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Article

Bioprospecting macroalgae, marine and terrestrial invertebrates & their associated microbiota

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Abstract: The present review aims the discussion of the impact of the bioprospection initiative developed by the projects associated to BIOprospecTA, a subprogram of the program BIOTA, supported by FAPESP. This review brings a summary of the main results produced by the projects investigating natural products (NPs) from non-plants organisms, as examples of the success of this initiative, focusing on the progresses achieved by the projects related to NPs from macroalgae, marine invertebrates, arthropods and associated microorganisms. Macroalgae are one of the most studied groups in Brazil with the isolation of many bioactive compounds including lipids, carotenoids, phycocolloids, lectins, mycosporine-like amino acids and halogenated compounds. Marine invertebrates and associated microorganisms have been more systematically studied in the last thirty years, revealing unique compounds, with potent biological activities. The venoms of Hymenopteran insects were also extensively studied, resulting in the identification of hundreds of peptides, which were used to create a chemical library that contributed for the identification of leader models for the development of antifungal, antiparasitic, and anticancer compounds. The built knowledge of Hymenopteran venoms permitted the development of an equine hyperimmune serum anti honeybee venom. Amongst the microorganisms associated with insects the bioprospecting strategy was to understand the molecular basis of intra- and interspecies interactions (Chemical Ecology), translating this knowledge to possible biotechnological applications. The results discussed here reinforce the importance of BIOprospecTA program on the development of research with highly innovative potential in Brazil.
Keywords: *Natural products; biological active compounds; bioeconomy; arthropods; insects; microbiota.*

Bioprospecção de macroalgas, invertebrados marinhos e terrestres e microbiota associada

Resumo: A presente revisão discute o impacto das iniciativas de bioprospecção desenvolvidas pelos projetos associados ao BIOprospecTA, subprograma do programa BIOTA, apoiado pela FAPESP. Esta revisão traz um resumo dos principais resultados produzidos pelos projetos de investigação de produtos naturais (PNs) de organismos não vegetais, como exemplos do sucesso desta iniciativa, com foco nos avanços alcançados pelos projetos relacionados a PNs de macroalgas, invertebrados marinhos, artrópodes e microrganismos associados. As macroalgas são um dos grupos mais estudados no Brasil com o isolamento de muitas substâncias bioativas, incluindo lipídios, carotenóides, ficocolóides, lectinas, aminoácidos do tipo micosporina e substâncias halogenadas. Invertebrados marinhos e microrganismos associados têm sido estudados de forma mais sistemática nos últimos trinta anos, revelando substâncias únicas, com potentes atividades biológicas. Os venenos de insetos himenópteros também foram amplamente estudados, resultando na identificação de centenas de peptídeos, que foram utilizados para criar uma biblioteca química que contribuiu para a identificação de modelos para o desenvolvimento de substâncias antifúngicas, antiparasitárias e anticancerígenas. O conhecimento construído dos venenos de himenópteros permitiu o desenvolvimento de um soro equino anti-peçonha de abelha. Dentre os microrganismos associados a insetos, a estratégia de bioprospecção foi compreender as bases moleculares das interações intra e interespécies (Ecologia Química), traduzindo esse conhecimento para possíveis aplicações biotecnológicas. Os resultados aqui discutidos reforçam a importância do programa BIOprospecTA no desenvolvimento de pesquisas com alto potencial inovador no Brasil.
Palavras-chave: *Produtos naturais; substâncias biologicamente ativas; bioeconomia; artrópodes; insetos; microbiota.*

Introduction: Historical Aspects

The use of the biodiversity and natural products (NPs) with nutritional and medicinal purposes in Brazil is undoubtable part of our development as a society since the arrival of Portuguese explorers (Valli et al. 2019), but in a broad sense the traditional knowledge was established long before by the native people inhabiting Brazil throughout the ancient times. Recognized as a megadiverse country, Brazil hosts around 15% of the estimated world biodiversity distributed along seven biomes, and the Brazilian scientific community is long aware of the chemical richness and its medicinal relevance. In this context, plant metabolites are the most studied ones, followed by fungi and marine organisms (Berlinck et al. 2017).

This review aims at the discussion of the impact of bioprospecting efforts using organisms other than plants under BIO*prospec*TA, a subprogram of the program BIOTA, supported by FAPESP, formally launched in 2002. The BIO*prospec*TA was created attempting to stimulate and support the search for NPs of potential economic value, recognizing the importance of biodiversity to a sustainable development (Joly & Bolzani 2017; Silva et al. in press).

Initially, to show a historical perspective, we searched the database (https://bv.fapesp.br/pt/proc6291/) of projects supported by FAPESP related to NPs since its foundation in 1962. A total 452 projects were retrieved, being only 44 projects in the period from 1962 and 1999 (period pre-BIOTA Program). These 44 projects could be divided into six different categories as follow: 4 projects related to isolation and structural characterization of novel NPs from plants; four projects related to isolation and characterization of novel NPs from marine organisms; three projects related to pharmacology of NPs; six projects related to the chemistry/biological properties of flavonoids; 13 projects related to the development of protocols of organic synthesis of NPs; and 14 projects related to the development of methods of extractions of NPs.

The 408 remaining projects corresponded to supported projects in the period between 2000 and 2021; from whose 51 are/were associated to BIOTA/BIO*prospec*TA Program, while 357 projects were not associated to the program. These projects may eventually become in the future partners of the program. The general profile of the projects not associated to BIOTA/BIO*prospec*TA is: 249 projects related to "Chemistry of NPs"; 23 projects related to "Pharmacology of NPs"; seven projects related to "Botanical Aspects of NPs"/"Phytochemistry"; 78 projects related to "Biological Actions" of NPs;

The central prospective focuses of the 51 projects associated with the BIOTA/BIO*prospec*TA Program are shown in Figure 1A. Probably due to the plant origin in NPs chemistry abroad (including Brazil), there is a large predominance of plant NPs in BIO*prospec*TA sub-program. Despite this, the biological variability is enormous, as expected by the richness of Brazilian biota. The applications involving these NPs are shown in Figure 1B, where it is possible to observe that the most of these projects are focused on the determination of a profile of biological activities for the NPs isolated and structurally assigned; apparently there is no structure-guided prospection within this group of projects, but the most of these projects are activity-guided.

