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Marine Genetic Resources and Bioprospecting in the Western Indian Ocean

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Opposite page: Nudibranchs are of interest in bioprospecting programmes and have been the source of dolastatins, under investigation for their anti-tumour activity. © Hendrik Martens / Shutterstock.

INTRODUCTION

Over the last few decades, increasing attention has been given to the commercial potential of exploiting marine genetic and associated natural product resources for a range of industries including pharmaceuticals, food and beverage, cosmetics, agriculture and industrial biotechnology (eg de la Calle 2009, Arrieta and others, 2010, Arnaud-Haond and others, 2011, Global Ocean Commission 2013, Martins and others, 2014). Furthermore, scientific and technological developments in molecular biology, genomics, and bioinformatics, have led to exciting new possibilities; whilst technological advances in observing and sampling the deep ocean have opened up previously unexplored areas to scientific research (Global Ocean Commission 2013). Since initial reports in the 1950s, some 23 570 natural products have been reported from marine organisms, growing at a rate of 4 per cent per year (Arrieta and others, 2010, Leal and Calado 2015). Only a small number of these products have reached the commercialised phase, yet marine bioprospecting provides significant economic opportunities with the global market for marine biotechnology products alone projected to reach US$ 4 900 million by 2018 (Global Industry Analysts Inc. 2013).

At the same time, the legal framework for marine genetic resources has become increasingly complex, characterised by a multiplicity of legal regimes and national and international laws. Marine genetic resources found within the EEZ are subject to national laws, and to provisions of the recently adopted Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilisation, an agreement under the Convention on Biological Diversity (CBD). The concept of "access and benefit sharing" (ABS) originated as a legal expression in the 1992 CBD arising from the unequal distribution of biodiversity throughout the world, the desire of biodiversity-poor but technology-rich industrialised countries to have continued access to these resources, and the determination of biodiversity-rich but technology-poor developing countries to benefit from the exploitation of their resources (Reid and others, 1993, Wynberg and Laird 2007). An agreement was reached requiring user countries to share benefits with provider countries, which in turn were required to facilitate access to their genetic resources. The Nagoya Protocol, which came into force in 2014, aims to create greater legal certainty for both providers and users of genetic resources by establishing clear and transparent procedures for access to genetic resources; and by helping to ensure the sharing of benefits once genetic resources leave the provider country through its new obligations related to compliance. In the high seas, natural resources are considered to be the "common heritage of humankind" and are subject to special rules under the United Nations Convention on the Law of the Sea (UNCLOS). Specialised ABS rules for these resources have not yet been developed.

What do these developments mean for countries of the Western Indian Ocean (WIO), whose territorial waters contain many marine genetic resources that are of growing interest to industries? With the exception of South Africa, most research, development and commercialisation of marine genetic resources is currently located outside of the WIO region, as is the ownership of associated intellectual property rights. A suite of challenging issues face policy-makers attempting to implement the Nagoya Protocol and ensure compliance with various other legal instruments. These include questions relating to ownership and benefit flows from the commercialisation of marine genetic resources; how research and development in WIO countries can be further stimulated; sustainable use of marine genetic resources, and minimising the threat of overexploitation; how the movement of marine genetic resources can be tracked and monitored; and guidance with regard to the exploitation of marine genetic resources in the high seas. This chapter provides an overview of these questions, beginning with a description of the potential value of marine genetic resources and the industries that utilise them; current research and development activities in the WIO region; and the central issues requiring attention by policy-makers and decision-makers.

THE NATURE AND SCOPE OF MARINE BIOPROSPECTING

Marine bioprospecting, the exploration of biological material in the marine environment for commercially valuable genetic and biochemical properties, is a rapidly expanding research and commercial activity. Whereas bioprospecting in the terrestrial environment can be traced back centuries, collecting and screening commercially valuable samples from the marine environment, dependent on the development of technological advances such as SCUBA diving, is as recent as the 1950s (Molinsky and others, 2009).

The marine environment presents important economic opportunities due to high levels of biodiversity and endemism, holding promise of biologically active chemical entities for the development of novel natural products (Davies-Coleman and Sunassee 2012, Leal and others, 2012, Martins and others, 2014). There is particular interest in marine species that live in extreme environments, such as hydrothermal vents, seamounts, cold seeps and submarine trenches ("extremophiles"), which trigger organisms to adopt new biosynthetic pathways that generate interesting compounds (Greiber 2011, Davies-Coleman and Sunassee 2012). In the 1970s and 1980s, marine macroalgae were a major focus of marine natural product research, but bioprospecting efforts have since focused on microorganisms and marine invertebrates (Leal and others, 2013). Increasing research is also focused on the potential of marine microalgae, especially in the food and cosmetics industries (Martins and others, 2014).

