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Review

An Overview on Marine Sponge-Symbiotic Bacteria as Unexhausted Sources for Natural Product Discovery

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Abstract: Microbial symbiotic communities of marine macro-organisms carry functional metabolic profiles different to the ones found terrestrially and within surrounding marine environments. These symbiotic bacteria have increasingly been a focus of microbiologists working in marine environments due to a wide array of reported bioactive compounds of therapeutic importance resulting in various patent registrations. Revelations of symbiont-directed host specific functions and the true nature of host-symbiont interactions, combined with metagenomic advances detecting functional gene clusters, will inevitably open new avenues for identification and discovery of novel bioactive compounds of biotechnological value from marine resources. This review article provides an overview on bioactive marine symbiotic organisms with specific emphasis placed on the sponge-associated ones and invites the international scientific community to contribute towards establishment of in-depth information of the environmental parameters defining selection and acquisition of true symbionts by the host organisms.

Keywords: marine symbiotic bacteria; sponge symbionts; genomic advances; metagenomics; marine biodiscovery; marine biotechnology

1. Introduction

There has been much advancement in the discovery of biologically active natural products that have been used to improve health care and agriculture practices over the last few decades [1,2]. Terrestrial plants and microorganisms have been the largest contributors to natural product discovery, however, today these natural resources have become somewhat exhausted due to culturing and supply difficulties of the producing organism or the repetition of compounds being isolated from known prolific producers such as actinobacteria and fungi which is inefficient and costly [2,3]. Furthermore, due to the emergence and re-emergence of multi-drug resistant (MDR) microorganisms [4], the quest to find novel biologically active natural compounds from a range of other biological resources is gaining importance [5–7].

Antibiotics have generally come from a small set of microbial scaffold molecules [8] that have had their use extended by synthetic modifications. However, with growing resistance appearing among pathogenic microorganisms the discovery of new, as yet unseen, molecular scaffolds is of high importance [4]. The rise in resistance to antibiotics, chemotherapeutic agents, and pesticides are major threats to healthcare and agriculture and without effective antibiotics, routine surgical procedures may not be possible or high risk; also, huge quantities of agricultural products may be lost without effective pesticides [9]. Therefore, there is an important need for new natural products to produce compounds that counteract resistant microorganisms, especially in severe infections and in MDR

cancers, as well as inhibit the growth of cancer cells, prevent or control chronic diseases such as acquired immunodeficiency syndrome (AIDS), asthma, diabetes, and even degenerative diseases such as Alzheimer's [10–13].

The marine environment in particular has attracted much attention as a source of natural product discovery due to its vast biodiversity, the variety of environmental conditions and natural compound production by marine plants, invertebrates, and their microbial communities [2]. Since many algal and invertebrate phyla are found only in the sea, they can possess different biosynthetic pathways from their terrestrial counterparts and may potentially encode for novel metabolites [14,15]. Biologically active metabolites have been isolated from algae, bryozoans, sponges, mollusks, corals, tunicates, ascidians, and microorganisms [12,16,17] and have exhibited a range of properties with biotechnological value [18,19]. Marine invertebrates (Porifera, Bryozoa, Cnidaria, and Chordata) in particular have been the largest contributors to marine natural compound production and these compounds have shown potent activity in a range of in vitro and in vivo assays [10]. The phyla Porifera (sponges) and Cnidaria (corals, jellyfish) have been two main sources of the novel marine natural compounds [17].

Marine natural product discovery was only truly established during the 1960s and rapidly expanded with an increase in the number of bioactive compounds with biotechnological potential [11,17,20–22]. Over 15,000 marine natural products have been isolated from marine invertebrates [23] [24] with over 30% of these having been derived from sponges [25]. A large number of highly active anti-cancer compounds have been isolated from marine invertebrates, including eleutherobin (*Eleutherobia* corals), sarcodictyin (*Stolonigeran* coral) [26], cytarabine (sponge-*Tectitethya crypta*) [17], and bryostatins (bryozoan-*Bugula neritine*) [23,27]. Furthermore, a comparative study carried out based on statistical data from the United States (US) National Cancer Institute has indicated that marine invertebrates are a preferred source of bioactive compounds due to a much higher level of cytotoxicity exhibited by these compounds [10]. It is known that many of these marine invertebrates contain a diverse range of microbial communities living symbiotically or transiently with their host and that some of these invertebrate-derived compounds are in fact produced by the symbiotic bacteria residing within these organisms rather than the invertebrate itself [28]. In contrast to this large number of isolated compounds, only a few have made it to clinical trials, let alone received approval by the US Food and Drug Administration (FDA) or European Agency for the Evaluation of Medicinal Products (EMEA) for use in the marketplace. This low number of compounds on the market might be a reflection of the fact that most compounds are restricted to the preclinical phase due to limited funding and supply of the compound [22,29–32]. This fact is further implicated by the complexity of the marine environment and the impact of biotic and abiotic factors on compound production, both in quality and quantity [33]. This makes the production of these compounds, either via aquarium culture of the invertebrate (e.g., sponge) [31] or growth of the producing microorganism under laboratory conditions, a priority. Unfortunately, such unnatural settings hamper reproducibility, especially when a particular compound of interest is targeted [6,34,35] therefore, mimicking ideal growth and production conditions is of great importance as this may aid in the challenge of supply by isolating and culturing the producing microorganism. Another exciting avenue focuses on microbial genomics targeting biosynthetic gene clusters that are responsible for producing important compounds and choosing a suitable bacterial host into which the specific genes would be cloned and the compounds expressed. Furthermore, genomics may allow for the activation of silent biosynthetic gene pathways that may encode novel unexpressed metabolites, thereby discovering these important metabolites that may not be expressed under classical screening-based methods [36,37].

This review aims to briefly summarize symbiotic relationships within the marine environment with emphasis on sponge-microbial relationships and the production of important natural products by sponges and their microbial community as well as culturing method concepts and genomic analysis that have been developed to induce activation of silent biosynthetic genes and the production of natural products.

2. Symbiosis in Marine Environments

Symbiotic relationships are those that occur between two or more organisms living in close physical association over time, as described by Anton de Bary [38,39]. Symbiotic relationships are vast and diverse within the marine environment and many marine organisms such as invertebrates as well as other marine animals live in symbiosis with their microbial communities [40,41]. In the case of marine invertebrates, due to their constant filter feeding and their exposure to an array of microorganisms in the surrounding sea water, this may contribute to establishing symbiotic relationships between the invertebrates and beneficial microorganisms [42]. These symbiotic relationships provide support and protection to the microbial symbionts and the host organism [43], as well as provide nutritional requirements for both the symbiont and the host [44–47]. For example Sulphur-oxidizing mutualistic bacteria provide invertebrates living in deep-sea hydrothermal vents with fixed carbon and in return obtain oxygen and reduced inorganic compounds from the invertebrate host [48]. Symbiosis can also contribute towards the host defense mechanisms [44,46,49,50], where compounds are produced by symbiotic microorganisms to protect themselves and the host from pathogens and predators [51,52]. Examples of symbiosis within the marine environment include *Alteromonas* mediated protection of the crustacean *Palaemon macrodactylus* shrimp against infection by *Lagenidium callinectes* through the production of the antifungal compound 2,3-indolinedione [53] as well as the production of a defense enzyme, phospholipase A2 (PLA2) (an established antibacterial protein), detected in a bacterium *Streptomyces dendra* sp. nov. MSI051, isolated from the sponge *Dendrilla nigra* with the functional role of protecting the sponge against predators or fouling factors within their environment [17,33].

3. The Sponge Host and Its Symbiotic Microbial Community

Sponges are sessile, ancient metazoans from the phylum Porifera [49,54–57] that date back about 600 million years [58,59] and the fact that sponges have survived in different and extreme environments for as long as they have demonstrates that modern sponges are highly evolved and successful organisms [60]. Approximately 8500 valid sponge species have been described to date [61]. Sponges are filter feeders that encounter a variety of microorganisms that may be retained within the sponge either extracellularly or intracellularly. Sponge-associated microorganisms may either be transient food sources, symbiotic microorganisms, or pathogens [62–67] and sponges can distinguish between food bacteria and bacterial symbionts. For example, the sponge *Aplysina aerophoba* was used in a study testing uptake rates of bacterial isolates and experimental evidence was provided that demonstrated that this sponge could distinguish between food bacteria, which was phagocytized, and bacterial symbionts [68]. Microorganisms either reside on the outer layers of the sponge, otherwise more permanently within the mesohyl of the sponge (please refer to the Queensland Museum website for sponge structure http://www.qm.qld.gov.au/microsites/biodiscovery/03sponges-and-corals/structure-of-sponges.html.

