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REVIEW

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Marine microbial bioprospecting: Exploitation of marine biodiversity towards biotechnological applications—a review

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Abstract

The increase in the human population causes an increase in the demand for nutritional supplies and energy resources. Thus, the novel, natural, and renewable resources became of great interest. Here comes the optimistic role of bioprospecting as a promising tool to isolate novel and interesting molecules and microorganisms from the marine environment as alternatives to the existing resources. Bioprospecting of marine metabolites and microorganisms with high biotechnological potentials has gained wide interest due to the variability and richness of the marine environment. Indeed, the existence of extreme conditions that increases the adaptability of marine organisms, especially planktons, allow the presence of interesting biological species that are able to produce novel compounds with multiple health benefits and high economical value. This review aims to provide a comprehensive overview of marine microbial bioprospecting as a growing field of interest. It emphasizes functional bioprospecting that facilitates the discovery of interesting metabolites. Marine bioprospecting was also discussed from a legal aspect for the first time, focusing on the shortcomings of international law. We also summarized the challenges facing bioprospecting in the marine environment including economic feasibility issues.

KEYWORDS

biodiversity, bioprospecting, biotechnology, functional bioprospecting, marine environment, metabolites

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Abbreviations: ABNJ, Areas Beyond National Jurisdiction; eDNA, environmental DNA; FACS, fluorescence-activated cell sorting; GS, gas chromatography; HPLC, high performance liquid chromatography; MS, mass spectroscopy (i.e. HPLC and GC); NGS, next-generation sequencing; NMR, nuclear magnetic resonance; SAR11, name of tiny micro-organism first found in the Sargasso Sea; UN-CBD, United Nations' Convention on Biological Diversity.

1 | INTRODUCTION

The increasing world's population is accompanied by an increase in income and global economy, followed by rising food, energy, and biological resources demand [1]. It is predicted that providing a sustainable source of food to meet the need of approximately 10 billion people will be a big challenge by 2050 [2]. Indeed, conventional agriculture will no longer be able to sustain the increasing population and food security will be a major world challenge [3]. Thus, food shortage is an expected outcome, which can result in malnutrition and cause the development of human diseases due to an unbalanced intake of nutrients [4]. Specifically, protein is one of the main nutritional compounds that will be lacking in the future, which necessitates pursuing alternatives to meet consumption requirements [5]. Consumers' preference for meat-based diets to acquire protein requirements has been a major risk facing sustainable protein production. Simply because when compared to plant-based diets, meat production requires much more water, energy, and land space [6].

Contributing to almost half of the global annual primary production, oceans are considered an important source of nutrition and a promising alternative for food security [7]. Oceans host huge ecological and biological diversity [3]. This variability allows the production of valuable biological compounds of benefit to mankind in nutrition, agriculture, remediation, and health [8].

This review focuses on marine microbial bioprospecting and functional bioprospecting as a tool for discovering interesting microorganisms and biological metabolites and providing new means of innovation. We also discuss the importance of marine biotechnology and the exploitation of its resources in providing an alternative source of pharmaceuticals, nutraceuticals, and bioenergy. Legal constraints regulating marine exploitation were discussed for the first time. Further, challenges facing the improvement of biotechnology were highlighted.

2 | BIODIVERSITY AND MARINE RESOURCES

Covering more than 70% of the earth, the marine environment is the most diversified ecosystem [9,10]. Microbial marine species account for over 95% of the total marine biomass [11]. They include viruses, bacteria, phytoplankton (photosynthetic planktons), and zooplankton (grazing planktons) present in the water column, sediments, or in associations. Since it encompasses an array of natural extreme environmental conditions (e.g., in polar regions, hydrothermal vents, etc.), and is continuously exposed to anthropogenic stressors [12], marine ecosystems have some of the most adaptive organisms tolerating extreme salinities, temperatures, and pressure [9]. Such adaptation capabilities drive a great amount of genetic and functional diversity [13], enabling the production of molecules that promote biotechnological applications. Marine microorganisms are receiving high attention in this aspect as they are believed to be a promising source of molecules that contribute to the development of pharmaceuticals, targeting health-threatening illnesses [8]. For instance, algal-driven products are of especially high interest as they provide some novel opportunities such as high-value lipids, pigments, and exopolysaccharides [14–18]. Furthermore, various marine bacterial and fungal species proved to produce a wide diversity of new compounds that have therapeutic potential working as antibiotics [19]. Marine yeast-derived biomolecules have also shown interesting properties for various potential applications including the production of biosurfactants [20].