The present review brings a summary of the main results produced by the projects investigating NPs from Non-Plants organisms. Some of these projects are being presented here as examples of the success of this initiative: NPs from macroalgae, NPs from marine invertebrates and associated microorganisms and, NPs from arthropods and microorganisms associated with insects.

1. Macroalgae

Macroalgae are the basis of the food web, mainly in the aquatic ecosystems. The biodiversity of macroalgae and their endophytic organisms (fungi and bacteria) is enormous and needs to be elucidated and described (Godinho et al. 2019). Ecologically speaking, algae are the major primary producers, responsible for about half of the O_2 generation, the main organisms responsible for the assimilation of nitrate and for the most of the dimethylsulfide released to the atmosphere (Cardozo et al. 2007). Macroalgae are indeed the main food source for larval stages of some crustacean and fish species, for zooplankton (rotifers, copepods, and brine shrimps), and for bivalve mollusks in all their growth stages. Their nutritional value is dependent on different characteristics including shape, size, digestibility, and toxicity. The determinant in establishing the food quality transferred to the other trophic levels of the food web are the biochemical composition of the macroalgae (amino acids, fatty acids, sterols, sugars, minerals, and vitamins) (Carigan et al. 2009). Marine macroalgae are subject to different environmental stresses such as tides, long exposure to UV light, temperature variation (Horta et al. 2012; Sissini et al. 2016), and therefore, in order to survive, they have

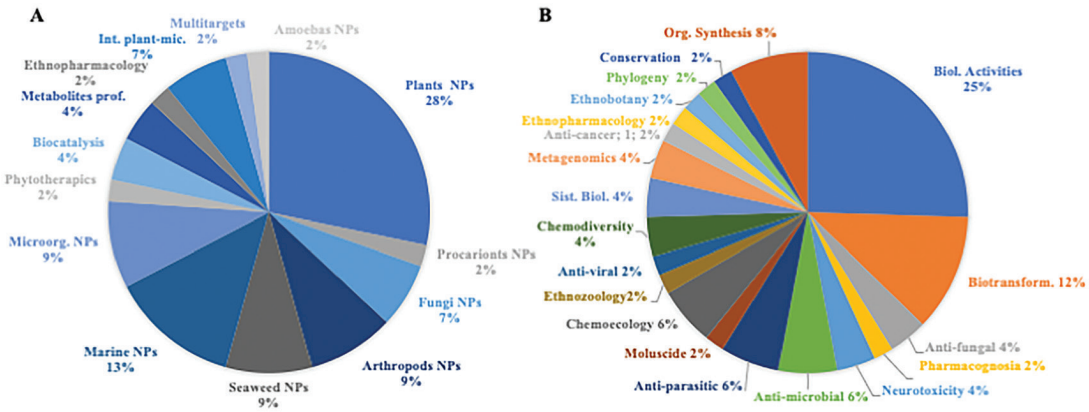

Figure 1. (A) Origin of the natural products (NPs) from projects associated with the BIOTA/BIOprospecTA Program. (B) Applications involving these NPs focus on the following targets.

to develop defense strategies that result in an enormous diversity of metabolites from different metabolic pathways (Cardozo et al. 2011).

NPs play an important role in the drug discovery process (Cragg & Newman 2013) thus, the search of new algal chemical compounds, a new class of source to natural products, has proved to be an essential area of pharmaceutical study. Reports have been published presenting isolated compounds from algae with biological activity, showing their ability to produce metabolites with high complexity and enormous diversity of pharmacological and/or biological properties (Mayer & Hamman 2004). Regarding the bioproducts, recent trends in drug research from natural sources suggest macroalgae, because of sophisticated chemical structures, as promising groups to furnish novel biochemical active substances (Singh et al. 2005).

Recently, some macroalgae have their genome sequenced. The metabolic pathways which increase the yield of compounds with economic value have been studied to be genetically modified. Thus, with the available genomes, surely the production and value of algae will increase (Alves-Lima et al. 2017; Falcao et al., 2008).

Macroalgae products, with potential economic impact, have been applied in the food, pharmaceutical, cosmetic, bioenergy, agricultural, and veterinarian industries (Cardozo et al. 2006, 2007, Gressler et al. 2010; Simas-Rodrigues et al. 2015). In the last 20 years, after Biota-Bio*Prospec*TA Open Research Program from Fapesp, and creation of Redealgas (Rede Nacional em Biotecnologia de Macroalgas), the Brazilian production of publication, patents, and products described from marine macroalgae have increased significantly.

Macroalgae NPs have broadly been used with high aggregated value. Macroalgae are source of fibers, minerals, steroids, antioxidants, vitamins, pigments, lectins, polysaccharides, halogenated compounds, polyketides, polyunsaturated fatty acids (specially omega 3 and 6 families), mycosporine-like amino acids, proteins, and other lipids which make them largely consumed in many countries. (Cardozo et al. 2007; Gressler et al. 2009, 2011; Martins et al, 2016). Furthermore, isolated compounds, extracts and fractionated extracts have been reported to have important biological activities, including anti-inflammatory, neglected diseases such as leishmanicidal, trypanocidal **(**Torres et al. 2014; Falkenberg et al. 2019; Rangel et al. 2019; Clementino et al. 2020; 2021**)**, schistosomicidal (Stein et al. 2021), antioxidant and UV absorber (Rangel et al. 2020; Tavares et al. 2020a; 2020b), anticancer (Vieira et al. 2016; Santos-Pirath et al. 2020, Gambato et al. 2014), biofilms for drug release (Paniz et al. 2020) and microbicidal properties as antifungal (Stein et al. 2011), antivirus (Cirne-Santos et al. 2020**),** antifouling **(**Salgado et al. 2008, Carvalho et al. 2017). Due to the different uses and wide availability of these photosynthetic organisms, the interest has turned from wild harvest to farming and controlled cultivation.

