Applications of Metabolities Extracted from Macroalgae to Fight Neglected Diseases in Brazil

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Microorganisms provoke neglected diseases. However, social factors intensified those affected by them. Macroalgae are photosynthetic beings that live in oceans. They are divided into three categories: green, red, and brown algae. These groups are known for having metabolites with various applications in biotechnology and natural products chemistry. The present work aimed to discuss, through bibliographic review, the applications of substances extracted from macroalgae to the treatment of forgotten diseases in Brazil. This research concludes that literature has studies focused on the presence and absence of these compounds, namely its qualitative aspects, in which pharmacological, pharmacodynamic, and reaction mechanisms fields of these bioactive constituents are described.
Keywords: Neglected Diseases. Macroalgae. Metabolites.

Introduction

Algae are organisms with photosynthetic capacity located in aquatic and continental environments. They provide protection and food resources for fish and invertebrates. They are divided into macroalgae (multicellular individuals) and microalgae (unicellular individuals). Three major taxa are: *Rhodophyta*, *Phaeophyta*, and *Chlorophyta*, also referred to as red, brown, and green algae, respectively [1,2].

Therefore, macroalgae are responsible for a large portion of the worldwide produced algae biomass, opening spaces for research development due to its vast production of metabolites and providing relevance to studies regarding pharmaceutical products used to fight infectious agents. Among the metabolites emphasized in previous studies, the caulerpin, a derivative of the *Caulerpa*, seaweeds in the family *Caulerpaceae* and phylum *Chlorophyta*. This compound has antitumor and antimicrobial activities, as the *Spatoglossum schroederi* seaweed, a member of the phylum *Phaeophyta*, which has a bioactive compound (fucoidan) with pharmacological activity. Likewise, the phylum *Rhodophyta* has shown antimalarial activity in literature, these red algae are located in the state of Ceará, reaching the southern limit of the state of Espírito Santo [1,4].

Currently, neglected diseases in Brazil are caused by infectious and parasitic pathogens that endemically affect vulnerable populations in developing countries, which lack positive therapeutic actions such as vaccines and medical diagnosis. These factors can damage communities that already do not have access to health-related resources, preventing them from better assistance and contributing to unequal reality. According to the Fundação Getulio Vargas (FGV), the prediction was that, in February 2021, 27.2 million people in Brazil would be living in poverty, which represents 12.83% of the Brazilian population. Thus, the growing cases of forgotten diseases in Brazil, such as dengue, Chagas disease, tuberculosis, malaria, cancer, leishmaniasis, and others, are inevitable [2,3].

The present work aims to highlight, through a bibliographic review, the management and application of metabolites from macroalgae to fight neglected diseases in Brazil.

Materials and Methods

We did literature research using papers published throughout the last 11 years (2010-2021)

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in the following databases: Instituto Nacional da Propriedade Industrial (INPI), Google Scholar, Scientific Electronic Library Online (SciELO), Periódico CAPES, Science Direct, and Espacenet. During the investigation, we searched for the words "seaweed and neglected diseases in Brazil", "green algae", "red algae", "golden algae", "seaweeds and metabolites", as well as "seaweeds and biopharmaceuticals", using the Portuguese, English, and Spanish languages. All studies were selected according to our subject of interest, and the pre-selected materials consisted of articles, doctoral thesis, and thesis.

Results and Discussion

We gathered 25 scientific materials, including original scientific articles, doctoral theses, masters' dissertations, and patent documents. Due to its continental dimensions, Brazil has a big coastline with potential for finding several species of macroalgae. It facilitates the opportunity of developing new pharmaceutical products for the treatment of neglected diseases and their consequences resulting from the current management methods.

On the other hand, neglected diseases are current for Brazilian citizens, causing a decrease in the well-being in the affected people. In addition, most of the existing drug treatments have demonstrated short-and long-term side effects, such as anticholinergics and opioids used for diarrhea, antimonials employed to treat leishmaniasis, and chemotherapy for various types of cancer [1,(24,25)]. Furthermore, several microorganisms acquire chemical resistance, owing to the prolonged use of treatments and indiscriminate lack of medical control for neglected diseases [3].

The unsuccessful therapeutic initiatives mentioned in the literature incentivates the research community to study therapies and medicines derived from natural resources, as well as the use of inputs extracted from macroalgae.The studies present a reduction of side effects and positive actions against such diseases when compared with the traditional one. Such applications are encouraged by the World Health Organization [4-6].

Dichloromethane and methanol extracts of *Dictyota mertensi* collected at the Itapuama Beach, Pernambuco-Brazil, exhibited 100% of leishmanicidal and cytotoxic activities, inhibiting the growth of promastigotes in the form of *Leishmania amazonensis in vitro*. Inputs from *Lobophora variegata*, *Padina gymnospora*, *Hypnea musciformis*, *Ulva fasciata*, *Ulva lactuca*, and *Caulerpa prolifera* collected from the coast of Ceará, are useful in the inhibition of *S. aureus* and *Salmonella* with the antibiotic-resistance profile. *L. variegata* and *H. musciformis* exhibited antimicrobial activity against *Vibrio harveyi*, which resists six types of industrial drugs, besides being a human and marine zoonotic pathogen.Methanol and ethanol-based raw materials obtained from *Padina gymnospora*, *U. lactuca*, and *C. prolifera* managed to neutralize the dengue virus type 3, an occurrence for the Brazilian health scenario, which seasonally faces outbreaks of dengue and correlated illnesses [7,(20-25)].*Spatoglossum schroederi*, *Udotea flabellum*, and *Gracilaria birdiae* - taken from substrates that originated in the coast of Rio Grande do Norte - showed parasite reduction and antimalarial activity against the *Plasmodium falciparum* species, expressing advantage compared to chloroquine. Other algae species such as *C. glomerata*, *D. dichotoma*, *S. furcellata S. natans*, and *U. lactuca* also have the antispasmodic operation following the action of meroditerpenes, tocopherols, b-tocopheryl-hydroquinone, and d-tocopheryl-hydroquinone. Sesquiterpenes from *L. dendoidrea*, obtained in the herbarium of the Universidade Federal do Rio de Janeiro (URFJ), reacted to leishmaniasis [8]. Fractions of *Prasiola crispa* contain a high leishmanicidal effect with efficiency, aside from having no toxicity to humans [9]. Inputs acquired

through solvent extraction using *S. vulgare*, *P. flagellifera*, *U. fasciata* collected on the coast of Bahia, demonstrated the following percentages of HIV inhibition: 89.92%, 37.18%, and 35.85%, respectively [10].

The genus *Gracilaria* has species with antibiotic activity in their extracts analyzed during *in vitro* studies, which tested their effects on Gram-positive and Gram-negative bacteria, such as *Vibrio cholera*, *Staphylococcus aureus*, *Shigella dysenteriae*, *Salmonella paratyphi*, and *Pseudomonas aeruginosa*. Soxhlet extraction using ethanol and methanol on *Gracilaria debilis*, *G. cervicornis*, *G. corticata*, *G. domigensis*, and *G. debilisi* generate inputs employed as antibacterial agents for multidrug-resistant organisms in severe cases of infections. Whereas *Gracilaria bursa-pastoris* and *Gracilaria* sp., when in contact with methanol, provide citrullinylarginine (Figure 1), a compound with antiretroviral activity regarding the human immunodeficiency virus (HIV), the herpes simplex virus (HSV), and the human papillomavirus (HPV) [11]. However, the reactions involved in these processes are unknown due to the lack of further research on such compounds, thus highlighting the need to assess the toxicity levels produced by prostaglandins, obtained from the mentioned algae through bioassays [12]. These species are found in Brazil from the coast of Ceará to the state of Espírito Santo [13].

Table 1 shows more applications of chemical inputs obtained from macroalgae in neglected diseases.

Conclusion

Based on many social problems surrounding neglected diseases in Brazil, the use of chemical compounds extracted from macroalgae to the direct and indirect treatment of pathologies should be well-studied. Besides, these compounds reduce side effects caused by conventional treatments and improve the well-being of vulnerable Brazilian populations.

Despite many metabolites discovered in marine and coastal macroalgae, the pharmacological and pharmacodynamic descriptions and the mechanisms of the action are still superficially explored to fight diseases.

So, further studies are needed to elucidate the interaction between these compounds and neglected diseases. Therefore, the scientific usage of the marine environment has to be aligned with the current societal sustainable mentality, highlighting the need to provide investments for studies focused on the mechanisms of action of these compounds.

Figure 1. Structure of citrullinylarginine.

