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Challenges for the Development and Use of Marine Natural Products

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ABSTRACT

Marine environments are known to be difficult and complex. To survive in hostile environments, living organisms have developed functional and metabolic adaptive mechanisms, which we are still far from knowing and taking full advantage of. Many compounds of marine origin are structurally complex and have unique functionalities, whose potential goes beyond pharmaceuticals, reaching cosmeceuticals, nutraceuticals, biomaterials and energy. Based on knowledge and technical development, cooperation between academia and industry allows for the sustainable use of marine resources. The present survey does not aim to be exhaustive, we intend to have an idea of the present situation and of future prospects.

KEYWORDS: Marine biodiversity; Marine natural products; Marine bioactive compounds

I. INTRODUCTION

Oceans importance is unquestionable to our planet. They are the largest ecosystem on Earth, containing 97% of the planet's water and are its main life support. They correspond to about 2/3 of its surface and include all marine water (1; 2; 3). For geographical and historical reasons, we consider the existence of 5 oceans: Atlantic, Artic, Indian, Pacific and Antarctic, but in reality they are all interconnected, so there is only one global ocean, a single large body of water that surrounds all the land masses. It is interesting to note that the reality does justice to the origin of the word ocean, from both the Greek *okeanos*, and the Latin *oceanus*, the name of a river that surrounded all the known lands at that time (4). Humans occupy only about 1/3 of the planet, i.e. the continents and some islands, but we all recognize the influence of oceans in the history of human civilization, over the centuries. Universal history shows that many peoples increased prestige, power and supremacy through their connection to the sea, the use of its resources and intense maritime trade. Marine sciences deal with the study of the oceans, their structure and functioning, encompassing physical, chemical, geological and biological aspects, as well as the ocean-atmosphere interaction. In general terms, all these areas of study carry out basic and applied research, which allow advancing knowledge of the physical, chemical, geological and biological processes of the oceans and coastal regions, including their interactions with the terrestrial, hydrological and atmospheric systems (5). We can imagine the magnitude of this task, which requires high levels of cooperation, both national and internationally. It is a multidisciplinary area that deals with a high level of scientific and technological knowledge and seeks to find sustainable uses and also new applications to the marine resources. Combining fundamental and applied research on the oceans is considered the most promising strategy to improve the quality of human life not only in terms of pharmaceuticals, but also in food, biomaterials and energy (3; 5; 6).

II. OCEANS, GLOBAL WEATHER AND CLIMATE SYSTEMS

Reality points to climate changes on our planet (7). The marine environment is under threat due to all types of human actions that generate pollution, such as all sorts of industrial processes, maritime oil exploration, maritime transport, maritime tourism, agricultural wastes from nutrient leaching, etc. All these has global impacts and are the result of technological developments, but also of policies that were not always adjusted to local realities (8; 9).

Although not yet sufficiently studied, we already know that the oceans play an important regulatory role on our planet's global climate. The existence of a large volume of surface water and its thermal capacity make it work as an effective buffer against any variation in the climate system. One of the consequences of the increase in the concentration of atmospheric CO_2 is the imbalance of the so-called greenhouse effect, leading to an increase in the temperature of the planet and to climate change. The fixation of CO_2 through the photosynthesis of marine autotrophic organisms, such as planktonic algae, and its dissolution through the superficial movements of water masses, confer great efficiency to the ocean in the sequestration of atmospheric CO_2, contributing with at least 50% of Earth's oxygen (6; 8).

The increase in the average temperature of the planet can have several effects on the oceans: i) the acidification of the waters leads to a reduction in the capacity to absorb and retain CO_2, with negative impacts on marine ecosystems and aquaculture; ii) the melting of ice and the consequent increase in the volume and mass of water, leads to a rise in the average level of the oceans; iii) the change in the wind and rainfall regime with the consequent modification in ocean currents can cause extreme phenomena, such as cyclones, hurricanes and deviations in the monsoon regime and even the triggering of a new ice age in the northern hemisphere. Some of these aspects have led to local interventions, the so-called mitigation tactic, such as algae culture, also called seaweed farming, for environmental reasons to reduce local waters pollution and acidification and to increase CO_2 absorption (10; 11; 12).

