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Phaeurus antarcticus and its endophytic fungi: Chemical diversity of a hidden pharmacy underneath the Antarctic Ocean

Phaeurus antarcticus e seus fungos endofíticos: Diversidade química de uma farmácia oculta sob o oceano Antártico

Gustavo Souza dos Santos

Ribeirão Preto
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“Man is the most insane species. He worships an invisible God and destroys a visible nature. Unaware that this nature he’s destroying is this God he’s worshiping.”

— Hubert Reeve

RESUMO

SANTOS, G. S. ***Phaeurus antarcticus* e seus fungos endofíticos: Diversidade química de uma farmácia oculta sob o oceano Antártico.** 2022. 367f. Tese (Doutorado). Faculdade de Ciências Farmacêuticas de Ribeirão Preto – Universidade de São Paulo, Ribeirão Preto, 2022.

Capítulo I: O perfil químico e as atividades antibacteriana, antiparasitária e inseticida da alga *P. antarcticus* foram investigados. O extrato hexânico (HX) e suas frações exibiram atividade bacteriostática e bactericida seletiva contra *Staphylococcus. aureus*. As frações HX-FC e HX-FD apresentaram atividade antiparasitária frente a *Leishmania amazonensis* e *Neospora caninum*. O extrato HX e a fração HX-FC apresentaram potencial inseticida frente a larvas de *Aedes aegypti*. Através de análises em CG-EM, e combinação de análises estatísticas multivariadas (OPLS-DA) com a construção de redes moleculares (GNPS) foi possível anotar terpenos, esteroides ácidos graxos e álcoois nas frações bioativas. **Capítulo II**: Utilizando técnicas metabolômicas (CLUE-EM/RMN ^{1}H) combinadas a análises estatísticas multivariadas (PCA, OPLS-DA) a variabilidade espacial de metabólitos secundários da alga *P. antarcticus* e a atividade antibiofilme dos extratos e frações foram avaliados frente a *S. aureus* resistente à meticilina e oxacilina (MRSA). Os resultados revelaram que as mudanças no perfil químico não foram sítio específicas e podem estar relacionadas a diferentes estágios do ciclo de vida das algas coletadas. Porfirinas, terpenos e carotenoides foram anotados como sustâncias discriminantes. O ácido linoleico (1) e o fucosterol (2) foram isolados das frações bioativas e apresentaram atividade antibiofilme frente a MRSA. **Capítulo III:** O extrato e frações do fungo *Penicillium purpurogenum* foram submetidos a avaliação das atividades antibacteriana, antiparasitária, imunomoduladora e fotoprotetora. O fracionamento bioguiado levou ao isolamento de seis policetídeos: 5,6,8-triidroxi-4-(1´-hidroxietil) isocumarina (3), aspergilumarina A (4), aspergilumarina B (5) berkeleyacetal C (6), sescandelina (7) e vermistatina (8). O potencial fotoprotetor, imunomodulador e leishmanicida das substâncias foi avaliado. As substâncias 3, 4, 7 e 8 apresentaram fotoestabilidade e atividade fotoprotetora frente a radiação UVB-UVA. As substâncias 3, 6, 7 e 8 apresentaram potencial imunomodulador, reduzindo a produção de espécies reativas de oxigênio em neutrófilos humanos estimulados pelo PMA sem efeitos citotóxicos. A substância 6 apresentou atividade leishmanicida frente a amastigotas de *L. amazonensis*. **Capítulo IV:** O perfil químico (CLUE-EM/ RMN ^{1}H) e a atividade antibiofilme frente a MRSA de 21 linhagens fúngicas foram investigados. O fracionamento do extrato do fungo *Epicoccum nigrum*, levou ao isolamento das epicozarinas A – B (9-10) e C (12) e de um terpeno (11) inédito. As substâncias 9 – 12 exibiram atividade antibiofilme contra MRSA. Dentre estas, a substância 11 apresentou maior inibição da formação de pré-biofilme e ruptura do biofilme formado. Diante do contexto global, este trabalho buscou a obtenção de novos produtos biotecnológicos, considerando os Objetivos do Desenvolvimento Sustentável das Nações Unidas. Os resultados obtidos fornecem novas informações quimio-taxonômicas e potencial biotecnológico dos organismos marinhos da Antártica como produtores de biomoléculas de interesse farmacêutico, enfatizando a importância da bioprospecção para a conservação de organismos ainda pouco conhecidos.

Palavras-chave: Produtos naturais marinhos, Fungos antárticos, Macroalgas antárticas, Fotoproteção, Antimicrobianos, Doenças negligenciadas, Atividade imunomoduladora, Metabolômica

ABSTRACT

SANTOS, G. S. ***Phaeurus antarcticus*** **and its endophytic fungi: Chemical diversity of a hidden pharmacy underneath the Antarctic Ocean.** 2022. 367f. Thesis (Doctoral). Faculdade de Ciências Farmacêuticas de Ribeirão Preto – Universidade de São Paulo, Ribeirão Preto, 2022.

Chapter I: The chemical profile and antibacterial, antiparasitic, and insecticidal activities of the seaweed *P. antarcticus* were investigated. The hexane extract (HX) and its fractions exhibited selective antibacterial activity against *Staphylococcus aureus*. Fractions HX-FC and HX-FD showed the highest antiparasitic activity against *Leishmania amazonensis* and *Neospora caninum*. The HX extract and the HX-FC fraction presented insecticidal potential against *Aedes aegypti* larvae. Through GC-MS analysis and the combination of multivariate statistical analyses (OPLS-DA) and the construction of molecular networks (GNPS), it was possible to annotate terpenes, steroids, fatty acids, and alcohols in the bioactive fractions. **Chapter II:** Using metabolomics techniques (UPLC-HRMS/^{1}H NMR) and multivariate statistical analysis (PCA, OPLS-DA), the spatial variability of secondary metabolites of the seaweed *P. antarcticus* and the antibiofilm activity of extracts and fractions were evaluated against S. aureus resistant to methicillin-oxacillin (MRSA). The results revealed that the changes in the chemical profile were not site-specific and could be related to different life cycle stages of the collected algae. Porphyrins, terpenes, and carotenoids were annotated as discriminating compounds. Linoleic acid (1) and fucosterol (2) were isolated from the bioactive fractions and showed antibiofilm activity against MRSA. **Chapter III:** The extract and fractions of the fungus *Penicillium purpurogenum* were evaluated for antibacterial, antiparasitic, immunomodulatory, and photoprotective activities. The bioguided fractionation led to the isolation of six polyketides: 5,6,8-trihydroxy-4-(1'-hydroxyethyl) isocoumarin (3), aspergillumarin A (4), aspergillumarin B (5), Berkeleyacetal C (6), sescandelin (7), and vermistatin (8). Compounds 3, 4, 7, and 8 presented photostability and photoprotective activities against UVB-UVA. Compounds 3, 6, 7, and 8 presented immunomodulatory activity by down-regulating the production of reactive oxygen species in PMA-stimulated human neutrophils without cytotoxic effects. Compound 6 presented leishmanicidal activity against amastigotes of *L. amazonensis*. **Chapter IV:** The chemical profile (UPLC-HRMS/^{1}H NMR) and antibiofilm activity against MRSA of 21 fungal strains were investigated. Among them, the fractionation of the extract of the fungus *Epicoccum nigrum* led to the isolation of epicorazines A–B (9–10) and C (12) as well as a new terpenoid (11). Compound 9–12 exhibited antibiofilm activity against MRSA. Among these, compound 11 showed the highest inhibition of pre-biofilm formation and rupture of the formed biofilm. Given the global context, this work sought to obtain new biotechnological products, considering the United Nations Sustainable Development Goals. The results obtained provide new information about the chemotaxonomy and biotechnological potential of Antarctic marine organisms as producers of biomolecules of pharmaceutical interest, emphasizing the importance of bioprospecting for the conservation of understudied organisms.

