Bioprospecting Sponge-Associated Microbes for Antimicrobial Compounds

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Abstract: Sponges are the most prolific marine organisms with respect to their arsenal of bioactive compounds including antimicrobials. However, the majority of these substances are probably not produced by the sponge itself, but rather by bacteria or fungi that are associated with their host. This review for the first time provides a comprehensive overview of antimicrobial compounds that are known to be produced by sponge-associated microbes. We discuss the current state-of-the-art by grouping the bioactive compounds produced by sponge-associated microorganisms in four categories: antiviral, antibacterial, antifungal and antiprotozoal compounds. Based on in vitro activity tests, identified targets of potent antimicrobial substances derived from sponge-associated microbes include: human immunodeficiency virus 1 (HIV-1) (2-undecyl-4-quinolone, sorbicillactone A and chartarutine B); influenza A (H1N1) virus (truncatol M); nosocomial Gram positive bacteria (thiopeptide YM-266183, YM-266184, mayamycin and kocurin); Escherichia coli (sydonic acid), Chlamydia trachomatis (naphthacene glycoside SF2446A2); Plasmodium spp. (manzamine A and quinolone 1); Leishmania donovani (manzamine A and valinomycin); Trypanosoma brucei (valinomycin and staurosporine); Candida albicans and dermatophytic fungi (saadamycin, 5,7-dimethoxy-4-p-methoxylphenylcoumarin and YM-202204). Thirty-five bacterial and 12 fungal genera associated with sponges that produce antimicrobials were identified, with Streptomyces, Pseudovibrio, Bacillus, Aspergillus and Penicillium as the prominent producers of antimicrobial compounds. Furthermore culture-independent approaches to more comprehensively exploit the genetic richness of antimicrobial compound-producing pathways from sponge-associated bacteria are addressed.

Keywords: antimicrobial compounds; sponges; sponge-associated microbes

1. Introduction

Antimicrobial resistance (AMR) is an emerging global threat, decreasing the possibilities for prevention and treatment of infectious diseases caused by viruses, bacteria, parasites and fungi [1,2]. A global surveillance report by the World Health Organization (WHO) [2] indicated an increase of morbidity and mortality of infectious diseases due to AMR, which could lead to a world-wide economic loss of up to 100 trillion US dollars (USD) in 2050 as the result of a 2%-3% reduction in the gross domestic product (GDP) [1]. A conservative estimation is that AMR now annually attributes to 700,000 deaths globally, with a potential leap to 10 million in 2050 [1]. AMR is a response of microorganisms against antimicrobial compounds, which can arise via several mechanisms such as chromosomal mutations [1], binding site modifications [2] or horizontal transfer of genes conferring resistance [3]. For several pathogenic bacteria such as Staphylococcus aureus [4],
The emergence of multi drug resistant (MDR) strains has been reported, which make infections with these strains increasingly difficult to treat with currently available antibiotics [3].

In the context of the arms race between humans and infectious agents, the discovery and development of new types of antimicrobial compounds with pronounced bioactivity and clinical significance are urgent [4,5]. The efforts to modify existing drugs are often not effective to overcome the mutation rate of pathogens and do not lead to the introduction of new classes of antimicrobial compounds [6]. The terrestrial environment has been the main focus of microbial-derived drug discovery since the first report on Penicillin in 1929 [7], followed by the booming of new classes of antibiotics in 1960s [8]. Although novel antimicrobials are still being discovered from the soil niche, e.g., turbomycin A and B [9] and teixobactin [10], there are issues with de-replication, which significantly reduces the discovery rate of new compounds from heavily screened environments [11].

In comparison with soils, the marine environment has been largely neglected for discovery of antibiotics until recently, mainly because of accessibility issues, but yet hold a huge biodiversity and potential novelty of antimicrobial compounds [12]. Of many marine organisms, sponges (phylum Porifera) are considered as the most prolific source of therapeutic compounds as these animals harbour a large variety of secondary metabolites, many of which are beneficial for human health purposes [13–17]. The “Supply Issue” is the main obstacle to exploit the biological activity of sponges’ metabolites since a large quantity of biomaterial is required for experimental purposes [13]. Interestingly, in recent years an increasing number of studies highlighted that many active substances from sponges are of bacterial origin due to similarity to chemical structures found in terrestrial microorganisms [13–15]. Furthermore, several studies have reported a wide diversity of antimicrobial activities from sponge-associated microbes, which make these microbial communities a valuable source for novel antimicrobials [14,16–20].

This review highlights the current knowledge of antimicrobial compounds produced by sponge-associated microbes. Our definition of “antimicrobial” is not limited to antibacterial agents, but also includes compounds active against viruses, fungi and infectious protozoa. For each of the four biological activities, a few substances are highlighted because of their high activity, along with the most complete overview to date of other known compounds with antimicrobial activity from sponge-associated microorganisms. To compare different bioactive compounds and crude extracts, inhibitory concentrations of substances reviewed have been as much as possible expressed in the same unit (µg/mL). Original articles use minimum inhibitory concentrations (MIC), half maximum inhibitory concentrations (IC$_{50}$) and the concentration of a drug that give the half-maximal response (EC$_{50}$). As they are not easily converted, we stucked to the original measures.

Moreover, we analyzed the distribution of bacterial and fungal genera associated with sponges that have been reported to produce antimicrobial compounds to identify the most prolific genera. In addition, the potential for application of metagenomics to complement culture-dependent antimicrobial screening strategies is also discussed.

### 2. Antiviral Compounds

New antiviral compounds are needed due to the increased occurrence of diseases caused by viral infections and because of antiviral escape strategies [21]. Marine organisms, and sponges in particular, have been shown to be a valuable source for antivirals. For example, the discovery of the nucleosides spongothymidine and spongouridine from the sponge *Tethya crypta* was the basis for the compound Ara-A (vidarabine) that is active against the herpes simplex virus [21–24].

Screening of sponge-associated microbes yielded several prospective anti-HIV-1 (human immunodeficiency virus-1) compounds (Table 1 and Figure 1). Bultel-Poncé et al. [25] isolated *Pseudomonas* sp. 1531-E7 from the marine sponge *Homophymia* sp. resulting in the discovery of the antiviral compound 2-undecyl-4-quinolone (1) (Figure 1). The compound had an IC$_{50}$ concentration as low as $10^{-3}$ µg/mL in vitro against HIV-1. Bringmann et al. [26] elucidated the chemical structure
of sorbicillactone A (2) which was isolated from Penicillium chrysogenum, a fungus associated with the sponge Ircinia fasciculata. Sorbicillactone A displayed cytoprotective effects on HIV-1-infected cells of the human cell line H9 at concentrations of 0.1–1 µg/mL. In addition, in vitro testing using H9 cells indicated that sorbicillactone A reduced the appearance of the HIV-1 protein up to 70% at a concentration of 0.3 µg/mL [26]. The sponge-associated fungus Stachybotrys chartarum MXH-X73 produces the compound stachybotrin D (3), which exhibited anti-HIV-1 activity by targeting reverse transcriptase [27]. At EC<sub>50</sub> concentrations from 2.73 µg/mL to 10.51 µg/mL, stachybotrin D was active not only against the wild type HIV-1 but also against several non-nucleoside reverse transcriptase inhibitor (NNRTI) resistant HIV-1 strains. Li et al. [28] reported identification of three other anti-HIV-1 compounds from Stachybotrys chartarum: chartarutine B, G, and H. Of these three chartarutine compounds, chartarutine B (4) showed the lowest concentration that resulted in 50% inhibition of HIV-1 (IC<sub>50</sub> of 1.81 µg/mL), followed by chartarutine G (IC<sub>50</sub> of 2.05 µg/mL) and chartarutine H (IC<sub>50</sub> of 2.05 µg/mL), respectively.

Sponge-associated microbes have also been found to produce anti-influenza compounds (Table 1). Zhao et al. [29] elucidated 14 new isoprenylated cyclohexanols coined as truncateols A-N from the sponge-associated fungus Truncatella angustata, and these compounds were tested in vitro against the influenza A (H1N1) virus. Truncateols C, E and M displayed bioactivity against H1N1, with truncateol M (5) being the most potent inhibitor, as shown by its IC<sub>50</sub> value of 2.91 µg/mL. This inhibitory concentration was almost six fold lower than that of the positive control oseltamivir at 14.52 µg/mL. Truncateol M was predicted to be active at the late stage of the virus infection, likely during the assembly or release step of the virion [29] due to resemblance of the inhibition patterns observed for neuraminidase-inhibitor drugs, e.g., zanamivir and oseltamivir [30]. In addition, the presence of a chlorine atom in the chemical structure of truncateol M is of particular interest since halogenation often enhances bioactivity of a given compound [31,32].
Table 1. Bioactive compounds with antiviral activity from sponge-associated microbes.

| Sponge            | Origin (Depth)         | Microorganism            | Phylum          | Compound                  | Property                                      | Target                          | Reference     |
|-------------------|------------------------|--------------------------|-----------------|---------------------------|-----------------------------------------------|---------------------------------|---------------|
| Homophymia sp.    | Touho, New Caledonia (ND) | Pseudomonas sp. 1531-E7  | Proteobacteria  | 2-undecyl-4-quinolone     | IC₅₀ (10⁻³ µg/mL)                            | HIV-1                           | [25]          |
| Ircinia fasciculata | Bight of Fetovaia, Italy (17.5 m) | Penicillium chrysogenum | Ascomycota      | Sorbicillactone A         | Reducing protein expression and activity of reverse transcriptase (0.3-1 µg/mL) | HIV-1                           | [26]          |
| Xestospongia testudinaria | Paracel Islands (ND) | Stachybotrys chartarum MXH-X73 | Ascomycota      | Stachybotrin D            | EC₅₀ (3.71 µg/mL)                            | HIV-1                           | [27]          |
| Xestospongia testudinaria | Paracel Islands (ND) | Stachybotrys chartarum MXH-X73 | Ascomycota      | Stachybotrin D            | EC₅₀ (10.51 µg/mL)                            | NNRTI resistant HIV-1 RT-L100I, K103N | [27]          |
| Xestospongia testudinaria | Paracel Islands (ND) | Stachybotrys chartarum MXH-X73 | Ascomycota      | Stachybotrin D            | EC₅₀ (5.87 µg/mL)                            | NNRTI resistant HIV-1 RT-L100I, K103N | [27]          |
| Xestospongia testudinaria | Paracel Islands (ND) | Stachybotrys chartarum MXH-X73 | Ascomycota      | Stachybotrin D            | EC₅₀ (2.73 µg/mL)                            | NNRTI resistant HIV-1 RT-L100I, K103N | [27]          |
| Niphates sp.      | Beibuwan Bay, China (10 m) | Stachybotrys chartarum | Ascomycota      | Chartarutine B            | IC₅₀ (1.81 µg/mL)                            | HIV-1                           | [28]          |
| Niphates sp.      | Beibuwan Bay, China (10 m) | Stachybotrys chartarum | Ascomycota      | Chartarutine G            | IC₅₀ (0.35 µg/mL)                            | HIV-1                           | [28]          |
| Niphates sp.      | Beibuwan Bay, China (10 m) | Stachybotrys chartarum | Ascomycota      | Chartarutine H            | IC₅₀ (0.35 µg/mL)                            | HIV-1                           | [28]          |
| Amphimedon sp.    | Yongxin island, China (10 m) | Truncatella angustata | Ascomycota      | Truncateol M              | IC₅₀ (2.91 µg/mL)                            | H1N1                            | [29]          |
| Capsellpora sp.   | Sanya, China (ND)      | Epicoccum sp. JJY40      | Ascomycota      | Pyronepolyene C-glucoside iso-D8646-2-6 | IC₅₀ (56.06 µg/mL) | H1N1 | [33] |
| Capsellpora sp.   | Sanya, China (ND)      | Epicoccum sp. JJY40      | Ascomycota      | Pyronepolyene C-glucoside, 8646-2-6 | IC₅₀ (62.07 µg/mL) | H1N1 | [33] |
| Unidentified      | Naozhou Sea, China (ND) | Aspergillus terreus MXH-23 | Ascomycota      | Butyrolactone III         | Percentage of inhibition (53.9% ± 0.53% at 50 µg/L) | H1N1 | [34] |
| Unidentified      | Naozhou Sea, China (ND) | Aspergillus terreus MXH-23 | Ascomycota      | 5-[(3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-6-yl)(methyl)-3-hydroxy-4(4-hydroxyphenyl)-2H1-furanone] | Percentage of inhibition (57.8% ± 1.99% at 50 µg/L) | H1N1 | [34] |
| Unidentified      | Paracel Islands (ND)   | Aspergillus sydowi ZSDS1-F6 | Ascomycota      | (Z)-5-(Hydroxy(methyl)2-(60-methylhept-20-en-20-y1)-phenol | IC₅₀ (14.30 µg/mL) | H3N2 | [35] |
| Unidentified      | Paracel Islands (ND)   | Aspergillus sydowi ZSDS1-F6 | Ascomycota      | Diorcinol              | IC₅₀ (15.31 µg/mL)                            | H3N2 | [35] |
Table 1. Cont.

| Unidentified Paracel slands (ND) | Aspergillus sydowii ZSDS1-F6 | Ascomycota | Cordyol C | IC₅₀ (19.33 µg/mL) | H3N2 | [35] |
|----------------------------------|-----------------------------|------------|-----------|-------------------|------|------|
| Unidentified Paracel Islands (ND) | Stachybotrys sp. HH1 ZSDS1F1-2 | Ascomycota | Stachybotrytisphenone B | IC₅₀ (10.2 µg/mL) | Enterovirus 71 (EV71) | [36] |
| Unidentified Paracel Islands (ND) | Stachybotrys sp. HH1 ZSDS1F1-2 | Ascomycota | Griseofulvin A | IC₅₀ (16.94 µg/mL) | Enterovirus 71 (EV71) | [36] |
| Unidentified Paracel Islands (ND) | Stachybotrys sp. HH1 ZSDS1F1-2 | Ascomycota | 3,6,9-Trihydroxy-1-methylxanthone | IC₅₀ (10.4 µg/mL) | Enterovirus 71 (EV71) | [36] |
| Petromica citrina Saco do Poço, Brazil (5–15 m) | Bacillus sp. B555 | Firmicutes | Unidentified | IC₅₀ (27.35 µg/mL) EC₅₀ (>500 µg/mL) | Bovine viral diarrhea | [37] |
| Petromica citrina Saco do Poço, Brazil (5–15 m) | Bacillus sp. B584 | Firmicutes | Unidentified | IC₅₀ (10.24 µg/mL) EC₅₀ (277 µg/mL) | Bovine viral diarrhea | [37] |
| Petromica citrina Saco do Poço, Brazil (5–15 m) | Bacillus sp. B616 | Firmicutes | Unidentified | IC₅₀ (47 µg/mL) EC₅₀ (1508 µg/mL) | Bovine viral diarrhea | [37] |

Table 1 is organised according to the target viruses. IC₅₀: half maximum inhibitory concentration; EC₅₀: the concentration of a drug that give the half-maximal response; ND: not determined; HIV: human immunodeficiency virus; H1N1 and H3N2 are influenza A virus subtypes.
3. Antibacterial Compounds

The screening procedure for antibacterial activity often includes both Gram positive and Gram negative target strains, including, e.g., Staphylococcus spp., Streptococcus spp., Bacillus spp., Clostridium spp., Escherichia spp., and Pseudomonas spp. From a medical point of view, these genera receive attention because they are well represented among the causative agents for human infectious diseases, such as pneumonia, urinary tract and blood stream infections [38,39]. Microbial isolates from marine sponges have been shown to exhibit bioactivity against a wide spectrum of pathogenic bacteria (Table 2). The novel thiopeptide antibiotics YM-266183 (6) and YM-266184 (7) (Figure 2), which were isolated from the sponge-associated bacterium Bacillus cereus QN03323, showed antibacterial activity against nosocomial infectious Gram positive bacteria in vitro [40,41]. Both YM-266183 and YM-266184 effectively inhibited Staphylococcus aureus and vancomycin-resistant Enterococcus faecium as indicated by minimal inhibition concentration (MIC) values as low as 0.025 µg/mL. In addition, compound YM-266184 was found particularly active against methicillin resistant Staphylococcus aureus (MRSA) with a MIC of 0.39 µg/mL. Compound YM-266183 also inhibited MRSA but required a two-fold higher concentration of the pure compound. Bioactivity of these thiopeptides was also observed against Streptococcus epidermidis and Enterococcus spp. (Table 2). The compound kocurin (8) was identified from three sponge-associated actinobacteria: Kocuria marina F-276,310, Kocuria palustris F-276,345, and Micrococcus yunnanensis F-256,446 [42,43]. Kocurin is a new member of the thiazyol peptide family and exhibited anti-MRSA activity with an MIC of 0.25 µg/mL, which to date is the most potent anti-MRSA compound reported from sponge-associated microbes. Scheenemaan et al. [44] isolated Streptomycetes sp. HB202 from the sponge Haliclona simulans, which lead to discovery of the polyketide mayamycin. In vitro assays with mayamycin (9) showed bioactivity against S. aureus and MRSA with IC₅₀ values of 1.16 µg/mL and 0.58 µg/mL respectively, along with an IC₅₀ of 0.14 µg/mL against Staphylococcus epidermidis [45].

Although many studies on antibacterial activity from sponge-associated microbes included Gram negative strains (Table 2), reports on pronounced antibacterial compounds active against Gram negative bacteria are limited in comparison to those that inhibit Gram positive strains. One of the examples of an inhibitor of a Gram negative bacterium is the compound naphthacene glycoside SF2446A2 (10) isolated from Streptomycetes sp. RV15 that was originally obtained from the marine sponge Dysidea tupha [46]. Naphthacene glycoside SF2446A2 (10) inhibited the Gram-negative bacterium Chlamydia trachomatis at an IC₅₀ value of 2.81 ± 0.24 µg/mL. Reimer et al. [46] underlined that compound 10 not only effectively inhibited the formation of chlamydial inclusion bodies during the primary infection but also affected the ability of C. trachomatis in producing viable progeny during the developmental cycle. Chlamydia trachomatis is an obligate intracellular Gram negative bacterium which is a leading cause of sexually transmitted diseases, and currently no methods are available to treat this infectious microorganism [46,47]. Li et al. [48] isolated four new bisabolane-typesesquiterpenoids: aspergiterpenoid A, (−)-sydonol, (−)-sydonic acid, (−)-5-(hydroxymethyl)-2-(2′,6′,6′-trimethyltetrahydro-2H-pyran-2-yl)phenol and a known compound (Z)-5-(Hydroxymethyl)-2-(6′-methylhept-2′-en-2′-yl)phenol from a sponge-associated Aspergillus sp. (Table 2). Of these five substances, the compound sydonic acid (11) exhibited the lowest MIC value against Escherichia coli at 1.33 µg/mL. This is the lowest inhibition concentration against E.coli reported from a compound produced by sponge-associated microbes although the inhibition concentration is still higher than the positive control ciprofloxacin (0.21 µg/mL) (Table 2).

Pruksakorn et al. [49] reported three prospective anti-tuberculosis compounds: trichoderin A (12), A1 and B from the sponge-associated fungus Trichoderma sp. 05F148. Both under standard aerobic growth and dormancy-inducing hypoxic conditions, these three compounds inhibited Mycobacterium smegmatis, M. bovis BCG, and M. tuberculosis H37Rv with MIC values in the range of 0.02–2.0 µg/mL. Of these three compounds, trichoderin A was the most potent compound indicated by the lowest MIC values against those Mycobacterium strains. Additional analysis revealed that bioactivity of trichoderin A is based on its ability to inhibit adenosine triphosphate (ATP) synthesis.
of mycobacteria [50]. Compounds such as trichoderin A are particularly important because in many cases, pathogens such as Campylobacter spp., Helicobacter pylori, and Legionella pneumophila are difficult to treat due to the fact that they are present in a dormant state [51]. Such physiologically inactive cells highly contribute to the need for prolonged antibiotic treatments, which may lead to the emergence of resistant strains [52,53].

