The essential of marine biotechnology

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Abstract

Coastal countries have traditionally relied on the marine resources for finding new economic endeavors, e.g. fishing, food, transport, recreation, tourism, ocean energy, desalination and seabed mining. Modern societies and lifestyle resulted in an increased demand for dietary diversity, better health and well-being, new biomedicines, natural cosmeceuticals, and sustainable energy sources. These societal challenges stimulated the interest of researchers on the underexplored marine environments as sustainable sources of biomolecules and biomass, and are addressed in the emerging field of marine (blue) biotechnology. The blue biotechnology provides opportunities for a wide range of initiatives of commercial interest for the pharmaceutical, med-tech, cosmetic, nutraceutical, food, feed, agricultural and related industries. This article depicts the essence, opportunities, responsibilities and challenges encountered in marine biotechnology and outlines the attainment and valorization of bio-inspired products from marine organisms or biomass. First, the diversity of marine bioresources including the overview of marine organisms and their potential for biotechnological uses are described. This is followed by the methodology for exploration of these resources and the main use case scenarios in energy, food and feed, agronomy, bioremediation and climate change, cosmeceuticals, bio-inspired materials, healthcare and well-being sectors. The aspects in the fields of legislation, funding and bioeconomy are provided with the emphasis on the importance of communication and stakeholder engagement at all levels of biotechnology development. Finally, the important overarching concepts, such as the quadruple helix and Responsible Research and Innovation are highlighted as important to follow within the marine biotechnology field. The authors of this review are collaborating under the European funded Cooperation in Science and Technology (COST) Action Ocean4Biotech – European transdisciplinary networking platform for marine biotechnology and focus the study on the European state of affairs.

1 Introduction

Marine environments provide a plethora of ecosystem services leading to societal benefit (Townsed et al., 2018). These services are mostly linked to supporting services (primary production and nutrient cycling), provisioning services (such as food) and cultural services, lately including tourism. The recent advancements of science and technology have facilitated the implementation of marine biotechnology, where marine organisms and their compounds are identified, extracted and used for applications in various sectors, ranging from food/feed to pharmaceutical and biomedical industries, to benefit society. Life in marine environments is diverse with wide environmental gradients in the physical, chemical and hydrological parameters such as temperature, light intensity, salinity and pressure. Marine organisms have adapted to these environments by developing a broad spectrum of forms, functions and strategies that play a crucial role for survival in the existing multitude of highly competitive ecosystems and ensure the adaptation and thriving of the organisms in these diverse conditions. Among the vast array of evolutionary traits present in extant marine phyla, the production of biomolecules is one of the most interesting for biotechnology. The biomolecules mediate chemical communications between organisms, act as a protective barrier against adverse environmental conditions, serve as weapons for catching prey or for protection against predators, pathogens, or harmful UV radiation and are primordial in many other life-sustaining processes. Biomolecules have evolved to improve the organism's performance in its environment and can act *in vivo* even at low concentrations to counteract the effect of their dilution at sea. The unique and complex structures of many marine metabolites enable the discovery of new and innovative applications with a commercial interest. Over 50% of the medicines we currently use originate from natural compounds, and this percentage is much higher for anticancer and antimicrobial treatment agents (Newman and Cragg, 2020). Apart from biomolecules, other properties and functions of marine organisms can also be beneficial and of interest to various industries, including the filtration and metabolism of compounds and organic matter, as well as intricate and inventive biochemical and biofabrication processes. However, we agree that marine resources are still underexplored and undervalorized.

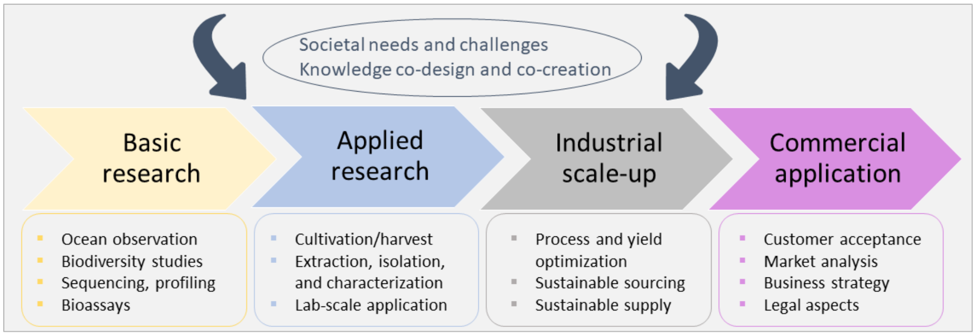

Figure 1: A simplified representation of the marine biotechnology pipeline that appears to be intrinsically interdisciplinary, combining basic and applied research with industry and business sectors.

A simplified marine biotechnology workflow (Figure 1) depicts that product development from marine organisms is an inherently transdisciplinary and multidimensional task. The scientific community, industry, policymakers and the general public have a role to play in this process. Initially, the scientific community, by following ethical and legal guidelines, conducts systematic bioprospecting and screenings of marine organisms, elucidates the structure of bioactive molecules and their mechanisms of action, and sets up the protocols and product development. Often the financing of product development is dictated by the societal needs and challenges (such as health, well-being or environmental protection). However, marine biotechnology is an inherently transdisciplinary process, hence the co-design of process and co-creation of knowledge is a necessary step in advancing the pipeline to ensure a faster product uptake. This also involves the collection of information about people's perceived and actual needs, which is of paramount importance. Outreach activities are therefore conducted to engage the public in protecting marine environment and its sustainable use. The feedback, provided by the general public to both the scientific and industrial communities, either through directed questionnaires (in case of market research and analyses to provide feedback on e.g. novel food or cosmeceuticals), workshops or other means of communication, often represents a key milestone in terms of consumer acceptance of novel developments. Subsequent steps in new marine product development, e.g. scale-up, delivery format, validation of potency toxicity, *in vivo* testing and implementation of statistically powered pre-clinical studies are generally performed by the pharmaceutical, biotechnological, biomedical and food/nutraceuticals sectors.

The present article reviews some of the important aspects of the marine biotechnology workflow. After this introductory Section 1, in Section 2, we first elaborate on the hotspots of marine biodiversity, from water column and sediments, microbial biofilms, beach wrack, to side streams. Section 3 introduces the main marine organisms being targeted for biotechnological research. Section 4 gives an overview on the general marine biotechnology pipeline and its key elements: organism isolation, data analysis and storage, chemical methods for characterization and isolation of compounds. Production and scaling-up to guarantee sufficient supply at the industrial level are presented in Section 5. Section 6 presents interesting use case scenarios where marine biotechnology can significantly address societal challenges such as energy production, agronomy, bioremediation, food, feed, bio-inspired materials, cosmetics and pharmaceuticals. Further, the legislative and ethical issues arising from the development of marine biotechnology should not be overlooked and they are presented in Section 7. A brief introduction to the marine bioeconomy is presented in Section 8. Finally, Section 9 concludes by discussing the importance of science communication both to raise consumer awareness on new products and establish new collaborations on one hand and implement knowledge transfer channels with stakeholders from the industrial, governmental and public sectors, on the other. The establishment of efficient communication that enables productive collaboration efforts is essential for the market entry and successful commercialization of marine biotechnology products.

2 Marine biodiversity habitats

The marine environment with its unique physico-chemical characteristics offers an untapped source of yet undiscovered organisms (Figure 2) for the production of commercially interesting chemical compounds. Ecological observations by marine biologists and their collaboration with chemists, supported with the availability of advanced techniques to access the ocean, fueled the increase in knowledge levels from the mid 20th century on. By the turn of the century, marine natural products chemistry was a mature and fully established subfield of chemistry with a focus on isolation and the structure elucidation of secondary metabolites (Baslow, 1969; Faulkner, 2000; Gerwick et al., 2012).

Although carrageenans or other polysaccharides extracted from seaweeds were used as food additives and in cosmetics since the 1930s, modern marine biotechnology expanded after the 1970s with the intensification of research on marine organisms and their products (Rotter et al., 2020a). The first studies focused on natural products isolated from representative organisms of the ecosystems like sessile macroorganisms including sponges, ascidians, cnidarians, corals and tunicates, and they revealed a unique chemical diversity of bioactive metabolites (de la Calle, 2017). Multicellular organisms from all types of habitats were also reported to host highly complex and specialized microbiota (the holobiont concept, Margulis, 1991; Simon et al., 2019). These symbiotic microbial communities have major impacts on the fitness and function of their hosts and they certainly contribute to the production of some secondary metabolites that play important roles against predators, pathogens or fouling organisms (Wilkins et al., 2019). This is especially true for soft-bodied, sessile organisms such as cnidarians and sponges that are the best-studied invertebrates and the most prolific source of bioactive molecules (Mehbub et al., 2014). In fact, microorganisms make up approximately 40-60% of the sponge biomass (Yarden, 2014) and many bioactive molecules have been demonstrated or predicted to have a microbial origin (Gerwick and Fenner, 2013). Microorganisms represent nearly 90% of the living biomass in the oceans and are fundamental for the function and the health of marine ecosystems by managing biogeochemical balances (de la Calle, 2017; Alvarez-Yela et al., 2019). They can produce a plethora of secondary metabolites with less stringent ethical and environmental requirements for research and product scale-up capability. Due to the broad range of manipulation possibilities, microorganisms are gaining importance for sustainable marine biotechnology and almost 60% of the new marine natural products nowadays are derived from microorganisms (Carroll et al., 2019). Nevertheless, macroorganisms still represent an active source and field of research for novel metabolites.

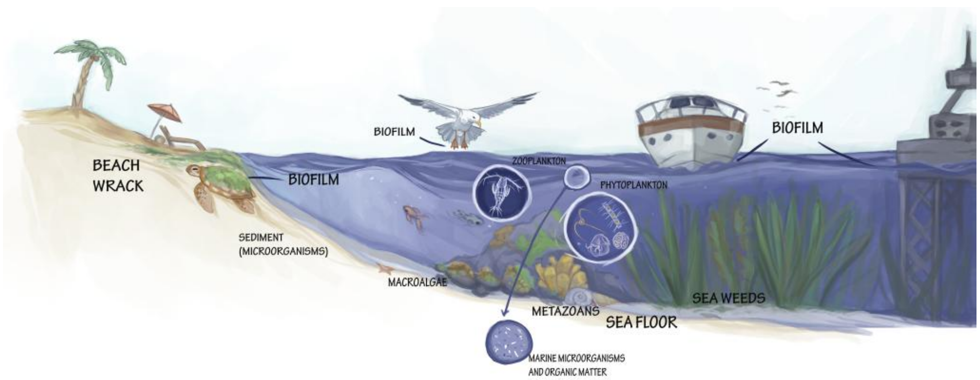

Figure 2: Various locations and taxa with valorization potential for marine biotechnology.

Since the early XXI century, the exploration of marine microbial biodiversity has been driven by the development of high-throughput molecular methods such as high throughput screening and High Throughput Sequencing (HTS), and their direct application on intact seawater samples without requiring any prior isolation or cultivation of individual microorganisms (Shokralla et al., 2012; Seymour, 2019). This sequencing approach utilizes specific gene regions (barcodes) to provide massive amounts of genetic data on the various microbial communities with continuing improvements in data quality, read length and bioinformatic analysis methods, leading to a better representation of the genetic-based taxonomy diversity of the sample. HTS methods detect both the most abundant community members but also the rare species, which cannot otherwise be retrieved by traditional cultivation-dependent methods. The Global Ocean Sample Expedition (GOS[1]) led by J. Craig Venter Institute is exemplary for that.

The isolation of DNA from environmental samples – eDNA - is already well established in the field of microbiology and marine monitoring (Díaz-Ferguson and Moyer, 2014; Pawlowski et al., 2018). Metabolic engineering is being used for the characterization of bacterial communities in sediments since the 1980’s (Ogram et al., 1987) and monitoring entire microbial populations in seawater samples (Venter et al., 2004). However, this approach has been applied to the analyses of macroorganisms only in recent years (Thomsen et al., 2012; Kelly et al., 2017; Jeunen et al., 2019). The study of eDNA in the water column (Keuter et al., 2015) or in the sediments (Keuter and Rinkevich, 2016) has received considerable attention for high-throughput biomonitoring using metabarcoding of multiple target gene regions, as well as for integrating eDNA metabarcoding with the biological assessment of aquatic ecosystems (Pawlowski et al., 2018). In addition, targeted species detection using qPCR assays have been implemented for both micro- and macroorganisms (Gargan et al.,2017; Hernández-López et al., 2019) in seawater samples. The potential for using eDNA in aquatic ecosystems has been the topic of several concerted actions (like DNAqua-Net COST Action[2]; Leese et al., 2016) and there have been considerable efforts to standardize DNA approaches to supplement or replace the existing methods, often dictated by regulatory frameworks such as the EU Water Framework Directive– WFD (Directive 2000/60/EC) and the Marine Strategy

[1] https://www.jcvi.org/research/gos

[2] https://dnaqua.net/

Framework Directive – MSFD (Directive 2008/56/EC). The biodiversity knowledge of marine microorganisms has been improved with the adaptation of various DNA barcoding protocols and approaches (Leese et al., 2016; Paz et al., 2018; Weigand et al., 2019). Although metagenomic data generated from eDNA samples can provide vast amounts of new information, datasets from complex microbial communities are difficult to process. Metagenome assemblies and their functional annotations are challenging. A large fraction (>50%) of the detected genes have no assigned function. The use of functional metagenomics applications and tools (including metagenomics coupled with activity screening/enzyme screening, meta-transcriptomics, meta-proteomics, meta-metabolomics), is key to solve this problem. One of the most used applications of functional metagenomics is an activity-based screening of metagenomcis libraries. Enzyme discovery is currently the largest field of its application, including marine enzymes (Hårdeman and Sjöling, 2007).

HTS offers a culture-independent characterization of microbial diversity, but the biotechnological exploitation of marine microorganisms often requires their cultivation in pure cultures and the optimization of yield production for the compounds of interest. It is estimated that up to 87% of microorganisms are unculturable under the current laboratory cultivation techniques (Wade, 2002; Lloyd et al., 2018). This is the 'great plate anomaly', a consequence of the difficulties in mimicking their natural environment, i.e. application of finely-tuned conditions for various parameters, such as temperature, salinity, oxygen, agitation and pressure, and use of species-specific growth substrates with trace elements. Additionally, cell-to-cell interactions, occurring both between symbiotic and competing organisms in the natural environment may be absent under laboratory conditions in pure cultures (Joint et al., 2010). Other strategies, like mimicking *in situ* nutritional composition and physico-chemical conditions as well as the addition of signaling molecules are used to increase the diversity of isolated marine microorganisms (Bruns et al., 2003). It is however important to realize the limitations of methods and tools, for example, the reliance on specific filters for bacterial isolation, 0.22 micron, that will fail to capture the smaller bacteria (Hug et al., 2016; Ghuneim et al., 2018). Hence, the establishment of pure microbial cultures remains one of the main hurdles in the discovery of bioactive constituents in microorganisms. To increase the number of harnessed microbes, a new generation of culture approaches has been developed that mimic the proximity of cells in their natural habitat and exploit interspecific physiological interactions. Several techniques, such as diffusion chambers (Kaeberlein et al., 2002), the iChip (Nichols et al., 2010), as well as the recently developed miniaturized culture chips (Chianese et al., 2018) have been employed to address microbial cultivation problems. Another reason preventing the wider valorization of marine microorganisms is that some cannot exist in nature without their symbionts: often microorganisms that are associated or in symbiosis with marine macroorganisms are the true metabolic source of marine natural products. Approximately 90% (19 out of 21) of marine natural products entering clinical trials have their origin in symbiotic microorganisms (Gerwick and Fenner, 2013). To uncover the potential of these species, many microbiological studies are focusing on bulk-community dynamics and how the performance of ecosystems is supported and influenced by individual species and time-species interaction (Kouzuma and Watanabe, 2014). Such advancements in the field of microbial ecology provide robust background knowledge for biotechnological exploitation. Hence, as natural communities are complex and difficult to assess, characterize and cultivate in artificial conditions, researchers use synthetic microbial communities of reduced complexity in their laboratory studies. These artificial communities are prepared by retaining only the microorganisms carrying out a specific biosynthetic process, as well as those providing culture stability and performance, to enable their use in biotechnological applications (Großkopf and Soyer, 2014).

Currently, the integrative "omics" approach provides comprehensive information describing the particular community through sophisticated analysis from genes to proteins and metabolites. Shotgun metagenome analysis allows us to extract genomes of the dominant organisms to link the enzymes of interests directly to organisms. Functional metagenomics is an excellent tool for studying gene function of mixed microbial communities, with a focus on genomic analysis of unculturable microbes and correlation with their particular functions in the environment (Lam et al., 2015). The conventional approach to construction and screening of metagenomic libraries, which led to the finding of many novel bioactive compounds as well as microbial physiological and metabolic features has been improved by sequencing of complete microbial genomes from selected niches. Genome mining can reveal the unlocked bioactive potential of marine organisms by utilizing the constantly evolving sequencing technologies and software tools in combination with phenotypic *in vitro* assays. This approach can facilitate natural products discovery by identifying a large number of clusters encoding different potential bioactivities within genera (Machado et al., 2015). Metatranscriptomics and metaproteomics, important for further functional analysis of microbial community composition, may indicate their role in many crucial processes as carbon metabolism and nutrition acquisition (Shi et al., 2009). With the development of *in situ* molecular tools (such as fluorescence in situ hybridization - FISH), it is possible to quantify and follow the dynamics of specific bacterial groups (Pizzetti et al., 2011; Fazi et al., 2020). Such tools may also help to uncover if microbial communities with explicit characteristics can favor biosynthesis processes for specific compounds of interest. To maximize the biotechnological potential of our oceans it is thus essential to exploit microbial communities with their complex networking systems engaged in cooperation and competition.

2.1 Water column, sea floor and sediments

Primary production is the key driver for life on Earth, and about half of the biologically mediated carbon fixation is undertaken by marine phytoplankton (50 ± 28 Gt C/year, Fahey et al., 2017). Spatial and temporal distribution patterns and the abundances of phytoplankton, bacterioplankton and viruses depend on a combination of physico-chemical parameters (e.g. light availability, nutrient supply, water column stratification) and biological processes (e.g. microbial activity, zooplankton grazing pressure, viral lysis) (Field et al., 1998; Kirchman 2000; Mousing et al., 2016). Continental shelves support a disproportional amount (around 20%) of global ocean primary production (Behrenfeld et al 2005; Jahnke, 2010) whilst only covering 9% of the ocean area (Simpson and Sharples 2012).