Keywords: Marine natural products, Antarctic fungi, Antarctic seaweed, Photoprotection, Antimicrobials, Neglected diseases, Immunomodulatory activity, Metabolomics

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LIST OF ABREVIATIONS

ASW	Artificial seawater
COSY	Correlation spectroscopy
EtOAc	Ethyl acetate
GC-MS	Gas chromatography mass spectrometry
h	hour
HMBC	Heteronuclear Multiple Bound Correlation
HRMS	High resolution mass spectrometry
HSQC	Heteronuclear Single Quantum Correlation
HX	Hexane
m/z	mass over charge
MeOH	Methanol
min	minutes
MPLC	Medium pressure liquid chromatography
NMR	Nuclear magnetic resonance
NSW	Natural seawater
OPLS-DA	Orthogonal partial least squares discriminant analysis
PCA	Principal component analysis
R*t*	Retention time
TLC	Thin layer chromatography
UVR	Ultraviolet radiation
VLC	Vacuum liquid chromatography

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1. INTRODUCTION

1.1 The Antarctic continent

Antartica is known as the "Continent of Superlatives" and represents one of the world's last frontiers. The continental landscape is characterized by rash climate conditions, such as extremely low temperatures, strong seasonal shifts in solar radiation, high ultraviolet exposure in the summer and darkness in winter, and heavy seasonal changes in ice cover (DINASQUET et al., 2018; WENZEL et al., 2016).

The continent is home to remote locations with pristine and little-studied ecosystems, each with their own distinct characteristics (Fig. 1). Surrounded by an ocean, the world's highest, driest, windiest, and coldest continent possess very distinctive environmental conditions that play an important role in the distribution and development of life (WENZEL et al., 2016).

Figure 1. Antarctic glacier near the Comandante Ferraz Brazilian Antarctic Base.

Source: G. S. SANTOS (2017).

The Antarctic biodiversity is mainly dominated by marine organisms, seabirds and microorganisms and lacks terrestrial mammalian predators (Fig. 2). In fact, until

the establishment of scientific bases, even humans were absent from the continent (MELTOFTE, 2019).

Figure 2. . Antarctic fauna. **A** – *Pygoscelis antarcticus*; **B** – *Pygoscelis adeliae*; **C** – *Pygoscelis papua*; **D** – *Macronectes giganteus*; **E** – *Hydrurga leptonyx*; **F** – *Mirounga leonina.*

Source: M. JATOBÁ – SeCom - UNB (2017).

Despite the geographical isolation, Antarctica is not protected from the impacts of anthropogenic activities and climate change effects. Human activities such as oil prospection, overfishing, pollution, and the constant release of greenhouse gases all exert pressure on the Antarctic ecosystems (DINASQUET et al., 2018; WAUCHOPE; SHAW; TERAUDS, 2019).

Between 1908 and 1943, seven countries claimed Antarctic territories, to avoid conflicts and further territorial claims, the Antarctic Treaty was created in 1959. The Treaty sets aside disputes over territorial claims and promotes peaceful use and scientific cooperation in the region (DODDS, 2010). Later, the Protocol on Environmental Protection to the Antarctic Treaty was signed in Madrid on October 4, 1991. The protocol established the continent as an International Natural Reserve devoted to peace and science. The protocol provided environmental protection, including a ban on mining and mineral exploration; the intentional introduction of non-native species; strict regulations on disturbance to native species; waste management; and environmental impact assessment requirements (WAUCHOPE; SHAW; TERAUDS, 2019).

The severe environmental conditions are the bottleneck for studying organisms derived from polar regions. The cost of logistics is high, and specialized equipment is required to explore the poles. The climate conditions make it difficult to access the poles but do not limit biological communities' development (SOLDATOU; BAKER, 2017). However, behind the white and frozen landscapes, the Antarctic marine environment harbors a rich and underexplored biodiversity with unmeasurable biotechnological potential. To survive and overcome abiotic and ecological pressures such as food and space competition, predation, high UV ray exposure and low temperatures, polar organisms evolved different adaptation strategies, including the production of secondary metabolites (LEBAR; HEIMBEGNER; BAKER, 2007; RANGEL et al., 2020; TEIXEIRA et al., 2021).

Recent numbers demonstrate the growing interest of natural products scientists in marine-derived molecules. For example, only in 2020, 1407 new compounds were isolated from marine organisms while only 332 were reported in 1984 (CARROL et al., 2021). According to a literature review, until 2016, about 30 000 publications regarding marine natural products have been listed in the MarinLit database, but only 3% of the total reported natural products from cold environments (SOLDATOU; BAKER, 2017). (BLUNT et al., 2017; CARROLL et al., 2021). Despite the lower number of studies when compared to tropical regions, Antarctica represents a hotspot of bioprospection. In 2013, when then last survey was made there were patents registered for 439 Antarctic species highlighting the biotechnological potential of polar organisms (NÚÑEZ-PONS et al., 2020).

1. 2 The Brazilian Antarctic Program and the University of São Paulo

Brazil signed the Antarctic Treaty in 1975, and with the establishment of the Brazilian Antarctic Program (PROANTAR) the Brazilian Antarctic Missions began in 1982. Later, in 1983, these efforts enabled the country to be considered as a consultant member of the Antarctic Treaty. Since then, Brazil participates in the decision-making and policies regarding the future of the continent (MARINHA DO BRASIL, 2016).

The first Brazilian Antarctic expedition (OPERANTAR I) was carried out on board of the oceanographic survey ship Barão de Tefé (Marinha do Brasil) and on the oceanographic ship Prof. Wladimir Besnard from the Institute of Oceanography of the University of São Paulo (MARINHA DO BRASIL, 2016). The oceanographic ship Prof. Wladimir Besnard (Fig. 3) was built with funds provided by the Brazilian Federal agencies and State government of São Paulo. Thus, the University of São Paulo was pioneer in the Antarctic expeditions and until now has contributed to the advance of Antarctic science.

Figure 3. Oceanographic ship Prof. Wladimir Besnard.