A large portion of the sponge mass, 35–60% [40], may be composed of microorganisms [58,69,70] and these include cyanobacteria, heterotrophic bacteria, fungi as well as unicellular algae [38,71]. Classical symbiosis, which involves only a single or relatively few symbiotic species per host, appears to be challenged when observing sponges that contain a mixture of sponge specialists (present in only one species), sponge associates (not found in the surrounding seawater), and generalists (found in sponges and seawater) [59,72]. However, microorganisms living within the sponge hosts may be sponge specific and this is evidenced by the fact that distantly related sponges from different geographical locations harbor similar microbial groups that have not been detected in the surrounding seawater or other marine habitats [40]. An example is that of the sponge *Halichondria panacea* which is common to the Adriatic Sea, North Sea, and the Baltic Sea. Specimens of the sponge were collected at these different marine locations and found to have the same genera of bacteria housed within the mesohyl of the sponge specimens dominated by the genus *Rhodobacter*. These findings suggest a symbiotic relationship between these bacteria and the sponge host [33,73]. Another is that of

the sponge *Scleritoderma cyanea* collected at a depth of 242 m off the coast of Curacao and another *Scleritoderma* sp. collected from a depth of 255 m off Bonaire that housed microbial communities like uncultivatable microorganisms collected from the shallow water sponges *Theonella swinhoei* and *A. aerophoba* [40,74]. Many of these sponge symbiotic bacteria are believed to be obtained through both vertical transmission from mother sponge to their offspring [75,76] as well as horizontal transmission from the surrounding seawater [77–82].

Sponge nutrition, health, and chemical defenses have been found to profoundly rely on these symbiotic microorganisms [65], nitrogen fixation by symbionts benefits sponges in nutrient-limited reef environments [83] while symbionts benefit from the nutrients (e.g., oxygen and inorganic compounds) and protection provided by the sponge host [64]. Other sponge isolates were also found to be phylogenetically related to anaerobic/microaerophilic microorganisms, suggesting that anaerobic conditions are produced within the sponge, perhaps due to localized active respiration and minimal water circulation [63]. Determining the nature of symbiotic relationships and exact functional roles of the sponge-associated symbionts is difficult [64] especially as most symbionts are challenging to culture independently from their hosts [62].

4. Diversity of Sponge Symbiotic Microorganisms

Twenty-eight bacterial phyla have been recorded as associated with sponges, this is based on both cultivation-independent and -dependent techniques [69]. The dominant bacterial groups that have so far been detected within sponges are of the phyla Proteobacteria (Alpha, Beta, Gamma, and Delta), Nitrospira, Cyanobacteria, Bacteroidetes, Actinobacteria, Chloroflexi, Planctomycetes, Acidobacteria, Gemmatimonadetes, and Verrucomicrobia [40,46,59,63,64,66,67,84–86]. A sponge-specific group of bacteria has also been discovered using molecular tools and has been proposed as a new phylum, 'Poribacteria'. Its members were reported to be uncultivable within the laboratory and could not be amplified using existing 16S rDNA primers [85,87] but only through the use of specific primers [67]. Recently another new phylum, 'Tectobacteria' has also been proposed which contains three phylogenetic clades, two of which have been largely recovered from marine sponges. The largest of these clades contains the candidate genus *Entotheonella* which appears to be widely distributed in marine sponges from geographically distant locations [88].

Although largely variable, some species are consistently present in sponge microbial communities and these include Proteobacteria, Actinobacteria, Acidobacteria, Bacteroidetes, Chloroflexi, Cyanobacteria, and Firmicutes [52,59,67,72,89–91]. Examples of these variable results include detection of high levels of similar microbial communities among two different sponge species, *Myxilla incrustans* and *Haliclona rufescens* [89], as well as between sponge species from different sponge genera *Haliclona* and *Cinachyra* [92]. Webster and Hill [93] revealed the existence of an Alphaproteobacterium (NW001), which was consistently present in samples of *Rhopaloeides odorabile* sampled across a variety of locations and seasons. This bacterium of the genus *Pseudovibrio*, has now been identified in multiple studies as a dominant member of the cultivable sponge microbial community [93–98]. The presence of Alphaproteobacteria from sponges collected in Brazil was also reported [99] and their existence was linked with the quorum sensing systems commonly found in this group of bacteria, which allows cell-to-cell communication and may be involved in the symbiotic interactions between bacteria and their hosts [99,100].

Hentschel et al. (2002) [59] noted the existence of phylogenetically diverse, distinct, microbial communities composed of Gamma-I, Actino-I, Actino-III, Acido-I, and Bacteroid-I and these taxa were specifically associated with numerous geographically and taxonomically distant sponges [59]. Regardless of their host sponge geographic location [55] many microorganisms identified within sponges were found to be closely related [65,87], such an existence might be an indication of development of similar requirements and characteristics by the sponge symbiotic microorganisms to adapt to life in the mesohyl [59].

Simister et al. (2013) [101] studied two different sponge species (*Ancorina alata* and *Tethya stolonifera*) using RNA (16S rRNA)-based amplicon pyrosequencing and bulk stable isotope analysis (d13C and d15N). They identified a total of 4468 unique operational taxonomic units (OTUs). These OTUs were affiliated with 26 bacterial phyla. Bacterial communities of both sponge species were reported to be remarkably stable throughout their monitoring period, driven by a small number of OTUs that dominated their respective communities [101]. In another study by Erwin et al. [102] bacterial symbionts in *Ircinia* spp. exhibited host-species specific structure and remarkable stability under large fluctuations in temperature and irradiance. Their monitoring revealed persistent sponge-specific bacterial taxa with phylogenetic lineages capable of photosynthesis, nitrite oxidation, and sulfate reduction. They noted that seasonal stability of the sponge microbiota again supported the hypothesis of host-specific, stable associations between bacteria and sponge [102]. The sponge family *Irciniidae* have been proposed as an appropriate model for microbiological and biotechnological research as they are agreeable to mariculture (a branch of aquaculture) and laboratory maintenance and can be used as targets for metabolite harvesting [38]. Other sponge species that have been investigated extensively include *Aplysina aerophoba* from the Mediterranean Sea, *Rhopaloedies odorabile* from the Great Barrier Reef and *Ircinia* spp. from the Caribbean, and these sponge species too have become model host sponges. Further long-term studies on key sponge species is likely to advance our understanding of sponge-microorganisms interactions and will allow researchers to obtain important information from a group of relevant hosts that may represent sponge species as a whole [38].

5. Sponge-Derived Bioactive Compounds

The phylum Porifera currently consists of 25 orders, 128 families, and 680 genera, all of which are divided between four classes: *Calcarea*, *Demospongiae*, *Homoscleromorpha*, and *Hexactinellida* [61,103,104]. *Demospongiae* is the largest and most studied of these classes with its most bioactive orders being: *Halichondrida*, *Poecilosclerida*, and *Dictyoceratida* as well as many other orders being described with bioactive metabolite production [46,61]. The lack of physical defense mechanisms in sponges are believed to have contributed towards the evolution of chemical defense mechanisms against predators and pathogens [46,49,51,86]. Sponges have been known to produce a variety of bioactive compounds—such as polyketides, alkaloids, macrolides, porphyrins, sterols, peptides, and terpenes—many of which exhibit anticancer, antitumor, anti-inflammatory, antimicrobial, antifungal or antiviral properties [46,49,54,76,85,99,105–107]. Bergmann et al. [108] isolated the first nucleosides, spongothymidine and spongouridine, from the Caribbean sponge *Tectitethya crypta* which led to the production of vidarabine (Ara-A) (Figure 1) with enhanced antiviral activity and cytarabine (Ara-C) (Figure 1) an anticancer agent [109]. Examples of other important compounds isolated from sponge species are given in Table 1 [110]. The sponge *T. swinhoei* is a typical example of diverse and unique chemistry and associated biosynthetic enzymes and more than 40 complex polyketide and peptide natural compounds have been isolated from a single *T. swinhoei* chemotype [15,88].

Most sponge-derived bioactive compound syntheses are the result of a cooperative efforts between both the sponge host and their microbial symbionts, and their synthesis may thus be triggered by the precursor compounds supplied by either the host or the symbiont [34].

