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52° Congresso SIBM: Possibili applicazioni biotecnologiche degli organismi marini: dalle molecole bioattive al biorisanamento

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TRENDS IN STUDY AND APPLICATION OF MARINE RESOURCES

TENDENZE NELLO STUDIO E NELL'APPLICAZIONE DELLE RISORSE MARINE

Abstract *- Oceans cover almost 70% of the earth's surface and are characterized by enormous biological and chemical diversity. Purified marine compounds and/or bioactive complex mixtures can be used for the creation of innovative products with potential application in pharmaceutical, nutraceutical, and other industries. Multidisciplinary approaches have been in fact reported to identify bioactive compounds, biocompatible components, gene clusters and innovative eco-sustainable processes. Recently, there has been a growing interest in the exploration of the marine habitat also thanks to the advancement of sampling, cultivation, molecular biology and bioinformatics technologies. The platforms for the identification of bioactivity, the optimization of biomass production, the development of sustainable protocols and innovative methods for extraction of biomaterials, and the use of wasted or underutilized biomass are currently between the main hot topics.*

Key-words: *Marine biotechnology, marine natural products, eco-sustainable, circular economy, marine organisms*

Introduction – The demand for new drugs for the treatment and prevention of human pathologies, such as cancer or infectious diseases, has triggered a growing interest in marine sources. Currently, there are 14 approved drugs of marine origin on the market (Tab. 1), of which 9 are used for the treatment of cancer. In addition, there are 23 compounds used in clinical trials (as reported at https://www.midwestern.edu/departments/marinepharmacology/clinical-pipeline). As shown in Tab. 1, chemical classes of the bioactive compounds are very variable, including nucleosides, peptides, omega-3 fatty acids, together with alkaloids, a macrolide or antibody drug conjugates.

Tab. 1 - Marine derived drugs on the market. Marine organism from which the original compound was isolated, commercial name, manufacturing company, and application are reported. * Food and Drug Administration (FDA) Approved. **Australia Dec 2018 Approved (modified from https://www.midwestern.edu/departments/marinepharmacology/clinical-pipeline). ADC: Antibody Drug Conjugate; Ara-A: 9-β-D-arabinofuranosyladenine; Ara-C: Cytosine Arabinoside; MMAE: Monomethylauristatin E; MMAF: Monomethylauristatin F.
*Farmaci di derivazione marina sul mercato. Vengono riportati l'organismo marino da cui è stato isolato il composto originale, il nome commerciale, l'azienda produttrice e l'applicazione. *Approvato dalla Food and Drug Administration (FDA). **Approvato per l'Australia nel dicembre 2018 (modificato da https://www.midwestern.edu/departments/marinepharmacology/clinical-pipeline). ADC: coniugato farmaco-anticorpo; Ara-A: 9-β-D-arabinofuranosiladenina; Ara-C: citosina arabinoside; MMAE: monometilauristatina E; MMAF: monometilauristatina F.*

Compound	Marine organism	Commercial name	Company	Disease	Chemical class
Belantama-mafodotin-blmf	Mollusk-cyanobacterium	Blenrep™ (2020)*	GlaxoSmithKline	Cancer: Relapsed/refractory	ADC (MMAF)

