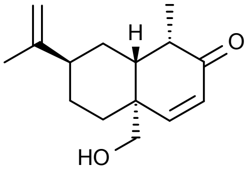

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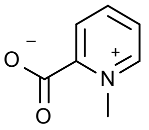
Antarctic molluscs, and in particular sea slugs have afforded an extensive number of bioactive metabolites, many of ecological significance as mediators of antipredation protection against sea stars (*O. validus*).[4,14] The lamellarian gastropod *Marseniopsis mollis* was found to harbor homarine (**31**) in all body tissues analyzed: the mantle, foot, and viscera. This compound is significantly active, and is suggested to be obtained from the ingestion of epizooites containing homarine (hydroids and bryozoans) that foul the tunic of the ascidian *Cnemidocarpa verrucosa*, which is where the gastropod is normally sited.[78]



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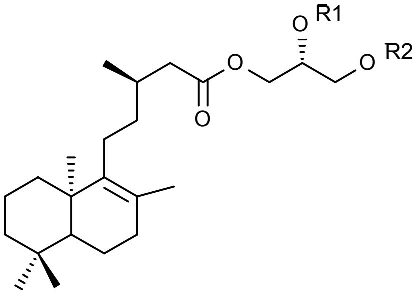
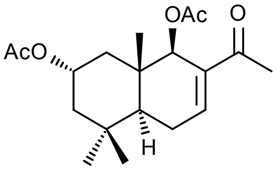
Homarine is found is several organisms in nature, encompassing opistobranch molluscs, hydroids, gorgonians, crustaceans, and the Antarctic soft coral *Gersemia antarctica*,[68,23] and has been described to possess a broad spectrum of bioactivities (e.g., antimicrobial against bacteria and diatoms, antifeedant, morphogenesis inductor). Indeed, this compound could be passed through the trophic chain, and be retained by certain consumers for their own defense.[2,3,24] This is likely the case of *M. mollis*. Likewise, *Tritoniella belli* seems to obtain antipredatory defense by sequestering chimil alcohol while feeding on its preferential prey, the soft coral *Clavularia frankliniana*.[76,78,79]

Sea slugs have well differentiated organs and are well suited for precise dissections for the study of metabolites distribution. Dorid nudibranchs are in this sense well known for allocating chemical defenses in specific tissues or structures, optimizing protection expenses from the energetic budget.[80,29] *Austrodoris kerguelenensis* synthesizes a series of diterpene diacylglycerides, which effectively defend them from sea stars (e.g., **32-33**), along with the corresponding monoacylglycerides, and monoacylglycerides of regular fatty acids.[81,82] Several other terpenoids with no attributed ecological role, such as the austrodorins A and B, and the two nor-sesquiterpenes austrodoral and austrodoric acid, have also being afforded by different collections of the species.[83–87] Indeed, the wide array of terpene glycerides in *A. kerguelenensis* indicates the existence of several chemotypes, with terpene synthase variants involved in the biosynthesis of these bioactive molecules.[88]



32: R1 - H; R2 - Ac
33: R2 = Ac; R2 = H

Bathydoris hodgsoni also produces *de novo* the feeding deterrent sesquiterpene, hodgsonal (**34**).[89–91] In both species, the defensive products (*i.e.*, diterpene acylglycerides and monoglycerides (**32-33**) from *A. kerguelenensis* and hogsonal (**34**) from *B. hodgsoni*) are allocated towards the most exposed structures: the mantle and papillae.[82] This pattern of defense distribution falls into the premises of the ODT, which for Antarctic prey organisms predicts the accumulation of bioactivity towards the outer body layers to reduce most influencing predators' attacks.[25] In general, sea stars are mobile macropredators that extrude their cardiac stomach against their victims and start extra-oral digestion from the surface.[92] Amphipods feed with minute peripheral bites, but similarly, only prolonged feeding would allow access to internal tissues.



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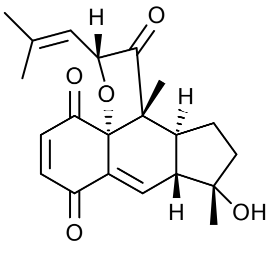
Other examples in which the postulates of the ODT are met include, the demosponges *Latrunculia apicalis,* found to concentrate discorhabdin G (**7**) in its outermost regions,[93] and *Suberites* sp., a spherical sponge revealing higher bioactivity and 90% suberitenone A sequestration in surface layers.[62] Opposed chemical defense distributions, displaying higher bioactive signals towards the internal regions (harboring the zooids), as compared to the more exposed external structures (the colonial tunics), have been reported in some Antarctic ascidians in the genera *Aplidium* and *Synoicum*.



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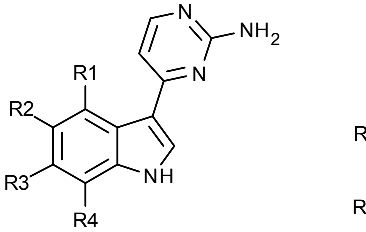
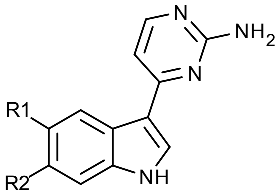
The meroterpenoid rossinone B (**35**) for instance, causes strong feeding rejection to sea stars (*O. validus*) and amphipods (*C. femoratus*), and constitutes the major deterrent metabolite obtained from the species *Aplydium fuegiense*. This compound is present in very low quantities in the external tunic, whereas in the internal region (zooids) it is highly abundant, and it is found along with its minor related derivatives 2,3-epoxy-rossinone B, 3-epi-rossinone B, and 5,6- epoxy-rossinone B, with no revealed functionalities. Similarly, feeding deterrence assays on dissected *Synoicum adareanum* colonies of the 'Black&White' morphotype suggest the same pattern of inner defense distribution, even if the responsible molecules have not yet been elucidated.[94] This characteristic internal distribution of defensive products probably reflects the storage of deterrents within the gonads for the production of complex, chemically protected larvae, which is common in colonial ascidians.[95] It is likely that this strategy also accomplishes the principles of the ODT; as an effective protection of the offspring, by defending valuable reproductive tissues, might be more relevant for the species survival than protecting the adult from sub-lethal external aggressions, specially in colonial organisms.[25] On a different plane, the ascidians *Aplidium meridianum* and *A. falklandicum* possess the bioactive indole alkaloids, the meridianins A-G (**36-42**).[96,97] These remarkably potent repellents occur in elevated concentrations in the zooids and the outer tunic (sometimes in slight higher amounts towards the tunics), providing sea star and amphipod avoidance throughout the whole colonies.[98,94]



