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Editorial Open Access

New Trends in Marine Natural Products

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Editorial

Public interest in substances with marine origin is very recent in comparison to that of terrestrial plants that dates back to our origins as nomadic hunter-gatherers. Our ancestors made the distinction between edible plants - some of which they eventually cultivated as humans became sedentary - and toxic substances that could serve as remedies once properly prepared and administered during special ceremonies by medicine men who are still highly respected in existing tribal systems worldwide. Several paralyzing substances and venoms were (and still are) used as aids for game hunting. Other neuroactive substances, mostly from toxic mushrooms, have been traditionally used as entrancing agents by witch doctors and more recently by westerners in search of mind-expanding (or mind-blowing) experiences.

Marine ethnopharmacology, on the other hand, has no real historical background except for isolated examples e.g. the use reported centuries ago of the red alga domoi as cure against roundworm infestation in Japanese infants. Traditional non health-oriented uses of marine substances are also uncommon, such as that of toxic holothurian skin exudates by Filippino fishermen to facilitate catches of coral reef fish.

Research on marine natural substances unfolds under three different periods, each of which brings its significant contribution to knowledge and human welfare. This is fuelled by scientific curiosity, facilitated by novel technologies, and sometimes hastened by health issues.

Several discoveries by isolated pioneers have landmarked the early 20th century, e.g. the discoveries of squalene, of astaxanthine and of Tyrian purple. But it was the publication in 1973 by Paul J. Scheuer of his historical textbook [1] that set off marine natural products as a scientific field in its own right. Following this, a growing number of American, European and Japanese scientific teams - public and private - have systematically explored and exploited a now easily accessible resource taxa by taxa, using safer SCUBA diving equipment and trawling along extensive transects. This has yielded the discovery of completely novel series of molecules with hitherto unknown terrestrial equivalents. For example, cyclic polyethers produced by microalgae, volatile halocarbons and tissue-bound terpenes of red algae, linear diterpenes and merediterpenes of brown algae, chlorinated diterpenes of cnidarians, bryostatins of bryozoans, saponins of echinoderms, non-ribosomal cyclic peptides of ascidians, sulfated polysaccharides from red and brown algae, and dozens of examples with original structures isolated from multiple sources [2].

Health concerns, with the competitive quest for original types of bioactive molecules that could inspire new generations of drugs, then took precedence. This led to extensive sourcing from marine organisms and to the characterization of metabolites extracted and analyzed onboard of specially outfitted vessels [3]. Very soon though, biologists were facing identification problems using existing taxonomic keys, while chemists/biochemists were puzzled by new biosynthetic challenges. Both communities became gradually interested in the defensive roles of tissue-bound substances and in the signaling functions of diffusible metabolites, all conferring selective advantages to the source organisms in highly competitive environments. Four major areas linked to marine natural products emerged gradually in the short late-1980's-to-early-1990's period between a hundred or so research groups from major economically developed nations: (i) taxonomy - using molecular criteria and approaches in addition to classical morphological criteria, (ii) chemical characterization using adapted extraction methods, improved separation techniques and higher resolution analytical instruments, (iii) biosynthetic investigations that hinted at alien origins (associated microbiota) of investigated molecules, and (iv) chemical ecology and ecological chemistry that are not strictly equivalent. Biologists study the effects of so-called secondary metabolites on target organisms and communities, while chemists study the chemical repertoire of a given species and how it varies throughout its geographic range (ecochemotypes), between seasons, and under induced stress.

These various specializations are clearly emerging in two publications that landmarked this period [4], as well as in the MaNaPro international symposia (International Symposium of Marine Natural Products) held every four years since its launching in Aberdeen (Scotland) in 1975.

By the early nineties, most major marine phyla had been investigated chemically, albeit superficially, though protists (e.g. foraminifers and ciliates) and minor groups of multicellular eukaryotes (e.g. sipunculid or peanut worms, chaetognaths and brachiopods) have not been properly explored chemically to date.