Fan et al. [111] noted that microbial communities from sponges have similar functional profiles that are different from the surrounding environment and core functions investigated within each sponge species revealed the presence of specific functions and interactions between host and symbiont [69,111]. The special digestive strategies of sponges are aided by symbiotic microbial enzymes such as the protease, lipase, chitinase, and agarase activities found in sponge-associated bacteria that are responsible for hydrolyzing complex compounds into nutritionally low-molecular weight compounds [112].

Once isolated from their hosts, many symbiotic microorganisms have been found to produce structurally similar, if not identical, compounds to those originally isolated from their sponge hosts suggesting these microorganisms may be responsible for this compound production rather than

the host itself [77,113–115]. One example is that of an anti-*Bacillus* compound isolated from the extracts of the sponge *Hyatella* sp. that was also found to be produced by an associated *Vibrio* isolate [116]. The isolation of theopalauamide (Figure 1), an antifungal compound, from the sponge *T. swinhoei* was also found to be related to fractions from unicellular bacteria [117] within extracts of *T. swinhoei*. The bacterium was later identified as a δ-Proteobacterium related to myxobacteria called *Entotheonella palauensis* [33,118].

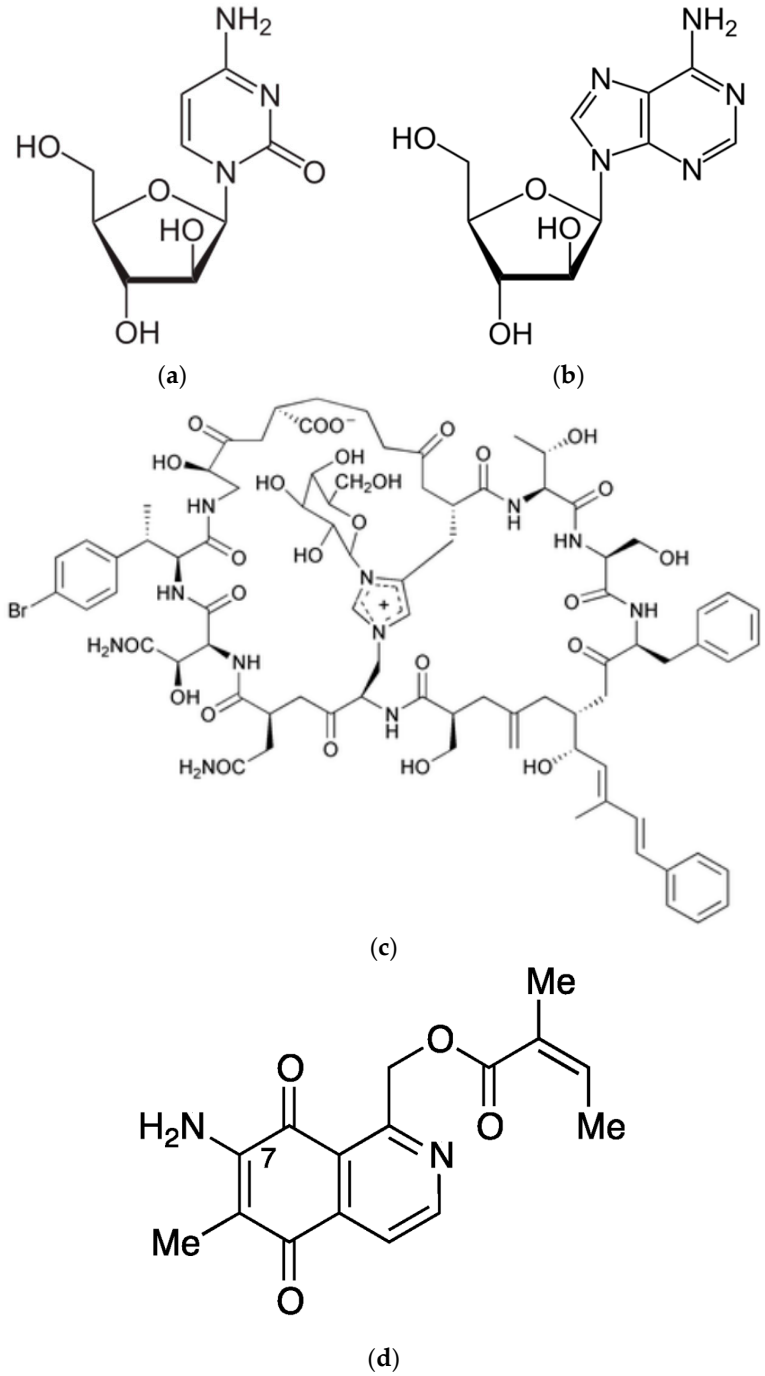


Figure 1. The molecular structure of sponge-derived compounds (**a**) Ara-C (cytarabine) an anticancer agent; (**b**) Ara-A (vidarabine) an antiviral agent [119]; (**c**) theopalauamide an antifungal agent [110]; and (**d**) cibrostatin 3 an antibacterial agent [120].

Table 1. Biologically active compounds with antibacterial, antiviral, antifungal, and antiprotozoal activity from marine sponges [110].

Sponge	Compound	Class	Target	References
	Antibacterial			
Acanthostrongylophora sp.	6-hydroxymanzamine E	Alkaloid	*Mycobacterium tuberculosis*	[121]
Oceanapia sp.	C14 acetylenic acid	Fatty acid	*E. coli*, *P. aeruginosa*, *B. subtillis* and *S. aureus*	[122]
Discodermia sp.	Polydiscamide A	Peptide	*B. subtilis*	[123]
Cribrochalina sp.	Cribrostatin 3	Alkaloid	*N. gonorrheae* (antibiotic-resistant strain)	[120]
Myrmekioderma styx	(*S*)-(+)-curcuphenol	Sesquiterpene	*M. tuberculosis*	[124]
Pachychalina sp.	Cyclostellettamines A-I, K-L	Nitrogenous	*S. aureus* (MRSA strain), *P. aeruginosa* (antibiotic-resistant strain), *M. tuberculosis*	[125,126]
Aka coralliphaga	Corallidictyals A-D	Hydroquinones	*S. aureus*	[127]
Melophlus sarassinorum	Melophlin C	Nitrogen heterocycles	*B. subtilis* and *S. aureus*	[128]
	Antiviral			
Cryptotethya crypta	Ara-A	Nucleoside	HSV-1, HSV-2, VZV	[108]
Theonella sp.	Papuamides A–D	Cyclic depsipeptides	HIV-1	[129]
Dysidea avara	Avarol	Sesquiterpene hydroquinone	HIV-1	[130]
Hamigera tarangaensis	Hamigeran B	Phenolic macrolide	herpes and polio viruses	[131]
Mycale sp.	Mycalamide A-B	Nucleosides	A59 coronavirus, HSV-1	[132]
	Antifungal			
Acanthostrongylophora sp.	Manzamine A	Alkaloid	*C. neoformans*	[133]
Discodermia sp.	Discobahamin A-B	Peptides	*C. albicans*	[134]
Leucetta cf. *chagosensis*	Naamine D	Alkaloid	*C. neoformans*	[135]
Discodermia sp.	Discobahamin A-B	Peptides	*C. albicans*	[134]
Luffariella variabilis	Secomanoalide	Sesterterpenoid	*C. glabrata*, *C. krusei* and *C. albicans*	[136]
	Antiprotozoal			
Pachymatisma johnstonii	Pachymatismin	Glycoprotein	*Leishmania* sp.	[137]
Acanthella sp.	Kalihinol A	Kalihinane diterpenoids	*P. falciparum*	[138]
Cymbastela hooperi	Diisocyanoadociane	Tetracyclic diterpene	*P. falciparum*	[139]
Monanchora unguifera	Mirabilin B	Alkaloid	*L. donovani*	[140]