36: A: R1 = OH; R2 = R3 = R4 = H
37: B: R1 = OH; R2 = R4 = H; R3 = Br
38: C: R1 = R3 = R4 = H; R2 = Br
39: D: R1 = R2 = R4 = H; R3 = Br
40: E: R1 = OH; R2 = R3 = H; R4 = Br



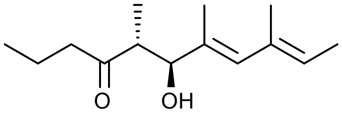
41: F: R1 = R2 = Br
42: G: R1 = R2 = H

Further variabilities from the expected external chemical storage may be observed in prey with large open body areas, in which small consumers may access to the inner regions to forage, promoting different (or a lack of) defense distributions. This has been proposed as the major reason why many Antarctic demosponge and hexactinellid species with conspicuous oscula do not exhibit clear allocation of bioactive agents.[99,45,50,49]

A notable proportion of the metabolites described herein have proved multifaceted deterrence/avoidance to more than one predator. This, in agreement with the OT, would be a mechanism for conserving energy, and the same compounds could be providing different activities to affect various predators.[26] It is likely also that homolog taste receptors, responding to similar stimuli, might had been retained in evolution among distinct consumers, facilitating broad effectiveness of antipredatory repellents.[100,24] A factor to be considered jointly with feeding deterrents is nutritional quality, as high food quality may mask the stimuli that elicit predators' avoidance when nutrients bind to repellent metabolites or compete with these for enzymes. In fact, some defensive agents are more or only effective along with low quality foods. This means that nutritive prey should concentrate larger amounts of, or more potent types of, defenses, or alternatively, weak defense could be accompanied by poor nutrient content.[38,101,24] In this regard, hexaxtinellid sponges contain a large proportion of inorganic matter (silica spicules), which suggests that they should not require defensive chemicals, for not representing a profitable or attractive diet to predators.[63,102] However in Antarctica *Odontaster* sea stars and *Austrodoris* nudibrachs readily feed upon them.[12,63] It has been proposed that these sponges might combine a low nutritional value with weak defense (e.g., 5α-cholestan-3β-one (**10**) along with other potential substances) to cope with predation pressures.[45] Similarly, in certain fibrous, less profitable organismal structures, analogous antipredatory strategies may take place. For instance in the tunics of certain ascidians deterrents are known to be less concentrated, like in *Synoicum adareanum* (morphotype Black&White), or the rossinone B (**35**) in *Aplidium fuegiense*.[47] The interference between chemical defenses and nutritional value was recently addressed by testing the efficacy of five types of deterrent compounds at different concentrations against *Cheirimedon femoratus*, and using diets of distinct energy content. It was found that the products that most interacted with energy content were those that occurred in nature at the highest concentrations (wax esters and meridianins), no matter their bioactive potency as deterrents. While other metabolites, less abundant within the source organisms (rossinone B (**35**), glassponsine (**11**), 5α-cholestan-3β-one (**10**)) seem to depend on a threshold concentration to provide activity, independently of the nutritional value of the food items.[51]

3.4 Interspecific chemical refuges

There are several unique ecological networks in the Antarctic ecosystems mediated by chemistry. One of the better decribed is the 'antagonistic symbiosis' engaging the pelagic mollusc *Clione antarctica*, a pteropod, and the amphipod *Hyperiella dilatata*.[103,104] *Clione antarctica* elaborates pteroenone (**43**),[105,106] which promotes repellence to several fish consumers. *H. dilatata* has the ability to capture (abduct) *C. antarctica* from the water column, and position it on its dorsum (like a backpack), obtaining this way protection from fish attacks.[103]



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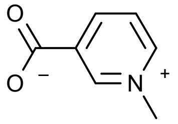
Other peculiar relationships involve repellent macroalgae holding large densities of small amphipod mesograzers, and acting as biosubstrata (e.g., *Desmarestia menziesii* and *D. anceps*). Such seaweed possess deterrents towards the associated mesograzers and other larger consumers (fish), and offer a chemically defended refuge to the mesograzers from prospective fish predators (e.g., *Notothenia coriiceps*). In return, the seaweed get benefit from amphipods because these remove epiphytic algae.[107–111] Analogous chemical refuges have been proposed in Antarctic deterrent sponges hosting dense amphipod populations.[43] Interestingly, the small crustaceans normally prefer feeding on undefended species different from their defended host substrata, which explains why edible species, like the algae *Palmaria decipiens*, attract much less associated fauna in the field. Recently though, the amphipod *Paradexamine fissicauda* was described to benefit from its ability to both live on and readily consume chemically defended macroalgae, being able to sequester potent antifeedants (mixtures of halogenated monoterpenes) from the red seaweed *Plocamium cartilagineum* for its own protection.[112] It is noteworthy that consumers feeding on defended items pay metabolic costs as well. On the one hand because they might require detoxification mechanisms to withstand ingested defensive chemicals; and in the other, because if focusing on weakly protected prey, these often represent poor quality diets, maybe not compensating for the investment in digestion. Specialist predators, which usually consist on small animals (sea slugs, amphipods), live and feed on their chemically defended hosts, while obtaining habitat and protection. This sedentary lifestyle affords haven against predation, but also reduces physiological performance due to the ingestion of poorly assorted and less profitable diets.[24]