III. MARINE ECOSYSTEMS

Marine ecosystems are under the influence of the oceans and differ greatly from other ecosystems on our planet. They include very diverse habitats with complex, competitive and aggressive environmental conditions, from coastal zones to remote and deep areas in open sea, which cover, for instance, rocky coasts, sandy beaches, swamps, mangroves, reefs, hydrothermal vents, polar and abyssal regions. These differences lead to the emergence of a huge biological diversity to which periodic daily changes in physical and chemical conditions can be added. In some coastal areas, the tidal effect as well as salinity variations, temperature, light availability and oxygen levels. Deep areas have more constant conditions, like the pressure, that increases with depth, and the absence of light, which limit the autotrophic life forms (7; 13; 14).

Despite these variables, some ecosystems are very productive, especially estuaries, mangroves and coral reefs. As a whole, marine habitats have more than 80% of plant and animal species of our planet. About 36 animal phyla are known and 34 of them exist in the marine environment, 15 of which are exclusive to this type of environment (3; 13; 15). It is estimated that this enormous biodiversity includes more than a million different species of animals, such as corals, sponges, mollusks, echinoderms, jellyfish, tunicates, bryozoans, fish and marine mammals and more than a billion species of microorganisms, including viruses, bacteria, cyanobacteria, protozoa, fungi and microalgae and also the macroalgae, which include thousands of species of seaweed belonging to three phyla, Chlorophyta, Rhodophyta and Phaeophyta (1; 3; 13; 15; 16). All these marine organisms survive because they developed special mechanisms of adaptation, including symbiotic interactions that may involve unique biochemical pathways leading to the synthesis of secondary metabolites, many of them unknown in terrestrial organisms. The vast majority of natural products are secondary metabolites of different chemical groups, usually with a low molecular weight, resulting from essential metabolic pathways. They do not interfere in basic survival functions, but in biotic and abiotic relationships, i.e., with other living beings and with the environment, performing the most varied functions, among others: communication between species, defense against competitors and predators, pheromones and also as reserve compounds.

IV. MARINE BIODIVERSITY

When we talk about the use of marine resources, we immediately think on activities, related to human food, mainly fishing and aquaculture, the latter with a greater increase in recent times, although humans have a long tradition on marine organism’s culture, already practiced by the Egyptians, since 2000 BC (3). Aquaculture deals with the exploitation or breeding, under controlled conditions, of aquatic organisms, not only fish, but also for example, crustaceans, bivalves and algae. There are other practices with a high impact on the world economy, such as maritime transports, the oil and natural gas exploration and all kinds of activities involving tourism and leisure. Until recently, a number of other activities have gone unnoticed, but due to various circumstances, they have been brought to the fore in more recent times. These include the exploitation of all types of biological resources, i.e. of marine biodiversity as a whole.

Despite great progress in drug synthesis and design, natural products remain a major resource for the pharmaceutical industry (16). Terrestrial sources, mainly angiosperm plants, have been their main font. The development of pharmacological resistance to traditional therapies and the difficulties in treating new diseases have forced the search and development of new drugs (17; 18). This horizon was greatly expanded with the search for biologically active compounds derived from marine organisms. In fact, in recent years, untapped marine resources have been considered the greatest source to meet the needs, not only of drug candidates, but also of food, cosmetics, biomaterials and energy (1; 3; 18).

The drug discovery process in marine natural products is not very different from the processes used in other natural products, or in synthesis compounds. In a first phase, research focuses on identifying molecules with certain biological effects. Then, and already in the pre-clinical tests, its focus is the optimization of the pharmacokinetic and pharmacodynamic properties tested in animals. In a third and final phase, clinical trials focus on the study of their efficacy and safety in humans (13; 19; 20; 21; 22; 23).