6. Production of Natural Products by Sponge Symbionts

Bacterial genera associated with sponges that are known to produce biologically active compounds include Alphaproteobacteria, Betaproteobacteria, Gammaproteobacteria, Actinobacteria, Acidobacteria, Fumicates, Cyanobacteria, Chloroflexi, 'Poribacteria', Bacteriodetes and Verrucomicrobia [52,141]. Marine-derived bioactive compounds have been reported to have functional roles within their symbiotic environments as well as have biotechnological uses as antimicrobials, anticancer agents, pigments, vitamins, and enzymes used in industry [141–145]. These compounds, that in nature are produced as a defense against competitors, predators, and pathogens [20,107,115,146] providing the host organism with competitive advantages in the environment by increasing their access to space and nutrients through elimination of the competitors [6,57,147], may exhibit antibacterial, antiviral, antifungal, antimicrobial, or cytotoxic properties that can and have been used in therapeutic agents in the pharmaceutical industry [106,148,149]. Examples of bioactive compounds produced by sponge-associated bacteria are given in Table 2. Although we know that these sponge bacteria can produce novel compounds, the compounds might only be produced under conditions specific to the marine-sponge environment (e.g., certain salt concentration, hydrostatic pressure, competition by other microorganisms and marine nutrients) and not under standard laboratory conditions. In the laboratory, fermentation of marine bacteria within liquid growth media has been the main method used to try and activate compound production [145,150,151] but standard laboratory fermentation conditions (that do not possess these specific sponge-marine conditions) may not be conducive to

triggering the expression of all bacterial biosynthetic pathways involved in the production of the potentially novel compounds [14]. However, the fermentation of cultivable sponge-symbiotic bacteria in the laboratory is a highly promising and stable option for discovering novel compounds from sponges [152] while conserving the natural sponge population [153]. Recently, a study carried out by Nicacio et al. [154] revealed that some of the first natural products (e.g., bromotyrosine-derived alkaloids) isolated from *Verongida* sponges only, have also for the first time been isolated from a marine bacterium, *Pseudovibrio denitrificans* (Ab134) isolated from tissue of the sponge *Arenosclera brasiliensis*. These bromotyrosine-derived alkaloids include fistularin-3,11-hydroxyaerothionin, verongidoic acid, aerothionin, homopurpuroceratic acid B, purealidin L, and aplysinamisine II. This bacterium was chosen for further investigation based on the antibacterial activity displayed in agar plate assays as well as aiding in further examination of these bromotyrosine-derived alkaloids [154].

The analysis of microbial genomes has also gained much interest as entire genomes are now able to be sequenced and with the use of genomics capabilities, specific genes involved in compound production may be targeted. Furthermore, the activation of silent biosynthetic gene clusters that are not expressed under standard laboratory conditions may be aided by the use of different culturing conditions which is also a favorable option [155]. Polybrominated diphenyl ethers (PBDEs), that are spread throughout the marine environment and resemble brominated flame retardants, have mainly been isolated from marine sponges of the order *Dysideidae*. However, the production source of these PDBEs within these sponges was previously unknown. A study carried out by Agarwal et al. [156] has now reported the discovery of biosynthetic gene clusters through the metagenome mining approach of the sponge-microbiome and identified association of these biosynthetic gene clusters within a sponge-associated cyanobacterial endosymbiont. Thus, investigating bioactive marine sponges through metagenomics may reveal the biosynthetic gene clusters which can then be incorporated into microorganisms that may be easily be grown within the laboratory [156].

The candidate phylum 'Tectobacteria', to which the uncultivated '*Candidatus* Entotheonella' members belong, are associated with the sponge *Theonella swinhoei* which is a known source of many unique biologically active natural products. This bacterial group is only distantly related to cultivated organisms and '*Ca.* Entotheonella' phylotypes contain many additional genes for currently unknown metabolites. Following the identification of a biosynthetic pathway (*poy* pathway) from the whole-sponge total DNA library of *T. swinhoei* that produces polytheonamide studies were carried out to identify the bacterial producer responsible for its production. Polymerase chain reaction (PCR) based analysis of single bacterial and host particles in wells in a microtiter plate based on polytheonamide and universal 16S ribosomal RNA gene sequences suggested that this *poy* cluster is part of a bacterium belonging to the candidate genus 'Entotheonella'. The sequence data obtained showed the presence of two 'Entotheonella' phylotypes with large, ca. nine megabase genomes proposed to be '*Candidatus* Entotheonella factor' and '*Candidatus* Entotheonella gemina'. Apart from this *poy* cluster, the 'E. factor' possesses gene clusters for almost all biologically active polyketide and peptide natural products previously isolated from *T. swinhoei*. These include onamides [157], cyclotheonamides [158], keramamides [159], and konbamides [160] to name a few [15,88]. Lackner et al. [161] carried out investigations into this fascinating bacterial group through genomic and chemical methods and have suggested a metabolic model of '*Ca.* Entotheonella' which may aid in targeted laboratory cultivation of these important microorganisms responsible for producing numerous significant biologically active natural products [161]. A metagenomic analysis of the Japanese marine sponge, *Discodermia calyx*, was carried out by Nakashima et al. [162] that identified a hybrid type I polyketide synthase-nonribosomal peptide synthetase gene (*kas.*) (Figure 2). Following a bioinformatics analysis of this gene it is proposed that this gene may be involved in the biosynthesis of a tetrapepetide, kasumigamide (Figure 3) with antialgal properties, that was previously isolated from a cyanobacterium, *Microcystis aeruginosa* NIES-87, found in freshwater. This same tetrapeptide was also found in extracts of the sponge *D. calyx* and the producing bacterium was identified as an 'Entotheonella' species. Furthermore, the analysis of the *kas* gene homologs found the presences of this *kas* gene in two other bacteria from the same phyla.

Due to the production of kasumigamide by distantly related bacteria horizontal gene transfer has been suggested and the potential for wider distribution of this gene across other bacterial groups [162]. Examples of other compound structures produced by sponge-associated bacteria are given in Figure 4.

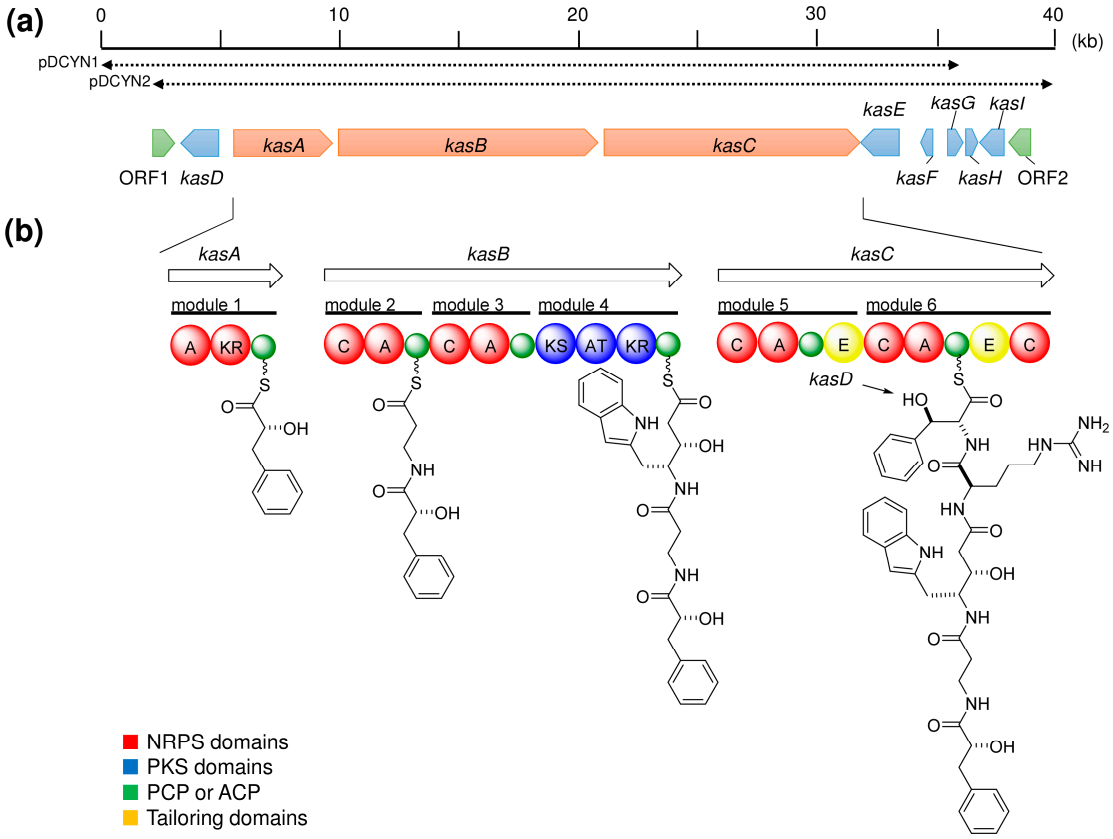


Figure 2. The biosynthetic gene cluster and proposed biosynthetic pathway to kasumigamide investigated by Nakashima, Egami, Kimura, Wakimoto, and Abe [162]. (**a**) ORFs encoded in the putative kasumigamide biosynthetic gene cluster, *kasA-I*. Double-headed arrows show the location of pDCYN1-2. The ORFs related to PKS-NRPS are highlighted in red. Putative transposases are coloured in green. (**b**) The domain organization and proposed biosynthetic pathway to kasumigamide [162].