As mentioned, several categories of chemical compounds have been isolated from macroalgae and below we described the ones mostly used in industries, including lipids, carotenoids, phycocolloids, lectins, mycosporine-like amino acids (MAA) and halogenated compounds.

Macroalgae synthesized fatty acids and they can be transferred to upper levels of the food web. Polyunsaturated fatty acids (PUFAs) are the main product of macroalgae. PUFAs are essential for normal cell function and have entered the biomedical and nutraceutical areas because of their biological role in certain clinical condition such as obesity and cardiovascular diseases so common in Western society (Gill & Valivety 1997, Sayanova & Napier 2004; Berneira et al. 2020; 2021; Santi et al. 2021). Moreover, PUFAs play key roles in electron and oxygen transport and tissue metabolism, including the regulation of membrane fluidity, as well as thermal adaptation (Funk 2001; Santos et al. 2019). Additionally, public perception of healthy food and lifestyle has brought PUFAs to the attention of the consumers (Pereira et al. 2017; Teixeira et al. 2019). It is increasing the interest in a typical PUFAs family (ω-3) named eicosapentaenoic acid (EPA – 20:5 $\Delta^{5,8,11,14,17}$ ω-3). Because of its physiological importance and future pharmacological and nutraceutical perspectives, the ω-3 and ω-6 PUFA consumption is increasing around the world to the annual worldwide demand for EPA to approximately 300 tons, US$ 1 billion/year and growing market of 12% per year (Sánches et al. 1999).

Carotenoids produced by algae are natural pigments and have sophisticated chemical structures and therefore, very difficult to be synthesized in laboratories. More than 600 different carotenoids have been identified to date displaying important biological functions in algae, bacteria, plants, and animals (Di Mascio et al. 1995; Hollnagel et al., 1996). ß-carotene has a worldwide market of 0,5 billion dollar per year used as antioxidant, precursor of vitamins, pigments, and colorant. The carotenoid astaxanthin is a red pigment common to several aquatic organisms including macro and microalgae, shrimps, lobsters, and fishes, such as salmon and trout. Crustaceans are unable to synthesize carotenoids *de novo* and require astaxanthin to be supplied in the diet to render adequate and live-colored seafood for market acceptance (Pinto et al. 2000; Meyers & Latscha, 1997). The unicellular alga *Haematococcus pluvialis* has been potentially explored by biotechnology companies as a source of astaxanthin (Sommer et al. 1992). Astaxanthin enhances power, burst, resistance and high antioxidant capability, and therefore has been used by high performance athletes, as a nutrition factor and has a market of US$ 200 million/year.

Macroalgae produce phycocolloids which are polysaccharides of high molecular weight composed of polymers of sugars units. They are the main structural components of seaweed cell walls and may be involved in recognition mechanisms between macroalgae and pathogens (Potin et al. 1999). Agar, carrageenan and alginate are the main polysaccharides from macroalgae used as food, antioxidant, antiviral, antitumoral, anticoagulant and cosmetic (Mayer & Lehmann 2001, Mayer & Hamann 2004, Smit 2004). The wide use of these compounds is based on their gelling, emulsifying and viscosifying properties, which generate an increasing commercial and scientific interest. The market of 50 thousand tons/year (growth market of 7% year) of agar and carrageenan runs over US$ 500 million/year.

Lectins are carbohydrate-binding proteins and are largely produced by macroalgae. In basic, pharmaceutical, and medical sciences, lectins are useful for detection of disease-related alterations of glycan synthesis including infectious agents (viruses, bacteria, fungi, parasites) (Rudiger & Gabius, 2001). Phycolectins have low molecular masses, with high specificity for complex oligossaccharides or glycoproteins and no requirement for metal ions (Rogers & Hori 1993, Hori et al. 1990). However, few studies have been found in literature up to now, characterization, and mainly, biological properties of these proteins in macroalgae. The worldwide market for lectins is huge and the products extracted from macroalga can fulfill this gap for lectins.

Mycosporine-like amino acids (MAA) are a family of compounds involved in the protection of aquatic organisms against UV radiation.

They are a cyclohexenone or cyclohexenimine chromophore conjugated with one or two amino acids, with an absorption maximum ranging from 310 to 360 nm (Cardozo et al. 2007; 2008; Teixeira et al. 2021). They are synthesized by algae and fungi and are present in many marine and freshwater organisms (Gröniger et al. 2000, Shick & Dunlap, 2002, Rezanka et al. 2004). MAA are up to 20 known identified and some of these structures are shown in Figure 2 (Carreto et al. 2005). Some marine organisms acquire MAA by diet transfer, symbiotic or bacterial associations (Shick et al. 1992, Stochaj et al. 1994, Carrol & Shick 1996). MAA are more abundant in algae of tropical regions, and they have similar function of flavonoids of higher plants (Fuentes-Leon et al. 2020). Experiments of photodegradation and photosensitization with several MAA evidenced their role as a stable and effective sunscreen compound (Whitehead & Hedges, 2005). MAA have been commercially explored as suncare products for skin protection, skin cancer protection, premature skin aging, and UV blockage of non-biological materials as photostabilizing additives in plastic, paint, and varnish industries (Bandaranayake 1998). The market for cosmetic UV protection is multimillionaire ranging around US$ 15 billion/year until 2030 and is a growing market of 11% a year.