The study of marine organisms began in the middle of the 20th century with the isolation of two nucleosides, spongouridine and spongothymidine, in a Caribbean sponge, *Tethya crypta* (syn. *Cryptotethya crypta*) (1; 3; 22; 23). Later, these compounds allowed the development of two drugs, Ara-C (cytarabine, an agent that fights leukemia) and Ara-A (vidarabine, an antiviral agent) (19; 22; 23; 24). In the 1950s and 1960s, a screening program for materials from land plants and from marine organisms was launched, carried out by the Cooperative Drug Discovery Program, of the National Cancer Institute of the United States of America. Following these works, it was noticed that some extracts of marine organisms had more antitumor activity than those of terrestrial origin. These actions were a stimulus for cooperation between academia and pharmaceutical companies. In the 1960s, the development of the cephalosporin class of antibiotics took place, starting from cephalosporin C, isolated some years before, in cultures of *Acremonium chrysogenum* (syn. *Cephalosporium acremonium*), a fungus from the Mediterranean waters of Sardinia. However, it was the discovery of large amounts of prostaglandins from the octocoral *Plexaura homomalla*, in 1978, that sparked investment by the pharmaceutical industry. Since then, research on marine natural products has led to the isolation and identification of numerous compounds, belonging to different chemical groups, such as alkaloids, lactones, phenols, quinones, xanthones, tannins, terpenes, saponins, fatty acids, glycosides, polyketides and peptides, among others (2; 13; 14; 23). All these classes of compounds have different biological activities such as: cytotoxic, antiviral, antibacterial, anti-tuberculosis, antifungal, antioxidant, anti-inflammatory, analgesic, antidiabetic, immunomodulatory and anticoagulant (1; 3; 21). Cytotoxic compounds accounted for more than half of new products of marine origin discovered until now, followed by compounds with antibacterial activity. The largest group of isolated bioactive compounds are the peptides (1; 3; 21). Among the marine-derived drugs approved by the Food and Drug Administration and the European Medicines Agency are ten cytotoxic drugs, one antiviral and one analgesic (25). Marine invertebrates are about 60% of all marine animals, presenting themselves as the main source of natural products from this environment. About 47.1% come from sponges (Phylum Porifera), 33.5% from corals and jellyfish (Phylum Cnidaria) and 7.4% from echinoderms (Phylum *Echinodermata*), 6.0% from tunicates (Phylum Chordata) and 5,0% from mollusks (Phylum Mollusca) respectively (8). Although isolated from marine invertebrates, many of the bioactive compounds with high pharmacological interest are produced by microorganisms associated in symbiosis with other species (13; 26; 27; 28; 29). Through the culture of microorganisms, fermentation processes and even their possible genetic recombination, we can obtain marine natural products for biosynthetic production in sufficient amounts to be able to carry out all clinical trials and eventual future drug production (30). Contrary to what happens with the collection of invertebrates, the isolation of these compounds in microorganisms has no impact on marine environment. In this way, microorganisms are promoters for industrial processes, which presents an important challenge for the sustainable production of marine origin compounds (26; 30; 31).

Likewise, in addition to all the marine organisms mentioned above, micro and macroalgae are also the subject of interest and research. Nowadays the potential of algae extends into the most diverse areas, from intervening in water decontamination (32), improving water retention and consistency of sandy soils, or be applied in antifouling and anticorrosive coatings for ships (33). Marine organisms, including red macroalgae synthesize these active compounds as a means of chemical defense to prevent fouling on their own surfaces (34). Algae do the synthesis of other high-value chemicals, such as biofuels, degradable bioplastics, and of course bioactive compounds applied to health, cosmetics and food (1; 3). The cosmetic industry has a new class of products, the cosmeceuticals. They are a combination of cosmetics and pharmaceuticals, where bioactive compounds are added to traditional creams, lotions and ointments with the aim of preventing and treating (6; 27; 35). The cosmetic industry is increasingly focused on the search for new molecules and therefore the use of marine natural products is not surprising (6). Microalgae are the source of some of today's most innovative skin care products. Some have excellent moisturizing and antioxidant properties that enhance cell regeneration and the protection of skin homeostasis, also playing an important role as carriers of the bioactive compounds. Marine carbohydrates are biopolymers known since classical antiquity. Sulfated polysaccharides, such as agar, carrageenan, fucoidin and alginates, isolated from marine macroalgae and some marine invertebrates, provide a good source of antioxidants and anti-aging molecules, used in the cosmeceutical industry and in plastic surgery (27; 35; 36; 37).

In some areas of the world, the aquaculture of both macro and microalgae have become an important practice, providing work, food benefits for humans and animals, due to its excellent nutritional characteristics, working as food supplements, promoting the maintenance of health. The addition of microalgae to food formulations allows the enrichment of their carbohydrates, proteins, fatty acids, vitamins and minerals content (38; 39; 40; 41). Some species of microalgae can also be a source of some antioxidant pigments from the carotenoid group, such as beta-carotene, lutein, zeaxanthin, fucoxanthin or astaxanthin. These pigments can be extracted for commercialization in their pure form, or added to nutraceutical and cosmetic formulations, creating considerable added value (42).

