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# Marine Sponges as Natural Oceanic Biofactories for Sustainable Drug Discovery

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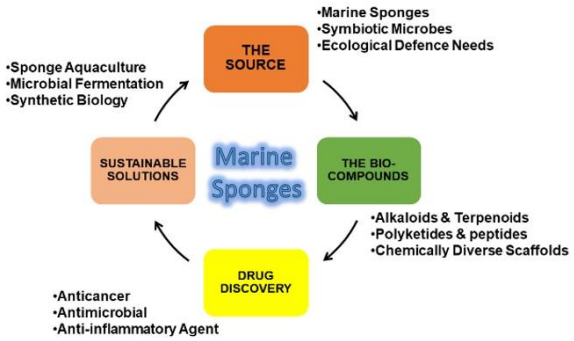
**Abstract:** Marine sponges (MS) are attracting a growing interest from the pharmaceutical industry due to their bioactive compounds. A large number of studies being done from MS as regards drug discovery, a multitude of reports on both bioprospecting to separation in addition to synthesis up to biological evaluation exist. The pharmaceutical potential of Actinobacteria and some other notable bioactive molecules, including kryptosiphon crypta, dragmacidin, phorboxazoles, and spirolides is excellent. Drug development can be a promising route from MS compounds, but the marine-derived drugs have been hindered by roadblocks such as sustainable supply of source organisms, process conditions and regulatory approval. Examples of the contribution of marine biodiversity to human health can be seen with compounds already in use such as eribulin, a chemotherapy agent obtained from Halichondria sponges and new drug leads from MS; advancements in biotechnology, chemical ecology and metagenomics have provided novel approaches to tackling existing problems helping pave the way for sustainable discovery and exploitation of potential clinically-relevant products found within the Antarctic environment. This review article reports the bioactive molecules exist from early periods of marine sponges, e.g. halichondrin B and papuamine, as well as their bioreactors for biosynthesis of natural products and natural/bioproducts of commercial importance. It will discuss how sponge–microbe symbiosis matters both in terms of driving innovation in drug discovery, informing sustainability challenges and now also presenting innovative solutions to some these issues.




**Keywords:** *Marine sponges, drug discovery, bioactive compounds, bioprospecting, sustainable drug discovery*

## Contents



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## 1. Introduction

Marine natural products have become an integral part of the drug discovery process and a rich repository of structurally diverse biologically active molecules. Sponges (phylum Porifera) are considered to be excellent producers of chemicals and produce a wide variety of bioactive secondary metabolites with the severe potential for therapy. This prospecting opener delves into the significance of marine natural products in medicine discovery, special marine sponges as chemical factories with insight on natural oceanic

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biofactories and the demand for a sustainable usage of sea resources.[1,2] Marine ecosystems are an abundant source in which many novel bioactive compounds have changed a landscape of pharmaceutical development. Recent reviews keep saying that marine sponges are rich sources of metabolites with a wide range of chemical structures. A dedicated review of compounds reported from 2020 to 2023 listed 218 unique sponge-derived secondary metabolites, such as terpenoids, peptides, and alkaloids. Many of these had cytotoxic, antimicrobial, enzyme-inhibitory, anti-inflammatory, neuroprotective, or antibiofilm activities.[3] This sustained rate of discovery highlights the significance of sponges as reservoirs of pharmacologically valuable chemical diversity. The complexity of structure and the diversity of function embodied in marine natural products offer synthetic chemists access to privileged scaffolds that cannot necessarily be readily realized through exclusively synthetic means. This chemical diversity is important in the context of discovery for new drugs, especially in respect to issues like antibiotic resistance, reinforced by cancer and chronic diseases. As the earliest multicellular invertebrates, marine sponges have evolved to produce diverse secondary metabolites over millions of years with an ecological role and potential pharmacological value.[4] Being sessile and soft-bodied exposes them to predation and colonisation by microbes; consequently, both factors have driven the development of complex chemical defence systems.[1,5]

Sponges are part of a wide array of benthic communities in all the oceans, and they play crucial ecosystem roles, such as habitat provision and nutrient dynamics. As filter feeders, they gather microscopic food particles day by day, and thanks to various symbiotic relationships with numerous groups of microorganisms, have augmented their biosynthetic potential. Symbiotic marine microbes of sponges have a longer evolutionary history than the ones present in higher plants, which largely accounts for the chemical novelty and diversity of compounds produced from sponges. This partnership leads to the production of a complicated chemical library, which is composed of alkaloids, polyketides, peptides, terpenoids and other natural products (secondary metabolites), many of which have shown powerful antimicrobial, antiviral and anticancer anti-inflammatory activities.[6,7] The vision of marine sponges as natural huge multiniche biofactories appears to be the philosophy that lies in searching for a wide range of bioactive compounds, besides the scientific rationale that these animals are extreme producers. These organisms produce secondary metabolites acting as both chemical deterrents towards predators, including fish, turtles and invertebrates, and anti-settlement factors to inhibit fouling on the surfaces of the biologics. This biochemical richness of sponge-derived metabolites is unparalleled in nature. There are now about 9,800 recognized species of sponges in the world, most of which are found in marine areas and a lesser number in freshwater habitats[8] and each species realizes a very unique chemistry.[9] The metabolic pathways leading to their synthesis are typically complex and often involve both sponge cells and associated microbes, which results in such biofactories being efficient producers of specialized metabolites.[5,10]

The ecological importance of sponges is not confined to secondary metabolite production. They have important functions in benthic systems, such as nutrient cycling, as a substrate for different marine organisms and the stabilization of ecosystems. This ecological significance emphasizes the requirement to sustainably use marine sponges in drug discovery. Unsustainable harvesting or unregulated collection can disturb benthic communities, resulting in loss of biodiversity and ecosystem dysfunction. As such, sustainable harvesting is essential to the conservation of these natural resources by continuing access through its bioactive agents.[1,11] Biotechnological approaches are increasingly being applied for the management of sustainability problems. The culture of sponges presents a renewable biomass source, which helps to relieve the exploitation pressure on wild stocks. Moreover, with the further development of microbial fermentation and metagenomics technology, it is possible to cultivate sponge-associated microorganisms in vitro and manipulate their genetic compositions in order to produce bioactive compounds. “Industrial” biology using synthetic biology approaches, industrially desired, but ecologically risky, complex metabolic pathways can be reproduced in more readily cultured organisms, providing scalable production methods. These approaches not simply lend invaluable support to the programme of sustainable drug discovery but also make it more realistic to consider translating sponge metabolites for use in patient treatment.[10,12]

Nevertheless, in spite of the great promising value for marine sponges as resources of medicinal engineering, some problems persist. The sponge-microbe interactions complicate the discovery process of bioactive compounds. In addition, sustainable sourcing and scalability become barriers during the development from discovery to commercial drug production. Regulatory barriers and the requirement for extensive ecological impact assessments are, however, substantial obstacles. Nonetheless, advances in chemical ecology, biotechnology and marine conservation are increasingly breaking down the barriers, leading towards a sustainable path on marine sponge exploitation.[13,14] The ecological function of sponges and their chemical productivity emphasizes the need to harvest these organisms with responsibility in order to find a balance between drug development requirements and marine life preservation.[15] Improvements in aquaculture, microbial biotechnology and synthetic biology are promising approaches that will allow the sustainable exploitation of sponge-derived products, making sure that marine natural products chemistry remains an important source for drug discovery pipelines (Figure 1).

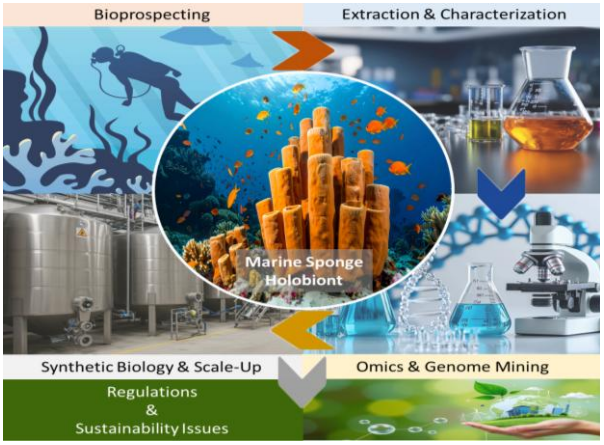


**Figure 1.** *Sustainable Drug Discovery Pipeline from Marine Sponges. Schematic representation of the integrated drug discovery pipeline originating from marine sponge holobionts. The process begins with sustainable bioprospecting and sample collection, followed by extraction and compound characterisation. Omics-driven genome mining identifies biosynthetic gene clusters, which are subsequently exploited through synthetic biology and microbial fermentation for scalable metabolite production. The pipeline operates within a regulatory and sustainability framework encompassing ethical bioprospecting, pharmacological evaluation, safety assessment, and compliance with international conventions, ensuring environmentally responsible and legally compliant translation into therapeutic development. (Source:* www.vecteezy.com)

## 2. The Biology, Ecology and Bionomic Potential of an Ancient Group of Animals, the Porifera-Marine Sponges

### 2.1. Fundamental Biology and Morphology

Sponges are simple metazoans that have porous bodies and elaborate internal canal systems. Many tiny holes called ostia allow saltwater to enter the sponge's structure, while bigger apertures called oscula allow it to depart after going through a filtering mechanism. These internal canals are lined by choanocytes, cells with a flagellum for movement of water. Choanocytes produce currents in the water and retain microscopical food particles, associated with an efficient filter-feeding process that is necessary for feeding/nutrient processing and metabolite accumulation. The skeletal system of the sponge is made up of silica or calcareous sponges and sponging fibres that offer structural support and help to keep the sponge's shape. This framework serves to reinforce the soft and sedentary body forms of sponges, which are in fact able to adapt to variable environmental conditions in marine habitats without losing their capacity for filter feeding.[16,17]