2.1 | Marine microbial-derived molecules with high added-value

Marine organism-derived molecules are produced as secondary metabolites that either stay inside the organism or get secreted [21]. Such products are most commonly polypeptides, nonribosomal peptides (e.g., vancomycin or daptomycin, actinomycin D, and cyclosporine), small molecules (e.g., lipopolysaccharides, polyphenols, alkaloids, etc.) [22], polyketides [23], or nucleic acids [24]. Many studies were oriented towards identifying the nature of marine-derived metabolites, which were mostly classified either as toxins or bioactive molecules,[25,26] to predict their potential application. Currently, about 7000 marine microbial-based bioactive molecules are being validated and used [8]. However, even with the current findings, marine habitats are poorly investigated, where more than 90% of marine species are not described yet [27]. This is driving scientists to expand their interest in exploring new tools and methods that enable them to identify and characterize novel molecules and compounds from the marine environment. Table 1 represents some of the important marine molecules contributing to innovations in a variety of fields such as medicine, pharmacology, aquaculture, food/feed supplements, cosmetics, and energy.

3 | MARINE MICROBIAL BIOPROSPECTING

In definition, marine biotechnology refers to the development of products and services through using the bioresources of marine environments [43]. It provides

TABLE 1 Marine-based molecules providing innovations in different fields.

Field	Activity	Source	References
Medicine and pharmacology	Anti-inflammatory	Diatom *Cylindrotheca closterium*	[28]
	Anticancer	Diatom *Skeletonema marinoi*	[28]
		Microalga *Isochrysis galbana*	[29]
	antimicrobial, antioxidant, anti-inflammatory	Bacterium *Nocardiopsis dassonvillei*	[30]
Nutraceuticals	C fatty acids	*Nanochloris atomus*	[17]
	Phycocyanin	*Leptolyngbia*	[18]
Nutrition	Dietary protein supplement	Lobster by-products	[31]
	β-carotene, neoxanthin, violaxanthin, and lutein production	Microalga *Tetraselmis* sp.	[32]
	Fucoxanthin, β-carotene production	Microalga *Isochrysis galbana*	[29]
Agriculture	Nitrogen-fixing biofertilizers	Cyanobacterium *Nostoc* sp.	[33]
	Nitrogen fixing and nutrient enriching biofertilizers	Cyanobacterium *Azolla-Anabaena*	[34]
Biofuels	Lipid production	Diatom *Cyclotella cryptica*	[35]
	Lipid production	Diatom *Mayamaea* sp.	[36]
	Bioethanol production	Yeast *Saccharomyces cerevisiae*	[37]
Cosmetics	Exopolysaccharides production	Bacterium *Alteromonas macleodii*	[38]
	Fucoidan production	Brown alga *Saccharina japonica*	[39]
Industry	Enzymatic bioremediation	Archea *Desulfurococcus* sp., *Pyrococcus* sp., *Thermococcus* sp.	[40]
	Enzymatic production of bioplastics	Bacterium *Burkholderia sacchari*	[41]
	Xylanolytic activity	Fungus *Aspergillus* sp.	[42]

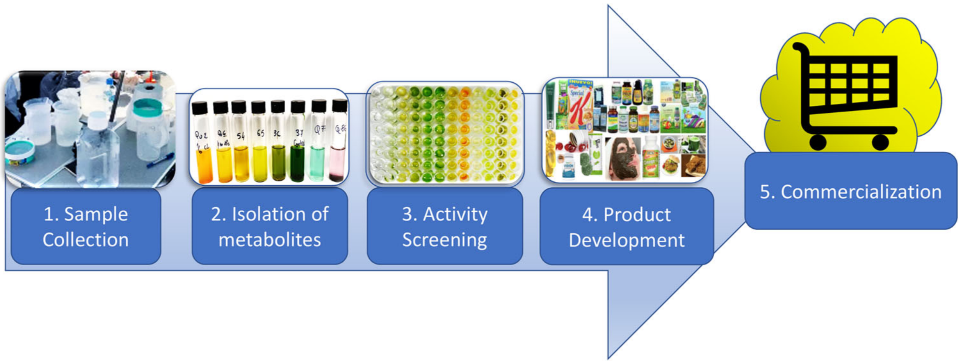

FIGURE 1 Phases of marine bioprospecting showcasing the different stages of how interesting microbial metabolites are investigated and then developed to reach the stage of commercialization of important products.