In parallel, the rising interest in microbial metabolites, often hampered by severe cultivation limitations, has not returned its promises to date. No bacterial chemical series and no novel chemical series specific to marine fungi have yet been reported, as one would expect from highly productive earlier investigations on many sessile invertebrates and algae. Only the Archaea, which represent one of the two [5,6] or three domains of life feature membrane lipids that are peculiar to this cell type.

By the turn of the century, advances in chemical ecology have demonstrated the sometimes unique microbial origin of target metabolites in host-microbe interactions, the host acting as an

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incubation chamber affording optimal conditions to microbial associates. Indeed, most isolated marine microbes cannot be cultivated *in vitro*, and only through a systems biology approach can we comprehend how complex and intricate photosymbiotic systems operate. Sessile invertebrates such as sponges, cnidarians, bryozoans and ascidians can then be viewed as holobionts [7] that include the invertebrate host and a range of microalgal, cyanobacterial, eubacterial, archaeal, fungal and viral associates. The symbiotic relationship can be obligate and highly host-specific, such as strains of *Poribacteria* for some sponges or *Endobugula* for specific bryozoans, simply host-specific as between cyanobacteria and their sponge host or between prochloron and their didemnid ascidian hosts, or merely functional as between zooxanthellae and their cnidarian host.

Free-living microorganisms that were little known before they became culture-friendly have revealed a huge potential for the production of useful substances such as ω-3 fatty acids that are produced at industrial scale by thraustochytrids, little ciliate-like protists. In other cases, successful cultivation of selected bacteria and fungi has reduced the sampling of natural sources and host organisms in the wild, thus avoiding environmental issues and political conflicts [8,9], yet, as already mentioned, most marine microorganisms escape successful cultivation [10].

From the late 90's, industrial applications have expanded for marine molecules and marine biotechnologies have emerged as a field of fundamental and applied research, and the first dedicated journal *Marine Biotechnology* covers a wide range of topics. Biomaterials, bioremediation, anti-biofouling strategies and nanotechnologies are now actively investigated and may enjoy spectacular developments in the near future [11].

More recently, the "omics" revolution now allows the study of metabolic responses at the scale of the single cell, of the isolated organ or of the whole organism when facing experimental stress or natural environmental changes. Ecochemotypes can be discriminated from true species on the basis of their metabolomes. Important biotechnological choices can be made in order to improve the productivity of a target compound. Microbiodiversity assessments of discrete (hosted microbiomes) to ocean-wide (global plankton) samples can be characterized without the need to formally identify or cultivate unknown biological entities (the vast majority), thanks to "meta-omics" techniques such as genomic barcoding [12].

A suite of experimental approaches can now link several scientific fields, i.e. genomics > transcriptomics > proteomics > metabolomics > fluxomics into large scientific multinational programs that coordinate the expertise of scientists with very different backgrounds.

Starting from the invariant genome (i.e. assuming no interfering mutations), molecular biologists (essentially by studying mRNAs) observe the participation of genes of interests in response to environmental changes or to induced stresses. Their up/down regulation manifests itself by the production of regulation proteins and key enzymes that in turn initiates the biosynthesis of organic molecules. The latter are of various classes, structural and functional, resident or exported according to the primary, secondary or sometimes dual role they are called to have. The characterization of the metabolome uses sophisticated extraction, separation and analytical procedures with instruments that are often coupled (mass spectrometers, NMR), the ever more bulky and complex data being analyzed by dedicated bioinformatics software using custom-made algorithms, now accessible to most laboratories. Finally, the overall metabolic performance of a biological system (single cell, isolated organ, whole organism or holobiont) can be modelled by fluxomics. Reaction kinetics of target metabolites can be quantified by e.g. isotopic labeling, in order to provide a general phenotypic performance assessment, which can in turn be complemented visually by microscopic or macroscopic imaging techniques that use specific molecular labels.

Each of these "omics" has progressively been diversified by benchtop specialists, as described in [13] yet with the final hope to get the Big Picture. Beyond our constant quest for investigating the unknown, the "omics revolution" [14-16] may also improve our vision of species evolution since the origin of life. Moreover it may increase social awareness by establishing key priorities and proposing adapted lifestyle improvements in order to prevent major biodiversity issues in the face of coming environmental changes.

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