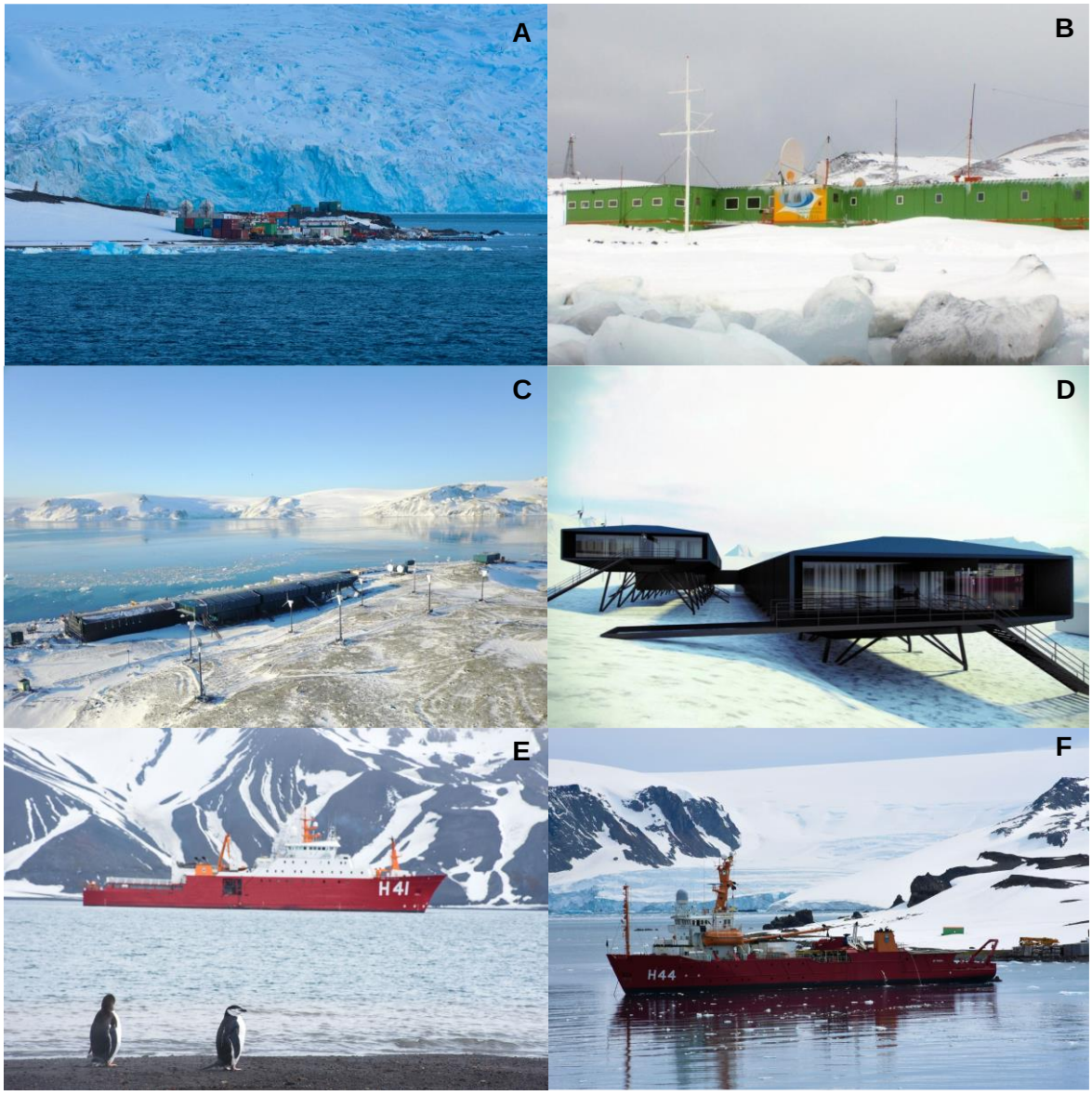
Source: https://www.io.usp.br/index.php/embarcacoes/n-oc-prof-w-besnard.html

The Brazilian Antarctic Base, Comandante Ferraz (Fig. 4A-B), was established in Admiralty Bay on King's George Island in 1984 and served as support for the expeditions until February 2012, when the structure was consumed by fire. After eight years since the accident, a new base was inaugurated in 2020 (Fig. 4C-D).

The Laboratory of Organic Chemistry of the Marine Environment has integrated two field expeditions to the continent, the first in 2015, when Dr. Hosana Maria Debonsi initiated the study of natural products derived from Antarctic seaweeds and their endophytic fungi, and the second in 2017, when samples of *P. antarcticus* used in this work were collected. The seaweed collection and isolation of fungi were conducted on

board the polar ship Almirante Maximiano H-41 (Fig. 4E) with the logistics support of the oceanographic ship Ary Rongel H-44 (Fig. 4F).

Figure 4. Brazil in Antarctica. **A**-**B** – Old Antarctic base; **C**-**D** – New Antarctic base; **E** – Polar ship Almirante Maximiano (H-41); **F** – Oceanographic ship Ary Rongel.



Source: SeCom – CIRM (2017); SeCIRM: https://www.marinha.mil.br/secirm/pt-br/proantar/nova-estacao (2019).

1. 3 Bioprospecting to Protect

The Antarctic Peninsula is one of the world's fastest warming regions. This environmental change has an impact on the planet's climate and will result in the loss of unknown biodiversity and imbalance in the continent's biological communities (SIEGERT et al., 2019). In this scenario, bioprospecting of polar organisms is essential to their conservation. Thus, continuous research is required to

investigate Antarctic life forms and their biotechnological potential. The majority of Antarctic derived natural products are extracted from marine organisms and, despite the growing number of reports, cold-water organisms are still underexplored (DOS SANTOS et al., 2021; SOLDATOU; BAKER, 2017).

The year 2021 started the United Nations Decade of Ocean Science for Sustainable Development (2021 – 2030) which targets the creation of a cooperative framework to benefit both ocean ecosystems and society through the achievements of ocean science. In addition, on July 8^{th,} 2021, the National Geographic Society recognized the surrounding waters of the Antarctic continent as the fifth ocean on Earth. In the present global context, there is no better opportunity to deepen our knowledge of the polar waters and gather resources from governments, industry, and academia to explore the hidden chemistry and biotechnological potential of polar marine organisms (DOS SANTOS et al., 2021).

This work aims to contribute to the University of São Paulo commitment to the United Nations Sustainable Development Goals (SDG's) agenda. Among the 17 SDG's, this work will contribute to numbers 3 ("Good Health and Well-Being") and 14 ("Life Below Water").

1. 4 Antarctic Natural products

Although the oceans occupy two-thirds of the earth's surface, marine biodiversity remains an untapped source of new natural products. Systematic investigations of marine natural products began only 50 years ago. However, marine natural products have demonstrated high diversity and structural complexity, which are not found in terrestrial organisms (CARROLL et al., 2021; IOANNOU; ROUSSIS, 2009).