Natural products are produced by many marine organisms as a chemical defence against predation, or as a response to inter-species competition for limited resources (Davies-Coleman and Sunasee 2012). A taxonomic analysis of new marine natural products discovered between 1990 and 2009 for invertebrates, indicated that the Phylum Porifera was the most abundant at 48.8 per cent, followed by Cnidaria (28.6 per cent); Echinodermata (8.2 per cent), Chordata (6.9 per cent) and Mollusca (5.8 per cent). Research points increasingly to symbiotic microbes as the source of the secondary metabolites of these larger organisms, biosynthesizing the natural products associated with their hosts (especially those found in sponges) (Marris 2006, Molinsky and others, 2009). This has led to a significantly increased research focus on marine microbes (Arrieta and others, 2010). Indeed, prokaryotes contribute 42 per cent of marine genes included in a patent analysis (Arrieta and others, 2010) and with the majority of microbes unexplored there is high potential for the development of useful products.

RESEARCH, DEVELOPMENT AND COMMERCIAL APPLICATIONS

A wide range of products include marine genetic resources, from those domesticated for food through to high-value cosmetic markets and high-end pharmaceuticals engineered for human health. Not all of these can be characterised as being produced as a result of bioprospecting, and uses range from the direct incorporation of seaweed in food supplements, for example, through to the use of bioactive ingredients in creams, lotions and ointments as cosmeceuticals, and the isolation of active compounds for the pharmaceutical industry. Investments in marine bioprospecting are typically extremely costly and risky due in part to the high costs of sampling in cases where this occurs in the deep sea, the low chances of success, and the significant regulatory hurdles for product approval. For example, it took more than three decades for Prialt®, the first pharmaceutical based on a marine source – the poison released by a tropical marine cone snail to paralyse its prey

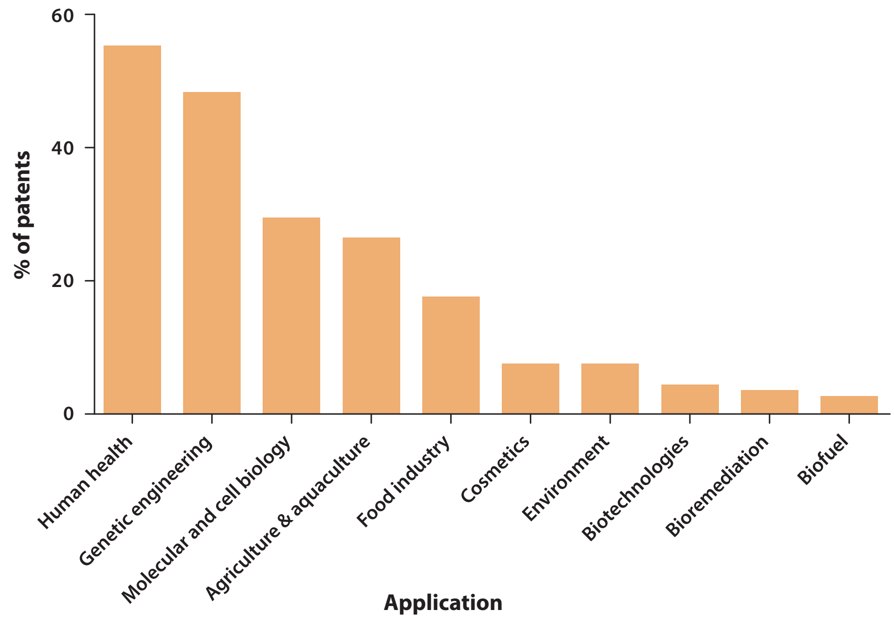

Figure 30.1. Synthesis of the uses proposed in the claims or description of 460 patents deposited at the International Patent Office and associated with genes isolated in marine organisms. Source: Arrieta and others, 2010.

– to be approved in the United States as a treatment for chronic pain (Marris 2006, Molinsky and others, 2009). Paradoxically, commercial supplies of Prialt®, a small polypeptide, were obtained through standard pharmaceutical manufacturing processes and exploitation of the natural source of this compound was never considered for supplying sufficient material for development. Regulatory hurdles are still significant but the time taken between the discovery of a molecule and product commercialisation have over the past decade significantly shortened due to technological advances in synthesising and scaling up production using biotechnology and aquaculture (Leal and others, 2014, Martins and others, 2014).