3.5 Fouling and microbial invasions

Biofouling is the accumulation of biota on the surface of another living host (epibiosis), progressively causing deterioration on the overgrown organism by reducing nutrient and gas exchange (e.g., interfering feeding currents). It is a successional process encompassing four major stages: 1) initial pre-colonizing step (the surface is covered with a conditioning film of organic polymers), 2) primary colonization (bacteria and diatoms adhesion and formation of a biofilm), 3) secondary colonization stages (the biofilm allows secondary colonizers as spores, propagules of macroalgae and protozoans to attach), and 4) later stages (tertiary macrofoulers settle, including ascidians, molluscs, and cnidarian species). Organisms have developed mechanisms to prevent heavy fouling, which majorly consist on physical periodic surface sloughing (sponges, soft corals, ascidians, algae), and the use of chemical defenses. Natural products may affect at all these multiple levels,[113] but the very limited data that exists in the Antarctic about antifoulants refer basically to inhibitors of primary microfoulers.[4,14] Antifoulants can involve insoluble products sequestered in the outer body surface, or soluble compounds released into the boundary layer surrounding the defending organisms (e.g., mucus secretions) to either repel or kill the fouling agents (reviewed in [113]).

Antarctic sessile macrobiota have been commonly observed invaded by epizoic diatoms, sometimes so heavily as to occlude filter feeding channels and clog pores, driving scientists to conclude that benthic diatoms are major fouling agents in the Southern Pole.[15,114,115] Comparable levels of diatom fouling are, to the best of our knowledge, unique to these high latitudes and not reported in tropical or temperate latitudes. This phenomenon is related to Southern Ocean's planktonic microalgal blooms in the early Austral summer, composed primarily of *Phaeocystis sp*. and pelagic and benthic diatoms.[116] In this context, some species often show no apparent epibiotic diatoms during the algal peak, whereas others have evident fouling, indicating the presence of antifoulants in the former.[15] Bioassays to test potential defenses against diatom invasions showed that antifouling properties are prominent among Antarctic macroalgae.[117] Similarly, sponge extracts have revealed in several occassions to cause high mortality in sympatric diatoms (*Syndroposis sp*.[118] and strain McM-C5 chain-forming, araphid pennate diatom in the class Fragilariophyceae).[15] This outcome contrasts to the general lack of antibacterial chemically based protection found among Antarctic sponges,[118] and also in ascidians.[119] Studies addressing the antifouling potential of Antarctic ascidians against epibiotic microalgae are limited to the analysis of McClintock et al. in 2004,[120] recording activity against chain-forming pennate diatoms in *Distaplia cylindrica*. However, the fact that many colonial species are conspicuously devoid of fouling, suggests that many ascidians should rely on chemical defenses. Recently, as opposed to sponges and ascidians, the less studied Bryozoa have revealed notable properties against bacteria.[121]

In spite of the premises of the OT, some level of specificity for chemical defenses against diatom fouling was suggested, as most demosponge species lacking antipredatory and/or antibacterial activities, effectively inhibited diatom growth.[15] Some other researches though, indicate the opposite. The soft coral *Alcyonium antarcticum (A. paessleri)* for instance, possesses antifouling agents competent concurrently against bacteria and diatoms.[122] Further multipurpose properties have been attributed to isolated compounds, such as the discorhabdins C (**6**) and G (**7**) from the sponge *Latrunculia apicalis*,[59] and the meridianins A-G (**36-42**) from the ascidians *Aplidium falklandicum* and *A. meridianum*, providing antifeedant protection and antifouling/antimicrobial activities to unidentified marine bacteria.[47] Suberitenones A and B (**8-9**) were also active in both asteroid tube-foot retraction assays and in antibiotic tests towards potentially fouling invertebrate-associated bacteria (isolate 28.2, from *Halecium arboreum* and isolate 22.3, from *Acodontaster conspicuus*).[61]



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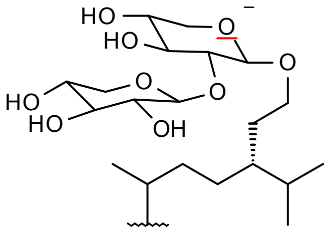
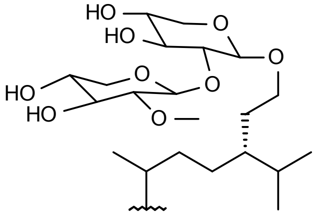
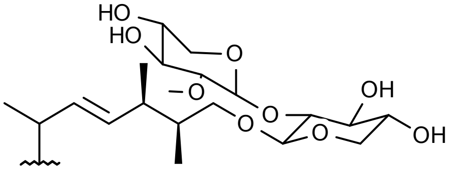
Homarine (**31**) and trigonelline (**44**), two water-borne widely extended metabolites extracted in the Antarctic from the soft coral *Gersemia antarctica* and the gastropod *Marseniopsis mollis,* cause among other activities, growth inhibition in sympatric microbes such as *Alteromonas* sp, *Moraxella* sp and *Psychrobacter* sp.[79,68,27] Finally Ainigmaptilone A (**30**) from the gorgonian *Ainigmaptilon antarcticus* provides, in addition to sea star repellence, antifouling/antimicrobial properties,[77] towards bacterial strains isolated by De Marino et al. (1997):[123] McM18.1 isolated from surface of *Odontaster validus*, McM13.3 from the sponge *Dendrilla membranosa,* McM32.2 from sponge *Leucetta leptorhapsis,* and McM11.5 isolated from the water column; and inhibition against diatoms cultured by Amsler et al. (2000): [15] strain McM-C5, a chain-forming, araphid pennate diatom in the class Fragilariophyceae. In the study of De Marino et al. (1997),[123] several steroids providing potential roles in preventing bacterial fouling/infection, like the steroidal oligoglycosides acodontasterosides D-I (**45-50**), and some polyhydroxylated steroids (**51-53**) were purified from the sea star *Acodontaster conspicuus*.