Figure 2. Chemical structures of the antibacterial compounds YM-266183 (6), YM-266184 (7), kocurin (8), mayamycin (9), naphthacene glycoside SF2446A2 (10), sydonic acid (11) and trichoderin A (12).
### Table 2. Bioactive compounds with antibacterial activity from sponge-associated microbes.

| Sponge Origin (Depth) | Microorganism | Phylum | Compound | Property | Target | References |
|-----------------------|---------------|--------|----------|----------|--------|------------|
| *Halichondria japonica* Iriomote island, Japan (ND) | Bacillus cereus QNO3233 | Firmicutes | Thiopeptide YM-266183 | MIC (0.025 µg/mL) | *S. aureus* | [40,41] |
| *Halichondria japonica* Iriomote island, Japan (ND) | Bacillus cereus QNO3323 | Firmicutes | Thiopeptide YM-266184 | MIC (0.025 µg/mL) | *S. aureus* | [40,41] |
| *Halichondria panicea* Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB202 | Actinobacteria | Mayamycin | IC₅₀ (1.16 µg/mL) | *S. aureus* | [45] |
| *Sphacinospongia vagabunda* Red Sea (ND) | Micrococcus sp. ECG4 | Actinobacteria | Microcuside A | MIC (12.42 µg/mL) | *S. aureus* | NCTC 8325 | [54] |
| *Isodictya setifera* Ross island, Antarctica (30–40 m) | Pseudomonas aeruginosa | Proteobacteria | Phenazine-1-carboxylic acid | MIC (>4.99 µg/mL) | *S. aureus* | [55] |
| *Hymeniacidon perleve* Bohai Sea, China (ND) | Aspergillus versicolor MF359 | Ascomycota | 5-Methoxydihydrosterigmatocystin | MIC (12.5 µg/mL) | *S. aureus* | [56] |
| *Melophilus sp.* Lau group, Fiji islands (10 m) | Penicillium sp. FF001 | Ascomycota | Citrinin | MIC (1.95 µg/mL) | *S. aureus* | [57] |
| *Petrosia* sp. Jeju island, Korea (20 m) | Aspergillus versicolor | Ascomycota | Averantin | MIC (3.13 µg/mL) | *S. aureus* | SG511 | [58] |
| *Petrosia* sp. Jeju island, Korea (20 m) | Aspergillus versicolor | Ascomycota | Nidurufin | MIC (6.25 µg/mL) | *S. aureus* | SG511 | [58] |
| *Petrosia* sp. Jeju island, Korea (20 m) | Aspergillus versicolor | Ascomycota | Averantin and nidurufin | MIC (3.13 µg/mL) | *S. aureus* | 285 | [58] |
| *Petrosia* sp. Jeju island, Korea (20 m) | Aspergillus versicolor | Ascomycota | Nidurufin | MIC (3.13 µg/mL) | *S. aureus* | 503 | [58] |
| *Hymeniacidon perleve* Nam-i island, China (ND) | Pseudoalteromonas piscicida NJ6-3-1 | Ascomycota | Norharman (beta-carboline alkaloid) | MIC (50 µg/mL) | *S. aureus* | [59] |
| *Halichondria panicea* Bogil island, Korea (ND) | Eschscholzia sp. | Ascomycota | Chlorohydroaspyrones A | MIC (62.5 µg/mL) | *S. aureus* | [60] |
| *Halichondria panicea* Bogil island, Korea (ND) | Eschscholzia sp. | Ascomycota | Chlorohydroaspyrones B | MIC (62.5 µg/mL) | *S. aureus* | [60] |
| *Azinella sp.* South China Sea, China (ND) | Eupenicillium sp. | Ascomycota | αβ-Dehydrocurvularin | MIC (375 µg/mL) | *S. aureus* | [61] |
| *Haliclona sp.* Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas fluorescens H40, H41 and Pseudomonas aeruginosa H51 | Proteobacteria | Diketopiperazine | MIC (512 µg/mL) | *S. aureus* | [62] |
| *Spongia officinalis* Southeast Coast India (10–15 m) | Streptomyces sp. MAPS15 | Actinobacteria | 2-pyrrolidone | MIC (500 µg/mL) | *S. aureus* | PC6 | [63] |
| *Dysidea herbacea* Koror, Republic Palau (1 m) | Oscillatoria spongiae | Cyanobacteria | 2-(2',4'-dibromophenyl)-4,6-dibromophenol | ND | *S. aureus* | [64] |
| *Hyrtios altum* Aragusuku island, Japan (ND) | Vibrio sp. | Proteobacteria | Trisindoline | DOI (10 mm) | *S. aureus* | [65] |
| *Xestospongia testudinaria* Bidong Island, Malaysia (ND) | Serratia marcescens IBRL USM 84 | Proteobacteria | Prodigiosin | DOI (<9 mm) | *S. aureus* | [66] |
Table 2. Cont.

| Unidentified | Location | Actinobacteria | Compound | MIC/DOI | Source |
|--------------|----------|----------------|----------|---------|--------|
| Nocardopsis sp. | South China Sea (10 m) | 1,6-Dihydroxyphenazine | DOI (25 ± 0.6 mm) | S. aureus SJ51 | [67] |
| Bacillus subtilis | Banyuls-sur-Mer, France (5-15 m) | 1,6-Dimethoxyphenazine | DOI (21 ± 0.1 mm) | S. aureus SJ51 | [68] |
| Bacillus subtilis | West Coast of India (10 m) | Indole | DOI (7-10 mm) | S. aureus | [69] |
| Bacillus licheniformis | West Coast of India (10 m) | 3-Phenylpropionic | DOI (4-6 mm) | S. aureus | |
| Curvularia lunata | Bali Bata National Park, Indonesia (ND) | 1,3,8-Trihydroxy-6-methoxyanthraquinone (lunatin) | DOI (10 mm) | S. aureus | [70] |
| Streptomyces sp. | Vizhinjam coast, India (10–15 m) | Unidentified | MIC (68 ± 2.8 µg protein/mL) | S. aureus | [73] |
| Aspergillus flavus | Kovalam Coast, India (5-10 m) | Unidentified | DOI (3-5 mm) | S. aureus | [74] |
| Aspergillus fesae | Cagarras Archipelago, Brazil (4-20 m) | Unidentified | DOI (27 mm) | S. aureus | [75] |
| Pseudomonas fluorescens | Cagarras Archipelago, Brazil (4-20 m) | Unidentified | DOI (20 mm) | S. aureus | [76] |
| Pseudomonas fluorescens | Cagarras Archipelago, Brazil (4-20 m) | Unidentified | DOI (23 mm) | S. aureus | [77] |
| Pseudomonas aeruginosa | Cagarras Archipelago, Brazil (4-20 m) | DOI (20 mm) | S. aureus | [77] |
| Pseudomonas aeruginosa | Cagarras Archipelago, Brazil (4-20 m) | DOI (30 mm) | S. aureus | [77] |
| Species                  | Location                      | Isolated Bacteria                      | Community                | Source Material | Species | Reference |
|-------------------------|-------------------------------|----------------------------------------|--------------------------|-----------------|----------|-----------|
| *Pseudoceratina clavata* | Heron Island, Great Barrier Reef (14 m) | *Salinispora* sp. M102, M403, M412, M413, M414, SW10, SW15 and SW17 | Actinobacteria Unidentified | DOI (>5 mm) | S. aureus | [79]      |
| *Pseudoceratina clavata* | Heron Island, Australia (14 m) | *Salinispora* sp. SW02 | Actinobacteria Unidentified | DOI (>5 mm) | S. aureus | [79]      |
| *Dendrilla nigra*       | Southeast coast of India (ND) | *Streptomyces* sp. BITL7 | Actinobacteria Unidentified | DOI (16 mm) | S. aureus | [80]      |
| *Mycale sp.*            | GALEI Port, Fujian, China (ND) | *Streptomyces* sp. HNS004, HNS010 | Firmicutes Unidentified | DOI (15–30 mm) | S. aureus | [81]      |
| *Mycale sp.*            | GALEI Port, Fujian, China (ND) | *Vibrio* sp. HNS022, HNS029 | Proteobacteria Unidentified | DOI (15–30 mm) | S. aureus | [81]      |
| *Mycale sp.*            | GALEI Port, Fujian, China (ND) | *Streptomyces* sp. HNS054 | Actinobacteria Unidentified | DOI (15–30 mm) | S. aureus | [81]      |
| *Mycale sp.*            | GALEI Port, Fujian, China (ND) | *Bacillus* sp. HNS005 | Firmicutes Unidentified | DOI (10–15 mm) | S. aureus | [81]      |
| *Mycale sp.*            | GALEI Port, Fujian, China (ND) | *Colobia* sp. HNS027, *Streptomyces* sp. HNS047, HNS056, *Nocardiopsis* sp. HNS048, HNS051, HNS055, *Nocardiia* sp. HNS052 | Actinobacteria Unidentified | DOI (10–15 mm) | S. aureus | [81]      |
| *Mycale sp.*            | GALEI Port, Fujian, China (ND) | *Bacillus* sp. HNS015 | Firmicutes Unidentified | DOI (8–10 mm) | S. aureus | [81]      |
| *Mycale sp.*            | GALEI Port, Fujian, China (ND) | *Pseudomonas* sp. HNS021 | Proteobacteria Unidentified | DOI (8–10 mm) | S. aureus | [81]      |
| *Mycale sp.*            | GALEI Port, Fujian, China (ND) | *Colobia* sp. HNS023, *Vibrio* sp. HNS038, *Lebrenzia* sp. HNS033, *Streptomyces* sp. HNS049, *Nocardiopsis* sp. HNS058 | Actinobacteria Unidentified | DOI (8–10 mm) | S. aureus | [81]      |
Table 2. Cont.

| Unidentified | Location | Species | Class | Unidentified | DOI (mm) | S. aureus |
|--------------|----------|---------|-------|--------------|----------|----------|
| Streptomyces sp. RV15 | Rovinj, Croatia (3–20 m) | Actinobacteria | Unidentified | DOI (17 mm) | S. aureus [82] |
| Dietzia sp. EGe7 | Rovinj, Croatia (3–20 m) | Actinobacteria | Unidentified | DOI (13 mm) | S. aureus [82] |
| Microbacterium sp. EGe9 | Rovinj, Croatia (3–20 m) | Actinobacteria | Unidentified | DOI (13 mm) | S. aureus [82] |
| Micromonospora sp. RV115 | Rovinj, Croatia (3–20 m) | Actinobacteria | Unidentified | DOI (12 mm) | S. aureus [82] |
| Rhodococcus sp. EC33 | Rovinj, Croatia (3–20 m) | Actinobacteria | Unidentified | DOI (12 mm) | S. aureus [82] |
| Rubrobacter sp. RV113 | Rovinj, Croatia (3–20 m) | Actinobacteria | Unidentified | DOI (9 mm) | S. aureus [82] |

| Suberites carnosus | Lough Hyne, Co. Cork, Ireland (15 m) | Arthrobacter sp. W13C1 | Actinobacteria | Unidentified | ND | S. aureus [83] |
| Pseudovibrio sp. W13S4, W13S21, W13S23, W13S26, W13S3 | Lough Hyne, Co. Cork, Ireland (15 m) | Proteobacteria | Unidentified | ND | S. aureus [83] |

| Aplysina aerophoba and Aplysina cavernicola | Marseille and Banyuls sur Mer, France (ND) | Bacillus SB6, SB17, Enterococcus SB91 | Firmicutes | Unidentified | DOI (12–16 mm) | S. aureus [84] |
| Aplysina aerophoba and Aplysina cavernicola | Marseille and Banyuls sur Mer, France (ND) | Arthrobacter SB95 | Actinobacteria | Unidentified | DOI (12–16 mm) | S. aureus [84] |
| Aplysina aerophoba and Aplysina cavernicola | Marseille and Banyuls sur Mer, France (ND) | unidentified low G + C Gram positive SB122 and SB144 | Unidentified | Unidentified | DOI (12–16 mm) | S. aureus [84] |
| Aplysina aerophoba and Aplysina cavernicola | Marseille and Banyuls sur Mer, France (ND) | α-Proteobacteria SB6, SB85, SB63, SB89, SB197, SB202, SB207, SB214 | Proteobacteria | Unidentified | DOI (12–16 mm) | S. aureus [84] |
| Dysidea granulosa | Kavaratti Island, India (ND) | Enterobacter sp. TTAG | Proteobacteria | Unidentified | DOI (22 mm) | S. aureus [85] |
| Petrosia ficiformis | Paraggi, Ligurian Sea, Italy (8 m) | Rhodococcus sp. E1 | Actinobacteria | Unidentified | ND | S. aureus [86] |

| Unidentified | Location | Species | Class | Unidentified | MIC (µg/mL) | methicillin-resistant Staphylococcus aureus (MRSA) |
|--------------|----------|---------|-------|--------------|-------------|--------------------------------------------------|
| Bacillus cereus QNO3323 | Iriomote island, Japan (ND) | Firmicutes | Thiopeptide YM-266183 | MIC (0.78 µg/mL) | MRSA [40,41] |
| Bacillus cereus QNO3323 | Iriomote island, Japan (ND) | Firmicutes | Thiopeptide YM-266184 | MIC (0.39 µg/mL) | MRSA [40,41] |
| Streptomycetes sp. HB202 | Kiel Fjord, Baltic Sea, Germany (ND) | Actinobacteria | Mayamycin | IC50 (0.58 µg/mL) | MRSA [45] |
| Penicillium sp. FF001 | Lau group, Fiji islands (10 m) | Ascomycota | Citrinan | MIC (3.90 µg/mL) | MRSA [57] |
| Exophiala sp. | Bogil island, Korea (ND) | Ascomycota | Chlorohydroaspirones A | MIC (125 µg/mL) | MRSA [59] |
| Exophiala sp. | Bogil island, Korea (ND) | Ascomycota | Chlorohydroaspirones B | MIC (62.5 µg/mL) | MRSA [59] |
| Pseudomonas spp. RHLB 12 | Gulf of Mannar, India (ND) | Proteobacteria | Chromophore compound | DOI (4 mm) at 50 µM | MRSA [87] |
Table 2. Cont.

| Sample Code | Geographic Location | Isolated Organism | Phylum | Family | DOI | MRSA Status |
|-------------|---------------------|-------------------|--------|--------|-----|-------------|
| Xestospongia testudinaria | Bidong Island, Malaysia (ND) | Serratia marcescens | Proteobacteria | Prodigiosin | DOI (22.5 mm) | MRSA [66] |
| Halichondria sp. | West Coast of India (10 m) | Bacillus licheniformis | Firmicutes | Indole 3-phenylpropionic | DOI (4-6 mm) | MRSA [69] |
| Halichondria sp. | Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas fluorescens H40 | Proteobacteria | | Unidentified | MRSA [77] |
| Halichondria sp. | Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas fluorescens H41 | Proteobacteria | | Unidentified | MRSA [77] |
| Halichondria sp. | Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas aeruginosa H51 | Proteobacteria | | Unidentified | MRSA [77] |
| Axinella dissimilis | Guirrag Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio Ad30 | Proteobacteria | | Unidentified | ND MRSA [78] |
| Halichondria simulans | Guirrag Sound, Kilkieran Bay, Ireland (15 m) | Streptomyces sp. SM2 and SM4 | Actinobacteria | | Unidentified | ND MRSA [88] |
| Halichondria simulans | Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas fluorescens H40 | Proteobacteria | | Unidentified | DOI (20 mm) community-associated MRSA [77] |
| Halichondria simulans | Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas fluorescens H41 | Proteobacteria | | Unidentified | DOI (22 mm) community-associated MRSA [77] |
| Halichondria simulans | Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas aeruginosa H51 | Proteobacteria | | Unidentified | DOI (43 mm) community-associated MRSA [77] |
| Petromica citrina | Cagarras Archipelago, Brazil (4–20 m) | Bacillus pumilus PC31 | Firmicutes | | Unidentified | DOI (40 mm) community-associated MRSA [77] |
| Clathrina aurea | Cagarras Archipelago, Brazil (4–20 m) | Pseudovibrio ascidiaceicola Ca31 | Proteobacteria | | Unidentified | DOI (17 mm) community-associated MRSA [77] |
| Paraleucilla magna | Cagarras Archipelago, Brazil (4–20 m) | Pseudovibrio ascidiaceicola Pm31 | Proteobacteria | | Unidentified | DOI (25 mm) community-associated MRSA [77] |
| Mycale microeignata | Cagarras Archipelago, Brazil (4–20 m) | Pseudovibrio denitrificans Mm37 | Proteobacteria | | Unidentified | DOI (20 mm) community-associated MRSA [77] |
| Appenina aerophoba | Banyuls-sur-Mer, France (15 m) | Bacillus subtilis A202 | Firmicutes | | Iturin | ND multi drug-resistant S. aureus [68] |
| Halichondria panicea | Bogil Island, Korea (ND) | Exophiala sp. | Ascomycota | Chlorohydroaspyrones A | MIC (125 µg/mL) multi drug-resistant S. aureus [60] |
| Halichondria simulans | Guirrag Sound, Kilkieran Bay, Ireland (15 m) | Bacillus subtilis MMA7 | Firmicutes | Subtilomycin | ND heterogeneous vancomycin intermediate S. aureus (hVISA) [71] |
| Axinella dissimilis | Guirrag Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio Ad30 | Proteobacteria | | Unidentified | ND hVISA [78] |
| Species                        | Location                          | Strain/Species/Strain Description | Taxonomy         | MIC/DOI | Reference |
|-------------------------------|-----------------------------------|-----------------------------------|-----------------|---------|-----------|
| *Haliclona simulans*           | Gurraig Sound, Kilkieran, Ireland | *Streptomyces sp.* SM2 and SM4     | Proteobacteria   | ND      | [88]      |
| *Melophus sp.*                 | Lau group, Fiji islands (10 m)    | *Penicillium sp.* FF001            | Ascomycota      | MIC     | [57]      |
| *Halichondria panicea*         | Baltic Sea (ND)                   | *Streptomyces sp.* HB202           | Actinobacteria   | IC<sub>50</sub> | [45]      |
| *Halichondria panicea*         | Kiel Fjord, Baltic Sea, Germany   | *Streptomyces sp.* HB202           | Actinobacteria   | IC<sub>50</sub> | [89]      |
| *Asinella corrugata*           | Arvoredo Biological Marine Reserve, Brazil (ND) | *Penicillium sp.*                 | Ascomycota      | Dipeptide cis-cyclo(leucyl-tyrosyl) reducing 85% of biofilm formation at 1000 µg/mL | [91]      |
| unidentified sponge            | Vizhijam coast (10–12 m)          | *Aspergillus clavatus MFD15        | Ascomycota      | MIC (800 ± 10 µg/mL) | [91]      |
| *Spongia officinalis*          | Southeast Coast India (10–15 m)   | *Streptomyces sp.* MAPS15          | Actinobacteria   | MIC (500 µg/mL) | [63]      |
| *Xestospongia testudinaria*    | Bidong Island, Malaysia (ND)      | *Serratia marcescens IBRL USM 84  | Proteobacteria   | DOI (<9 mm) | [66]      |
| *Aplysina aerophoba*           | Banyuls-sur-Mer, France (5–15 m)  | *Bacillus subtilis A184*           | Firmicutes       | ND      | [68]      |
| *Aplysina aerophoba*           | Banyuls-sur-Mer, France (5–15 m)  | *Bacillus subtilis A190*           | Firmicutes       | ND      | [68]      |
| *Haliclona sp.*                | Cagarras Archipelago, Brazil (4–20 m) | *Pseudomonas fluorescens H40*     | Proteobacteria   | DOI (35 mm) | [77]      |
| *Haliclona sp.*                | Cagarras Archipelago, Brazil (4–20 m) | *Pseudomonas fluorescens H41*     | Proteobacteria   | DOI (30 mm) | [77]      |
| *Clathrina aurea*              | Cagarras Archipelago, Brazil (4–20 m) | *Pseudovibrio ascidiaceicola*     | Proteobacteria   | DOI (28 mm) | [77]      |
| *Petromica citrina*            | Cagarras Archipelago, Brazil (4–20 m) | *Bacillus pumilis Pc31*           | Firmicutes       | DOI (45 mm) | [77]      |
| *Clathrina aurantium*          | Cagarras Archipelago, Brazil (4–20 m) | *Pseudovibrio ascidiaceicola*     | Proteobacteria   | DOI (25 mm) | [77]      |
| *Paraleucilla magna*           | Cagarras Archipelago, Brazil (4–20 m) | *Pseudovibrio ascidiaceicola*     | Proteobacteria   | DOI (35 mm) | [77]      |
| Species                                | Location                                      | Isolate(s)                                      | Class/Order          | Resistance/Properties                        | Reference |
|----------------------------------------|-----------------------------------------------|------------------------------------------------|----------------------|-----------------------------------------------|-----------|
| *Mycale microsigmatosa*                | Cagarras Archipelago, Brazil (4-20 m)         | *Pseudovibrio denitrificans* Mm37              | Proteobacteria       | Unidentified                                  | [77]      |
| *Pseudoceratina clavata*               | Heron Island, Australia (14 m)                | *Salinispora sp.* M102, M403, M412, M413, M414, SW10, SW15, SW17 | Actinobacteria       | Unidentified                                  | [79]      |
| *Pseudoceratina clavata*               | Heron Island, Australia (14 m)                | *Salinispora sp.* SW02                         | Actinobacteria       | Unidentified                                  | [79]      |
| *Callyspongia diffusa*                 | Bay of Bengal, India (10-15 m)               | *Streptomyces sp.* CPS 13                      | Actinobacteria       | Unidentified                                  | [92]      |
| *Haliclona* sp.                        | Cagarras Archipelago, Brazil (4-20 m)         | *Pseudomonas fluorescens* H40                  | Proteobacteria       | Unidentified                                  | [77]      |
| *Haliclona* sp.                        | Cagarras Archipelago, Brazil (4-20 m)         | *Pseudomonas fluorescens* H41                  | Proteobacteria       | S. epidermidis 5% (susceptible to amp, cip, pen, lef) | [77]      |
| *Haliclona* sp.                        | Cagarras Archipelago, Brazil (4-20 m)         | *Pseudomonas aeruginosa* H51                   | Proteobacteria       | S. epidermidis 5%                              | [77]      |
| *Petromica citrina*                    | Cagarras Archipelago, Brazil (4-20 m)         | *Bacillus pumilus* Pc31                        | Firmicutes           | Unidentified                                  | [77]      |
| *Petromica citrina*                    | Cagarras Archipelago, Brazil (4-20 m)         | *Bacillus pumilus* Pc32                        | Firmicutes           | Unidentified                                  | [77]      |
| *Clathrina aurea*                      | Cagarras Archipelago, Brazil (4-20 m)         | *Pseudovibrio ascidiaceicola* Cc31             | Proteobacteria       | Unidentified                                  | [77]      |
| *Paraleucilla magna*                   | Cagarras Archipelago, Brazil (4-20 m)         | *Pseudovibrio ascidiaceicola* Pm31             | Proteobacteria       | S. epidermidis 5%                              | [77]      |
| *Mycale microsigmatosa*                | Cagarras Archipelago, Brazil (4-20 m)         | *Pseudovibrio denitrificans* Mm37              | Proteobacteria       | Unidentified                                  | [77]      |
| *Xestospongia testudinaria*            | Weizhou coral reef, China (ND)                | *Aspergillus* sp.                              | Ascomycota           | (Z)-5-(Hydroxymethyl)-2-((6'-methylhept-2'-en-2'-yl)phenol | Staphylococcus albus | [48] |
| *Haliclona* sp.                        | Cagarras Archipelago, Brazil (4-20 m)         | *Pseudomonas fluorescens* H40                  | Proteobacteria       | Unidentified                                  | [77]      |
| *Haliclona* sp.                        | Cagarras Archipelago, Brazil (4-20 m)         | *Pseudomonas fluorescens* H41                  | Proteobacteria       | S. haemolyticus                                | [77]      |
| *Haliclona* sp.                        | Cagarras Archipelago, Brazil (4-20 m)         | *Pseudomonas aeruginosa* H51                   | Proteobacteria       | S. haemolyticus                                | [77]      |
Table 2. Cont.