Figure 30.1 provides a synthesis of uses proposed in the claims of 460 patents (Arrieta and others, 2010), suggesting the predominance of the pharmaceutical and biotechnology industries for a range of applications from anti-cancer drugs through to applications in the fields of ecotoxicology, bioremediation, anti-fouling and biofuel production. A significant focus includes microalgae for large-scale production of polyunsaturated fatty acids for inclusion in dietary supplements; a range of biomedical applications such as fluorescent proteins, bone fillers and bioceramic coatings; polysaccharides derived from algae for use in the food and health sectors; and use of "extremozymes" in industrial applications (Arrieta and others, 2010, Silva and others, 2012, Laird 2013). Table 30.1 provides some examples of the types of marine natural products used in the pharmaceutical, food supplement, and personal care markets; the organisms they are extracted from; and the status of their development.

The considerable costs involved in marine bioprospecting research, alongside the advanced technologies and expertise required, have meant that most exploration has been undertaken by developed countries, notably, the United States of America, United Kingdom, Australia, Canada, Japan, Germany and Russia – but with the sampling often conducted in developing, tropical countries (Greiber 2011, Leal and others, 2012, Oldham and others, 2013). This is clearly illustrated in Figure 30.2 below. With the exception of South Africa and, to a lesser extent, Kenya, few WIO countries have engaged actively as research collaborators in international endeavours. In South Africa, Rhodes University has a long-standing bioprospecting collaboration with the National Cancer Institute, the Scripps Institution of Oceanography and pharmaceutical companies SmithKline Beecham (now GlaxoSmithKline) and Bristol-Myers Squibb, while the Oceanographic Research Institute in Kwazulu-Natal has had an active bioprospecting programme involving the University of Tel Aviv and the Spanish pharmaceutical company PharmaMar (Davies-Coleman and Sunassee 2012). A more recent player is the University of the Western Cape in Cape Town, South Africa, which, through its Institute for Microbial Biotechnology and Metagenomics, is engaged in marine microbial bioprospecting through PharmaSea, a large, EU funded

Table 30.1. Examples of marine natural products in the pharmaceutical, nutritional and personal care markets (Source: Global Ocean Commission 2013).

Category	Product	Organism	Status
Therapeutic	Yondelis® (cancer)	*Ecteinascidia turbinate* (ascidian)	US$ 78 million in 2012
Therapeutic	Prialt® (neuropathic Pain)	*Conus magus* (mollusc)	US$ 20 million in 2012
Therapeutic	Halaven® (cancer)	*Halichondria okadai* (sponge)	>US$ 200 million in 2011
Therapeutic	Salinisporamide (cancer)	*Salinispora tropica* (bacterium)	Phase 1
Therapeutic	Plinabulin (cancer)	*Aspergillus* sp. (fungus)	Phase 1
Biofilm inhibitor	Brominated furanones (quorum sensing inhibitor)	*Delisea pulchra* (red alga)	In trials
Sunscreen	Mycosporine like amino acids (UV absorbing)	*Coral zooxanthellae*	In trials
Cosmetic	Pseudopterosins (anti-inflammatory)	*Pseudopterogorgia elisabethae* (soft coral)	Commercialised
Cosmetic	Venuceane (anti-free radicals)	*Thermus thermophilus* (bacterium)	Commercialised
Nutrition	ω-3 fatty acids	*Crypthecodinium cohnii* (microalga)	Commercialised
Nutrition	Carotenoids (anti-oxidant)	*Dunaliella salina* (microalga)	Commercialised

project (www.pharma-sea.eu/partners/institutions/university-of-the-western-cape.html). The Kenya Marine and Fisheries Institute has been involved in bioprospecting initiatives as part of its collaboration with northern institutions. Although there has been research activity in other WIO countries such as Madagascar, these do not appear to be based on collaborative research programmes with the provider country.

Obtaining a sustainable supply of marine sources, often sparsely distributed, and located in inaccessible sites, presents a considerable challenge to product research and development. While bioprospecting typically requires the collection of only a limited amount of biomass in the discovery phase, recollection of interesting species, or scaling up for commercialisation may pose significant ecological threats. Key concerns include poor knowledge about the conservation status of many species, and the damage that may occur to the ecosystems in which they occur (Costello and others, 2010, Global Ocean Commission 2013).