The consumption of products of marine origin, fish, mollusks and algae is part of the eating habits of many populations, and even a cultural tradition. They are foods rich in many bioactive chemical groups, proteins and polysaccharides, among others. In addition to these, other marine organisms are also used in the production of various functional foods, dietary supplements and nutraceuticals products, which are important in the daily diet of humans, preventing disease. In addition to source of health and well-being, they also have antioxidant, gelling, preservative and emulsifying properties (41; 43; 44).

V. MARINE NATURAL PRODUCTS TODAY

Extending the research of marine biodiversity to deep sea environments, without being limited to organisms that can only be collected in coastal areas or by freediving, raises huge problems and can be a controversial issue for environmental reasons. New approaches have become necessary in the way of exploiting all the oceans resources. Advances in diving methods and in equipment for collection in deeper areas, such as manned submersibles or remotely operated vehicles, were achieved and allowed the exploration of underwater environments and access to previously unreachable organisms. Even so this type of access is limited as it has a very high cost, but on the other hand it also avoids environmental damages and encourages cooperation between institutions. At the same time, other technological developments took place, more specific and improved, in the isolation of compounds, which allowed the determination of their structure and identification, from small amounts of samples. Even other developments such as the use of molecular biotechnology and genome sequencing, all contributed to the use of marine natural products on a larger scale (13; 15; 17; 18) and also the implementation of synthesis methods make it possible to resort to genetically modified microorganisms for the production of substances with complex structures (1; 6; 19; 45). The structural elucidation of chemical compounds allows expanding the knowledge about their pharmacological actions and the clarification regarding their therapeutic targets also leads to the synthesis of new drugs. Chemical synthesis continues to be the industry's resource of choice to obtain the amount of material necessary to meet the needs of the market and the guarantor of its independence from the vulnerability of biological resources (1).

All this gave rise to the so-called blue economy, an economy based on the knowledge and technical development, which enables the sustainable use of ocean resources for human well-being and social equity. This is a long-term strategy aimed at supporting sustainable economic growth through ocean-related sectors and activities, like fisheries, aquaculture, tourism, energy and marine biotechnology (46). Biotechnology allows the use of some types of biological agents (organisms, cells, organelles, molecules) to obtain goods or ensure services, like the development of genetically modified organisms, to allow a set of knowledge that increase world food production and drug development (47). Marine biotechnology seeks molecules with a huge economic potential, in addition to promoting the development of the following technologies: i) biological technology to identify ecological stress points in the environment (e.g. molecular probes of harmful algal blooms to predict potential health risks); ii) molecular technology for identifying populations and emerging diseases, with a view to protecting fisheries and other biological resources (e.g. fish DNA mapping); iii) molecular technology for rapid diagnostic tests, which guarantee the safety of food resources, from aquaculture (e.g. application of PCR reactions to identify, in a single test and simultaneously, several pathogenic microbes). The good results in some of those areas, accelerated the integration of the concept in national and international maritime strategies (48; 49).

The potential of marine organisms can be used as a direct source of new compounds or as suppliers of model molecules, whose structures can be modified to obtain new compounds by chemical synthesis, or to enhance their mechanism of synergy (23; 50) Marine natural products are very attractive target molecules, as they act at low concentrations, are very selective against some malignant cells and develop low resistance (50). But marine molecules still have some disadvantages, for example, very high experimental cost, low yield in isolation processes, some structural complexity and consequent difficulty in its synthesis and limited therapeutic use, due to its high toxicity (51; 1; 3). Some of these difficulties have been overcome, with new molecular biology tools, using genetically modified bacteria for the production of substances with complex structures, advances in structural analysis techniques, and the correct use of aquaculture.

Despite the high number of new compounds with recognized biological activity, so far, few have been marketed as drugs.

Its approval for therapeutic use, only happens after many years of research. The whole process of research and development of new drugs is not easy, nor is success guaranteed from the outset, because statistically, out of every 5000 substances that enter the pre-clinical testing phase, only 5 go on to clinical studies and only one molecule results in medicine (52).

If the structural complexity of most marine natural products makes it difficult to produce new financially profitable drugs, the solution is to invest in understanding their mechanisms of action, determine the pharmacological group and try to create simpler molecules, with comparable therapeutic activity and with fewer side effects. This process, called structural simplification or function-oriented synthesis, is already in practice. The strategy involves the conjugation of small molecules-drug or their encapsulation in nanoparticles (13; 53). With the advances in molecular synthesis and modeling techniques, the tendency is for the original structure of natural products to be the basis for the development of new drugs, and not for them to be the active principle with therapeutic action (1). Currently, the interest does not come from the direct use of bio-resources, but from the isolation of bioactive compounds for subsequent synthesis and industrial production (13; 53).