multiple myeloma

Tab. 1 – continue

Compound	**Marine organism**	**Commercial name**	**Company**	**Disease**	**Chemical class**
Plitidepsin	Tunicate: Applidium albicans	Aplidin™ **	PharmaMar	Cancer: Multiple Myeloma, Leukemia, Lymphoma	Depsipeptide
Lurbinectedin	Tunicate	Zepzelca ™ (2020) *	PharmaMar	Cancer: Metastatic Small Cell Lung Cancer	Alkaloid
Enfortumab Vedotin-ejfv	Mollusk-cyanobacterium	PADCEV ™ (2019) *	Astellas Pharma & Seattle Genetics	Metastatic urothelial cancer	ADC (MMAE)
Polatuzumab vedotin (DCDS-4501A)	Mollusk-cyanobacterium	Polivy ™ (2019) *	Genetech/ Roche	Cancer: Non-Hodgkin lymphoma, Chronic lymphocytic leukemia, Lymphoma, B-Cell	ADC (MMAE)
Trabectedin (ET-743)	Tunicate	Yondelis® (2015) *	PharmaMar	Cancer: Soft Tissue Sarcoma and Ovarian Cancer	Alkaloid
Brentuximab vedotin (SGN-35)	Mollusk-cyanobacterium	Adcetris® (2011) *	Seattle Genetics	Cancer: Anaplastic large T-cell systemic malignant lymphoma, Hodgkin's disease	ADC (MMAE)
Eribulin Mesylate (E7389)	Sponge	Halaven® (2010) *	Eisai Inc.	Cancer: Metastatic Breast Cancer	Macrolide
Cytarabine (Ara-C)	Sponge	Cytosar-U® (1969) *	Pfizer	Cancer: Leukemia	Nucleoside
Omega-3-acid ethyl esters	Fish	Lovaza® (2004) *	GlaxoSmithKline	Hypertriglyceridemia	Omega-3 fatty acids
Eicosapenta enoic acid ethyl ester	Fish	Vascepa® (2012)*	Amarin	Hypertriglyceridemia	Omega-3 fatty acids

Tab. 1 – continue

Compound	**Marine organism**	**Commercial name**	**Company**	**Disease**	**Chemical class**
Omega-3-carboxylic acid	Fish	Epanova® (2014)*	AstraZeneca	Hypertriglyceridemia	Omega-3 fatty acids
Vidarabine (Ara-A)	Vira-A® (1976)*	Sponge	Mochida Pharmaceutical co.	Antiviral: Herpes Simplex Virus	Nucleoside
Ziconotide	Prialt® (2004) *	Cone snail	Jazz Pharmaceuticals	Pain: Severe Chronic Pain	Peptide

Since the first report of the biologically active marine natural compound (MNP) spongothymidine in 1950s, approximately 40,856 MNPs have been identified (according to MarinLit database updated to the 11 December 2023; https://marinlit.rsc.org/). When "marine natural product" is used as search filter of the literature available on the PubMed database, it is evident a clear increase in the interest and discoveries in this field, especially in the last 20 years. This means that this is a quite new field and the reason why there are only 14 marine-derived drugs on the market is that from the sampling of an organism, characterizing bioactivities of its raw extracts, identifying the bioactive compounds, performing clinical trials to commercialization, it takes about 20 years.

Various methods are used in drug discovery, including the bioactivity-guided fractionation, genome mining, omics approaches, genetic engineering, molecular networking and chemical synthesis (Lauritano *et al*., 2019).

Recent trends include the search for more eco-sustainable solutions, reducing impact on the marine environment and avoiding excessive use of marine resources, such as working on marine microorganisms, which can be more easily cultured in enclosed photobioreactors than macroorganisms, allowing more environment-friendly approaches (Saide *et al.*, 2021).

In addition to the pharmaceutical field, many other compounds, extracts and powders are actually used as ingredients of cosmeceutical and nutraceutical products (Alves *et al.*, 2020). Various marine ingredients, especially with antioxidant properties, have been in fact included in products available on the cosmetic market. For instance, DERMOCHLORELLA D/DP (by Codif) is a product based on an extract of the microalga *Chlorella vulgaris* Beijerinck*.* As reported on their website (https://www.codif-tn.com/en/principesactifs/dermochlorella-d/), DERMOCHLORELLA D is a concentrate of amino acids from *C. vulgaris* which acts as activator of collagen synthesis to mask dark circles. Another example is Skinrep, a water extract of the green microalga *Tetraselmis suecica* (Kylin) Butcher, which contains high carotenoid levels (e. g.