Technological advances over the past decade have, however, begun to address this "supply" concern (Davies-Coleman and Sunassee 2012, Leal and others, 2014). For example, aquaculture is increasingly being used to produce assemblages of marine invertebrate-microorganisms that can be manipulated to produce higher yields of target metabolites (Leal and others, 2014). The accelerated development of classical analytical technologies, such as nuclear magnetic spectroscopy and mass spectrometry, also means that new compounds can now be identified from mere micrograms of source material. Advances in biotechnology and new approaches to metagenomic mining are presenting ample scope for the scaling-up of marine bioprospecting in future, in particular for microorganisms (Molinsky and others, 2009, Leal and others, 2012, Martins

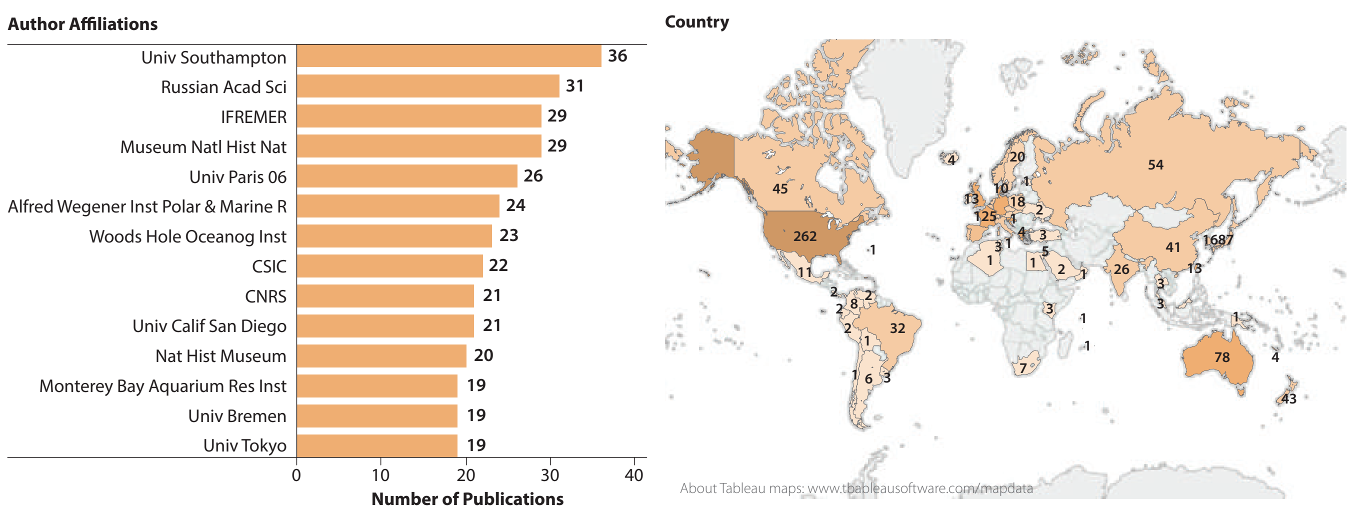

Figure 30.2. Author and country affiliations for scientific literature focused on marine genetic resources. Source: Oldham and others, 2013.