In recent years there has been a very significant increase in the number of patents worldwide in the field of marine biotechnology. If we look at these patents, we see that in most, microorganisms stand out, meaning bacteria, cyanobacteria and microalgae but also macroalgae. When we use "marine products" as a keyword, among the institutions holding the largest number of patents, the highest number, in descending order, are pharmaceutical, chemical, fuel and food industries (54; 55).

Natural products arouse curiosity in consumers and appeal to their consumption, especially in the areas of cosmetics and nutrition. Regarding the use of marine natural products there might be some constraints as mentioned in the report Blue Growth Scenarios and drivers for Sustainable Growth from the Oceans, Seas and Coasts carried out in 2012 for DG MARE (Directorate-General for Maritime Affairs and Fisheries) of the European Union. An example is the use of some of these products as food ingredients, as only a very small number of species are approved by the European Union, but their application is being studied in various consumer products (56)

There are several other benefits of blue economy, like the contribution to the preservation of marine environment and natural resources. Unfortunately, the oceans might be polluted by human activities, spills from shipping and industrial runoff. There are biological methods to prevent, reduce and combat some of these actions. They include the addition of microbes, nutrients or oxygen to stimulate bacterial growth and thus, through microbial action, manage to reduce pollution and its effects (57).

The transformation of all types of by-products, namely of the fishing industry is being implemented and associated with sustainable production processes, reducing chemical product recycling costs and greenhouse gas emissions. From fish wastes high-value proteins can be extracted reducing the uncontrolled use of resources (58; 59). Fish viscera and skin are recognized to be an important source of proteins as well as a source of antimicrobial compounds that contribute to provide a first barrier against pathogens' attack (59; 60).

Many natural compounds of marine origin have been tested and recognized for their antimicrobial activity, for their potential against multidrug-resistant bacterial infections and also for their antiviral activity (61), including against the SARS-CoV-2, through the use of a depsipeptide, isolated from the tunicate *Aplidium albicans* (62; 63; 64).

By the way, many experimental and diagnostic tools, nowadays very common and routine in applied research and development laboratories, are originated from marine organisms. In recent years we all heard about PCR (polymerase chain reaction), used in some Covid tests, but very few will know that the Taq polymerase enzyme, irreplaceable for PCR, was first isolated from the bacterium *Thermus aquaticus*, in hot springs. Other enzymes from hot springs and marine environments have been reported, such as Pfu, an enzyme from a marine thermophile, *Pyrococcus furiosus*, is now also used in PCR (6).

Under fluorescence microscopy the use of fluorophores allows the chemical localization of cellular components. GFP (green fluorescent protein) is used as a biomarker for labeling cell structures *in vitro* and *in vivo*, for instance the INCENP, i.e., inner centromere protein. It was isolated from the jellyfish *Aequorea Victoria*, whose discovery was awarded the Nobel Prize in Chemistry in 2008. There are other fluorescent proteins that have been isolated from marine organisms with unique characteristics for emitting light in the infrared region and with applications in several areas of biology (59; 65).

Accurate and rapid detection of pathogens is critical to implement preventive measures. Classified as a lipoglycan, lipopolysaccharides (LPS) are small amphiphilic molecules that are associated with Gram-negative bacteria. LAL, Limulus-Amoebocyte-Lysate, derived from the crab *Limulus polyphemus*, is used in the form of the LAL test for the sensitive detection of LPS from Gram-negative bacteria. The European Pharmacopoeia prescribes the LAL test to verify the absence of LPS in samples (6).

VI. CONCLUSIONS

The marine environment has great biological and chemical diversity and therefore has become an important option for prospecting resources that are known to have enormous potential, not only for therapeutic uses, but also as food, cosmetics, biomaterials and energy. From the cooperation between industry and academia, new scientific developments have emerged that have provided a solid foundation for the management of marine resources. The future of their exploitation involves the use of biotechnological strategies. For instance, the culture of different organisms combined with genetic engineering, will overcome the problems of harvesting and the lack of raw materials necessary for research and development of new products.

This gave rise to the so-called blue economy, an economy based on knowledge and technical development, which enables the sustainable use of ocean resources for human well-being and social equity. It should be borne in mind that results in this area are obtained in the medium and long term and public opinion must be involved throughout the process.