| Species                     | Location                              | Isolate   | Family             | Taxon                  | DOI (mm) | Susceptibilities                        |
|-----------------------------|---------------------------------------|-----------|--------------------|------------------------|----------|-----------------------------------------|
| *Petromica citrina*         | Cagarras Archipelago, Brazil (4–20 m) | Bacillus  | Firmicutes         | Unidentified DOI (40 mm)| S. haemolyticus [77] |
| *Petromica citrina*         | Cagarras Archipelago, Brazil (4–20 m) | Bacillus  | Firmicutes         | Unidentified DOI (40 mm)| S. haemolyticus [77] |
| *Clathrina aurea*           | Cagarras Archipelago, Brazil (4–20 m) | Pseudovibrio ascidiaceicola Ca31 | Proteobacteria | Unidentified DOI (38 mm)| S. haemolyticus [77] |
| *Pseudovibrio ascidiaceicola* | Cagarras Archipelago, Brazil (4–20 m) | Pseudovibrio ascidiaceicola Pm31 | Proteobacteria | Unidentified DOI (40 mm)| S. haemolyticus [77] |
| *Mycale microsigmatosa*     | Cagarras Archipelago, Brazil (4–20 m) | Pseudovibrio denitrificans Mm37 | Proteobacteria | Unidentified DOI (43 mm)| S. haemolyticus [77] |
| *Haliclona sp.*             | Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas fluorescens H40 | Proteobacteria | Unidentified DOI (19 mm)| S. haemolyticus 109s (susceptible to amp, gen, oxa, pen) [77] |
| *Haliclona sp.*             | Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas fluorescens H41 | Proteobacteria | Unidentified DOI (15 mm)| S. haemolyticus 109s [77] |
| *Petromica citrina*         | Cagarras Archipelago, Brazil (4–20 m) | Bacillus  | Firmicutes         | Unidentified DOI (31 mm)| S. haemolyticus 109s [77] |
| *Petromica citrina*         | Cagarras Archipelago, Brazil (4–20 m) | Bacillus  | Firmicutes         | Unidentified DOI (36 mm)| S. haemolyticus 109s [77] |
| *Clathrina aurea*           | Cagarras Archipelago, Brazil (4–20 m) | Pseudovibrio ascidiaceicola Ca31 | Proteobacteria | Unidentified DOI (23 mm)| S. haemolyticus 109s [77] |
| *Paraleucilla magna*        | Cagarras Archipelago, Brazil (4–20 m) | Pseudovibrio ascidiaceicola Pm31 | Proteobacteria | Unidentified DOI (30 mm)| S. haemolyticus 109s [77] |
| *Mycale microsigmatosa*     | Cagarras Archipelago, Brazil (4–20 m) | Pseudovibrio denitrificans Mm37 | Proteobacteria | Unidentified DOI (20 mm)| S. haemolyticus 109s [77] |
| *Haliclona sp.*             | Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas fluorescens H40 | Proteobacteria | Unidentified DOI (31 mm)| Staphylococcus hominis [77] |
| *Haliclona sp.*             | Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas fluorescens H41 | Proteobacteria | Unidentified DOI (28 mm)| S. hominis [77] |
| *Haliclona sp.*             | Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas aeruginosa H51 | Proteobacteria | Unidentified DOI (37 mm)| S. hominis [77] |
| *Petromica citrina*         | Cagarras Archipelago, Brazil (4–20 m) | Bacillus  | Firmicutes         | Unidentified DOI (41 mm)| S. hominis [77] |
| *Petromica citrina*         | Cagarras Archipelago, Brazil (4–20 m) | Bacillus  | Firmicutes         | Unidentified DOI (43 mm)| S. hominis [77] |
| *Clathrina aurea*           | Cagarras Archipelago, Brazil (4–20 m) | Pseudovibrio ascidiaceicola Ca31 | Proteobacteria | Unidentified DOI (23 mm)| S. hominis [77] |
| *Paraleucilla magna*        | Cagarras Archipelago, Brazil (4–20 m) | Pseudovibrio ascidiaceicola Pm31 | Proteobacteria | Unidentified DOI (25 mm)| S. hominis [77] |
Table 2. Cont.

| Species                  | Location                        | Associated Bacteria                  | Taxonomy                                | DOI (mm) | Antibiotic Resistance   |
|--------------------------|---------------------------------|--------------------------------------|-----------------------------------------|----------|--------------------------|
| *Mycale microsigmatosa*  | Cagarras Archipelago, Brazil (4–20 m) | *Pseudovibrio denitrificans* Mm37 | Proteobacteria Unidentified             | DOI (24 mm) | S. hominis [77]          |
| *Haliclona sp.*          | Cagarras Archipelago, Brazil (4–20 m) | *Pseudomonas fluorescens* H40 | Proteobacteria Unidentified             | DOI (25 mm) | S. hominis 79s (susceptible to amp, pen) [77] |
| *Haliclona sp.*          | Cagarras Archipelago, Brazil (4–20 m) | *Pseudomonas fluorescens* H41 | Proteobacteria Unidentified             | DOI (27 mm) | S. hominis 79s           |
| *Petromica citrina*      | Cagarras Archipelago, Brazil (4–20 m) | *Bacillus pumilus* Pc31 | Firmicutes Unidentified                 | DOI (35 mm) | S. hominis 79s           |
| *Petromica citrina*      | Cagarras Archipelago, Brazil (4–20 m) | *Bacillus pumilus* Pc32 | Firmicutes Unidentified                 | DOI (30 mm) | S. hominis 79s           |
| *Clathrina aurita*       | Cagarras Archipelago, Brazil (4–20 m) | *Pseudovibrio ascidiaceicola* Ca31 | Proteobacteria Unidentified             | DOI (25 mm) | S. hominis 79s           |
| *Paraleucilla magna*     | Cagarras Archipelago, Brazil (4–20 m) | *Pseudovibrio ascidiaceicola* Pm31 | Proteobacteria Unidentified             | DOI (25 mm) | S. hominis 79s           |
| *Mycale microsigmatosa*  | Cagarras Archipelago, Brazil (4–20 m) | *Pseudovibrio denitrificans* Mm37 | Proteobacteria Unidentified             | DOI (28 mm) | S. hominis 79s           |
| *Xestospongia testudinaria* | Bidong Island, Malaysia (ND) | *Serratia marcescens* IBRL USM 84 | Proteobacteria Prodigiosin              | DOI (<9 mm) | *Staphylococcus saprophyticus* [66] |
| *Halichondria panicea*   | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB202 | Actinobacteria Mayamycin | IC50 (3.71 µg/mL) | *Staphylococcus lentus* [45] |
| *Halichondria panicea*   | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB062 | Actinobacteria Unidentified             | ND       | S. lentus [44]           |
| *Halichondria panicea*   | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB117 | Actinobacteria Unidentified             | ND       | S. lentus [44]           |
| *Halichondria panicea*   | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB122 | Actinobacteria Unidentified             | ND       | S. lentus [44]           |
| *Halichondria panicea*   | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB132 | Actinobacteria Unidentified             | ND       | S. lentus [44]           |
| *Halichondria panicea*   | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB138 | Actinobacteria Unidentified             | ND       | S. lentus [44]           |
| *Halichondria panicea*   | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB149 | Actinobacteria Unidentified             | ND       | S. lentus [44]           |
| *Halichondria panicea*   | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB184 | Actinobacteria Unidentified             | ND       | S. lentus [44]           |
| *Halichondria panicea*   | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB253 | Actinobacteria Unidentified             | ND       | S. lentus [44]           |
| *Halichondria panicea*   | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB272 | Actinobacteria Unidentified             | ND       | S. lentus [44]           |
Table 2. Cont.

| Marine sponge | Collection site | Isolated strain | Taxonomic class | Phylogenetic group | Molecular markers | MIC | Source |
|---------------|----------------|-----------------|----------------|-------------------|------------------|-----|--------|
| *Halichondria panicea* | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB288 | Actinobacteria | Unidentified | ND | S. lentus | [44] |
| *Halichondria panicea* | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB298 | Actinobacteria | Unidentified | ND | S. lentus | [44] |
| *Halichondria panicea* | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB328 | Actinobacteria | Unidentified | ND | S. lentus | [44] |
| *Halichondria panicea* | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB375 | Actinobacteria | Unidentified | ND | S. lentus | [44] |
| *Halichondria panicea* | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB383 | Actinobacteria | Unidentified | ND | S. lentus | [44] |
| *Dendrilla nigra* | Southwest Coast of India (10-12 m) | *Nocardopsis dassonvillei* MAD08 | Actinobacteria | Unidentified | MIC (600 µg/mL) | Staphylococcus sp. | [93] |
| *Halichondria japonica* | Iriomote island, Japan (ND) | *Bacillus cereus* QNO3323 | Firmicutes | Thiopeptide YM-266183 | MIC (1.56 µg/mL) | Multi drug-resistant Strep. epidermidis | [40,41] |
| *Halichondria japonica* | Iriomote island, Japan (ND) | *Bacillus cereus* QNO3323 | Firmicutes | Thiopeptide YM-266184 | MIC (1.2 µg/mL) | MRSE | [40,41] |
| *Aplysina aerophoba* | Banyuls-sur-Mer, France (5-15 m) | *Bacillus subtilis* A202 | Firmicutes | Iturin | ND | Multi drug-resistant S. epidermidis | [68] |
| *Dysidea granulosa* | Kavaratti Island, India (ND) | *Enterobacter* sp. TTAG | Proteobacteria | Unidentified | DOI (23 mm), MIC crude extract (5 mg/mL) | Streptococcus sp. | [68] |
| *Petrosia sp.* | Jeju island, Korea (20 m) | *Aspergillus versicolor* | Ascomycota | Averantin | MIC (0.78 µg/mL) | Streptococcus pugenae 308A | [58] |
| *Petrosia sp.* | Jeju island, Korea (20 m) | *Aspergillus versicolor* | Ascomycota | Nidurufin | MIC (3.13 µg/mL) | Streptococcus pugenae 77A | [58] |
| *Petrosia sp.* | Jeju island, Korea (20 m) | *Aspergillus versicolor* | Ascomycota | Nidurufin | MIC (6.25 µg/mL) | Streptococcus pugenae 77A | [58] |
| *Halichondria sp.* | West Coast of India (10 m) | *Bacillus licheniformis* SAB1 | Firmicutes | Indole | DOI (1-3 mm) | Streptococcus pugenae | [69] |
| *Halichondria sp.* | West Coast of India (10 m) | *Bacillus licheniformis* SAB1 | Firmicutes | 3-Phenylpropionic | DOI (4-6 mm) | Streptococcus pugenae | [69] |
| *Haliclona simulans* | Curragean Sound Kilkieran Bay, Ireland (15 m) | *Streptomyces* sp. SM2 and SM4 | Actinobacteria | Unidentified | ND | Streptococcus pneumoniae | [88] |
| *Callyspongia diffusa* | Bay of Bengal, India (10-15 m) | *Saccharomonospora* sp. CPI 9 | Actinobacteria | Unidentified | ND | haemolytic Streptococcus sp (6-3) | [92] |
| *Halichondria japonica* | Iriomote island, Japan (ND) | *Bacillus cereus* QNO3323 | Firmicutes | Thiopeptide YM-266183 | MIC (1.56 µg/mL) | Bacillus subtilis ATCC 633 | [40,41] |
| *Halichondria japonica* | Iriomote island, Japan (ND) | *Bacillus cereus* QNO3323 | Firmicutes | Thiopeptide YM-266184 | MIC (1.56 µg/mL) | B. subtilis ATCC 633 | [40,41] |
| *Halichondria panicea* | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB202 | Actinobacteria | Mayamycin | IC₅₀ (3.71 µg/mL) | B. subtilis | [45] |
| *Halichondria panicea* | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB202 | Actinobacteria | Streptophenazines G | IC₅₀ (3.49 ± 0.38 µg/mL) | B. subtilis | [89] |
Table 2. Cont.

| Halichondria panacea | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB202 | Actinobacteria | Streptophenazines K | IC<sub>50</sub> (9.18 ± 2.89 µg/mL) | B. subtilis |
|----------------------|--------------------------------------|------------------------|----------------|---------------------|-------------------------------|-------------|
|                      |                                       |                        |                |                     |                               |             |
|                      | Halichondria panicea                  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB084 | Actinobacteria | Unidentified | ND | B. subtilis |
|                      | Halichondria panicea                  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB095 | Actinobacteria | Unidentified | ND | B. subtilis |
|                      | Halichondria panicea                  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB096 | Actinobacteria | Unidentified | ND | B. subtilis |
|                      | Halichondria panicea                  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB105 | Actinobacteria | Unidentified | ND | B. subtilis |
|                      | Halichondria panicea                  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB107 | Actinobacteria | Unidentified | ND | B. subtilis |
|                      | Halichondria panicea                  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB116 | Actinobacteria | Unidentified | ND | B. subtilis |
|                      | Halichondria panicea                  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB117 | Actinobacteria | Unidentified | ND | B. subtilis |
|                      | Halichondria panicea                  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB118 | Actinobacteria | Unidentified | ND | B. subtilis |
|                      | Halichondria panicea                  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB122 | Actinobacteria | Unidentified | ND | B. subtilis |
|                      | Halichondria panicea                  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB132 | Actinobacteria | Unidentified | ND | B. subtilis |
|                      | Halichondria panicea                  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB138 | Actinobacteria | Unidentified | ND | B. subtilis |
|                      | Halichondria panicea                  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB181 | Actinobacteria | Unidentified | ND | B. subtilis |
|                      | Halichondria panicea                  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB184 | Actinobacteria | Unidentified | ND | B. subtilis |
|                      | Halichondria panicea                  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB202 | Actinobacteria | Unidentified | ND | B. subtilis |
|                      | Halichondria panicea                  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB253 | Actinobacteria | Unidentified | ND | B. subtilis |
|                      | Halichondria panicea                  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB272 | Actinobacteria | Unidentified | ND | B. subtilis |
|                      | Halichondria panicea                  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB298 | Actinobacteria | Unidentified | ND | B. subtilis |
|                      | Halichondria panicea                  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB328 | Actinobacteria | Unidentified | ND | B. subtilis |
| Species                | Location                                      | Isolate          | Bacterial Class | Antimicrobial Activity                                                                 |
|-----------------------|-----------------------------------------------|------------------|----------------|----------------------------------------------------------------------------------------|
| *Halichondria panicea*| Kiel Fjord, Baltic Sea, Germany (ND)          | *Streptomyces* sp. HB375 | Actinobacteria | Unidentified, ND, B. subtilis [44]                                                    |
| *Halichondria panicea*| Kiel Fjord, Baltic Sea, Germany (ND)          | *Streptomyces* sp. HB383 | Actinobacteria | Unidentified, ND, B. subtilis [44]                                                    |
| *Callipoma sp.*      | Kyung-Po beach, Korea (12 m)                 | *Brevibacterium* sp. KMD 003 | Actinobacteria | 6-Hydroxymethyl-1-phenazine-carboxamide MIC (5.06 µg/mL), B. subtilis [64]              |
|                      |                                               | *Brevibacterium* sp. KMD 003 |               | 1,6-Phenazinedimethanol MIC (4.80 µg/mL), B. subtilis [64]                             |
| *Haliclona simulans* | Gurnag Sound, Kilkieran Bay, Ireland (15 m)  | *Streptomyces* sp. SM8 | Actinobacteria | Mixture Kitamycin A or B and Antimycin A3 or A7 MIC (7.42 µg/mL), B. subtilis [95]   |
|                      |                                               |                  |                | Antimycin A2, A8, A11 or A17 MIC (9.40 µg/mL), B. subtilis [95]                       |
|                      |                                               |                  |                | Antimycin A3 or A7, MIC (400 µg/mL), B. subtilis [95]                                |
| *Hymeniacidon perleve*| Bohai Sea, China (ND)                        | *Aspergillus* versicolor MF359 | Ascomycota     | 5-Methoxydihydrostreptomycin MIC (3.125 µg/mL), B. subtilis [56]                     |
| *Hymeniacidon perleve*| Nanji island, China (ND)                     | *Pseudalteromonas* piciicida NJ6-3-1 | Proteobacteria | Norharman (beta-carboline alkaloid) MIC (50 µg/mL), B. subtilis [59]                 |
|                      |                                               |                  |                | (-)-Sydonic acid MIC (0.66 µg/mL), B. subtilis [48]                                 |
|                      |                                               |                  |                | (-)-5-(Hydroxymethyl)-2-(6'-methylhept-2'-en-2'-yl)phenol MIC (2.33 µg/mL), B. subtilis [48] |
| *Xestospongia testudinaria* | Weizhou coral reef, China (ND) | *Aspergillus* sp. | Ascomycota     | 2-(2'-2',4'-Dibromophenyl)-4,6-dibromophenol ND, B. subtilis [64]                   |
| *Dysidea herbacea*   | Koror, Republic Palau (1 m)                  | *Oscillatoria* sp. | Cyanobacteria   | 2-(2'-2',4'-Dibromophenyl)-4,6-dibromophenol ND, B. subtilis [64]                   |
| *Hyrtios altum*      | Aragusuku island, Japan (ND)                 | *Vibrio* sp.     | Proteobacteria  | Trisiodihaline DOI (17 mm), B. subtilis [65]                                           |
| *Xestospongia testudinaria* | Bidorong Island, Malaysia (ND) | *Serratia marcescens* IBRL, USM 84 | Proteobacteria | Prodigiosin DOI (<9 mm), B. subtilis [66]                                             |
| *Niphates olemda*    | Bali Bata National Park, Indonesia (ND)      | *Curculiostrum* lunata | Ascomycota     | 1,2,8-Trimethoxy-6-methoxyhdroxiquinone (lunatin) DOI (9 mm), B. subtilis [70]       |
|                      |                                               |                  |                | Bisanthraquinone cytoskyrin A DOI (12 mm), B. subtilis [70]                          |
| *Hymeniacidon perleve*| Nanji island, China (ND)                     | *Pseudomonas* sp. NJ6-3-1 | Proteobacteria | Unidentified, ND, B. subtilis [74]                                                    |
| *Axinella dissimilis*| Gurnag Sound, Kilkieran Bay, Ireland (15 m)  | *Pseudodiplospira* AdX30 | Proteobacteria | Unidentified, ND, B. subtilis [78]                                                    |
| *Pseudoceratina chlorata* | Heron Island, Great Barrier Reef (14 m) | *Salinispora* sp. M102, M403, M412, M413, M414, SW02, SW10, SW 15 and SW 17 | Actinobacteria | Unidentified, ND, B. subtilis [79]                                                    |
### Table 2. Cont.