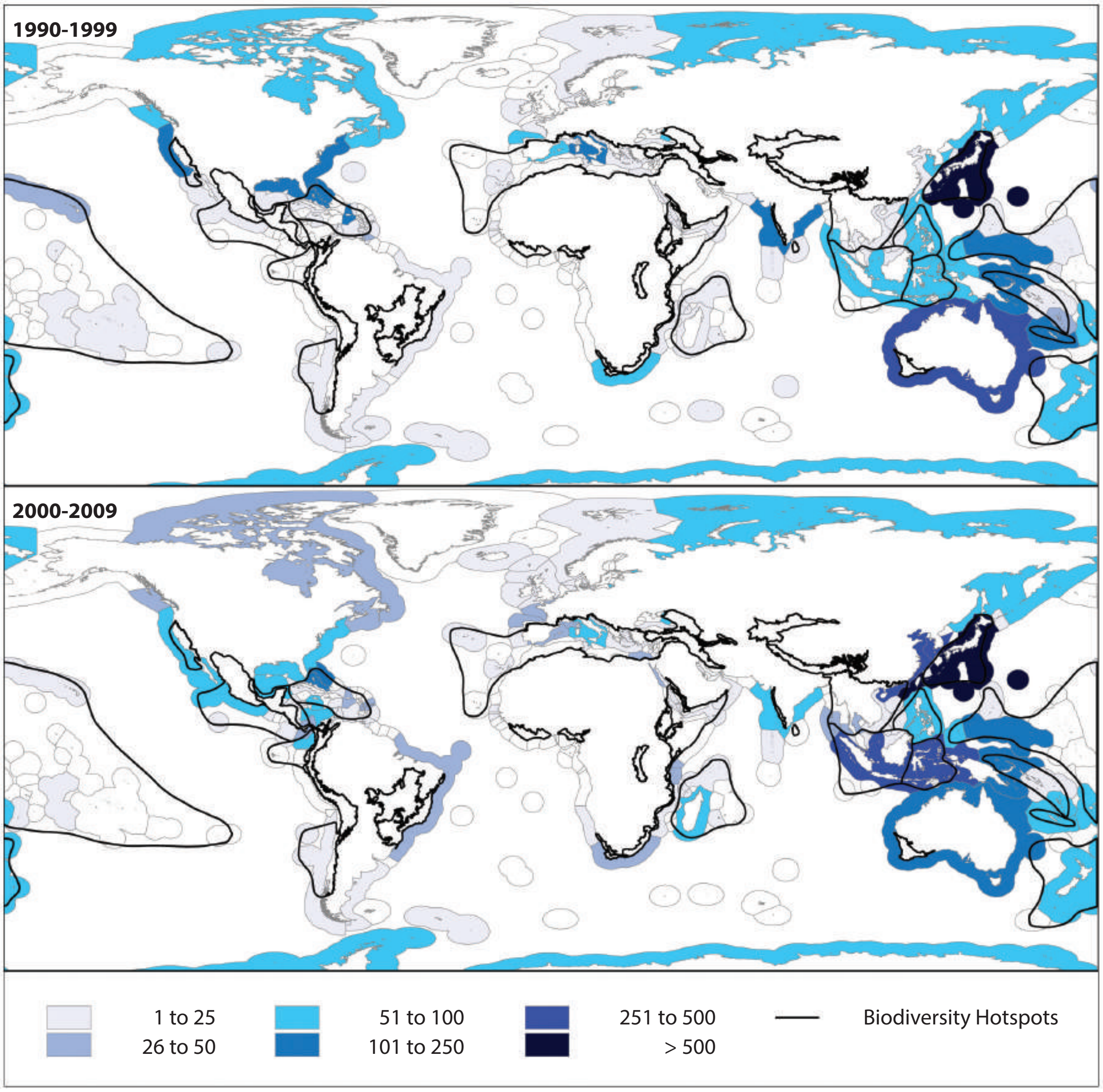

Figure 30.3. Number of new natural products from marine invertebrates for world Economic Exclusive Zones during the 1990s and 2000s. Boundaries of biodiversity hotspots are also presented. Source: Leal and others, 2012.

and others, 2014). 'Genome-mining', or metagenomic approaches, allow researchers to search directly within a sample for genes that produce enzymes with specific biocatalytic capabilities, rather than growing organisms in the laboratory as was previously necessary (Laird 2013).

NATURAL PRODUCT RESEARCH AND DEVELOPMENT IN THE WESTERN INDIAN OCEAN

Several areas in the WIO are of interest for natural products. Figure 30.3 illustrates trends in the discovery of new marine natural products from invertebrates over the last two decades. This demonstrates an increased interest in the WIO islands and east African coastline, although the most intense bioprospecting activity continues in Australasia. There is continued interest in the southern African coastline, linked to the occurrence of three biogeographical zones and high levels of endemism among marine organisms off the southern African coast (Costello and others, 2010, Davies-Coleman and Sunassee 2012). The presence of biodiversity hotspots in the WIO region also suggests that the area is likely to be of increasing interest for marine natural products. Only a small fraction of this biodiversity has been explored for its commercial potential (Davies-Coleman and Sunassee 2012).

Figure 30.4 presents a draft of occurrences in east and southern Africa of marine species in patent data, drawing from unpublished research conducted by Oldham and