Halogenated NPs are frequently reported metabolites in marine algae, particularly in red and brown algae. Halogenated class compounds may include indoles, terpenes, phenols, fatty acids and volatile halogenated hydrocarbons (Dembitsky & Srebnik 2002). In many cases these halogenated marine compounds display biological activities of pharmacological interest, including antibacterial (Machado et al. 2014, 2015), anti-parasites (Stein et al. 2015) and antitumoral (Pacheco et al. 2018). The notable producer of the halogenated compounds in the marine environment belongs to the genus *Laurencia* (Rhodophyta) (Faulkner 2001, Wright et al. 2003, Machado et al. 2019). It is estimated a 23-million-dollar market by 2026 and this can be very attractive for the macroalgae market.

2. *Marine invertebrates and microbiota*

Marine invertebrates have taken the attention of organic chemistry groups since the 1950s, and the number of isolated compounds had steadily increased throughout the years, especially in the past twenty years with the knowledge of the metabolic profusion of the microorganisms associated with the invertebrates (Papon et al. 2022). Since the beginning, it was evident that these molecules were able to interact with proteins and nucleic acids within the mammalian cells, modifying their function, thus conferring to these molecules powerful biological activities (Jimenez et al. 2020). Nowadays there are seventeen approved marine drugs, among them twelve are used to treat cancer (https://www.marinepharmacology.org/approved).

In Brazil, studies on marine natural products started back in 1960s by Prof. Tursch at Rio de Janeiro with the isolation of cholesterol from the sea urchin *Echinometra lucunter*, continuing for 20 years with a "phytochemistry" nature (Tursch et al. 1963, Kelecom 1997, Costa-Lotufo et al. 2006). It was only in the 1990s that robust screening programs collecting dozens of marine invertebrates were started (Berlinck et al. 2004), although before that, some very interesting molecules had been isolated from gorgonians, ascidians, mollusks, cnidarians, and sponges (Kelecom 1997). Prof. Roberto Berlinck from the University of São Paulo established the first screening program back in 1994 funded by FAPESP. His research team has been systematically studying marine natural products, mainly from sponges and ascidians, and more recently from microorganisms, revealing dozens of interesting bioactive molecules (Berlinck et al. 2004, Ióca et al. 2014, 2018). Among then, the tryptophan-derived compounds, isogranulatimide and granulatimide (Figure 3), isolated from the ascidian *Didemnum granulatum* drew special attention due to its inhibitory activity of G_2 cell cycle checkpoint, an important anticancer mechanism (Berlinck et al. 1998a; 1998b; Roberge et al. 1998). Brazilian sponges are also described as proficuous producers of anticancer compounds, and remain as the most studied group of invertebrates by Brazilian Researchers

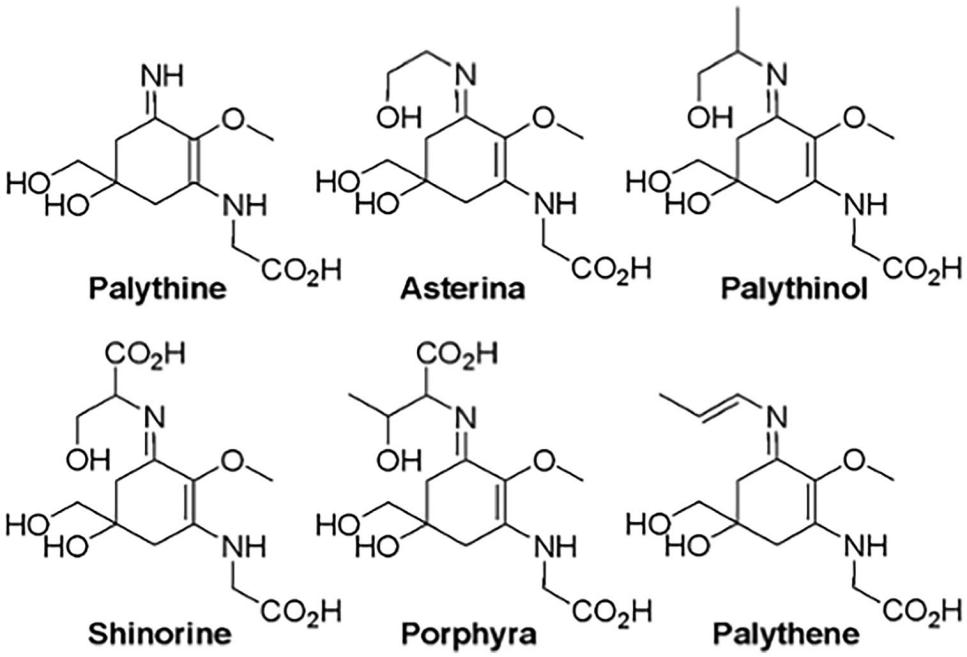

Figure 2. Mycosporine-like amino acids (MAA) structures isolated from macroalgae (modified from Cardozo et al, 2007).