Seaweeds have been used in food, traditional medicine, and agriculture since ancient times, and they were among the first marine organisms to be chemically analyzed (IOANNOU; ROUSSIS, 2009; MILLEDGE; NIELSEN; BAILEY, 2016). Secondary metabolite production is directly related to abiotic factors in both the marine and terrestrial environments (TEIXEIRA et al., 2019a). In this sense, the seas and oceans present a number of adverse conditions, such as changes in salinity, acidity, temperature, ultraviolet radiation incidence, and nutrient competition, that make this environment an excellent trigger for the production of differentiated metabolites (CONTE et al., 2021).

The polar regions, which include the Arctic and Antarctica, are considered the most extreme on earth (LIU et al., 2013). As a result, there is a limitation in the development of biological communities, and their biodiversity is dominated by marine organisms and microorganisms (GODINHO et al., 2013).

The Antarctic marine environment is characterized by high biological activity and biogeochemical cycling (BALDI et al., 2010). The intensity of biological activity and nutrient cycling in this environment is directly related to the high primary production that occurs during the summer (DUCKLOW et al., 2008; FONDA UMANI et al., 2005). Due to the isolation caused by the Antarctic Circumpolar Current, the benthic communities in the region are characterized by a high degree of endemism and the presence of cold-adapted species (WIENCKE et al., 2007).

In the Antarctic marine environment, seaweeds are important primary producers and plays an essential role in carbon cycling (NĘDZAREK, A., RAKUSA-SUSZCZEWSKI, 2004). In addition to primary production, seaweeds shelter a variety of associated organisms, including fish, invertebrates and microorganisms such as bacteria and fungi (LOQUE et al., 2010).

To survive the harsh conditions of the marine environment, seaweeds have developed/improved several defense strategies. Regarding secondary metabolites, these adaptations resulted in the production of diverse molecules biosynthesized by different metabolic pathways (IOANNOU; ROUSSIS, 2009). For example, to modulate microbial colonization on its surface and avoid herbivory, seaweeds produce compounds capable of balancing these ecological relationships and ensuring their survival (PERSSON et al., 2011). Abiotic factors such as increasing or decreasing temperature can also influence the metabolic profile displayed by macroalgae (FARIMAN; SHASTAN; ZAHEDI, 2016). For example, previous studies indicated the relationship between the decrease in water temperature and the increase in the production of polyunsaturated fatty acids (FARIMAN; SHASTAN; ZAHEDI, 2016; NOMURA et al., 2013).

In addition to the production of secondary metabolites, the association between seaweeds and microorganisms might characterize another form of defense and adaptation (SURYANARAYANAN, 2012). Marine fungi have been recognized as a prolific source of bioactive compounds. In the marine environment, they occur as spores, fragments of hyphae and mycelia and are classified into two distinct groups: obligate marine fungi and facultative marine fungi (JONES; KOHLMEYER;

KOHLMEYER, 1980). Obligate marine fungi are those that grow and sporulate exclusively in a marine or estuarine habitat, while marine facultative fungi are those found in freshwater or terrestrial environments, which are able to grow and possibly also sporulate in the marine environment (PANG et al., 2016).

In polar regions such as Antarctica, fungi are further classified as psychrophilic and psychrotolerant (HARDING et al., 2011). The endemic Antarctic fungi are classified as true psychrophilic because they are capable of growing and sporulate exclusively in the Antarctic environment. The so-called psychrotolerant are cosmopolitan ecotypes that resulted from an adaptation to the climatic conditions of Antarctica, thus being able to develop in the region (ROSA et al., 2019b).

Macroalgae are the second largest source of fungi in the marine environment, evidencing the ecological relationship between these two groups of organisms (BUGNI; IRELAND, 2004). The fungi that colonize the algal surface are called epiphytic and those capable of colonizing the tissues and internal parts of the algae are then called endophytic (SURYANARAYANAN, 2012). By definition, endophytic fungi are those that colonize or spend part of their life cycle inside the host tissue, in a relationship that can range from symbiotic-mutualistic to latent-pathogenic (BUGNI; IRELAND, 2004; JONES; KOHLMEYER; KOHLMEYER, 1980; SURYANARAYANAN, 2012).

Studies related to Antarctic seaweeds and their symbionts are limited by logistics and safety in the face of extreme conditions in these environments. A few studies describe the diversity and biotechnological potential of the fungal community associated with the Antarctic seaweeds *Acrosiphonia arcta*, *Adenocystis utricularis*, *Monostroma hariotii*, *Palmaria decipiens*, *Ulva intestinalis*, *Desmarestia menziesii* and *Phaeurus antarcticus*, however, the methodologies used in these works did not target the isolation of endophytic fungi. Furthermore, only the potential of crude extracts was investigated with no records of isolated compounds (FURBINO et al., 2014; GODINHO et al., 2013).

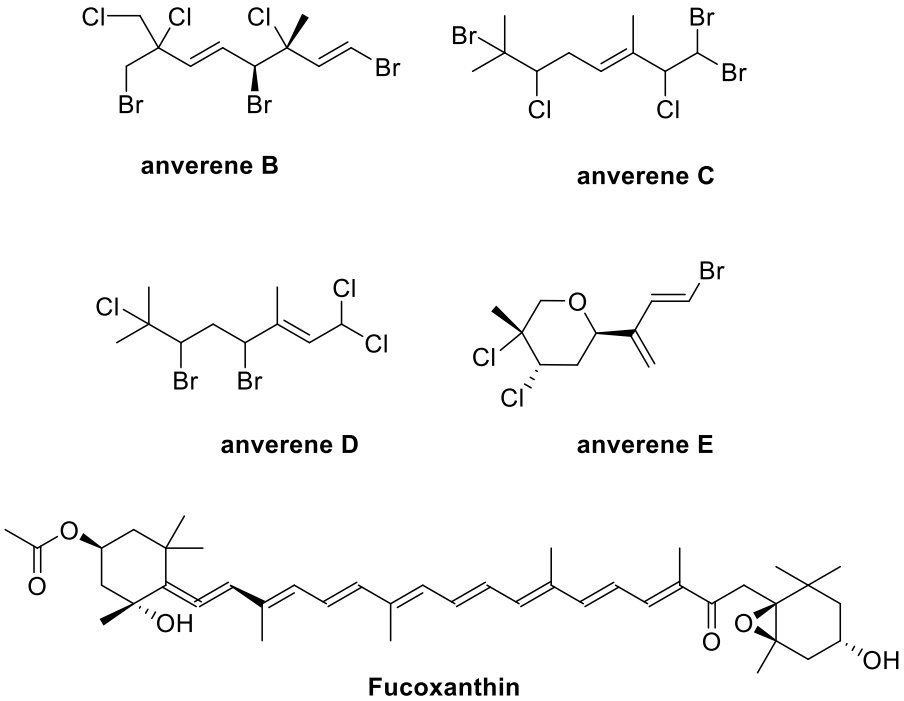
1. 4. 1 Natural products from Antarctic seaweed

Seaweeds are a rich source of secondary metabolites, including antibacterial, antifungal, antiparasitic and photoprotective compounds (FALKENBERG et al., 2019; SHANNON; ABU-GHANNAM, 2019). *Plocamium cartilagineum* is a red macroalga species widely distributed on the Antarctic Peninsula. Previous chemical investigations

of this macroalga led to the identification of different chemogroups (YOUNG et al., 2013). In a recent report, Shilling and co-workers (2019) isolated nine monoterpenes from three chemogroups of this alga, including four new compounds named anverenes B–E (Fig. 5). All isolated compounds were submitted to clonogenic survival assay using a human cervical cancer cell line (HeLa). Anverene D was the most active compound with IC_{50} value of 1.19 (SHILLING et al., 2019a).