| **Dendrilla nigra** | **Southeast coast of India (ND)** | **Streptomyces sp. BTL7** | **Actinobacteria** | **Unidentified** | **DOI (15 mm)** | **B. subtilis** |
|---------------------|----------------------------------|---------------------------|-------------------|----------------|----------------|----------------|
| **Mycale sp.**      | **Galei Port, Fujian, China (ND)** | **Bacillus sp. HNS004, HNS005** | **Firmicutes** | **Unidentified** | **DOI (8-10 mm)** | **B. subtilis** |
| **Mycale sp.**      | **Galei Port, Fujian, China (ND)** | **Pseudomonas sp. HNS021, HNS027, Vibrio sp. HNS038** | **Proteobacteria** | **Unidentified** | **DOI (8-10 mm)** | **B. subtilis** |
| **Mycale sp.**      | **Galei Port, Fujian, China (ND)** | **Labrevecia sp. HNS063, Streptomyces sp. HNS047, Nocardiopsis sp. HNS046, HNS053, HNS056, Cobetia sp. HNS023** | **Actinobacteria** | **Unidentified** | **DOI (8-10 mm)** | **B. subtilis** |
| **Mycale sp.**      | **Galei Port, Fujian, China (ND)** | **Bacillus sp. HNS005, HNS010** | **Firmicutes** | **Unidentified** | **DOI (10-15 mm)** | **B. subtilis** |
| **Mycale sp.**      | **Galei Port, Fujian, China (ND)** | **Streptomyces sp. HNS049, HNS056** | **Actinobacteria** | **Unidentified** | **DOI (10-15 mm)** | **B. subtilis** |
| **Mycale sp.**      | **Galei Port, Fujian, China (ND)** | **Vibrio sp. HNS022, HNS028** | **Firmicutes** | **Unidentified** | **DOI (15-30 mm)** | **B. subtilis** |
| **Mycale sp.**      | **Galei Port, Fujian, China (ND)** | **Streptomyces sp. HNS054** | **Actinobacteria** | **Unidentified** | **DOI (15-30 mm)** | **B. subtilis** |
| **Sigmadocia fibulatus** | **Hare Island, India (5-10 m)** | **Bacillus sp. SC3** | **Firmicutes** | **Unidentified** | **ND** | **B. subtilis** |
| **Amphilectus fucorum** | **Lough Hyne, Ireland (6-15 m)** | **Pseudovibrio sp. 113V** | **Proteobacteria** | **Unidentified** | **ND** | **B. subtilis** |
| **Eurypon major**   | **Lough Hyne, Ireland (6-15 m)** | **Pseudovibrio sp. 107L, 108L, 109L** | **Proteobacteria** | **Unidentified** | **ND** | **B. subtilis** |
| **Suberites carnosus** | **Lough Hyne, Co. Cork, Ireland (15 m)** | **Arthrobacter sp. W13C11** | **Actinobacteria** | **Unidentified** | **ND** | **B. subtilis** |
| **Suberites carnosus** | **Lough Hyne, Co. Cork, Ireland (15 m)** | **Pseudovibrio sp. W13S4, W13S21, W13S26, W13S31** | **Unidentified** | **ND** | **B. subtilis** |
| **Halioclis similans** | **Garraig Sound, Kilkieran Bay, Ireland (15 m)** | **Streptomyces sp. SM2 and SM4** | **Actinobacteria** | **Unidentified** | **ND** | **B. subtilis** |
| **Isodictya setifera** | **Ross island, Antarctica (30-40 m)** | **Pseudomonas aeruginosa** | **Proteobacteria** | **Phenazine-1-carboxylic acid and phenazine-1-carboxamide** | **MIC (<0.49 µg/mL)** | **Bacillus cereus** |
| **Xestospongia testudinaria** | **Weizhou coral reef, China (ND)** | **Aspergillus sp.** | **Ascomycota** | **(Z)-5-(Hydroxymethyl)2-β'-methylhept-2'-en-2'-y1pheno1** | **MIC (2.33 µg/mL)** | **B. cereus** |
| **Xestospongia testudinaria** | **Bidong Island, Malaysia (ND)** | **Serratia marcescens IBRL USM 84** | **Proteobacteria** | **Prodigiosin** | **DOI (10-14 mm)** | **B. cereus** |
| **Dendrilla nigra** | **Vizhinjam coast, India (10-15 m)** | **Streptomyces sp. MS005** | **Actinobacteria** | **Unidentified** | **MIC (46 ± 1.62 µg protein/mL)** | **B. cereus** |
| **Asinella disimilis** | **Garraig Sound, Kilkieran Bay, Ireland (15 m)** | **Pseudovibrio Ad30** | **Proteobacteria** | **Unidentified** | **ND** | **B. cereus** |
| Name                        | Location                          | Isolate(s)                              | Taxonomy                                | Compound                  | Activity           | Reference |
|-----------------------------|-----------------------------------|------------------------------------------|------------------------------------------|---------------------------|--------------------|-----------|
| *Dendrilla nigra*           | Southeast coast of India (ND)     | Streptomyces sp. BTL7                   | Actinobacteria                           | Unidentified              | DOI (16 mm)        | [80]      |
| *Haliclona simulans*        | Gurraig Sound Kilkieran Bay, Ireland (15 m) | Streptomyces sp. SM2 and SM4             | Actinobacteria                           | Unidentified              | ND                 | [88]      |
| *Xestospongia testudinaria* | Bidong Island, Malaysia (ND)      | *Serratia marcescens IBRL USM 84        | Proteobacteria                           | Prodigiosin               | DOI (10-14 mm)     | [66]      |
| *Xestospongia testudinaria* | Bidong Island, Malaysia (ND)      | *Serratia marcescens IBRL USM 84        | Proteobacteria                           | Prodigiosin               | DOI (<9 mm)        | [66]      |
| **unidentified**            | South China Sea (10 m)            | **Nocardiapys sp.** 13-33-15 and 15-12-13 | Actinobacteria                           | **1,6-Dihydroxyphenazine** | **DOI (16 ± 0.5 mm)** | **[67]** |
| *Aplysina aerophoba*        | Banyuls-sur-Mer, France (5-15 m)  | *Bacillus subtilis* A184                 | Firmicutes                               | Surfactin, iturin, fengycin | ND                 | [68]      |
| *Aplysina aerophoba*        | Banyuls-sur-Mer, France (5-15 m)  | *Bacillus subtilis* A190                 | Firmicutes                               | Surfactin                 | ND                 | [68]      |
| *Aplysina aerophoba*        | Banyuls-sur-Mer, France (5-15 m)  | *Bacillus subtilis* A202                 | Firmicutes                               | Iturin                    | ND                 | [68]      |
| *Haliclona simulans*        | Gurraig Sound Kilkieran Bay, Ireland (15 m) | *Bacillus subtilis* MMA7                | Firmicutes                               | Subtilomycin              | ND                 | [71]      |
| *Dysidea aurata*            | Mediterranean sea (ND)            | *Actinomycetopsis* sp. EC49             | Actinobacteria                           | 1,6-Dihydroxyphenazine (result of the co-culture) | DOI (11 mm)        | **Bacillus sp.** P25 | [98]      |
| *Spheciospongia vagabunda*  | Red Sea (ND)                      | *Nocardiapys* sp. RV163                 |                                            |                           |                    |           |
| *Callyspongia diffusa*      | Bay of Bengal, India (10-15 m)    | *Streptomyces* sp. CPI 13               | Actinobacteria                           | Unidentified              | DOI (6.6 mm)       | **Bacillus sp.** | [92]      |
| *Callyspongia diffusa*      | Bay of Bengal, India (10-15 m)    | *Micromonospora* sp. CPI 12             | Actinobacteria                           | Unidentified              | DOI (8 mm)         | **Bacillus sp.** | [92]      |
| *Halichona sp.*             | Cagarras Archipelago, Brazil (4-20 m) | *Pseudomonas fluorescens* H40          | Proteobacteria                           | Unidentified              | DOI (19 mm)        | **Entenococcus faecalis** | [77]      |
| *Halichona sp.*             | Cagarras Archipelago, Brazil (4-20 m) | *Pseudomonas fluorescens* H41          | Proteobacteria                           | Unidentified              | DOI (17 mm)        | **E. faecalis** | [77]      |
| *Halichona sp.*             | Cagarras Archipelago, Brazil (4-20 m) | *Pseudomonas aeruginosa* H51          | Proteobacteria                           | Unidentified              | DOI (32 mm)        | **E. faecalis** | [77]      |
| *Clathrina aura*            | Cagarras Archipelago, Brazil (4-20 m) | *Pseudorhizobium asadiaciella* Ca31   | Proteobacteria                           | Unidentified              | DOI (11 mm),       | **E. faecalis** | [77]      |
| *Paraleucilla magna*        | Cagarras Archipelago, Brazil (4-20 m) | *Pseudorhizobium asadiaciella* Pm31   | Proteobacteria                           | Unidentified              | DOI (12 mm),       | **E. faecalis** | [77]      |
| *Mycale microsigmatosa*     | Cagarras Archipelago, Brazil (4-20 m) | *Pseudorhizobium densitricans* Mm37   | Proteobacteria                           | Unidentified              | DOI (14 mm)        | **E. faecalis** | [77]      |
Table 2. Cont.

| Species                          | Location                  | Isolate      | Family               | Genus          | DOI (mm) | Species | MIC (µg/mL)          | Reference |
|---------------------------------|---------------------------|--------------|---------------------|----------------|----------|---------|---------------------|-----------|
| unidentified                    | Rovinj, Croatia (3–20 m)  | Streptomyces | Actinobacteria      | Unidentified   | DOI (11 mm) | E. faecalis | [82]                |           |
| unidentified                    | Rovinj, Croatia (3–20 m)  | Microbacterium | Actinobacteria    | Unidentified   | DOI (9 mm)  | E. faecalis | [82]                |           |
| unidentified                    | Rovinj, Croatia (3–20 m)  | Micromonospora | Actinobacteria  | Unidentified   | DOI (10 mm) | E. faecalis | [82]                |           |
| unidentified                    | Rovinj, Croatia (3–20 m)  | Rhodococcus  | Actinobacteria      | Unidentified   | DOI (8 mm)  | E. faecalis | [82]                |           |
| Halocondria japonica            | Iriomote island, Japan (ND) | Bacillus cereus | Firmicutes | Unidentified   | DOI (11 mm) | Thiopeptide YM-266183 | MIC (0.1 µg/mL) | E. faecalis CAY 04_3 | [40,41] |
| Halocondria japonica            | Iriomote island, Japan (ND) | Bacillus cereus | Firmicutes | Unidentified   | DOI (9 mm)  | Thiopeptide YM-266184 | MIC (0.025 µg/mL) | E. faecalis CAY 04_3 | [40,41] |
| Sphheciospongia vagabunda       | Red Sea (ND)              | Micrococcus  | Actinobacteria      | Unidentified   | DOI (11 mm) | Microhaside A | MIC (9.55 µg/mL) | E. faecalis JH212 | [54]     |
| Halocondria japonica            | Iriomote island, Japan (ND) | Bacillus cereus | Firmicutes | Unidentified   | DOI (11 mm) | E. faecalis SAE (susceptible to van) | E. faecalis | [77]        |
| Clathrina aures                  | Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas fluorescens | Proteobacteria | Unidentified   | DOI (20 mm) | E. faecalis SAE | [77]                |           |
| Mycale microsignatosa           | Cagarras Archipelago, Brazil (4–20 m) | Pseudotrethrix denitrificans | Proteobacteria | Unidentified   | DOI (12 mm) | E. faecalis SAE | [77]                |           |
| Halocondria japonica            | Iriomote island, Japan (ND) | Bacillus cereus | Firmicutes | Unidentified   | DOI (11 mm) | Thiopeptide YM-266183 | MIC (0.025 µg/mL) | E. faecalis SAE | [77]     |
| Halocondria japonica            | Iriomote island, Japan (ND) | Bacillus cereus | Firmicutes | Unidentified   | DOI (11 mm) | Thiopeptide YM-266184 | MIC (0.05 µg/mL) | Vancomycin-Resistant E. faecium CAY 09_2 | [40,41] |
| Halocondria japonica            | Iriomote island, Japan (ND) | Bacillus cereus | Firmicutes | Unidentified   | DOI (11 mm) | Thiopeptide YM-266183 | MIC (0.025 µg/mL) | Vancomycin-Resistant E. faecium CAY 09_2 | [40,41] |
| Melophus sp.                    | Lau group, Fiji islands (10 m) | Penicillium | Ascomycota          | Citrinin       | MIC (1.95 µg/mL) | Vancomycin-resistant E. faecium | [57]                |           |
| Haloconida similis              | Curragh Sound Kilkieran Bay, Ireland (15 m) | Bacillus subtilis | Firmicutes | Subtilomycin   | ND        | E. faecium | [71]                |           |
| Haloconida sp.                  | Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas fluorescens | Proteobacteria | Unidentified   | DOI (18 mm) | E. faecium | [77]                |           |
| Haloconida sp.                  | Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas aeruginosa | Proteobacteria | Unidentified   | DOI (21 mm) | E. faecium | [77]                |           |
| Haloconida sp.                  | Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas aeruginosa | Proteobacteria | Unidentified   | DOI (30 mm) | E. faecium | [77]                |           |
| Dragmacidonreticulatus          | Cagarras Archipelago, Brazil (4–20 m) | Bacillus pumilus | Firmicutes | Unidentified   | DOI (20 mm) | E. faecium | [77]                |           |
| Petromica citrina               | Cagarras Archipelago, Brazil (4–20 m) | Bacillus pumilus | Firmicutes | Unidentified   | DOI (23 mm) | E. faecium | [77]                |           |
| Petromica citrina               | Cagarras Archipelago, Brazil (4–20 m) | Bacillus pumilus | Firmicutes | Unidentified   | DOI (20 mm) | E. faecium | [77]                |           |
| Clathrina aures                  | Cagarras Archipelago, Brazil (4–20 m) | Pseudotrethrix asiadiacicotector | Proteobacteria | Unidentified   | DOI (22 mm) | E. faecium | [77]                |           |
Table 2. Cont.

| Species                  | Environment                          | Isolate/Strain        | Kingdom                  | Phylum                | Class                      | Genus         | Species                        | MIC/MNC/NC (µg/mL) | Sensitivity                        |
|--------------------------|--------------------------------------|-----------------------|--------------------------|-----------------------|----------------------------|----------------|--------------------------------|-------------------|-----------------------------------|
| **Glycera magnifica**    | Cagarras Archipelago, Brazil (4-20 m) | *Pseudovibrio*        | Proteobacteria           | Unidentified          | DOI (20 mm)                | *E. faecium*  | [77]                           |                   |                                   |
| **Mycale microsigmatosa**| Cagarras Archipelago, Brazil (4-20 m) | *Pseudovibrio*        | Proteobacteria           | Unidentified          | DOI (15 mm)                | *E. faecium*  | [77]                           |                   |                                   |
| **Axinella dissimilis**  | Gurraig Sound, Kilieran Bay, Ireland (15 m) | *Pseudovibrio*        | Proteobacteria           | Unidentified          | ND                         | *E. faecium*  | [78]                           |                   |                                   |
| **Axinella dissimilis**  | Gurraig Sound, Kilieran Bay, Ireland (15 m) | *Pseudovibrio*        | Proteobacteria           | Unidentified          | ND                         | Vancomycin-resistant *Enterococcus* sp. | [78]          |                                   |
| **Callyspongia sp.**     | Kyung-Po beach, Korea (12 m)          | *Brevibacterium*      | Actinobacteria           | 6-Hydroxymethyl-1-phenazine-carboxamide | MIC (1.26 µg/mL) | *Enterococcus hirae*           | [94]              |                                   |
| **Haliclona sp.**        | Cagarras Archipelago, Brazil (4-20 m) | *Pseudomonas*         | Proteobacteria           | Unidentified          | DOI (22 mm)                | *Enterobacter cloacae* | [77]          |                                   |
| **Haliclona sp.**        | Cagarras Archipelago, Brazil (4-20 m) | *Pseudomonas*         | Proteobacteria           | Unidentified          | DOI (25 mm)                | *E. cloacae*  | [77]                           |                   |                                   |
| **Haliclona sp.**        | Cagarras Archipelago, Brazil (4-20 m) | *Pseudomonas*         | Proteobacteria           | Unidentified          | DOI (18 mm)                | *E. cloacae*  | [77]                           |                   |                                   |
| **Callyspongia diffusa** | Southwest Coast of India (6-7 m)     | *Shewanella algae*    | Proteobacteria           | 1,6-Phenazinedimethanol | MIC (1.20 µg/mL) | *E. hirae*    | [94]                           |                   |                                   |
| **Haliclona sp.**        | Cagarras Archipelago, Brazil (4-20 m) | *Pseudomonas*         | Proteobacteria           | Unidentified          | DOI (19 mm)                | *E. cloacae AE* (susceptible to amp, cef, fos, let) | [77]          |                                   |
| **Haliclona sp.**        | Cagarras Archipelago, Brazil (4-20 m) | *Pseudomonas*         | Proteobacteria           | Unidentified          | DOI (12 mm)                | *E. cloacae AE* | [77]                           |                   |                                   |
| **Haliclona sp.**        | Cagarras Archipelago, Brazil (4-20 m) | *Pseudomonas*         | Proteobacteria           | Unidentified          | DOI (23 mm)                | *E. cloacae AE* | [77]                           |                   |                                   |
| **Petromica citrina**    | Cagarras Archipelago, Brazil (4-20 m) | *Bacillus*            | Firmicutes               | Unidentified          | DOI (20 mm)                | *E. cloacae AE* | [77]                           |                   |                                   |
| **Petromica citrina**    | Cagarras Archipelago, Brazil (4-20 m) | *Bacillus*            | Firmicutes               | Unidentified          | DOI (20 mm)                | *E. cloacae AE* | [77]                           |                   |                                   |
| **Haliclona sp.**        | Cagarras Archipelago, Brazil (4-20 m) | *Pseudomonas*         | Proteobacteria           | Unidentified          | DOI (28 mm)                | *Enterobacter hafniae* | [77]          |                                   |
| **Haliclona sp.**        | Cagarras Archipelago, Brazil (4-20 m) | *Pseudomonas*         | Proteobacteria           | Unidentified          | DOI (21 mm)                | *E. hafniae*  | [77]                           |                   |                                   |
| **Haliclona sp.**        | Cagarras Archipelago, Brazil (4-20 m) | *Pseudomonas*         | Proteobacteria           | Unidentified          | DOI (23 mm)                | *E. hafniae*  | [77]                           |                   |                                   |
| **Petromica citrina**    | Cagarras Archipelago, Brazil (4-20 m) | *Bacillus*            | Firmicutes               | Unidentified          | DOI (18 mm)                | *E. hafniae*  | [77]                           |                   |                                   |
| **Axinella dissimilis**  | Gurraig Sound, Kilieran Bay, Ireland (15 m) | *Pseudovibrio*        | Proteobacteria           | Unidentified          | ND                         | *Enterobacter aerogenes* | [78]          |                                   |
| Organism | Source | Isolated Bacteria | Isolated Compounds | MIC (µg/mL) | Reference |
|----------|--------|-------------------|-------------------|-------------|-----------|
| Xestospongia testudinaria | Weizhou coral reef, China (ND) | Aspergillus sp. | (−)-Sydonic acid | 1.33 | [48] |
|  |  |  | (Z)-5-(Hydroxymethyl)-2-[(6S)-methylhept-2-en-2-yl]phenol | 2.33 |  |
|  |  |  | Aspergiterpenoid A | 4.72 |  |
|  |  |  | (−)-Sydonol | 5.04 |  |
| Halocordia japonica | Iriomote island, Japan (ND) | Bacillus cereus QNO3323 | Thiopeptide YM-266183 | >100 | [40,41] |
|  |  |  | Thiopeptide YM-266184 | >100 |  |
| Unidentified sponge | Vizhijam coast (10–12 m) | Aspergillus clavatus MFD15 | 1H-1,2,4-Triazole-3-carboxaldehyde-5-methyl | 2-Pyrrolidone |  |
|  |  |  | 800 |  |
| Spongia officinalis | Southeast Coast India (10–15 m) | Streptomyces sp. MAPS15 | E. coli PC1 | 400 | [63] |
| Dysidea herbasca | Koror, Republic Palau (1 m) | Oscillatoria spongialis | E. coli | 2-(2′,4′-Dibromophenyl)-4,6-dibromophenol |  |
|  |  |  | E. coli | ND |  |
| Hryptios altum | Aragusuku island, Japan (ND) | Vibrio sp | Trisandoline | DOI (16 mm) |  |
|  |  |  | Prodigiosin | DOI (≤9 mm) |  |
| Xestospongia testudinaria | Bidong Island, Malaysia (ND) | Serratia marcescens IBRL USM 84 | E. coli | 2-Pyrrolidone |  |
|  |  |  | E. coli | 400 |  |
| Unidentified | South China Sea (10 m) | Nocardopsis sp. 13-33-15 and 13-12-13 | E. coli SJ42 | 1,6-Dihydroxyphenazin |  |
|  |  |  | E. coli SJ42 | DOI (8 ± 0.4 mm) |  |
| Aplysina aerophoba | Banyuls-sur-Mer, France (5–15 m) | Bacillus subtilis A184 | E. coli | Surfactin |  |
|  |  |  | E. coli | Iturin Fengycin |  |
|  |  |  | E. coli | ND |  |
| Aplysina aerophoba | Banyuls-sur-Mer, France (5–15 m) | Bacillus subtilis A190 | E. coli | Surfactin |  |
|  |  |  | E. coli | ND |  |
| Niphates olemda | Bali Bata National Park, Indonesia (ND) | Curvularia lunata | E. coli HBI-101 | 1,3,8-Trithydroxy-6-methoxyantraquinone (lanatin) |  |
|  |  |  | E. coli HBI-101 | DOI (11 mm) |  |
| Niphates olemda | Bali Bata National Park, Indonesia (ND) | Curvularia lunata | E. coli | Bisanthraquinone cytoskyrin A |  |
|  |  |  | E. coli | DOI (11 mm) |  |
| Niphates olemda | Bali Bata National Park, Indonesia (ND) | Curvularia lunata | E. coli HBI-101 | 1,3,8-Trithydroxy-6-methoxyantraquinone (lanatin) |  |
|  |  |  | E. coli HBI-101 | DOI (10.5 mm) |  |
| Niphates olemda | Bali Bata National Park, Indonesia (ND) | Curvularia lunata | E. coli HBI-101 | Bisanthraquinone cytoskyrin A |  |
|  |  |  | E. coli HBI-101 | DOI (9 mm) |  |
| Polymastia boletiformis, Axinella dissimilis and Haliclonia simulans | Gurraig Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. W64, W69, W89, W74 | E. coli | Tropolodithiacid |  |
|  |  |  | E. coli | DOI (> 2 mm) |  |
### Table 2. Cont.