Authors Contribution

MM, PS and TG did the bibliographic search and GT developed the concept and wrote all sections.

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Conflicts of Interest

All the authors have no conflicts of interest to declare.

REFERENCES

1. Costa-Lotufo, L., Wilke, D., Jimenez, P., Epifanio, R. 2009. Marine organisms as a source of new pharmaceuticals: History and perspectives. Quimica Nova, 32:703-16.
2. Newman, D., Cragg, G. 2016. Drugs and Drug Candidates from Marine Sources: An Assessment of the Current “state of Play. Planta Medica, 82: 775-89. Doi:10.1055/s-0042-101353
3. Lindequist, U. 2016. Marine-derived pharmaceuticals - challenges and opportunities. Biomolecules & Therapeutics, 24: 561-71
4. https://ciberduvidas.iscte-iul.pt/artigos/rubricas/idioma/oceano/4951
5. https://comum.rcaap.pt/bitstream/10400.26/13007/1/Couceiro%2c%20T%c3%a2nia%20Alexandra%20Candeias.pdf
6. Jaspars, M., De Pascale, D., Andersen, J., Reyes, F., Crawford, A., Ianora, A. 2016. The marine biodiscovery pipeline and ocean medicines of tomorrow. *Journal of the Marine* Biological *Association UK,* 96: 151-8.
7. Cavicchioli, R., Ripple, W., Timmis, K. 2019. Scientists’ warning to humanity: microorganisms and climate change. *Nature Reviews Microbiology*, 17: 569–586. https://doi.org/10.1038/s41579-019-0222-5
8. https://unstats.un.org/sdgs/report/2021/The-Sustainable-Development-Goals-Report-2021.pdf
9. https://unstats.un.org/sdgs/report/2022/The-Sustainable-Development-Goals-Report-2022.pdf
10. https://oceanservice.noaa.gov/facts/ocean-oxygen.html
11. Special Report on the Ocean and Cryosphere in a Changing Climate. 2019. https://doi.org/10.1017/9781009157964.001
12. http://oxfordre.com/environmentalscience/view/10.1093/acrefore/9780199389414.001. 0001/acrefore-9780199389414-e-12
13. Cappello, E. and Nieri, P. 2021. From Life in the Sea to the Clinic: The Marine Drugs Approved and under Clinical Trial, Life, 11:1–19. https://doi.org/10.3390/life11121390
14. Altmann, K. 2017. Drugs from the oceans: Marine natural products as leads for drug discovery. Chimia 71: 646–651. https://doi.org/10.2533/chimia.2017.646
15. Donia, M. and Hamann, M. 2003. Marine natural products and their potential applications as anti-infective agents. Lancet Infectious Diseases, 3: 338-348.
16. Felício, R., Oliveira, A., Debonsi, H. 2012. Bioprospecção a partir dos oceanos: conectando a descoberta de novos fármacos aos produtos naturais marinhos. Ciência e Cultura, 64: 39-42.
17. Newman, D., Cragg, G. 2012. Natural products as sources of new drugs over the 30 years from 1981 to 2010. Journal of Natural Products, 75: 311-335.
18. Cragg, G., Newman, D. 2013. Natural products: A continuing source of novel drug leads. *Biochimica et Biophysica Acta - General Subjects*, 1830: 3670–3695 https://doi.org/10.1016/j.bbagen.2013.02.008
19. Glaser, K., Mayer, A. 2009. A renaissance in marine pharmacology: From preclinical curiosity to clinical reality. Biochemical Pharmacology, 78: 440-448.
20. Rangel, M., Falkenberg, M. 2015. An overview of the marine natural products in clinical trials and on the market. Journal of *Coastal Life* Medicine, 3: 421-428.
21. Ghareeb, M., Tammam, M., El-Demerdash, A., Atanasov, A. 2020. Insights about clinically approved and preclinically investigated marine natural products. *Current Research* in *Biotechnology*, 2: 88-102. https://doi.org/10.1016/j.crbiot.2020.09.001
22. 22. Lu, Y., Li, H., Li, Q., Wu, Y. 2021. Application of marine natural products in drug research. *Bioorganic & Medicinal Chemistry*, 35: 1-30. DOI: 10.1016/j.bmc.2021.116058
23. 23. Murti, Y., Agrawal, T. 2010. Marine derived pharmaceuticals- development of natural health products from marine biodiversity. *International*

Journal of *Chemical Technology Research*, 2: 2198-2217.