Tavares and co-workers (2020) described the isolation of fucoxanthin from *Desmarestia anceps*. Fucoxanthin presented UVA and UVB absorption, photostability when incorporated into a sunscreen formulation, and antioxidant activity after UVA induction of ROS production on reconstructed human skin. This compound presented photoprotective properties and potential to be used as a UV-booster on sunscreens (TAVARES et al., 2020a).

Figure 5. Compounds isolated from Antarctic seaweeds.



1. 4. 2 Natural products from Antarctic marine fungi

In the period ranging from January 2018 to December 2021, fungi were the second most prospected Antarctic organism, highlighting the interest of natural products researchers in this new reservoir of bioactive molecules. Herein examples of metabolites isolated from Antarctic derived fungi and their bioactivity reported in the

review article Natural Products from Poles: Structural diversity and biological activities are described (DOS SANTOS et al., 2021).

The chemical investigation of the Antarctic fungus *Aspergillus sydowii* SP-1 led to the isolation of the new alkaloid acremolin C together with the four known compounds cyclo-(*L*-Trp-*L*-Phe), (4-hydroxyphenylacetic acid, (7*S*)-(+)-hydroxysydonic acid, and (7*S*,11*S*)-(+)-12-hydroxysydonic acid (Fig. 6). These compounds were screened against *Staphylococcus aureus*, *Staphylococcus epidermidis*, methicillin resistant *S. aureus* (MRSA), and methicillin-resistant *S. epidermidis* (MRSE). Acremolin C presented inhibition activities against MRSA and MRSE with MIC values of 32 and 16 µg/mL, respectively, while compounds cyclo-(*L*-Trp-*L*-Phe), 4-hydroxyphenylacetic acid, and (7*S*,11*S*)-(+)-12-hydroxysydonic acid presented higher inhibition effects against MRSA and MRSE with MIC values ranging from 0.5 to 1 µg/mL (LI et al., 2018).

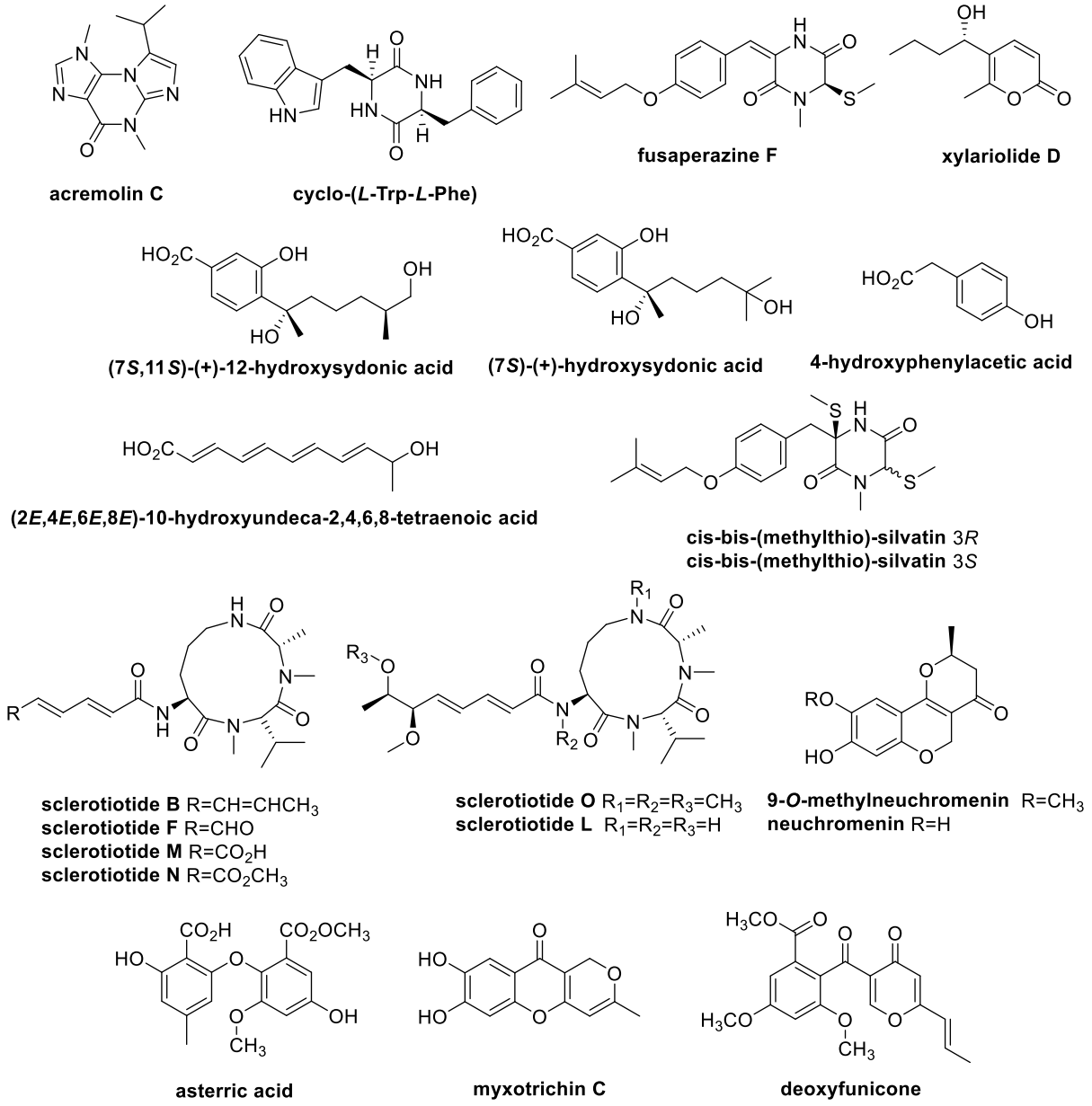
A fungal isolate from marine sediment collected from Prydz Bay, Antarctica was identified as a *Penicillium crustosum* strain which produced the new polyene compound (2*E*,4*E*,6*E*,8*E*)-10-hydroxyundeca-2,4,6,8-tetraenoic acid, and a new diketopiperazine named fusaperazine F, together with the known compounds *cis*-bis-(methylthio)-silvatin and xylariolide D (Fig. 6). Fusaperazine F exhibited bioactivity against K562 cells, with an IC_{50} value of 12.7 µM (LIU et al., 2019).