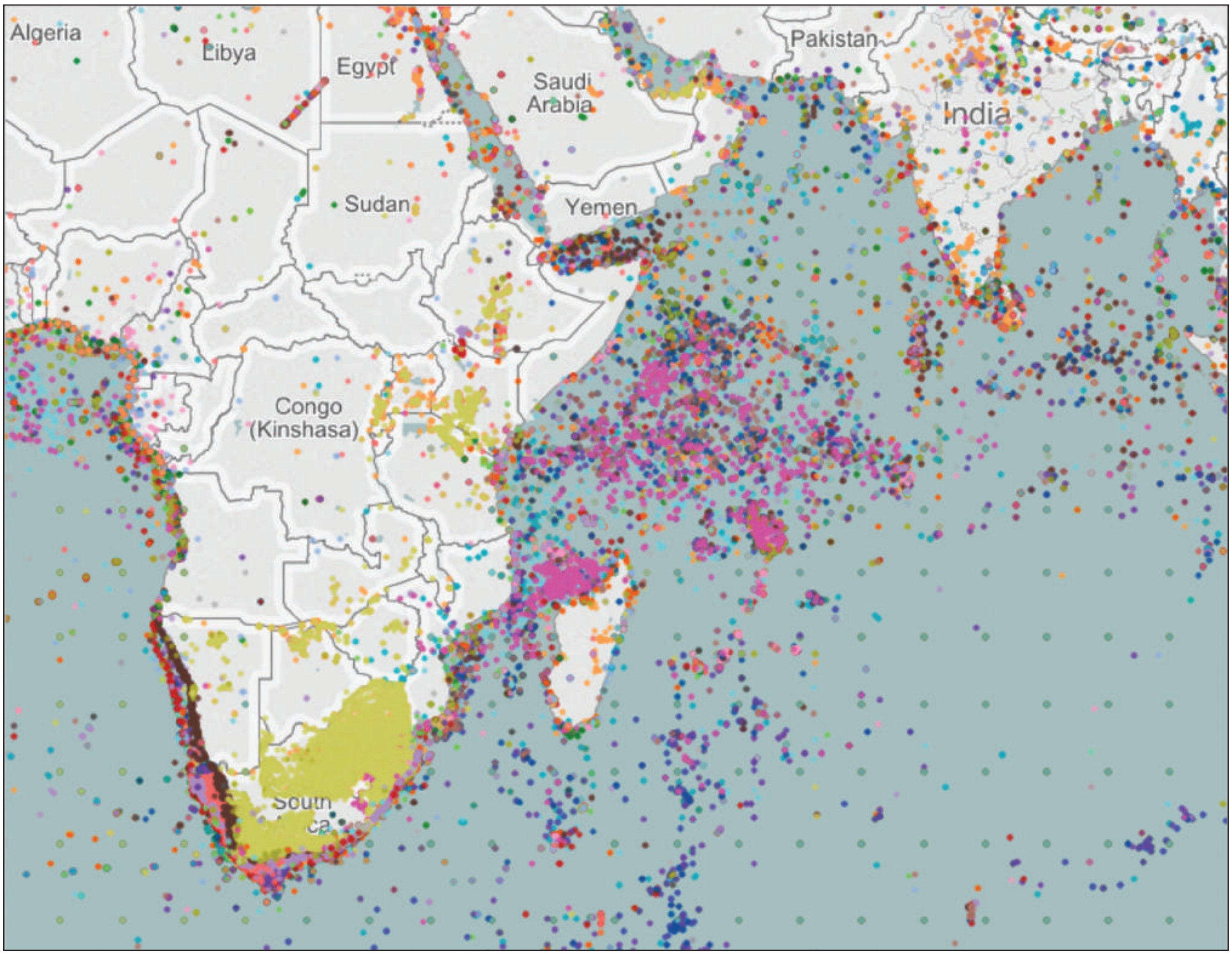

Figure 30.4. African occurrences of marine species in patent data. Source: Oldham and others (2013), Oldham and others (2014). Colours represent different species.

others (2013) and based on data from the Global Biodiversity Information Facility (GBIF). It is important to note that occurrence data does not necessarily mean the species was collected from the area. Although incomplete, it does give a picture of activity in the region. An especially noteworthy finding is the fact that natural product research mainly concentrates on marine invertebrates *inside* national jurisdictions (Oldham and others, 2013). Similarly, the majority of marketed products have been derived from organisms from inside national jurisdictions with limited exceptions for enzymes from extremophiles and Antarctic krill as a source of nutraceutical products (Oldham and others, 2013).

While there is increased global interest in marine microorganisms and microalgae for the pharmaceutical, cosmetic and food industries, there is a lack of knowledge about the distribution and occurrence of commercially interesting taxonomic groups in the WIO region. However, it is likely that there is significant potential in the WIO region to generate interesting new leads and that industry interest in the region will increase.

Major constraints that prevent this potential from being realised are the low levels of scientific and technical capacity that exist in most countries, with the possible exception of South Africa, and insufficient biodiversity knowledge. Without concerted efforts to strengthen this capacity and improve knowledge, benefits derived from the region's genetic resources are likely to continue to be reaped by developed countries. The Nagoya Protocol provides an important platform around which a new model of equitable research partnerships can evolve, not only between research institutions from WIO countries and those from the developed world, but also between research institutions and industry discovery and development programmes.