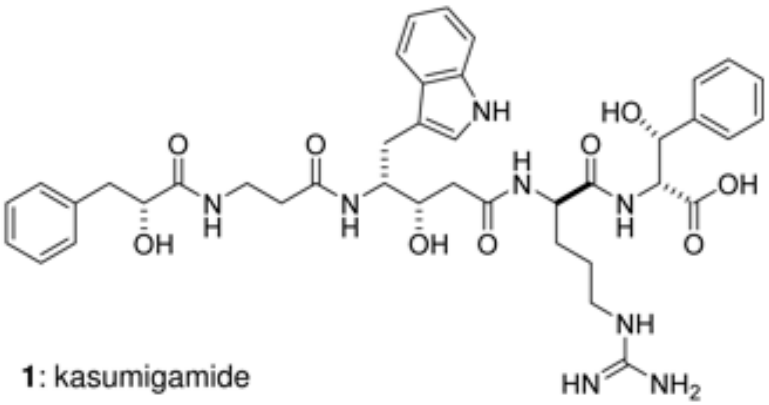


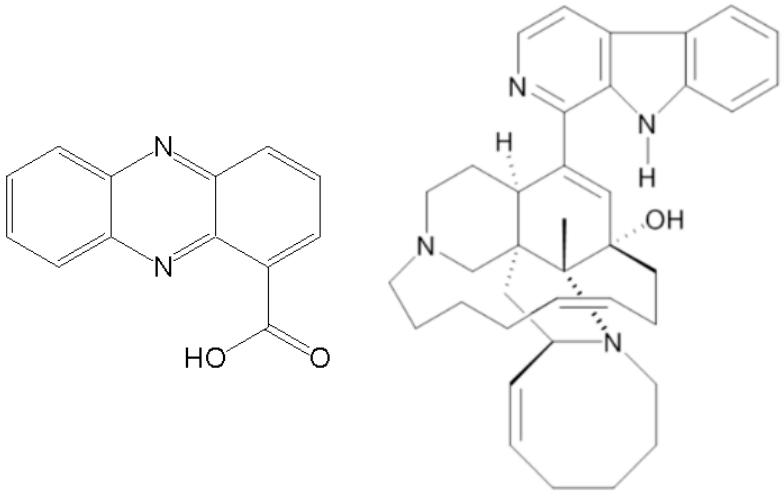
Figure 3. The molecular structure of kasumigamide an antialgal tetrapeptide [162].

Table 2. Biologically active compounds with antibacterial, antiviral, antifungal, and antiprotozoal activity from sponge-associated microorganisms [110,163].

Sponge	Location	Microorganism	Phylum	Compound	Target	References
			Antibacterial			
Halichondria japonica	Iriomote island, Japan	*Bacillus cereus* QNO3323	Firmicutes	Thiopeptide YM-266183	*Staphylococcus aureus*	[164,165]
Spheciospongia vagabunda	Red Sea	*Micrococcus* sp. EG45	Actinobacteria	Microluside A	*S. aureus* NCTC 8325	[166]
Isodictya setifera	Ross island, Antartica (30–40 m)	*Pseudomonas aeruginosa*	Proteobacteria	Phenazine-1-carboxylic acid	*S. aureus*	[167]
Pseudoceratina clavata	Heron Island, Great Barrier Reef (14 m)	*Salinispora* sp. M102, M403, M412, M413, M414, SW10, SW15 and SW17	Actinobacteria	Unidentified	*S. aureus*	[168]
Haliclona sp.	Cagarras Archipelago, Brazil (4–20 m)	*Pseudomonas fluorescens* H40, H41 and *Pseudomonas aeruginosa* H51	Proteobacteria	Diketopipe-razine	*S. aureus*	[169]
Aplysina aerophoba	Banyuls-sur-Mer, France (5–15 m)	*Bacillus subtilis* A190	Firmicutes	Surfactin	*S. aureus*, *Staphylococcus epidermidis* *Bacillus megaterium*, *Clavibacter michiganensis*, *Proteus vulgaris* and *Escherichia coli*	[170]
Haliclona sp.	Cagarras Archipelago, Brazil (4–20 m)	*Pseudomonas fluorescens* H40, H41 and *Pseudomonas aeruginosa* H51	Proteobacteria	Diketopiperazine cyclo-(L-Leu-L-Pro)	*P. aeruginosa*	[169]
Isodictya setifera	Ross island, Antarctica (30–40 m)	*Pseudomonas aeruginosa*	Proteobacteria	Phenazine-1-carboxylic acid and phenazine-1-carboxamide	*Micrococcus luteus*, *S. aureus*, *Bacillus cereus*	[167]
Hyatella sp.	Unknown	*Vibrio* sp.	Proteobacteria	Polyketide-peptide compound	*Bacillus* sp.	[116]
Haliclonaocculata	Gulf of Mannar, India	*Bacillus licheniformis* T6-1	Firmicutes	Fluorophore compound	*Salmonella typhi*	[171]
			Antiviral			
Homophymia sp.	Touho, New Caledonia	*Pseudomonas* sp. 1531-E7	Proteobacteria	2-undecyl-4-quinolone	HIV-1	[172]
Ircinia fasciculata	Bight of Fetovaia, Italy (17.5 m)	*Penicillium chrysogenum*	Ascomycota	Sorbicillactone A	HIV-1	[173]
Callyspongia sp.	Sanya, China	*Epicoccum* sp. JJY40	Ascomycota	Pyronepolyene C-glucoside iso-D8646-2-6	H1N1	[174]
Xestospongia testudinaria	Paracel Islands	*Stachybotrys chartarum* MXH-X73	Ascomycota	Stachybotrin D	NNRTI resistant HIV-1RT-L100I, K103N	[175]
Unidentified	Paracel Islands	*Aspergillus sydowii* ZSDS1-F6	Ascomycota	(*Z*)-5-(Hydroxymethyl)-2-(60)-methylhept-20-en-20-yl)-phenol	H3N2	[176]
			Antifungal			
Aplysina fistularis	Sharm El-Sheikh, Egypt	*Streptomyces* sp. Hedaya48	Actinobacteria	Saadamycin	*Candida albicans*, *Trichophyton rubrum*, *Microsporum gypseum*, *Epidermophyton floccosum*, *Fusarium oxysporum*, *Cryptococcus humicolus*, *Aspergillus fumigatus*, *Trichophyton mentagrophyte*, *Epidermophyton floccosum*	[177]

Table 2. *Cont.*

Sponge	Location	Microorganism	Phylum	Compound	Target	References
Aplysina fistularis	Sharm El-Sheikh, Egypt	*Streptomyces* sp. Hedaya48	Actinobacteria	5,7-Dimethoxy-4-pmethoxylphenylcoumarin	*T. rubrum*, *T. mentagrophyte*, *C. albicans*, *M. gypseum*, *E. floccosum*, *F. oxysporum*, *C. humicolus*	[177]
Halichondria japonica	Iriomote Island, Japan	*Phoma* sp. Q60596	Ascomycota	YM-202204	*C. albicans*, *Cryptococcus neoformans*, *Saccharomyces cerevisiae*	[178]
Halichondria sp.	West Coast of India (10 m)	*Bacillus* sp. SAB1	Firmicutes	4,41-Oxybis (3-phenylpropionic acid)	*C. albicans*, *Aspergillus niger*, *Rhodotorula* sp., *Vibrio cholerae*	[179]
Halichondria sp.	West Coast of India (10 m)	*Bacillus* sp. SAB1	Firmicutes	3-Phenylpropionic acid	*A. niger*, *Rhodotorula* sp., *C. albicans*	[179]
Myxilla incrustans	The Caribbean Island of Dominica	*Microsphaeropsis* sp.	Ascomycota	Microsphaeropsisin	*Eurotium repens*, *Ustilago violacea*	[180]
Ectyoplasia ferox	The Caribbean Island of Dominica	*Coniothyrium* sp.	Ascomycota	(3R)-6-Methoxymellein	*E. repens*, *U. violacea*	[180]
Ectyoplasia ferox	The Caribbean Island of Dominica	*Coniothyrium* sp.	Ascomycota	Phenylethanol	*U. violacea*, *E. repens*	[180]
			Antiprotozoal			
Acanthostrongylophora ingens	Manado, Indonesia	*Micromonospora* sp. M42	Actinobacteria	Manzamine A	*Plasmodium falciparum*, *Plasmodium berghei*	[122,181–184]
Homophymia sp.	Touho, New Caledonia	*Pseudomonas* sp. 1531-E7	Proteobacteria	2-Undecyl-4-quinolone	*P. falciparum*	[172]
Aplysina aerophoba	Rovinj, Croatia (3–20 m)	*Micromonospora* sp. RV115	Actinobacteria	Diazepinomicin	*Trypanosoma brucei*	[185]
Spheciospongia vagabunda	Red Sea	*Actinokinespora* sp. EG49	Actinobacteria	Actinosporin A	*T. brucei*	[186]
Aplysina polypoides	Rovinj, Croatia (3–20 m)	*Streptomyces* sp. 34	Actinobacteria	Valinomycin	*T. brucei*, *Leishmania major*	[187]