#### 2.1.1. Cellular Plasticity

Sponges are characterized by extraordinary cellular malleability: cells dedifferentiate, trans differentiate and migrate around the animals. This plasticity enables sponges to rearrange their cellular structure during environmental changes or wounding. This flexibility is essential for survival, allowing responses to changing internal and external conditions as well as support for the interdependent activities of cells in metabolism that are not necessarily defined by primary metabolic products.[18,19]

#### 2.1.2. Regenerative Capacity

The impressive ability of marine sponges to regenerate is one of their most striking biological features. They have a high capacity for proliferation and differentiation to replace lost or damaged tissues. This regenerative capability is not only beneficial for healing physical injuries, but it also contributes to asexual reproduction processes such as fission. To ensure the persistence of sponge populations, which is essential for the maintenance of their ecological niche and seamless bioactive metabolite production, regeneration is a valid alternative.[19–21]

#### 2.1.3. Filter-Feeding and Metabolite Accumulation

The filter-feeding capacity of sponges is the core of their ecological role and potential as a biofactory. Sponges continuously flush copious amounts of seawater through their canal systems and efficiently filter out planktonic material, bacteria, and organic detritus on which they feed. This feeding mode also requires the storage of metabolites originating from both sponge cells and their symbiotic microbiota. The accumulated metabolites consist of a wide array of secondary compounds, several with ecologically relevant functions as defenses against predators and fouling organisms. The interdependence of filter-feeding and metabolite production highlights the role that sponges play as natural bioreactors by manufacturing complex structural and biologically active products which they use in various survival and ecological roles. All in all, such biological characteristics as cellular plasticity, regenerative capabilities and advanced filter-feeding underlie the ecological success of marine sponges and their extraordinary prospects as producers of new bioactive compounds.[22,23]

### 2.2. Ecological and Chemical Defence Adaptations

Sponges have a variety of ecological specializations that help them to persist in very different and at times extreme marine habitats. Everything from their rather unique body shape to the way they feed through filter-feeding and reproduce as hermaphrodites all contributes to their ability to live. However, one of the most important adaptations driving their ecological success is a remarkably complex and effective chemistry defence system that is tightly integrated with chemical ecology and secondary metabolite production.[9]

#### 2.2.1. Chemical Ecology

The chemical ecology of the marine sponge embraces two main aspects: the production and release of bioactive secondary metabolites for mediating contact towards other organisms or the environment. Not having a nervous system or hard/sheathed body to protect them, sponges have had to rely on chemical mechanisms to prevent predation, microbial settlement and overgrowth (fouling) by other organisms. Such chemical defences are essential due to their sessile lifestyle, being permanently exposed to a variety of potential enemies. Regulation of water movement through their permeable integuments, for both feeding and defence, is an adaptive feature. The oscula of a sponge can be opened and closed to increase feeding rates as food supplies increase and protect the sponge from agents in the environment during periods of low food. Furthermore, other activities such as reversing of water flow following environmental disturbances promote canal health and reduce clogging (e.g., indirectly supporting chemical defence by increasing metabolic activity and metabolite production).[24]

#### 2.2.2. Production of secondary metabolites under ecological pressure

Secondary metabolites from marine sponges are a structurally diverse group of compounds produced by the sponges to defend against predation, competition and microbial fouling. These are mainly composed of alkaloids, terpenoids, polyketides and peptides, as well as other classes of biologically active molecules. They are also frequently inducible, produced more in response to a stress such as evidence of predation or the presence of fouling organisms.[25,26] Chemical defences can have several ecological roles: deterring fish, turtles and invertebrate predators; inhibiting the settlement and growth of fouling organisms, including bacteria and algae, as well as competition with benthic species. This pleiotropy points to the evolutionary advantage of metabolite network diversity and creativity.[27] These microbes represent a major source of chemical diversity, and many of the metabolites isolated are only reported from sponge-microbe complexes. Such mutualistic interaction expands the sponge's chemical defence against changing natural conditions in nature, allowing for a dynamic and adaptive response.[17]

### 2.3. Sponge Microbe Symbioses as Biofactories

Marine sponges host extremely diverse and intricate microbial communities which contribute to their biofactory potential. This symbiosis greatly increases the ability of sponges to synthesize a large diversity of bioactive secondary metabolites, which play important ecological roles and can have valuable applications in the pharmaceutical industry.[28]

#### 2.3.1. Microbial Diversity

Collagenous sponges harbour complex bacterial, archaeal, fungal and microalgal consortia that reside in the mesohyl. These microbiotic communities may represent a significant fraction of the sponge biomass, in some cases being over 40% by volume. This diversity includes several phyla, such as Proteobacteria, Actinobacteria, Cyanobacteria and Acidobacteria. This microbiological richness may provide the holobiont with metabolic versatility and thus allow for biosynthesis of structurally unusual compounds which are infrequently found in marine organisms.[29,30]

#### 2.3.2. Biosynthetic Gene Clusters (BCG)

Secondary metabolites in sponge holobionts are biosynthetically encoded by a polyketide-/non-ribosomal peptide synthase (PKS/NRPS) gene cluster distributed among both the sponge cells and their accompanying

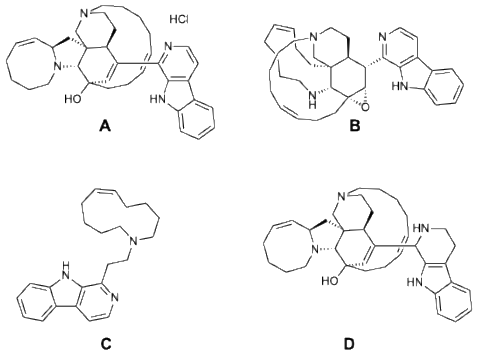


**Figure 2.** *Structural representations and diversity of the manzamine alkaloid family. (A) Manzamine A (shown as the hydrochloride salt), illustrating the complex polycyclic core architecture attached to the β-carboline moiety. (B) Manzamine B, displaying variations in the oxygenated polycyclic framework. (C) Manzamine C, highlighting a simplified azacyclooctadecene macrocyclic structure. (D) 8-Hydroxymanzamine A, an analog featuring a targeted hydroxyl substitution on the β -carboline ring system. All chemical structures were prepared with the assistance of PubChem and ChemSketch*

microorganisms. Such BGCs encompass the genes involved in the production of polyketides, non-ribosomal peptides, terpenoids, and alkaloids. Advances in metagenomic and genomic sequencing have shown that many BGCs originate from symbiotic microorganisms rather than from the sponge host.[31] This genomic observation emphasizes the significance of symbiotic microorganisms as the true producers of a number of bioactive compounds associated with sponges. Functional expression of these gene clusters is mediated by intricate regulatory networks and interspecies metabolic exchanges among sponge-microbe communities. The occurrence of horizontally transferred genes and modular gene organizations can also increase the chemical variability and modularity in these biosynthetic pathways and provide adaptability.[32] Metagenomic surveys of sponges with higher microbial symbiotic association have revealed an unexpectedly large collection of biosynthetic gene clusters. One study documents ~5082 distinct clusters across diverse sponge metagenomes, including PKS, NRPS, terpene, and RiPP biosynthetic families. This emphasizes the vast unexplored potential for novel natural product discovery and for activating cryptic pathways.[10]

#### 2.3.3. Metabolite Origin (Host *vs*. Symbiont)

The exact source of sponge metabolites is difficult to assign because the host-symbiont relationship is very close. Although some compounds are produced by sponge cells themselves, the majority of them are synthesized by microorganisms that agreed to be included in their host. Studies using isotopic labelling, metagenomics and chemical profiling have implied that a significant number of structurally novel metabolites with pharmaceutical properties are products of microorganisms. The holobiont concept views the sponge and its microbiome as a holistic functional unit, with metabolite production being generated via collective biosynthesis.[33] This cooperation allows the formation of compounds neither computer alone mediates production of, increasing ecological fitness to the sponge and promoting a broader repertory of bioactive natural products for drug development. Knowledge of the mechanisms of mutual symbiosis between sponge and microbe (biosynthetic pathways control, metabolite exchange) is crucial for future sustainable production strategies. Cultures of symbionts, metagenomic exploitation and synthetic biology strategies focused on BGCs open a perspective for scaled production of valuable sponge metabolites without damaging the natural marine environment.[34]

## 3. Chemo-diversity of Bioactive Compounds from Marine Sponge

Marine sponges are one of the most productive sources of structurally diverse secondary metabolites that have had significant pharmacological applications. This chemical variety reflects the diverse biosynthetic potential of the sponge host and its attendant microbial associates. Alkaloids, terpenoids, polyketides, peptides and macrolides are the main classes of bioactive products isolated from marine sponges with distinct structures and pharmacological features .[14,25,35]

### 3.1. Bioactive Metabolites and Their Major Classes

#### 3.1.1. Alkaloids

Alkaloids, natural nitrogenous heterocyclic compounds, have been extensively described in marine sponges. Such metabolites are frequently characterized by strong antimicrobial, antimalarial and cytotoxic activities. The manzamines are a family of structurally complex polycyclic β-carboline alkaloids possessing fused tetra- or penta-cyclic ring systems, which exhibit wide-ranging bioactivity (Figure 2). Another novel group unique to sponges, troxoviridins, are bromopyrrole alkaloids which are derived from the oroidin precursor and have various biological activities, such as antitumor activity and antimicrobial activity.[1,5,36]