| Polymastia boletiformis, Axinella dissimilis and Haliclona simulans | Polynemus sp. | Proteobacteria | Unidentified | DOI (2–2 mm) | E. coli |
|---|---|---|---|---|---|
| Gurraig Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. JIC5, JIC6, JIC17, W62, W65, W71, W99, WC43, W85, W78, W94, W96, WME1, WM33, WM34, WM48, WC13, WC21, WC22, WC30, WC32, WC41, HC6, HMMA3 | Proteobacteria | Unidentified | DOI (>2 mm) | E. coli |

| Dendrilla nigra | Southwest Coast of India | Nocardiopsis dassonvillei MAD08 | Actinobacteria | Unidentified | MIC (300 µg/mL) | E. coli PC1 |
|---|---|---|---|---|---|---|
| Axinella dissimilis | Gurraig Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. Ad30 | Proteobacteria | Unidentified | DOI (1-3 mm) | E. coli |

| Hydmaniacodon perleve | Nandi Island, China (ND) | Pseudomonas sp. NJ6-3-1 | Proteobacteria | Unidentified | DOI (15 mm) | E. coli |

| Callip sponsa | Kovalam Coast, India (5-10 m) | Aspergillus flavus GL815344 | Ascomycota | Unidentified | DOI (42 mm) | E. coli |

| Haliclona sp. | Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas fluorescens H40 | Proteobacteria | Unidentified | DOI (22 mm) | E. coli |

| Haliclona sp. | Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas fluorescens H41 | Proteobacteria | Unidentified | DOI (25 mm) | E. coli |

| Haliclona sp. | Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas aeruginosa H51 | Proteobacteria | Unidentified | DOI (18 mm) | E. coli |

| Batrmecia citrina | Cagarras Archipelago, Brazil (4-20 m) | Bacillus pumilus P31 | Proteobacteria | Unidentified | DOI (16 mm) | E. coli |

| Micromonospora | Cagarras Archipelago, Brazil (4-20 m) | Micromonospora CPI 12 | Actinobacteria | Unidentified | DOI (7.5 mm) | E. coli |

| Axinella dissimilis | Gurraig Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. Ad30 | Proteobacteria | Unidentified | DOI (10-15 mm) | E. coli |

| Callip sponsa | Bay of Bengal, India (10-15 m) | Micromonospora sp. CPI 12 | Actinobacteria | Unidentified | DOI (26 mm) | E. coli |

| Sigmadocia fibulatus | Hare Island, India (5-10 m) | Bacillus sp. SC3 | Firmicutes | Unidentified | DOI (2-2 mm) | E. coli |
### Table 2. Cont.

| Organism                        | Location                                                   | Isolate(s) | Phylum                        | Unidentified (DOI) | Reference |
|---------------------------------|------------------------------------------------------------|------------|-------------------------------|--------------------|-----------|
| *Aplysina aerophoba* and *Aplysina cavernicola* | Marseille and Banyuls sur Mer, France (ND) | Bacillus SB8, SB17 | Firmicutes                     | Unidentified (DOI 12–16 mm) | [84]      |
| *Aplysina aerophoba* and *Aplysina cavernicola* | Marseille and Banyuls sur Mer, France (ND) | *Enterococcus* SB91 | Proteobacteria                  | Unidentified (DOI 12–16 mm) | [84]      |
| *Aplysina aerophoba* and *Aplysina cavernicola* | Marseille and Banyuls sur Mer, France (ND) | *Arthrobacter* SB95 | Actinobacteria                  | Unidentified (DOI 12–16 mm) | [84]      |
| *Aplysina aerophoba* and *Aplysina cavernicola* | Marseille and Banyuls sur Mer, France (ND) | unidentifed low G + C Gram positive SB122 and SB144 | | Unidentified (DOI 12–16 mm) | [84]      |
| *Aplysina aerophoba* and *Aplysina cavernicola* | Marseille and Banyuls sur Mer, France (ND) | α-Proteobacteria SB6, SB55, SB63, SB89, SB156, SB197, SB202, SB207, SB214, | Proteobacteria                  | Unidentified (DOI 12–16 mm) | [84]      |
| *Halichondria panicea* | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB107 | Actinobacteria                  | ND | [44]      |
| *Halichondria panicea* | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB132 | Actinobacteria                  | ND | [44]      |
| *Halichondria panicea* | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB253 | Actinobacteria                  | ND | [44]      |
| *Halichondria panicea* | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB298 | Actinobacteria                  | ND | [44]      |
| *Amphilectus fucorum* | Lough Hyne, Ireland (8–15 m) | *Pseudovibrio* sp. 117V, 115 V and 112 V | | Unidentified (ND) | [97]      |
| *Amphilectus fucorum* | Lough Hyne, Ireland (8–15 m) | *Pseudovibrio* sp. 113V | | Unidentified (ND) | [97]      |
| *Eurypon major* | Lough Hyne, Ireland (8–15 m) | *Pseudovibrio* sp. 107L, 108L, 109L | | Unidentified (ND) | [97]      |
| *Haliclona simulans* | Gurraig Sound Kilkieran Bay, Ireland (15 m) | *Streptomyces* sp. SM2 and SM4 | | Unidentified (DOI 25 mm) | [88]      |
| *Dysidea granulosa* | Kavaratti Island, India (ND) | *Enterobacter* sp. TTAG | | Unidentified (ND) | [85]      |
| *Calyptraea diffusa* | Southwest Coast of India (6–7 m) | *Shewanella* alga VCDB KC623651 | | Unidentified (DOI 10 mm) | [99]      |
| *Haliclonia sp.* | Cagarras Archipeloago, Brazil (4–20 m) | *Pseudomonas* fluorescens H40 | Proteobacteria                  | Unidentified (DOI 20 mm) | [77]      |
| *Haliclonia sp.* | Cagarras Archipeloago, Brazil (4–20 m) | *Pseudomonas* fluorescens H41 | Proteobacteria                  | Unidentified (DOI 17 mm) | [77]      |
| *Haliclonia sp.* | Cagarras Archipeloago, Brazil (4–20 m) | *Pseudomonas* aeruginosa H51 | Proteobacteria                  | Unidentified (DOI 20 mm) | [77]      |
| *Petromica citrina* | Cagarras Archipeloago, Brazil (4–20 m) | *Bacillus* pumilus P33 | Firmicutes                     | Unidentified (DOI 35 mm) | [77]      |
| Species                     | Location                          | Bacteria                          | Genus                        | Species | Taxonomy | Growth Zone | MIC/IC50 | Reference |
|----------------------------|-----------------------------------|-----------------------------------|------------------------------|---------|----------|-------------|----------|-----------|
| *Petromica citrina*        | Cagarras Archipelago, Brazil (4–20 m) | *Bacillus pumilus* PC32          | Firmicutes                   | Unidentified | DOI (39 mm) | E. coli 54AE | [77]     |           |
| *Clathrina aura*           | Cagarras Archipelago, Brazil (4–20 m) | *Pseudovibrio ascidiaceicola* Ca31 | Proteobacteria               | Unidentified | DOI (15 mm) | E. coli 54AE | [77]     |           |
| *Paraleucilla magna*       | Cagarras Archipelago, Brazil (4–20 m) | *Pseudovibrio ascidiaceicola* Pm31 | Proteobacteria               | Unidentified | DOI (21 mm) | E. coli 54AE | [77]     |           |
| *Mycale microsagittosa*    | Cagarras Archipelago, Brazil (4–20 m) | *Pseudovibrio denitrificans* Mm37 | Proteobacteria               | Unidentified | DOI (25 mm) | E. coli 54AE | [77]     |           |
| *Petrelasma ficoformis*    | Panaggy, Ligurian Sea, Italy (8 m)  | *Pseudoalteromonas* sp. F6         | Proteobacteria               | Unidentified | ND       | *Escherichia faecalis* | [86]     |           |
| *Halichondria panicea*     | Kiel Fjord, Baltic Sea, Germany (ND) | *Streptomyces* sp. HB202          | Actinobacteria               | *Mayamycin* | IC50 (1.16 µg/mL) | *Klebsiella pneumonia* | [45]     |           |
| *Spongia officinalis*      | Southeast Coast, India (10–15 m)   | *Streptomyces* sp. MAPS15         | Actinobacteria               | 2-Pyrrolidone | MIC (700 µg/mL) | *K. pneumonia PC7* | [63]     |           |
| *Haliclona sp.*            | Cagarras Archipelago, Brazil (4–20 m) | *Pseudomonas fluorescens* H40     | Proteobacteria               | Unidentified | DOI (25 mm) | *K. pneumonia* | [77]     |           |
| *Haliclona sp.*            | Cagarras Archipelago, Brazil (4–20 m) | *Pseudomonas fluorescens* H41     | Proteobacteria               | Unidentified | DOI (24 mm) | *K. pneumonia* | [77]     |           |
| *Dendrilla nigra*          | Southeast coast of India (ND)      | *Streptomyces* sp. BTL7           | Actinobacteria               | Unidentified | DOI (<10 mm) | *K. pneumonia* | [80]     |           |
| *Calypsochonia diffusa*    | Bay of Bengal, India (10–15 m)     | *Streptomyces* sp. CPI 13         | Actinobacteria               | Unidentified | DOI (9.2 mm) | *K. pneumonia* | [92]     |           |
| *Calypsochonia diffusa*    | Bay of Bengal, India (10–15 m)     | *Saccharomonospora* sp. CPI 3     | Actinobacteria               | Unidentified | DOI (6.3 mm) | *K. pneumonia* | [92]     |           |
| *Dipsida granulosa*        | Cagarras Archipelago, Brazil (4–20 m) | *Entrobacter* sp. TTAG             | Proteobacteria               | Unidentified | DOI (22 mm) | *K. pneumonia* | [85]     |           |
| *Haliclona sp.*            | Cagarras Archipelago, Brazil (4–20 m) | *Pseudomonas fluorescens* H40     | Proteobacteria               | Unidentified | DOI (18 mm) | *K. pneumonia 52 AE* | [77]     |           |
| *Haliclona sp.*            | Cagarras Archipelago, Brazil (4–20 m) | *Pseudomonas fluorescens* H41     | Proteobacteria               | Unidentified | DOI (15 mm) | *K. pneumonia 52 AE* | [77]     |           |
| *Haliclona sp.*            | Cagarras Archipelago, Brazil (4–20 m) | *Pseudomonas aeruginosa* H51      | Proteobacteria               | Unidentified | DOI (21 mm) | *K. pneumonia 52 AE* | [77]     |           |
| *Haliclona sp.*            | Cagarras Archipelago, Brazil (4–20 m) | *Pseudomonas fluorescens* H40     | Proteobacteria               | Unidentified | DOI (16 mm) | *K. pneumonia 19AE* (susceptible to amp, atm, caz, cpd, fox) | [77]     |           |
| *Haliclona sp.*            | Cagarras Archipelago, Brazil (4–20 m) | *Pseudomonas fluorescens* H41     | Proteobacteria               | Unidentified | DOI (20 mm) | *K. pneumonia 19AE* | [77]     |           |
| *Haliclona sp.*            | Cagarras Archipelago, Brazil (4–20 m) | *Pseudomonas aeruginosa* H51      | Proteobacteria               | Unidentified | DOI (32 mm) | *K. pneumonia 19AE* | [77]     |           |
| *Haliclona sp.*            | Cagarras Archipelago, Brazil (4–20 m) | *Pseudomonas fluorescens* H40     | Proteobacteria               | Unidentified | DOI (20 mm) | *Neisseria gonorrhoeae* | [77]     |           |
Table 2. Cont.

| Haliclona sp. | Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas fluorescens H41 | Proteobacteria | Unidentified | DOI (27 mm) | N. gonorrhoeae [77] |
|--------------|--------------------------------------|----------------------------|----------------|--------------|-------------|---------------------|
| Haliclona sp. | Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas aeruginosa H51 | Proteobacteria | Unidentified | DOI (52 mm) | N. gonorrhoeae [77] |
| Petromica citrina | Cagarras Archipelago, Brazil (4-20 m) | Bacillus pumilus Pc31 | Firmicutes | Unidentified | DOI (28 mm) | N. gonorrhoeae [77] |
| Petromica citrina | Cagarras Archipelago, Brazil (4-20 m) | Bacillus pumilus Pc32 | Firmicutes | Unidentified | DOI (29 mm) | N. gonorrhoeae [77] |
| Haliclona sp. | Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas fluorescens H40 | Proteobacteria | Unidentified | DOI (24 mm) | N. gonorrhoeae 4277 (susceptible to pen) [77] |
| Haliclona sp. | Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas fluorescens H41 | Proteobacteria | Unidentified | DOI (24 mm) | N. gonorrhoeae 4277 [77] |
| Haliclona sp. | Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas aeruginosa H51 | Proteobacteria | Unidentified | DOI (32 mm) | N. gonorrhoeae 4277 [77] |
| Petromica citrina | Cagarras Archipelago, Brazil (4-20 m) | Bacillus pumilus Pc31 | Firmicutes | Unidentified | DOI (32 mm) | N. gonorrhoeae 4277 [77] |
| Petromica citrina | Cagarras Archipelago, Brazil (4-20 m) | Bacillus pumilus Pc32 | Firmicutes | Unidentified | DOI (32 mm) | N. gonorrhoeae 4277 [77] |
| Haliclona sp. | Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas fluorescens H40 | Proteobacteria | Unidentified | DOI (24 mm) | N. gonorrhoeae 4957 (susceptible to cip) [77] |
| Haliclona sp. | Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas fluorescens H41 | Proteobacteria | Unidentified | DOI (29 mm) | N. gonorrhoeae 4957 [77] |
| Haliclona sp. | Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas aeruginosa H51 | Proteobacteria | Unidentified | DOI (36 mm) | N. gonorrhoeae 4957 [77] |
| Petromica citrina | Cagarras Archipelago, Brazil (4-20 m) | Bacillus pumilus Pc31 | Firmicutes | Unidentified | DOI (23 mm) | N. gonorrhoeae 4957 [77] |
| Petromica citrina | Cagarras Archipelago, Brazil (4-20 m) | Bacillus pumilus Pc32 | Firmicutes | Unidentified | DOI (23 mm) | N. gonorrhoeae 4957 [77] |
| Haliclona sp. | Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas fluorescens H40 | Proteobacteria | Unidentified | DOI (20 mm) | N. gonorrhoeae 5728 (cip, pen, het) [77] |
| Haliclona sp. | Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas fluorescens H41 | Proteobacteria | Unidentified | DOI (19 mm) | N. gonorrhoeae 5728 [77] |
| Haliclona sp. | Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas aeruginosa H51 | Proteobacteria | Unidentified | DOI (46 mm) | N. gonorrhoeae 5728 [77] |
| Petromica citrina | Cagarras Archipelago, Brazil (4-20 m) | Bacillus pumilus Pc31 | Firmicutes | Unidentified | DOI (29 mm) | N. gonorrhoeae 5728 [77] |
| Petromica citrina | Cagarras Archipelago, Brazil (4-20 m) | Bacillus pumilus Pc32 | Firmicutes | Unidentified | DOI (32 mm) | N. gonorrhoeae 5728 [77] |
| Haliclona sp. | Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas fluorescens H40 | Proteobacteria | Unidentified | DOI (18 mm) | N. gonorrhoeae 5729 (susceptible to azm, pen, het) [77] |
Table 2. Cont.

| Organism                             | Location                        | Bacteria                          | Group     | DOI (mm)         | Organism                          |
|--------------------------------------|---------------------------------|-----------------------------------|-----------|-----------------|-----------------------------------|
| Haliclona sp. Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas fluorescens H41 | Proteobacteria | Unidentified | DOI (16 mm) | N. gonorrhoeae 5729 [77] |
| Haliclona sp. Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas aeruginosa H51 | Proteobacteria | Unidentified | DOI (35 mm) | N. gonorrhoeae 5729 [77] |
| Petromica cirrina Cagarras Archipelago, Brazil (4–20 m) | Bacillus pumilus Pc31 | Firmicutes | Unidentified | DOI (25 mm) | N. gonorrhoeae 5729 [77] |
| Petromica cirrina Cagarras Archipelago, Brazil (4–20 m) | Bacillus pumilus Pc32 | Firmicutes | Unidentified | DOI (32 mm) | N. gonorrhoeae 5729 [77] |
| Haliclona sp. Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas fluorescens H40 | Proteobacteria | Unidentified | DOI (20 mm) | N. gonorrhoeae 6002 (susceptible to tet) [77] |
| Haliclona sp. Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas fluorescens H41 | Proteobacteria | Unidentified | DOI (26 mm) | N. gonorrhoeae 6002 [77] |
| Petromica cirrina Cagarras Archipelago, Brazil (4–20 m) | Bacillus pumilus H51 | Proteobacteria | Unidentified | DOI (28 mm) | N. gonorrhoeae 6002 [77] |
| Petromica cirrina Cagarras Archipelago, Brazil (4–20 m) | Bacillus pumilus Pc32 | Firmicutes | Unidentified | DOI (28 mm) | N. gonorrhoeae 6002 [77] |
| Haliclamaocculata Gulf of Mannar, India (ND) | Bacillus licheniformis T6-1 | Firmicutes | Fluorophore compound | DOI (6 mm) at 50 µM | Salmonella typhi [87] |
| Dysidea granulosa | Kavaratti Island, India (ND) | Enterobacter sp. TTAG | Proteobacteria | Unidentified | DOI (19 mm) | S. typhi [85] |
| Callipogonia diffusa | Southeast Coast of India (6-7 m) | Shewanella alga VCD8 KC62851 | Proteobacteria | Unidentified | DOI (11 mm) | S. typhi [99] |
| Dendrilla nigra | Southeast coast of India (ND) | Streptomycetes sp. BTL7 | Actinobacteria | Unidentified | DOI (16 mm) | S. typhi [85] |
| Axinella dissimilis | Garraig Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. W64, W69, W89, W74 | Proteobacteria | Unidentified | ND | Salmonella typhimurium [78] |
| Polymastia boletiformis, Axinella dissimilis and Haliclona simulans | Garraig Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. W64, W69, W89, W74 | Proteobacteria | Unidentified | ND | Salmonella typhimurium [72] |
| Polymastia boletiformis, Axinella dissimilis and Haliclona simulans | Garraig Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. HC5, W63, W65, W71, W99, W96, WM40, WC32, WC41, HC6 | Proteobacteria | Unidentified | DOI (≥2 mm) | S. typhimurium [72] |
| Polymastia boletiformis, Axinella dissimilis and Haliclona simulans | Garraig Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. W10, W62, WC43, W85, W78, W94, WM31, WM34, WC33, WC21, WC30 | Proteobacteria | Unidentified | DOI (≥1 mm) | S. typhimurium [72] |
| Haliclama sp. | Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas fluorescens H40 | Proteobacteria | Unidentified | DOI (21 mm) | Salmonella enterica [77] |
| Haliclama sp. | Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas fluorescens H41 | Proteobacteria | Unidentified | DOI (17 mm) | S. enterica [77] |
| Haliclama sp. | Cagarras Archipelago, Brazil (4–20 m) | Pseudomonas aeruginosa H51 | Proteobacteria | Unidentified | DOI (25 mm) | S. enterica [77] |
Table 2. Cont.