Seafloor provides diverse habitats for organisms. Besides forming stromatolites in the surface sediments, cyanobacteria can secrete or excrete extracellular polymeric substances (EPS) (Golubic et al., 2002) that can further stabilize sediments and protect them from antimicrobial compounds and other various biotic and abiotic stressors (Costa et al., 2018). Ocean sediments cover the great majority of the Earth´s surface and host many more bacterial phyla and individual species, the biosynthetic capabilities of which are largely unknown. This is particularly true for the poorly accessible deep systems. Phylogenetic studies from the ultra-oligotrophic eastern Mediterranean Sea have shown that sediments down to 4393 m depth host a vast diversity of bacteria and archaea (Polymenakou et al., 2015). More importantly, a large fraction of 16S rDNA sequences retrieved from the same environment (~12%) could not be associated with any known taxonomic division, implying the presence of novel bacterial species (Polymenakou et al., 2009). Recently, the most important step forward in elucidating world-wide eukaryotic biodiversity were cross-oceanic expeditions such as Malaspina, Tara Oceans and Biosope (Grob et al., 2007; Claustre et al., 2008; Bork et al., 2015; Duarte, 2015; de Vargas et al., 2015). These studies have also confirmed that much of the eukaryotic plankton diversity in the euphotic zone is still unknown and has not been previously sequenced from cultured strains. The Tara Oceans dataset also provided significant new knowledge to protistan diversity, as it resulted in an increase of the estimated mean tree-length by 453%, reaching >100% in 43 lineages (de Vargas et al., 2015).

Several maritime ecoregions have been much less explored for their biodiversity in macroorganisms in regions of the world where marine science is less supported or regions that are difficult to access, such as the polar regions, the west coasts of Africa and South America or some remote islands of the Pacific or the Atlantic (Carroll et al., 2019). Given that the world´s ocean average depth is 2,000 m, the advent of diving and vessel-operated sampling equipment and techniques, such as dredges, collectors and remotely operated vehicles (ROVs), allowed exploring previously inaccessible environments (such as hydrothermal vents and deep-sea), opening new prospects and horizons for marine biotechnology. The exploration of these extreme environments requires specific equipment, skills and resources for long cruises, which include systematic mapping, especially in the deep ocean and seabed.

Submarine caves were recently recognized as biodiversity hotspots (Gerovasileiou and Voultsiadou, 2012; Gerovasileiou et al., 2015), with the majority of them being largely unexplored. The organisms hosted in these environments are of particular biotechnological interest. A range of autochthonous mesophilic and thermotolerant microorganisms have been reported from submarine caves and cavities, characterized by elevated concentrations of hydrogen sulphide, H_2S (Canganella et al., 2006), while methanogenic and sulphate reducing microbial species with potential applications in biogas production and bioremediation have been isolated from similar environments (Polymenakou et al., 2018). Besides biogas production, the biotechnological interest of bacteria originating from unique submarine caves could be even greater in terms of their secondary metabolites. Overall, we propose that regional national or even transnational initiatives should be fostered to set-up long-term inventories of marine biomaterial open to the public with a strong emphasis on taxonomy and geographic information (Leal et al., 2016). National initiatives have been supported in Europe, for instance in Norway and Ireland with the construction of a National Marine Biodiscovery Laboratory in Ireland[3] (Gabrielsen, 2012).

2.2 Biofilms

Biofilm formation (Figure 2) is an important life-strategy for microorganisms to adapt to the wide range of within aquatic environments. Biofilms are complex and dynamic prokaryotic and eukaryotic microbial communities and represent a novel species bank of hidden microbial diversity, sources of secondary metabolites and functional potential in the ocean (Battin et al., 2003; Zhang et al., 2019b). The scarcity of some microbial species in seawater prevents their capture in global sequencing efforts and they can only be detected when their relative abundance increases during biofilm formation. The biofilm microbiome can be analyzed by metagenomic approaches such as Illumina and visualized by microscopic imaging techniques such as CARDFISH (Parrot et al., 2019). Controlled surface biofilm offers advantages to the organism due to the production of secondary metabolites. Mass spectrometry imaging (MSI) techniques, such as DESI-MSI permit the identification and spatial distribution and localization of marine microbial natural products in the biofilm (Papazian et al., 2019; Parrot et al., 2019).

The main component of biofilms, that represent up to 90 % of the dry biomass, are extracellular polymeric substances (EPS), which comprise polysaccharides, proteins, extracellular DNA, lipids and other substances, forming a complex 3-D structure holding cells nearby (Flemming and

[3] http://www.imbd.ie/

Wingender, 2010). This matrix of EPS keeps the biofilm attached to the colonized surface (Battin et al., 2007; Flemming and Wingender, 2010). Exopolysaccharides can remain bound to the cell surface or be directly released into the aquatic environment. The assessment of the distribution of specific microbes within the biofilm and their exopolysaccharide composition is of crucial importance for biotechnological applications (Pereira et al., 2009; Lupini et al., 2011; Fazi et al., 2016). EPS composition varies greatly depending on the microorganisms present and environmental conditions (e.g. shear forces, temperature, nutrient availability) and therefore represents an untapped resource of novel compounds (Di Pippo et al., 2013). These suggest different biosynthesis mechanisms, that are, in turn, dependent on environmental and growth conditions (De Philippis and Vincenzini, 2003; Pereira et al., 2009). EPS are responsible for adhesion to the surface, aggregation of bacterial cells, cohesion within the biofilm, retention of water, protection, and enzymatic activity (Žutić et al., 1999). Furthermore, they are important for absorption of organic and inorganic compounds, exchange of genetic material, storage of excess carbon and they can serve as a nutrient source (Flemming and Wingender, 2010). These features can be exploited in different applications. Many different bioactivities such as high antioxidant capacity, antiviral and antifugal are available from extracts of marine seagrasses such as *Halodule uninervis* or *Posidonia oceanica* (Bibi et al., 2018; Benito-González et al., 2019). The biodegradable and sustainable carbohydrate-based materials in biofilms provide mechanical stability and can be exploited as packaging materials, films, prosthetics, food stabilizers and texturizers, industrial gums, bioflocculants, emulsifiers, viscosity enhancers, medicines, soil conditioners, and biosorbents (Li et al., 2001; Roca et al., 2016). The extracellular proteins and enzymes can find interesting applications in medical biofilm dispersion or bioconversion processes. The EPS also contains biosurfactants with antimicrobial activity and extracellular lipids with surface-active properties that can disperse hydrophobic substances, which can be useful for enhanced oil recovery or bioremediation of oil spills (Baldi et al., 1999; Flemming and Wingender, 2010). Understanding the molecular mechanisms behind various secondary metabolites that are used for interspecies communication within biofilms will be useful in combating the biofilm-forming pathogenic bacteria (Barcelos et al., 2020).

Biofilms are also involved in marine biofouling, and defined as the accumulation of microorganisms, algae, and aquatic animals on biotic and abiotic surfaces, including human-made structures that are immersed in seawater (Amara et al., 2018). The environmental impact of biofouling is significant due to the reduction of the water flow and the increase of debris deposition below the aquaculture farms (Fitridge et al., 2012). Biofouling can seriously affect environmental integrity and consequently impact the worldwide economy. Ships' hulls can increase fuel consumption by up to 40% due to the increased drag and weight of the ships (Amara et al., 2018) and can also increase ship propulsion up to 70% (Trepos et al., 2014), resulting in a rise in carbon dioxide and sulphur dioxide emissions by 384 and 3.6 million tons per year, respectively (Martins et al., 2018). The transport delays, the hull repairs and the biocorrosion cost an additional 150 billion dollars per year (Schultz, 2007; Hellio et al., 2015). Moreover, ships might transport invasive fouling species, thus threatening indigenous aquatic life forms (Martins et al., 2018). The use of antifouling paints incorporating biocides like heavy metals and tributyltin was the chemical answer to the fouling issue, but these substances are known to leach into the water and pose deleterious effects to many non-target species (Yebra et al., 2004; Amara et al., 2018). Marine natural products, originating from bacteria as well as higher organisms, can represent an environmentally friendly alternative to synthetic biocides (Eguía and Trueba, 2007; Adnan et al., 2018) and an economically advantageous solution to foul-release polymers (Trepos et al., 2014b; Chen and Qian, 2017; Pereira et al., 2020). In particular, the compounds that inhibit quorum sensing signals that regulate the microbial colonization, formation of aggregates could mitigate the impact of biofilms (de Carvalho, 2018; Salehiziri et al., 2020).

Biofilms are useful as a core part of the nitrification bioreactors, operated in recirculated aquaculture systems and called biofilters, as they convert excreted ammonia from animals to nitrates. This restores healthy conditions for farmed fish and shrimp. Aquaculture biofilms have a complex microbiome, which composition varies depending on the farmed species and culture conditions. However, these biofilms can also harbor pathogens that can be harmful to cultured fish. Therefore, careful manipulation of microbial communities associated with fish and their environment can improve water quality at farms and reduce the abundance of fish pathogens (Bentzon-Tilia et al., 2016; Bartelme et al., 2017; Brailo et al., 2019).

2.3 Beach wrack

Beach wrack (Figure 2) consists of organic material (mainly seagrasses) washed ashore by storms, tides, and wind. According to the European Commission Regulation (EC) No 574/2004 and the European Waste Catalogue (EWC), waste from beaches is defined as “municipal wastes not otherwise specified” (Wilk and Chojnacka, 2015). Therefore, specific regulations of each country are implemented concerning the collection of municipal solid waste (Guillén et al., 2014) which typically results in large amounts of unexploited beach wrack. Moreover, the removal of wrack eliminates valuable nutrients that may affect sandy beach and dune ecosystem's food chains, and it can cause a reduction in species abundance and diversity (Defeo et al., 2009). For example, the role of *Posidonia oceanica* ‘banquettes’ (dead leaves and broken rhizomes with leaf bundles) is fundamental in protecting beaches from erosion, and its removal can have a dramatic negative impact on *P. oceanica* ecosystem services, including the conservation of beaches (Boudouresque et al., 2016). On the other hand, the high deposition of beach cast is due to the blooms of opportunistic macroalgae following elevated nutrient loading. In such cases, a removal of beach cast is seen as a mitigation action to remove excess nutrients in marine environments (Weinberger et al., 2019). The collection of beach wrack could therefore be connected to an interesting biotechnological application, but such interventions should also take into account the ecological role that algae and plant debris play in the coastal ecosystems (Guillén et al., 2014). Collection and handling methods should therefore be tailored to fit the particular characteristics of each coastal system, including the type of the dominant species and the quantities of biomass. Solutions should then be verified from economical, technical and environmental perspectives.

As beach wrack often includes contaminants, the decay of this biomass can lead to the reintroduction of toxic pollutants into the aquatic environment. Before the implementation of industrial agriculture practices in the 20th century, beach wrack was used in Europe as a fertilizer (Emadodin et al., 2020). The high salt content was reduced by leaving the biomass on the shore for weeks to months so that the salt could be washed out by the rain. The implementation of adapted recycling methods should be included for further processing of wrack biomass before its removal from the coastal ecosystem. Besides high salt content, sand removal is another obstacle for the immediate utilization of beach wrack. New technologies, including the magnetic modification of marine biomass with magnetic iron oxide nano- and microparticles and its subsequent application for the removal of important pollutants can be considered (Angelova et al., 2016; Safarik et al., 2016; Safarik et al., 2020).

Coastal biomass displays good biotransformation potential for biogas, which is comparable to higher plants containing high amounts of lignin. Besides biogas production, the bioactive substances of this biomass (mainly exopolysaccharides) can be used to develop cosmetics, as well as for pharmaceutical and biomedical products (Barbot et al., 2016). This biomass may also be used for the removal of various types of contaminants by biosorption (Mazur et al., 2018). Hence, there is interest in the adoption of circular economy principles for the sustainable management of coastal wrack biomass. This can enable the production of valuable solutions, while at least partially substituting the use of fossil fuels, the use of electricity at a biogas plant and the use of chemical fertilizers (using degassed or gasified/torrefied biomass), thus avoiding “dig and dump” practices and landfill emissions. The implementation of these methods can also contribute to local small-scale energy unit development in coastal regions (Klavins et al., 2019).

2.4 Seafood industry by-products/side stream valorization

Among the different marine resources, fish represent the main commodity; of the 171 million tons of global production, about 88% was used for direct human consumption in 2018 (FAO, 2018). Due to a lack of adequate infrastructures and services to ensure proper handling and preservation of the fish products throughout the whole value chain, 20-80% of marketed fish biomass is discarded or is wasted between landing and consumption (Gustavsson et al., 2011; Ghaly et al., 2013). In addition, large quantities of marine by-products are generated mainly as a result of fish and shellfish processing by industrial-scale fisheries and aquaculture (Rustad, 2003; Ferraro et al., 2010; Radziemska et al., 2019). Additionally, the phycocolloid industry also generates considerable amounts of seaweed by-products that are good sources of plant protein, cellulosic material and contain taste-active amino acids. They can also be used in food flavoring (Laohakunjit et al., 2014), animal feed (Hong et al., 2015) or as feedstock biomass for bioenergy (Ge et al., 2011).

The by-products are often treated as waste, despite containing valuable compounds. The biorefinery concept integrates biomass conversion processes and equipment to produce value-added chemicals, fuels, power and heat from various types of side stream (waste) biomass. In this context, marine biorefinery employs recycled/reutilization of marine waste biomaterials to produce higher-value biologically active ingredients/components, such as minerals, proteins, peptides, lipids, long-chain ω-3 fatty acids, enzymes, and polysaccharides (Nisticò, 2017; Kratky and Zamazal, 2020; Kumar et al., 2020; Prabha et al., 2020). The process typically includes trimmings, skins and chitin residues from crustacean species, heads, frames (bone with attached flesh) and viscera. Only a small portion of cut-offs is further processed, mostly into fish meal and fish oil, while a part is processed to extract value-added compounds that can be used in the pharmaceutical and nutraceutical products (Senevirathne and Kim, 2012) for prevention and management of various disease conditions, such as those associated with metabolic syndromes (Harnedy and FitzGerald, 2012). Collagen can be used for wound healing dressings, drug delivery, tissue engineering, as an antibiofilm agent, nutritional supplement, or as and ingredient in cosmetics and pharmaceutical products (Abinaya and Gayathri, 2019; Shalaby et al., 2019). Gelatin and chondroitin have applications in the food, cosmetic and biomedical sectors. Chitin and chitosan resulting from shellfish are other examples of marine by-products with applications in the food, agriculture and biomedicine sectors (Kim et al., 2006). Hydroxyapatite derived from fish bone has demonstrated relevance for dental and medical applications (Kim et al., 2006) and can also be used as feed or fertilizers in agriculture or horticultural use. Cephalopod ink sac is considered a by-product that is discharged by most processing industries (Hossain et al., 2019). However, the ink from squid and cuttlefish, can be a potential source of bioactive compounds, such as antioxidant, antimicrobial or chemopreventive agents (Smiline Girija et al., 2008; Zhong et al., 2009; Shankar et al., 2019). Moreover, microbes that live in fishes’ slimy mucus coating can be explored as drug-leads for the pharmaceutical industry (Estes et al., 2019). The main challenge for the valorization of all aforementioned by-products is their very short shelf-life, implying that the processing steps should be fast enough to prevent oxidation and microbial degradation.

3 Marine organisms and their potential application in biotechnology

All marine organisms have the potential for biotechnological valorization (Figure 2). Table 1 presents the different types of marine organisms and their main biotechnological applications currently being developed, while a more detailed discussion on this topic follows in subsequent sections.

Table 1: An short, non-exhaustive list of the current uses of marine organisms.

Organism	Use	Representative taxa	Challenges
Metazoans	Medicine (human), cosmetics	*Ecteinascidia turbinata*, *Conus magus, Mycale hentscheli*, mollusks, sponges	Sourcing and supply sustainability
Seaweeds	Food, feed, medicine, cosmetics, nutraceuticals, biofertilizers/soils conditioners, biomaterials, bioremediations, sustainable energy	*Laminaria hyperborea, Laminaria digitata Ascophyllum nodosum, Euchema denticulatum, Porphyra/Pyropia spp., Saccharina japonica, Saccharina latissima, Undaria pinnatifida, Gelidium sesquipedale, Pterocladiella capillacea, Furcellaria lumbricalis, Palmaria, Alaria, Fucus, Ulva spp., Sargassum, Gracilaria*	Sourcing and supply sustainability Yield optimization, disease management
Microalgae	Sustainable energy, cosmetics, food, feed, biofertilizers, bioremediation	Chlorophyta, Cryptophyta, Dinoflagellata, Ochrophyta, *Haematococcus*, *Spirulina*, *Chlorella, Isochrysis Tetraselmis*	Bioprospecting and yield optimization (1 – increase in biomass/volume ratio and 2 – increase yield of compound production)
Bacteria and Archaea	Medicine, cosmetics, biomaterials, bioremediation, biofertilizers	Actinobacteria, Cyanobacteria, Firmicutes, *Pyrococcus*, *Thermococcus, Bacillus, Pseudoalteromonas, Alteromonas, Salinispora tropica*	Culturing for nonculturable species, yield optimization
Fungi	Bioremediation, medicine, cosmetics, feed/food, biofertilizers	*Penicillium*, *Aspergillus*, *Fusarium*, *Cladosporium*	Limited in-depth understanding, yield optimization
Viruses	Medicine	mycoviruses	Limited in-depth understanding, yield optimization

3.1 Metazoans

Most initial studies on marine natural products focused on marine metazoans such as sponges, soft corals (after sponges the second best-studied marine organisms), cnidarians, gastropods and tunicates, as they were representative organisms of the studied marine ecosystems and relatively easy to collect by scuba diving (reviewed in Molinski et al., 2009). The first described drugs from the sea that were used in clinical trials decades after their discoveries were vidarabine (ara-A) and cytarabine (ara-C), two chemical derivatives of ribo-pentosyl nucleosides extracted in the 1950s from a Caribbean marine sponge, *Tectitethya crypta (=Cryptotethya crypta de Laubenfels, 1949)* (Bergman et al., 1951). Other early drugs originating from the sea was ziconotide, a synthetic form of ω-conotoxin, extracted from the Pacific cone snail *Conus magus* and commercialized under the trade name Prialt for the treatment of chronic pain (Olivera et al., 1985; Jones et al., 2001), ω-3 acid ethyl esters (Lovaza) from fish for hyperlipidemia conditions, the anticancer drugs Eribulin Masylate (E7389) macrolide marketed as Halaven, and Monomethyl auristatin E derived from dolastatin peptides isolated from marine shell-less mollusk *Dolabella auricularia* commercialized as Adcetris (Jimenez et al., 2019). In 2007, about 40 years after its initial extraction from the Caribbean ascidian *Ecteinascidia turbinata*, ecteinascidin-743 (ET-743), also known as trabectedin or its trade name Yondelis, was the first marine-derived drug to be approved for anticancer treatments (Rinehart et al., 1990; Corey et al., 1996; Martinez et al., 2000; Aune et al., 2004). Multiple strategies were tested to produce the drug at an industrial scale, including mariculture and total synthesis, and eventually a semisynthetic process starting from cyanosafracin B, an antibiotic obtained by fermentation of *Pseudomonas fluorescens*, solved the problem (Cuevas et al., 2000; Cuevas and Francesh, 2009). Since then, the discovery of marine-derived compounds extracted from metazoans is expanding (Molinski et al., 2009; Rocha et al., 2011) and sponges and cnidarians are the most prominent as far as novel marine natural products discovery is concerned (Qi and Ma, 2017; Blunt et al., 2018; Carroll et al., 2020). The annual number of the new compounds reported for each from the aforementioned two phyla is consistently high at approximately 200 along the past decade, while the respective number for other widely investigated marine phyla, such as mollusks, echinoderms and tunicates (subphylum Chordata), is limited between 8 to 50 for the same period (Carroll et al., 2020). Bryozoans are acknowledged as an understudied group of marine metazoans concerning metabolites production, with the newly discovered natural products fluctuating from zero to slightly over 10 over the last few years (Blunt et al., 2018; Carroll et al., 2020). Those pronounced differences in marine product discovery either reflect an innate trend towards the production of complex secondary metabolites (Leal et al., 2012) or the study effort towards a phylum or another taxonomic group, often due to the lack of taxonomic expertise for some groups. Yet, the pronounced differences in discovered marine products do not appear to reflect the biodiversity included within each group, since sponges, cnidarians, bryozoans and echinoderms each include a comparable number (6289 to 11873) of accepted species (Costello and Chaudhary, 2017; WoRMS Editorial Board, 2020). At the same time, mollusks are one of the richest marine metazoan phyla in terms of biodiversity with 48803 extant species (WoRMS Editorial Board, 2020) but a poor source of novel marine products (17 new metabolites in 2017, according to Carroll et al. 2020). Chemical diversity is an interesting measure to assess the potential of each metazoan phylum towards the production of novel marine products. Blunt et al. (2018) compiled a principal component analysis of different physico-chemical properties for compounds isolated from 15 different marine phyla, and highlighted the large numbers of chemicals produced by sponges. Moreover, fine-tuning of the extraction process has been shown to increase metabolic diversity in marine sponge extracts (Bayona et al., 2018). While sponges and cnidarians, in particular corals, can be cultured on a large-scale to support drug discovery (Duckworth and Battershill, 2003; Leal et al., 2013), the provision of marine invertebrates in sufficient quantities for implementing a battery of activity tests on their natural products is challenging as sustainable supply should be ensured.