#### 3.1.2. Terpenoids

Marine sponges make a lot of terpenoids, which are secondary metabolites. These are best described as natural products that come from isoprene instead of polymers with low molecular weights. Sesquiterpenoids, sesterterpenoids, and triterpenoids are some examples. They all have different structures. There should be another figure that shows examples of structures such as avarol, manoalide, and stellettin B. For example, manoalide from Luffariella variabilis is known to stop inflammation by blocking phospholipase A2. Avarol from Dysidea avara has been shown to be cytostatic and antimicrobial, and stellettin B from Jaspis stellifera has been shown to be very effective against cancer. These examples show that the wide range of structures found in terpenoids from sponges is closely linked to their wide range of biological activity (Figure 3).[37]

#### 3.1.3. Polyketides

Polyketides are structurally diverse secondary metabolites that are synthesized via polyketide synthase pathways and are most of the time reported to be isolated from marine sponges. These chemical substances usually have complex macrocyclic structures or polyoxygenated frameworks, and possess a wide range of biological activities, including anticancer,

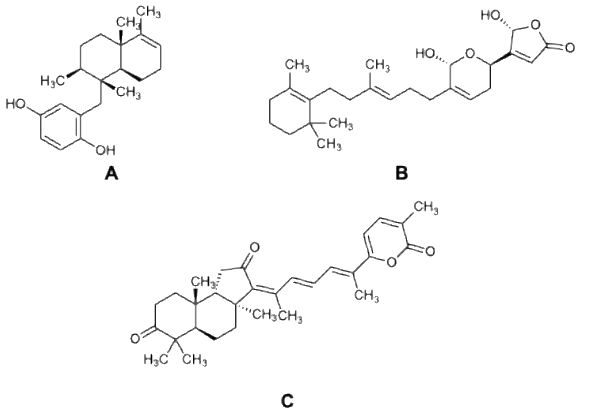


**Figure 3.** *Representative chemical structures of bioactive terpenoids isolated from marine sponges. (A) Avarol, a sesquiterpenoid derivative from Dysidea avara with known cytostatic and antimicrobial activities. (B) Manoalide, a sesterterpenoid from Luffariella variabilis recognized for anti-inflammatory properties via phospholipase A2 inhibition. (C) Stellettin B, an isomalabaricane triterpenoid from Jaspis stellifera exhibiting significant anticancer efficacy. All chemical structures were prepared with the assistance of PubChem and ChemSketch*

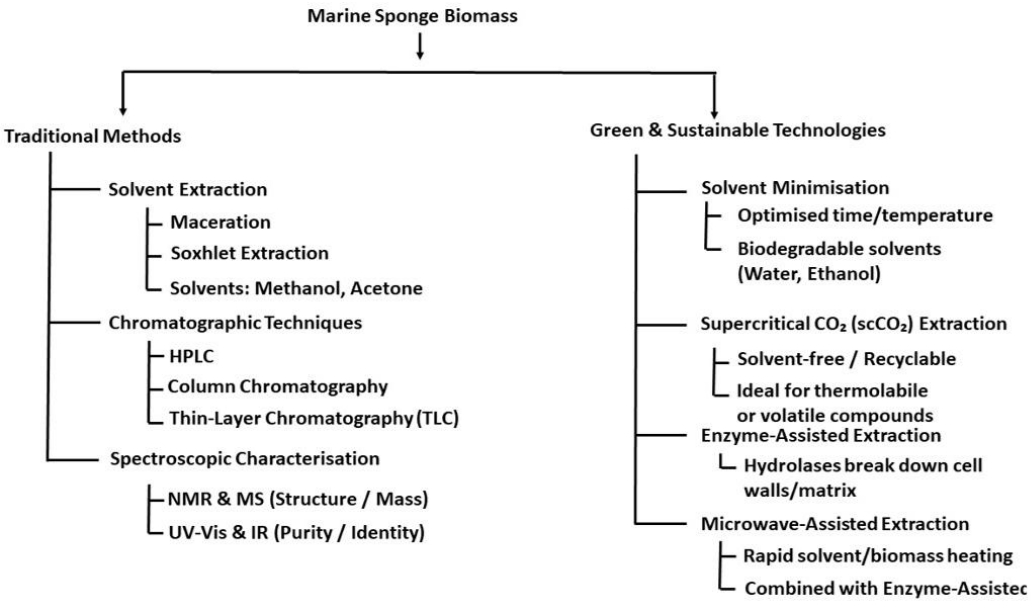


**Figure 3.** *Comparison of methodological approaches for processing marine sponge biomass. The schematic outlines two primary pathways for the extraction and analysis of marine sponge-derived compounds: Traditional Methods and Green & Sustainable Technologies. The traditional pipeline relies heavily on conventional solvent extraction techniques (such as maceration and Soxhlet extraction using organic solvents like methanol and acetone), followed by standard chromatographic separation (HPLC, column chromatography, and TLC) and comprehensive spectroscopic characterization (NMR, MS, UV-Vis, and IR). In contrast, the right panel highlights modern green and sustainable technologies aimed at reducing environmental impact. These include solvent minimization strategies (utilizing optimized conditions and biodegradable solvents like water and ethanol), supercritical $CO_2$ ($scCO_2$) extraction for volatile and thermolabile compounds, enzyme-assisted extraction utilizing hydrolases to break down cellular matrices, and microwave-assisted extraction for rapid heating, which can also be coupled with enzymatic methods.*

antibacterial, and antifungal effects. Figure 4 with different structures of representative sponge-derived polyketides such as halichondrin B, discodermolide, calyculin A, and tedanolide will be included to show their structural diversity. Their

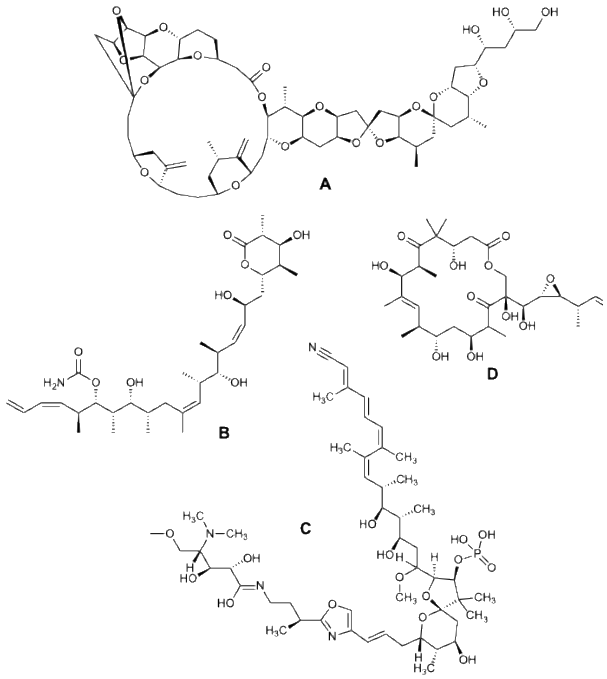


**Figure 4.** *Structural diversity of representative polyketides isolated from marine sponges. (A) Halichondrin B, a complex macrocyclic polyether and the structural inspiration for the anticancer drug eribulin. (B) Discodermolide, a polyhydroxylated lactone with potent cytotoxic properties. (C) Calyculin A, a spiroketal-containing polyketide utilized as a potent biochemical tool. (D) Tedanolide, a highly substituted macrolide exhibiting significant therapeutic potential. These structures highlight the complex macrocyclic and polyoxygenated frameworks characteristic of sponge-derived polyketide metabolites. All chemical structures were prepared with the assistance of PubChem and ChemSketch.*

biomedical importance is exemplified by halichondrin B, which led to the anticancer drug eribulin, while other compounds have served as highly potent cytotoxic agents or biochemical tools, thus illustrating the therapeutic and pharmaceutical value of marine sponge-derived metabolites.[38]

### 3.1.4. Peptides and Macrolides

Marine sponge-derived peptides and macrolides are significant bioactive metabolites, and their chemical structures should be depicted in the figure. Uncommon amino acids are found in peptides like discodermin A that have a broad-spectrum antibacterial as well as enzyme inhibitory activity, so they have a therapeutic significance. Similarly, sponge-derived macrolides like swinholide A and tedanolide have powerful cytotoxic and potential anticancer effects. It is clear from these examples that marine sponge metabolites are quite different, chemically, but they could also be antibacterial and anticancer agents (Figure 5).[39]

## 3.2. Biosynthesis Pathways and Metabolic Origins

The biosynthetic routes get their foundations in the oxidative acetylenic chemistry. These biosynthesis pathways have structural origins of terpene, and certain heptaketides from anthraceneyl usolic acids lead to both natural and steric-functional type compounds.[40]

### 3.2.1. Host-Derived Metabolites

Some secondary metabolites are produced by sponge cells themselves, mostly serving for defence against predators and fouling agents. This includes a few terpenoids and peptides for which biosynthetic genes reside in the sponge genome. The sponge's cellular plasticity and capability of regeneration facilitated the biosynthesis and storage of such compounds.[41]

### 3.2.2. Microbial Biosynthesis

A large group of complex bioactive metabolites are derived from symbiotic microorganisms living within the bodies of sponges. Such microorganisms, including bacteria, archaea, fungi and microalgae, harbour biosynthetic gene clusters

(BGC) encoding enzymes for polyketides as well as alkaloids, terpenoids and peptides. Studies using metagenomics have shown that the vast majority of BGCs are microbial in nature, emphasising the importance of symbionts for generating structurally new and pharmacologically active compounds.[42] A study has reported at least 270 structurally novel antimicrobial metabolites between 2012 and 2022 are mainly produced by actinomycetes and filamentous fungi assocuated with marine sponges. These findings support the concept of the sponge holobiont, where the sponge and its microbial symbionts function together as a unified chemical system rather than as separate organisms.[6]