A strain of *Aspergillus insulicola* HDN151418 was isolated from an unidentified sponge sample collected 410 m deep from Prydz Bay, Antarctica. Using a UV-HPLC guided approach, three new tripeptides named sclerotiotide M, sclerotiotide N, and sclerotiotide O were isolated from this fungus together with the known compounds, sclerotiotide L, sclerotiotide F and sclerotiotide B (Fig. 6). Sclerotiotide M presented potent antimicrobial activity towards *Bacillus cereus, Proteus mirabilis, Mycobacterium phlei, Edwardsiella tarda* and *B. subtilis* with MIC values ranging from 1.56–6.25 µM. Sclerotiotide N was most active against *E. tarda* with MIC value of 1.56 µM (SUN et al., 2020).

A new polyketide named 9-*O*-methylneuchromenin, together with the four known compounds neuchromenin, asterric acid, myxotrichin C, and deoxyfunicone (Fig. 6) were isolated from the fungus *Penicillium glabrum* (SF-7123). The compounds 9-*O*-methylneuchromenin, asterric acid and myxotrichin C presented inhibitory activity of nitric oxide (NO) in lipopolysaccharide (LPS)-stimulated BV2 microglial cells, with IC_{50} values of 2.7 µM, 28.1 µM, and 10.6 µM respectively. These compounds also

downregulated the production of NO in LPS-stimulated RAW264.7 macrophages. Additionally, 9-*O*-methylneuchromenin downregulated NO synthase and cyclooxygenase-2 and inflammatory pathways dependent on nuclear factor kappa B and protein kinase in BV2 and RAW264.7 cells. Myxotrichin C and deoxyfunicone were found to inhibit the protein tyrosine phosphate 1B with IC_{50} values of 19.2 µM and 24.3 µM (HA et al., 2020).

Figure 6. Compounds isolated from Antarctic-derived fungi.



1. 5 The seaweed *Phaeurus antarcticus*

Phaeurus antarcticus Skottsberg (Fig. 7) is a brown seaweed endemic to the Antarctic Peninsula and adjacent islands south of the Antarctic convergence. It occurs in the coastal and sub-coastal areas at depths that vary between 8 and 10 meters. It belongs to the order *Desmarestiales*, family Desmarestiaceae, and genus *Phaeurus*. *P. antarcticus* is considered one of the most primitive species in its family due to the simple structure of its thallus (CLAYTON; WIENCKE, 1990).

Currently, there are few works describing the chemical composition of *P. antarcticus* (IKEN et al., 2009a; TEIXEIRA et al., 2019b), and the biological activity of isolated molecules from this alga have not been reported. Additionally, reports addressing the diversity of endophytic fungi associated with this seaweed and their biotechnological potential are scarce (FURBINO et al., 2014; GODINHO et al., 2013), highlighting the relevance of the chemical investigation and bioactivities of *P. antarcticus* and its endophytic fungi.

Figure 7. The seaweed *Phaeurus antarcticus.*

Source: GODINHO et al., (2013); ALGAEBASE: https://www.algaebase.org/search/genus/detail/?genus_id=42681.

1. 6 Metabolomic and chemometrics approaches

In natural products research metabolomics has been defined as the comprehensive and quantitative analysis of all metabolites produced by a given organism. The metabolomic approach is often used to target distinct chemical profiles and avoid the isolation of known compounds with previously described bioactivities (ZHAO; ZHANG; LI, 2018).

Metabolomic analysis is divided into targeted and non-targeted studies. In targeted studies, the search is focused on predefined metabolic pathways or

compound classes. On the other hand, in non-targeted studies, all the metabolites present in extracts/fractions will be recorded and often large datasets are generated. Data acquisition in natural products metabolomic studies commonly relies in hyphenated techniques such as gas chromatography coupled to mass spectrometry (GC-MS) and liquid chromatography coupled to mass spectrometry (LC-MS) or nuclear magnetic resonance (NMR) (ZHAO; ZHANG; LI, 2018).

Usually, non-targeted studies needed to be coupled to chemometric approaches such as multivariate analysis, or computational techniques such as the Global Natural Products Social Molecular Networking workflows to allow data mining and a comprehensive understanding of metabolic patterns (DEMARQUE et al., 2020; GRIFFITHS et al., 2010; YANG et al., 2013).

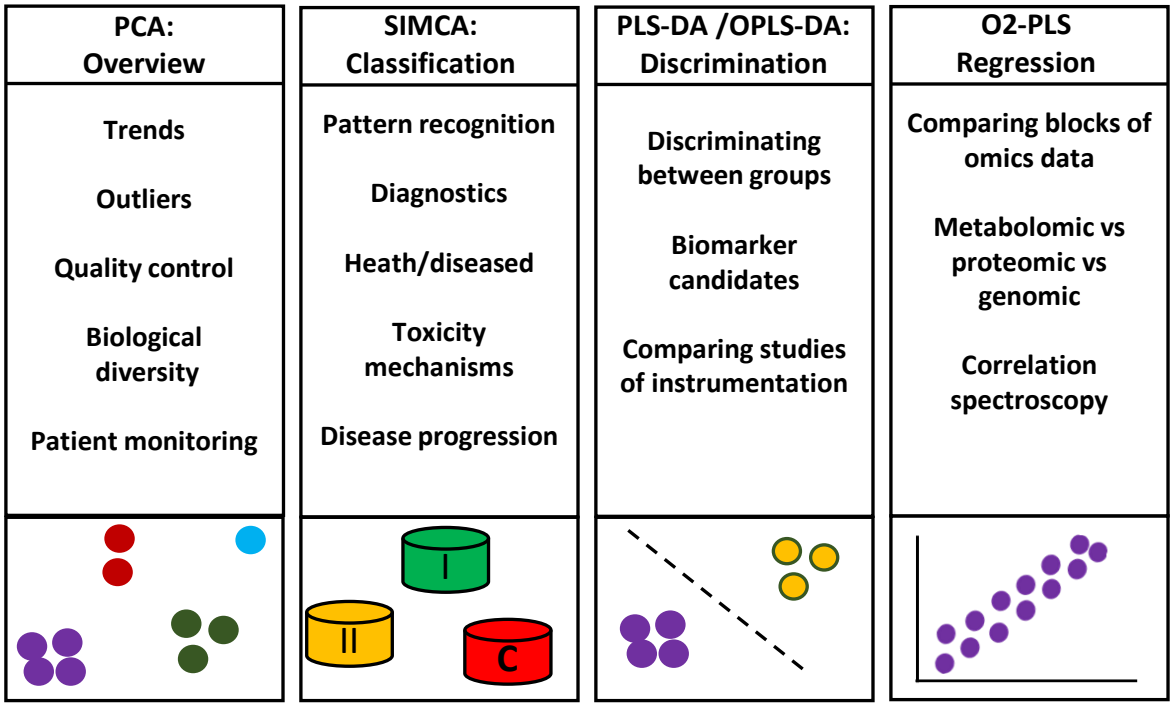
Chemometrics aims to extract chemically relevant information from data produced in chemical experiments relying on mathematical models. For example, a measurement of the chemodiversity of molecules produced by different organisms can be obtained by evaluating the size of the chemical space visualized by a multivariate analyses (MVA) such as the principal component analysis (PCA) (WOLFENDER et al., 2019).

