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Editorial: Sustainable production of marine natural products - from discovery to application

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Editorial on the Research Topic
Sustainable production of marine natural products - from discovery to application

Marine natural products are distinct by their structural diversity and unique chemical functionalization. However, most compounds discovered in marine macro-organisms are detected in minute quantities, which demands significant amounts of biomass to generate sufficient compounds for industrial application. In most cases this practice is significantly damaging fragile marine ecosystems, such as coral reefs. Today, advanced analytical tools, particularly applying comprehensive system biology approaches, allow the identification of selective biosynthetic pathways. Deciphering complex systems biology data to identify specific natural product encoding biosynthetic pathways is increasingly automated by use of advanced bioinformatics tools. The advances in analytical methods in synergy with sophisticated bioinformatics centered algorithms, provide a knowledge gain that create the basis for synthetic biology approaches enabling sustainable and scalable production of marine bioactives in recombinant microbial hosts.

Marine invertebrates have long been of particular interest for the discovery of bioactive compounds. While coral and sponges have proven time and again a particularly rich resource, the authors of "*UV-B Protective and Antioxidant Activities of Protein Hydrolysate From Sea Cucumber (Holothuria scabra) Using Enzymatic Hydrolysis*" demonstrated that peptides from the sea cucumber (*Holothuria scabra*) may be used as antioxidants with a protective effect against UV-B induced skin cell damage (Doungapai et al.). Papain, alcalase, or flavourzyme were used to obtain sea cucumber protein hydrolysate powders for analysis. Six peptides were identified which should be further evaluated for their application efficacy, reaction mechanism, and bioavailability in pre-clinical and human trials.

Using an integrated *de novo* transcriptomic and proteomic analysis, Zhang et al. in "*Discovery of 194 Unreported Conopeptides and Identification of a New Protein Disulfide Isomerase in Conus caracteristicus Using Integrated Transcriptomic and Proteomic Analysis*" provided novel insights into the pharmaceutically attractive conopeptides

from the venom duct (VD) and venom bulb (VB) of the cone snail *C. caracteristicus*. The authors described 194 previously unreported conopeptide precursors, identified two conotoxins at the protein level and detected a novel protein disulfide isomerase (PDI) gene. The information obtained supports future investigations of Conus gene evolution and toxin function for use in pharmaceutics.

A multi-informative molecular networking (MIMN) approach for the in-depth analysis of *Lendenfeldia* sp. sponge extracts was proposed by Chen et al. in "*Chemometric-Guided Exploration of Marine Anti-Neurofibroma Leads*". In particular, the authors investigated leads with the potential to downregulate the chemokine/cytokine expressions for the development of anti-neurofibroma candidates. The reduction of CXCL10 expression and inhibition of several other inflammatory chemokines of *Lendenfeldia* sp. sponge extracts were of particular interest. Scalarane of *Lendenfeldia* sp. extracts dominated the anti-chemokine effect.

In the article "*Comparative analysis of assembly algorithms to optimize biosynthetic gene cluster identification in novel marine actinomycete genomes*" by Tizabi et al., the microbial community of the sponge *Xestospongia muta* was investigated for their pharmaceutically relevant metabolites. A novel assemblage of Actinobacteria in the sponge were explored for compounds inhibiting *M. tuberculosis* using a bioinformatics approach. SPAdes, A5-miseq, and Shovill, three bioinformatic assembly algorithms, where used to identify biosynthetic gene clusters of compounds with known anti-TB activity. Strains of *Micromonospora* and *Streptomyces* within the mesohyl matrix of *X. muta* related to BCGs previously reported to encode compounds that inhibit *M. tuberculosis*.

Using novel bioengineering tools for the targeted production of known metabolites in a recombinant host may provide a sustainable route to scale and provide a cost-effective approach for the manufacture of valuable metabolites. The production of docosahexaenoic acid (DHA) by metabolic engineering in the marine protist *Aurantiochytrium* sp. was explored by Liang et al. in "*Metabolic Engineering to Improve Docosahexaenoic Acid Production in Marine Protist Aurantiochytrium sp. by Disrupting 2,4-Dienoyl-CoA Reductase*". In the article, the authors describe the production of DHA by disrupting polyunsaturated fatty acid beta-oxidation *via* knockout of the 2,4-dienyl-CoA reductase (*DECR*) gene by UV mutagenesis. Fatty acid methyl esters (FAMEs) were analyzed by GC-MS and showed that knockout of *DECR* substantially enhanced the DHA percentage yield.

Using marine bacteria as novel means for the production of high value products was highlighted by Vijay et al. in "*Native Production of Prodigiosin in the Estuarine Bacterium, Vibrio gazogenes PB1, and Identification of the Associated pig Genes*". Here, the authors have shown the production of prodigiosin in a promising bacterial host, the estuarine bacterium *Vibrio gazogenes* PB1, using lysogengy broth medium supplemented with NaCl. Prodigiosin was identified as a promising apoptotic agent, antibiotic, and fungicide. Under batch conditions, the authors could observe the production of prodigiosin was influenced by glucose, ammonium chloride, inorganic phosphate ions, and pH.

Underutilized marine resources have been the focus of "*Mesopelagic Fish Protein Hydrolysates and Extracts: A Source of Novel Anti-Hypertensive and Anti-Diabetic Peptides*" Authors Naik et al. demonstrated that proteins from mesopelagic fish and zooplankton may be a potential source of inhibitors of Angiotensin-1-converting enzyme (ACE-1; EC. 3.4.15.1), Acetylcholinesterase (AChE; EC 3.1.1.7), and Dipeptidyl peptidase IV (DPP-IV; EC 3.4.14.5) which are linked with Type-2 diabetes and metabolic syndrome.

In addition to using underutilized marine resources, the use of marine fishing waste allows for transition into a circular bio-economy while generating value adding natural products that have various applications ranging from food over chemical to pharmaceutical applications. As such, processing crustacean and bivalve processing side streams (CBPS) may yield a variety of high value products as shown in the review article "*Valorisation of crustacean and bivalve processing side streams for industrial fast time-to-market products: A review from the European Union regulation perspective*" by Zou et al. With side stream wastes making up to 75% of the whole mass of shellfish-based food products, this resource may yield protein, lipids, carotenoids, minerals and chitins of high commercial value, depending on the extraction process. However, products must comply with market regulations. The authors have chosen to highlight implications for these added value products considering EU regulations with a focus on animal feeds, bio-pesticide/stimulants, and cosmetic ingredients.

In summary, this article collection demonstrates the intensified development in the field of aquatic biotechnology and signals new route to sustainable materials, bioactives and consumer products. The continued development of updated and new bioinformatics tools, potentially aided by AI in the near future, will allow for a robust increase in the development of environmentally and economically-sustainable systems to produce bioactives from marine sources. These methodologies can be adapted to produce bioactives from other environmental sources.

Author contributions

All authors were equally involved in the development, drafting, and correction of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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