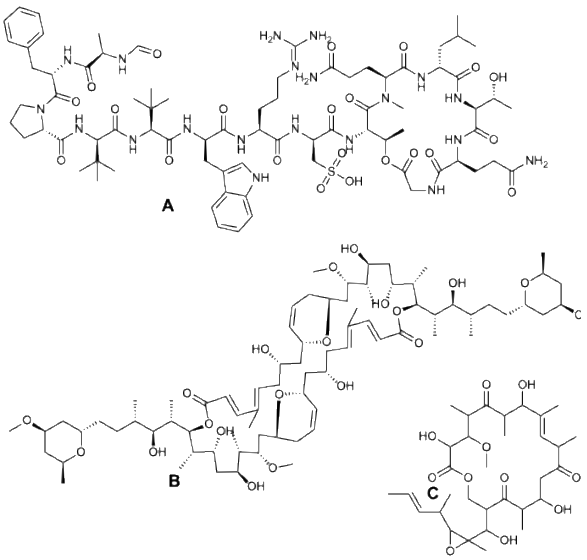


**Figure 5.** *Chemical structures of representative bioactive peptides and macrolides derived from marine sponges. (A) Discodermin A, a complex tetradecapeptide containing uncommon amino acids, known for broad-spectrum antibacterial and enzyme inhibitory activities. (B) Swinholide A, a massive dimeric dilactone macrolide exhibiting potent cytotoxicity. (C) Tedanolide, an 18-membered macrolide with significant anticancer potential. These structures illustrate the diverse chemical architectures responsible for the therapeutic properties of marine sponge metabolites. All chemical structures were prepared with the assistance of PubChem and ChemSketch.*

### 3.2.3. Mixed Biosynthetic Routes

And in some cases, biosynthesis is supported by overall metabolic crosstalk between the sponge host and its associated microorganisms. The holobiont is proposed as a functional system in which the metabolome ultimately reflects enzymatic activities from both partners that intersect to produce chemical products not produced from either partner alone. These dual biosynthetic pathways from divergent kingdoms of life contribute to the chemical richness and environmental adaptiveness that enable the sponge to serve as a natural aquatic biofactory. This chemical diversity, influenced by evolutionary and ecological factors, has been identified as the key factor for sponges not only to survive but also to be a source of valuable scaffolds in drug discovery. Knowledge of the biosynthetic origins and pathways is important for the sustainable production processes and efficient pharmaceutical utilisation of sponge natural products.[41,43]

## 4. Extraction, Characterization and Sustainable Processing

The two primary milestones for harnessing the pharmaceutical potential of marine sponges (MSs) are the isolation and characterisation of bioactive compounds obtained from MSs. In addition, sustainable and eco-friendly techniques for the isolation of these natural products are definitely important both in preservation of the environment as well as keeping the stability of the compounds.[12,13] Solvent-aided solid-liquid extraction has been used in the extraction of sponge metabolite using standard procedures. Commonly used solvents are methanol, ethanol, acetone, trichloromethane and water either singularly or in combinations to allow for the selection of different polarity compounds. Maceration involves the room temperature soaking of sponge biomass in solvent with constant stirring, while Soxhlet extraction pertains to forced dynamic refluxing to maximize compound yield. These processes are commonplace, but would necessitate using risky amounts of solvent with long process times resulting in high solvent usage and thermal degradation of thermolabile components due to heating.[5,44] After solvent extraction, the compounds are isolated by chromatographic methods such as high-performance liquid chromatography (HPLC), column and thin-layer chromatography. It enables the fractionation based on polarity or molecular size or affinity for the isolation of bioactive metabolites. Preparative chromatography has continued to develop with improved resolution and performance toward secondary analysis and bioactivity-based fractionation.[45] The structural determination of the isolated compounds is achieved by mean of spectroscopical methods like nuclear magnetic resonance(NMR), mass(MS) UV-Vis MD infrared (IR). While NMR provides structural and stereoisomeric information, the mass spectrum (MS) gives us molecular weight and fragmentation pattern. All these approaches serve to validate the compound identity and quality, both vital for drug testing and synthetic optimization.[46] The minimization of the use of solvents is searched through the optimization of extraction conditions such as, type and volume of solvents, temperature and time of contact to obtain high yields with a minimum environmental impact. Green chemistry[46] ideally initiates fewer dangerous and more biodegradable solvents (i.e., water and ethanol).[47] Supercritical $CO_2$ ($scCO_2$) extraction provides an environment-friendly approach, which employs $CO_2$ separating power versatility under supercritical conditions to selectively extract non- to moderately polar compounds in the absence of organic solvents. This method might as well be promising with leaving the extraction under low-temperature conditions, using less solvent after extraction, and prompt separation of product and solvent. $scCO_2$ extraction is particularly appropriate for thermolabile and volatile metabolites, allowing immediate preservation of bioactivity and even recycling of solvents.[13,44] To release intracellular metabolite, the enzyme-assisted extraction method is designed to creak sponge cell walls and extracellular matrix by means of a specific hydrolase for convenient solvent penetration. Moreover, the extraction cost is not only cheaper but also exhibits a higher extraction rate and selectivity of zeaxanthin under mild conditions when compared with classical methods. New technologies such as "microwave-assisted extraction (MAE)" are being applied for selective (homo or hetero) undirected and directed extractions of bioactives from a multicultural matrix by combining both the quick microwave energy that heats the solvent and biomass rapidly, ultimately speeding up the extraction rate or improving yield compared to conventional approaches. MaE actually represents a sustainable and scalable alternative for traditional techniques since it reduces the extraction time and solvent volume. Yet enzyme-assisted microwave has an even more efficient technique. These green extraction technologies can also be applied to conventional methods and improve the bioactives recovery from marine sponges as well as increase sustainability and feasibility of different pharmaceutical applications (Figure 6).[48]

## 5. Pharmacological Actions and Potential for the Discovery of Promising Drugs

Marine sponges are one of the richest natural sources of biologically active compounds with a wide range of

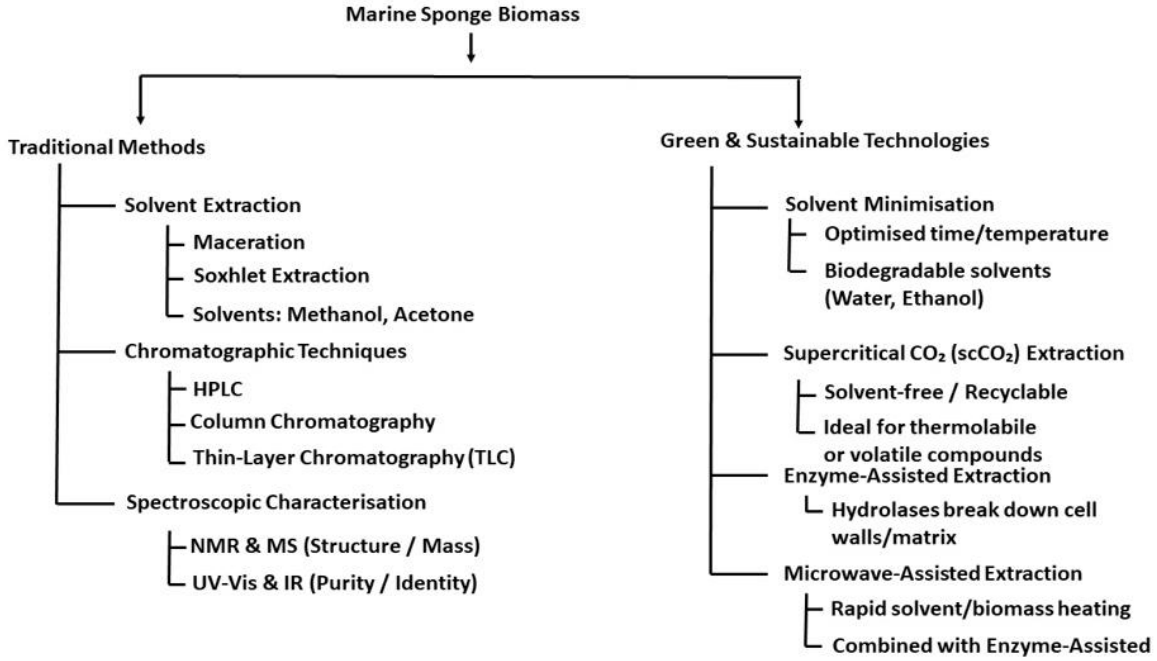


**Figure 6.** *Overview of extraction and analytical methodologies for marine sponge biomass, comparing traditional approaches with modern green and sustainable technologies. Traditional methods rely on conventional solvent extraction, chromatography, and spectroscopy, whereas sustainable technologies emphasize solvent minimization, supercritical $CO_2$ ($scCO_2$), enzymatic degradation, and microwave-assisted extraction.*

pharmacological actions. Their broad chemical diversity and ecological specializations have yielded a wealth of metabolites with potential applications in medicine. This section summarises the significant pharmacological features, including anticancer, antimicrobial and antiviral properties, anti-inflammatory effects, neuroprotective activity and immunosuppressive effects that emphasize the importance of marine sponges as a source for drug discovery.[49]

### 5.1. Anticancer and Cytotoxic Agents

The marine sponges are also recognized for their production of several compounds with anticancer and cytotoxic potential. These metabolites frequently hit at key cellular pathways implicated in tumour progression and metastasis. Multiple sponge-derived metabolites have been identified as inhibitors of protein kinase C (PKC), a crucial regulator of cellular signaling, with its dysregulation associated with cancer and various pathological conditions. Consequently, PKC-inhibitory metabolites derived from marine sponges persist in garnering interest as potential candidates for therapeutic advancement.[50] The overactivation of PKC is involved in pathological states, and its blocking may lead to inhibition of adherence and proliferation of cancer cells. Compounds, e.g., octa- and nonaprenylhydroquinonesulfates from *Sarcotragus* sp., have shown a potential fucosyltransferase inhibitory effect that can lead to the control of inflammation and cancer. Several sponge-derived metabolites are capable of initiating apoptosis, have an effect on microtubule dynamics or inhibit DNA replication and provide promising leads in anticancer drug research. These series encompass polyketides, alkaloids and peptides with different modes of action. The cytotoxicity of these compounds is frequently associated with selectivity for cancer cells, which brings reduced toxicity to normal tissues. Their unique structures give rise to the potential to develop novel chemotherapeutic agents which have not shown cross-resistance.[51,52]