opportunities in discovering and developing chemical compounds, pharmaceuticals, nutraceuticals, enzymes, and bioactive molecules through bioprospecting [44]. Bioprospecting is an organized search of beneficial products derived from living organisms (e.g., plants, animals, microorganisms) to improve human life [45]. Since oceans are believed to have huge genetic diversity, marine bioprospecting has been receiving a lot of attention.

As summarized in Figure 1, marine bioprospecting is made of several phases including (a) sample collection and bioprospecting, (b) isolation of interesting metabolites,

(c) activity screening and product development, and (d) finally commercialization [46]. Even though these steps are applied to the bioprospecting of all organisms, planktonic communities seem to be mostly targeted in bioprospecting activity. Cyanobacteria, for instance, were documented to produce cyclopeptides which could be used in drugs to fight cancer [47]. Brown algae were also documented to produce fucoxanthin which was used as anticancer treatment [48] and antidiabetes medication [49]. In addition, red algae and diatoms were shown to produce domoic acid known for its anthelmintic activity [50]. Further, fungi were documented to produce cephalosporin P which exhibits antibacterial activity [51].

Plankton bioprospecting usually targets organisms living in extreme conditions to increase the chance of discovering interesting molecules whether as primary or secondary metabolites [52–54]. For instance, the polymerase chain reaction DNA polymerase (Taq polymerase) which is extensively used in molecular biology laboratories, was isolated from the thermotolerant bacterium *Thermus aquaticus* [55]. It also considers meroplanktons (organisms who live as planktons during one stage of their lives only, such as the larvae stage) a potential source of novel metabolites that are produced to defend them against predators [11]. For instance, it was documented that novel molecules used in defense mechanisms are produced by Antarctic sea star eggs [56], ascidian larvae [57,58], bryozoan larvae and *Luffariella variabilis* larvae [59], and *Polychaeta* [60] at the young stages of life only and not in their mature stages.

Planktons are targeted by bio-prospectors not only due to their ability to produce novel molecules but also due to their rapid biomass production [59]. Having a short replication time, planktons are providing an advantage of minimal energy requirements, lower cost of production, and faster production of the metabolite of interest [11].

3.1 | Microbial bioprospecting strategies

The traditional marine bioprospecting activities rely on cultural methodologies that include microscopy, selective media, Gram-staining, and biochemical identification [61]. Mainly, two strategies have been developed and used for the marine microbial bioprospecting such as (i) nutrient enrichment of the sample prior to culture then isolation, and (ii) isolation of single-cell followed by nutrient enrichment and culture. Generally, as summarised in Figure 2, bioprospecting starts with collecting the environmental sample, then enriching the sample with nutrients to enhance the growth of microbes, and finally comes the step of isolating the cultured microorganisms [62]. Such simple methodologies provide qualitative and quantitative data of high sensitivity and reliability on the microbial species [63]. Even though conventional culturing methods deliver valuable information, it is still highly limiting bioprospection