violaxanthin, neoxanthin, antheraxanthin and loroxanthin esters). Skinrep, thanks to its strong antioxidant, anti-inflammatory and repairing activity, is used for a daily anti-aging cream with SPF 30+ UVB / UVA named Anti-age UV Shield, a new anti-pollution cosmetic named Urban Serum, and a daily lip treatment named Bioactive Lip Care (https://www.biosearchsrl.com/a-new-anti-age-algal-formulation/). Carotenoids, with their UV-protecting effects have found market applications as well, such as the product Mousse Exquise based on extracts of the microalga *Dunaliella salina* (Dunal) Teodoresco for face deep cleansing (https://www.eclae.com/en/products/mousse-exquise). Similarly, products from macroalgae have found market access, including ''Short Range of Cosmetic Food Ingredients from the Sea'' by Codif Technologie Naturelle (https://www.codif-tn.com/en/), launched in 2020 which include Matrigenics 14G (based on extracts of the brown macroalga *Undaria pinnatifida* (Harvey) Suringar), that has anti-ageing and anti-wrinkle properties. They also produced an oil obtained by supercritical CO_2 extraction from *U. pinnatifida,* named WAKAPAMP LIPS, for lip care applications.
Regarding the nutraceutical sector, multiple compounds, derived from marine microorganisms, sponges, seaweeds, cnidarians, bryozoans, molluscs, tunicates, echinoderms, crustaceans, fish and mammals, found applications or are under consideration for possible market uses, from processing to storage of the food production process (Ghosh *et al.*, 2022). Molecules include marine animal and plant lipids, polysaccharides, chitosan, pigments, vitamins and peptides. Thanks to their antioxidant, anti-inflammatory, anti-obesity and other properties, these compounds have been considered for health-promoting activities such as the prevention osteoporosis, Alzheimer's disease, and cardiovascular disease, to boost the immune system and to induce general wellbeing (Ghosh *et al.*, 2022). For example, chitosan, a sugar coming from the outer skeleton of some marine organisms, including crabs, lobsters, and shrimps, is at the base of various products for possible weight and fat control, as well as for maintaining normal cholesterol levels in the blood (e.g. https://www.slowfarma.com/longlife-chitosan-84-tavolette.html). Crustacean copepod derived oil has been suggested to be a valuable substitute of fish and krill oil as alternative omega-3 source. The product named Calanus® oil (https://www.biogrators.com/prodotti/calanus-oil/) is based on lipids derived from the copepod *Calanus finmarchicus* (Gunnerus, 1770) and showed beneficial properties with anti-inflammatory and anti-obesogenic activities. Possible source of these ingredients may also be fish discards, including seafood processing industry, favoring a circular economy strategy for marine resources. Marine lipids have been extensively studied also for possible biodiesel applications, even if there are still no products available due to the high costs of production and low lipid yields to satisfy global biodiesel needs.
Human activities produce a negative impact on the environment and marine environments are exposed to pollution by various chemicals, ranging from heavy metals, hydrocarbons and various xenobiotics, including antibiotics discharged by humans. These molecules cause deleterious impacts on the environment, by altering microbial community composition, distribution and functions. Many studies are focused on innovative bioremediation techniques, including the use of marine organisms as well as purified enzymes for the reduction of the most harmful contaminants (Thatoi *et al.*, 2014; Vingiani *et al.*, 2022). As example, the project