### 5.2. Antimicrobial and Antiviral Compounds

The emergence of multidrug-resistant bacteria and methicillin-resistant Staphylococcus aureus (MRSA, among them) has further increased the demand for new antimicrobials. Marine sponges represent a great reservoir of antibacterial products active against terrestrial and marine bacteria.[53] For instance, the extracts of arctic sponges are highly potent, and moderate to strong antimicrobial activity ($IC_{50}$) has been recorded as their activity. Alkaloids, peptides, and terpenoids derived from sponges have been reported to possess bactericidal and/or bacteriostatic activity against multidrug-resistant strains. Furthermore, antifungal agents such as jaspamide, a cyclodepsipeptide that demonstrates potent activities against Candida spp., are promising compounds to treat invasive mycoses in immunosuppressed hosts. Another significant pharmacological aspect of sponge substances is their antiviral effect6. A number of these compounds have shown antiviral activity against such viruses as HIV, herpes simplex or poliovirus. There is also an increasing and urgent necessity for novel antiviral compounds, particularly for persistent and emerging viral diseases, which makes marine sponge metabolites promising candidates. The inhibitory mechanisms of these compounds on viral entry, replication, or assembly may contribute to the development of new antiviral drugs.

### 5.3. Anti-inflammatory and neuroprotective activity

Neuroprotective marine sponges are medicinal and serve as a group. Anti-inflammatory compounds in these animals work against a drug such as aspirin or ibuprofen (NSAID). For instance, manoalide (a sesterterpenoid compound from Luffariella variabilis) has been reported to suppress the activity of phospholipase $A_2$ ($PLA_2$), a key enzyme involved in the formation of pro-inflammatory mediators. This inhibition is advantageous because it reduces tissue damage and inflammation. Certain sponge metabolites have been shown to have neuroprotective properties, which may either reduce oxidative stress, decrease neuroinflammation, or maintain the integrity of neurones. These endeavours provide paths for the development of therapeutics for neurodegenerative diseases. Immunosuppressive agents from sponges are useful in the treatment of hypersensitivity reactions, autoimmune diseases and organ transplantations. Other metabolites decrease their T-cell proliferation or level of nitric oxide synthase, which has an immunomodulatory effect. These agents are specific and

potent and might be suitable for safer immunosuppression therapy. The significance of marine sponge metabolites in drug development is emphasised due to their wide range of pharmacological activity. Their distinct structure and ability to interact with a particular biological target provide enormous promise for the creation of novel medications to address untreated illnesses.[54]

## 6. Sponges uses in Drug Discovery and Biotechnology

Marine sponges have emerged as significant sources in the biotechnological and pharmaceutical sectors due to their exceptional capacity to generate secondary metabolites that are both physiologically active and architecturally varied. Yet, the continuous and scaled-up source of these biologically active compounds is still a major bottleneck. To combat these challenges, sophisticated growing practices, cell cultures, microbial fermentation, and synthetic biology have been developed and improved. Together these strategies work toward a sustainable, green synthesis platform for sponge-derived therapeutics.[55]

## 6.1. Sponge Aquaculture and Mariculture

Aquaculture and mariculture are core technologies for sustainable biomass production of marine sponges, minimizing the impact on ecosystems caused by wild harvesting and protecting marine biodiversity.[13,15]

### 6.1.1 Biomass Sustainability

Aquaculture of sponges in marine or artificial conditions leads to controlled year-round biomass production. Wild sponge fragments or larvae are source organisms, collected and placed (spat-on-rope) on natural ropes deployed in propagating areas of coastal water, where growth conditions approximate those found in the ocean. Aimed at investigating the growth in controlled conditions for larval/juvenile production, ex situ systems are composed of tanks, raceways or flow-through seawater facilities, depending on where environmental factors such as temperature, salinity, light intensity and nutrients are systematically analyzed and artificially managed.

### 6.1.2 Controlled Metabolite Production

Environmental parameters such as light, temperature, nutrient levels and current velocity strongly affect the amount and composition of sponge secondary metabolites. Aquaculture enables targeted optimization of these parameters to enhance biosynthesis of the desired compounds. As an example, the exposure to certain stress stimuli or elicitation can induce overexpression of biosynthetic pathways and increase metabolite production. Finally, these genetic traits in metabolite production can be enhanced by selective breeding and clonal propagation within the aquaculture system to ensure reproducibility and quality control are maintained. Mariculture also makes it possible to culture rare or slow-growing sponge species which are not possible to find in a sustainable way.[56]

## 6.2. Culture of Sponge

Culture technology of animal cells is a promising approach for the sustainable supply of metabolites, as it allows sponge cells to be proliferated without the need for whole organisms. But sponges have some unique biology that presents several hurdles.[57]

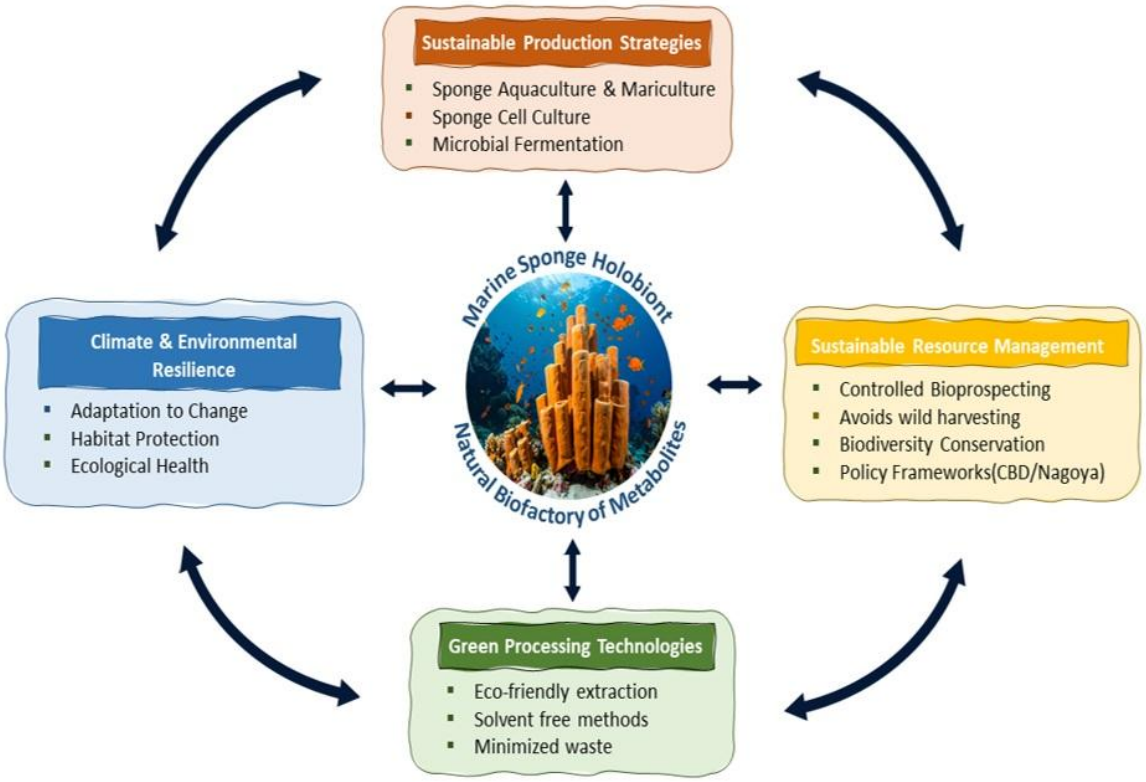


**Figure 7.** *Integrated Sustainability Model for Marine Sponge–Based Drug Discovery. Conceptual framework illustrating a circular sustainability model for marine sponge–derived drug discovery. The central marine sponge holobiont (sponge and associated microbial symbionts) is supported by four integrated pillars: sustainable resource management, sustainable production strategies, green processing technologies, and climate–environmental resilience. These interconnected approaches collectively reduce dependence on wild harvesting, promote scalable biotechnological production, ensure biodiversity conservation, and strengthen the long-term sustainability of the pharmaceutical pipeline.* (*Source: bioart.niaid.nih.gov, www.vecteezy.com)*

### 6.2.1 Totipotency and Cellular Plasticity

A sponge cell is totipotent it can give rise to all other cell types in the organism, and these dissociated cells can reassemble in culture and make a functional sponge. This cellular flexibility explains, at least theoretically, the possibility of generating in vitro continuous cell lines able to produce secondary metabolites. Yet, preservation of cell viability, proliferation and differentiation has been possible only by replicating the complex cellular microenvironments, such as symbioses with bacteria or specific biochemical signaling systems.[19]

#### 6.2.1.1 Challenges in Culture Establishment

It is known that so far it has been impracticable to establish long-term, stable sponge cell lines due to the complex relationship between sponges and their microbes and between sponges and the environment. Primary cultures are generally short-lived and often yield low amounts of metabolites. Monocultures may suffer due to the lack of natural microbial consortia and lower biosynthetic potential. Additionally, the metabolic rate and growth of sponge cells are relatively slow as compared to other cell types grown in cultures, which further hampers scale-up efforts.[58]

#### 6.2.1.2 Applications and Advances

Despite limitations, sponge cell cultures represent useful systems for investigating biosynthetic pathways, conducting bioassays and testing pharmaceutical activities in controlled environments. Recently, these efforts produced co-cultures of sponge cells and symbiotic bacteria to reactivate metabolic activities and improved culture media by specifically adding various nutrients and factors stimulating growth, as well as engineering bioreactors for achieving higher cell density and rate of metabolite production. These technology advances are necessary to address the existing bottlenecks for the large-scale in vitro production of sponge compounds.[59]

### 6.3 Microorganism Fermentation and Synthetic Biology

Since a large number of marine sponge metabolites are generated by their associated microorganisms, fermentation and genetic manipulation of the microorganisms could be an excellent method for a sustainable resource of drugs.