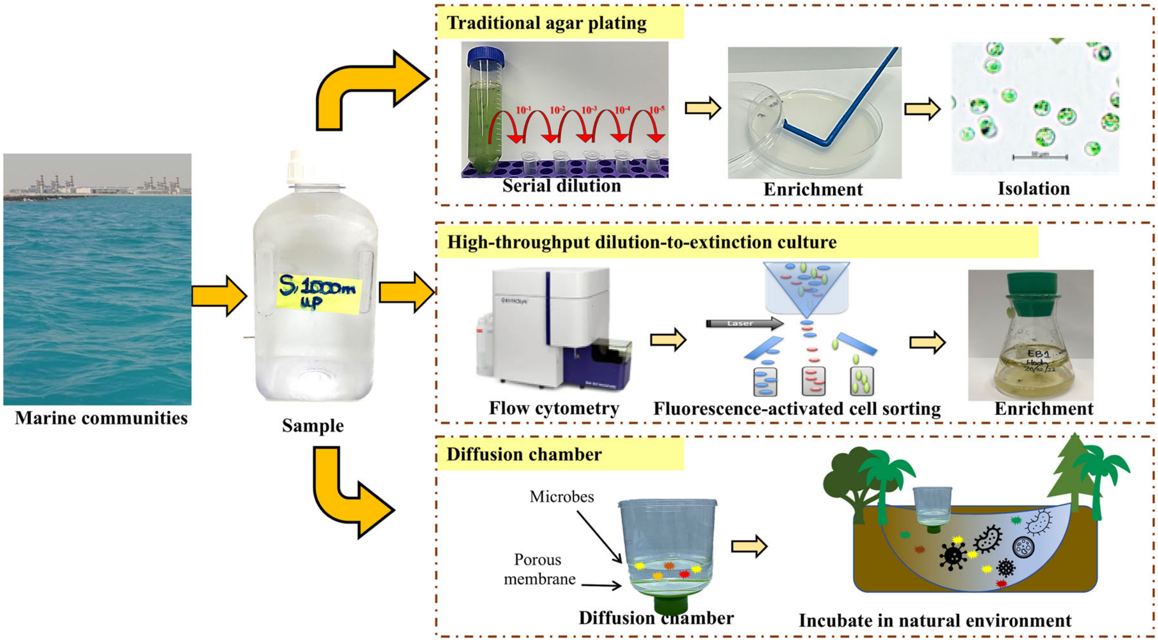

FIGURE 2 Microbial bioprospecting strategies. Traditional agar plating that starts with enriching the sample then isolation of microorganisms. High-throughput dilution-to-extinction culture where organisms are isolated then enriched. Diffusion chamber where microorganisms are incubated in their natural environment in a confined manner.

[61]. In fact, currently, only 0.1% of the seawater microbial species are cultivable in laboratories [64]. In other words, relying on conventional laboratory techniques results in missing out on more than 99% of the marine microbial species. The noncultivability of some microbial species may be due to the smaller microbial populations competing with the dominant microbial species, or inhibition of growth of fastidious microbes which are incapable of growing in vitro [65]. Overall conventional bioprospection can lead to an underestimation of microorganisms that are uncultivable, subdominant, or slow growing [66].

Based on this legacy, culture-dependent bioprospecting is continuously developing to overcome the shortcomings of traditional culturing and provide innovative culturing strategies [67]. Coupling basic biology and ecology with high-throughput cultivation techniques resulted in increasing the amount of culturable marine microbial species and led to the isolation of new microbial species such as the first representatives of SAR 11 clade [68]. Unlike the traditional isolation strategy, the single-cell isolation strategy starts with isolating the microorganism of interest and then enriching single cells to enhance their growth [69]. One of the most sensitive and effective techniques used to isolate marine microorganisms is high-throughput dilution-to-extinction culture [70]. This technique usually involves coupling flow cytometry with fluorescence-activated cell sorting (FACS) to increase productivity and reduce the cost of bioprospecting [71]. High-throughput dilution-to-extinction overcomes the time-consuming nature of traditional culturing, where it measures the fluorescence properties of thousands of cells in a second [72]. In this technique, samples are drained through the flow cell, and guided to sheath fluid such as culture medium or phosphate-buffered saline. Utilizing hydrodynamic focusing allow cells to pass one by one to receive the laser, then the scattering light will be detected and converted to an electric signal of a certain voltage. Thus, data will be generated for each cell individually. Then the coupled FACS work on the separation of the cells by vibrating the nozzle of the flow cell. The vibration causes the outflowing liquid to separate into small, charged droplets containing selected individual cells. As summarised in Figure 2, upon passing through the deflection plates, the droplets deflect and are collected into separate collection systems (e.g., microtiter plate, tubes) based on their charge [72].