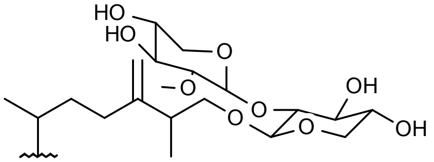
45: R = OH



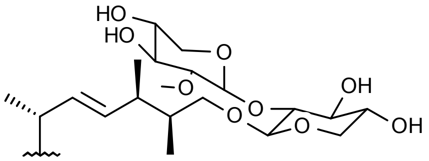
47: R = OH



46: R = OH



48: R = OH



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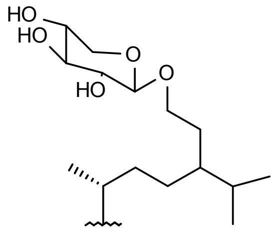

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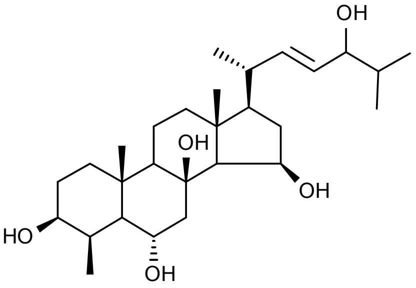
The steroidal diglycosides acodontasterosides D (**45**), E (**46**), F (**47**), and I (**50**) and polyhydroxylated steroids 15 (**51**) and 18 (**52**) all showed inhibition against McM13.3 and McM32.2; acodontasteroside G (**48**) was affective against McM32.2; acodontasteroside H (**49**) showed activity against McM11.5; and steroid 19 (**53**) was active against McM13.3.[123]



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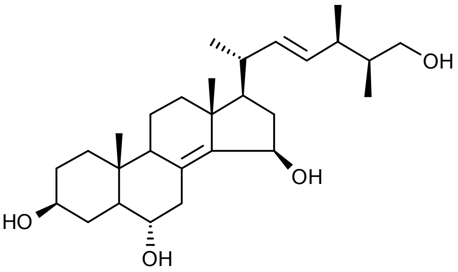

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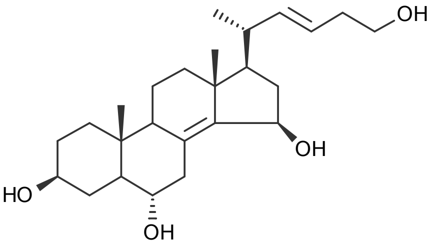

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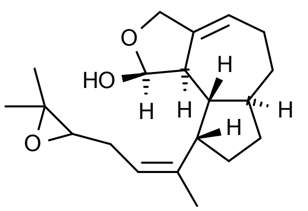
As previously mentioned, there are also mutual interspecific interactions that involve antifouling mechanisms undertaken by associated mesograzer Amphipoda removing epiphytes, including diatoms, from their host macroalgae.[42,111,110]

3.6 Competition for space and/or resources

Antarctic ecosystems are highly competitive environments in terms of space, but also in general resources, due to the long periods of limiting light and nutrients input. Organisms here must fight for their niche while maintaining a good balance of the integral energy budget to fulfill basic functions.[124] Despite the evident participation of allelochemicals mediating competitive interactions, very scarce work has been performed in these communities on this particular topic.[4,14] The fact that chemical defense is supposed to be metabolically expensive, partly explains why defended organisms are not typically space colonizers.[38,125,36] Several authors have proposed the hypothesis of a negative correlation between growth rate and protection, suggesting that slow-growth species are more likely to possess chemical defenses.[13,126] Accordingly, the predominant long-lived and slow-growing Antarctic biota is known to be in general well protected, excluding some punctual exceptions. Among such exceptional cases is the fast-growing sponge *Mycale acerata*, which is heavily preyed upon by the spongivorous sea star *Perknaster fuscus*, and has been repeatedly found to lack deterrent chemistry.[4,14,13] In Antarctic benthic communities this demosponge is actually considered one of the major space-dominating competitors. Thus, at the community level, this focused predation driven by *P. fuscus* may control competitive exclusion of slow-growing species.[13] Several water-borne products from the soft coral *Alcyonium antarcticum (A. paessleri)*, reported to yield antipredation protection, did as well demonstrate the ability to induce tissue necrosis to the colonizer sponge *M. acerata*. All this suggested the existence bioactive products exuded within the coral mucus, working synergistically for several ecological functions.[68] Other fast growing species, described as pioneer colonizers after major sea bottom disturbances (e.g., iceberg scouting) may as well represent space competitors, nonetheless no chemical ecology assays have been conducted against them.[127,128]

Indirect, time delayed, chemically mediated interactions can as well modulate relevant competitive encounters among species. Examples of such relationships may include emission of allelochemicals by a certain organism, promoting reduced physiological or reproductive performance in potential competing species. These events of indirect and transgenerational protection have been reported in temperate waters,[2,3] but they are poorly understood in Antarctica.[4,14] In the Southern Ocean, several species have proved to contain chemicals that induce death or low viability in early stages of the common Antarctic sea urchin *Sterechinus neumayeri*.[129–133] The ciliate *Euplotes focardii* further emits the diterpenoids epoxyfocardin (**54**) and focardin (**55**), which cause cytotoxicity to gametes of co-occurring ciliate communities of *Euplotes focardii* strain TN-1 line A, *E. focardii* TN-1 line B and *E. nobilii* AC-3, this way displacing potential competitors.[134]



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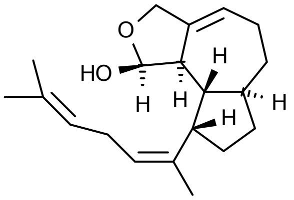

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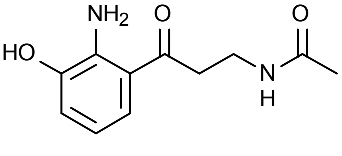
Eribusinone (**56**) from the demosponge *Isodictya erinacea* was found to mediate another singular allelopathic interaction, by promoting reduced molt events and increased mortality in the omnivore amphipod *Orchomene plebs,* when the amphipod was fed on eribusinone (**56**) enriched diets.[55]



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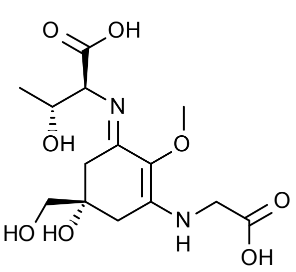
These strategies are likely to contribute in controlling population abundances and reduce future potential competitive pressures.