ACCESS AND BENEFIT SHARING

Marine biodiscovery, or bioprospecting, depends upon access to marine organisms, which in turn is governed by multiple legal regimes and national and international laws (Figure 30.5). Marine genetic resources found within the Exclusive Economic Zone (EEZ) are subject to national laws, and to the CBD and the Nagoya Protocol. This means that coastal states have the sovereign right to allow, prohibit and regulate marine bioprospecting in the EEZ; that users of genetic resources who wish to access this material must obtain prior informed consent from national competent authorities; and there must be mutually agreed terms on access and the sharing of benefits.

In practice, it has been extremely difficult to implement ABS principles for marine genetic resources, due in large part to their widespread occurrence and the challenges of determining ownership, but also to the evolving nature of ABS law and policy, and the absence of workable policy approaches in many countries (UNCTAD 2014). In all likelihood, therefore, most cases of marine bioprospecting in the EEZ have not been approved by national authorities, thus leaving the patent applicant and commercial entities as sole beneficiaries (UNCTAD 2014). Increased awareness is, however, leading to recognition of the importance of ABS in bioprospecting initiatives, articulated largely through research collaborations between developed and developing country institutions. The very low chances of commercial success and long-term nature of natural product research suggest that non-monetary benefits associated with scientific engagement and technology transfer are likely to be some of the more significant benefits to emerge from marine bioprospecting in the short-term.

In the high seas, or Areas Beyond National Jurisdiction (ABNJ), natural resources are considered to be the "common heritage of humankind" and are subject to the provisions of UNCLOS. Specialised ABS rules for these resources have not yet been developed and UN members are presently debating the desirability of a new international instrument arising from the conservation and sustainable use of marine biodiversity in these areas (Global Ocean Commission 2013). A central question is whether the benefits arising from the commercial use of these resources should be shared by the entire international community, or whether the States and corporations with the intellectual and technological know-how to exploit these resources should benefit. Unsurprisingly, the G77, which comprises countries that largely do not have suitable scientific and technological capacity, are supportive of an ABS regime that distributes benefits from this common resource more equitably. To date, the debate has focused largely on the *potential* economic value of marine genetic resources, as most research has been on resources from inside national jurisdictions (Oldham and others, 2013).

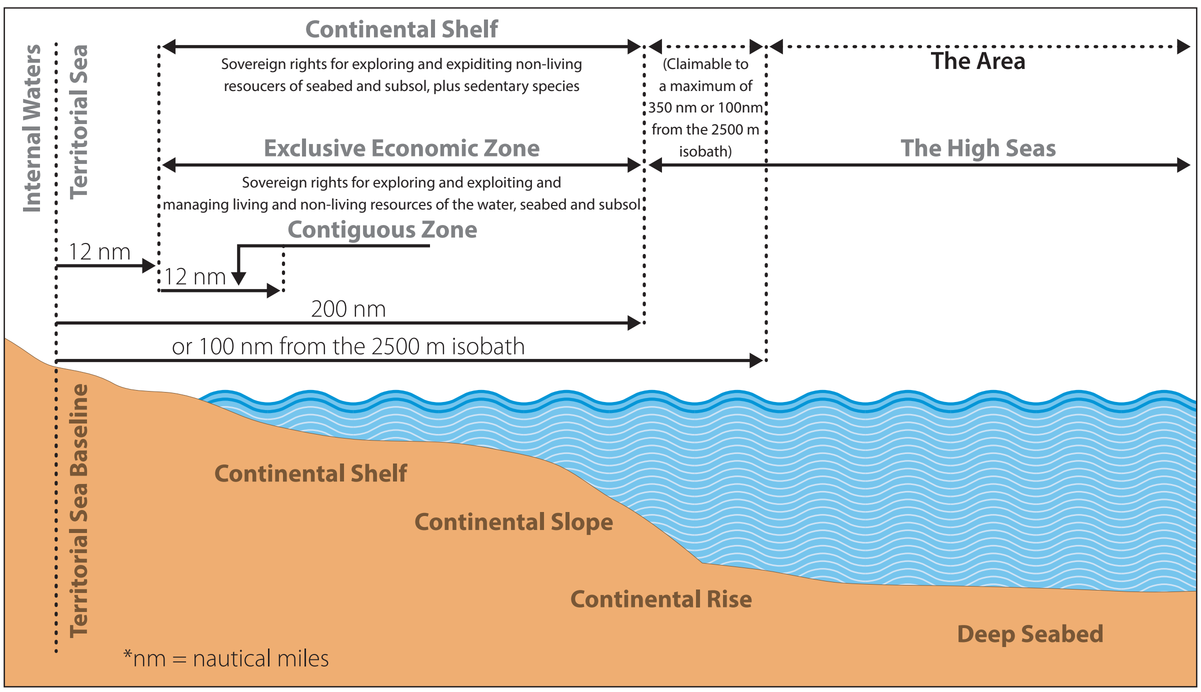

Figure 30.5. Cross-section of legal regimes governing marine resources in geographical zones. Source: Canadian Department of Fisheries and Oceans (www.charts.gc.ca/about-apropos/fs-fd/008-eng.asp)