Another technique that has been recently used to culture marine environmental microbial cells is the diffusion chamber (Figure 2). The principle of the diffusion chamber is to inoculate the environmental microbes in agar matrix inside of porous membranes [69]. Those chambers are incubated in the natural environment (e.g., the sea), allowing the nutrients and other essential growth factors to diffuse through the membranes reaching the inoculated trapped cells without introducing the outer microbial communities into the chamber [73].

3.2 | Culture-independent functional bioprospecting

Discovering novel products through bioprospecting usually happens by focusing on target species following a stepwise procedure. Since the discovery of potential market value for such molecules, companies are aiming to find novel approaches that make the process more time-efficient [74]. Therefore, there is a specific interest in bioinformatics as it accelerates the discovery of interesting molecules and strains by identifying the genetic coding [75]. Studying the genomic, metagenomic, or transcriptomic profiling of marine water samples through next-generation sequencing (NGS) offers an advanced methodology for discovering novel compounds [76]. Marine biotechnology has benefited from NGS and the development of sequencing projects, which resulted in advancing the omics approach including proteomics and metabolomics to understand the structure and function of novel molecules [77]. It also provides a prediction of the action of the discovered molecule on certain species or the surrounding environment [8]. After the identification of molecules of interest through omics, either the organism is isolated, or the gene of interest is isolated and reinserted in another organism that will have recombinant DNA [8]. Isolated species or recombinant species are scaled up in a controlled manner, using bioreactors, for instance, to produce large quantities of the molecule of interest without altering the wild population [78]. This is important to maintain ecosystem balance and process sustainability [78].

3.2.1 | Genomics and metagenomics

To investigate the biotechnological potential of any marine organism, studying its genome is required [79]. After sequencing, it is critical to investigate the gene-coding region of the genome through computational analysis to identify the functional gene content [80]. This process can be facilitated by metagenomic analysis that sequences the environmental DNA without the need for cultivation [81,82]. This approach will provide an advantage in biotechnological studies since a minimal fraction of the existing microorganisms are culturable using conventional methods [83]. Metagenomic studies also enable studying mixed microbial communities from a certain environment, which increase the chance of discovering interesting functions such as the production of novel extermoenzymes, novel anticancer, antibacterial, and antifungal compounds [84].

As such, Manoharan et al. [85] studied the sediments of Mexican coasts to look for Asgard Archaea through metagenomics. The results of 16 rRNA sequencing revealed the presence of both Lokiarchaeota and Thorarchaeota, possessing reductive dehalogenase genes, which indicates their ability to metabolize halogenated organic compounds.

Additionally, Colonia, et al. [86] investigated marine thraustochytrids which are lipid accumulating protists found in mangroves and coastal seawaters of southern Brazil. Metagenomics was used to identify the existence of microorganisms that accumulate lipid. Total DNA was extracted from the mangrove and coastal samples, then sequenced using Illumina MiSeq. Samples containing Labyrinthulomycetes were identified and selectively chosen to do direct plating and pollen baiting isolation. After the high-throughput screening, biomass production, and lipid characterization, it was found that *Aurantiochytrium* sp. achieved the highest biomass and lipid production which could be used as diet supplement.

3.2.2 | Transcriptomics and proteomics

Transcriptomics is the study of the transcriptome of the organism, which includes all RNA transcripts. Transcriptome studies are an efficient way of discovering the functionality of the genetic material of an organism since it solely focuses on studying the expressed part of the genome, which is transcribed [87]. Transcriptomic technologies include microarrays and RNAseq [88]. Microarray is a microscopic chip having specific probes of known DNA sequences or genes. It is a tool used to detect the expression of genes by quantifying certain transcripts as they hybridize (i.e., bind) to the chip's probes which have complementary sequences [89]. Microarrays advancements gave the probes high specificity and increased sensitivity through fluorescence detection [89]. RNAseq on the other hand is the sequencing of transcript cDNAs, which is advancing with the advancement of high-throughput sequencing technologies [90].

Proteomics on the other hand is the analysis of the proteins produced by an organism and the identification of its physiochemical properties [91]. It is a study that complements the metagenomics and transcriptomics analysis where data comparison will reveal the genes responsible for protein production. The study of protein composition is usually carried out using chromatography, enzymatic digestion, electrophoresis, Edman degradation, and mass spectroscopy [92]. Traditionally, Edman degradation was the most used proteomics analysis. However, due to its low throughput and requirement of a huge quantity of samples, it is not preferred to rely on it [93]. On the other hand, the advancement of mass spectroscopy enabled cost-efficient identification of the proteome with high sensitivity [94].