3.7 Photodamage from UV radiation

The ozonosphere, atmospheric UV filter layer, is diminished within the polar vortex (persistent, large-scale cyclone on either of the planet's poles), particularly over the Southern Hemisphere. Within the Antarctic vortex chlorine, which catalyzes the photochemical destruction of ozone (O_3), accumulates during the winter. This leads to a peak of O_3 depletion in the spring, when the sunlight returns to the Austral latitudes from September to early December.[16] The ozone hole has negative consequences to living beings due to the resultant increased surface UV (UV-B) levels, capable to disrupt DNA bonding, and cause genetic damage.[135] In response to this, Antarctic communities adapted to O_3 depletion, have been found to possess mycosporine-like amino acids (MAAs) (**57**-**66**).[136–140]



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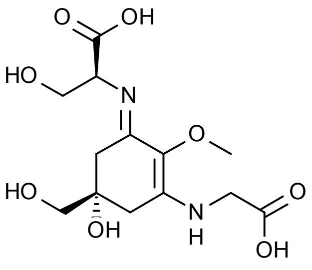

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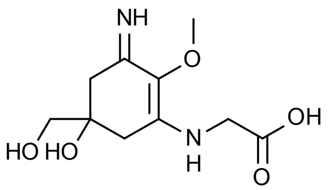

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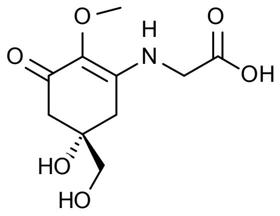

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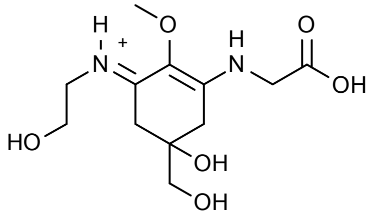

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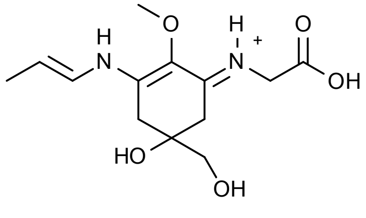

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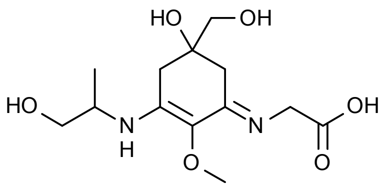
MAAs are UV-protecting molecules widespread in microbes (reason why they are called 'microbial sunscreens'), as well as in some multi-cellular organisms, mostly algae. They are thought to be transferred through the trophic chain, and/or to be obtained from symbiotic partnerships in other organisms. MAAs are synthesized in response to UV-B, and, besides their photo-protective capabilities, they are effective antioxidant molecules and participate in cellular tolerance to desiccation, salt, and heat stress. So far there are up to 20 known MAAs identified.[17]



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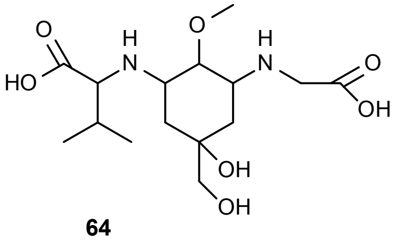

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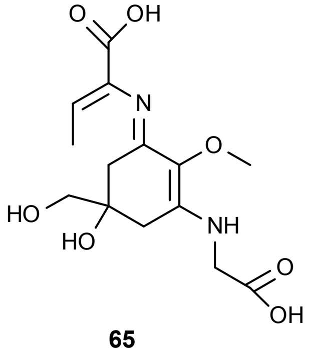
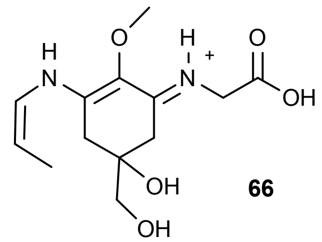


65



66

In the Antarctic, the most common MMAs found, almost in all marine taxa are: porphyra-334 (**57**), shinorine (**58**), palythine (**59**), mycosporine-glycine (**60**), asterina-330 (**61**), palythene (**62**), palythinol (**63**), mycosporine-glycine:valine (**64**), palythenic acid (**65**) and usujirene (**66**). Some other compounds with indirect photoprotectant functions include UV-absorbing pigments from *Palmaria decipiens* and *Enteromorpha bulbosa*[141] and carotenoids from *Leptosomia simplex*.[138]

3.8 Reproduction assistance

The harsh conditions of Antarctica, recording the coldest temperatures on Earth, challenge in many manners biological and physiological processes, and particularly concerning is the success of sex and reproduction. Therefore species here have assumed strategies to cope with the extreme seasonality, which periodically limits resources, and reduces the chances of sexual (gamete) encounters. Some of the mechanisms adopted include significant accumulations of lipidic compounds both,[142] to resist freezing, and to struggle through lapses of unavailable food supply, including the production of yolky eggs and embryos. Despite the marked seasonality, benthic species tend to reproduce all year-round, with lecithotrophic larvae that experience slow developmental rates until settling as adults.[143,124] These larval stages represent an important energetic investment, and are usually chemically defended against predation to resist relatively long intervals of exposition in the water column.[144] Planktonic organisms instead, are specially affected by ice dynamics, since a great part of the population gets trapped during the winter within the ice packs, and becomes relatively inactive, or dead.[142] The allelochemicals that mediate sex take part of the so-called pheromones (secreted factors that trigger social responses in members of the same species), which often promote interaction, and may further convey information about genotype. In marine environments, pheromones can create three-dimensional trails to assist gamete fertilization.[145]