### 6.3.1. Cultivation of Symbionts

The culture and isolation of sponge-associated micro-organisms such as bacteria, fungi or microalgae allow the ex situ production of bioactive metabolites. Advancements in metagenomics and microbial ecology allowed the isolation and cultivation of hitherto uncultivable symbionts by mimicking the in situ microenvironment of sponges and improving culture conditions. Scaled-up controlled fermentative processes may generate large amounts of active compounds and hence reduce the demand for sponge biomass.[12]

### 6.3.2. Heterologous Expression of Biosynthetic Pathways

Synthetic biology approaches include cloning sponge symbiont BGCs into well-characterized, fast-growing microbial hosts such as Escherichia coli, Streptomyces or yeast. This heterologous host expression produces complex natural products in a scalable and controlled manner while avoiding the difficulties associated with cultivating native symbionts. It is possible to manipulate genes to express, stabilize, and produce more.[60]

#### 6.3.2.1 Metabolic Engineering and Pathway Optimization

Genetic and metabolic engineering can also be used to improvise the precursor supply, enzyme expression, and regulation networks in host strains. By utilizing methods including promoter engineering, gene knockouts and pathway refactoring, the efficiency of biosynthesis can be enhanced and new analogues produced with better pharmacological properties. Bioactive chemical manufacturing and discovery are facilitated by the combination of synthetic biology and genome mining.[61]

#### 6.3.2.2 Omics and Computational Integration

System-level data integration of metagenomics, transcriptomics, proteomics and metabolomics offers a holistic view into biosynthetic pathways and regulatory circuits. Computer algorithms and data learning can be used to predict gene cluster function and optimize metabolic flux. These methodologies inform the synthetic biology initiative to rationally engineer industrially robust production strains. Taken together, these biotechnological strategies provide eco-friendly options to the wild collection of sponges as a source for marine natural products to be used in the pharmaceutical industry. A concerted effort towards the discovery of new chemical entities from sponges, in combination with modern approaches for cultivation and cell biology, including studies on microbial symbionts as the likely source of many sponge natural products, is necessary to unveil the therapeutic potential held by these organisms and their associated microbiomes without destroying marine ecosystems.[9]

## 7. Sustainability Issues in Sponge Drug Discovery

Studying marine sponges for the discovery of novel bioactive compounds is confronted with major challenges regarding sustainability. Those issues include ecological, environmental, technical and economic dimensions that may need to be borne in mind by further consideration of a responsible and sustainable utilisation of sponge resources (Figure 7).[13,56]

### 7.1. Overharvesting and Biodiversity Loss

The overharvesting of marine sponges for extraction of bioactive compounds is the most serious threat to marine biodiversity and stability in benthic ecosystems. Many sponge species are sessile, have a slow growth rate and are extremely susceptible to intensive collections. It also results in the possible depletion of populations, changes to community structure and loss of genetic diversity, which have downstream consequences for ecosystem processes which utilize these marine products, such as nutrient cycling and habitat provision for other marine organisms. The ecosystem goods and services sponges supply include filtering high nutrient loads, harboring a wide diversity of marine fauna and resulting in benthic-pelagic coupling. Sponge populations acting as these critical ecosystem engineers are negatively affected by such disruption, capable of sparking a 'domino' or 'cascading' impact throughout marine habitats. Loss of sponge diversity also is a loss of chemical diversity, thereby reducing the chance of discovering new therapeutic agents. To counteract these effects, sustainable harvesting techniques including quotas, seasonal closures, and selective gathering methods are essential. Furthermore, a combination of aquaculture and mariculture methodologies can help relieve pressure on wild stocks by offering alternative sources of biomass. In order to enhance ecosystem-based management

of sponges, conservation programs should include community involvement and regulatory measures.[1,56]

## 7.2. Environmental Change and Habitat Destruction

Numerous benthic environments are home to sponges; however, they are increasingly under stress from human stress and environmental unpredictability. Overarching climate change stressors such as ocean warming, acidification and novel salinity regimes impact sponge physiology, distribution and reproduction success. Increased temperatures may cause stress responses, slow growth rates, and enhanced susceptibility to diseases; acidification may interfere with skeletal deposition and metabolic processes. Sponge populations are further threatened by habitat degradation through pollution, siltation, eutrophication, and destructive practices such as bomb fishing. Sponge tissues are enriched with contaminants, including heavy metals, hydrocarbons and microplastics that might modify the metabolite profiles and the bioactivity. Sedimentation also decreases water clarity and may impede sponge canal systems, thus affecting filter-feeding capabilities and the health of sponges.

These environmental pressures endanger sponge survival and have an impact on the number and quality of bioactive compounds (BACs) that they produce and thus drug discovery. Protection of a sponge's habitat may be provided through monitoring environmental parameters and establishing MPAs. Recovery programmes and pollution mitigation are also key for ecosystem resilience, ensuring the survival of sponge populations.[62]

## 7.3. Technical and Economic Constraints

The translation of sponge-associated bioactives from discovery to marketable drugs is inhibited by several technical and financial challenges. The low natural abundance of most of the target compounds results in high amounts of sponge biomass required, which is difficult to obtain sustainably. Extraction and purification methods can be relatively expensive in terms of resources, increasing the need to optimize these processes for increased yield and decreased cost. Culture of both sponges and the symbionts for mass production is fraught with biological limitations sponge growth rates are slow, they have complex symbiotic dependencies and they are inherently difficult to simulate in situ environmental conditions outside the sponge. To date, most of the sponge cell culture systems are at their early stages of development, and only low metabolite productivity has been demonstrated. Economic hurdles such as expensive R&D (research and development) costs, long preclinical and clinical testing timeframes, and tough regulation are all challenges to be addressed. Management of IP and market competition also add to the complexity of commercialization routes. The perception of sponge-based drug development as a high-investment, high-risk, low-return undertaking could discourage investors. To tackle these barriers, multidisciplinary efforts are needed to integrate marine biotechnology, synthetic biology, and process engineering for the construction of sustainable production systems. The cytotoxicity and anti-inflammation of such terpenoids may be exerted through the induction of apoptosis in tumour cells. Developments in heterologous expression of biosynthetic gene clusters and fermentation technologies can improve feasibility. Mutually beneficial collaborations between academia, industry and regulatory agencies are required to address technical challenges as well as economic issues, which can help good integration of marine sponge natural products into pharmaceutical pipelines.[1,56]

## 7.4. Approaches toward Sustainable Drug Discovery from Marine Sponges

Marine sponges are a prolific source of the structurally unique bioactive compounds towards promising pharmaceutical applications. Nonetheless, the sustainable utilisation of these resources is mandatory to maintain marine biodiversity and achieve the long-lasting exploitation of sponge-derived natural products. Sustainability challenges must be addressed through rulers that integrate ecological, biotechnological, chemical and agro-policy approaches. This review highlights some of the major solution-focused approaches and emphasizes sustainable bioprospecting, aquaculture-based production, microbial and genome-guided metabolite discovery, green chemistry principles and conformance to international policy guidelines.[13]

## 7.5. Sustainable Bioprospecting

Sustainable bioprospecting sets the scene for environmentally responsible sponge exploration, with minimal disruption of the ecosystem and a high probability of new bioactive discovery. This method includes selective sampling strategies of small tissue biopsies or older organisms in order to 'save' the remaining population. Ecological studies such as population surveys and reproductive cycle investigations are used to guide the timing and intensity of collection so that it does not interfere with key life-history stages. Limiting bioprospecting in ecologically strategic or protected zones, like no-take areas and marine protected areas (MPAs), also offers protection to sponge habitats. Involving local communities and stakeholders ensures stewardship, compliance with sustainable practices and fair benefit-sharing. Open data and documentation provide a foundation for adaptive management and ecological transparency. Combining ecological insights with ethical management leads to sustainable bioprospecting that should ensure survival of the sponge populations and conservation of a chemical reservoir for drug development.[46,63]

## 7.6. Aquaculture-Based Production

Scale-up from wild sponge collection has been successfully achieved by cultivating sponges in aquaculture/mariculture environments in a sustainable, ecologically friendly manner, further ensuring reliable control regarding biomass availability for pharmaceutical production. In situ farming: The larvae or sponge fragments are attached to artificial substrata that are introduced into open seawater systems, and sponges grow on these while being exposed to natural conditions; however, site selection is crucial for a trade-off between productivity and environmental considerations. Ex situ culture in controlled tank or raceway facilities allows accurate control of environmental conditions (e.g., temperature, salinity, light and nutrient availability) to maximize growth rates and synthesize secondary metabolites. The manipulation of abiotic factors and the use of elicitors or mild stressors can increase the production of bioactive molecules, increasing also yield and reproducibility. Phenotypic features related to metabolite production are additionally increased through selective breeding and clonal propagation in aquaculture systems. Furthermore, sponge culture has the potential to provide beneficial ecosystem services such as water filtration and may be considered environmentally friendly. In a general sense, aquaculture eases pressure on natural populations, is in line with conservation goals, and stabilizes supply chains for sponge-based pharmaceuticals.[13,56]

## 7.7. Microbial and Genome-Guided Metabolite Discovery

The technological developments in genomics, metagenomics and synthetic biology have turned marine sponge drug discovery to the microbial symbionts that are majorly responsible for the production of metabolites.