(**a**) (**b**)

Figure 4. The molecular structures of compounds produced by sponge-associated bacteria (**a**) phenazine-1-carboxylic acid with antibacterial activity [168] and (**b**) manzamine A with antiprotozoal activity [122,164].

7. Detection and Isolation of Sponge-Symbiotic Bacteria

There are a large number of uncultivable microorganisms within the marine environment [49], with estimates of the detectable microbial diversity by culture-dependent methods being slightly varied depending on the substrate or species examined [49,188]. The cultivable community were found to represent less than 1% to as high as 5% of the total microbial community [62,65,93,189]. Regardless of the exact percentage, molecular investigations revealed that the cultivable community represents only a fraction of the total microbial community [79,113]. Although culture-dependent methods have many limitations they provide key information on their uncultivable relatives [190,191]. Wilson et al. [192] indicated that the ability of current culture-dependent methods to identify new bacteria has been underestimated since only 47% of the isolates they cultured from surface-attached marine bacteria including sponge species in Sydney Harbor were able to be classified to a known genus [192].

Culture-independent methods such as molecular and metagenomic approaches on the other hand, have increased our understanding of the uncultivable microbial community composition and the metabolic pathways responsible to produce potentially beneficial compounds [6,49,63,85,113]. The most commonly utilized and well known culture-independent method of describing the total.

Microbial community is sequence analysis of the 16S rRNA gene and this phylogenetic marker that can be used to determine species diversity in a sample [59]. Webster, Wilson, Blackall, and Hill [63] used the comprehensive 16S rRNA-based molecular approach to describe the microbial community composition in *Rhopaloeides odorabile.* Their approach combined with rational design of culturing methods revealed a large diversity of bacteria associated with this sponge, many of which were only distantly related to previously described bacteria [63]. Sipkema et al. [193] used the same approach and cultured 10–14% of the community of a *Haliclona* sponge, a higher cultivability rate than previously recorded for sponge-associated bacteria. They also mimicked the inner structure of the sponge by applying floating polycarbonate filters to low nutrient media. Such an approach once again confirmed the use of alternative cultivation methods to culture previously uncultivated species [193].

While culture-dependent isolation methods based on the nutritional requirements of taxonomically close relatives can provide information on the microorganisms of interest, advances in genomics, metagenomics, proteomics, transciptomics, and expression systems currently enable the discovery and production of novel compounds while completely bypassing the laboratory cultivation process of the organisms of interest [57,113,194].

8. Genomic Advances Changing the Scene of Marine Biodiscovery

Complete genome sequences of actinobacteria and fungi in the early 2000s revealed that these microorganisms have a greater potential to produce novel, specialized metabolites than previously shown from classical bioactivity screening [37]. Recently, full genome sequencing of a sponge-associated *Pseudovibrio* species has enabled further insights into their metabolic capacities, specifically, the genomic potential of *Pseudovibrio* species to attach to host cells, interact with the eukaryotic cell machinery, produce secondary metabolites, and supply the host with co-factors [194]. Crowley et al. [195] indicated that varying physiological growth conditions, gene expression and biological analysis (in addition to the knowledge gained through genome sequencing of members of the genus *Pseudovibrio*) may lead to the identification of genes involved in the production of secondary metabolites, optimum growth parameters and gene expression; eventually leading to the development of novel bioactive compounds [195].

Combined metaproteogenomic approaches (study of all genes/protein samples recovered from environmental sources) by Liu et al. [196] have also recently provided novel information on the activities, physiology, and interactions of sponge-associated microbial communities [196].

9. Metagenomics

Metagenomics is the culture-independent genomic analysis of DNA extracted from organisms in environmental samples, which has been developed to answer fundamental questions related to microbial-host ecology [197,198]. To extract biotechnologically relevant information from metagenomic libraries, two diverse types of analyses have been used. The first approach targets function (libraries are screened for the expression of specific traits), and the second one is based on screening for specific sequences [52,57,194,199–201].

Natural compounds derived from sponges and their bacteria have been mostly complex polyketides with the polyketide synthase genes (PKS) responsible for their biosynthesis [202]. Metagenomic techniques have enabled the discovery of novel gene clusters particularly those responsible for polyketide synthases (PKS), non-ribosomal peptide synthases (NRPS), isoprenoid synthases, and terpenoid synthases [57,113,203–205]. Many studies on PKS and NRPS gene clusters from the sponge metagenome have also found that they are most closely related to other sponge-derived sequences suggesting the possibility of sponge-specific clusters [204–206]. Further detection of ketosynthase (KS) gene domains in sponge bacterial symbionts indicated their involvement in the biosynthesis of secondary metabolites [202].

The production of calyculins with cytotoxic properties and calyculin-related compounds have been isolated from *Discodermia calyx* and many different Pacific Ocean sponge genera which suggests a symbiotic producer. Furthermore, the production of calyculins has not been reported from any other organisms. Upon further investigation, a biosynthetic gene cluster (*trans*-acyl transferase (AT) type I PKS) of calyculin A (Figure 5) was identified by sponge metagenome mining approach which revealed the microbial symbiont possessing this specific gene cluster belong to the candidate genus 'Entotheonella' [115]. Heterotrophic bacteria associated with two samples of the marine sponge, *Erylus discophorus*, were screened for their capacity to produce bioactive compounds against a panel of human pathogens [142]. Their search of PKS-I and NRPS genes in 59 of the bioactive bacteria cultured from the sponge samples suggested the presence of PKS-I genes in 12 strains, NRPS genes in 3 strains, and both sets of genes in 3 strains. Moreover, while PKS and NRPS biosynthetic routes are known to be conserved in marine systems, in some cases additional, novel catalytic enzymes responsible for the unique functional groups found solely in marine natural products have also been reported [206]. Differential gene expression in relation to its symbiotic state was also identified in the Mediterranean sponge, *Petrosia ficiformis* [207].

Using a metatranscriptomics approach (correlates the transcriptomes of a group of interacting microorganisms), Radax et al. [208] investigated the microbial community of the marine sponge *Geodia barrette* and identified a wide range of putative functional gene transcripts from over 10 different

phyla among the bacterial mRNA-tags. They reported that the most abundant mRNAs were those encoding key metabolic enzymes of nitrification from ammonia-oxidizing *Archaea* as well as candidate genes involved in related processes [208].

The use of metagenomics, although highly useful and a very promising avenue to continue natural product discovery, has some limitations such as with heterologous gene expression, the use of in silico analysis has been estimated to identify only 40% of metabolic activities with random cloning of environmental DNA into *Escherichia coli* [201]. Heterologous gene expression has been identified as an enormous challenge that limits the confidence of metagenomics approaches to access the full metabolic potential of biosynthetic pathways [209–211]. The biosynthetic PKS and NRPS gene clusters also require specific induction in order to obtain a specific metabolite and without these inducing conditions, metabolites may be unexpressed [212,213], and even if the expression of a particular gene pathway is successful it may not produce the same or all of the expected metabolites [52,202]. Therefore, the use and development of alternative bacterial hosts for gene expression, alternative expression systems and multi-host shuttle vectors are required to overcome the metagenomics limitations [193].