Multivariate statistical analysis of the data generated from GC/LC-MS and NMR can be performed to visualize data patterns through unsupervised clustering such as PCA, using soft independent modelling by class analogy (SIMCA), or supervised clustering such as partial least squares (PLS), partial least squares discriminant analysis (PLS-DA) and orthogonal partial least square discriminant analysis (OPLS-DA). Additionally, multivariate models can find relations among correlated variables, as is often the case in metabolomics studies, and possess the ability to distinguish systematic variation from noise (ROBOTTI; MARENGO, 2016; WOLD; ESBENSEN; GELADI, 1987).

Supervised analysis such as OPLS-DA can be useful to discriminate between two classes, such as healthy versus diseased, allowing us to target disease biomarkers or drug targets for treatments. In natural products research, this approach can be used to discriminate between bioactive and inactive fractions and, thus, allows prioritizing the isolation of specific metabolites responsible for bioactivity (WOLD; ESBENSEN; GELADI, 1987).

An illustration of the possible applications for each multivariate models is shown in figure 8.

Figure 8. Multivariate models and their applicability.



Adapted from (WOLD; ESBENSEN; GELADI, 1987).

1. 7 Investigated biological activities

1. 7. 1 Photoprotection

The skin is the primary body protection against external damages such as mechanical lesions and microbial infections. When exposed to sunlight human skin triggers the production of vitamin D and β-endorphin which display beneficial health effects (MEAD, 2008).

However, the deleterious effect of continuous skin exposure to ultraviolet radiation (UVR) has been known since 1960. Unprotected or prolonged exposure to UVR leads to numerous changes in the skin, such as actinic keratosis, which has been identified as a precursor of non-melanoma skin cancer and squamous cell carcinoma. These conditions are related with UVA radiation, because of its ability to penetrate deeper in the skin (RAFFA et al., 2019).

Concerns regarding the effects of global warming have also been discussed in the context of skin related diseases since there is decrease of the stratospheric ozone layer and consequently an increase of UVR reaching the Earth's surface. The UV portion of the magnetic spectrum includes long wave UVA radiation (320-400 nm),

medium wave UVB (280-320) and short wave UVC radiation (100-280 nm) (MU et al., 2021; SLOMINSKI; PAWELEK, 1998; URBAN et al., 2016).

In this context, sunscreens formulations represent an additional protection against UVR damage. However, recent studies have demonstrated the toxic potential of UV filters to human health, including DNA damage, penetration into placenta, alteration of spermatozoids and endocrine functions (JESUS et al., 2022).

Additionally, UV filters such as benzophenone-3 and octyl methoxycinnamate are harmful to marine organisms, especially corals. Benzophenone-3 was considered toxic to larval forms of the coral *Stylophora pistillata* and cytotoxicity was observed to other six coral species (DOWNS et al., 2016).

Compounds derived from natural sources have been studied to as photoprotective components against the damage produced by UV radiation. Marine derived compounds such as mycosporins, alkaloids, isocoumarins (present in fungi), mycosporin-like amino acids (MAAs, found in cyanobacteria, algae, and animals) have stood out as new candidates for sunscreens formulations and represent a source of new photoprotective compounds (MACIEL et al., 2018; SINGH et al., 2017; THIESEN et al., 2017).

1. 7. 2 Neutrophils as new drugs target for chronic inflammatory diseases

Neutrophils are polymorphonuclear and phagocytic leukocytes that function as the first line of defense against pathogenic organisms. In fact, they are the most abundant leukocytes in blood, and, from the circulation, they are mobilized to sites of inflammation and/or infection (ROSALES, 2020). When their receptors interact with antigens in the pathogen's cell wall, mechanisms such as the production of reactive oxygen (ROS) species and the release of neutrophil extracellular traps are activated (NETs)(HIRSCHFELD et al., 2017).

However, in the chronic inflammatory process hyperactivity of neutrophils leads to increased ROS production, resulting in an imbalance in redox homeostasis. The deregulation in neutrophils functions promotes exacerbated oxidative stress and consequently irreversible cellular and tissue damage (AMULIC et al., 2012; MORTAZ et al., 2018).

In fact, both inefficiency and exacerbation of neutrophil responses contribute to the pathophysiology of several diseases. In particular, chronic inflammatory diseases such as systemic lupus erythematosus (SLE) (TOLLER-KAWAHISA et al., 2015). In

this context, molecules with the ability to regulate neutrophil function such as ROS production might represent an alternative to the development of new therapeutic agents for this disease.

1. 7. 3 Leishmaniasis

Leishmaniasis is caused by more than twenty species of Leishmania and is transmitted to humans by the bite of infected female phlebotomine sandflies (TORRES-GUERRERO et al., 2017). The disease affects humans and animals, causing public health problems especially in underdeveloped and developing countries (DOS SANTOS VARJÃO et al., 2022).

There are three main forms of the disease: cutaneous leishmaniasis (CL), visceral leishmaniasis (VL), and mucocutaneous leishmaniasis (MCL). The most common form of leishmaniasis is CL, which is caused by the *L. amazonensis* species. Currently, CL affects 12 million people globally, and 2 million new cases occur each year. CL is endemic in almost 100 countries 350 million people are at risk of contracting the disease (DE VRIES; SCHALLIG, 2022).

Pharmacotherapy for the treatment of leishmaniasis is represented by a few chemotherapeutic agents, such as pentavalent antimonials, amphotericin B, paromomycin, and miltefosine, which have several limitations regarding toxicity and lack of efficacy in endemic areas (TORRES-GUERRERO et al. 2017; FALKENBERG et al. 2019).

Due to the toxicity of existing therapies, as well as the emergence of resistant forms of *Leishmania*, there is an increased need for the development of more effective and less toxic antileishmanial drugs.

1. 7. 4 Neosporosis

Neosporosis is caused by the etiological agent *Neospora caninum*. This parasite infects mammalian species, like cattle, sheep, goats, horses, and dogs. Neosporosis causes abortion in cattle and neuromuscular disorders in dogs. The economic loss related to neosporosis in milk and livestock production is estimated at billions of dollars per annum. In addition, despite the efforts of industry and scientific community *Neosporosis* still does not have a specific treatment. For this reason, when animals

are diagnosed with Neosporosis they are sacrificed to avoid a disease outbreak (PEREIRA et al. 2017).

The investigation of natural products as anti-*Neospora* agents is very limited and has been focused on plant extracts (LEESOMBUN; BOONMASAWAI; NISHIKAWA, 2017; SEO et al., 2013). The first report of marine-derived compounds against *N. caninum* was published by our research group and revealed that the Antarctic seaweed *D. antarctica* presented anti-Neospora activity, highlighting the potential of marine-derived natural products in the prospection of new anti-Neospora treatments (DOS SANTOS et al., 2020).