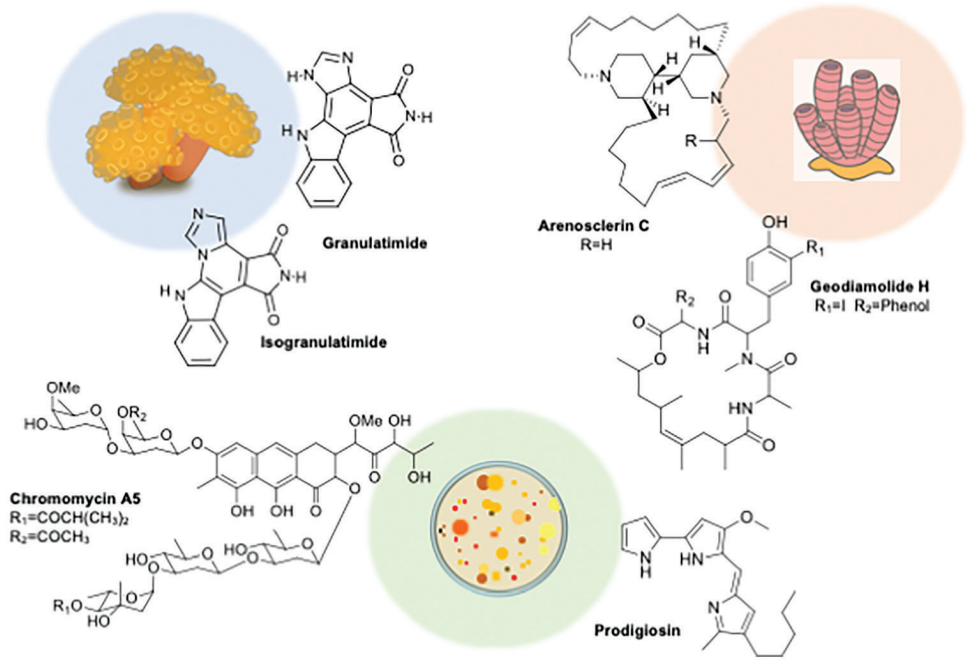

Figure 3. Examples of natural products isolated from Brazilian marine organisms.

(Ióca et al. 2018). As good examples, arenosclerin A and haliclonacyclamine E (Figure 3), isolated from the Brazilian endemic sponge *Arenosclera brasiliensis*, caused tubulin disorganization, while geodiamolide H (Figure 3), isolated from *Geodia corticostylifera*, caused accumulation of actin, both in breast cancer cells (Torres et al. 2000; Prado et al. 2004; Rangel et al. 2006; Freitas et al. 2008). An overview of the isolated compounds showed alkaloids as the main group of isolated compounds, followed by polyketides and terpenes (Ióca et al., 2018).

By far, the most studied biological activity of compounds isolated from marine invertebrates and microorganisms was cytotoxicity against cancer cells. Wilke et al. (2021) showed that 238 species of invertebrates and microorganisms were evaluated for the anticancer potential, leading to the isolation of 393 compounds; among them, 61 showed anticancer properties. Some of these compounds were already known, but the novelty is related to the modulated target and the mechanism of action. For example, it was shown that the progininines, red-pigmented alkaloids isolated from a *Pseudoalteromonas* sp. strain recovered from marine sediments, directly targets the inhibitor of apoptosis protein, survivin, modulating the proliferation of melanoma cells (Branco et al. 2020). Prodigiosin (Figure 3) was first isolated from *Serratia marcescens*, in 1962, but it is produced in many gram positive and gram negative bacteria. Its chemical structure, actually, inspired the development of obatoclax, a BH3 mimetic synthetic compound that acts as a pharmacological pan-inhibitor of anti-apoptotic members of the BCL2 family, and reached clinical trials for leukemia and lymphoma patients (Townsend et al. 2021).

Another promising finding was the description of the transcription factor TBX2 modulation by chromomycins (Sahm et al. 2020). Using a bioaffinity chromatography technique, it was evidenced that chromomycin A5 (Figure 3) was able to directly bind TBX2. The TBX2 transcription factor is overexpressed in several cancers, including melanoma, sarcoma and breast cancer, where it contributes to key oncogenic processes including the promotion of proliferation and bypass of senescence. Importantly, based on compelling biological evidence, TBX2 has been considered as a potential target for new anticancer therapies, but with no previously described modulators. Chromomycins are long known bacterial metabolites with DNA-binding properties. During the 1960s, chromomycin A3 reached phase II clinical trials, but did not advance, mainly due to lack of efficacy (Falkson et al. 1966). Nonetheless, the observance of TBX2 direct affinity makes visiting old data very important, since not only because chromomycin A5 is more potent, but the correct selection of patients can open new possibilities in the clinical successful use of these old drugs.

Those are only two examples of exciting anticancer applications of marine microbial compounds, but during the past twenty years, some microorganisms collections have been created with the support of BIOTA/BIO*prospec*TA program, housing thousands of bacterial and fungi strains that can be studied with the most distinct applications. Although the most exciting results are cancer related, many other activities have indeed been screened, including leishmanicidal, trypanocidal, antiplasmodium, antibiotic and antifungal, among others (Ióca et al. 2014; 2018; Oliveira et al. in press).

3. *Terrestrial invertebrates and microbiota*

3.1. *Natural products from arthropods*

The venoms of the social Hymenoptera consist of a complex mixture of proteins, peptides, and low molecular mass compounds. These insects evolved their venoms to prevent the presence of predators, keeping them far from the colonies; the venom of these species is not used to promote lethal actions, but to produce mnemonical actions in the victims of their stinging due to the uncomfortable effects caused by the venoms such as: pain, local burning, edema, swelling, bradycardia, tachycardia, and headache; however, some-times are observed systemic effects like respiratory and/or kidney failure (Palma 2013).

The consequences of stinging accidents caused by social Hymenoptera insects may be classified into three types: i) those in which the victims are stung a single/few times, and react presenting only local inflammation; ii) those in which the victims are stung a single/few times, and react presenting extensive inflammation and systemic reactions; iii) those in which the victims are stung multiple times, and react presenting severe envenoming shock (Perez-Riverol et al. 2017). Considering the situations described above, it was decided to focus the prospective approach targeting the molecules responsible for each type of sting accident.

The peptide toxins of these venoms cause the largest inflammatory processes known at the level of skin and organs. Peptide components represent about 70% of social Hymenoptera venom composition and are responsible for a series of actions such as mast cell degranulation, chemotaxis of polymorphonucleated leukocytes, hemolysis, muscle contraction, and cytolysis. Until five years ago, only a few tenths of these peptides were reported in the literature; however, as result of massive spectroscopic investments made by the BIO*prospec*TA Program, nowadays many hundreds of polycationic peptides (mastoparans, chemotactic peptides, and kinins,) are known (Dias et al. 2015). In addition to permit understanding in detail the most of inflammatory processes caused by the peptide components, it was built a peptide library that contributed to our prospective initiative, leading to the identification of peptide structures as leader models for the rational development of antibacterial and antifungal compounds (Singulani et al. 2021), antiparasitic compounds (Vinhote et al. 2017), and anticancer (Leite et al. 2015) compounds.