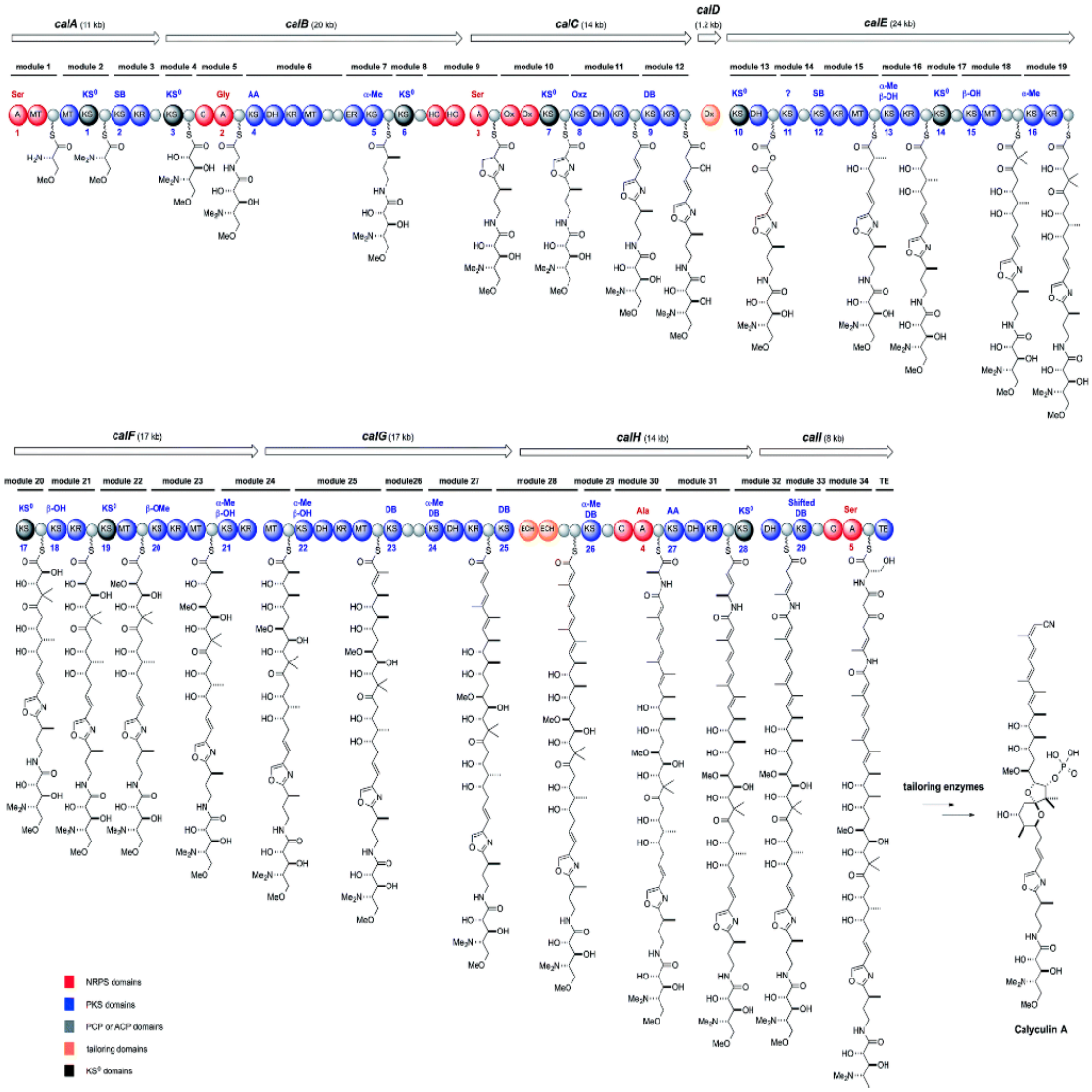


Figure 5. The biosynthetic gene cluster and proposed pathway of calyculin A [214] investigated by Wakimoto, Egami, Nakashima, Wakimoto, Mori, Awakawa, Ito, Kenmoku, Asakawa, Piel, and Abe [115].

10. Cryptic/Silent Biosynthetic Pathways

Continuous discovery of new cryptic or silent gene pathways that are not active under standard laboratory conditions supports the fact that one organism can produce many different compounds [214–218]. The failure to produce certain natural products can be attributed to the poor expression or silence of the biosynthetic gene cluster.

Expression of the cryptic regulatory genes, either pathway-specific regulatory genes or global regulatory genes, can lead to the production of novel compounds [219]. Moreover, gene clusters within bioactive microorganisms may define the production of many compounds as the subunit genes can exist in differing orders. As these clusters are organized in a linear fashion, the compounds produced may vary greatly depending on the order of the subunit genes [57]. There have been a large number of biosynthetic genes clusters reported to be responsible for natural product production, but only a small number of these therapeutic natural products have resulted from functional metagenomics screening and the number of new drugs is greatly under-represented [201]. The development and use of next-generation sequencing (NGS) technologies has increased the rate as well as reduced the cost of generating genomic data [220]. Researchers are now using NGS to identify cryptic biosynthetic pathways responsible to produce a novel metabolite by generating a draft genome of the producing organisms. The draft genome may be used to identify cryptic pathways by analyzing the genome using bioinformatics [221–223]. Combinatorial biosynthesis is a technique that exploits this gene cluster organization within the pathway through genetic manipulation (addition, deletion, and reorganization of genes and amino acids) of these clusters with the aim of creating new pathways responsible to produce novel compounds [57,224,225]. Pathways could also be genetically altered to produce structurally novel analogs with improved pharmacological profiles [226]. One widely used computational tool used to identify these cryptic biosynthetic gene clusters is antiSMASH (antibiotics and secondary metabolite analysis shell) [227] which allows the input of multiple related sequences, direct analysis of protein sequences, and detection of added classes of specialized metabolite biosynthetic gene clusters [228]. AntiSMASH analysis was used with *Vibrio harveyi*, isolated from the sponge *Tectitethya crypta*, which noted six potential secondary metabolites pathways, three were bacteriocins, one encoded the osmolyte ectoine, one potential vibrioferrin pathway, and one potentially encoding for enterobactin [229]. Draft genomes made up for sponge associated actinobacterial isolates (*Micromonospora* sp. RV43, *Rubrobacter* sp. RV113 and *Nocardiopsis* sp. RV163), isolated from the Mediterranean sponge, *Aplysina aerophoba*, were also analysed for the presence of gene clusters encoding secondary metabolites using antiSMASH (as well as NapDos pipelines) and this outlined the chemical wealth of the sponge associated actinobacteria and the efficacy of genome mining for discovering genomic potential of these isolates [230].

Discovery of cryptic pathways may not only be used to activate silent gene clusters and detect novel compounds but may also improve the production of compounds that are already expressed [225]. These new techniques and discoveries in heterologous gene expression could therefore potentially eliminate the supply problem from the marine macro-organisms and can be used for the production of these compounds not only for clinical trials but also for subsequent commercial uses [231]. Due to the rise in the number of whole genomes sequences now available, a large number of cryptic biosynthetic gene clusters can now be found in publically available databases [37].

Chemosynthetic symbioses between chemosynthetic bacteria and marine invertebrates occur in a wide range of habitats ranging from cold seeps, to shallow-water coastal sediments and continental margins [232,233]. Recent molecular methods have revealed the true nature of these symbioses and identified different lineages of chemosynthetic bacteria associated with their hosts. Again, recent genomic and proteomic analyses have revealed that these chemosynthetic symbionts have developed a remarkable range of different metabolic pathways to gain energy from the environment and feed their hosts [233]. Such in-depth understanding of these genomic advances can deliver marine-derived potent therapeutic agents.

11. Altering Growth Conditions and Co-Cultivation of Microorganisms

Changing the growth conditions of some compound producing microorganisms may be used to induce a change in the expression of metabolite biosynthetic gene clusters by either increasing the production of a certain compound or inducing the expression of a completely new compound. 'OSMAC' is the term for 'one strain many compounds', which is the ability of a single strain to produce different compounds when grown under differing conditions [156]. The culturing of a marine fungus, *Spicaria elegans*, which was grown under 10 different culture conditions was shown to produce a range of new compounds including the novel spicochalasin A, five new aspochalasins M-Q, and two known aspochalasins [234]. This method was also used to isolate two new *O*-glycosylated angucyclines, actinosporins A and B from the broth culture of *Actinokineospora* sp. strain EG49 (from a Red Sea sponge *Spheciospongia vagabunda*) [186]. Other microorganisms subjected to the OSMAC method have also expressed a variety of compounds previously unseen when culturing these microorganisms in only one set of culture conditions [235].