67:`NPEDWFTPDTCAYG-DSNTAWTTCTTPGQTCYT-CCSSCFDVVGEQACQ-MS--AQC`

68:`DIEDFYTSETCPYKNDSQLAWDTCSGGTGNCGTVCCGQCFSFPVSQSCAGMADSNDCPNA`

The information about these types of molecules in the Antarctic is limited to the protein pheromones En-1 (**67**) and En-2 (**68**), produced by the protozoan ciliate *Euplotes nobilii* (strain AC-1) to promote mating induction.[146]

3.9 Miscellaneous

3.7.1 Pigments in defense. Marine invertebrates are often brilliantly colored independently whether they inhabit in shallow waters exposed to light, or in dark areas. Color characteristics are the result of several different processes, and serve various purposes. Pigments may belong to all the major structural classes of natural products, but the predominant ones are nitrogenous compounds. Frequently, pigments are employed by photosynthetic organisms in energy capture, photoprotection, and as antioxidants, but they can perform further relevant roles, including protection against other organisms. In this sense pigments may act directly as chemical defenses, as many are themselves bioactive; and additionally they may also function indirectly through aposematism. Aposematism is an antipredation adaptation consisting on a warning coloration that advises visual predators about the unprofitability, or presence of repellents in a prey item. The color warning represents a primary defense mechanism, and the non-visible chemical defenses are secondary. Aposematic adaptation is so successful that often undefended organisms have evolved to mimic such color warning (batesian mimicry). Moreover, aposematic species also come to resemble one another, expanding the significance and efficacy of a particular pattern in a process called müllerian mimicry.[166] The discorhabdins from *Latrunculia apicalis* (**6**-**7**), 4,5,8-trihydroxyquinoline-2-carboxylic acid from *Dendrilla membranosa*, an uncharacterized purple product from *Kirkpatrickia variolosa*, the tryptophan-related eribusinone (**56**) from *Isodictya erinacea,* and, to a lesser extent, the suberitenones (**8**-**9**) from *Suberites sp*., are all bioactive vivid pigments from Antarctic sponges (revised in [62,4,14]) Besides the strongly active, bright yellow meridianins (**36**-**42**) are present in several colonial *Aplidium* and *Synoicum* ascidians, as well as in sponges.[164,165,98,47] It is compelling that all these pigments, which are responsible for the intense colorations of the species that harbor them, operate in a marine system like the Antarctic, where visually oriented predators such as fish are generally lacking. It was hypothesized that pigmented chemical defenses in modern Antarctic fauna may constitute 'relict pigments' that evolved under aposematic selection in ancient (~22 million years ago), warmer Antarctic seas when visual consumers, including fish and turtles, were important predators.[104] Consequently, those pigment compounds with inherent antifoulant and/or antifeedant properties were retained under selective pressure in several species for providing ecological advantages, even if the aposematic coloration did not fulfill a function anymore. Indeed, apart from these cases, there seems to be trend in certain Antarctic groups (e.g., *Leucetta* and some other sponges in the genera *Haliclona* and *Calyx*), reporting colorless representatives, while temperate and tropical counterparts are colored.[14]

3.7.2 Microbial symbiosis. Currently, organisms are no longer seen as single pluricellular beings, but as 'holobionts': metaorganisms formed by a macroscopic host harboring an array of functionally dynamic assemblages of Bacteria, Archaea, Fungi, Virus, and algal symbionts.[147] Biochemical diversity resides majorly in microorganisms, reason why multicellular metazoans, limited in metabolic potential, have become greatly dependent on microbial symbionts, thereby expanding their ecological capacities. This is often attributed to a metabolic exchange, taking place between commensal microbes and holobionts, including the sharing of nutrients, and also ecologically functional compounds. Still, two major aspects about the role natural products play in symbiotic partnerships need to be disentangled: 1) what are the chemical mechanisms involved in the "cross-talk" between microorganisms and hosts to structure and maintain symbiotic microbiomes; 2) which bioactive metabolites enrolled in holobiont allelopathy really derive from symbionts.[147,148]

Microbial partnerships in Antarctic marine organisms have been suggested in many groups, yet experimental evidence of these relationships is in most cases insufficient. Several studies have catalogued associated microbiomes in invertebrates like the soft coral *Alcyonium antarcticum,*[149] or the colonial ascidian *Synoicum adareanum*.[150] Other analyses have detected more specific associated microbiota, such as blue-green prokaryotic microbes containing the pigment 2-vinylpheophorbide-a5 in echiurid worms;[151] non-photosynthetic bacteria discovered on the foot of the bivalve *Lissarca notorcadensis*,[152] the gills of the bivalve *Thyasira falklandica*,[153] the epidermis of the limpet *Laevipilina antarctica*,[154] or in the gut of the blood-sucking Antarctic fish isopod parasite *Gnathia calva*;[155] and bacterial and ciliate symbionts within the gut and stomach of the krill *Euphausia superba*.[156] There are also outstanding cases, such as certain metabolically active diatoms located inside hexactinellids living at ~100 m depth. It was suggested in such affair a symbiotic interaction, in which light is transmitted to the microalgae thanks to the optic properties of the silica spicules acting as fiber glass, and in return the sponges would get essential nutrients from the photosynthates.[157] From this discovery, endosymbiotic diatoms have been proposed in other