Sponges are prominent candidates for bioproduction-oriented cultivation, due to their simple body plan and regenerative capacity, and their richness in bioactive substances. While sponge farming in the open sea has been proposed (and often accomplished) as an effective strategy to resolve the supply bottleneck and ensure sustainable production of sponge-derived compounds (Duckworth, 2009), it is still limited by the necessity to destructively collect primary material from wild populations in various phases of the cultivation. Little progress has been made towards 'closed life cycle cultivation', i.e. successfully inducing reproduction and recruitment of larvae to the aquaculture (Abdul Wahab et al., 2012). Cell culturing can provide advantages in terms of control of desirable parameters and fine-tuning of production (Sipkema et al., 2005), while recent advances have shown potential for the establishment of sponge cell lines (Conkling et al., 2019). Some advances have been made towards sustainable processes for the production of sponge metabolites (Pérez-López et al., 2014).

Since many marine macroinvertebrates host massive associations with microbes, the origin of the metabolite might be the organism itself, its symbiont (e.g. bacteria) or food (e.g. algae) of the metazoan (Loureiro et al., 2018). Hence, metazoans can act as concentrators of natural compounds. For example, the antitumor depsipeptide kahalalide F (Shilabin and Hamann, 2011; Salazar et al., 2013), produced by the alga *Bryopsis* ssp. (Hamann et al., 1996) at very low concentrations, was originally identified from the sea slug *Elysia rufecens* that feed on these algae and accumulated this natural compound at 5,000 fold higher concentrations (Hamann et al., 1996).

3.2 Macroalgae

Seaweeds, or marine macroalgae, represent an overlooked bioresource, but they have gained wide interest in recent years as a result of their increasing popularity in the human diet. The term "seaweed" includes macroscopic and multicellular marine red, green and brown algae. Seaweeds are a rich source of proteins, minerals, iodine, vitamins, non-digestible polysaccharides, and bioactive compounds with potential health benefits. From the ecological point of view, seaweeds demonstrate high interactions and inter-relationships with various other marine species and the surrounding environment. They are present in several habitats: the intertidal zone, tropical reefs and to a lesser extent in salt marshes. The actual distribution of seaweed species is controlled by several environmental and biological factors. Dense beds of large brown seaweeds (i.e. *Fucales* and *Sargassum* species) are frequently found together with red and green algae of smaller size. The competition for space between species in these areas is strong, and the removal of one species can impact the structure of the whole community. Certain seaweeds can be invasive in some regions and their exploitation for biotechnology applications showed promising results and has been already used for skincare products (Rotter et al., 2020b). In this way the adverse effects on local biodiversity can be mitigated. In addition to their nutritional value, seaweeds exhibit antimicrobial, immunostimulatory and antioxidant properties (Gupta and Abu-Ghannam, 2011). Due to the growing demand for marine proteins and lipids in the fishfeed industry over the last 20 years, the use of seaweed extracts as prophylactic and therapeutic agents in shellfish and fish aquaculture has become increasingly popular (Vatsos and Rebours, 2015). There are also other macroalgal biomolecules (mainly polysaccharides and carotenoids) that can be used as a functional food, nutraceuticals and cosmeceuticals. In 2016 alone, over 32.8 million tons of seaweed were reported to be produced from capture and aquaculture worldwide, and the seaweed production, including brown, red and green seaweeds, increased around 10% annually in the last three years, mainly due to an increase in the aquaculture sector (EC, 2020). Globally, over 95% of seaweeds are produced through aquaculture (FAO, 2018) with Asian countries being the leaders in this activity, whereas European seaweed production is primarily based on the harvesting of natural resources (FAO, 2018; Ferdouse et al., 2018), primarily kelp (*Laminariales*) and in smaller volumes knotted wrack (*Ascophyllum nodosum*) for production of alginate and seaweed meal. *Saccharina latissima* is presently the species that are cultivated in Europe on a large scale. European seaweed harvest was approximately 390,000 tons in 2000 (FAO[4]) and has since declined to reach 273,240 tons in 2019 (FAO - Fisheries and Aquaculture Information and Statistics Branch - 18/12/2019). The opening of new applications and markets (i.e. biofuel, feed and food supplements, food ingredients, nutraceuticals, cosmetics) has further increased the demand for seaweed biomass and it has contributed to the development of aquaculture on several species (Stévant et al., 2017). The yield of the active substances extracted from seaweed is ranging from less than 1% up to 40% of the dry algal mass, depending on various factors, such as target metabolite, species and season (Pereira and Costa-Lotufo, 2012). To increase the value of commercial seaweeds it is important to study the remaining biomass after the extraction of the target substances to find future applications, for example with *Gelidium sesquipedale* and *Pterocladiella capillacea* after agar extraction (Matos et al., 2020). Although many seaweed extracts are known to exhibit immunostimulatory properties, which can contribute to health protection, in most studies these effects were never examined in parallel with the antimicrobial effects. Indeed, understanding the physiological effects of seaweeds or seaweed extracts is a complicated task, they can exhibit different properties depending on the geographical origin and season of harvest. The extraction method of the bioactive components is also an important factor that can affect the efficacy of the final extracts. Furthermore, seaweed derived therapeutics need careful management of administration (Rasch et al., 2004; Mata et al., 2013; Thanigaivel et al., 2014; Vatsos and Rebours, 2014). The feasibility of using any of these extracts on a commercial scale needs to be examined to define the extraction cost and reveal how the extracts can be delivered under intensive farming conditions. It is finally worth mentioning that seaweeds can act as habitats for endophytes (Flewelling et al., 2015; Manomi et al., 2015; Mandelare et al., 2018). Endophytes are microorganisms (bacteria and fungi) that live in the plant tissue without causing external symptoms and in many cases support the plant immunity and growth under extreme or unfavorable conditions and against pathogens and pests (Liarzi and Ezra, 2014; Bacon and White, 2016; Gouda et al., 2016). Endophytes were demonstrated as a rich source of secondary metabolites with potential for use in medical, agricultural and industrial applications (Liarzi and Ezra 2014; Gouda et al 2016).

Seagrasses are higher plants that live in marine environments; along with seaweeds, they play a significant role in coastal ecosystems as they provide food, habitat, and are nursery areas for numerous vertebrates and invertebrates. Seagarsses are rich in secondary metabolites like polyphenols, flavonoids and fatty acids which are the key factors that are involved in the adaptation to changing biotic and abiotic environments and for the defense mechanism (Custódio et al. 2015). They have potential cytotoxic, antimicrobial, and antifouling activity (Zidorn, 2016). Zosteric acid from the genus *Zostera* is one of the most promising natural antifoulant due to its low bioaccumulation and no ecotoxicity effects (Vilas-Boas et al., 2017).

3.3 Microalgae

Microalgae are the major primary producers in marine environments. As photosynthetic organisms, they can convert light and carbon dioxide into algal biomass with high contents of carbohydrates, lipids, proteins and a variety of primary and secondary metabolites (Vignesh and Barik, 2019). They serve as a food source or food additives for higher organisms. Diatoms alone account for ~40% of the total carbon fixation in oceans and contribute to approximately 20% of the global oxygen production

[4] http://www.fao.org/fishery/statistics/global-aquaculture-production/en

(Vincent and Bowler 2019). Microalgae have high growth rates and short generation times. On average, they can double their biomass in two-five days. Microalgal biomass yields have been reported to be up to 20 kg/m^2/year for microalgal cultures (Varshney et al., 2015) and they have the potential of transforming 9–10% of solar energy into biomass with a theoretical yield of about 77 g of biomass/m^2/day, which is about 280 ton/ha/year (Melis, 2009; Formighieri et al, 2012), even though practical yields in large scale cultivation are much lower (e.g. 23 g/m2/day, Novoveska et al., 2016). As their specific growth rate is 5-10 times higher than those of terrestrial plants, the interest in microalgal biotechnology has increased over the last decades. Microalgal biomass could be considered as genuine "cell factories" for the biological synthesis of bioactive substances used in the production of food, feed, high-value chemicals and other biotechnological applications (de Morais et al., 2015; de Vera et al., 2018). Large-scale cultivation of marine microalgae is usually performed on land, although near-shore cultivation facilities have been tested (Wiley et al. 2013). Saltwater is pumped from the ocean and introduced into ponds or bioreactors where marine microalgae are cultivated on a larger scale. While land is still needed for microalgae cultivation, this does not have to be the high-quality arable land required for agricultural activities. Microalgal production may utilize wastewater as a nutrient source and/or recycled CO_2 from industrial facilities or geothermal power plants.

Microalgae-based production combines several bioprocesses: cultivation, harvesting, extraction and the isolation of active components. Parameters to be controlled in cultures include levels of carbon dioxide, light, oxygen, temperature, pH, and nutrients as they have a crucial effect on biomass activity and productivity. The control of predators in industrial scale microalgae production must also be considered (Rego et al., 2015). The biochemical composition of microalgae can be manipulated by optimizing parameters or by applying specific environmental stress conditions, such as variations in nitrate concentration, light spectrum and intensity or salinity, to induce microalgae to produce a high concentration of target bioactive compounds (Markou and Nerantzis, 2013; Yu et al., 2015a; Vu et al., 2016; Chokshi et al., 2017; Smerilli et al., 2017).

Microalgal species can produce valuable compounds including antioxidants, enzyme polymers, lipids, polyunsaturated fatty acids, peptides, vitamins, toxins and sterols (Moreno-Garcia et al., 2017). The main components of microalgae are lipids, proteins, and carbohydrates. Microalgae also contain pigments such as chlorophylls, carotenoids, keto-carotenoids and phycobiliproteins (Zullaikah et al., 2019). Due to their precious contents, microalgae are considered as a promising feedstock for renewable and sustainable energy, cosmetics, food/feed industry both as whole biomass and as nutritional components, colorants or stabilizing antioxidants and for the synthesis of antimicrobial, antiviral, antibacterial and anticancer drugs (Suganya et al., 2016; Moreno-Garcia et al., 2017). Microalgal biomass can also be used in bio-surfactants, bio-emulsifiers, and bioplastics. Unused biomass can be used as fertilizers or it can be digested for biomethane production. Among microalgae, marine dinoflagellates are efficient producers of bioactive substances, including biotoxins, some of the largest, most complex and powerful non-protein molecules known in nature (Daranas et al., 2001). These molecules are of great interest not only due to their negative impact on seafood safety, but also for their potential uses in biomedical and pharmaceutical applications (de Vera et al., 2018). Nonetheless, the supply of these metabolites remains a challenge due to their low cellular abundance and the tremendous difficulties involved in large-scale microalgae production (Gallardo-Rodríguez et al., 2012; Molina-Miras et al., 2018).

Currently, the most lucrative large-scale production systems focus on a pigment (Novoveská et al., 2019), for example, the production of β-carotene from genus *Dunaliella*. *Nannochloropsis* species-rich in ω-3 fatty acids are used for eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) production. The cultivation of *Haematococcus pluvialis* in large quantities for the commercial production of astaxanthin has also attracted worldwide interest, as this compound is considered to be a "super antioxidant" with numerous applications, ranging from human nutraceuticals and cosmetics to aquaculture feed additives and beverages (Kim et al., 2016; Shah et al., 2016). Many other marine microalgae are being investigated as they are genetically adapted to a variety of environmental conditions. The basis of these adaptations and/or acclimation mechanisms are still being uncovered (Mühlroth et al. 2013; Brembu et al., 2017a; Brembu et al., 2017b; Mühlroth et al. 2017; Alipanah et al., 2018; Sharma et al. 2020). Consequently, several research groups have been bioprospecting new microalgal strains that accumulate bioactive compounds of interest (Nelson et al, 2013; Bohutskyi et al., 2015; Erdoğan et al., 2016[5]).

Selection and breeding of marine algae lags some 10,000 years behind similar activities for terrestrial plants. Recent developments in the fields of molecular biology, genomics and genetic engineering have enabled the implementation of detailed functional studies and precise editing of traits/properties of marine microalgae (Nymark et al., 2016; 2017; Kroth et al., 2018; Sharma et al., 2018; Serif et al., 2018; Slattery et al., 2018; Nymark et al., 2019; Sharma et al., 2020). The molecular biology and genomics tool-box for marine microalgae is growing rapidly and we will soon be able to optimize growth, stack properties and transfer complete metabolic pathways from one species to another or from other types of organisms (Noda et al., 2016; Slattery et al., 2018; Nymark et al., 2019; Sharma et al., 2020).

3.4 Bacteria and archaea

Marine environments are known to host unique forms of microbial life (Poli et al., 2017). So far, an increasing number of thermophilic, halophilic, alkalophilic, psychrophilic, piezophilic and polyextremophilic microorganisms (mostly bacteria and archaea) have been isolated that are capable of proliferating even under extreme conditions as a result of their adaptation strategies involving diverse cellular metabolic mechanisms. As the survival strategies of extremophiles are often novel and unique, these microorganisms are frequently characterized by extraordinary phenotypic traits that are accompanied by the production of novel secondary metabolites or enzymes of biotechnological interest. An example is the enzymes of thermophilic or psychrophilic bacteria that are capable of degrading polysaccharides, proteins and lipids for various applications in food industry or modifying exopolysaccharides for tissue engineering (Poli et al., 2017). In a recent study, bacteria were isolated across the water column of the CO_2-venting Kolumbo submarine volcano (northeast Santorini, Greece) and the strains originating from the hydrothermally active zone in the crater's floor (500 m depth) were found to be several-fold more tolerant to acidity, antibiotics and arsenic, compared to the strains isolated from overlying surface waters (Mandalakis et al., 2019). Assuming that the large differences in phenotypic traits imply a genetic adaptation of species to harsh environmental conditions and thus differences in their biosynthetic capacity, the biotechnological potential of bacteria from deep hydrothermal systems deserves an in-depth investigation.

Many archaea are extremophiles. Enzymes derived from extremophiles (extremozymes) are superior to the traditional catalysts because they can perform industrial processes even under harsh conditions, under which conventional proteins are completely denatured (Egorova and Antranikian, 2005). Hyperthermophiles, whose preferred growth temperatures lie above 80 °C, consist mostly of archaea. Ideal extremozymes for application in a sustainable biorefinery with lignocellulosic waste material as feedstock should exhibit high specific activities at high temperatures combined with superior

[5] http://www.egemacc.com/en/

thermostability (Krüger et al., 2018). Over 120 genomes of hyperthermophiles have been completely sequenced and are publicly available (Krüger et al., 2018). Interesting strains belonging to extremophilic archaea that grow at elevated temperatures have been studied in detail such as the genera found in marine environment *Pyrococcus*, *Thermococcus* or *Thermotoga* (Krüger et al., 2018). Thermostable archaeal enzymes were reported to have higher stability towards high pressure, detergents, organic solvents, and proteolytic degradation (Sana, 2015). However, marine organisms, especially those in biofilms or adapted to live in extreme environments, such as hyperthermophiles, may be recalcitrant to typical lysis methods, hindering protein extraction or modifying the yield of this important step. The hyperthermophile and radiotolerant archaeon *Thermococcus gammatolerans* which was isolated about 2,000 m deep in the Pacific Ocean, is a typical example of such a difficult non-model organism (Zivanovic et al., 2009; Hartman et al., 2014). Chitin is the second most abundant polysaccharide after cellulose, but its use as a feedstock is limited by the inability to hydrolyze it into simple sugars. Several chitinases have been characterized by extremely thermophilic archaea from marine biotopes (Straub et al., 2018, Chen et al., 2019). Recently, the first thermophilic chitinase able to hydrolyze the reducing end of chitin was reported in *Thermococcus chitonophagus*, potentially expanding the opportunities for using this material (Andronopoulou and Vorgias, 2004; Horiuchi et al., 2016).

Halophilic archaea (haloarchaea) comprise a group of microorganisms from hypersaline environments, such as solar salterns, saltlakes and salt deposits. These microorganisms can synthesize and accumulate both C40 and C50 carotenoids (Giani et al., 2019). The bioactivity of the carotenoid extracts of some haloarchaea indicates their antioxidant, antihemolytic and anticancer activity (Galasso et al., 2017; Hou and Cui, 2018). The main haloarchaeal carotenoid, bacterioruberin, a C50 carotenoid, presents a higher antioxidant ability when compared to other commercially available carotenoids, such as beta-carotene (Yatsunami et al., 2014).

Some groups of bacteria, like actinobacteria and cyanobacteria, stand out for their capacity to synthesize secondary metabolites. About 660 new natural products from marine bacteria were discovered between 1997 and 2008, with 33% and 39% of them originating from cyanobacteria and actinobacteria (Williams, 2009). Since then, the new hits from marine bacteria exhibited an accelerated increase. The number of marine bacterial natural products identified each year from 2010 to 2012 was approximately 115, from 2013 to 2015 was 161, while it increased to 179 in 2016 (Blunt et al., 2018). It is estimated that 10% of all marine bacteria are actinomycetes (Subramani and Aalbersberg, 2013; Subramani and Sipkema, 2019). With less than 1% of the actinomycetes isolated and identified so far, the marine environment represents a highly promising resource in the field of biodiscovery. Between 2007 and 2017, 177 new actinobacterial species belonging to 29 novel genera and 3 novel families were described (Subramani and Sipkema, 2019). The Gram-positive actinobacteria are a major chemically prolific source of bioactive metabolites with anticancer, antimicrobial, antiparasitic, anti-inflammatory, antibiofilm activities, and anti-fouling, among others (Prieto-Davó et al., 2016; Bauermeister et al., 2018; Bauermeister et al., 2019; Girão et al., 2019; Cartuche et al., 2019; 2020). There are several marine-derived actinomycete metabolites described. Marinone and neomarinone, a pair of sesquiterpene napthoquinones, generated considerable interest in the biosynthesis community because terpenes are extremely rare in bacteria and because the biosynthetic gene cluster could represent a unique mechanism to produce hybrid polyketides through combinatorial biology (Pathirana et al., 1992). Cyclomarin A, a cyclic heptapeptide, also generated interest due to its uniquely modified amino acids and potent anti-inflammatory activity (Renner et al., 1999; Lee and Suh, 2016). The obligate marine actinomycetes from species *Salinispora tropica* produce salinosporamide A, a unique and highly potent β-lactone-γ-lactam proteasome inhibitor currently in Phase III of clinical trials for the treatment of cancer (Mincer et al., 2002; Feling et al., 2003; Fenical et al., 2009), clearly illustrates the importance of these microorganisms (Potts et al., 2011). Marinomycins A-D is also chemically unique, bioactive metabolites with potent cytotoxicity towards HCT-116 human colon carcinoma, possessing unprecedented polyol-polyene carbon skeletons presenting unique biological activities evaluated *in vivo* tumor models (Kwon et al., 2006) and currently in clinical trials. *Streptomyces* sp. is a potential source of novel anti-cancer compounds as they exhibit significant *in vitro* cytotoxicity and pronounced selectivity in a diversity of cancer cell lines (Hughes et al., 2009a, 2009b) and have also shown potent antibiotic activity against several human pathogenic strains (Nam et al., 2010; Jang et al., 2013). However, as non-medical applications require less strict bioassays for certification, a recent trend for *Streptomyces*-derived antimicrobial compounds is their use in antifouling and antibiofilm products due to their capacity to inhibit the growth of biofilm-forming species (Cheng et al., 2013; Bauermeister et al., 2019; Pereira et al., 2020).