Maghembe et al. [95] provided a detailed review on the use of omics for bioprospecting. Part of the review was providing different examples where transcriptomics was applied for drug discovery from bacterial and microalgal species found in different environments. Specifically to the marine environment, in Ren et al. [96] study, docosahexaenoic acid (DHA) fermentation at various phases by *Schizochytrium* sp. was studied using transcriptomic analysis at four different growth stages. This allowed for the identification of various potential genes which play a role in cell transition from growth, to lipid accumulation, to lipid turnover. Identification of these genes allows better understanding of the lipid metabolic pathways, which, inturn, can be used to enhance lipid metabolism and increase the production of DHA.

3.2.3 | Metabolomics

This branch of omics focuses on studying the metabolomes (low molecular weight metabolites produced internally in the tissues, cells, or fluids) of the organisms [97]. It allows the identification of useful biological metabolites produced at normal conditions or under stressful environmental conditions [97]. This is because the metabolome is a product of gene expression and protein production which are directly affected by physiological and environmental inductions [98]. Thus, metabolomics is often coupled with genomics or transcriptomics to reach a holistic conclusion.

Unlike other omics approaches, metabolomics faces the difficulty of measuring and identifying the produced metabolites since they have diversified physiochemical characteristics [97]. Thus, the metabolites identification process does not have a specific bioanalytical tool. Instead, several tools and techniques need to be applied to have a comprehensive view of the metabolome. The most used detection tools are mass spectroscopy (i.e., high-performance liquid chromatography and gas chromatography) mass spectrometry, and nuclear magnetic resonance (NMR) spectroscopy [99]. In their study, Paulus et al. [100] isolated *Actinobacterium streptomyces* sp. from marine sediments samples in Trondheim Fjord, Norway. Genomic DNA was isolated from the strain and then it was sequenced using two MiSEQ libraries (Illumina). Assembly of the shotgun reads was performed with the Newbler v2.8 assembler (Roche). They also conducted detailed metabolomic analyses using mass spectroscopy. The results of their study revealed that the isolated strain produces 18 secondary metabolites as well as new bioactive molecules which makes it a promising strain for the production of new natural compounds.

When comparing the different omics approaches, it can be seen that the genomics and metagenomics approach produces a huge set of data that needs to be analyzed which takes a long time and requires expertise [101]. For instance, if one is considering the proteomics approach, then the results will be restricted to the detectable proteins, where proteins of low concentrations are not likely to be identified [102]. Looking into metabolomics, the detection of metabolites often requires utilizing more than one detection tool to cover most metabolites [97]. Generally, it is recommended to combine more than one approach to have an idea of the genetic coding and the corresponding produced molecule, to facilitate future application.

4 | MARINE BIOPROSPECTING IN THE LEGAL CONTEXT

The continuous progression of the bio-industry and the consequent increase in bioprospecting activities comes with the risk of depleting marine resources over time. It is crucial that marine bioprospecting activities be regulated by establishing laws that ensure that bioprospecting activities do not alter the sustainability of the marine environment [103]. Generally, marine-oriented environmental laws and constitutions worldwide are focused on the conservation of diversity. For example, one of the most significant international treaties that ensures the sustainability of marine biodiversity is the United Nations Convention on Biological Diversity (UN-CBD) [104]. This treaty emphasizes the importance of conserving diversity and using sustainable means for consuming any of the environment's resources, all the while sharing the genetic resource benefits fairly and equitably [104]. With the increase in world population leading to heavy exploitation of marine resources, many other international subsidiary agreements, legal instruments, and organizations have been established to regulate the use of marine biodiversity (Table 2).

From the above-mentioned information, it can be clearly seen that most international treaties and agreements for the protection of marine resources are generally based on the sustainable use and conservation of biodiversity. None of the above-mentioned legal instruments directly mention the use of marine resources for bioprospecting, hence failing to provide any restrictions on the bioprospecting-based exploitation of marine resources. This creates a gray area of when bioprospecting is useful for the environment and when it is causing damage, as it is not being regulated officially.