24. 24. Jimenez, P., Wilke, D., Costa-Lotufo, L. 2018. Marine drugs for cancer: surfacing biotechnological innovations from the oceans. Clinics, 73: 1-7.
25. 25. Marine Pharmacology. Clinical Pipeline: Approved Marine Drugs. 2021 https://www.marinepharmacology.org/approved
26. Gerwick, W., Fenner, A. 2013. Drug discovery from marine microbes. Microbial Ecology, 65: 800-806.
27. Martins, A., Vieira, H., Gaspar, H., Santos, S. 2014. Marketed marine natural products in the pharmaceutical and cosmeceutical industries: tips for success. Mar Drugs, 12: 1066-1101.
28. Kim, S., Wijesekara, I. 2010. Development and biological activities of marine-derived bioactive peptides: A review. Journal of Functional Foods, 2:1-9.
29. Kiuru, P., D'Auria, M., Muller, C., Tammela, P., Vuorela, H., Yli-Kauhaluoma, J. 2014. Exploring marine resources for bioactive compounds. *Planta Medica*, 80: 1234-1246. https://doi.org/10.1055/s-0034-1383001
30. Javed, F., Qadir, M., Janbaz, K., Ali, M. 2011. Novel drugs from marine microorganisms. Critical Reviews in Microbiology, 37: 245-249. https://doi.org/10.3109/1040841X.2011.576234
31. Núñez-Montero, K. and Barrientos, L. 2018. Advances in antarctic research for antimicrobial discovery: A comprehensive narrative review of bacteria from antarctic environments as potential sources of novel antibiotic compounds against human pathogens and microorganisms of industrial importance. Antibiotics 7. https://doi.org/10.3390/antibiotics7040090
32. https://oceanographicmagazine.com/features/cleaning-rivers/
33. Jessica, G-B. 2022. Marine Natural Products: A Promising Source of Environmentally Friendly Antifouling Agents for the Maritime Industries. Frontiers in Marine Science. https://doi.org/10.3389/fmars.2022.858757
34. Dahms, H., Dobretsov, S. 2017. Antifouling compounds from marine macroalgae. Marine Drugs 15, 1-16. https://doi.org/10.3390/md15090265
35. Corinaldesi, C., Barone, G., Marcellini, F., Dell´Anno, A., Danovaro, R. 2017. Marine microbial-derived molecules and their potential use in cosmeceutical and cosmetic products. Marine Drugs. 5: 1-21. DOI:10.3390/md15040118
36. Lin, S-K. 2013. Marine Nutraceuticals: Prospects and Perspectives. Marine Drugs, 11:1300–1303. https://doi.org/10.3390/md11041300
37. Suleria, H., Osborne, S., Masci, P., Gobe, G. 2015. Marine-based nutraceuticals: An innovative trend in the food and supplement industries. Marine Drugs, 13: 6336–6351. https://doi.org/10.3390/md13106336
38. Ruocco, N., Costantini, S., Guariniello, S., Costantini, M. 2016. Polysaccharides from the marine environment with pharmacological, cosmeceutical and nutraceutical potential. Molecules, 21: 1-16.
39. Ahmed, A., Adel, M., Karimi, P., Peidayesh, M. 2014. Pharmaceutical, Cosmeceutical and Traditional Applications of Marine Carbohydrates. Fundamentals and Applications. Advances in Food and Nutrition Research, 73: 197-220. https://doi.org/10.1016/B978-0-12-800268-.00010-X.
40. Alves, A., Sousa, E., Kijjoa, A., Pinto, M. 2020. Marine-derived compounds with potential use as cosmeceuticals and nutricosmetics. Molecules. 25: 2536. https://doi.org/10.3390/molecules 25112536
41. https://www.fao.org/3/x5822e/x5822e03.htm
42. Sirohi, P., Verma, H., Singh, S., Singh, V., Pandey, J., Khusharia, S., Kumar, D., Teotia, P., Kumar, A. 2022. Microalgal Carotenoids: Therapeutic Application and Latest Approaches to Enhance the Production. Current Issues in Molecular Biology, 44: 6257-6279. https://doi.org/10.3390 /cimb44120427
43. Tahergorabi, R., Matak, K., Jaczynski, J. 2014. Fish protein isolate: Development of functional foods with nutraceutical ingredients. Journal of Functional Foods, 18: 1-11.
44. Ananey-Obiri, D., Tahergorabi, R. 2018. Development and Characterization of Fish-Based Superfoods. Current Topics on Superfoods. http://dx.doi.org/10.5772/intechopen.73588
45. Mayer, A., Glaser, K., Cuevas, C. 2010. The odyssey of marine pharmaceuticals: a current pipeline perspective. Trends in Pharmacological Sciences, 31: 255-65.
46. https://unric.org/en/blue-economy-oceans-as-the-next-great-economic-frontier/
47. Biotechnology IUPAC Goldbook. 2014. doi:10.1351/goldbook.B00666.
48. Freitas, A. C., Rodrigues, D., Rocha-Santos, T., Gomes, A., Duarte, A. 2012. Marine biotechnology advances towards applications in new functional foods. Biotechnology Advances, 30: 1506-1515.
49. Daniotti, S., Re, I. 2021. Marine biotechnology: challenges and development market trends for the enhancement of biotic resources in industrial pharmaceutical and food applications. A statistical analysis of scientific literature and business models. Marine Drugs, 19: 61. http://dx.doi.org/10.3390/md19020061
50. Vinothkumar, S., Parameswaran, P. 2013. Recent advances in marine drug research. Biotechnology Advances, 31: 1826-1845.