Peptides are the most abundant group of bioactive compounds produced by cyanobacteria, constituting nearly 65% of their bioactive metabolites (Chlipala et al., 2011). The most common biological activity displayed by cyanobacterial compounds is cytotoxicity and proteases inhibitory activity (Dittmann et al., 2015; Demay et al. 2019).

Marine Firmicutes and Proteobacteria have been also shown to produce diverse bioactive compounds, like indole derivatives, alkaloids, polyenes, macrolides, peptides, and terpenoids (Soliev et al., 2011). Firmicutes represent 7% of the bioactive secondary metabolites produced by microorganisms. The genus *Bacillus* is a relevant representative of the Firmicute phylum and is a common dweller of the marine environment. It shows high thermal tolerance and rapid growth in liquid media (Stincone and Brandelli, 2020). Species of the genus *Bacillus* are a prolific source of structurally diverse classes of secondary metabolites and among them macrolactins, cyclic macrolactones consisting of 24-membered ring lactones, stand out due to their antimicrobial, anticancer, antialgal and anti-viral activities (Gustafson et al., 1989; Li et al., 2007; Azumi et al., 2008; Berrue et al., 2009; Mondol et al., 2013).

Though Proteobacteria is the most abundant phylum in the ocean, representing 55% of ocean bacteria (Sunagawa et al., 2015), these bacteria are scarcely explored in terms of biotechnological potential. Recent genome mining studies have however demonstrated that marine Proteobacteria hold many biosynthetic gene clusters in their genomes that may be responsible for the production of bioactive compounds (Buijs et al., 2019). More than 15% of their genome is dedicated to natural products biosynthesis with structural features that include halogenation, sulfur-containing heterocycles, non-ribosomal peptides, and polyketides with unusual biosynthetic pathways (Timmermans et al., 2017), remaining an attractive source of new drug leads and cell factories (Buijs et al., 2019). For example, more than 20 biosynthetic gene clusters (BGCs) are found in a single genome of pigmented *Pseudoalteromonas* strains (Paulsen et al., 2019), comparable to the prolific phylum Actinobacteria. Apart from their important ecological role in marine ecosystems, marine members of *Pseudoalteromonas* have proven to be important producers of various antibiotics (Bowman, 2007; Fehér et al., 2010; Chen et al., 2012). A *Pseudoalteromonas* strain isolated from Huon Estuary in southern Tasmania, Australia also shows potent algicidal activity on harmful algae species implicated in bloom events (Lovejoy et al., 1998). Additionally, these microorganisms have also been found to produce several pigmented compounds with antifouling activity (Holmström et al., 2002; Egan et al., 2001, 2002).

The main challenge still remains the establishment of pure cultures of all bacterial divisions, an essential prerequisite for the development of marine biodiscovery. While genomics allows access to the genetic information of uncultured microorganisms, the availability of the organisms is essential to develop its full potential (Joint et al., 2010).

3.5 Fungi

Marine fungi are widespread in the oceans and colonize different ecological niches; they are found associated with organisms of all trophic levels and can act as saprobes, symbionts and parasites (Wang et al., 2012; Raghukumar, 2017; Poli et al., 2018). Despite the increasing effort of marine mycologists to contribute to the discovery of new species (Abdel-Wahab et al., 2017; Bovio et al., 2018; Devadatha et al., 2018; Poli et al., 2019, 2020), marine fungi are still an understudied group compared to other marine microorganisms (Tisthammer et al., 2016). Jones and collaborators (2015) estimated that about 10,000 marine fungi are still waiting to be described. Marine fungal strains can be isolated from different substrates, such as invertebrates, decaying wood, seawater, sediments, seaweeds and mangrove detritus. Many factors influence the occurrence and distribution of marine fungi including hydrogen ion activity, hydrostatic pressure, ionic composition and concentration, osmotic response, oxygen availability, salinity, tidal exposure, temperature, availability of substrates for growth (Pang et al., 2016). Since fungi are major marine decomposers, their distribution and seasonal variability typically follow the abundance of the organic matter and its seasonal variability. The highest levels of fungal biomass are encountered in coastal environments and the upper 30 m of the sea surface, rather than in deep seawaters (Wang et al., 2012). On the contrary, deep-sea sediments represent the sink for organic matter creating a habitat where fungi are the dominant eukaryotic microbes (Nicoletti and Andolfi, 2018). Around 120 fungal species have been retrieved from sediments of deep-sea hydrothermal vents (Xu et al., 2018). Several other substrates have been investigated for the isolation of marine fungi, however, due to the increasing interest in natural products, the most studied fungal communities are those associated with invertebrates, algae and plants (Garzoli et al., 2015; Bovio et al., 2017; Gnavi et al., 2017; Raghukumar, 2017; Garzoli et al., 2018; Marchese et al., 2020). However, the uncultivable fungi, described by using HTS techniques, still represent the major component of the marine fungal community (Comeau et al., 2016; Rämä et al., 2017; Xu et al., 2018). Marine fungi can produce hydrolytic and/or oxidative enzymes including alginate lyase, amylase, cellulase, chitinase, glucosidase, inulinase, keratinase, ligninase, lipase, nuclease, phytase, protease, and xylanase (Bonugli-Santos et al., 2015). These enzymes can have their optimum activity at temperatures ranging from 35 to 70°C, and at pH values spanning from 3.0 to 11.0. The ability of marine fungi to adapt to high saline conditions and extreme pH represents a major biological advantage over terrestrial fungi, and it gives them a higher versatility in biotechnological applications.

Marine fungi produce diverse bioactive molecules (Silber et al., 2016). Besides, their biotechnological potential is still incontestable: among the 1,277 new natural products described in 2016, marine fungi account for 36% of these newly described molecules (Blunt et al., 2018). In comparison, the respective percentage of molecules originating from marine bacteria was only 14%. In five years (2010-2015), 285 antibacterial and antifungal compounds were isolated from marine fungi (Nicoletti and Andolfi, 2018). The first reported group of bioactive compounds from marine fungi were cephalosporins, a class of β-lactam antibiotics originally isolated from the *Acremonium chrysogenum* (which was previously known as *Cephalosporium*) by Giussepe Brotzu in 1945. Most of the published work on secondary metabolites of marine fungi has focused on just a few genera, mainly *Penicillium*, *Aspergillus*, *Fusarium* and *Cladosporium* (Imhoff, 2016; Marchese et al., 2020). Marine fungi are found to be a promising source of pharmacologically active metabolites (Imhoff, 2016), with novel anti-cancer, anti-bacterial, anti-viral, anti-plasmodial, anti-inflammatory, but rarely antifouling, activities (Rajasekar et al., 2012; Bovio et al., 2019a). They are also useful in the production of biosurfactants (Cicatiello et al., 2017; Pitocchi et al., 2020), enzymes (Nicoletti and Andolfi, 2018) and bioremediation (Bovio et al., 2017). Interestingly, endophytic fungi that are associated with seaweeds and macroalgae produce biologically active secondary metabolite with antibacterial, antifungal anticancer and other beneficial properties (Mathan et al., 2013; de Felício et al., 2015; Teixeira et al., 2019). Furthermore, marine fungal enzymes can be used for cleaning, textile, leather, biofuel, pulp, and paper industries; for food and beverages; for animal feed; for environmental, pharmaceutical and cosmetic applications (Bonugli-Santos et al., 2015).

3.6 Thraustochytrids

The thraustochytrids represent a unique protist group of eukaryotic microorganisms that provides bioactive compounds including antimicrobial agents. These marine heterotrophic protists (a fungus-like clade of *Stramenopiles*, (class Labyrinthula of the Chromista Kingdom), in contrast to their common referral as microalgae, are in fact not microalgae because they are not photosynthetic and lack plastids (Leyland et al., 2017). Under culture conditions that change from one species to the others, each one of the thraustochytrid taxa develops ectoplasmic networks generated by a unique organelle termed the sagenogen (or sagenogenetosome). Some growing cells exhibit gliding mobility associated with the ectoplasmic networks. Their reproduction activities involve the formation of heterokont, biflagellate zoospores (Porter, 1990). Yet, the level of diversity of thraustochytrids remains to be uncovered since an increasing number of strains and species are being recovered. Thraustochytrid species are usually characterized by either their developmental modes, sorus form or their spore type (Porter, 1990). However, these traditional systematic approaches are not enough, as just a limited list of morphological characters are available, a status that facilitated the development of molecular markers, of which the most common are the 18S rDNA sequences (Mo et al., 2002). Yet, due to the limitation of 18S rRNA clone library construction and the emerged cultivation-dependent approaches, the full diversity of thraustochytrid species is not even partly elucidated (Liu et al., 2017).

Thraustochytrids, considered as oleaginous microorganisms, are developing into an increasingly important marine source of polyunsaturated fatty acids (PUFAs) for a wide range of biotechnological applications (primarily for the industrial production of the ω-3 fatty acid docosahexaenoic [DHA]). They are however also known to be pathogens of edible invertebrates and common contaminants of marine invertebrate cell cultures (Ilan et al., 1996; Rinkevich and Rabinowitz, 1993; Rinkevich, 1999; Bowels et al., 1999; Rabinowitz et al., 2006) as they are found on surfaces and within the bodies of most marine organisms. Based on these characteristics, the thraustochytrids are considered as an alternative to fish oil and an eco-friendly solution to overfishing. In addition, they are further known to produce saturated fatty acid which are renewable sources of biofuels, for biodiesel, and as a potential source of squalene and carotenoids, two other commercially important compounds that show an increasing market potential (Aasen et al., 2016). Thraustochytrid strains are now available that produce enzymes with multiple hydrolytic activities that have potential in diverse industrial applications and that secrete various commercially important enzymes, a wide range of them being secreted constitutively, including agarases, amylases, pectinases, chitinases and carrageenases (Shirodkar et al., 2017). They are probably the only eukaryotic group that may digest tar balls. Further, the oil from one strain of thraustochytrids (*Schizochytrium* sp.) has been designated safe for human and for animal consumption by the U.S. FDA. Thus, it is not surprising to find that 731 patents on thraustochytrids were published just between 1999 and 2018 (United States and Eurasia are top in the list), with most patents targeting the chemical and human disciplines, leading by ω-3 oils biosynthesis patents (Colonia et al., 2020).

The thraustochytrids have been isolated from a wide range of marine habitats including the open sea (where they were collected by 'pollen traps') and the deep sea, and are commonly found in waters rich in organic materials. They are particularly abundant in mangrove environments where they are major colonizers, feeding on decaying materials (Morabito et al., 2019) while playing important ecological roles as active degraders of organic materials and primary consumers (Mo and Rinkevich, 2001). The thraustochytrids, as other heterotrophic marine protists, can consume dissolved organic matter and particulate organic matter as energy sources, and as a result, they are considered to share a distinct ecological niche in marine ecosystems with potentially significant roles in marine biogeochemical cycles (Liu et al., 2017).

The development of the research on thraustochytrids has largely facilitated the exploration of novel thraustochytrid strains and species from various marine habitats and ecological niches, and since the beginning of this century, research efforts are involved in fermentative trials, to select appropriate thraustochytrid strains for the industry and for the initiation of best culture conditions to obtain high yields (Rabinowitz et al., 2006; Xie et al., 2017). Further, thraustochytrids have novel extracellular lipases, for which sequences have not yet been elucidated (Ishibashi et al., 2019). Some thraustochytrids including species of *Schizochytrium* and *Aurantiochytrium* produce long-chain polyunsaturated lipids like docosahexaenoic acid (DHA, C22:5 n3) and docosapentaenoic acid (DPA, C22:5 n6) (Heggeseth et al., 2019). To produce their DHA, thraustochytrids use a sophisticated system that differs from the classical fatty acid synthase system (synthesized by a polyketide synthase, instead of by the standard fatty acid synthesis), yet, very little has been developed regarding process optimization and their optimal use (Aasen et al., 2016).

3.7 Viruses

While viruses are identified as pathogens in many marine organisms, little research effort has been put towards their presumed role as associated organisms. There are an estimated 10^{30} virioplankton in the world's oceans, the majority of which are bacteriophages (Parsons et al., 2012). Viruses can live as virioplankton, which is a dynamic component of marine environments, with a turnover time of 2–4 days or associated with macro- or microorganisms encompassing enormous genetic diversity and serving as a reservoir of genes for prokaryotic communities (Angly et al., 2006; Dinsdale et al., 2008). The presence of viruses and virus-like particles (VLPs) in association with corals (Blackall et al. 2015), sea cucumbers (Nerva et al., 2019a) and sponges (Webster and Taylor 2011) has been reported using morphological and molecular approaches. In the sponge phylum, elaborate microscopical studies have demonstrated a variety of morphological entities that can be hosted in different body compartments of the host, such as within the cells of the sponge or the associated microbes, or the extracellular matrix and the epithelium (Pascelli et al. 2018). While functional, mutualistic roles have been envisaged for viruses and VLPs associated with corals (van Oppen et al. 2009), relevant studies have been lacking in sponges. Specifically, most marine viruses are cyanophages and are important players in biogeochemical cycles and drivers of the evolution of their hosts (Brussaard et al., 2008) by influencing microbial population size through their lytic capacity, altering their metabolic output and providing an immensely diverse pool of genetic material available for horizontal gene transfer. Only recently, viruses infecting and replicating in marine fungi were reported and many new mycoviruses were identified in a handful of studies (Nerva et al., 2016; 2018; 2019b). Contrary to most bacterial viruses, mycoviruses do not cause lysis of the fungal host cell and accumulate to high levels without specific cytotoxic effects as persistent and often cryptic infections creating multi-level interactions with their hosts: they can modulate host behavior to successfully spread and survive in the environment and provide adaptive advantages (Mehle et al., 2012; Selman et al., 2012; Son et al., 2015). Very recently it has also been highlighted how mycoviruses can modulate the production of secondary metabolites for example mycotoxins (Nerva et al., 2019b). Based on this evidence, the search for mycoviruses within each fungal isolate and the investigation of their contribution to biosynthetic processes is of high biotechnological interest, and it may open a new avenue in the discovery of unique natural products..

By some estimations, bacteriophages are the most abundant entities on this planet (Harada et al., 2018). Their valorization in early anti-infection trials was hampered by the discovery of antibiotics but it is being reintroduced due to the global emergence of antibiotic resistance (Coffey et al., 2010). Bacteriophages can be used as an alternative for antibiotics, either against resistant pathogens (Mattey and Spencer, 2008) as well as can be used to steer aquaculture processes that relies on a massive use of antibiotics (Culot et al., 2019). Additionally, bacteriophage biotechnology is directed to control bacterial pathogens in important crops and to limit the risk of pathogens reaching food chains by decontamination of livestock (Harada et al., 2018). Bacteriophages can also be used as cost-efficient, highly stable and specific biosensors to effectively detect pathogenic bacteria (Singh et al., 2020).

4 Methodology for exploration of marine bioresources

4.1 Data analysis, storage and sharing

Omics approaches have become increasingly popular in recent decades due to decreasing costs of DNA sequencing, the availability of mass spectrometry (metabolomics, lipidomics, proteomics) and bioinformatics development. The major limitations that prevent taking full advantage of the rapidly growing volumes of biological data from omics technologies, are the lack of standardization and/or description of experimental/sampling conditions. Other limitations are the lack of user-friendly bioinformatic annotation pipeline tools and well-curated and populated data repositories (Glöckner and Joint, 2010) and well curated and populated sequence repositories. These tools would enable faster detection of new marine species and their biomolecules and faster adoption of molecular protocols that are necessarily coupled with subsequent network analyses, bioinformatics and biostatistics. Typically, biodiversity data is generated from long-term monitoring campaigns or novel exploratory expeditions and are presented as lists of species presence and (relative) abundance. As these lists can be lengthy, their manual inspection is time-consuming and limits access to important pieces of information. Visualizing these data using network analysis tools can uncover important associations and relations between species in a specific location (Orlando-Bonaca and Rotter, 2018; Mozetič et al., 2019). Importantly, other traits can be included in the biodiversity datasets (i.e. chemodiversity, physical parameters), which can uncover complex network associations of marine organisms and their compounds and can help to determine the target organisms for biotechnological exploitation. Bioinformatics approaches are typically developed and used for assembly, alignment, gene/genome annotation, function prediction and data integration. After determining the species and compounds of interest, the next step is to compare the organism growth / metabolic engineering conditions, productivity and yields of the compound(s) of interest. Novel approaches such as the use of Solid-Phase Microextraction (SPME) have been recently demonstrated as a successful means of non-invasive untargeted metabolome screening of marine organisms (Bojko et al., 2019). This method comprises the use of specially coated probes that combine metabolite sampling and extraction in a single step, thus allowing *in vivo* metabolomic screening in the marine environment, while allowing both polar and non-polar metabolites to be extracted efficiently (Reyes-Garcés et al., 2018), thus emerging as a useful field tool to discover novel compounds of interest from complex marine holobionts. Statistical models are then often used for the determination of differential expression of genes or metabolites of interest and determination of optimization protocols. These are necessary steps for the development of scale-up production protocols.