1. 7. 5 Antibacterial and antibiofilm

Antibiotic resistance is one of the biggest threats to global health. Despite the fact that antibiotic resistance occurs naturally, this process has been accelerated by the misuse of antibiotics in human and animal health. The advent of multidrug resistant bacteria is rapidly rising, causing diseases such as severe pneumonia, tuberculosis, blood poisoning, gonorrhea, and food borne diseases. Due to the new resistance mechanisms evolved by bacteria, these diseases are becoming harder, and sometimes impossible to treat (ASLAM et al., 2018; WHO, 2022).

Biofilm forming bacteria are a major public health concern due to biofilm's ability to withstand external stresses and contribute to the persistence of chronic infections (DE LA FUENTE-NÚÑEZ et al., 2013). Biofilms are immobile microbial communities which can colonize and grow on different surfaces such as medical implants and catheters. In biofilms, bacterial populations are crammed by extra cellular matrix (ECM) which possesses bacterial secreted polymers such as exopolysaccharides (EPS), extracellular DNA, proteins amyloidogenic proteins (SHARMA; MISBA; KHAN, 2019; WHITCHURCH et al., 2002).

It is estimated that 80% of chronic and recurrent microbial infections are caused by bacterial biofilms. Microbial biofilms display different resistance mechanisms when not observed in planktonic cells, including lower cell permeability, efflux pumps, drug modifying enzymes and drug neutralizing proteins. These characteristics make the search for antibiofilm compounds an important initiative in order to aid in the fight against microbial resistance (SHARMA; MISBA; KHAN, 2019).

1. 7. 6 *Aedes aegypti* control

The *Aedes aegypti* mosquito is the vector responsible for the transmission of viral pathogens such as dengue, chikungunya, yellow fever and zika viruses. This species, native to Africa, is now distributed to all continents (KRAEMER et al., 2015; MCGREGOR; CONNELLY, 2021).

In Brazil, this mosquito has been responsible for the outbreaks of dengue, chikungunya, and zika viruses. The country has been facing an uninterrupted dengue epidemic since 1986 (VALLE; NACIF PIMENTA; AGUIAR, 2016). The WHO recommends that since there is no treatment for the viral diseases transmitted by *A. aegypti*, combating the vector is the most efficient strategy for controlling outbreaks (BENELLI, 2015).

Recently, the Brazilian National Dengue Control Program has promoted the replacement of highly toxic synthetic insecticides (organophosphates, pyrethroids and carbamates) for more environmentally friendly compounds, such as pyrethroids (cypermethrin and deltamethrin). However, they still display toxicity to the environment (PILON et al., 2022). In this context, we aimed to prospect new insecticidal compounds from Antarctic marine organisms in order to contribute to the development of safer and ecofriendly alternatives to those currently on the market.

1. 8 Preface

This doctoral thesis is divided into four chapters. Chapters I and III were developed in the School of Pharmaceutical Sciences of Ribeirão Preto – University of São Paulo, Brazil. Chapters II and IV were developed in the Strathclyde Institute of Pharmacy and Biomedical Sciences – University of Strathclyde, United Kingdom.

Parts of the introduction of this thesis were published as a review article “Natural Products from the Poles: Structural Diversity and Biological Activities” in the Brazilian Journal of Pharmacognosy.

Chapter I describes the evaluation of the antibacterial, antiparasitic, and insecticidal potential of the seaweed *Phaeurus antarcticus* and the annotation of bioactive metabolites through the combination of multivariate analysis and GC-MS Molecular Networking.

Chapter II provides an insight into the spatial variability of secondary metabolite production and the antibiofilm activity of *P. antarcticus*, through the combination of proton nuclear magnetic resonance (^{1}H NMR) and high-resolution mass spectrometry (HRMS) data and multivariate analysis.

Chapter III presents the isolation of photoprotective, immunomodulatory, and antileishmanial compounds from the endophytic fungi *Penicillium purpurogenum*.

Chapter IV reports the metabolomic profiling of endophytic fungi isolated from *P. antarcticus* collected in different locations in the South Shetland Islands and the isolation of antibiofilm compounds from the fungus *Epicoccum nigrum.*

5. 5 CONCLUSION

A total of 27 fungal strains were isolated from the inner tissues of the seaweed *Phaeurus antarcticus* collected in different locations across the Antarctic Peninsula. Sequencing of the ITS region led to the identification of fungi belonging to the *Arthrinium, Cladosporium, Curvularia, Epicoccum, Nigrospora, Penidiella, Penicillium* and *Periconia* genera. Additional sequencing experiments of the ACT region led to the identification of six *Cladosporium* species associated with this seaweed. A chemical profiling of 21 strains was achieved by proton NMR, HRMS and multivariate analysis. The strains identified as *Penidiella aggregata* and *Cladosporium halotolerans* presented unique chemical constituents and appeared as outliers in the PCA scatter plot. In the PCA loading scatter plot was possible to target the unique secondary metabolites responsible for the chemical distinction. In the *C. halotolerans* extracts, nitrogen containing compounds were annotated (rigidiusculamide A, huaspenone C, stachyline A, monascuskaochroman). In the *Penidiella* extracts, a polyketide, (sporminarin A), was annotated as discriminant metabolite. Despite the unique chemical profiles, in the antibiofilm evaluation *Penidiella* and *C. halotolerans* extracts were not among the most active samples against methicillin and oxacillin resistant *S. aureus.* The antibiofilm assays revealed that *P. terrigenum*, *C. perangustum* (LMC 1016) and *E. nigrum* extracts exhibited the highest antibacterial and antibiofilm effects.

A chemotaxonomic study was conducted with the *Cladosporium* isolates using proton NMR and HRMS data combined to the molecular identification results. A PLS-DA model was constructed to visualize the distribution of metabolites among the six different species of *Cladosporium.* Results revealed that the clustering observed in the phylogenetic tree was similar to the clustering observed in the PLS-DA model, indicating that the closest related strains also presented similar chemical profiles. These findings are an important contribution to the understanding of chemosystematics of Antarctic derived *Cladosporium* and could be used to guide future bioprospection and ecological investigations.

In the search for antibacterial and antibiofilm compounds, the fungus *E. nigrum* presented a more diverse chemical profile when compared to *P. terrigenum* and *C. perangustum* (LMC1016). For this reason, the strain was selected for large scale fermentation and isolation of metabolites. The purification of bioactive fractions led to the isolation of 4 metabolites, epicorazine A (9), epicorazine B (10),

epicorazine C (12), and a novel terpene (11). Epicorazine A – C exhibited MIC and MBEC values of 50 µg/mL, 200 µg/mL and 25 µg/mL, respectively, but no effect on post-biofilm viability was observed. Compound 11 presented MIC and MBEC values of 25 µg/mL and was able to inhibit 100% of post-biofilm viability at a concentration of 100 µg/mL .

In conclusion, fungi endophytes associated with the seaweed *P. antarcticus* presented a diverse chemical profile, that could source novel antimicrobial and antibiofilm compounds. *E. nigrum* produced interesting sulfur containing metabolites with potential biotechnological applications in the pharmaceutical industry. Thus, despite the highly cytotoxic effects of the isolated compounds reported in the literature, *in vivo* models are encouraged to assess the toxic potential of epicorazines.

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