51. Haefner, B. 2003. Drugs from the deep: marine natural products as drug candidates. Drug Discovery Today, 8: 536-544.
52. Akhondzadeh S. 2016. The Importance of Clinical Trials in Drug Development. Avicenna Journal Medical Biotechnology, 8:151. PMID: 27920881; PMCID: PMC5124250.
53. Wang, E., Sorolla, M., Krishnan, P., Sorolla, A. 2020. From seabed to bedside: A review on promising marine anticancer compounds. Biomolecules, 10: 248. http://dx.doi.org/doi:10.3390/biom10020248
54. Shinde P, Banerjee P, Mandhare A. 2019. Marine natural products as source of new drugs: a patent review (2015-2018). Expert Opin Ther Pat. 2019 Apr; 29: 283-309. https://doi.org/10.1080/13543776.2019.1598972
55. Banerjee P, Mandhare A, Bagalkote V. 2022. Marine natural products as source of new drugs: an updated patent review (July 2018-July 2021). Expert Opinion on Therapeutic Patents. 2022 Mar;32(3):317-363. https://doi.org/10.1080/13543776.2022.2012150
56. DG. Blue Growth - scenarios and drivers for sustainable growth from the oceans, seas and coasts. Final Report. Eur Comm [Internet]. 2012; (August):126.
57. Azubuike, C., Chikere, C., Okpokwasili, G. 2016. Bioremediation techniques - classification based on site of application: principles, advantages, limitations and prospects. World Journal of Microbiology and Biotechnology, 32: 180. https://doi.org/10.1007/s11274-016-2137-x
58. Caruso, G., Floris, R., Serangeli, C., Di Paola, L. 2020. Fishery Wastes as a Yet Undiscovered Treasure from the Sea: Biomolecules Sources, Extraction Methods and Valorization. Marine Drugs. 18: 622. https://doi.org/10.3390/md18120622
59. https://www.researchgate.net/profile/Jean-Pascal-Berge/publication/262808270_Adding_value_to_fish_processing_by-products/links/02e7e538ecacd000cf000000/Adding-value-to-fish-processing-by-products.pdf
60. Dash, S., Das, S., Samal, J., Thatoi, H. 2018. Epidermal mucus, a major determinant in fish health: A review. Iranian Journal of *Veterinary Research*, 19: 72-81.
61. Yasir, M. 2018. Analysis of bacterial communities and characterization of antimicrobial strains from cave microbiota. Brazilian Journal of Microbiology, 49: 248–257. doi:10.1016/j.bjm.2017.08.005
62. Taglialatela-Scafati, O. 2021. New hopes for drugs against COVID-19 come from the sea. Marine Drugs, 19: 104. https://doi.org/10.3390/md19020104
63. PharmaMar 2021. Molecular Pharmacodynamics. https://pharmamar.com/molecular-pharmacodynamics/?lang=en
64. Martinez, M. 2021. Plitidepsin: a repurposed drug for the treatment of COVID-19. Antimicrobial Agents Chemotherapy, 65: e00200-21. https://doi.org/10.1128/AAC.00200-21
65. Burgess, J. 2012. New and emerging analytical techniques for marine biotechnology. Current Opinion in Biotechnology, 23: 29-33. https://doi.org/10.1016/j.copbio.2011.12.007.