TABLE 2 Legal instruments and organizations regulating the exploitation of marine resources

Instrument	Description	References
Global Ocean Commission	International entitative aiming to reduce the degradation of the marine environment with a special focus on seas beyond the exclusive economic zones. In addition to recommending amendments to the UNCLOS.	[105]
European Micro B3	A project that works on setting a legal framework for creating a data base containing the genomes and metagenomes of marine microorganisms. It is also targeting standardization of microorganisms sampling.	[106]
Valencia declaration	Urging international regulation of marine activities beyond national jurisdictions to ensure the balance between human's benefit and protection of marine biodiversity.	[107]
Bonn guidelines	Providing assistance to governments in implementing access and benefit-sharing measures of genetic resources under the CBD.	[108]
United Nations Convention on the Law of the Seas (UNCLOS)	An international agreement that establishes guidelines for the exploitation of marine resources and limiting the national rights of a country in the world's ocean.	[109]
Nagoya protocol	Supplementary agreement to the CBD, promoting access and benefit sharing of genetic resources. Adopted in October 2010 and entered into force October 2014.	[110]
International Seabed Authority	Organization established by the UNCLOS, aiming to regulate the prospecting and exploitation of marine minerals in international seabed areas.	[111]

Furthermore, in recent years, increased bioprospecting has also led to novel marine organisms being found, leading to a higher number of marine gene patents [112]. A downside is that only a handful of countries (e.g., United States, Germany, Japan, France) are benefitting from these marine bioprospecting findings. These countries benefit from access to the international waters due to having advanced technologies, which allow bioprospecting on a larger scale with efficiency. Any novel genes are patented by these countries and the distribution of information becomes limited to researchers from other countries. In one instance, enzymes found in hydrothermal vents located in international waters or areas beyond national jurisdiction (ABNJ) were patented and used for biofuel production leading to a profit of 150 million dollars. Although these marine resources are found in areas not owned by a specific country, no laws are in place which stop them from being patented [113]. This creates a research gap and keeps important scientific findings away from people which may be important for the betterment of human lives.

5 | CHALLENGES FACING MARINE MICROBIAL BIOPROSPECTING

Despite being a very promising field of science, there are still various challenges facing marine bioprospecting. The challenges vary starting from the stage of discovery of interesting metabolites or organisms and ending by the commercialization.

5.1 | Culturability and identification of the microorganisms

Culturing microbial species from environmental samples can be challenging and difficult due to the lack in knowledge about their nutritional requirements [114]. This reduces the feasibility of adapting some strains to lab conditions [115]. Therefore, correct identification of microorganisms is an important part of the bioprospecting process. Despite the development of biochemical identification techniques, it can be occasionally difficult to differentiate between closely related species [116]. Rare and novel species create yet a bigger difficulty since their biochemical profiles are not found in databanks [116].

Further, some species might simply be in an unculturable state [117]. The viable but not culturable state of some microorganisms is a survival mechanism adopted when the environmental conditions are not favorable. Under such state, the microorganism is alive but fails to grow on a routine growth medium [118]. Relying on conventional microbiological cultivation techniques makes the prospecting of such microorganisms and exploring their metabolites virtually impossible [114]. In addition, even in cases of successful culturing, isolating a specific interesting microbial species is yet another challenge. Some marine microbial communities are characterized by a symbiotic relationship, where both microbial species depend on the existence of one another to survive [119]. This was documented in many studies, for instance, Sandhya and Vijayan [120] showed that the marine microalga *Isochrysis galbana* can be associated with a bacterial species such as *Alteromonas* sp. and *Labrenzia* sp. in a mutually beneficial relationship, that enhances the productivity of both organisms. The study revealed that the production of growth stimulatory compounds like siderophores and antioxidants by the bacterial species are possibly the enhancers of algal growth. Another study showed that B1 and B12 vitamins that are required for the growth of marine dinoflagellate *Lingulodinium polyedrum*, are supplied by the bacterial communities associated with this alga [121]. In other words, attempting to isolate a species that live symbiotically with another, might result in growth reduction or even death of the targeted species.