ABBaCo "Pilot experiments for the environmental restoration and balneability of the Bagnoli-Coroglio coastal area" funded by MIUR and coordinated by Stazione Zoologica Anton Dohrn (2017-2020) aimed to develop new approaches for the remediation and environmental restoration of the coastal area of Bagnoli-Coroglio, where a former industrial plant induced land and sea contamination. In particular, the project proposed to identify the environmental benchmark of the area; ii) assess its present health status, iii) study the effects of contaminated sediments on biodiversity and ecosystem functioning, iv) assess the combined effects of multiple stressors; (v) experimenting innovative methods of transplantation (such as *Posidonia oceanica* Delille replanting). New environmental technologies, such as bioremediation and bioaugmentation, were investigated as well (https://www.szn.it/index.php/it/ricerca/ecologia-marina-integrata/progetti-di-ricerca-emi/abbaco). Another example is the project LIFE SEDREMED (https://life-sedremed.eu/it/homepage/; 2021-2025) which proposes to develop a prototype for the use of microorganisms within the sediments and increase their bioremediation capacities thanks to the transmission of electric current, both at laboratory-scale and on-site. In addition to the use of entire organisms, various studies have also shown the possibility of using purified or partially purified enzymes from marine organisms to detoxify a specific toxicant/pollutant. Promising results are available from bacteria, but recent papers have shown also for microalgae differential expression of enzymes involved in the degradation of a pollutant after exposure with it, confirming that they may be responsible of the remediation activity and suggesting future studies for enzyme purification (Vingiani *et al.*, 2022). As for the case of the first in silico identification of two putative di-n-butyl phthalate (DBP) hydrolases in the transcriptome of the marine diatom *Cylindrotheca closterium* (Ehrenberg) Reimann & J.C.Lewin. The expression level analyses of the two enzymes upon exposure of *C. closterium* to different concentrations of DBP for 24 and 48 hrs, showed a concentration-dependent up-regulation, highlighting their potential role in phthalate degradation.

Another biotechnological field which has recently attracted a lot of attention and is rapidly evolving is the use of marine organisms to obtain biomaterials, such as chitin, chitosan, and marine-derived collagen (Wan *et al.*, 2021). Collagen is in fact a promising natural biomaterial used to build scaffolds in tissue engineering, wet wound dressing, biomedical devices, dermal implants as well as nutricosmetic, food and beverages. For regenerative medicine, mainly bovine and porcine collagen has been used until now. This was considered risky for the transmission of diseases from animals to humans (e. g. transmissible spongiform encephalopathy and bovine spongiform encephalopathy). In addition, the use of animal derived products is sometimes prevented by specific needs or personal choices and by religious constraints. Several studies and projects are focusing on the identification of alternative and sustainable collagen sources, which may be represented by marine waste from fisheries and fish processing industries being fully in line with the European efforts to reduce and/or replace terrestrial animals and their derived products in research and favoring the circular economy and the use of underutilized products, including marine discards. Another biomaterial example, derived from marine microalgal species, is characterized by diatom biosilica frustules. They have high biocompatibility and can be functionalized on the surface, making them suitable for drug loading, biosensing chip and regenerative medicine for biomedical applications. For instance, the diatom *Chaetoceros* sp. frustules modified by iron oxide nanoparticles and conjugated with the monoclonal antibody Trastuzumab were studied to detect circulating breast cancer cells, SKBR3 cells (HER2 positive cells), from HER2-negative cells under a magnetic field. The optical properties of the silica allowed to detect this interaction by fluorescence microscopy, suggesting *Chaetoceros* silica frustules as promising eco-friendly biomaterials for the targeted administration of drugs to specific sites (Esfandyari *et al.*, 2020).

Materials and methods – Information reported in this paper has been retrieved by searching the literature available on the PubMed database. Regarding the updated approved marine drugs on the market or others in clinical trials, I referred to the webpage https://www.midwestern.edu/departments/marinepharmacology/clinical-pipeline, maintained by the Marine Pharmacology Department at the Midwestern University.

Conclusions – Recent publications have highlighted how marine organisms, their purified compounds along with extracts or marine waste, such as fish waste, marine food industry waste and beached species, may find applications in various market sectors including pharmaceutical, nutraceutical, cosmeceutical, bioremediation, biomaterial, aquaculture and biodiesel production. The zero-waste strategy and circular economy are between the most discussed hot topics. The interest in the subject is also underlined by the number of regional, national and European funded projects in the sector aimed at improving the exploitation of marine organisms for the discovery of new products and services.

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