| Species                        | Location                                    | Isolated Bacteria                                      | Source/Target    | MIC or IC50 Value       | Reference |
|--------------------------------|---------------------------------------------|--------------------------------------------------------|------------------|-------------------------|-----------|
| **Clathrina aurea**            | Cagarras Archipelago, Brazil (4-20 m)       | Pseudovibrio ascidiaceicola Ca31                        | Proteobacteria   | Unidentified            | [77]      |
| **Paraleucilla magna**         | Cagarras Archipelago, Brazil (4-20 m)       | Pseudovibrio ascidiaceicola Pm31                       | Proteobacteria   | Unidentified            | [77]      |
| **Mycale microsigmatosa**      | Cagarras Archipelago, Brazil (4-20 m)       | Pseudovibrio denitrificans Mm37                        | Proteobacteria   | Unidentified            | [77]      |
| **Halichondria panicea**       | Kiel Fjord, Baltic Sea, Germany (ND)        | Streptomyces sp. HB202                                  | Actinobacteria   | Mayamycin IC50 (1.16 µg/mL) | [45]      |
| **Halichondria sp.**           | Cagarras Archipelago, Brazil (4-20 m)       | Pseudomonas fluorescens H40, H41 and Pseudomonas aeruginosa H51 | Proteobacteria   | Diketopiperazine cyclo-(L-Leu-L-Pro) MIC (512 µg/mL) | [62]      |
| **Halichondria sp.**           | West Coast of India (10 m)                  | Bacillus licheniformis Sab1                             | Firmicutes       | Indole DOI (4-6 mm)     | [69]      |
| **Halichondria sp.**           | West Coast of India (10 m)                  | Bacillus licheniformis Sab1                             | Firmicutes       | 3-Phenylpyrroline DOI (4-6 mm) | [69]      |
| **Halichondria sp.**           | Cagarras Archipelago, Brazil (4-20 m)       | Pseudomonas fluorescens H40                             | Proteobacteria   | Unidentified            | [77]      |
| **Petrovima citrina**          | Cagarras Archipelago, Brazil (4-20 m)       | Bacillus pumilus Pc31                                   | Firmicutes       | Unidentified            | [77]      |
| **Petrovima citrina**          | Cagarras Archipelago, Brazil (4-20 m)       | Bacillus pumilus Pc32                                   | Firmicutes       | Unidentified            | [77]      |
| **Halichondria sp.**           | Cagarras Archipelago, Brazil (4-20 m)       | Pseudomonas aeruginosa H51                              | Proteobacteria   | Unidentified            | [77]      |
| **Clathrina aurea**            | Cagarras Archipelago, Brazil (4-20 m)       | Pseudovibrio ascidiaceicola Ca31                        | Proteobacteria   | Unidentified            | [77]      |
| **Paraleucilla magna**         | Cagarras Archipelago, Brazil (4-20 m)       | Pseudovibrio ascidiaceicola Pm31                       | Proteobacteria   | Unidentified            | [77]      |
| **Mycale microsigmatosa**      | Cagarras Archipelago, Brazil (4-20 m)       | Pseudovibrio denitrificans Mm37                        | Proteobacteria   | Unidentified            | [77]      |
| **Axinella dissimilis**        | Gurraig Sound, Kilkieran Bay, Ireland (15 m)| Pseudovibrio Ad30                                      | Proteobacteria   | ND                      | [78]      |
| **Dendrilla nigra**            | Southeast coast of India (ND)               | Streptomyces sp. BTL7                                  | Actinobacteria   | Unidentified            | [80]      |
| **Callyspongia diffusa**       | Bay of Bengal, India (10-15 m)              | Streptomyces sp. CPI 13                                 | Actinobacteria   | Unidentified            | [92]      |
| **Callyspongia diffusa**       | Bay of Bengal, India (10-15 m)              | Micromonospora sp. CPI 12                              | Actinobacteria   | Unidentified            | [92]      |
| **Callyspongia diffusa**       | Bay of Bengal, India (10-15 m)              | Saccharomonospora sp. CPI 9                            | Actinobacteria   | Unidentified            | [92]      |
| **Callyspongia diffusa**       | Bay of Bengal, India (10-15 m)              | Saccharomonospora sp. CPI 3                            | Actinobacteria   | Unidentified            | [92]      |
### Table 2. Cont.

| Species                  | Location                                      | Bioactive Compound                                  | MIC (μg/mL)            | Source                          |
|--------------------------|-----------------------------------------------|------------------------------------------------------|------------------------|---------------------------------|
| *Haliclona sp.*          | Cagarras Archipelago, Brazil (4–20 m)         | *Pseudomonas aeruginosa* H51                         | Unidentified           | DOI (32 mm)                     | *P. aeruginosa* 3AE (susceptible to atm, tsp) [77] |
| *Haliclona sp.*          | Cagarras Archipelago, Brazil (4–20 m)         | *Pseudomonas aeruginosa* H40                         | Unidentified           | DOI (20 mm)                     | *P. aeruginosa* 3AE [77] |
| *Clathria aurea*         | Cagarras Archipelago, Brazil (4–20 m)         | *Pseudovibrio ascidiaceicola* Ca31                   | Unidentified           | DOI (14 mm)                     | *P. aeruginosa* 3AE [77] |
| *Paraleucilla magna*     | Cagarras Archipelago, Brazil (4–20 m)         | *Pseudovibrio ascidiaceicola* Ps13                   | Unidentified           | DOI (12 mm)                     | *P. aeruginosa* 3AE [77] |
| *Mycale microsigmata*    | Cagarras Archipelago, Brazil (4–20 m)         | *Pseudovibrio denitrificans* Mm37                   | Unidentified           | DOI (15 mm)                     | *P. aeruginosa* 3AE [77] |
| *Halichondria panicea*   | Kiel Fjord, Baltic Sea, Germany (ND)          | *Streptomyces* sp. HB107                             | Actinobacteria         | Unidentified                    | *P. fluorescens* [44] |
| *Halichondria panicea*   | Kiel Fjord, Baltic Sea, Germany (ND)          | *Streptomyces* sp. HB202                             | Actinobacteria         | Unidentified                    | *P. fluorescens* [44] |
| *Halichondria panicea*   | Kiel Fjord, Baltic Sea, Germany (ND)          | *Streptomyces* sp. HB107                             | Unidentified           | ND                              | *P. fluorescens* [44] |
| *Halichondria panicea*   | Kiel Fjord, Baltic Sea, Germany (ND)          | *Streptomyces* sp. HB138                             | Unidentified           | ND                              | *P. fluorescens* [44] |
| *Halichondria panicea*   | Kiel Fjord, Baltic Sea, Germany (ND)          | *Streptomyces* sp. HB272                             | Unidentified           | ND                              | *P. fluorescens* [44] |
| *Halichondria panicea*   | Kiel Fjord, Baltic Sea, Germany (ND)          | *Streptomyces* sp. HB289                             | Unidentified           | ND                              | *P. fluorescens* [44] |
| *Callyspongia sp.*       | Kyung-Po beach, Korea (12 m)                  | *Breithiobacterium* sp. KMD 003                      | Actinobacteria         | 6-Hydroxymethyl-1-phenazine-carboxamide | *Micrococcus luteus* [94] |
| *Isodictya setifera*     | Ross Island, Antarctica (30–40 m)             | *Pseudomonas aeruginosa*                             | Proteobacteria         | Phenazine-1-carboxylic acid and phenazine-1-carboxamide | *M. luteus* [55] |
| *Dendrilla nigra*        | Southeast coast of India (ND)                 | *Streptomyces* sp. BTL7                             | Actinobacteria         | Unidentified                    | *M. luteus* [80] |
| *Callyspongia diffusa*   | Bay of Bengal, India (10–15 m)                | *Saccharomonospora* sp. CPI 9                       | Actinobacteria         | 1,6-Dihydroxyphenazine         | *M. luteus* [92] |
| *Callyspongia diffusa*   | Bay of Bengal, India (10–15 m)                | *Saccharomonospora* sp. CPI 3                       | Unidentified           | DOI (6.6 mm)                    | *M. luteus* [92] |
| *Xestospongia testudinaria* | South China Sea (10 m)          | *Nocardopsis* sp. 13-33-15 and 13-12-13             | Actinobacteria         | 1,6-Dihydroxyphenazine         | *M. luteus* [87] |
| *Xestospongia testudinaria* | South China Sea (10 m)          | *Nocardopsis* sp. 13-33-15 and 13-12-13             | Actinobacteria         | 1,6-Dimethoxyphenazine         | *M. luteus* [87] |
| *Xestospongia testudinaria* | Weizhou coral reef, China (ND)             | *Aspergillus* sp.                                    | Ascomycota             | (−)-Sydonic acid                | *Micrococcus tetragenus* [48] |
Table 2. Cont.

| Organism                        | Location                                      | Isolate                                | Microorganism          | Genus                        | IC50 (µg/mL) |
|---------------------------------|-----------------------------------------------|----------------------------------------|------------------------|------------------------------|--------------|
| *Xestospongia testudinaria*     | Weizhou coral reef, China (ND)                | Aspergillus sp.                        | Ascomycota             | (Z)-5-(Hydroxymethyl)-2-(6'-methylhept-2'-en-2'-yl)phenol | M. tetragenus | [48] |
| *Xestospongia testudinaria*     | Weizhou coral reef, China (ND)                | Aspergillus sp.                        | Ascomycota             | Aspergiterpenoid A           | M. tetragenus | [48] |
| *Xestospongia testudinaria*     | Weizhou coral reef, China (ND)                | Aspergillus sp.                        | Ascomycota             | (–)-Sydonol                  | M. tetragenus | [48] |
| *Xestospongia testudinaria*     | Bidong Island, Malaysia (ND)                  | Serratia marcescens IBRL USM 84       | Proteobacteria         | Prodigiosin                  | Micrococcus sp. | [66] |
| *Petrosia ficiformis*           | Paraggi, Ligurian Sea, Italy (8 m)            | Rhodococcus sp. E1                    | Actinobacteria         | Unidentified                | ND           | Micrococcus sp. | [86] |
| *Halichondria panicea*          | Kiel Fjord, Baltic Sea, Germany (ND)         | Streptomyces sp. HB202                | Actinobacteria         | Mayamycin                    | Brevibacterium epidermidis | [45] |
| *Halichondria panicea*          | Kiel Fjord, Baltic Sea, Germany (ND)         | Streptomyces sp. HB202                | Actinobacteria         | Mayamycin                    | Dermabacter hominis | [45] |
| *Halichondria panicea*          | Kiel Fjord, Baltic Sea, Germany (ND)         | Streptomyces sp. HB202                | Actinobacteria         | Mayamycin                    | Propionibacterium acnes | [45] |
| *Halichondria panicea*          | Kiel Fjord, Baltic Sea, Germany (ND)         | Streptomyces sp. HB202                | Actinobacteria         | Mayamycin                    | Xanthomonas campestris | [45] |
| *Dysidea tupha*                 | Rovinj, Croatia (ND)                         | Streptomyces sp. RV15                 | Actinobacteria         | Naphthaene glycoside SF2446A2 | Chlamydia trachomatis | [46] |
| unidentified                    | ND                                            | Trichoderma sp. 05F48                 | Ascomycota             | Trichodermin A               | M. smegmatis | [49] |
| unidentified                    | ND                                            | Trichoderma sp. 05F48                 | Ascomycota             | Trichodermin A               | M. smegmatis | [49] |
| unidentified                    | ND                                            | Trichoderma sp. 05F48                 | Ascomycota             | Trichodermin A               | M. smegmatis | [49] |
| unidentified                    | ND                                            | Trichoderma sp. 05F48                 | Ascomycota             | Trichodermin A               | M. bovis BCG  | [49] |
| unidentified                    | ND                                            | Trichoderma sp. 05F48                 | Ascomycota             | Trichodermin A               | M. tuberculosis H37rv | [49] |
| unidentified                    | ND                                            | Trichoderma sp. 05F48                 | Ascomycota             | Trichodermin A               | M. tuberculosis H37rv | [49] |
| unidentified                    | ND                                            | Trichoderma sp. 05F48                 | Ascomycota             | Trichodermin A               | M. tuberculosis H37rv | [49] |
| *Xestospongia testudinaria*     | Weizhou coral reef, China (ND)                | Aspergillus sp.                        | Ascomycota             | (–)-Sydonic acid             | V. parahaemolyticus | [48] |
| *Asbestopluma hypogea*          | La Ciotat, France (17 m)                      | Streptomyces sp. SICA                 | Actinobacteria         | Unidentified                | ND           | V. parahaemolyticus | [100] |
| *Mycale sp.*                    | Gulei Port, Fujian, China (ND)                | Bacillus sp. HNS010                   | Firmicutes             | Unidentified                | DOI (8–10 mm) | V. parahaemolyticus | [81] |
| Table 2. Cont. |
|----------------|
| **Mycale sp.** | Gulei Port, Fujian, China (ND) | Coilotha sp. HNS023; Noctiluopsis HNS055; HNS058 | Actinobacteria | Unidentified | DOI (8-10 mm) | V. parahaemolyticus [81] |
| **Mycale sp.** | Gulei Port, Fujian, China (ND) | Streptomyces sp. HNS054 | Actinobacteria | Unidentified | DOI (10-15 mm) | V. parahaemolyticus [81] |
| **Phorbas tenacior** | Mediterranean Sea, Marseille, France (15 m) | Citricoccus sp. P1S7 | Actinobacteria | Unidentified | DOI (3-6 mm) | V. parahaemolyticus [101] |
| **Phorbas tenacior** | Mediterranean Sea, Marseille, France (15 m) | Pseudovibrio sp. P1Ma4 and Vibrio sp. P1MaNa1 | Proteobacteria | Unidentified | DOI (2-3 mm) | V. parahaemolyticus [101] |
| **Xestospongia testudinaria** | Weizhou coral reef, China (ND) | Aspergillus sp. | Ascomycota | SD-3 (1.33 µg/mL) | V. parahaemolyticus [101] |
| **Haliclona simulans** | Guillaum Sound, Kilkieran Bay, Ireland (15 m) | Bacillus subtilis MMA7 | Firmicutes | Subtilomycin | ND | V. anguillarum [71] |
| **Polymastia boletiformis, Axinella dissimilis and Haliclona simulans** | Guillaum Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. W64, | Proteobacteria | Tropodithietic acid | DOI (3-4 mm) | V. anguillarum [72] |
| **Polymastia boletiformis, Axinella dissimilis and Haliclona simulans** | Guillaum Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. W69, W99, | Proteobacteria | Tropodithietic acid | DOI (2-2 mm) | V. anguillarum [72] |
| **Polymastia boletiformis, Axinella dissimilis and Haliclona simulans** | Guillaum Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. W74 | Proteobacteria | Tropodithietic acid | DOI (3-2 mm) | V. anguillarum [72] |
| **Polymastia boletiformis, Axinella dissimilis and Haliclona simulans** | Guillaum Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. JC6, JC17, WM33, WC15, WC22 | Proteobacteria | Unidentified | DOI (3-1 mm) | V. anguillarum [72] |
| **Polymastia boletiformis, Axinella dissimilis and Haliclona simulans** | Guillaum Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. W62, W71, WC43, WC78, W94, W96, WM38, WC13, WC21, WC30, WC32, WC41, WMMA3 | Proteobacteria | Unidentified | DOI (3-2 mm) | V. anguillarum [72] |
| **Phorbas tenacior** | Mediterranean Sea, Marseille, France (15 m) | Citricoccus sp. P1S7 | Actinobacteria | Unidentified | DOI (3-6 mm) | V. anguillarum [101] |
| **Callyspongia diffusa** | Southwest Coast of India (6-7 m) | Streptomyces sp. VCD8 KGC623651 | Proteobacteria | Unidentified | DOI (10 mm) | V. anguillarum [99] |
| **Dendrilla nigra** | Southeast coast of India (ND) | Streptomyces sp. BTL7 | Actinobacteria | Unidentified | DOI (5 mm), MIC (176 g protein/mL) | V. anguillarum [80] |
| **Phorbas tenacior** | Mediterranean Sea, Marseille, France (15 m) | Citricoccus sp. P1S7 | Actinobacteria | Unidentified | DOI (3-6 mm) | V. anguillarum [101] |
| Species                     | Location                        | Organism(s)                               | Bacteria/Phylum                        | Metabolite                          | DOI (mm) | Reference |
|-----------------------------|---------------------------------|-------------------------------------------|----------------------------------------|-------------------------------------|----------|-----------|
| *Dysidea herbacea*          | Koror, Republic Palaua (1 m)    | *Oscillatoria spongiae*                   | Cyanobacteria                          | 2-(2',4'-Dibromophenyl)-4,6-dibromo- | ND       | [64]      |
| *Halichondria sp.*          | West Coast of India (10 m)      | *Bacillus licheniformis* SABI             | Firmicutes                             | 4,4'-Oxybis(3-phenylpropionic acid) | DOI (4-6 mm) | [69]      |
| *Mycate sp.*                | Gaeli Port, Fujian, China (ND) | *Vibrio sp.* HNS02, HNS029, Stretomyces sp. HNS049, HNS054, Nocardopsis sp. HNS055 | Proteobacteria                         | Unidentified VI (8-10 mm)          | V. harveyi | [81]      |
| *Callipogonia diffusa*      | Southwest Coast of India (6-7 m)| *Vibrio sp.* HNS02, HNS029, Stretomyces sp. HNS049, HNS054, Nocardopsis sp. HNS055 | Proteobacteria                         | Unidentified VI (14 mm)            | V. harveyi | [98]      |
| *Asbestopluma hypogea*      | La Ciota, France (17 m)         | *Streptomyces sp.* SICA                   | Actinobacteria                         | Unidentified VI (3-5 mm)            | V. sp. 2SW | [100]     |
| *Asbestopluma hypogea*      | La Ciota, France (17 m)         | *Streptomyces sp.* SICA                   | Actinobacteria                         | Unidentified VI (3-5 mm)            | V. sp. 2SW | [100]     |
| *Xestospongia testudinaria* | Bidong Island, Malaysia (ND)    | *Serratia marcescens* IBRL, USM 84       | Proteobacteria                         | Prodigiosin VI (10-14 mm)           | A. tumefaciens | [66]      |
| *Asbestopluma aerophoba*    | Banyuls-sur-Mer, France (5-15 m)| *Bacillus subtilis* A184                  | Firmicutes                             | Surfactin iturin fengycin VI (ND)   | ND       | [68]      |
| *Hymeniacidon porleve*      | Nani Island, China (ND)         | *Pseudomonas sp.* NJ6-3-1                 | Proteobacteria                         | Unidentified VI (3-5 mm)            | tumefaciens | [74]      |
| *Xestospongia testudinaria* | Bidong Island, Malaysia (ND)    | *Serratia marcescens* IBRL, USM 84       | Proteobacteria                         | Prodigiosin VI (10-14 mm)           | A. tumefaciens | [66]      |
| *Halichona sp.*             | Cagarras Archipelago, Brazil (4-20 m) | *Pseudomonas fluorescens* H40             | Proteobacteria                         | Unidentified VI (20 mm)            | humannii | [77]      |
| *Halichona sp.*             | Cagarras Archipelago, Brazil (4-20 m) | *Pseudomonas fluorescens* H40             | Proteobacteria                         | Unidentified VI (20 mm)            | humannii | [77]      |
| *Halichona sp.*             | Cagarras Archipelago, Brazil (4-20 m) | *Pseudomonas fluorescens* H40             | Proteobacteria                         | Unidentified VI (19 mm)            | Acinetobacter calcoaceticus | [77]      |
| *Halichona sp.*             | Cagarras Archipelago, Brazil (4-20 m) | *Pseudomonas fluorescens* H41             | Proteobacteria                         | Unidentified VI (18 mm)            | calcoaceticus | [77]      |
| *Halichona sp.*             | Cagarras Archipelago, Brazil (4-20 m) | *Pseudomonas aeruginosa* H51             | Proteobacteria                         | Unidentified VI (30 mm)            | calcoaceticus | [77]      |
| *Petromica citrina*         | Cagarras Archipelago, Brazil (4-20 m) | *Bacillus pumilus* Pc31                  | Firmicutes                             | Unidentified VI (35 mm)            | calcoaceticus | [77]      |
| *Petromica citrina*         | Cagarras Archipelago, Brazil (4-20 m) | *Bacillus pumilus* Pc32                  | Firmicutes                             | Unidentified VI (30 mm)            | calcoaceticus | [77]      |
| *Clathrina aurea*           | Cagarras Archipelago, Brazil (4-20 m) | *Pseudovibrio acidoviscida* Ca31          | Proteobacteria                         | Unidentified VI (18 mm)            | calcoaceticus | [77]      |
| *Paraleucilla magna*        | Cagarras Archipelago, Brazil (4-20 m) | *Pseudovibrio acidoviscida* Pm31          | Proteobacteria                         | Unidentified VI (23 mm)            | calcoaceticus | [77]      |
| *Mycate microsigmatosa*     | Cagarras Archipelago, Brazil (4-20 m) | *Pseudovibrio densitriaticus* Mm37        | Firmicutes                             | Unidentified VI (23 mm)            | calcoaceticus | [77]      |
### Table 2. Cont.