Metagenomic exploration of sponge-associated microbiomes reveals genetic treasures, including biosynthetic gene clusters (BGCs) encoding enzymes for the production of secondary metabolites, which otherwise remain cryptic and unknown in their biologically stimulating products. Genome-driven bioprospecting associates gene clusters with known and putative chemical structures and bioactivities to enable more efficient targeting of new drug discovery. Existing generation of bioactive metabolites is supported through symbiotic efficient culture based on genomic knowledge and robust growth conditions. Synthetic biology tools port BGCs into genetically amenable hosts such as Escherichia coli, Streptomyces, or yeast for tunable and large-scale biosynthesis. Metabolic engineering is used to optimize the supply of precursors, expression of enzymes and regulation of pathways, increasing yield as well as generating new analogues with better pharmacological profiles. Additionally, these approaches can be combined with computational modelling and machine learning to improve the characterisation of pathways and production strategies. This genome-based approach reduces reliance on sponge biomass, reduces environmental stress and increases the speed of natural product discovery and cultivation in these marine-derived natural products.[42,64]

## 7.8. Green Chemistry and Life-Cycle Assessment

Green processes Sustainable drug discovery will require that the extraction, processing and manufacture of starting materials need to be under environmentally friendly conditions in line with green chemical principles and life cycle assessment (LCA) approaches. Additionally, replacement of toxic and poisonous solvents with less harmful, biodegradable or innocuous alternatives (e.g., ethanol or $scCO_2$) along with reducing solvent usage limits the environmental impact as well as health hazards. Microwave-assisted, ultrasound-assisted and enzyme-assisted extractions are energy-saving technologies that reduce the processing time and energy consumption. In an effort to reduce carbon footprints, process development introduces the principles of waste minimization, solvent recycling and product yield/purity enhancements. Use of biomass from either aquaculture or microbial fermentation as the source material provides sustainable feedstocks that avoid depleting wild populations. The LCA is a complete assessment of all the environmental impacts on the product life cycle, from the hotspots to directing improvements towards Process intensification, through the use of combined unit operations into continuous flow systems, improves efficiency and scalability with a smaller resource footprint. Application of green chemistry and LCA principles in marine sponge drug discovery will comply with international efforts towards sustainability and CSR.[65,66]

## 7.9. Policy Frameworks

International policy instruments, including the Convention on Biological Diversity (CBD) and the Nagoya Protocol, provide legal and ethical principles relating to the fair and equitable use of marine genetic resources, among which are sponges. The CBD calls for conservation, sustainable use, and equitable sharing of benefits from genetic resources with the PIC and MAT in place between resource providers and users. The protocol details a series of access and benefit-sharing (ABS) procedures to ensure source countries and local communities receive fair benefits from both commercial exploitation and non-commercial utilisation. Legally, certainty and trust are generated through the observance of national ABS legislation, permit issuing and transparent benefit-sharing agreements. These frameworks promote the creation of marine protected areas, guidelines for sustainable harvesting, and capacity-aiding projects to protect marine biodiversity and facilitate scientific research. Government, academia, industry and local community partners should be encouraged to collaborate on research to facilitate sharing of knowledge: the key word here is sustainability. IP protection reconciles innovation incentives and access and benefit sharing, motivating responsible drug development. Compliance with these policy frameworks has the potential to redirect marine sponge-based drug discovery in a manner that is conducted ethically, legally and sustainably and contributes toward global biodiversity protection and equitable development.[67]

# 8. Sponge-Derived Drugs and Lead Compounds as Case Studies

Marine sponges had been one of the most fruitful sources of bioactive compounds, which led to drug candidates, clinical candidates and promising leads from their symbiotic microbiota.[5,68]

## 8.1. Approved Drugs

The clinical relevance of sponge-derived metabolites has previously been highlighted in multiple marine sponge compounds, which have progressed to approved drugs.[69,70]

### 8.1.1. Cytarabine

Originally derived from nucleoside analogues (spongothymidine and spongouridine) found in the Caribbean sponge Cryptotethya crypta, cytarabine (1-β-D-arabinofuranosylcytosine) remains a workhorse chemotherapy for haematologic malignancies, particularly acute myeloid leukaemia and non-Hodgkin's lymphoma. Structurally, it is a pyrimidine nucleoside analogue that differs from the endogenous nucleoside cytidine by the substitution of an arabinose sugar for ribose, creating a unique 2'-hydroxyl group stereochemistry (Figure 8). Its action consists of the inhibition of DNA synthesis in rapidly dividing cancer cells; after intracellular phosphorylation, it competes with deoxycytidine triphosphate for incorporation into DNA, leading to steric hindrance, chain termination, and cellular apoptosis.

### 8.1.2. Eribulin Mesylate

A halichondrin B synthetic analogue derived from the marine sponge Halichondria okadai, eribulin is FDA approved for metastatic breast cancer and liposarcoma. Structurally, eribulin is a complex, fully synthetic macrocyclic ketone. It represents a structurally simplified analogue of the right-hand (macrolactone) pharmacophore of the naturally occurring halichondrin B (Figure 8). It is a highly potent microtubule dynamics inhibitor that binds to a specific site on the vinca domain of tubulin, blocking the growth phase of microtubules without affecting the shortening phase. This unique structural interaction causes the formation of mitotic spindle abortion, irreversible mitotic blockade, and ultimately tumour cell death.

### 8.1.3. Vidarabine

A further nucleoside analogue isolated from Cryptotethya crypta, vidarabine (9-β-D-arabinofuranosyladenine) was amongst the first drugs used in the treatment of viral infections, notably those caused by herpes simplex viruses. Structurally, vidarabine is a purine nucleoside analogue and the arabinosyl epimer of adenosine, containing an arabinose sugar moiety instead of a ribose (Figure 8). Upon intracellular activation to its triphosphate derivative, it acts as a competitive inhibitor of viral DNA polymerase and incorporates into the viral DNA chain, prematurely terminating DNA synthesis. These case studies illustrate how sponge reticulate scaffolds have been rationally deconstructed and manufactured for clinical application, highlighting the role of marine sponges in drug discovery.

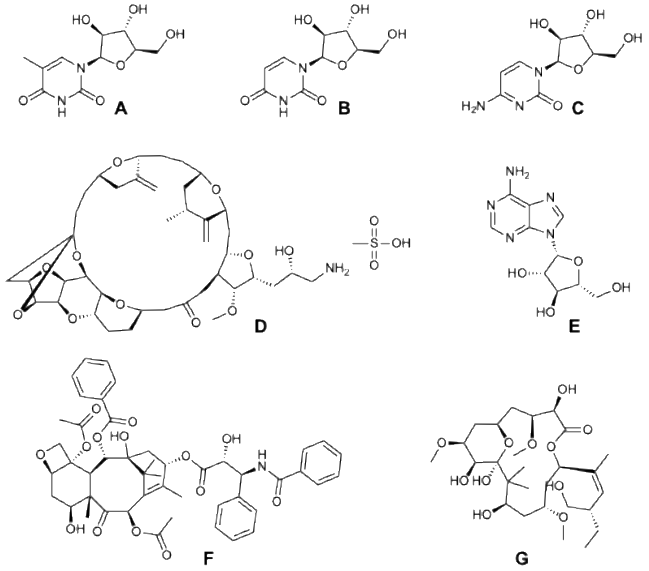


**Figure 8.** Chemical structures of cytarabine and its marine-derived natural precursors. (A) Spongothymidine, an original nucleoside analogue isolated from the Caribbean marine sponge *Cryptotethya crypta*. (B) Spongouridine, a second foundational nucleoside analogue derived from *C. crypta*. (C) Cytarabine β-D-arabinofuranosylcytosine), an approved synthetic antineoplastic drug. The structure highlights the critical substitution of an arabinose sugar, featuring the unique 2'-hydroxyl stereochemistry essential for its mechanism of action in inhibiting DNA synthesis. (D) Eribulin mesylate, an FDA-approved, fully synthetic macrocyclic ketone. Eribulin represents a structurally simplified analogue of the active right-hand (macrolactone) pharmacophore of halichondrin B. (E) Vidarabine (9-β-D-arabinofuranosyladenine), a marine-derived nucleoside analogue. The structure highlights its configuration as the arabinosyl epimer of adenosine, where the substitution of an arabinose sugar provides the structural basis for its inhibition of viral DNA polymerase. (F) Paclitaxel (Taxol), a widely utilized plant-derived taxane. While both compounds promote microtubule stability and polymerization, discodermolide interacts with a distinct pharmacological binding site on the tubulin polymer, offering therapeutic potential against taxane-resistant malignancies. (G) Chemical structure of Peloruside A. Isolated from the marine sponge *Mycale hentscheli*, this complex macrolide functions as a potent microtubule-stabilizing agent and is currently in preclinical development for its anticancer properties. *All chemical structures were prepared with the assistance of PubChem and ChemSketch.*

## 8.2. Clinical Candidates

There are many substances that have been isolated from sponges and are studied in clinical settings with the goal of utilizing their therapeutic potential.

### 8.2.1. Discodermolide

Isolated originally from Discodermia dissoluta, this polyketide demonstrates taxane-like potentiation of microtubule stability but binds to different sites than those used by the taxanes (Figure 8). Several different cancers form harbours, and they have reached trials in humans, where researchers hope to prove that they can combat resistance to current chemotherapies.

### 8.2.2. Halichondrin analogues

Another class of eribulin, other halichondrin B analogues, are in preclinical or early clinical development with the goal of attempting to enhance pharmacokinetics and decrease toxicity.

#### 8.2.2.1. Peloruside A

Peloruside A was derived from Mycale hentscheli, and it is another microtubule-stabilizing compound with potential anticancer activity in preclinical development (Figure 8).