5.2 | Adequate preservation techniques

Since microorganisms and their associated activities have a key role in maintaining the stability and functionality of ecosystems, it is important to safeguard their existence. With the current global changes and habitat destruction, the preservation of valuable microbial diversity became a necessity. In which, the microorganisms of interest are protected and maintained in their desired status, for the stability of the ecosystems in addition to research applications [122]. In pharmaceutical and food industries, for instance, preservation is significantly essential to maintain the microbial communities of interest [123]. Conceptually, preserving microorganisms is forcing them into anabiosis through lowering their metabolic activity [124]; which allows the storage of the organism for long time periods. The continuous research in this field led to the development of various preservation techniques including continuous subculturing, agar beads preservation, silica gel storage, desiccation, liquid drying, spray drying, vitrification, cryopreservation, and lyophilization (freeze-drying) [125]. Due to their reliability and effectiveness for long-term storage, cryopreservation and freeze-drying are considered the most valuable and popular preservation techniques [123]. However, the high costs associated with such techniques are a major drawback [126]. Further, the effectiveness of these two techniques does not apply to all microorganisms [127]. Different microorganisms require different preservation protocols which need to be optimized to suit their specific characteristics [128]. Also, the chosen preservation protocol must be validated in terms of efficiency, reliability, and reproducibility by conducting pre and post characterization of the preserved microorganisms; which limits the applicability of microbial preservation [129].

5.3 | Bioinformatics bottlenecks

Bioinformatic tools proved to be an efficient way of discovering genes encoding interesting biological compounds [130]. However, the lack of adequate development of databases due to the small number of specialized taxonomists, lack of bioinformatics experts, and the difficulty in data analysis is a major drawback of this approach [8]. Therefore, the discovery of novel molecules through bioinformatics would be restricted to the available information found in databases. In addition, processing the datasets generated from the bioinformatic analysis is complicated as there is still a lack in the standardization of software usability which limits the applicability of this tool [131].

5.4 | Economics of producing valuable biobased products

Operational cost is one of the most important factors that should be considered in biotechnological approaches. Overcoming the problems of economic viability and production costs is important for the commercial production of the biobased product [131]. When considering the market value, biobased products should be very competitive with the already existing alternatives in terms of price and efficiency. Therefore, optimization of the production and operation costs are needed to enhance the product's commercial viability. In case of microalgae for instance, even though many studies are targeting production optimization, most of them are demonstrations of lab-scale, or semi-industrial scale, and not large-scale production [132]. At the laboratory scale, culturing is well-situated since it takes place under controlled and optimized conditions. However, mimicking the same conditions during large-scale production is difficult which hinders its success [133]. In fact, environmental conditions play an important role in deciding the behavior of the organism and the metabolites produced. Even after overcoming the large-scale production obstacle, harvesting the microorganism or desired product is yet another challenge. Harvesting along with product purification rely heavily on the characteristics of the product and the producing cells. This requires intensive study and correct characterization of the microorganism to choose the most suitable and cost-effective downstream processing approaches. As a way of increasing the cost-efficiency of commercialization, genetic engineering of microorganisms has gained interest. However, as reviewed by Hegde et al. [134] for instance, even though genetic engineering of microorganisms to enhance the quality and quantity of produced biodiesel is successful at the lab scale, many obstacles are still facing the shift to large scale production and commercialization mainly due to economic feasibility related issues.

6 | CONCLUSION

In conclusion, oceans are characterized by unique ecosystems exposed to a variety of extreme conditions. This creates a huge pool of genetic diversity and increases the probability of having specialized coding sequences that enables the organisms to cope with such harsh conditions. Marine biotechnology provides the opportunity of utilizing such biological resources for mankind's benefit, which is usually undertaken by bioprospecting which provides a systemic search of beneficial products. In this regard, plankton bioprospecting has gained special interest as it provides several advantages over other organisms.

The bioprospecting strategies are developing continuously to reduce the required time and cost, and to enhance the outcome. It escalated from the traditional culture-dependent techniques to novel functional bioprospecting that does not require culturing. Still, the advancement of marine bioprospecting is being held back by a number of obstacles, including a lack in the development of bioinformatics, the difficulty of large-scale production and product purification, production variability, and maintaining cost-efficiency.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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