| Species                      | Location                                      | Isolate/Strain       | Taxonomy       | Metabolite          | DOI (mm) | Reference |
|------------------------------|-----------------------------------------------|----------------------|----------------|--------------------|----------|-----------|
| **Petromica citrina**        | Cagarras Archipelago, Brazil (4-20 m)         | Bacillus pumilus Pc31| Firmicutes     | Unidentified       | DOI (45 mm) | [77]      |
| **Petromica citrina**        | Cagarras Archipelago, Brazil (4-20 m)         | Bacillus pumilus Pc32| Firmicutes     | Unidentified       | DOI (45 mm) | [77]      |
| **Halichondria sp.**         | West Coast of India (10 m)                    | Bacillus licheniformis SAR1 | Firmicutes | Indole          | DOI (1-3 mm) | [69]      |
| **Halichondria sp.**         | West Coast of India (10 m)                    | Bacillus licheniformis SAR1 | Firmicutes | 3-Phenylpropionic | DOI (4-6 mm) | [69]      |
| **Xestospongia testudinaria**| Bulong Island, Malaysia (ND)                  | Serratia marcescens IBRL USM 84 | Proteobacteria | Prodigiosin       | DOI (<9 mm) | [66]      |
| **Aplysina aerophoba**       | Banyuls-sur-Mer, France (5-15 m)              | Bacillus subtilis A184 | Firmicutes   | Surfactin Iturin Fengycin | ND | Ceribacter michiganensis [68] |
| **Aplysina aerophoba**       | Banyuls-sur-Mer, France (5-15 m)              | Bacillus subtilis A190 | Firmicutes   | Surfactin        | ND | Ceribacter michiganensis [68] |
| **Aplysina aerophoba**       | Banyuls-sur-Mer, France (5-15 m)              | Bacillus subtilis A202 | Firmicutes   | Iturin           | ND | Ceribacter michiganensis [68] |
| **Aplysina aerophoba**       | Banyuls-sur-Mer, France (5-15 m)              | Bacillus subtilis A184 | Firmicutes   | Surfactin Iturin Fengycin | ND | Proteus vulgaris [68] |
| **Aplysina aerophoba**       | Banyuls-sur-Mer, France (5-15 m)              | Bacillus subtilis A202 | Firmicutes   | Iturin           | ND | Proteus vulgaris [68] |
| **Callyspongia diffusa**     | Southwest Coast of India (6-7 m)              | Sheanella algei VCD8 KC628631 | Proteobacteria | Unidentified | DOI (10 mm) | Proteus vulgaris [99] |
| **Callyspongia diffusa**     | Bay of Bengal, India (10-15 m)                | Micromonospora sp. CPI 12 | Actinobacteria | Unidentified | DOI (8 mm) | Proteus mirabilis [92] |
| **Callyspongia diffusa**     | Bay of Bengal, India (10-15 m)                | Saccharomonospora sp. CPI 9 | Actinobacteria | Unidentified | DOI (6 mm) | Proteus mirabilis [92] |
| **Dysidea aurata**           | Mediterranean sea (ND)                        | Actinomycetes sp. EG49 | Actinobacteria | 1,6-Dihydroxyphenazine (result of co-culture) | DOI (15 mm) | Actinomycetes sp. EG49 [98] |
| **Spheciospongia vagabunda** | Red Sea (ND)                                  | Nocardia sp. RV163 | Actinobacteria |                 |           |           |
| **Halichondria simulans**    | Gurraig Sound Kilkieran Bay, Ireland (15 m)   | Bacillus subtilis MMA7 | Firmicutes   | Subtilomycin       | ND | Listeria monocytogenes [71] |
| **Axinella dissimilis**      | Gurraig Sound, Kilkieran Bay, Ireland (15 m)  | Pseudovibrio Ad30 | Proteobacteria | Unidentified       | ND | Listeria monocytogenes [71] |
| **Halichondria simulans**    | Gurraig Sound Kilkieran Bay, Ireland (15 m)   | Streptomyces sp. SM2 and SM4 | Actinobacteria | Unidentified       | ND | Listeria monocytogenes [88] |
| **Halichondria simulans**    | Gurraig Sound Kilkieran Bay, Ireland (15 m)   | Bacillus subtilis MMA7 | Firmicutes   | Subtilomycin       | ND | Listeria innocua [71] |
| **Halichondria simulans**    | Gurraig Sound Kilkieran Bay, Ireland (15 m)   | Bacillus subtilis MMA7 | Firmicutes   | Subtilomycin       | ND | Clostridium spongens [71] |
### Table 2. Cont.

| **Axinella dissimilis** | **Gurraig Sound, Kilkieran Bay, Ireland (15 m)** | **Pseudovibrio Ad30** | **Proteobacteria** | **Unidentified** | **ND** | **Clostridium perfringens** | [78] |
|-------------------------|-----------------------------------------------|-----------------------|--------------------|-----------------|-------|-----------------------------|-----|

| **Axinella dissimilis** | **Gurraig Sound, Kilkieran Bay, Ireland (15 m)** | **Pseudovibrio Ad30** | **Proteobacteria** | **Unidentified** | **ND** | **Clostridium difficile** | [78] |

| **Dendrilla nigra** | **Southeast coast of India (15 m)** | **Streptomyces sp. BTL7** | **Actinobacteria** | **Unidentified** | **DOI (10 mm)** | **Clostridium botulinum** | [88] |

| **Haliclona simulans** | **Gurraig Sound, Kilkieran Bay, Ireland (15 m)** | **Streptomyces sp. SM2 and SM4** | **Actinobacteria** | **Unidentified** | **ND** | **Clostridium difficile** | [88] |

| **Haliclona simulans** | **Gurraig Sound, Kilkieran Bay, Ireland (15 m)** | **Bacillus subtilis MMA7** | **Firmicutes** | **Subtilomycin** | **ND** | **Lactobacillus lactis** | [71] |

| **Callyspongia diffusa** | **Southwest Coast of India (6–7 m)** | **Shewanella algae VCDB KC623651** | **Firmicutes** | **Unidentified** | **DOI (10 mm)** | **L. lactis** | [98] |

| **Haliclona simulans** | **Gurraig Sound, Kilkieran Bay, Ireland (15 m)** | **Bacillus subtilis MMA7** | **Firmicutes** | **Subtilomycin** | **ND** | **Alphomomas sp.** | [71] |

| **Polymastia boletiformis, Axinella dissimilis and Haliclona simulans** | **Gurraig Sound, Kilkieran Bay, Ireland (15 m)** | **Pseudovibrio sp. W64, W69, W89, W74** | **Proteobacteria** | **Tropodithietic acid** | **DOI (>4 mm)** | **Yersinia ruckerri** | [72] |

| **Polymastia boletiformis, Axinella dissimilis and Haliclona simulans** | **Gurraig Sound, Kilkieran Bay, Ireland (15 m)** | **Pseudovibrio sp. JIC5, JIC17, W10, W62, W63, W65, W71, W99, W85, W96, WM31, WM34, WM40, WC13, WC22, WC30, WC32, WC41, HC6** | **Proteobacteria** | **Unidentified** | **DOI (>4 mm)** | **Y. ruckerri** | [72] |

| **Polymastia boletiformis, Axinella dissimilis and Haliclona simulans** | **Gurraig Sound, Kilkieran Bay, Ireland (15 m)** | **Pseudovibrio sp. WC43, W79, W94, WM32, WC21, HMMA3** | **Proteobacteria** | **Unidentified** | **DOI (>4 mm)** | **Y. ruckerri** | [72] |

| **Polymastia boletiformis, Axinella dissimilis and Haliclona simulans** | **Gurraig Sound, Kilkieran Bay, Ireland (15 m)** | **Pseudovibrio sp. WC6, WC15** | **Proteobacteria** | **Unidentified** | **DOI (>1 mm)** | **Y. ruckerri** | [72] |

| **Polymastia boletiformis, Axinella dissimilis and Haliclona simulans** | **Gurraig Sound, Kilkieran Bay, Ireland (15 m)** | **Pseudovibrio sp. JIC6, JIC17, W10, W62, W65, W71, W85, WM31, WM34, WM40, WC13, WC22, WC41, HC6** | **Proteobacteria** | **Tropodithietic acid** | **DOI (>4 mm)** | **Edwardsiella tarda** | [72] |

| **Polymastia boletiformis, Axinella dissimilis and Haliclona simulans** | **Gurraig Sound, Kilkieran Bay, Ireland (15 m)** | **Pseudovibrio sp. W64, W69, W89** | **Proteobacteria** | **Tropodithietic acid** | **DOI (>2 mm)** | **E. tarda** | [72] |

| **Polymastia boletiformis, Axinella dissimilis and Haliclona simulans** | **Gurraig Sound, Kilkieran Bay, Ireland (15 m)** | **Pseudovibrio sp. JIC5, W63, W99** | **Proteobacteria** | **Unidentified** | **DOI (>4 mm)** | **E. tarda** | [72] |

| **Polymastia boletiformis, Axinella dissimilis and Haliclona simulans** | **Gurraig Sound, Kilkieran Bay, Ireland (15 m)** | **Pseudovibrio sp. JIC6, JIC17, W10, W62, W65, W71, W85, W96, WM31, WM34, WM40, WC13, WC22, WC41, HC6** | **Proteobacteria** | **Unidentified** | **DOI (>2 mm)** | **E. tarda** | [72] |
| Table 2. Cont. |
|----------------|
| **Polypodium boletiformis, Axinella dissimilis and Haliclona simulans** | Gurraig Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. W78, W94, WM33, WC21, WC30, HMMA3 | Proteobacteria | Unidentified | DOI (>1 mm) | E. tarda [72] |
| **Polypodium boletiformis, Axinella dissimilis and Haliclona simulans** | Gurraig Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. W64, W74 | Proteobacteria | Tropodithietic acid | DOI (>4 mm) | M. morganii [72] |
| **Polypodium boletiformis, Axinella dissimilis and Haliclona simulans** | Gurraig Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. W69, W89 | Proteobacteria | Tropodithietic acid | DOI (>2 mm) | M. morganii [72] |
| **Polypodium boletiformis, Axinella dissimilis and Haliclona simulans** | Gurraig Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. JIC5, W62, W65, W71, W99, W78, WM34, HC6 | Proteobacteria | Unidentified | DOI (>4 mm) | M. morganii [72] |
| **Polypodium boletiformis, Axinella dissimilis and Haliclona simulans** | Gurraig Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. JIC17, W94, W96, WM40, WC13, WC21, WC32, WC41 | Proteobacteria | Unidentified | DOI (>2 mm) | M. morganii [72] |
| **Polymastia boletiformis, Axinella dissimilis and Haliclona simulans** | Gurraig Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. W64, W69, W89 | Proteobacteria | Tropodithietic acid | DOI (>2 mm) | P. sputorum [72] |
| **Polymastia boletiformis, Axinella dissimilis and Haliclona simulans** | Gurraig Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. W74 | Proteobacteria | Tropodithietic acid | DOI (>1 mm) | P. sputorum [72] |
| **Polymastia boletiformis, Axinella dissimilis and Haliclona simulans** | Gurraig Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. W63 | Proteobacteria | Tropodithietic acid | DOI (4 mm) | P. sputorum [72] |
| **Polymastia boletiformis, Axinella dissimilis and Haliclona simulans** | Gurraig Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. W62, WM40 | Proteobacteria | Unidentified | DOI (>2 mm) | P. sputorum [72] |
| **Polymastia boletiformis, Axinella dissimilis and Haliclona simulans** | Gurraig Sound, Kilkieran Bay, Ireland (15 m) | Pseudovibrio sp. JIC5, JIC6, JIC17, W10, W15, W71, W99, WC43, W85, W78, W96, WM34, WC32, HC6 | Proteobacteria | Unidentified | DOI (>1 mm) | P. sputorum [72] |
| **Haliclona sp.** | Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas fluorescens H40 | Proteobacteria | Unidentified | DOI (23 mm) | Corynebacterium fimii [77] |
| **Haliclona sp.** | Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas fluorescens H41 | Proteobacteria | Unidentified | DOI (26 mm) | Corynebacterium fimii [77] |
| **Haliclona sp.** | Cagarras Archipelago, Brazil (4-20 m) | Pseudomonas aeruginosa HS1 | Proteobacteria | Unidentified | DOI (43 mm) | Corynebacterium fimii [77] |
| **Haliclona sp.** | Cagarras Archipelago, Brazil (4-20 m) | Virgibacillus pantothenticus H31 | Firmicutes | Unidentified | DOI (17 mm) | Corynebacterium fimii [77] |
Table 2. Cont.

| Species                 | Location                                       | Bacillus sp.          | Firmicutes     | Unidentified | DOI (mm) | Corynebacterium sp. |
|-------------------------|------------------------------------------------|-----------------------|----------------|--------------|----------|---------------------|
| Haliclona sp.           | Cagarras Archipelago, Brazil (4–20 m)          | Bacillus flexus H42   | Firmicutes     | Unidentified | DOI (21 mm) | Corynebacterium fini |
| Dragmacidon reticulatus | Cagarras Archipelago, Brazil (4–20 m)          | Bacillus pumilus D031 | Firmicutes     | Unidentified | DOI (20 mm) | Corynebacterium fini |
| Petromica cirrina       | Cagarras Archipelago, Brazil (4–20 m)          | Bacillus pumilus P31  | Firmicutes     | Unidentified | DOI (46 mm) | Corynebacterium fini |
| Petromica cirrina       | Cagarras Archipelago, Brazil (4–20 m)          | Bacillus pumilus P32  | Firmicutes     | Unidentified | DOI (42 mm) | Corynebacterium fini |
| Clathrina aurea         | Cagarras Archipelago, Brazil (4–20 m)          | Pseudovibrio ascidiaceicola Ca31 | Proteobacteria | Unidentified | DOI (31 mm) | Corynebacterium fini |
| Paraleucilla magna      | Cagarras Archipelago, Brazil (4–20 m)          | Pseudovibrio ascidiaceicola Pm31 | Proteobacteria | Unidentified | DOI (24 mm) | Corynebacterium fini |
| Paraleucilla magna      | Cagarras Archipelago, Brazil (4–20 m)          | Pseudovibrio ascidiaceicola Pm52 | Proteobacteria | Unidentified | DOI (15 mm) | Corynebacterium fini |
| Mycale microsigmatosa   | Cagarras Archipelago, Brazil (4–20 m)          | Pseudovibrio desitriescens Mm37 | Proteobacteria | Unidentified | DOI (34 mm) | Corynebacterium fini |
| Clathrina aurea         | Cagarras Archipelago, Brazil (4–20 m)          | Pseudomonas fluorescens H40 | Proteobacteria | Unidentified | DOI (17 mm) | S. marcescens        |
| Haliclona sp.           | Cagarras Archipelago, Brazil (4–20 m)          | Pseudomonas fluorescens H41 | Proteobacteria | Unidentified | DOI (18 mm) | S. marcescens        |
| Haliclona sp.           | Cagarras Archipelago, Brazil (4–20 m)          | Pseudomonas aeruginosa H51 | Proteobacteria | Unidentified | DOI (20 mm) | S. marcescens        |
| Clathrina aurea         | Cagarras Archipelago, Brazil (4–20 m)          | Pseudovibrio ascidiaceicola Ca31 | Proteobacteria | Unidentified | DOI (13 mm) | Stenotrophomonas maltophilia |
| Paraleucilla magna      | Cagarras Archipelago, Brazil (4–20 m)          | Pseudovibrio ascidiaceicola Pm31 | Proteobacteria | Unidentified | DOI (13 mm) | S. maltophilia       |
| Mycale microsigmatosa   | Cagarras Archipelago, Brazil (4–20 m)          | Pseudovibrio desitriescens Mm37 | Proteobacteria | Unidentified | DOI (15 mm) | S. maltophilia       |
| Haliclona sp.           | Cagarras Archipelago, Brazil (4–20 m)          | Pseudomonas fluorescens H40 | Proteobacteria | Unidentified | DOI (19 mm) | Citrobacter freundii |
| Haliclona sp.           | Cagarras Archipelago, Brazil (4–20 m)          | Pseudomonas aeruginosa H51 | Proteobacteria | Unidentified | DOI (16 mm) | C. freundii          |
| Haliclona sp.           | Cagarras Archipelago, Brazil (4–20 m)          | Pseudomonas fluorescens H41 | Proteobacteria | Unidentified | DOI (26 mm) | C. freundii          |
| Paraleucilla magna      | Cagarras Archipelago, Brazil (4–20 m)          | Pseudovibrio ascidiaceicola Pm31 | Proteobacteria | Unidentified | DOI (10 mm) | C. freundii          |
| Xestospongia testudinaria | Weizhou coral reef, China (ND)                | Aspergillus sp.       | Ascomycota     | (-)-Sydonic acid | MIC (0.66 µg/mL) | Sarcomyx lutea |
| Dysidea herbecia        | Koror, Republic Palau (1 m)                     | Oscillatorium spongillae | Cyanobacteria  | 2-(2',4',4'-Dibromophenyl)-4,6-dibromophenol | ND | Synechococcus sp. |
| Location                          | Sample Source | Organism          | Genus                  | Species               | Actinobacteria | Unidentified | MIC (µg protein/mL) | Unidentified | Biofilm bacterium | Reference |
|----------------------------------|---------------|-------------------|-----------------------|-----------------------|-----------------|--------------|--------------------|--------------|-------------------|-----------|
| Asbestopluma hypogea             | La Ciotat, France (17 m) | Streptomyces sp. SICA | Actinobacteria | Unidentified | ND | Ruegeria sp. S138W | [100] |
| Asbestopluma hypogea             | La Ciotat, France (17 m) | Streptomyces sp. SICA | Actinobacteria | Unidentified | ND | Sulfitobacter sp. S16SW | [100] |
| Asbestopluma hypogea             | La Ciotat, France (17 m) | Streptomyces sp. SICA | Actinobacteria | Unidentified | ND | Pseudoalteromonas distincta | [100] |
| Phorbas tenacior                  | Mediterranean Sea, Marseille, France (15 m) | Citricoccus sp.P157 | Actinobacteria | Unidentified | 3–6 mm | P. distincta | [101] |
| Phorbas tenacior                  | Mediterranean Sea, Marseille, France (15 m) | Pseudovibrio sp. P1Ma4 and Vibrio sp. P1MaNaal1 | Proteobacteria | Unidentified | 2–3 mm | P. distincta | [101] |
| Dendrilla nigra                  | Vizhinjam coast, India (10–15 m) | Streptomyces sp. MS0051 | Actinobacteria | Unidentified | MIC (32 ± 0.61 µg protein/mL) | unidentified biofilm bacterium EB1 | [73] |
| Dendrilla nigra                  | Vizhinjam coast, India (10–15 m) | Streptomyces sp. MS0051 | Actinobacteria | Unidentified | MIC (34 ± 2.18 µg protein/mL) | unidentified biofilm bacterium EB4 | [73] |
| Halichondria panicea             | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB107 | Actinobacteria | Unidentified | ND | Xanthomonas campestris | [44] |
| Halichondria panicea             | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB132 | Actinobacteria | Unidentified | ND | X. campestris | [44] |
| Halichondria panicea             | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB138 | Actinobacteria | Unidentified | ND | X. campestris | [44] |
| Halichondria panicea             | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB202 | Actinobacteria | Unidentified | ND | X. campestris | [44] |
| Halichondria panicea             | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB253 | Actinobacteria | Unidentified | ND | X. campestris | [44] |
| Halichondria panicea             | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB291 | Actinobacteria | Unidentified | ND | X. campestris | [44] |
| Halichondria panicea             | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB298 | Actinobacteria | Unidentified | ND | X. campestris | [44] |
| Halichondria panicea             | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB132 | Actinobacteria | Unidentified | ND | Erwinia amylovora | [44] |
| Halichondria panicea             | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB202 | Actinobacteria | Unidentified | ND | E. amylovora | [44] |
| Halichondria panicea             | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB320 | Actinobacteria | Unidentified | ND | E. amylovora | [44] |
| Halichondria panicea             | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB328 | Actinobacteria | Unidentified | ND | E. amylovora | [44] |
| Halichondria panicea             | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB100 | Actinobacteria | Unidentified | ND | Ralstonia solanacearum | [44] |
| Halichondria panicea             | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB107 | Actinobacteria | Unidentified | ND | R. solanacearum | [44] |
| Halichondria panicea             | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB117 | Actinobacteria | Unidentified | ND | R. solanacearum | [44] |
| Species                  | Location                        | Isolate                     | Phylum        | Identification | DOI (mm) | Source                                      | Reference |
|-------------------------|---------------------------------|-----------------------------|---------------|----------------|----------|---------------------------------------------|-----------|
| *Halichondria panicea*  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB142 | Actinobacteria | Unidentified | ND       | *R. solanacearum*                           | [44]      |
| *Halichondria panicea*  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB156 | Actinobacteria | Unidentified | ND       | *R. solanacearum*                           | [44]      |
| *Halichondria panicea*  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB238 | Actinobacteria | Unidentified | ND       | *R. solanacearum*                           | [44]      |
| *Halichondria panicea*  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB253 | Actinobacteria | Unidentified | ND       | *R. solanacearum*                           | [44]      |
| *Halichondria panicea*  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB254 | Actinobacteria | Unidentified | ND       | *R. solanacearum*                           | [44]      |
| *Halichondria panicea*  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB272 | Actinobacteria | Unidentified | ND       | *R. solanacearum*                           | [44]      |
| *Halichondria panicea*  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB274 | Actinobacteria | Unidentified | ND       | *R. solanacearum*                           | [44]      |
| *Halichondria panicea*  | Kiel Fjord, Baltic Sea, Germany (ND) | Streptomyces sp. HB375 | Actinobacteria | Unidentified | ND       | *R. solanacearum*                           | [44]      |
| *Pseudoceratina clavata* | Heron Island, Great Barrier Reef (14 m) | Salinispora sp. M101 | Actinobacteria | Unidentified | DOI (>5 mm) | unidentified marine bacterial isolate SW09 | [79]      |
| *Pseudoceratina clavata* | Heron Island, Great Barrier Reef (14 m) | Salinispora sp. M102, M403, M413 | Actinobacteria | Unidentified | DOI (>5 mm) | unidentified marine bacterial isolate SW09 | [79]      |
| *Pseudoceratina clavata* | Heron Island, Great Barrier Reef (14 m) | Salinispora sp. M412 | Actinobacteria | Unidentified | DOI (>5 mm) | unidentified marine bacterial isolate SW09 | [79]      |
| *Pseudoceratina clavata* | Heron Island, Great Barrier Reef (14 m) | Salinispora sp. M414, SW10, SW 15 and SW 17 | Actinobacteria | Unidentified | DOI (>5 mm) | unidentified marine bacterial isolate SW09 | [79]      |
| *Pseudoceratina clavata* | Heron Island, Great Barrier Reef (14 m) | Salinispora sp. SW02 | Actinobacteria | Unidentified | DOI (>5 mm) | unidentified marine bacterial isolate SW09 | [79]      |
| *Pseudoceratina clavata* | Heron Island, Great Barrier Reef (14 m) | Salinispora sp. SW02 | Actinobacteria | Unidentified | DOI (>5 mm) | unidentified marine bacterial isolate SW09 | [79]      |
| *Pseudoceratina clavata* | Heron Island, Great Barrier Reef (14 m) | Salinispora sp. SW02 | Actinobacteria | Unidentified | DOI (>5 mm) | unidentified marine bacterial isolate SW09 | [79]      |
| *Pseudoceratina clavata* | Heron Island, Great Barrier Reef (14 m) | Salinispora sp. SW02 | Actinobacteria | Unidentified | DOI (>5 mm) | unidentified marine bacterial isolate SW09 | [79]      |
| *Pseudoceratina clavata* | Heron Island, Great Barrier Reef (14 m) | Salinispora sp. SW02 | Actinobacteria | Unidentified | DOI (>5 mm) | unidentified marine bacterial isolate SW09 | [79]      |
| *Pseudoceratina clavata* | Heron Island, Great Barrier Reef (14 m) | Salinispora sp. SW02 | Actinobacteria | Unidentified | DOI (>5 mm) | unidentified marine bacterial isolate SW09 | [79]      |
| *Pseudoceratina clavata* | Heron Island, Great Barrier Reef (14 m) | Salinispora sp. M101 | Actinobacteria | Unidentified | DOI (>5 mm) | unidentified marine bacterial isolate SW09 | [79]      |
Table 2. Cont.