Co-cultivation may also induce the expression of cryptic biosynthetic gene clusters as microorganisms occupying the same environment may be able to carry out crosstalk, for example, *Aspergillus fumigatus* was co-cultivated with *Streptomyces rapamycinicus* which induced the expression of a usually silent polyketide biosynthetic gene cluster which led to the discovery of an uncommon class of polyphenols named fumicyclines [236]. Two sponge-derived actinomycetes, *Actinokineospora* sp. EG49 and *Nocardiopsis* sp. RV163, were also cultured together which induced the biosynthesis of three compounds that were not detected when each actinomycete was cultivated alone [5].

Quorum sensing which is small-compound-signaling between microorganisms, mainly bacteria may be responsible for the production of unseen compounds when co-culturing. Bacterial communication is carried out by the acyl homoserine lactone (AHL) regulatory system and is used to mediate the colonizing traits of the bacterial community such as, virulence, congregation, and biofilm formation [237–239] which are essential for establishment of symbiotic or pathogenic relationships with other microorganisms and their host organism [240]. This may be of interest to researchers because these small-compound-signaling molecules may influence production of novel secondary metabolites. Trialing the addition of quorum sensing molecules (for bacterial communication) within media could be of benefit; they may act as either a trigger for activation of biosynthetic pathways and secondary metabolite production, or promote microbial growth.

12. Status of Marine Sponge-Microbial Natural Product Discovery

Sustainable harvesting of compounds and the conservation of producer organisms, such as sponges, is an issue that should be vigorously evaluated and carefully considered as survival of many marine sponge species are under threat due to climate change and anthropogenic activities [241,242]. The main anthropogenic activities include overfishing and exploitation, biological invasions, and pollution (mostly oil but also sewage, heavy metals, radioactive waste, garbage, and chemicals). The change in climate threatens to dramatically effect sea level and ocean currents as well as increase the incidence and prevalence of various diseases [241].

Obstacles associated with the in vitro growth of symbionts as well as the supply of the host may be overcome via aquaculture [30,217,243,244] and chemical synthesis (semi-synthesis, synthesis, and synthesis of simpler analogues) if processes are refined and improved [245]. Symbiont cultivation may also be a viable solution to overcome the supply and sustainability issues associated with wild harvest of marine macro-organisms to obtain useable amounts of the compounds of interest [25,77,246]. This approach can at least provide a more efficient method for determining the regulation and functionality of the metabolic pathways in question [31]. Furthermore, improved understanding of the symbiont occurrence and diversity within a host may lead to successful cultivation of these microorganisms independent of their hosts [33]. Examples include the use of sponge extract agar by Webster and Hill [93] to effectively culture sponge bacteria after molecular examination of the microbial community where standard isolation methods have failed [93]. Exploitation of the AHL-mediated signaling

systems used by bacteria to communicate with one another has also resulted in increased cultivability of bacteria by adding the AHLs into the marine growth media [247].

Selective extraction of certain characteristics may also be achieved through molecular approaches whereby the functional genes of interest can be cloned into cultivable hosts 35,247]. Genomics can now deliver bioactive compounds with therapeutic value from symbiotic bacteria [248].

13. Ecological Impact of the Surrounding Environment on Sponges and Their Microbial Communities

Although the ability of sponges and their microbial communities to produce important bioactive natural products with a range of uses has been reported worldwide, the impact that the geographical and environmental factors at the different collection sites have on the sponge species and their associated microorganisms is still only vaguely highlighted and very little information is given on the features of the collection sites. To date, most studies have focused on how sponge microbial communities respond to different environmental factors established through host-specific microbial responses to nutrients, temperature, and sediments [249]. By accurately collecting biogeographical data related to sponge classification and ecological observations, when collecting the sponge samples from different locations, this may aid in the ability of other researchers to examine sponges from other locations with similar biogeographical features or target known stressors which may increase the range of natural products identified [21]. For example, observing the level of predation surrounding the sponges, owing to the production of defense metabolites or whether the sponges have a surrounding bare zone (uninhabited area around the sponge due to inhibition of growth of other marine organisms by toxic sponge metabolites) may inform other researchers about the stressors within that environment. Numerous studies have also revealed that, within the northern high latitudes, the occurrence of defense compounds appears to be much less that in tropical environments or the Antarctic [250]. Whether sponges are collected within oligotrophic offshore locations or turbid inshore locations may also play a key role in the diversity of the microbial community within the sponge. A study carried out by Luter et al. [250] reported that the microbial community differed considerably with regards to species diversity and richness for the sponge species *Carteriospongia foliascens* when collected at inshore and offshore locations which suggests that this sponge species relies on environmental factors for their specialist microbiome. Collection of the sponge samples of *C. foliascens* from different geographical locations (e.g., Torres Strait, Red Sea, and Great Barrier Reef) also revealed that the abundance of certain bacterial classes also differs between location, for example sponge samples from Torres Strait have a higher abundance of *Cyanobacteria* compared to samples from Fantome and Orpheus Islands, which have a higher abundance of *Bacteriodetes*, therefore the ratio of *Cyanobacteria* to *Bacteriodetes* increases for these sponge samples in oligotrophic offshore environments [250]. Targeting environments known to produce novel natural products due to metabolic specialization such as, extreme environments, may also result in the identification of novel natural products. Furthermore, parameters such as ocean acidification and rises in sea surface temperature can affect sponges in a number of ways including changes to their cellular and physiological processes, disruption to acid base physiology, metabolic suppression, and loss of function by symbiotic microbial communities [251] which can have considerable impact on the type of compounds produced. Whether pollutants are present within the surrounding ocean is also reported to impact sponges, from a study carried out by Webster et al. [252] that demonstrated the extreme reduction in the diversity and abundance of bacteria associated with the Great Barrier Reef sponge *Rhopaloeides odorabile* after exposure to copper. Therefore, changes in sponge microbial communities may also be a good bio-indicator of pollution within their environment [252]. Due to the production of a range of compounds by a macro/microorganism being significantly affected with different environmental parameters, the same taxa or strain may be considered to be from different locations and may have the ability to produce a few different compounds depending on the environmental parameters [21]. By recording all these observations accurately, relational databases may be produced and natural product discovery may be optimized

with accurate geo-spatial referencing and effective visualization tools. A number of visualization tools (e.g., Worldwind (NASA Ames Research Center, Moffett Field, CA, USA), Google Earth™ (Google Incorporated, Santa Clara, CA, USA)) and web databases (e.g., Pubchem) now exist which can be channeled for natural product discovery research [21].

14. Conclusions and Outlook

The diversity in naturally produced compounds, especially those from marine organisms, has a variety of potential biotechnological, pharmaceutical, commercial, industrial, and environmental applications [253–256]. To mass produce and utilize bioactive compounds the biology, physiology, and metabolism of the producer marine macro- and microorganisms must be fully understood to adapt target directed and objective cultivation methods. Sound understanding of the ecology [33,91] and functional diversity of marine symbionts [257], in particular those associated with sponges [83], and correlating such understanding with the rationale of symbiont-aided host bioactive metabolite production in marine environments will improve prospects of generating drug leads from sponge sources [25,33,53,54,85,258,259]. However, one of the important aspects of the sponge-symbiont related biodiscovery has been the lack of in-depth information on the environmental conditions and stress factors surrounding the host which define this specific interaction. The composition of host associated microflora is naturally influenced by these surrounding factors. Most of the published research studies fail to provide information on the current directions, overflows, presence, or absence of pollutants as well as the characteristics of the sediments or reefs at the sponge sampling sites. Response of host sponges to such surrounding factors and how they might interfere with the selective acquisition of the microflora during the filter feeding activity of the host remains unclear. As a result, determining the existence of the true symbiotic associations between the host and the microorganisms is difficult. This is increasingly the case when non-marine origin actinomycete taxa are reported to be present in the sponges. Environmental factors which might be the reason of the possible transitory interaction are not defined, such as the presence of organic matter and terrestrial run-offs. Authors with this introductory review paper would like to invite the international scientific community to share such information to be able to improve understanding on the existence of true symbiotic relationships between the host and symbiotic bacteria. Such information will in turn aid in the establishment of the rationale on the occurrence of symbionts in the sponge whether they occur coincidentally in the surrounding waters because of other man-made or natural events or due to true ecological existence in the location under study.

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