Antarctic species.[114,158] Indeed, the Porifera are of the best studied groups, in terms of microbiology, showing a wide array of associated microbiota including archaea, bacteria, diatoms and dinoflagellates.[159,160] Symbiotic microorganisms are often involved in the production of natural products in tropical and temperate marine organisms, however, in the Antarctic this is still an important open question starting to be approached.[160,148] The diketopiperazines (DKP) and phenazine alkaloids, with no known ecological role, were isolated from the bacterium *Pseudomonas aeruginosa* associated with the Antarctic sponge *Isodictya setifera*.[161] In the colonial ascidian *Synoicum adareanum,* alpha and gamma classes of symbiotic Proteobacteria, falling in the *Pseudovibrio* and *Microbulbifer* genera, were also shown to biosynthesize the macrolide palmerolide A. This polyketide is a potential antimelanoma drug with no demonstrated ecological properties.[162,163,150] Finally, there are circumstances that bring about the suspicion of certain functional natural products being originated from microbial associates. The meridianins (**36**-**42**), as an illustration, are multifaceted allelochemicals, which have been afforded by the ascidians *Aplidium meridianum, A. falklandicum* and a *Synoicum sp*., and meridianin A was also reported from the Southern Ocean sponge *Psammoclema sp.* (*Psammopemma sp.)* [164,165,98,47] The fact of being found in different Antarctic species, genera and taxa, have leaded various authors to suspect that these potent alkaloids could be produced by a common microorganism; which partnership would have been retained in the several groups for the beneficial bioactivities provided.[47] On the opposite side, there examples of single species providing inconsistent secondary metabolite profiles, like that observed in the terpenoid patterns of the soft corals *Alcyonium antarcticum*[69–71] and *A. rosseum*; or the glass sponge *Anoxycalyx (Scolymstra) joubini* yieding glassponsine (**11**) in only one sample of the collection, after analyzing various conspecifics.[65,51] In these species different microbiomes might be providing diverse molecules, yet further investigation should clarify these and other analogous cases.

4. Conclusions

Marine chemical ecology research continues to highlight the importance of chemical cues and allelopathy as lead forms of communication for a variety of processes in marine communities in general, and particularly among many Antarctic taxa, such as Rhodophyta, Ciliata, Porifera, Cnidaria, Mollusca, Echinodermata, Ascidiacea, and others. Nonetheless, further study requires expansion over many more groups, and attention should be taken on increasing field experimentation in order to obtain more realistic results. Additionally, much needs to be learned yet on the identity of the bioactive compounds involved in the communities and how these operate, as a large number of activities not included in this review, refer to complex mixtures of compounds contained within crude organic extracts.[4,14,49] Ecological roles for marine natural products include anti-predation, prevention of fouling, overgrowth and microbial invasions, reproduction assistance, and UV photoprotection. The most studied activity though, is predator deterrence, in which most antifeedants act, not through toxicity, but eliciting bad taste to the potential prey, and it is not clear whether certain moieties are more effective than others.[3,7,8,51] Regarding antifouling, strategies in Antarctic systems seem to operate differently from other regions. Here, a few species have been found to possess compounds yielding antibacterial inhibition, whereas several experiments point out an extended presence of antidiatom agents still to be identified.[122,15,117,119,118,121] This is pertinent, as diatoms are major fouling components in Southern Pole latitudes.[15] Scarce studies have addressed spatial competition processes in the Antarctic benthos, but there is evidence of growth inhibitors to avoid displacement by fast-growing space-dominating species.[68,13] Photoprotection with mycosporine-like amino acids is broadly extended in shallow marine taxa, in accordance to the consequences of the O_3 hole and the elevated UV-B light impacting polar latitudes ([139] and reviewed in [4]). Moreover, the harsh conditions and acute seasonal changes in nutrient supply and ice formation, have driven species to adopt strategies to facilitate reproduction through molecules (pheromones) that favor mating,[146] and to produce chemically protected larval stages.[144] Interestingly, it is plausible that deterrent metabolites with bright colorations and retained in evolution for their bioactivities, might have promoted aposematism in the antique warmer (temperate/subtropical) Antarctic ecosystem; warning about defensive chemistry or toxicity when visual predators were abundant.[166] Practically nothing is known about microbial symbioses in Antarctic communities and the chemical ecology (allelochemistry) involved. A few studies have recognized secondary metabolites produced by microorganisms in association with marine organisms, yet the ecological role is still to be determined.[161,163,150] In fact, this circumstance is believed to be quite common among macroalgae and invertebrates, becoming, to a certain extent, metabolically dependent on their symbiotic microbiome.[167,160,5,148] In general, variability in chemistry and defensive bioactivities among conspecific individuals likely responds to different reasons, among which: interspecific (genetic, phenotypic) variable chemotypes, chemical defense induction (acclimatization), or symbiotic origin of certain metabolites.[8] As the field of chemical ecology continues to progress and expand to more remote areas like Antarctica, there are additional crucial aspects to examine about the roles natural products play in symbiotic partnerships, and also how environmental changes affect chemically-mediated interactions for understanding the overall impact of climate change on marine ecosystems. To this end, collaborations should be put together among ecologists, natural product chemists, physiologists, biochemists, molecular biologists and microbiologists. Within Antarctica itself, efforts should be taken over to compensate the asymmetric status of knowledge; since the vast majority of chemical ecology studies come from McMurdo Sound and Antarctic Peninsula, followed by other areas, such as the Weddell Sea, and some Subantarctic Islands, whereas almost nothing has been reported from areas like Ross, Davis and Bellinghausen Seas.[4,14] This and other reviews on the topic underline the maintenance of metabolic pathways related to the production of natural products that bestow evolutionary advantage. High latitudes and cold temperatures do not reduce ecological pressures nor do they limit organisms' metabolic capacities. Ultimately, high biodiversity of Antarctic communities, and concomitant organism-on-organism ecological interactions has driven chemical diversity: 'chemodiversity recapitulates biodiversity'. The Southern Ocean is indeed a prolific resource of bioactive chemicals awaiting to be understood and exploited.