The proteins represent about 20% of venom composition amongst the social Hymenoptera; they are physiologically responsible by lytic actions to facilitate the diffusion of toxins through the victims' bodies. Until 10 years ago almost nothing was known about the venom composition of Hymenopteran insects endemic to Brazilian fauna. In the last ten years the investments of BIO*prospec*TA Program (FAPESP) in the human resources training, as well in the set-up of high-level Proteomic Laboratory resulted in the identifications of hundreds of proteins in the venoms of several species of wasps, bees and ants. The knowledge of the detailed protein composition of these venoms, in turn, permitted the clear understanding of the complex mechanism of envenoming caused by the stinging of social Hymenoptera against humans. The detailed knowledge about the proteins and peptides composition of the venom from Africanized Honeybee (*A. mellifera*), permitted us to develop a consortium between University of São Paulo State (UNESP), University of São Paulo (USP) and Butantan Institute, to exploit the immunoproteomics of Africanized honeybee venom to horse IgG, which resulted in the development of an equine hyperimmune anti-honeybee venom serum (Guidolin et al. 2008) used for treating patients that were stung multiple times during a massive attack of the Africanized honeybee (Santos et al. 2013).

The immunoreactivity to human IgE by some venom proteins make them important allergens of social Hymenoptera venoms, resulting in immediate hypersensitivity reactions, which cause anaphylaxis. Currently the treatment (Venom Immunotherapy -VIT) is performed by injecting regularly increasing doses of very diluted insect venom under patients skin, until achieve the concentration of a natural stinging action; the immune system produces protective components (IgE, IgG1, IgG4, IgA, and various types of cytokines), making the body getting used to the allergens. The VIT is a very effective treatment to prevent severe systemic reactions; however, it is expensive, requires a long training of the medical staff, and is time-consuming. In addition to this, there is a very limited availability of standardized commercial venom extracts. Due to the absence of information about the occurrence of crossed immune reactions between the venoms from different Hymenoptera species, the VIT must be performed with the use of species-specific venom extract, which is very difficult in Brazil due to the very high number of endemic social Hymenoptera species.

Purified natural/ recombinant allergens also have been used for desensitization of allergic patients; however, due to the high number of allergens and the richness of Brazilian fauna of social Hymenoptera, it is necessary much effort to overcome the difficult of allergen supplying for this purpose. Currently there are 75 allergens chemically and immunologically characterized from 31 species of social Hymenoptera; however only three of these allergens from two species of social wasps, endemic from Brazil, are included in this list (www.allergen.org); only a few of these allergens are available commercially. The knowledge about immune crossed reaction between homologous individual allergens from the venoms of different Hymenopteran species could contribute to increase the availability of material for diagnosis and therapy of insect venom desensitization.

Considering the need to develop a quick, safe, and reliable method of identification of the stinger species of social Hymenoptera, just analyzing patients' blood, it was invested in infrastructure for microsequencing the five major allergens from the venoms of endemic species of Brazilian fauna: hyaluronidase from Africanized *Apis mellifera* (Api m2); hyaluronidase (Poly p2) and phospholipase A1 (Poly p1) from the social wasp *Polybia paulista*; phospholipase A1 (Sol i1) and antigen-5 (Sol i3) from the fire-ant *Solenopsis invicta*. The sequences of these proteins were synthesized as partially overlapping heptapeptides (with four amino acid residues common between neighbor peptides) using the strategy of SPOT synthesis on membranes; 1058 peptides were synthesized to cover the complete sequence of the five allergens. These membranes were submitted to immunoblotting with the sera of Brazilian and European Hymenoptera venom-allergic patients, revealing a total of 29 linear epitopes reactive to sIgG and sIgE, common to both cohorts (Brazilian and European). The peptides corresponding to these epitopes were synthesized on solid phase, purified and submitted to bioassays of cytotoxicity, hemolysis, and histamine release from mast cells; none of them were active in these assays. Therefore, these peptides may be used for the diagnosis of Hymenoptera venom sensitivity, as well for the therapy of patients desensitization to insect venom. This initiative will permit in a short future the GMP production of synthetic peptides for Component Resolved Diagnosis (CRD) and a safe treatment of allergy to Hymenoptera venom.

3.2. Microorganisms associated to insects

Traditionally, bioprospecting projects in Brazil have either randomly chosen the genetic resources to be screened in bioassays; or alternatively, the selection has also been based on ethnopharmacological or chemotaxonomic information. Despite being successful to some extent, these approaches neglect the ecological functions the NPs (or specialized metabolites in this case) play in their natural context. Unveiling the ecological functions of small molecules may represent a prolific strategy not only to understand the molecular basis of intra- and

interspecies interactions (Chemical Ecology), but also to translate this knowledge to possible biotechnological applications of the specialized metabolites. Symbiotic systems where different organisms interact among themselves serve as remarkable sources to align Chemical Ecology and Natural Products discovery. The focus on the small molecules that mediate the interspecies interactions can result in **(i)** understanding of the molecular basis of the symbiotic interactions; **(ii)** discovering specialized metabolites hits for pharmaceutical and agrochemical development, and **(iii)** designing strategies for biodiversity conservation and supporting public policies.

Several symbiotic systems exist in Nature and deserve attention. Insects dominate the known diversity of living organisms, comprising about 1 million species described and making up 83.5% of all species in the Phylum Arthropoda (Stork 2018). As other organisms, insects establish different types of symbiotic associations with microbes (bacteria, fungi, yeasts, and viruses), spanning from parasitism to mutualism. Microorganisms usually play important roles in metabolic, nutritional, and defensive symbiosis in the beneficial associations with insects. Microbes living in the gut or within specialized cells of the insect can provide nutrients and/or help the host to digest food. Social insects are particularly interesting, since some of them have evolved mutualistic interactions with fungi in which nutrient exchange between species is mandatory for the association, as observed in attine ants in the Neotropics and termites in Africa (Ramadhar et al. 2014, Biedermann & Vega 2020). Insects may also rely on molecular defenses from symbiotic microbes to cope with environmental threats, such as microbial entomopathogens. These molecules have evolved through complex multipartite interactions and have been selected for compatibility with an animal host, being considered privileged scaffolds for natural products discovery (Van Arnam et al. 2018), thus offering fruitful opportunities for research in the field.