| Pseudoceratina clavata | Heron Island, Great Barrier Reef (14 m) | Salinispora sp. M102, M403, M413 | Actinobacteria | Unidentified | DOI (>5 mm) | unidentified bacterial isolate DE05 (γ-proteobacteria) | [79] |
|------------------------|-----------------------------------------|----------------------------------|----------------|--------------|-------------|------------------------------------------------------|-----|
| Pseudoceratina clavata | Heron Island, Great Barrier Reef (14 m) | Salinispora sp. M412             | Actinobacteria | Unidentified | DOI (>5 mm) | unidentified bacterial isolate DE05 (γ-proteobacteria) | [79] |
| Pseudoceratina clavata | Heron Island, Great Barrier Reef (14 m) | Salinispora sp. M414, SW10, SW 15 and SW 17 | Actinobacteria | Unidentified | DOI (>5 mm) | Unidentified bacterial isolate DE05 (γ-proteobacteria) | [79] |
| Pseudoceratina clavata | Heron Island, Great Barrier Reef (14 m) | Salinispora sp. SW02             | Actinobacteria | Unidentified | DOI (>5 mm) | Unidentified bacterial isolate DE05 (γ-proteobacteria) | [79] |

Table 2 is organised according to the target bacteria. IC<sub>50</sub>: half maximum inhibitory concentration; MIC: minimum inhibitory concentration; DOI: diameter of inhibition; ND: not determined. Susceptible to [77]: amp = ampicillin; atm = aztreonam; azm = azithromycin; caz = ceftazidimine; cef = cefalotin; chl = chloramphenicol; cip = ciprofloxacin; cpd = cefpodoxime; fox = cefoxitin; gen = gentamicin; oxa = oxacillin; pen = penicillin; sxt = trimethoprim/sulfamethoxazole; tet = tetracycline; tzp = piperacillin/tazobactam; van = vancomycin.
4. Antifungal Activity

The incidence rate of fungal infections has increased significantly over the past decades. This is mainly caused by clinical use of antibacterial drugs and immunosuppressive agents after organ transplantation, cancer chemotherapy, and advances in surgery [102,103]. Several fungal species that often cause human infections include Candida albicans, Candida glabrata, Cryptococcus neoformans and Aspergillus fumigatus [102,104,105]. The story becomes more complex as many of these pathogenic fungi develop resistance against available antifungal drugs, which will prolong duration of treatments [106].

Screening for antifungals is often focused on finding compounds active against Candida albicans, the prominent agent for candidiasis (Table 3). Invasive candidiasis is accounted as the most common nosocomial fungal infection resulting in an average mortality rate between 25%–38% [103]. El-Gendy et al. [107] isolated Streptomyces sp. Hedaya 48 from the sponge Aplysina fistularis and identified two compounds: the novel compound saadamycin (13) and the known compound 5,7-dimethoxy-4-p-methoxylphenylcoumarin (14) (Figure 3). Bioassays indicated that both saadamycin and 5,7-dimethoxy-4-p-methoxylphenylcoumarin displayed pronounced antifungal activity against Candida albicans with MIC values of 2.22 µg/mL and 15 µg/mL, respectively. In addition, both compounds displayed bioactivity against some pathogenic dermatophytes (skin-infecting fungi), such as Epidermophyton floccosum, Trichophyton rubrum, Trichophyton mentagrophytes, Microsporum gypseum, Aspergillus niger, Aspergillus fumigatus, Fusarium oxysporum, and Cryptococcus humicolus (Table 3). Further analysis showed that saadamycin displayed a more potent bioactivity indicated by a 3875 fold lower MIC than that of the reference compound, miconazole, whereas 5,7-dimethoxy-4-p-methoxylphenylcoumarin was around a 200 fold more potent than miconazole.

Antifungal activity was also detected from the sponge-associated fungus Phoma sp. Q60596. The sponge-derived fungus produced a new lactone compound, YM-202204 (15) [108], which was effective against C. albicans (IC80 of 6.25 µg/mL), along with Cryptococcus neoformans (IC80 of 1.56 µg/mL), Saccharomyces cerevisiae (IC80 of 1.56 µg/mL) and Aspergillus fumigatus (IC80 of 12.5 µg/mL). Furthermore, Nagai et al. [108] showed that YM-202204 was able to block the glycoprophatidylinositol (GPI) anchor, an important structure for protein attachment in the membrane of eukaryotic cells and one of the targets in developing antifungal drugs [109,110].
Table 3. Bioactive compounds with antifungal activity from sponge-associated microbes.

| Sponge                  | Origin (Depth)            | Microorganism     | Phylum        | Compound                  | Property               | Target          | Reference |
|-------------------------|---------------------------|-------------------|---------------|---------------------------|------------------------|-----------------|-----------|
| Aplysina fistularis     | Sharm El-Sheikh, Egypt (ND)| Streptomyces sp. Hedaya48 | Actinobacteria | Saadamycin               | MIC (2.22 µg/mL)       | C. albicans     | [107]    |
| Aplysina fistularis     | Sharm El-Sheikh, Egypt (ND)| Streptomyces sp. Hedaya48 | Actinobacteria | 5,7-Dimethoxy-4-p-methoxyphenylcoumarin | MIC (15 µg/mL)       | C. albicans     | [107]    |
| Halichondria japonica  | Iriomote island, Japan (ND)| Phoma sp. Q60596 | Ascomycota    | YM-202204               | IC₅₀ (6.25 µg/mL)     | C. albicans     | [108]    |
| Haliclona simulans      | Graig Sound Kilkieran Bay, Ireland (15 m) | Streptomyces sp. SM8 | Actinobacteria | Antimycin A2, A8, A11, or A17 | MIC (210 µg/mL) | C. albicans | [95]    |
| Haliclona simulans      | Graig Sound Kilkieran Bay, Ireland (15 m) | Streptomyces sp. SM8 | Actinobacteria | Antimycin A3 or A7       | MIC (80 µg/mL)        | C. albicans     | [95]    |
| Haliclona simulans      | Graig Sound Kilkieran Bay, Ireland (15 m) | Streptomyces sp. SM8 | Actinobacteria | Antimycin A2, A8, A11, or A17, antimycin A3 or A7 | MIC (90 µg/mL) | C. albicans | [95]    |
| Halichondria sp.        | West Coast of India (10 m) | Bacillus sp. SAB1 | Firmicutes    | 3-Phenylpropionic acid | DOI (7–10 mm) at 50 µg/disk | C. albicans | [69]    |
| Halichondria sp.        | West Coast of India (10 m) | Bacillus sp. SAB1 | Firmicutes    | 4,4’-Oxybis(3-phenylpropionic acid) | DOI (4–6 mm) at 50 µg/disk | C. albicans | [69]    |
| Xestospongia exigua     | Bali Sea, Indonesia (ND) | Penicillium cf. montanense | Ascomycota   | Xestodecalactone B       | MIC (28.03 µg/disk) | C. albicans | [111] |
| unidentified            | Iriomote island, Japan (ND) | Streptomyces sp. Ni-80 | Actinobacteria | Urauchinycins A and B | MIC (10 µg/mL)        | C. albicans | [112] |
| Haliclona sp.           | Tateyama, Japan (ND) | Streptomyces humbergensis | Actinobacteria | Unidentified            | DOI (5 mm)             | C. albicans | [113] |
| Haliclona sp.           | Tateyama, Japan (ND) | Streptomyces jarenssis | Actinobacteria | Unidentified            | DOI (11 mm)            | C. albicans | [113] |
| unidentified            | Nagura Bay, Ishigaki, Japan (ND) | Streptomyces albifluorae | Actinobacteria | Unidentified            | DOI (16 mm)            | C. albicans | [113] |
| unidentified            | Nagura Bay, Ishigaki, Japan (ND) | Streptomyces variabilis | Actinobacteria | Unidentified            | DOI (19 mm)            | C. albicans | [113] |
| unidentified            | Nagura Bay, Ishigaki, Japan (ND) | Streptomyces latenspurus | Actinobacteria | Unidentified            | DOI (24 mm)            | C. albicans | [113] |
| Sphacelospongia ragahunda | Rovinj, Croatia (3–20 m) | Actinokineospora sp. EG49 | Actinobacteria | Unidentified            | DOI (12 mm)            | C. albicans | [82]    |
| Dysidea tupha           | Rovinj, Croatia (3–20 m) | Streptomyces sp. RV15 | Actinobacteria | Unidentified            | DOI (4–6 mm)           | C. albicans | [82]    |
| Sigmodiacis filubatus   | Hare Island, India (5-10 m) | Bacillus sp. SC3 | Firmicutes    | Unidentified            | DOI (15 mm)            | C. albicans | [96]    |
| Sigmodiacis filubatus   | Hare Island, India (5-10 m) | Pseudomonas sp. SC11 | Proteobacteria | Unidentified            | DOI (7 mm)             | C. albicans | [96]    |
| Echinodictyum sp.       | Hare Island, India (5-10 m) | Idiomarina baltica SA7 | Proteobacteria | Unidentified            | DOI (10 mm)            | C. albicans | [96]    |
| Spheciospongia vagabunda | Hare Island, India (5-10 m) | Staphylococcus equorum SB11 | Firmicutes    | Unidentified            | DOI (10 mm)            | C. albicans | [96]    |
| Aplysina aerophoba      | Banyuls-sur-Mer, France (5-15 m) | Bacillus subtilis A184 | Firmicutes    | Surfactin, iturin, and fengycin | ND | C. albicans | [68]    |
| Organism | Location | Bacteria | Proteobacteria | Actinobacteria | MIC (µg/mL) | Pathogen |
|----------|----------|----------|----------------|---------------|-------------|----------|
| Aplysina aerophoba | Banyuls-sur-Mer, France (5–15 m) | Bacillus subtilis A190 | Firmicutes | Surfactin | ND | C. albicans [68] |
| Aplysina aerophoba | Banyuls-sur-Mer, France (5–15 m) | Bacillus subtilis A202 | Firmicutes | Iturin | ND | C. albicans [68] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio sp. SC-C1-5 | Proteobacteria | Unidentified | ND | C. albicans [83] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio sp. BSw21697 | Proteobacteria | Unidentified | ND | C. albicans [83] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio splendidus LGP32 | Proteobacteria | Unidentified | ND | C. albicans [83] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Bacillus amyloliquefaciens | Proteobacteria | Unidentified | ND | C. albicans [83] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio sp. SC-C1-5 | Proteobacteria | Unidentified | ND | C. albicans [83] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio splendidus LGP32 | Proteobacteria | Unidentified | ND | C. albicans [83] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Bacillus amyloliquefaciens | Proteobacteria | Unidentified | ND | C. albicans [83] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio splendidus LGP32 | Proteobacteria | Unidentified | ND | C. albicans [83] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio splendidus LGP32 | Proteobacteria | Unidentified | ND | C. albicans [83] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio splendidus LGP32 | Proteobacteria | Unidentified | ND | C. albicans [83] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio splendidus LGP32 | Proteobacteria | Unidentified | ND | C. albicans [83] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio splendidus LGP32 | Proteobacteria | Unidentified | ND | C. albicans [83] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio splendidus LGP32 | Proteobacteria | Unidentified | ND | C. albicans [83] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio splendidus LGP32 | Proteobacteria | Unidentified | ND | C. albicans [83] |
| Aplysina fistularis | Sharm El-Sheikh, Egypt (ND) | Streptomyces sp. Hedaya48 | Actinobacteria | Saadamycin | MIC (5 µg/mL) | T. rubrum [107] |
| Aplysina fistularis | Sharm El-Sheikh, Egypt (ND) | Streptomyces sp. Hedaya48 | Actinobacteria | 5,7-Dimethoxy-4-p-methoxylphenylcoumarin | MIC (7.5 µg/mL) | T. rubrum [107] |
| Aplysina fistularis | Sharm El-Sheikh, Egypt (ND) | Streptomyces sp. Hedaya48 | Actinobacteria | Saadamycin | MIC (1.5 µg/mL) | T. mentagrophytes [107] |
| Aplysina fistularis | Sharm El-Sheikh, Egypt (ND) | Streptomyces sp. Hedaya48 | Actinobacteria | 5,7-Dimethoxy-4-p-methoxylphenylcoumarin | MIC (90 µg/mL) | T. mentagrophytes [107] |
| Aplysina fistularis | Sharm El-Sheikh, Egypt (ND) | Streptomyces sp. Hedaya48 | Actinobacteria | Saadamycin | MIC (1.25 µg/mL) | M. gypseum [107] |
| Aplysina fistularis | Sharm El-Sheikh, Egypt (ND) | Streptomyces sp. Hedaya48 | Actinobacteria | 5,7-Dimethoxy-4-p-methoxylphenylcoumarin | MIC (100 µg/mL) | M. gypseum [107] |
### Table 3. Cont.

| Sample Location | Organism | Taxonomy | Compound | MIC/IC₅₀ | Pathogen | Reference |
|-----------------|----------|----------|----------|---------|----------|-----------|
| Aplysina fistularis Sharm El-Sheikh, Egypt (ND) | Streptomyces sp. Hedaya48 | Actinobacteria | Saadamycin | MIC (1.0 µg/mL) | Epidermophyton floccosum | [107] |
| Aplysina fistularis Sharm El-Sheikh, Egypt (ND) | Streptomyces sp. Hedaya48 | Actinobacteria | 5,7-Dimethoxy-4-p-methoxylphenylcoumarin | MIC (50 µg/mL) | Fusarium oxysporum | [107] |
| Aplysina fistularis Sharm El-Sheikh, Egypt (ND) | Streptomyces sp. Hedaya48 | Actinobacteria | Saadamycin | MIC (1.2 µg/mL) | F. oxysporum | [107] |
| Aplysina fistularis Sharm El-Sheikh, Egypt (ND) | Streptomyces sp. Hedaya48 | Actinobacteria | 5,7-Dimethoxy-4-p-methoxylphenylcoumarin | MIC (22 µg/mL) | Cryptococcus humicolus | [107] |
| Aplysina fistularis Sharm El-Sheikh, Egypt (ND) | Streptomyces sp. Hedaya48 | Actinobacteria | Saadamycin | MIC (5.16 µg/mL) | Cryptococcus neoformans | [108] |
| Aplysina fistularis Sharm El-Sheikh, Egypt (ND) | Streptomyces sp. Hedaya48 | Actinobacteria | 5,7-Dimethoxy-4-p-methoxylphenyl-coumarin | MIC (10 µg/mL) | A. fumigatus | [107] |
| Halichondria japonica Iriomote island, Japan (ND) | Phoma sp. Q60596 | Ascomycota | YM-202204 | IC₅₀ (1.56 µg/mL) | A. fumigatus | [108] |
| Aplysina fistularis Sharm El-Sheikh, Egypt (ND) | Streptomyces sp. Hedaya48 | Actinobacteria | Saadamycin | MIC (1.6 µg/mL) | Aspergillus fumigatus | [107] |
| Leucosolenia sp. Lough Hyne, Co. Cork, Ireland (15 m) | Staphylococcus saprophyticus | Firmicutes | Unidentified | ND | A. fumigatus | [83] |
| Leucosolenia sp. Lough Hyne, Co. Cork, Ireland (15 m) | Staphylococcus sp. HJBR03 | Firmicutes | Unidentified | ND | A. fumigatus | [83] |
| Leucosolenia sp. Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio litoralis MANCO2P | Proteobacteria | Unidentified | ND | A. fumigatus | [83] |
| Leucosolenia sp. Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio sp. SC-C1-5 | Proteobacteria | Unidentified | ND | A. fumigatus | [83] |
| Leucosolenia sp. Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio sp. BSw21667 | Proteobacteria | Unidentified | ND | A. fumigatus | [83] |
| Leucosolenia sp. Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio splendidus LGP32 | Proteobacteria | Unidentified | ND | A. fumigatus | [83] |
| Leucosolenia sp. Lough Hyne, Co. Cork, Ireland (15 m) | