

DISCOVERY AND DEVELOPMENT OF POTENTIAL CHEMOTHERAPEUTIC AGENTS FROM MARINE INVERTEBRATES AND ASSOCIATED MICROORGANISMS

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Ascidian Didemnum sp.

The aim of this project is the chemical investigation of biologically active crude extracts obtained from marine invertebrates and marine microorganisms collected in different regions of the Brazilian coastline. Extracts of marine invertebrates active as cytotoxic and antituberculosis, as well as with antimicrobial activity against both antibiotic-sensitive and antibiotic-resistant human pathogenic microbes and of inhibition of specific enzymes implied in the life cycle of pathogenic protozoa, will be subjected to dereplication by LC-PDA-MS before a chromatographic

fractionation toward the isolation of biologically active compounds. Marine fungi and bacteria isolated from marine invertebrates will be grown in optimized artificial media in order to produce secondary metabolites. Extracts from marine microbes growth media will be subjected to the same above mentioned bioassays. A new set of bioassays related to the inhibition or stimulation of chemical mediators implied in immunomodulation processes will be applied to the whole crude extract collection in order to search for active extracts. Dereplication by LC-PDAMS analysis in order to get information about crude extracts chemical profiles will provide basis for the isolation of novel bioactive compounds. Pure chemical entities obtained from marine invertebrates and microorganisms will be identified and evaluated in the bioassays in which the original crude extract was active, aiming to obtain information on their mechanism of action.

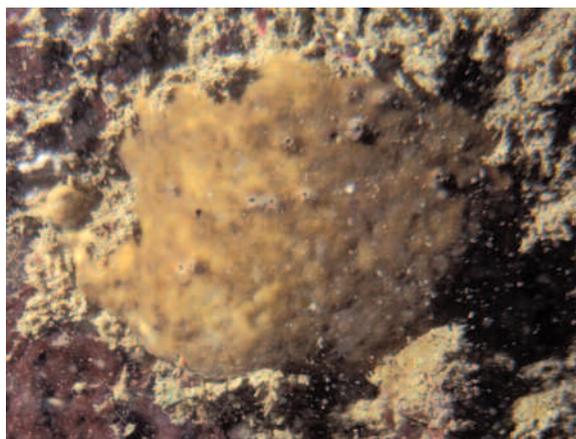
SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

We have screened > 1500 crude extracts from both marine invertebrates and microorganisms in cytotoxicity, anti-Leishmania, antimicrobial and anti-inflammatory bioassays. Several active extracts were investigated. Pure compounds have been isolated from both marine invertebrate and microbes. These include polycyclic bis-piperidine alkaloids from Haplosclerid sponges that displayed cytotoxic and anti-Leishmanial activities, cytotoxic alkaloids from a nudibranch of the genus *Tambja*, anti-Leishmanial and anti-neuroinflammatory polyketides from the marine sponge *Plakortis angulospiculatus*, anti-bacterial modified diketopiperazines from two ascidians of the genus *Didemnum* and anti-tuberculosis polybrominated tyrosine derivatives from marine sponges. The investigation of marine-derived fungi culture media led to the isolation of several bioactive metabolites, mostly with antibiotic activity.

Aiming to overcome the low yield production of secondary metabolites by marine-derived fungal strains, we have developed a method for the optimization of secondary metabolites production in culture media. Consequently, it has been possible to isolate and identify minor metabolites produced in tiny amounts under standard culture conditions. The method is currently being improved and further explored in the production of bioactive natural products by marine-derived fungal strains.

The exploitation of marine biological sources of natural products has been very productive, and showed promising results towards the finding of new lead compounds for drug discovery. Although the compounds so far isolated are structurally too complex to be considered as drug leads, the finding of novel bioactive compounds from the São Paulo state and Brazilian coastline biodiversity shows the importance of a continuous search for such chemical entities with a potential for the development of new drug candidates.

Sponge Plakortis angulospiculatus



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