The highest diversity of insects in the world is found in Brazil (Rafael et al. 2009), so ecological-based research of specialized metabolites mediating insect-microbial symbiosis would represent a new and underexplored approach in the field of Natural Products Chemistry in the country. Previous remarkable results have described specialized metabolites mediating microbial symbiosis in termites, beetles, wasps and Attine ants (Van Arnam et al. 2018, Schmidt et al. 2022, Kroiss et al. 2010), all collected outside Brazil. These data were the basis for the establishment of the first International Cooperative Biodiversity Group (ICBG) in Brazil, bringing together a team of researchers from the US (Harvard Medical School, University of Wisconsin-Madison) and Brazil (University of São Paulo). This unique Thematic Project was jointly funded by the Fogarty International Center/National Institutes of Health (FIC/NIH) and FAPESP (2013/50954-0, 2014-2020) in the BIOTA Program (Pupo et al. 2017).

The multilateral symbiosis in fungus-growing ants (Formicidae: Myrmicinae: Attini: Attina) was the main focus of the ICBG. These ants originated in a single ancestral attine in Amazon around 45 million years ago (Hölldobler & Wilson 1990) and collect plant matter to feed it to basidiomycete fungi they cultivate for food in subterranean chambers in an obligate symbiosis (Schultz & Brady 2008). Other microorganisms in this multipartite symbiosis are a specialized pathogenic fungus (genus *Escovopsis*), which can suppress the fungal cultivar and eradicate the insect colony (Currie et al. 1999a), and a symbiotic actinobacteria (usually in the genus *Pseudonocardia*), which produces small molecules that selectively inhibit the pathogenic fungus (Currie et al. 1999b, Cafaro & Currie 2005). Several antimicrobial NPs produced by the symbiotic actinobacteria from ants collected in Central America have been identified in this system (Van Arnam et al. 2018).

Recent results obtained with bacterial symbionts of ants collected in different Brazilian biomes (Amazon, Cerrado and Atlantic Forest) significantly expanded the existing chemical repertoire of bacterial defenses in this system. *Streptomyces* sp. ISID311, associated with *Cyphomyrmex* ants, produced the new polyketide cyphomycin (Figure 4), active against *Escovopsis* (Chevrette et al. 2019). Cyphomycin inhibited multidrug resistant fungal pathogens strains, reducing *Candida albicans* infection in mouse candidiasis models (Chevrette et al. 2019; Bugni et al. 2021). Additionally, cyphomycin and two structurally related analogues showed antiprotozoal activity

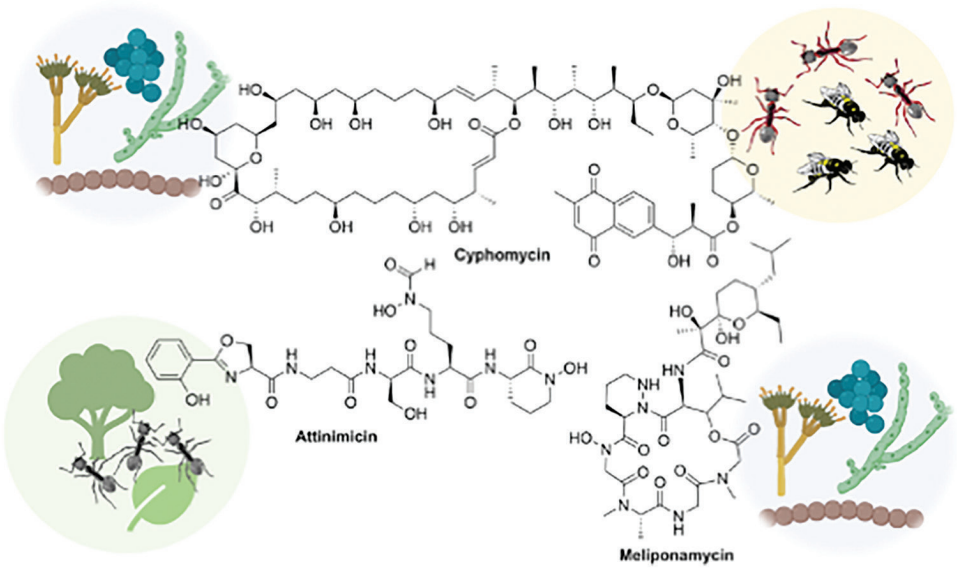

Figure 4. New natural products from Brazilian insect microbiomes.

against *Leishmania donovani*, with good selectivity indexes (Ortega et al. 2021). Similarly, antifungal polyethers and piericidins also showed antileishmanial activity with good selectivity (Ortega et al. 2019). These compounds were produced by multiple *Streptomyces* strains isolated from *Atta sexdens*, *Acromyrmex rugosus rugosus*, and *Cyphomyrmex* ants (Ortega et al. 2019).

A comprehensive chemical and genomic analysis of 42 *Pseudonocardia* strains associated with different attine species collected in multiple sites in Brazil revealed that 73% of the strains produce a new non-ribosomal peptide named attinimicin (Figure 4), as part of the bacterial chemical defenses against *Escovopsis* (Fukuda et al. 2021a). Attinimicin was detected *in situ* in ant and fungal garden samples directly analyzed by LC-MS/MS, reinforcing its ecological role. Metabolomics and phylogenetic analyses showed the geographic dispersion of the attinimicin biosynthetic gene cluster in Brazilian *Pseudonocardia* spp., pointing this compound as the first specialized metabolite from ant-associated bacteria with such broad geographic distribution. Additionally, attinimicin also showed *in vivo* antifungal activity against human pathogens (Fukuda et al. 2021a).