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† Electronic Supplementary Information (ESI) available: **Table 1:** Known natural products with ecological activity in Antarctic marine ecosystems. See DOI: 10.1039/b000000x/

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REVIEW

Electronic Supplementary Information (ESI)

Table 1: Known natural products with ecological activity in Antarctic marine ecosystems.

PHYLUM	SPECIES	METABOLITE	CODE	ACTIVITY	REFERENCES
RHODOPHYTA	*Plocamium cartilagineum*	Averene	**1**	D_A	Ankisetty et al., 2004
		Epi-plocamene-D	**2**	D_A	
		Halogenated monoterpenes		D_F	Amsler et al. 2013
CILIATA	*Euplotes focardii*	Epoxyfocardin	**54**	C_G	Guella et al. 1996
		Focardin	**55**	C_G	
	Euplotes nobilii (strain AC-1)	Pheromone En-1	**67**	Ph	Felici et al. 1999
		Pheromone En-2	**68**	Ph	
PORIFERA	*Anoxycalyx (Scolymastra) joubini*	Glassponsine	**11**	D_A	Núñez-Pons & Avila 2014
	Crella sp.	Norselic acid A	**12**	D_A	Ma et al. 2009
	Dendrilla membranosa	Picolinic acid	**3**	T_S	Baker et al. 1993, 1995
		7-Methyladenine	**4**	T_S	
	Isodictya erinacea	p-Hydroxybenzaldehyde	**5**	T_S	Baker and Yoshida, 1994; Moon et al., 2000
		Erebusinone	**56**	Mo	Amsler et al., 2001
	Kirkpatrickia variolosa	Uncharacterized purple pigment		T_S	Baker et al. 1994
	Latrunculia apicalis	Discorhabdin C and G	**6**	T_S; A_B	Yang et al. 1995
		Discorhabdin G	**7**	A_B; D_S	Furrow et al. 2003
	Rossellidae spp.	5α-Cholestan-3β-one	**10**	D_A; D_S	Núñez-Pons et al. 2012
	Suberites sp.	Suberitenones A and B	**8-9**	T_S; A_B	Baker et al., 1997
CNIDARIA	*Ainigmaptilon antarcticus*	Ainigmaptilon A	**30**	D_S; A_B; A_D	Iken and Baker, 2003
	Alcyonium antarcticum (= *A. paessleri*)	Water-borne Cholesterol	**13**	T_S; Co	Slattery et al., 1997a
		22-Dehydrocholesterol	**14**	T_S; Co	
		22-Dehydro-7-hydroxy-cholesterol	**15**	T_S; Co	
		Wax esters	**27-28**	D_A; D_S	Núñez-Pons et al. 2013
	Alcyonium grandis	Illudalenes 1-9	**16-24**	D_A; D_S	
		Wax esters	**27-28**	D_A; D_S	
	Alcyonium hadonii	Wax esters	**27-28**	D_A; D_S	
	Alcyonium paucilobulatum	Wax esters	**27-28**	D_A; D_S	
	Alcyonium rosseum	Illudalenes 10-11	**25-26**	D_A; D_S	

		Wax esters	**27-28**	D_A; D_S	
	Clavularia frankliniana	Chimyl alcohol	**29**	D_S	McClintock et al., 1994c
	Gersemia antarctica	Homarine	**31**	A_B	Slattery et al. 1997a
		Trigonelline	**44**	A_B	
MOLLUSCA	*Austrodoris kerguelenensis*	Diterpene monoacylglycerides	**32-33**	D_S	Iken et al., 2002
		Diterpene diacylglycerides		D_S	
		Monoacylglycerides from fatty acids		D_S	
	Bathydoris hodgsoni	Hodgsonal	**34**	D_S	Avila et al., 2000
	Clione antarctica	Pteroenone	**43**	D_F	Yoshida et al., 1995
	Marseniopsis mollis	Homarine	**31**	D_S	McClintock et al., 1994a
	Tritoniella belli	Chimyl alcohol	**29**	D_S	McClintock et al., 1994c
ECHINODERMATA	*Acodontaster conspicuus*	Acodontasterosides D, E, F, G, H, I	**45-50**	A_B	De Marino et al. 1997
		Steroids 15, 18, 19	**51-53**	A_B	De Marino et al. 1998
CHORDATA	*Aplidium falklandicum*	Meridianins A-G	**36-42**	D_A; D_S; A_B	Núñez-Pons et al., 2010
	Aplidium meridianum	Meridianins A-G	**36-42**	D_A; D_S; A_B	
	Aplidium fuegiense	Rossinone B	**35**	D_A; D_S	Carbone et al. 2012; Núñez-Pons et al., 2012
ARTHROPODA	*Paradexamine fissicauda*	Halogenated monoterpenes		D_F	Amsler et al. 2013
SEVERAL TAXA		Porphyra-334	**57**	UVph	Karentz et al. 1991; Karentz 1994; McClintock & Karentz 1997; Karentz & Bosch 2001; Hoyer et al. 2003
		Shinorine	**58**	UVph	
		Palythine	**59**	UVph	
		Mycosporine-glycine	**60**	UVph	
		Asterina-330	**61**	UVph	
		Palythene	**62**	UVph	
		Palythinol	**63**	UVph	
		Mycosporine-glycine:valine	**64**	UVph	
		Palythenic acid	**65**	UVph	
		Usujirene	**66**	UVph	

Ecological activities

T_S: Tube-foot retraction in seastars

D_A: Deterrent against amphipods

D_S: Deterrent against seastars

D_F: Deterrent against fish

Co: Competitors avoidance

A_B: Antibacterial

A_D: Antifouling against diatoms

C_G: Cytotoxicity to gametes of sympatric spp.

Ph: Mating induction (pheromone)

Mo: Molting inhibition on crustaceans

UVph: UV-B Photoprotection