Classical taxonomy, based on morphology is still the basis of the (macro)species description. However, bioprospecting of marine microorganisms using state-of-the-art molecular methods generates vast amounts of data. By digitalizing these data, scientists are now offered rapid access to biodiversity data that can be integrated, thus providing information on distribution and genome diversity (La Salle et al., 2016). However, not all data are open access, as data providers may have their policies concerning privacy and confidentiality, which limits scientists to share their experience and collaboration. Importantly, any data provider should develop internal metadata guidelines that provide minimal information about the data stored that will enable their use in the future. In 2011, the European Commission (EC) launched a new Open Data Strategy for Europe after realizing that data generated by the public sectors are vast and although financed by the public funds, data are not always available and accessible. Hence, the EC highlighted the unused potential of public sector data to spur innovation, economic growth, and answer to societal challenges such as food security and healthcare[6]. As a result, Europe now hosts at least two infrastructure initiatives, publicly hosting many marine microbial strains: MIRRI (Microbial resource research infrastructure[7]) and EMBRC (the European marine biological resource center[8]). MIRRI is an infrastructure initiative for preserving microbes that can be cultured for future exploitation and providing coordinated actions to facilitate access to genetic resources – data, microbial strains and expertise. EMBRC and LIFEWATCH connect marine stations that provide direct access to the sea, marine resources and different services. Also useful for marine biotechnology development are databases of chemical structure: ChemSpider[9]; databases of carbohydrate structures and other glycobiology-related fields (e.g. Glycosmos, Glycomics at Expasy, GlyGen, CarboMet[10]); MarinLit[11], a database of marine natural products literature that has been active since the 1970s, and the newly developed Natural Products Atlas[12], an open-access database for microbial natural products discovery (van Santen et al., 2019). These databases play an important role in facilitating track and trace of the specimen and the chemical compounds they synthesize, thus enabling a rapid dereplication (Blunt et al., 2012; Collins, 2019a). Importantly, the policymaking and scientific community are supporting the public availability of all information and materials from these databases to avoid the fragmentation of expertise, unequal database access, and the estimated $10 billion annual losses due to incorrect reference material (Collins, 2019a).

4.2 The chemical inventory

There is a wide range of marine natural products, from relatively small primary and secondary metabolites, with molecular weight usually lower than 1,500 Da, which comprises around 34,000 compounds according to the latest version of the marine natural products database MarinLit[11], with a wide range of biological activities, to macromolecules such as enzymes and polysaccharides.

[6] https://ec.europa.eu/digital-single-market/en/open-data

[7] https://www.mirri.org/home.html

[8] http://www.embrc.eu/

[9] http://www.chemspider.com/

[10] https://glycosmos.org/, https://www.expasy.org/glycomics, https://glygen.org/, https://carbomet.eu/

[11] http://pubs.rsc.org/marinlit/

[12] https://www.npatlas.org/joomla/

Proteins, carbohydrates and lipids from marine organisms are crucial in our diet, but can also be involved in the development of novel processes for the production of higher added value compounds. A wide range of applications has been described for marine enzymes in the food industry and human health, and marine polysaccharides have also found multiple biomedical and tissue engineering uses (Fernandes, 2014; Eswara Rao et al., 2017; Joshi et al., 2019). However, only a fraction of the enzymes derived from marine organisms have been isolated and characterized. Hence, enzymes as biocatalysts from marine organisms are a relatively untapped resource for discoveries.

Dereplication is a crucial step in any natural product discovery used to identify known metabolites in complex and heterogeneous matrices with a broad concentration of bioactive molecules, preventing the re-isolation and re-characterization of known bioactive compounds (Gaudencio and Pereira, 2015; Kildgaard et al., 2017). The last two decades have seen a revolution in the development of new dereplication strategies. These usually consist of the combination of analytical techniques: chromatography (usually HPLC or uHPLC) with a detection method, mass spectrometry (MS) in the high resolution (HRMS) mode and/or with ion fragmentation (MS/MS), or nuclear magnetic resonance (NMR). The remarkable advances in analytical instrumentation along with the development of suitable databases have enabled the development of the fast dereplication processes required in current drug discovery programs based on natural products (Pérez-Victoria et al., 2016). The use of LC-MS/MS based molecular network workflows enable the unearthing of the real chemical inventory of chemical extracts and downstream fractions, and significantly increase the annotation rate of metabolites (Oppong-Danquah et al., 2018), allowing the targeted isolation of new metabolites (Li et al., 2018). Furthermore, biological activities can be mapped into such networks, facilitating the rapid discovery of (new) compounds that are responsible for bioactivity (Fan et al., 2019).

Recently, open-access knowledge bases containing tandem mass (MS/MS) spectrometry data such as the Global Natural Products Social Molecular Networking (GNPS[13]) or structures of microbial natural products (The Natural Products Atlas[12]) are greatly enhancing the efficiency of dereplication processes leading to the identification of new molecules and natural product scaffolds (Wang et al., 2016). Small Molecule Accurate Recognition Technology (SMART), using NMR data, constitutes a step forward in the automatic identification or classification of new natural products, especially when combined with GNPS. Metabolite identification based on HR-MS/MS and NMR along with freely accessible and commercial databases were reviewed by Wolfender et al., 2019. The next steps are: (i) the use of databases ZINC or Reaxys for virtual ligand screening[14] and discovery to predict binding sites based on chemical similarity to known ligands to identify protein targets of bioactive molecules (Sterling and Irwin, 2015; Cockroft et al., 2019), and (ii) the use genomic data in combination with molecular networks enabling dereplication also at the frontier between chemistry and biology.

4.3 Production of secondary metabolites by microbes

The efficiency and rate of secondary metabolites production by microorganisms are closely dependent on their growing conditions and potential for up-scaling. Indeed, one of the driving forces for the production of specific metabolites, compared to the constitutive ones that are usually produced in any conditions, is the simulation of the marine microbes-native environment, including the interactions with other microorganisms as usually occurs in nature (Takahashi et al., 2013; Vallet

[13] http://gnps.ucsd.edu

[14] http://zinc.docking.org/; https://www.reaxys.com

et al., 2017). As a consequence, standard conditions will not always support fungal or bacterial production of interesting secondary metabolites (Reich and Labes, 2017). To increase the availability of microbial biomass and minimize the environmental damage impacts of organismal collections, new strategies are needed to develop sustainable *in vitro* approaches for the cultivation of whole organisms or of individual cell types from targeted marine species (Rinkevich 1999, 2005, 2011; Barnay-Verdier et al., 2013; Ventura et al., 2018, Maristem COST Action[15]). This is also of importance for sponges and corals, which host endosymbiotic intracellular microorganisms. The appropriate cultivation settings should provide the optimal conditions for the holobionts (Rinkevich, 1999).

When cultured, microorganisms do not always continue to produce the same metabolites (Wijffels, 2008). To mimic the naturally occurring interactions, the co-culture (solid media) or mixed fermentation (liquid media) with other organisms have been demonstrated to stimulate the production of secondary metabolites (Romano et al., 2018), some modulating the quorum sensing, with application both in antibiotics and anticancer in pharma sectors (Bertrand et al., 2014). The interactions can be modulated to mimic the natural environment for chemical-ecological study, including symbiosis studies; and for example specific antagonistic organisms can be introduced to promote the synthesis of antibiotics (Bertrand et al., 2014; Romano et al., 2018; Bovio et al., 2019b). Enhanced lipid production in microalgae has for example been documented in co-cultivation of microalgae and bacteria, including cyanobacteria (Ferro et al., 2019; Gautam et al., 2019; Toyama et al., 2019), as well as in co-cultivation of microalgae and fungi (Arora et al., 2019). Growth-enhancement in microalgae has been documented in co-cultivation of microalgae with other microalgae (Ishika et al., 2019), as well as with fungi (Wang et al., 2019) and protozoa (Li et al., 2019).

In 2002, Bode and collaborators highlighted that the modification of cultivation parameters such as temperature or salinity can activate silent genes that determine the synthesis of new secondary metabolites; this method is called OSMAC approach (One Strain - Many Compounds, Bode et al., 2002). Today, the manipulation of the fermentation conditions and the use of epigenetic modifiers (i.e. 5-azacytidine and suberoyl bis-hydroxamic acid) are widely recognized as an effective tool to stimulate the production of secondary metabolites and find new bioactive molecules in microorganisms (Adpressa and Loesgen, 2016; González-Menéndez et al., 2016; Romano et al., 2018).

4.4 Extraction, fractionation, isolation, structure elucidation and biological activity screening

There is a great need for exploring new extraction protocols to identify bioactive ingredients. Extraction is the first step to obtain natural products from organisms. Several extractions methods can be applied, depending on the characteristic of the compounds of interest. At lab scale, maceration or percolation with solvents (organic or water) at room temperature are the methods most commonly used. The selection of the solvent depends on the solubility of the metabolites of interest, but there are other aspects such as cost and safety that are considered. To increase efficiency, avoid the use of large amounts of solvents and reduce extraction time, some greener extraction methods have been developed such as supercritical fluid extraction - SFC (Essien et al., 2020), subcritical water extraction - SWE (Zhang et al., 2020), a moderate electric field - MEF (Gavahian et al., 2018), ultrasound (Kumari et al., 2018), pressurized liquid extraction - PLE, microwave-assisted extraction - MAE and enzyme-assisted extraction - EAE (Grosso et al., 2015). They all share the advantages of

[15] http://maristem.eu/

time reduction, optimized solvent consumption and yield and selectivity increase, therefore making these procedures more suitable for industrial processes.

Organisms that grow in liquid media require several steps to obtain biomass for biochemical extraction. Biorefinery is costly and requires a long biomass processing that involves multiple unit operations, including cultivation, harvesting, product extraction and stabilization. All of these contribute to the commercial competitiveness of bioproducts. One major bottleneck is the initial amount of biomass of organisms available at the beginning of the process. Another issue is the differences in bioactive molecules produced by the same organisms but grown under different environmental conditions or different seasons. Homogenization can take place only if they can be cultivated under the same conditions, which is not always possible. The extraction method involves several steps including cell disruption, utilization of supercritical fluid extraction, chemicals or enzymes. Extraction, which directly impacts the product properties, is one of the main commercial constraints for the production of fuels, foods, and feeds, and also of high-value products like polysaccharides and pigments. It is not easy to generalize extraction, as it is a highly specific process and strongly depends on the desired products (Rizwan et al., 2018). Recently, it has been suggested that "milking" of secondary metabolites from marine organisms can significantly reduce the time and cost of this process (Hejazi and Wijffels, 2004; Kim et al., 2016). "Milking" is a term used to describe non-destructive regenerative extraction of target metabolites from marine organisms while keeping the cells metabolically active just like producing milk from cows. Unlike conventional biorefinery, which requires a time-consuming cultivation step and intensively energy-consuming harvesting and cell disruption steps, the milking process does not require the reculturing of cells from the exponential stage of the cultivation process nor harvesting and cell disruption (Hejazi and Wijffels, 2004). Milking has been demonstrated in two microalgal species; *Dunaliella salina* for β-carotene and *Botryococcus brauni* for hydrocarbon (Hejazi et al., 2004; Moheimanni et al., 2014). These microalgae have a weak/no cell wall and release storage compounds to the cultivation medium under stress (exocytosis), which remains the prerequisite for the success of milking.

Generally, crude extracts consist of a complex mixture of natural products that require several fractionation steps to obtain pure compounds. The separation method used depends on the physical or chemical properties of the individual natural product and the amount needed. Chromatography, especially column chromatography, is the main method used to obtain pure natural products from a complex mixture. Several chromatographic options can be used depending on the polarity, size or ionic strength of the compounds of interest. Ideally, the process would involve a one-step purification and a scale-up system that allows working with small amounts of crude extract that are at the same time relevant for the industrial level (Ebada et al., 2008; Zhang et al., 2018).

Suitable and standardized scalable extraction and purification methods are not yet established. New separation techniques are necessary, capable of treating dilute solutions or solutions containing only minute amounts of target molecules in the presence of vast amounts of accompanying compounds in both small and large-scale processes, even in the presence of particulate matter. In addition to standard separation procedures, applications of magnetically stabilized fluidized beds or magnetically modified two-phase systems can be used successfully for the separation of natural products (Safarik and Safarikova, 2004). In most cases, magnetic carriers bearing an immobilized affinity or hydrophobic ligand or ion-exchange groups, or magnetic biopolymer particles having affinity to the isolated molecule are mixed with a sample containing target compound(s). Following an incubation period when the target compound(s) bind to the magnetic particles, the whole magnetic complex is easily and rapidly removed from the sample using an appropriate magnetic separator. After washing out the contaminants, the isolated target compound(s) can be eluted and used for further work. All the steps of the purification procedure can take place in one single vessel. The separation process can be performed directly in crude samples containing suspended solid material (Safarik and Safarikova, 2004). Magnetic techniques based on the application of magnetic nano- and microparticles have been successfully used for the preconcentration, detection and determination of different types of xenobiotics, viruses, microbial pathogens and protozoan parasites in water samples (Safarik et al., 2012). Currently, magnetic solid-phase extraction (Safarikova and Safarik, 1999) is one of the most often used preconcentration procedure used in (bio)analytical chemistry.

The structure elucidation of secondary metabolites is of critical importance, especially when developing products for the pharmaceutical sector. No risks can be taken, especially considering the tragic case with the sedative drug thalidomide (Thalidomid®) prescribed to relieve pregnancy nausea, in which one of the stereoisomers had the diseased bioactivity and the other caused birth defects in thousands of children. This tragedy marked a turning point in product testing, resulting in the development of systematic toxicity testing (Kim and Scialli, 2011). Marine natural products have unique complex chemical scaffolds, and their structure elucidation is obtained through HR-MS, 1D and 2D NMR data analysis. Computer techniques are being developed to aid structure elucidation such as Computer-Assisted Structure Elucidation (Soong et al., 2020). However, these are not fully implemented in practice. To determine the absolute configuration methods, single-crystal X-ray diffraction and Mosher´s are often used. Recently, the elucidation of biosynthetic pathways through genomic sequencing is also used to support the absolute configuration assignment.

Screening for biological activity of marine extracts or extracted compounds is an important next step in determining their applicability for a specific purpose. It is typically done using *in vitro*, *ex vivo* or *in vivo* approaches. The bioassay-guided identification and purification of novel compounds is common practice (Strömstedt et al., 2014; White et al., 2019). First, the selection of the extraction protocol may affect the possibility of testing for biological activity, as not all solvents used for extractions are biocompatible. Second, an array of selected bioassays can be performed to discover novel bioactive compounds, encompassing for example antimicrobial, anticancer, antiviral, antiparasitic, anti-inflammatory, nematotoxic, or entomotoxic activities. These bioassays are usually very specific, fast and often in a high-throughput format. They test for individual bioactivity, such as inhibition of a specific enzyme, or inhibition of bacterial growth using only one bacterial species. Since the amount of the extracted material is usually limited, a limited array of bioassays can be performed on a given extract. Therefore, the choice of bioassays and their quality determine the potential of the extract/compound for future applicability. In contrast to the use of dereplication to avoid the rediscovery of compounds from different extracts/bioresources, the use of different bioassays for the same extract is encouraged to avoid missed opportunities for alternative bioactivity. Namely, there is a myriad of bioactive compounds in any extract and it is becoming accepted that any compound can execute multiple bioactivities. Repurposing of compounds with known bioactivity for a different one is increasingly becoming an attractive proposition because it involves the use of de-risked compounds, with potentially lower overall development costs and shorter development timelines (Pushpakom et al., 2019). Importantly, as in any application the compounds in original or transformed form inevitably end up in the environment, an important bioassay to include in the screening process is the ecotoxicity assessment (Walker, 2008, Yan et al., 2019). Moreover, in the last decade *in silico* methods have been developing to assess both bioactivity and toxicity of known bioactive compounds and their synthetic analogs or novel compounds with known chemical structures (Yang et al., 2018, Liu et al., 2019).

Screening and preclinical validation have been essentially performed in rodents, mostly because, among the model organisms used in pharmaceutical and biomedical research, they have a large repository of genetic/molecular tools available and are genetically similar to humans. However, ethical and economic concerns associated with low throughput (Giacomotto and Ségalat, 2010), have potentiated the search for alternative models that may be used as the first line of screening, thus decreasing the burden on mammalian models, that still need to be used as a final step of validation before clinical trials. *In vitro* and *ex vivo* screenings using cell lines and tissues representative of both healthy and pathological human conditions, are currently used to identify biological activities of marine-derived extracts (Laizé et.al., 2014, Kolanti et al., 2016; Yuan et al., 2017, Carson et al., 2018a, Martínez Andrade et al., 2018, Sun et al., 2018). Nevertheless, the results obtained, even if promising, still need to be validated *in vivo*. Zebrafish has become a model of increasing interest for human disorders and it allows both low-throughput screenings using adults, and high-throughput screening using larvae, thus fitting the requirements to develop vertebrate whole-animal assays (Lee et al., 2017). The increasing number of molecular tools and the development of mutants and transgenic fish (Hwang et al., 2013; Cornet et al., 2018), capable of highlighting almost any given tissue (Chen et al., 2017), allowing *in vivo* follow-up of treatments through fluorescence microscopy is also an asset, associated to their easy maintenance, short life cycle, large progeny and translucent larvae.

5 Production upscaling

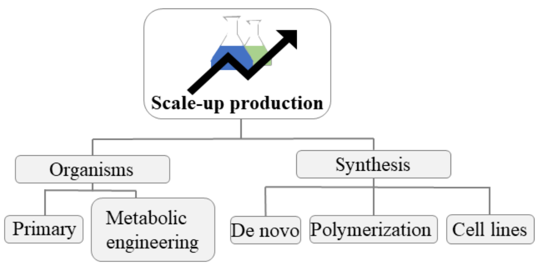

Figure 3: Production scale-up possibilities.

The long-term socioeconomic sustainability of production is an important aspect of marine biotechnology. It relies on the stakeholders' capabilities to manage the resource sustainably and to provide the social, economic and regulatory conditions to ensure a living income. Therefore, wild harvesting is not desirable as it could endanger the species itself or its associated species and impact the whole marine ecosystem. The product quality and quantity should also not be dependent on the seasonal fluctuations and abundance of biomass or its target compound. From an economic and social perspective, commercial/industrial activities preferably maintain regular volumes of production throughout the year. The translation of research laboratory discoveries into commercial items that entail obtaining and maintaining the supply levels are nowadays recognized as the major hurdle in bringing marine natural-product-based molecules to market (Newman and Cragg, 2020). With regards to sustainability and the zero-waste principle, an important consideration when growing marine biomass and isolating bioactive compounds is cascading, circular economy and zero waste/waste utilization. The biorefinery should be designed typically in a cascading approach to exploit all bioactive and not just the dominant or more economic compounds. The biological leftovers from a cascading process could ultimately be valorized as a feed or low end as bioenergy (Tedesco and Stokes, 2017; Álvarez-Viñas et al., 2019).

There are two general production upscaling methods (Figure 3). One is the growth of whole organisms in controlled production such as bioreactors or aquaculture for seaweed, sponges and corals and the other concerns the use of whole organisms or their synthesized molecules. In the first case (Figure 3, left), when the organisms that naturally produce the compounds of interest are used, the desired properties for scaled-up products are a short production cycle and a high yield per unit (Li et al., 2019). One of the possible approaches for product harvesting is to trap the secondary metabolites secreted by the invertebrate or associated microorganisms to the surrounding water. This strategy has the advantage of preserving the producer organism with no stress or injury. The proof of concept was described recently for a device that traps the secreted metabolites with Amberlite XAD-16 (Vlachou et al., 2018). Based on this concept, the group patented and built Somartex for testing in different marine locations[16]. Alternatively, compounds of interest can be produced with plasmid-based expression systems in well-established prokaryotic and eukaryotic hosts such as *Escherichia coli*, *Saccharomyces cerevisiae* (Kroll et al., 2010; Mao et al., 2017), the yeast genus *Pichia* as well as mammalian cell systems.