#### 8.2.2.2. Soblidotin (TZT-1027)

Soblidotin, a synthetic hemisuccinate analogue of dolastatin 10 based on the natural product isolated from sea sponges, was tested in patients with solid tumours for its cytotoxic and antiangiogenic activity (Figure 9).

Together, these clinical candidates constitute a continuing pipeline of sponge-derived agents moving towards therapeutic use based on their novel modes of action.

## 8.3. Symbiont-Derived Success Stories

The realization that most of the bioactive metabolites of sponges were/are indeed produced by their microbial symbionts challenges both drug discovery and sustainable production:

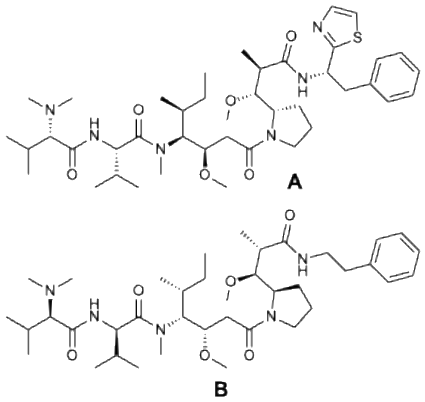


**Figure 9.** Chemical structures illustrating the development of the clinical candidate soblidotin. (A) Dolastatin 10, a highly potent natural marine product. (B) Soblidotin (TZT-1027), a synthetic analogue of dolastatin 10 engineered to retain potent cytotoxic and antiangiogenic activities while improving upon the therapeutic profile of its natural precursor for the treatment of solid tumors. *All chemical structures were prepared with the assistance of PubChem and ChemSketch.*

### 8.3.1. Salinosporamide A (Marizomib)

Originally derived from the marine actinomycete Salinispora tropica, a symbiont of marine sponges, salinosporamide is a highly potent proteasome inhibitor currently in clinical trials for multiple myeloma and glioblastoma. Its microbial source has enabled large-scale fermentation production. Bryostatin Analogues: Bryostatins are closely related natural products of bryozoans, but the polyketide structures produced by bacteria associated with sponges have stimulated synthesis of analogues that are under clinical trial as cancer chemotherapeutics and

immunomodulators. Other microbially produced metabolites: The advent of metagenomics and cultivation-based approaches has revealed a plethora of biosynthetic gene clusters in sponge microbiomes that code for novel compounds with medicinal properties. These findings facilitate heterologous expression and fermentation methods to mediate the supply problems, which are associated with sponge collection. Symbiont-derived compounds provide scalable and sustainable access to intricate bioactive structures, demonstrating the use of microbial technology in marine natural product drug development.[71,40]

## 9. Future Scope

The prospect of marine sponge-based drug discovery will make a significant leap to innovative achievements through the linking of new technologies and multidisciplinary strategies. Engineered oceanic biofactories, including those afforded by omics-centered discovery, AI (artificial intelligence), synthetic biology, or climate-resilient marine biotechnology, may provide means for sustainably accessing the abundant chemical diversity in sponges and their symbiotic microbiomes.

### 9.1. Omics-Driven Discovery

High-throughput omic techniques such as genomics, transcriptomics, proteomics and metabolomics are transforming the discovery of the biosynthetic capacity of marine sponges. These mechanisms allow us to obtain a systematic characterisation of sponge holobionts, including the genetic and metabolic architectures responsible for secondary metabolite production. Metagenomic sequencing reveals natural product BGCs from unculturable microbial symbionts, and transcriptomics and proteomics decipher gene expression profiles and enzymatic pathways working under specific environmental pressures. Metabolomics is complementary to these approaches by defining chemical phenotypes and linking metabolites to their various biosynthetic origins. Multi-omics integrating multimodal datasets enables systems-level understanding of sponge-microbe interactions and biosynthetic feedback control, providing insight for targeted bioprospecting and metabolic pathway engineering. And so omics-driven discovery shortens the time to discover new bioactive compounds and helps define how they should be produced sustainably.[42]

### 9.2. AI and Machine Learning

Artificial intelligence (AI) and machine learning techniques are more frequently applied to omics analysis, biosynthetic capabilities prediction, and natural product discovery pipeline optimization. By using artificial intelligence-based tools, genomic and metagenomic sequences can be mined efficiently for discovery or annotation of BGCs, chemical structures encoded by the producing organisms predicted, and candidates promoted for experimental validation. AI models may improve on compound dereplication, reducing redundancy and aiding the identification of new chemistries. Moreover, AI helps in designing synthetic pathways and enzyme function predictions that permit better pathway reconstitution in host organisms. In drug discovery, machine learning facilitates virtual screening, structure-activity relationship modelling and toxicity prediction and has led to an acceleration of the lead optimization process. By leveraging AI, marine natural product research transitions from intuition- and chance-based discovery mode to data-driven, predictive and scalable development mode with the prospect of overcoming historical impedance points in their discovery and development[72].For example, AI-assisted virtual screening of 2,504 marine sponge–derived compounds from the CMNP database against neurodegenerative targets (AChE, SLC6A4, 5-HT1A, TrkB, and GABA receptors) identified Xestosaprol J as a promising multi-target candidate with high binding energies. Molecular dynamics simulations further confirmed stable interaction with AChE, supporting its potential as a therapeutic lead. Similarly, in-silico screening of 272 marine sponge compounds against ERα of breast cancer identified six top candidates with docking scores comparable to standard drugs such as tamoxifen. Molecular dynamics simulations and MM/PBSA analysis further supported their stable binding and favorable drug-likeness properties.

### 9.3. Synthetic Biology Platforms

By rebuilding and optimizing biosynthesis pathways in genetically tractable microbial hosts, synthetic biology provides considerable capabilities to manipulate marine sponge biofactories. Cloning and heterologous expression of BGCs from sponge symbionts in bacteria or yeast provides an opportunity for large-scale production of complex NPs irrespective of the biomass/life cycle aspect associated with the source, sponges. Recent developments in DNA synthesis, genome editing and pathway refactoring now enable optimization of gene expression, enzyme activity and metabolic flux to increase yield and structural diversity. Modularity enables combinatorial biosynthesis to create new analogues with improved pharmacological activities. Synthetic biology can also allow the assembly of synthetic microbial consortia which reconstruct a sponge holobiont, together performing cooperative metabolism necessary for metabolite production. High-throughput screening and automation allow integration of iteration between design-build-test cycles. Evidently, sustainability, scalability and cost-effective production of marine sponge-derived therapeutics can be achieved through the various platforms proposed herein in response to supply issues and environmental considerations.[73]

### 9.4. Climate-Resilient Marine Biotechnology

Ecological changes such as ocean warming and acidification and pollution challenge marine sponge populations and the production of their metabolites. The development of climate-resilient marine biotechnology is essential for the protection and exploitation of sponge bioresources in an age of changing oceans. This deploys sponge and microbial symbiont strains with either naturally or artificially improved resistance to the abiotic stressful conditions that must be endured in order for stable metabolite biosynthesis to be established. Regulated aquaculture with environmental monitoring and adaptive management can help to alleviate climate impacts and stabilize biomass quality. Recent developments in synthetic biology can lead to the engineering of stable microbial production hosts for use under varying conditions. Moreover, predictive ecological modelling using omics and environmental data can inform conservation and sustainable exploitation scenarios. Climate-resilient strategies can secure the sustainability of marine sponge drug discovery despite global environmental challenges that stretch biotechnological innovation to converge with ecosystem conservation.[74]

## 10. Key Challenges, Emerging Opportunities, and Future Outlook

Marine sponges' chemical diversity, coupled with their complex biology, ecological defenses and sponge, microbe symbioses have made marine sponges an ever-abundant source of incredible new candidates such as alkaloids, terpenoids, polyketides, peptides and macrolides for drug discovery. The chemodiversity available from sponges continues to represent a valuable source of leads for therapeutic targeting of diseases such as anticancer, antimicrobial, antiviral, anti-inflammatory and neuroprotective even though effective clinical translation is still an unusually rare outcome.[1] However, cytarabine, vidarabine and

particularly eribulin show that the most clinically effective sponge-derived drugs are those whose structures can be optimized without hindering drug availability–in particular with regard to supply of sponges at production quantities—healthy ship shape rates with an ever-successful therapeutic driving license for metastatic breast cancer and unresectable or metastatic liposarcoma.[75] Such problems of toxicity, supply constraint, pharmacokinetics and inadequate efficacy have affected near all marine drugs that appeared to be making progress until now. Application of omics, biosynthetic gene clusters mining, artificial intelligence-led prioritization and heterologous expression have improved hit identification and source attribution; additionally, microbiomes associated with sponges are certain to unveil a wealth of new sources of biosynthetic potential in metagenomic investigations yet to be explored. Conversely, silent or incomplete gene clusters, uncertainties regarding whether the metabolites originate from host or symbiont sources, low production yields, and need for stringent preclinical and clinical validation put limitations on such products' real-world application.[76] Perhaps therefore, the most effective pipeline is likely to be one which fuses marine microbiology, synthetic biology, sustainable production methods, pharmacology and clinical development in order to convert the vast organic diversity of sponges into tangible therapeutics.[12]

Marine sponges are a great source of bioactive compounds with a wide range of structures that could be useful in finding new drugs, especially for diseases that are resistant to antibiotics, cancer, and inflammatory diseases. However, to make this potential real, we need long-term plans, since relying on wild harvesting is not good for the environment or for business. So, future progress should focus on environmentally friendly methods like aquaculture, microbial fermentation, synthetic biology, genome-guided discovery, and green chemistry. To make progress in this field, scientists from different fields will need to work together, protect biodiversity, improve farming systems, and combine omics and AI-based tools. The long-term future of sponge-based medicines depends on finding a balance between new medicines, protecting marine ecosystems, and responsible bioprospecting.

## Supporting Information

There is no supporting information for this article.

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