Serratia marcescens strains were frequently associated with *Atta sexdens rubropilosa* ("saúva") ants. These Gammaproteobacteria produce a family of pyrazines that includes members previously identified as ant trail pheromones in the host ants, an unprecedented example of convergent chemistry in this system (Silva-Junior et al. 2018).

Ants and plants can interact in myrmecophytic mutualistic relationships, such as *Azteca* ants and *Cecropia* plants. Microbial symbionts have been reported in this myrmecophyte interaction. Indeed, larvae of the symbiotic ant ingest black yeasts found inside plant domatia, indicating a nutritive function (Blatrix et al. 2012). Samples of *Cecropia-Azteca* collected in Atlantic Forest revealed *Pantoea*, *Rhizobium*, *Methylobacterium*, *Streptomyces* and *Pseudomonas* as the major cultivable genera of bacteria associated with this myrmecophyte (Fukuda et al. 2021b). *Pseudomonas* spp. isolates showed potent antimicrobial activity and potential for nitrogen fixation. The antifungal cyclic lipodepsipeptide viscosinamide was identified using a combination of chemical and genomic analyses. The results suggest *Pseudomonas* strains play an important role in the myrmecophytic symbiosis (Fukuda et al. 2021b).

Brazil harbors a high number of native stingless bees, another important group of social insects that has distinct microbial symbionts (de Paula et al. 2021). *Scaptotrigona depilis* larvae are dependent on the ingestion of a fungus that grows inside the brood cells to complete metamorphosis (Menezes et al. 2015). This singular discovery suggested a new symbiotic interaction, therefore efforts in the ICBG were also moved towards the chemical signaling of the microbial symbiosis in stingless bees. Indeed, the fungal food source was identified as an osmophilic yeast in the genus *Zygosaccharomyces*, which provides ergosterol to the larvae as a precursor for ecdysteroids biosynthesis (Paludo et al. 2018). *Candida* sp. and *Monascus ruber* are also present in the cerumen and their small molecules seem to modulate *Zygosaccharomyces* growth in the brood cells (Paludo et al. 2019). Ethanol and isoamyl alcohol, produced by *Candida* sp., stimulate *Zygosaccharomyces* sp. growth, while monascin and lovastatin are biosynthesized by *M. ruber*. Lovastatin inhibits the growth of *Zygosaccharomyces* sp., while monascin inhibits *Candida* sp. growth (Paludo et al. 2019).

As observed in attine ants, defensive microbial symbiosis also occurs in the stingless bee *Melipona scutellaris*. *Paenibacillus polymyxa* was isolated from larval food, and produces (*L*)-(−)-3-phenyllactic acid and a family of lipodepsipeptides named fusaricidins, all active against at some extent against entomopathogenic fungi and the honey bee bacterial pathogen *Paenibacillus larvae* (Menegatti et al. 2018). Interestingly, fusaricidins were also detected *in situ* in samples of larval food, supporting an ecological role in defensive symbiosis. Actinobacteria in the genera *Streptomyces* and *Micromonospora* were isolated from nurse and forager bees, and produced antibiotic polyketides (lobophorins and anthracyclines) active against *P. larvae* (Rodriguez-Hernandez et al. 2019). Two new cyclic hexadepsipeptides, meliponamycins A and B (Figure 4), isolated from *Streptomyces* sp. ICBG1318, presented strong activity against *P. larvae* and human pathogens *Staphylococcus aureus* and *Leishmania infantum* (Menegatti et al. 2020).

These results corroborated the initial hypothesis of the ICBG project to understand the ecological functions of microbial specialized metabolites in insect-microbe symbiosis and to align this chemical ecology knowledge to pharmacological applications (Menegatti et al. 2021). However, the chemistry behind insect-microbe interactions remains considerably to be deciphered. Uncounted species of insects and their microbiomes are out there awaiting to be studied and deserve further attention in new research projects.

Perspectives – New World Bioeconomy

There is a growing worldwide demand for renewable chemical compounds. Substances extracted from renewable materials are biologically better, more effective, and safer for human and animal food than those synthesized from other sources. Green extraction is based on some principles that contemplates (i) the use of renewable resources, (ii) the use of alternative solvents replacing petrochemicals ones, (iii) the reduction of energy consumption, (iv) the transformation of waste residue into co-products and/or by-products via processes that (v) do not degrade nor contaminate the raw material (Gorka & Wieczorek 2017, Ospina et al. 2017). These points are in complete agreement with the concept of circular economy, which demands eco-friendly innovations and sustainable feedstock to close the loop of the products life cycle (Prieto-Sandoval et al. 2018). Extraction of compounds using supercritical fluid technologies (with CO_2 and water) is recommended for food, cosmetic and pharmaceutical industries. Protocols for the full use of biomass (zero waste and CO_2 mitigation) to obtain chemicals of commercial interest are being developed or under development in countries that have know-how in sustainable technologies. Thus, both the development of technologies and applied research in the bioprospecting of new natural molecules and/or the discovery of new applications for already known chemicals are RD&I strategies in line with the New World Bioeconomy. The European Commission for Research and Innovation in Bioeconomy (Ronzon et al. 2017) estimates that changing the use of petroleum-derived compounds to biological ones will reduce CO_2 consumption to 2.5 billion tons per year from 2030. This new economic matrix is a fast-growing area capable of creating new markets and jobs. Products for the New World Bioeconomy (product versus commercial value),

indicate that chemical products are the ones with the highest return on the investment made.

Associate Editor

Carlos Joly

Conflicts of Interest

The authors declare that they have no conflict of interest related to the publication of this manuscript.

Ethics

This study did not involve human beings and/or clinical trials that should be approved by one Institutional Committee.

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