Table 30.2. Overview of signatories and parties to the Convention on Biological Diversity (CBD) and the Nagoya Protocol

Western Indian Ocean State	Ratified CBD	Ratified or signed Nagoya Protocol	ABS Measures
Somalia	Y	Signed (09-01-12)	No ABS measures in place (Fifth National Report on the Implementation of the CBD, Mogadishu, February 2014, CBD website).
Kenya	Y	Ratified	Framework legislation and regulations were promulgated in 2006, setting out provisions for access to genetic resources and benefit sharing. The Regulations include specific provisions authorising the Minister to issue guidelines for access to and exploitation of living and non-living resources in the continental shelf, Territorial Seas and the Exclusive Economic Zone. The Science, Technology and Innovation Act sets the framework for scientific research.
Tanzania	Y	Neither signed nor ratified	ABS measures under development.
Mozambique	Y	Ratified	ABS measures under development.
South Africa	Y	Ratified	One of the first WIO countries to develop ABS laws, South Africa's Biodiversity Act was promulgated in 2004, followed by Regulations on Bioprospecting, Access and Benefit Sharing in 2008. Marine genetic resources are included within the ambit of these laws.
Comoros	Y	Ratified	No ABS measures in place
Madagascar	Y	Ratified	ABS measures under development.
Mauritius	Y	Ratified	ABS measures under development.
Réunion (France)	Y	Ratified (EU approval)	France does not yet have national ABS legislation covering the whole of its territory.
Seychelles	Y	Ratified	ABS measures under development.

Table 30.2 provides a summary of WIO signatories and parties to the CBD and Nagoya Protocol, and the ABS measures in place in each country. All ten WIO states are party to the CBD, and eight are party to the Nagoya Protocol. The exception is Tanzania which has neither signed nor ratified the Nagoya Protocol. All countries, with the exception of South Africa, and to a lesser extent Kenya and the Seychelles, are still in the process of developing ABS legislation. While ABS regulations have been in place in South Africa since 2008, implementation continues to be problematic, confounded by definitional issues of scope, low capacity levels, and a permitting system widely believed to be excessively onerous (Wynberg 2014).

CONCLUSIONS AND RECOMMENDATIONS

The marine genetic resources of WIO countries are likely to continue to be attractive for natural product research, especially with the accelerated development of genomics and increased interest in microorganisms. While marine bioprospecting presents a number of important opportunities for WIO countries, these are currently not being optimised. Appropriate laws are not yet in place; the costs of research and technologies remains prohibitively high; scientific capacity is low; and there are significant gaps in taxonomic and ecological knowledge.

The following recommendations are made to address some of these challenges:

• WIO countries should develop or strengthen national and regional ABS laws for marine biodiversity in the EEZ, with an emphasis on ensuring sufficient control over access and benefits, but without impeding research endeavours. Laws should be clear, simple and implementable. Countries that are not yet party to the Nagoya Protocol should be encouraged to ratify the agreement.

• In line with Article 8 of the Nagoya Protocol, particular attention should be given to promoting research that contributes to the conservation and sustainable use of biodiversity. Regulations should include a requirement for an assessment of the environmental impact of collecting activities.

• As noted in Articles 22 and 23 of the Nagoya Protocol, marine bioprospecting should be regarded as an opportunity to build scientific capacity in WIO countries and to transfer appropriate technology and access to technology from developed countries and institutions.

• Considerable effort should be given towards improving scientific knowledge about the marine biodiversity of the WIO region, and in particular under-explored groups, including microorganisms and microalgae.

• In addition to capacity development and technology transfer, benefit sharing should include measures to strengthen the conservation of the area of collection and/or species collected. Countries should consider benefit-sharing measures to improve taxonomic knowledge and to improve access to raw and published data.

• Attention should be given to the possible development of a regional ABS approach for marine genetic resources in the WIO region, in line with the multilateral mechanism proposed by the Nagoya Protocol.

•Efforts should be undertaken to develop ABS rules for genetic resources in the high seas to ensure these potential benefits are gleaned by humanity as a whole.

• In international negotiations, WIO countries should support improved disclosure of the origin of material in patent applications to ensure greater transparency and improved tracking of the source of the material. Detailed information about the geographical and phylogenetic origins of marine genetic resources would help states to settle disputes over the ownership of material.

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