Instead of culturing the whole organism, another possible focus is to establish cell lines from marine invertebrates (Figure 3, right). So far, this has not been successfully implemented. Nevertheless, some research groups are working on the improvement of invertebrate cell culture and recently a substantial increase in both the rate and number of cell divisions in sponge cells has been reported by optimization of the nutrient medium (Conkling et al., 2019). The other upscaling method (Figure 3, right), especially used for compounds from animals, is *de novo* chemical synthesis, laboratory polymerization, or a combination of methods (such as chemical modification of natural precursor, mainly of bacterial origin). This method can be very costly with many steps and low yields due to the chemical complexity of the compounds that often have many functional groups and chiral centers. An example is halichondrin B, a potent cytotoxic macrolide isolated from the sea sponge *Halichondria okadai* with a staggering 32 stereocentres (Hirata and Uemura, 1986; Ledford, 2010). Its structurally simpler analog, eribulin, has 19 stereocentres and is an FDA-approved drug for the treatment of metastatic breast cancer. However, its supply still consists of a 62-step synthesis (Ledford, 2010). When an entirely chemical production is required, strategies will very much depend on the kind of structure to be synthesized, but in some particular cases, as the synthesis of peptides or their derivatives, solid-phase approaches have proved to be the method of choice for their efficient production (Martín et al., 2014). In addition, biosynthetic steps merged with chemical synthesis steps to offer a simplified option for the total synthesis of some natural products (Kirschning and Hahn, 2012). Recently, enzymatic synthesis mimicking natural biosynthesis is starting to be used to synthesize natural products (Greunke et al., 2017).

[16] http://pilotunit.com/technologies/innovative-technology/somartex

6 Use case scenarios

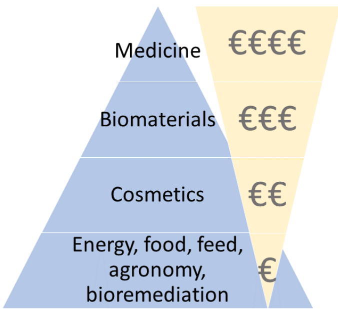

Figure 3: Marine biotechnology products pyramid value. Adapted from Day et al., 2016. The price / quantity ratio is depicted by the area of the triangles.

Marine biotechnology is considered to be one of the main pillars of bioeconomy. The main use case scenarios are discussed below, following the order of the marine biotechnology products pyramid value, presenting industrial sectors and products with substitution potential (Figure 4). A short, non-exhaustive overview presenting some of the European SMEs that specialize in delivering marine biotechnology products is included in Table 2.

The development of marine natural products is typically connected with enormous financial investments to sustain experimentation costs (Giugni and Giugni, 2010), especially in the medical sector. Intellectual property, primarily in the form of patents, facilitates the commercialization potential (Starling-Windhof et al., 2020). Since a growing number of marine-based drugs are entering clinical trials, there is a cumulative increase in the number of patents published in the last years (Mandhare et al., 2019).

6.1 Table 2: A non-exhaustive overview of the European SMEs offering marine biotechnology products.

Company	Website	Country	Product
EstAgar AS	http://estagar.ee/	Estonia	A texturant and gelling agent – furcellaran from the red seaweed *Furcellaria lumbricalis*
Ocean Basis	https://www.oceanbasis.de/en	Germany	Naturally occuring substances from the marine environment used for wellbeing (food, nutraceuticals, cosmetics)

6.2 Energy

In terms of bioenergy, microalgae have been widely tested for the production of biodiesel, especially due to their chemical composition and global abundance (Chisti, 2007; Schenk et al., 2008; Singh and Dhar, 2011). Marine microalgae can contain high levels of lipids and their doubling rates exceed most terrestrial plants, making them suitable for the production of biofuel. Together with a large liquid fuel market and the need to break the dependence on fossil fuels, renewable fuel generated from algae was a celebrated prospect. One of the approaches was to apply electro-extraction of valuable biofuel compounds from microalgae, avoiding the use of solvents and other chemicals (Brennan and Owende, 2010; Goettel et al., 2013). However, while the technology is well-known and technically feasible, producing biodiesel from microalgae is not economically convenient at the moment (Williams and Laurens, 2010; Quinn et al., 2015; Abdo et al., 2016; Novoveska et al., 2018). The main reason for this is that microalgae cannot be grown at sufficiently dense cultures due to their inherent demand for light. As the culture grows denser, the microalgae become light deprived due to self-shading, which limits the maximum achievable density of the culture. This in turn results in high harvesting costs when dilute biomass has to be separated from large volumes of water. Currently, the research on genetic modification of marine microalga *Nannochloropsis* and *Phaeodactylum tricornutum* for biofuel production is still ongoing to overcome these obstacles (Du et al., 2018; Nymark et al. 2019).

Seaweed aquaculture can contribute to a sustainable supply of biomass for profitable biofuel production with the advantage of not competing with food crops for land or freshwater resources (Borines et al., 2011; Fernand et al., 2017). However, biogas and bioethanol production should focus on the use of residual and overabundant marine biomass to avoid competition with the biomass requirements of the seaweed food industry. The simultaneous production of combustible biomethane and disposal of undesirable marine biomass in a synergistic waste management system is a concept with environmental and resource-conserving advantages (Barbot et al., 2016). In addition to the direct use of biomass for biofuel, seaweed can be used in renewable energy systems as a viable, economic and environmentally friendly alternative to solid electrolytes used in dye-sensitized photovoltaic cells. Research conducted by Bella et al. (2015) on derived products from algae using green chemistry and multivariate-based preparation methods and smart activation via spontaneous sublimation, provides a concrete starting point for third-generation solar cells. These findings are also supported by Anand and Suresh (2015) who suggested that the exploration of vast marine pigment resources for their potential use as sensitizers in solar cells could provide low-cost and environmentally friendly alternatives to expensive ruthenium metal complex.

6.3 Food, feed and nutraceuticals

A large portion of human food and animal feed may need to be sourced from sustainable marine origins to address future food supply challenges, i.e. an increasing human population and a decline in terrestrial food resources (Olsen, 2011).

Whole marine organisms can be a source for innovative or new foods, especially those that are adapted from other diets, such as seaweed or jellyfish. Seaweeds have traditionally been used in Asia and Northern Europe as a food and are recently becoming more popular throughout European cuisine, although they are still considered an unusual foodstuff (Barbier et al., 2020). There is a current trend of consumers adopting organic, local and "natural" foods from clean environments which should increase acceptance and popularity of marine sourced foods/food ingredients. Jellyfish have been an important food source in Chinese cuisine for over 1000 years (Hsieh et al., 2001). By adapting the harvesting (using local species), preprocessing (omitting the use of alum salts) and preparation techniques, jellyfish are more recently being introduced as a food source in western-style cuisine (also as part of scientific projects, supported by the European Commission; two of which are PULMO[17] and GoJelly[18]). Therefore, opportunities exist to develop food-friendly processing protocols. However, strict regulatory mechanisms (e.g. Novel Food Regulation (EU) No 2015/2283) are another important bottleneck in the delivery of novel food from marine organisms. A novel food

[17] https://cordis.europa.eu/project/id/708698

[18] https://gojelly.eu

is defined as food that was not consumed to a significant degree within the EU countries before 15 May 1997, when the first Regulation on novel foods came into force (Regulation (EC) No 258/97; 2015/2283). Furthermore, there may be some safety considerations due to the bioaccumulation of toxic substances, which may present a risk of chronic poisoning, thus favoring culturing rather than harvesting, where possible. Seaweeds can accumulate heavy metals (mercury, cadmium and lead) if present in the surrounding environment. Therefore, in the EU, the identification and registration of potential toxic substances are covered by the REACH Regulation (Regulation (EC) No 1907/2006) and the allowed threshold values for some heavy metals in seaweed which are used as dietary supplements are covered within the Commission Regulation 1881/2006.

In addition to whole organisms, *compounds* from fish, shellfish, micro- and macroalgae, bacteria and fungi are used in the food and feed industries as natural preservatives, pigments, stabilizers, gelling agents, functional food ingredients, nutraceuticals, dietary supplements and prebiotics (Boziaris, 2014). Nutrition products with bioactive ingredients are envisioned to have medical benefits such as anticancer, antiinflammatory, antioxidant, antiosteoporotic, antimicrobial, antidiabetic, hypocholesterolemic and adipogenesis inhibition. Marine-derived polymers are also used as gelling, stabilizing, thickening, flocculent and binding agents. Examples include polyunsaturated and ω-3 fatty acids, astaxanthin, chitin, chitosan, chitooligosaccharides, chondroitin sulfate and glucosamine from shark cartilage and crustacean by-products, and spirulin from cyanobacteria (Boziaris, 2014; Harnedy and FitzGerald, 2015; Suleria et al., 2016). Moreover, the food and beverage industries use cold-active enzymes derived from marine organisms in the processing of heat-sensitive ingredients/products. The use of such enzymes avoids heat-induced changes to the nutritional and organoleptic properties of foods (Nikolaivits et al., 2017). The efficient release of the bioactive compounds for application in the food and feed industries can be aided by marine-derived enzymes having unique catalytic specificity and the ability to operate under extreme conditions. If any compounds are considered novel foods, there may be additional requirements, e.g. the supply of a scientific dossier concerning their quality and safety, which may require human intervention studies to validate their efficacy and safety.

A scheme of the process of using marine organisms as a source of food or feed is shown in Figure 5. To efficiently use marine organisms as a source of food and feed, the process of identification, isolation and nutritional value analysis is used to select species that could be used to produce food and feed. The next step represents the establishment of cultivation systems and feeding experiments that generate sufficient quantities of food/feed, using a comparative analysis with a control group that uses classic food/feed sources to compare the overall quality and palatability with the existing products.

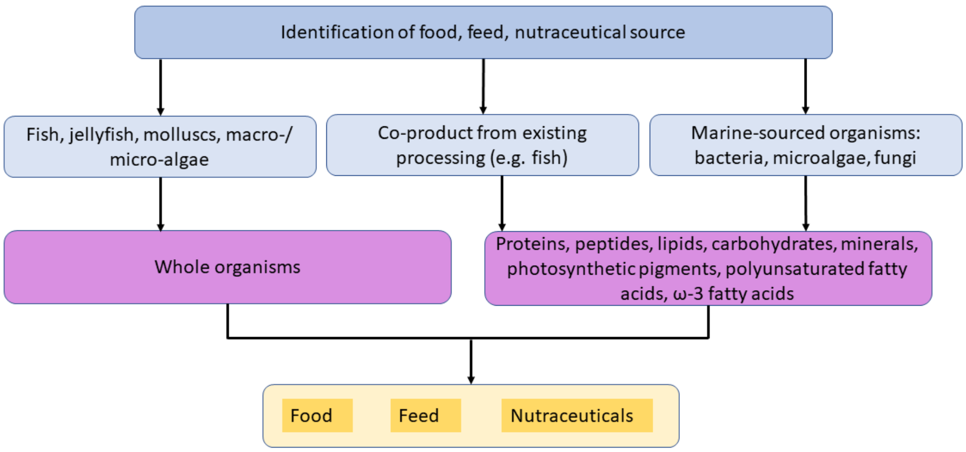

Figure 4: The workflow for using marine organisms as food or feed.

Fish meal is characterized by high protein content, digestible energy and balanced composition of essential amino acids, minerals and vitamins (Kaushik et al., 2004), while fish oil contains long-chain polyunsaturated fatty acids (PUFAs) and are mostly used in animal feed formulations to raise aquaculture and terrestrial livestocks. Although vast improvements have been made both in feed conversion efficiency and in utilizing waste streams (discards, offal), this situation is not sustainable (Guttormsen, 2002). The fish feed industry is therefore looking for sources of oils to replace fish oils and microalgae are a promising source, not only for essential lipids, but also for essential amino acids (Dineshbabu et al., 2019; Tibbetts et al., 2020). However, live feeds (in contrast to formulated feeds) are indispensable for the rearing of larvae of most marine fish species (Nielsen et al., 2017). Live feeds are usually based on *Artemia* or rotifers, while copepods are also becoming more common as live feeds, having a superior lipid composition, compared to other live feed organisms (Nielsen et al., 2017). To produce live feed organisms, the production of their prey organisms, typically microalgae, is necessary, and the microalgae have to be optimized for their content of essential lipids and amino acids to be the best feed for the zooplankton organisms (Vu et al., 2016).

6.4 Agronomy

Marine phytobiomass is currently being explored for different purposes in the agricultural sector (i.e. fertilizers, heat production in biogas plants, feeds) with large quantities available along the coastlines (Mossbauer et al., 2012). Historically, seagrasses and seaweeds were used as organic soil amendments in coastal areas to increase soil fertility and harvest yields (Acksel et al., 2017; Michalak and Chojnacka, 2018; Franzén et al., 2019). Marine biomass can also be used for crop protection. As an example, *Posidonia oceanica* was found do reduce weed pressure after application (Grassi et al., 2015) and the extraction of venom from jellyfish, namely *Rhopilema esculentum* and *Nemopilema nomurai*, can be used as a natural insecticide (Yu et al., 2005; Yu et al., 2015b). The chemical properties of marine biomass applied to land might also affect the microbial decomposition leading to improved soil structures and increased carbon sequestration rates with positive feedbacks to land restoration and the climate. Accordingly, the exploration of marine biomass and their extracts have the potential to push the agriculture sector towards new market chains and more sustainable production. However, the chemical characteristics of marine biomass may lead to a slow decay in the soil (Papazian et al., 2019). As a result, the short-term availability of nutrients is slower in comparison with other conventional fertilizers. In response to this, controlled composting processes were developed to increase nutrient use efficiency. They can however cause environmental trade-offs due to increased risk of N_2O and NH_3 releases during the compost production (Han et al., 2014). In addition, marine biomass can exceed the legal thresholds of undesired substances due to their ability to accumulate anthropogenic chemicals (Malea et al., 2018; Franzén et al., 2019). Thus, to use marine biomass directly as organic fertilizer in crop production with large quantities in the future, additional research and innovation is necessary to provide biomass with a homogenic structural and chemical quality. In any case, the establishment of either resilient production chains for processing beach wrack biomass (Emadodin et al., 2020) or a predictable yield of farmed seagrass and seaweed are necessary to ensure that the direct biomass use for agriculture will become economically resilient in the future (Chiaiese et al., 2018; Philis et al., 2018).

Plant biostimulants are nowadays used to enhance the nutrition efficiency, abiotic stress tolerance, crop yield and quality traits (du Jardin, 2015; Popko et al., 2018). Biostimulants are extracts derived from organic material that are able to stimulate the growth and development of several crops under both optimal and stressful conditions. Biostimulants are heterogenic, representing a composite of polysaccharides, minerals, vitamins, oils, fats, acids, pigments and hormons (EL Boukhari et al., 2020). Protein hydrolysates have been reported to exert stimulatory effects on plants (Colla et al., 2017). Extracts made by seaweeds, microalgae and cyanobacteria have been identified to contain phytohormones (as auxins, cytokinins, gibberellins) and plant growth regulators (as abscisic acid, jasmonic acid, polyamines, ethylene) which are known to play key roles in plant growth, development and defense (Sharma et al., 2014). Moreover, high protein content in some cyanobacteria with specific amino acid profiles are sought to provide amino acids for key phytohormones (Sharma et al., 2014; Garcia-Gonzalez and Sommerfeld, 2016; Chiaiese et al., 2018; Mógor et al., 2018). Microalgal extracts are therefore increasingly used as biostimulants and biofertilizers in agriculture. Biofertilizers are products containing living microorganisms or natural substances that can improve chemical and biological soil properties, stimulating plant growth, and restoring soil fertility (Ronga et al., 2019). Finally, chitosan can be used as a coating for fertilizers, pesticides, herbicides, nematocides, and insecticides for their controlled release to soil and chitosan films are used to coat seeds and leaves to prevent microbial infection (Sudha et al., 2014).

6.5 Bioremediation, ecosystem restoration, climate change mitigation

A schematic representation of the application of marine biotechnology for bioremediation (either using whole cells or their metabolites) is shown in Figure 6. Marine invertebrates have been used in antifouling management and control, particularly sponges (Stowe et al., 2011; Ganapiriya et al., 2012). Bacteria from the phyla proteobacteria, actinobacteria, cyanobacteria, bacteroidetes and firmicutes can be used as an alternative process for the degradation of aromatic pollutants, such as polycyclic aromatic hydrocarbons (Nikolaivits et al., 2017). These bacterial communities have a great biodegradation potential for various types of hydrocarbons, aromatics and carbohydrates in oil-polluted sediments and petroleum spills (Atlas and Hazen, 2011; Acosta-González and Marqués, 2016). Hydrocarbon-degrading bacterial taxa have been uncovered on plastic marine debris using HTS, which supports the theory of potential of plastic degradation in the ocean by consortia of microbial taxa (Zettler et al., 2015). Microorganisms synthesize enzymes that can degrade plastics, e.g. lipases, alkane hydroxylases, laccases and others. However, the interactions between plastic and microbial consortia need to be further investigated to provide realistic mitigation measures (Urbanek et al., 2018). Marine fungi represent potential bioremediation agents: fungi that produce lignin-degrading enzymes are used in decolorization of highly colored effluents from paper, pulp mills, textile and dye-making industries (D'Souza et al., 2006), they also have strong oil degradative capabilities (Simister et al., 2015; Bovio et al., 2016) or are used in the bioremoval of Cu and Zn from sediments (Cecchi et al., 2019). Both micro- and macroalgae have been shown to remove nutrients, heavy metals, some pharmaceutical compounds and even capture free-floating microplastics from surrounding waters (Sundbaek et al., 2018; Mondal et al., 2019; Bulgariu and Bulgariu, 2020). Additionally, seaweed farms provide habitat and shelter for a variety of marine organisms. Due to their high detoxification efficiency, low cost and demand for nutrients, seaweeds and seagrasses can be used as biosorbents to remove pollutants from wastewater (Pennesi et al., 2015).

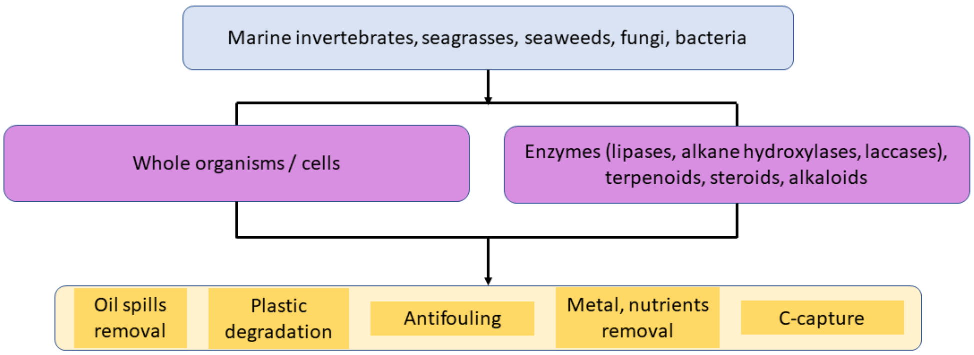

Figure 5: The potential of marine biotechnology for bioremediation.