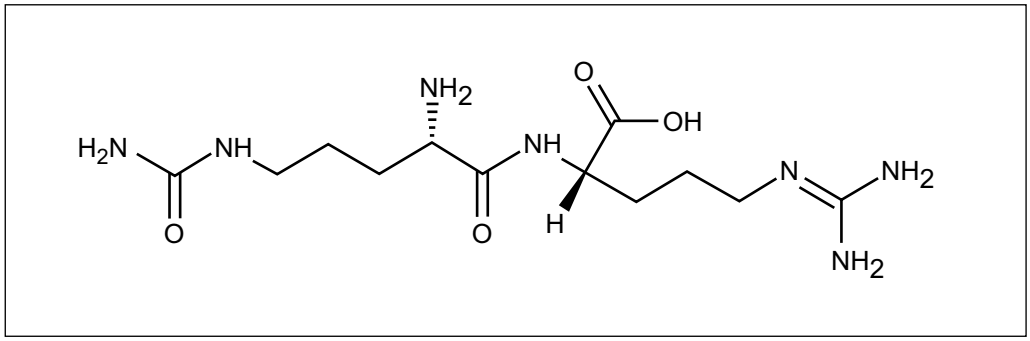

Table 1. Applications of macroalgae chemicals.

Species	Substance	Application	References
Octhodea secundiramea (red seaweed)	Halogenated, monoterpenes and octodens	Schistosomicidal activity	[14]
Byrothamnion triquetrum, *Gracilaria birdia*, and *Gracilaria caudata* (red seaweed)	Sulfated polysaccharides	Antinociceptive action generated by the treatment of neglected diseases and reduction of gastrointestinal lesions caused by antibiotics and acute antidiarrheal drugs	[1]
Dictyota caribea (brown seaweed)	Sulfated polysaccharides (fucoidans), diterpenes, primarymetabolites	*In vitro* macrophage activation for epidermal carcinomas, reduction of sarcoma 180	[15]
Caulerpa lentillifera (green seaweed)	Fucoidans	Apoptosis of sarcoma 180 and increased production of murine macrophages with M1 phenotype for antitumor activity	[15, 16]
Lobophora variegata (brown seaweed)	Polyunsaturated henecosanoid epoxide, apo-13'-fucoxanthinone, phytanyl glyceryl ether	Cytotoxicity against cancer cells and decrease in nitrous oxide responsible for HCT 116 derived inflammations	[17]
Laurencia intricata, *Laurencia obtusa*, *Laurencia microcladia*, *Leishmania mexicana*, *Laurencia scoparia*, *Undaria pinnatifida*, and *Plocamium cartilagineum* (red seaweed)	Diterpene, laurediterpineol, 7-hydroxyllaurane, bromolaurenisol, sesquiterpene, elatol, trichomonicide, β-bisabolene, fucoxanthin, terpenoids, polar fractions florotannins, sterols, alkaloid, and bromophenols	Antitumor activity against T47D cell lines and HIF-1 factors, both related to breast tumor cells. They are also inhibitors of K562 cells, epidermal, cervix, and myelogenous adenocarcinoma derivatives, lung and prostate tumors. They show a significant decrease in the action of helminth parasites and sexually transmitted infections	[8,18]
Gayralia oxysperma, *Monostroma nitidum*, and *Capsosiphon fulvescens* (green seaweed)	Rhamnans, sulfated, manoxylans, and sulfated heteroramnans	Inhibition of gastric tumor cells, Vero cells, human glioma, and herpes activity	[19]
Portieria hornemannii, *Plocamium cornutum*, and *Callophycus serratus* (red seaweed) *Udotea orientalis* (green seaweed)	Pentahalogenated terpenes, oxygenated monoterpenes, bromoficolides, aromatic sesquiterpenes, diterpenes, sulfated polysaccharides, and C-6 galactose	Inhibition of brain, kidney and, colon tumor cells. Antiplasmodic activity against *Plasmodium*, antimalarial, aside from anti-titrypanosomal activity opposed to *Trypanosoma cruzi* amastigotes, antiviral action *in vitro* against DENV-1, DENV- 2, DENV-3, and DENV-4	[20]
Cladophora glomerata, *Ulva prolifera*, and *Ulva lactuca* (red seaweed)	Indoleacetic acid, Indolebutyric acid, kinetin, polysaccharide extracts, and aqueous extracts	Antioxidant and anti-inflammatory actions, pancreatic fat breaking, antibacterial management against *Escherichia coli*	[21-23]

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