Microalgae also can bioaccumulate heavy metals. Therefore, they can be used in bioremediation of effluents from industries with toxic heavy metals (Dwivedi, 2012; Rath, 2012; Kumar et al., 2015; Zeraatkar et al., 2016). Among them, *Chlorella*, *Scenedesmus*, *Tetraselmis* and *Spirulina* are reported to bio-sequester toxic heavy metals with high uptake capacity (Pérez-Rama et al., 2002; Aksu and Dönmez, 2006; Gokhale et al., 2008; Şeker et al., 2008; Mirghaffari et al., 2015). Microalgae remove heavy metals through adsorption or absorption mechanisms. Roy et al. (1993) reported that the sorption of heavy metals is a two-step process. The first step is rapid surface adsorption by cell wall polysaccharides and other functional groups such as carboxyl, hydroxyl, sulphate and other charged groups, which differ in affinity and specificity for various organic and inorganic compounds (Crist et al., 1981; Volesky, 1990; Bulgariu and Gavrilescu, 2015). The second step is a slow process that requires energy for the uptake of heavy metals into the cell interior (Wang et al., 2010). Like other organisms, microalgae synthesize metal-binding peptides, namely the cysteine rich metallothionein, which neutralize the toxic effect caused by heavy metals (Cobbett and Goldsbrough, 2002; Perales-Vela et al., 2006).

In addition to heavy metal biosorption, microalgae have bioremediation potential of emerging contaminants (EC), primarily synthetic organic chemicals (Sutherland and Ralph, 2019). EC typically fall into several broad categories, including pharmaceuticals, personal care products, illicit drugs, artificial sweeteners, pesticides, plasticisers, and flame retardants (Petrie et al., 2015; Norvill et al., 2016; Tran and Gin, 2017). Reported rates for adsorption of EC have been variable, with adsorption rates reported to be from 0 to 100% (Peng et al., 2014; Guo et al., 2016; de Wilt et al., 2016; Ali et al., 2018; Gojkovic et al., 2019).

Macroalgae are dominant primary producers in coastal areas and open seas, but a substantial part of this biomass is transported to deep sea and sediment, where the macroalgal carbon is sequestered from the atmosphere (Krause-Jensen and Duarte, 2016; Ortega, 2019). Macroalgae have recently been getting attention due to their potential for C-capture which is important to mitigate climate change. Further, they are of strategic importance to provide bio-based fertilizers from marine organisms as the compost may increase the carbon storage within the soil, thus reducing carbon dioxide emissions (Radziemska et al., 2019). In addition, seaweed added as a feed additive has the potential to reduce methane emission from cattle. Ruminants, and mainly cattle are considered as a major culprit in the emission of greenhouse gas, mainly in the form of enteric methane (Herrero and Thornton, 2013) with a high impact on climate change. This causes high pressure on the livestock sector forced to take mitigating actions to reduce the production of greenhouse gasses, but on the other hand, it needs to increase production efficiency because of the ever-increasing population and the globally changing consumption patterns. Recently, the potential of the marine red seaweed *Asparagopsis taxiformis* added as a feed amendment to reduce enteric methane emission was evaluated. Ruminant production is the largest anthropogenic contributor to the global methane budget (Dangal et al., 2017). Dried *Asparagopsis* was added in (small) quantities up to 0.2% in the normal cattle diet. Methane reduction of 98% has been reported without inhibiting the fermentation process or live-weight-gain on beef cattle (Roque et al., 2019; Kinley, 2020). At this stage, a few -mainly tropical- seaweed species have been evaluated via *in vitro* studies for their methane reducing capacity (Machado, 2014).

Among metazoans, sponges have been investigated as a natural bioremediation solution (e.g. Fu et al., 2007; Stabili et al., 2009), due to their capacity, as active filter-feeders, to primarily feed on the ultraplankton fraction (less than 5 microns particle size) of the particulate matter (Pile, 1999), along with dissolved organic matter (de Goeij et al., 2008a,b) in the surrounding seawater. Additionally, sponges –or their microsymbionts– show the capacity to partake of and accumulate metallic trace elements, as well as various organic pollutants (Bauvais et al., 2015; Gentric et al., 2015), rendering them prominent candidate bioindicators or bioremediators.

6.6 Cosmetics and cosmeceuticals

Marine compounds recently started to be incorporated into skincare and make-up products. Their drug-like benefits produce pharmaceutical hybrids in which the bioactive ingredients are added to the topical or oral cosmetics to produce a cosmeceutical with enhanced proprieties. There are examples of products that are already on the market mostly from microorganisms (bacteria, microalgae, fungi), but also from macroalgae, fish and corals (Martins et al. 2014; Corinaldesi et al., 2017; Brunt and Burgess, 2018). Examples of substances of interest for cosmetic applications are (i) mycosporine-like amino acids (MAAs), produced by marine organisms under high UV stress (cyanobacteria, macro and microalgae). These compounds absorb UV radiation between 310-360 nm and are considered as photoprotective and antiageing agents (de la Coba et al., 2009); (ii) exopolysaccharides, produced by several microorganisms that increase the moisture content of the skin (Satpute et al., 2010); (iii) carotenoid and polyphenolic compounds that can act as antioxidants (Sachindra et al., 2007; Lopes et al., 2016); (iv) enzymes and peptides that may act as anti-aging agents by protecting collagen stores (Chen et al., 2011). Importantly, many of the marine skincare products that are already in the market are not pure compounds but treated extract or enriched mixtures (Martins et al., 2014).

Examples of cosmeceuticals used for hydrating, moisturizing, anti-wrinkle and anti-aging that use algae extracts are: Biotherm by Blue Therapy, La Mer, Elemis, OceanBasis, Guam algae by Lacote, and La Prairie. The use of microalgae extracts occurs in Dermochlorella DG by CODIF Reserche &

Nature, XCELL-30 by Greensea, Alguronic Acid by Algenist and Alguard by Frutarom. The use of fungal extracts occurs in Eyedeline and Brighlette by Lipotec. Resilience by Estée Lauder uses pseudopterosin typetricyclic diterpene glycosides isolated from gorgonians. They show wound-healing, anti-inflammatory and analgesic properties to prevent irritation caused by exposure to the sun or chemicals. Other interesting and potent marine-derived cosmetic ingredients are Hyadisine, Antarticine and Hyafini, derived from extremophilic marine microorganisms (Martins et al., 2014). Marine polymers are increasingly used in cosmetic products, e.g. SeaCode by Lipotec with a mixture of extracellular glycoproteins (GPs) and other glucidic exopolymers produced by fermentation of a *Pseudoalteromonas* sp. from Antarctic waters for soothing and reducing irritation of sensitive skin against chemicals, and with hydrating, anti-wrinkle and expression lines attenuator properties. Potassium alginate and fucoidan from brown algae, aluminum silicate from sea mud, chitin from crustaceans, shell 'powder' from oysters, and carrageenan from red algae are some examples of less differentiated but widely used marine active ingredients. Marine jellyfish and fish-derived collagen (developed also within the GoJelly project[18]) and gelatin are also excellent functional ingredients for the cosmetic industry. Nevertheless, the marine environment remains an undervalorized resource for cosmetic discovery.

6.7 Bio-inspired materials

Biomolecules and biomaterials from marine sources have useful characteristics such as increased salt tolerance, pressure tolerance, cold adaptivity, heat tolerance. They may have novel physical, chemical/stereochemical as well as original biochemical properties (Trincone, 2011). Although there are wide possibilities for use of marine-based products for development of bio-inspired materials in medicine, there are still several challenges that must be solved. For instance, the isolation and purification of the biopolymers play an important role in targeted drug delivery and control of the sustained drug release concentrations. Moreover, the reproducibility of materials composition maintaining the same properties from the same species, regions and even seasons, is another challenge that needs to be solved. Marine products are used for in-depth studies of functional marine biomaterials in biomedical field - biopolymers, biominerals and bioceramics. Applications of these materials include hard and soft tissue engineering, bio-adhesives, dental biomaterials, and drug and cell delivery systems. Bioactive ceramic materials are developed from corals, shells and sea urchins, using them as sources for hydroxyapatite synthesis, which is the main inorganic material in bone structure (Palavaniene et al., 2018; Pawelec and Planell, 2019; Haugen et al., 2019). The structural organization of marine organisms, particularly sponges, has inspired many technical solutions in fabrications of biomaterials, architecture and aerodynamics (Macha et al., 2019). Several sponge taxa are known to produce inorganic skeletal elements (spicules) composed of amorphous, hydrated silica, through an enzymatic process (Voigt et al., 2017). This process, along with properties of the sponge-produced siliceous structures has led to several mimicking attempts targeting biomaterials for mainly biomedical (Müller et al., 2006; Müller et al., 2007, Schröder et al., 2007; Barros et al., 2016) or optical applications (Müller et al., 2009). Silica-based materials are used in many high-tech products including microelectronics and optoelectronics while the silica-forming enzymes, silicateins, from both demosponges (marine and freshwater sponges) and hexactinellid sponges can be used for the production of highly-ordered inorganic–organic composite materials with defined optical, electrical, and mechanical properties (Schröder et al., 2009).

Recent developments of electronic devices that possess functionalities of biological synapses are used to advance in mapping the functions of the human brain. In this perspective, biocompatible artificial synapses based on seaweed matrix biopolymer (ι-carrageenan) with Ag dynamics added, has the potential for constructing neuromorphic systems, using an environmentally benign material (Kim and Lee, 2018). Oyster shells, chitin from the exoskeleton of crustaceans and collagen extracted from cartilaginous or bony fish skin byproducts can be used to produce biomedical scaffolds (Gheysari et al, 2020). Biopolymers, such as sodium alginate derived from marine brown algae, chitosan obtained by deacetylation of the chitin extracted from the exoskeleton of crabs and shrimps, and porous silica shell of marine diatoms are used for the development of drug and cell delivery systems, hydrogels and bioactive coatings and also scaffolds for next generation of tissue engineering products (Figure 7, Perale and Hilborn, 2016; Roman et al., 2019), and nanotoxicity studies (Ciglenečki-Jusić and Svetličić 2015). The potential of the isolated algal plasma membrane is also underexplored. The plasma membrane is highly permeable for anionic fluorescent dyes, thus a method for sealing reconstructed plasma membranes would increase the attractiveness of these transport vehicles towards the development of a new generation of drug delivery systems (Ivošević DeNardis et al., 2020). Collagen can also be extracted from jellyfish for the production of medical devices and biomaterials (such as scaffolds and hydrogels) useful for wound healing and regenerative medicine. This is the so-called next generation collagen by Jellagen PTY Ltd[19], already on the market as biomaterial for 2- and 3-D cell cultures and as a universal collagen scaffold. Fish-derived gelatin is another alternative to commonly used gelatin in medical devices, usually sourced from bovines or porcine hides and skins (GMIA, 2019). Indeed, marine-animal sourcing of gelatin can ensure a higher standard of safety as it does not carry the intrinsic risks of disease transmissions typical of farming animals (e.g. the Creutzfeldt Jakob disease risk, ISO 22442). These novel applications that represent a realistic alternative to currently used and sourced materials are foreseen in the new European regulatory framework for the medical devices industry, the Medical Devices Regulation (Regulation (EU) 2017/745).

Diatoms are very valuable in terms of their waste as they produce nanostructured and mesoporous biosilica shells (frustules) with a highly ordered hierarchical architecture. These unique, morphological, chemical and mechanical properties make the biosilicate of diatoms a very attractive nanomaterial for a wide range of applications (Petikapić et al., 2012). Diatom frustules have good mechanical properties, low density and a high surface area, hence they can be used as fillers to improve the mechanical properties of polymers (Lamastra et al., 2017). Some studies have shown that solid frustules increase the modulus and yield strength of the epoxy matrix (Taşdemirci et al., 2008; Gültürk et al., 2013). The application of various wastes as additives for composite production has attracted great interest to the scientific community due to its beneficial environmental effects: (i) waste material management, (ii) production of biodegradable products, and (iii) cost.

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The global study by Geyer et al. (2017) showed that in 2015 only 9% of world-wide plastics were recycled while 12% was incinerated and 79% was disposed to landfills and natural environment. This can represent an opportunity to use macroalgae and microalgae as a potential feedstock to produce sustainable, recyclable/and or compostable plastic while offsetting our carbon footprint. Algal biomass can be used for packaging in a variety of ways: firstly, raw seaweed fronds are pre-treated and used as single-use disposable plates (e.g. serving fish on a pre-treated, dried and shaped blade of seaweed). Secondly, several compounds can be extracted from algae to serve as precursors to produce films, lining for packaging or packaging material itself (bioplastics). Currently, the most common algae-based precursors for bioplastics are poly-lactic acid (PLA), polyhydroxyalkanoate (PHAs), starch, cellulose, proteins, lipids and other polysaccharides such as alginates and carrageenans (Zhang et al., 2019a). PLA is currently the compound with the most commercial interest. The monomer of PLA is a lactic acid which is derived from carbohydrates during

[19] www.jellagen.com

fermentation, and then polymerized into PLA. Many macroalgal and microalgal species are carbohydrate-rich and therefore suitable as a feedstock for PLA production. However, due to the slow degradation of PLA, there is an active ongoing search for other polymers (Jem and Tan, 2020). Also, macroalgae can serve as a substrate to cultivate marine bacteria capable of synthesizing PHAs, which are a biodegradable plastic alternative (Ghosh et al., 2019). Several species of cyanobacteria and microalgae have also been recorded to produce PHAs (Costa et al., 2019).

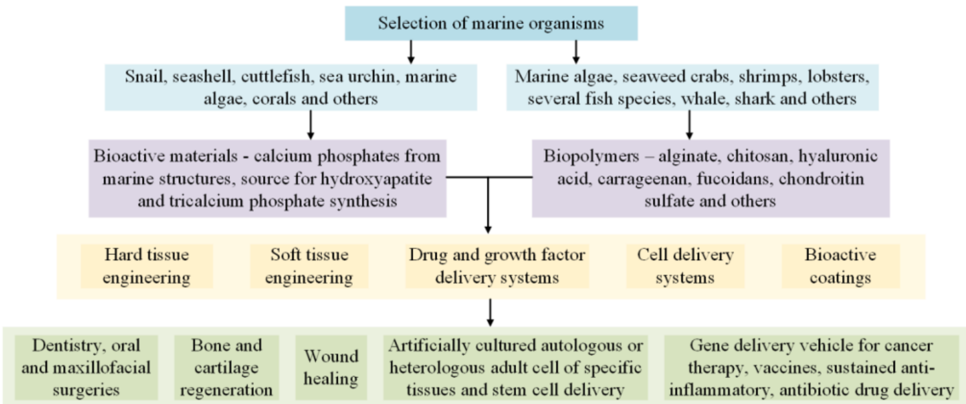

Figure 7: The workflow for using marine organisms as biomaterials.

6.8 Healthcare and well-being

The increasing standard of life inherently represents a growing demand for pharmaceuticals, nutraceuticals and cosmeceuticals. Marine organisms, such as algae, sponges, mollusks (including cone snails), cyanobacteria, actinobacteria, fungi, tunicates and fish synthesize metabolites with significant biological activities for therapeutic and industrial applications, with anticancer, anti-inflammatory, anti- and pro-osteogenic, anti-obesity, antimicrobial, antiviral, and anticoagulant activities (Majik et al., 2014; Surget et al., 2017; Carson et al., 2018a; Carson et al., 2018b; Jin et al., 2018; Kumar, 2019; Mayer et al., 2020). To date, there are ten clinically approved drugs of marine origin that include:cytarabine (Cytosar-U), trabectedin (Yondelis), eribulin (Halaven), brentuximab vedotin (Adcetris), plitidepsin (Aplidin) polatuzumab vedotin (Polivy), and enfortumab vedotin-ejfv (PADCEV) for cancer treatment, ziconotide (Prialt) for severe chronic pain, ω-3-acid ethyl esters (Lovaza) for hyper-triglyceridemia treatment, and ι-carrageenan (carragelose) and vidarabine (Vira-A; US discontinued[20]) for antiviral treatment (Martins et al., 2014; Jimenez et al., 2020). This number has prospects of increasing as Lurbinectedin (Zepsyre a novel ecteinascidin derivative, developed by PharmaMar for cancer treatment, was awarded Priority Review by FDA and the report was released in August 2020.

Other compounds originating from marine organisms are also used in healthcare. Carotenoids are pigments that serve as antioxidants with many health benefits including prevention or slowdown of

[20] https://www.midwestern.edu/departments/marinepharmacology/clinical-pipeline.xml, accessed on January 2nd 2020

some chronic diseases, cellular damage and aging. Specifically, carotenoids have the potential to reduce the risk of inflammation, heart disease, cancer (Griffiths et al., 2016), type 2 diabetes (Sluijs et al., 2015), obesity (Gammone et al., 2015) and even some neurodegenerative diseases (Cho et al., 2018). Phlorotannins are bioactive compounds from brown seaweeds with potential use in food, pharmaceutical and cosmeceutical industries (Li et al., 2011). The cyanobacteria from the Baltic Sea, both the bloom-forming species such as *Nodularia spumigena* (Fewer et al., 2013; Niedermeyer et al., 2014) and the species rarely recorded in the sea (Mazur-Marzec et al., 2015), produce metabolites of pharmaceutical potential. Dolastatin 10 produced by the cyanobacterium *Symploca* sp. showed potent *in vivo* anticancer activity, however, it was dropped from Phase II clinical trials due to its toxic side-effects (Hearn et al., 2006). Many analogues of dolastatin were synthesized and tested through the years and, currently, an antibody-drug conjugate (ADC), brentuximab vedotin (Adcetris) is used as a treatment for Hodgkin's lymphoma and anaplastic large cell lymphoma. (Tan, 2013). *Nostoc sphaeroides* and other cyanobacteria have been used for the treatment of diarrhea, hepatitis and hypertension. *N. sphaeroides* is also used as an important ingredient of medicines (Barsanti and Gualtieri, 2014). *N. ellipsosporum* produces a bioactive compound called cyanovirin, a low-molecular-weight protein with potent activity against various human immunodeficiency viruses type 1 (HIV-1), HIV-2 and simian immunodeficiency viruses, without damaging the host cells (Boyd et al., 1997; Dey et al., 2000). The extracts of the growth media and cell extracts of many unicellular microalgae *Chlamydomonas pyrenoidosa* and *Chlorella vulgaris* possess antibacterial activity against both Gram-negative and Gram-positive bacteria (Hussein et al., 2018). Similarly, extracts of diatoms, green algae and dinoflagellates have antifungal activities (Dewi et al., 2018). Genomes of higher eukaryotes encode hundreds of kinases, many of which having important roles in controlling the molecular machinery of cell proliferation, survival and motility. Recent studies of the arctic marine hydrozoan *Thuiaria breitfussi* revealed a family of bioactive breitfussins, molecules that act as cell-specific kinase inhibitors (Hansen et al. 2019). Two of the breitfussins were shown to selectively inhibit the survival of several cancer cell lines. The highest inhibition was verified for the triple negative breast cancer cell line MDA-MB-468. These results open a very promising avenue for the development of selective kinase inhibitors for use in cancer therapy. It is also worth noticing that the compounds were isolated from a sessile marine organism, which may hint on where to find potential cell active compounds (i.e. defense related molecules). Recently, fermented Pacific oyster extracts (Ihn et al., 2019) have proven to be efficient in inhibiting osteoclastogenesis in rodents, thus being proposed as a possible treatment for another highly prevalent human pathology, osteoporosis, which has greatly increased in the human population with the increase in life expectancy.

Among marine organisms, sponges have been considered as a “drug treasure” during the past 50 years, due to the huge diversity of their secondary metabolites with an equal variety of biotechnological properties (Schröder et al., 2003; Müller et al., 2004; Perdikaris et al., 2013). In the early 1950s, pharmaceutical interest for marine sponges started by the investigation of the Caribbean sponge *Tectitethya crypta* (=*Cryptotethya crypta* de Laubenfels, 1949) and extraction of the nucleosides: spongouridine (3-β-D-arabofuranosyluracil), spongothymidine (3-β-D-arabofuranosylthymine) and spongosine (9-β-D-ribofuranosyl-2-methoxyadenine) (Bergmann and Feeney, 1950; 1951; Bergmann and Burke, 1956). These unique nucleosides were the basis for the synthesis of the antiviral drug ara-A, as well as the first marine-derived anticancer agent, ara-C, currently used in the routine treatment of patients with leukemia and lymphoma (Proksch et al., 2002). Besides the above-mentioned bioactivities, sponges produce many immunosuppressive, neurosuppressive and muscle relaxant compounds (Anjum et al, 2016). Numerous bioactive substances, important in public health disease treatment and control, have been isolated from marine sponges. The most promising drugs are those for treatment of malaria, manzamines, with antiplasmodial (Youssaf et al., 2002) and even immunomodulating activity (Ang et al., 2001), as well as activities against atherosclerosis (Stead et al., 2000) and cardiovascular diseases (Barrese and Taglialatela, 2013). A group of particular interest is the microtubule-stabilizing drugs, potent macrolide secondary metabolites isolated from New Zeland marine sponge *Mycale hentscheli*: peloruside A, mycalamide A and pateamine as well as zampanolide from the Tongan sponge *Cacospongia mycofijiensis* (Miller, et al., 2010). Peloruside A and paclitaxel (Taxol) can stabilize microtubules by binding to β-tubulin and thus possess promising activity against cancer, neurodegenerative and autoimmune diseases (Kanakkanthara et al., 2016). A recently identified microbiome of sponge host *Mycale hentscheli* shows remarkable chemical diversity and biosyntethic potential of multiple symbionts, including microtubule-inhibiting and eukayotic translation-inhibiting bioactive compounds (Rust et al., 2020).

Jellyfish extracted molecules (proteins, peptides, mucins) have antioxidant, wound healing and antimicrobial properties (Merquiol et al., 2019; Nudelman et al., 2019). The most famous jellyfish-derived compound is a green fluorescent protein (GFP), one of the most important tools in molecular biology research, serving as a molecular marker alongside other that found important applications in wider scientific research, and was awarded a Nobel Prize in Chemistry in 2008 to Osamu Shimomura, Martin Chalfie and Roger Tsien.

7 Legislation and funding

The potential of marine biotechnology may significantly contribute to achieving 14 out of 17 United Nations (UN) Sustainable Development Goals (SDGs, Figure 8)[21]. First and foremost, the discovery of biodiversity and the sustainable use of marine bioresources contributes to SDG14 (Life below water). The new solutions and processes developed, such as new bioremediation or alternative fertilizers contribute to SDGs 6 (Clean water and sanitation), 13 (Climate action) and 15 (Life on land), respectively. Importantly, alternative food, feed and fertilizer sources contribute to SDG2 (Zero hunger). The use of marine algal biomass as an alternative energy source contributes to SDG 7 (Affordable and clean energy). The valorization of waste, also food by-products can contribute to the decrease of urban pollution (SDG11, Sustainable cities and communities). The development of new products in nutraceutical, cosmeceutical and medical industries contributes to SDG3 (Good health and well-being). Promotion of resource efficiency and technological development contribute to SDG12 (Responsible consumption and production) and 9 (Industry, innovation and infrastructure), respectively; the establishment of partnerships between governments, industry, civil society and the scientific sector contributes to SDG17 (Partnerships for the goals). Indirectly, successful biotechnological development can lead to new products, new industries and new job openings. With a proactive interregional collaboration, good practice examples can be taken by regions that are lagging in terms of regional development and job security,

Figure 8: Marine biotechnology can contribute to 14 of 17 UN sustainable development goals.

[21] https://sustainabledevelopment.un.org/?menu=1300

which contributes to SDGs 1 (No poverty), 10 (Reduced inequalities) and 8 (Decent work and economic growth).

Table 3: A list of European strategies and funding mechanisms that directly or indirectly include marine biotechnology.

Type	Name	Location	Link
Strategy	European Green Deal	EU	https://ec.europa.eu/info/sites/info/files/european-green-deal-communication_en.pdf
Strategy	European Technology Platform for Sustainable Chemistry	EU	http://www.suschem.org/
Strategy	European Bioeconomy Strategy (2012, revised 2018)	EU	https://ec.europa.eu/research/bioeconomy/pdf/ec_bioeconomy_strategy_2018.pdf
Strategy	Strategic Innovation & Research Agenda (SIRA) developed by EC and BIC	EU	https://www.bbi-europe.eu/sites/default/files/sira-2017.pdf
Strategy	Nordic Council of Ministers has "Ocean – Blue Growth in the North"	Regional	Nordic Council of Ministers, 2018
Funding	Framework Programme (Horizon H2020, Horizon Europe)	EU	https://ec.europa.eu/info/horizon-europe-next-research-and-innovation-framework-programme_en
Funding	Bio-based Industries Joint Undertaking (BBI-JU)	EU	https://www.bbi-europe.eu/
Funding	LIFE (L'Instrument Financier pour l'Environnement)	EU	https://ec.europa.eu/easme/en/life
Funding	ERA-Net Cofound	Limited country participation	https://ec.europa.eu/programmes/horizon2020/en/h2020-section/era-net
Funding	Interreg, Interreg Med, Interreg Baltic, Interreg Atlantic	Regional	https://interreg.eu/; https://interreg-med.eu/; https://www.interreg-baltic.eu/home.html; https://www.atlanticarea.eu/
Funding	Joint Programming Initiative Healthy and Productive Seas and Oceans (JPI Oceans)	Limited country participation	https://www.jpi-oceans.eu/
Funding	National, Bilateral	Limited to single country or bordering countries	

Table 3 briefly outlines the strategies and funding mechanisms in the EU that directly or indirectly tackle marine biotechnology. They can also serve as a tool for streamlining current efforts and consolidating future directions. Depending on the funding scheme these tools can act at European-, regional-, national- and bilateral-scale. The European Technology Platform for Sustainable Chemistry (SusChem) has issued a new Strategic innovation and research Agenda in 2019 with a vision where sustainable chemistry and biotechnology provide solutions for future generations. The SusChem priorities align well with the field of marine biotechnology as the priorities are (i) advanced materials and advanced processes for circular economy and resource efficiency, and (ii) low carbon economy towards mitigating climate change and protecting environmental and human health. The European Green Deal (COM(2019), 640) is an EU growth strategy to transition into a prosperous society with a resource-efficient and competitive economy. National funding mechanisms can sometimes provide partial financing through research programs and national projects. At the European- scale, Horizon2020 and its successor, Horizon Europe framework programs are the ones directly funded by the EU budget. The marine biotechnology sector significantly benefits from the Horizon funding mechanism, intending to directly address societal challenges and promote the development of innovative societies through international cooperation and collaboration of academic and industrial partners. These and other financing opportunities have limited country participation where the governmental organizations (national ministries) typically endorse the respective national participation. Therefore, the establishment of collaborations between scientific institutions and the policy-making sector is of extreme strategic importance. An example is the Action ERA-NET COFUND on Blue Bioeconomy – unlocking the potential of aquatic bioresources, which is currently running. Another source of funding at the European level stems from the European Regional Development Fund. Marine biotechnology is not uniformly represented as a strategic priority at the regional levels. The Interreg Baltic Sea Region, for example, has marine biotechnology at the core of blue growth. Marine biotechnology is also encompassed in the Interreg Mediterranean and Atlantic transnational collaborations. Another funding source is the European Maritime and Fisheries Fund. This is implemented at the national scale, through co-financing operational programs. Moreover, marine biotechnology is a part of the maritime economy, a high-potential economic sector. The co-funding programs come along with the national ones that are financed by the Public Investments Programs. Among the Joint Programming Initiatives (JPIs), JPI-Oceans has a priority in marine biotechnology, with limited country participation. To a lesser extent LIFE programs, funded by Environment Directorate-General, could also indirectly be used to better manage marine biodiversity.

During the whole development process, the policy framework imposes guidelines throughout the whole technology readiness level scale. The scientific and technological breakthroughs must also be addressed due to local, national and international policy that protects and promotes the ocean health and functioning aspects of ecosystems. In the field of marine biotechnology, the Convention on Biological Diversity (CBD) and the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization as well as the United Nations Convention on the Law of the Sea (UNCLOS) is of particular relevance (Barbier and Briand, 2014; Lallier et al., 2014). Nagoya protocol has clear implications for scientists working on genetic resources, including those doing biotechnology research on marine organisms, as well as any user of genetic resources along the biodiscovery pipeline (Broggiato et al., 2018). Bioprospecting, a term that defines screening for new organisms and their compounds with biotechnological value, is controlled at different levels. In Exclusive economic zones, these resources are under the sovereignty of the coastal country, which requires special permits to sample habitats of interest. In many cases, bioprospecting in the waters of a third country is allowed only if the country provides its access and use of the genetic resources either for commercial interest or for academic research, even if the material taken is of negligible intrinsic value. The 'gold mine' syndrome (according to which each crude sample contains a hidden treasure) hampers the ability of partners to agree on an a priori chain value (Querellou, 2010). The exclusive access to these potential economic benefits can only be obtained through patents associated with "marine genetic resources". However, the majority of patents are associated with microbial species. Another challenge is the access and benefit-sharing of resources collected in areas beyond national jurisdiction (Collins et al., 2019b). The ocean is a common good and negotiations are necessary to find the solution for the fair and equitable benefit sharing from the utilization of marine genetic resources (Rabone et al., 2019).

Overall, there are currently many legal and practical challenges along the pathway for the commercialization of products derived from marine organisms as legislation is not progressing at the same rate as technology. A serious burden that delays the market entry of products is the safety assessments and compliances for marine biotechnology products. Another clear practical challenge involves the potential spatial conflicts, in other words, the impacts of different existing marine uses such as tourism or maritime commerce, with the exploration and use of marine biota. The recent increase in interest in marine spatial planning over the past two decades has opened opportunities to overcome conflicts and to proactively determine simultaneous and integrated uses. The above mentioned Maritime Spatial Planning Directive (2014/89/EU) addresses this facet of marine uses, however, of note is the progress made by many non-EU countries who are also taking initiative to develop plans for their coastal and exclusive economic zones (see Collie et al., 2013; Portman, 2016; Smythe and McCann, 2018).

Marine exploitation needs increased governance practices as well as ethical practices. Hence, policy involvement is necessary while developing products and processes from marine sources and this may be ensured through the Responsible Research and Innovation concept (see more in Section 9). This new perspective of conducting science which has to be transdisciplinary and tackle the complex interactions between nature, society and governance is nowadays called the social-ecological systems (Folke et al., 2005; Rozzi et al., 2015; Nakicenovic et al., 2016). This new mode of governance, adapted to social-ecological systems takes into consideration different dimensions: economic (cost-efficiency), political, social, legal (European and national legislation) and scientific (environmental issues) ones. The marine biotechnology sector is thus complex, multi-dimensional and is facing uncertainties. Therefore, the adoption of governance adapted to social-ecological systems considering different aspects of this sector is challenging but necessary.

8 Bioeconomy

The European Commission defines blue bioeconomy as an exciting field of innovation, turning aquatic biomass into novel foods, feed, energy, packaging and much more[22]. This is also reflected in the revised EU Bioeconomy Strategy[23]. In the European Union, the blue economy (including all the sectors) reached €750 billion turnovers and employed close to 5 million people in 2018 (European Commission, 2020). Marine biotechnology is a niche within the ocean-based industries. As this is a growing field, it is projected that in 2030 many ocean-based industries will outperform the growth of the global economy as a whole, providing approximately 40 million full-time equivalent jobs (Rayner et al., 2019). In this aspect, the policy-making sector is aware that future marine research priorities

[22] https://ec.europa.eu/maritimeaffairs/press/blue-bioeconomy-forum-shape-future-blue-bioeconomy-europe_en

[23] https://ec.europa.eu/research/bioeconomy/index.cfm?pg=policy&lib=strategy

should include improved techniques for mass production and processing of marine biomass (European Commission, 2019). This imposes several challenges: (i) the need for harmonization and later standardization of processes, protocols and definitions; (ii) the need to establish ethical guidelines that will be endorsed and respected by national administrative authorities and concern the fair share and use of biological resources; (iii) the need to bridge the collaboration and communication gap between science and industry on one hand, and policymakers on the other. This entails some changes in the mode of action. For example, networking activities such as brokerage events and participatory workshops should be taken as a means of opportunity for the exchange of expertise, opinion and potential co-creation of strategic documents. (iv) There is a need to develop strategies for showcasing individual expertise, such as the creation of open access repositories of experts and their contacts (Rotter et al., xxx). (v) Finally, there is a need to sustain the investment into ocean observations that provide evidence of regulatory compliance and support the valuation of natural assets and ecosystem services (Rayner et al., 2019). Open science and access to data are of key importance here, enabling fair access to public knowledge.

9 Communication and stakeholder engagement in development finalization

Transdisciplinary collaborations, such as marine biotechnology, seek to produce knowledge through integration and collaboration to address societal challenges (Misra and Lotrecchiano, 2018). These complex collaborations are high-risk, high-impact and are needed to establish modern, innovative societies (Rotter et al., 2020b). On one hand, this demands the creation of teams with varying expertise, including scientific organization, industrial actors, policymakers and the civil society, i.e. the quadruple helix (Rotter et al., 2020b and Figure 4 therein). On the other hand, these collaborations need to establish efficient communication channels to share infrastructure, experts, expertise (Rotter et al., XXX) and data, which is endorsed by the open access policy of scientific information. These collaborations are endorsed by the Responsible Research and Innovation framework (RRI). RRI aims at an interactive process where societal actors, researchers and innovators actively cooperate to co-define, co-design and co-construct solutions, services and products that are socially acceptable, sustainable and resolve important societal issues (Schneider, 2019). This is an increasingly popular narrative in the European policy making sector, oriented towards publicly funded research that should be inclusive, sustainable and involve policymakers and the general public (von Schomberg, 2013; Jakobsen et al., 2019). There are three features within the RRI framework (Owen et al., 2012): (i) science is made for society defining societal challenges, setting targets and impact; (ii) science is made with society and innovations should be constantly iterated by monitoring the economic, social, environmental impact and including the general public and the policy-making sector; and (iii) science is responsible and should include the principle of openness, ethics and financial responsibility towards financers, technology or product users. As marine ecosystems become important in the quest for sustainable development, it is important to ensure that citizens will understand the cause-effect of societal actions and inactions and how human and ocean health are tightly connected. At the same time, citizens, scientists, policymakers and industry are responsible for the ocean's health to ensure sustainable and long-lasting marine resources. Thus, they are all an integral part of systemic innovation, where they must collaborate to co-design and co-create to ensure the uptake of the results in science, industry, policy and society. Thus, the RRI roadmap (Schneider, 2019) facilitates building trust among these diverse stakeholders, which is the prerequisite for systemic innovation. True and active involvement will increase our understanding of marine bio-based information, knowledge and upcoming marine bio-based products, and catalyze the increase of ocean literacy towards ocean health and sustainable marine biotechnology. Applying the RRI Roadmap will enable a faster industry uptake, where currently there is a lack of coordination and cooperation along the value chain as well as lack of knowledge and insufficient information exchange (Marine Board, 2010). Moreover, these barriers, together with the lack of effective training in the art of science communication, demand a structural change in the academic curricula, especially when training future marine biotechnologists. International marine biotechnology education programs (such as “A Blue Biotechnology Master for a Blue Career”) are a way to transferring knowledge from the scientific community to the industrial sector for blue biotechnology business development by employing high skilled graduates.

The overall marine biotechnology development pipeline includes biodiversity discovery roadmap, biomass/chemical compound production and biorefinery, as well as business development and communication. Here, the scientific community, the industrial sector, business development specialists, policymakers and the general public should work closely together. If the public perception of a certain product is not positive, the rest of the development may be put on hold. In fact, low public product awareness and acceptance is an important barrier for product commercialization. This is especially the case for commodity products, for which the consumers appreciation is decisive, in contract to high end products like medical drugs and industrially valorizable compounds. One solution is the financing of transdisciplinary collaborative networks (such as the European COST Action Ocean4Biotech, Rotter et al., 2020a), where representatives from transdisciplinary communities can co-create knowledge to develop solutions that are efficient, safe, of general public interest and legally feasible.

10 Conclusion

Oceans harbor a vast variety of organisms that offer a biological and chemical diversity with metabolic abilities unrivaled in terrestrial systems, which makes them an attractive target and an untapped and plentiful resource for marine bioprospecting. While the advances in bioprospecting reveal new knowledge about the biodiversity, we are still far from discovering the true potential of organisms to produce biotechnologically relevant compounds. Moreover, the identification of new compounds from marine organisms or the discovery of the real potential of already identified natural products becomes more challenging and more efficient screening and characterization pipelines are required. Getting access to a larger fraction of the biosynthetic diversity encoded in the genomes of newfangled organisms is required to accelerate the speed and probability of discovering new chemical scaffolds with biological activities. Moreover, many of the known organisms and bioactive compounds have not been exploited to their full commercial and possibly also functional potential. A sustainable supply of marine macroorganisms still poses a great challenge, which led to the great paradigm shift in the investigations of marine (symbiotic) microorganisms. With recent advances in biochemical, chemical and genetic methodologies and omics repertoire, some natural products with potent activity could enter clinical trials for further exploration of potential applications in industries such as feed, nutraceuticals and/or pharmaceuticals. Hence, any marine biotechnology development demands a coordinated multidisciplinary effort to transform the results of scientific research work and technological breakthroughs into industrial, economic and commercial successes. The result of these coordinated efforts is then the commercialization of innovative natural products and principles/methods such as new pharmaceuticals, novel food, feed, drug delivery methods, materials and more. These products have the potential to generate new jobs and contribute to national, regional and European economic development. Furthermore, another important aspect provided by marine biotechnology is that the microbial and cell cultures that are collected and, ideally, shared between research and industrial centers, are *de facto* contributing to maintenance, cataloging, conservation and sustainable use of marine biological diversity of areas beyond national jurisdiction (Collins, 2019a).

This manuscript presents the overall concept behind marine biotechnology - from the organisms, their source and industrial applications including the important aspects of legislation, economy and communication. We also presented some important overarching disciplines and concepts, including the quadruple helix and RRI. All of these are prerequisites to building efficient collaborations that will progress into developing products and services, sourced from the oceans. The way that applicative science is advancing is rapidly changing. Transdisciplinarity and communication are necessary prerequisites to advance and contribute to innovative societies. We are fully aware that the amount of knowledge that has to be acquired represents a potential bottleneck when providing new developments in this field, and we therefore hope this manuscript will serve as a useful starting guideline/reminder/check box covering the product development pipeline.

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AR designed the article concept and drafted the manuscript. All authors read, edited and approved of the final version of the manuscript.

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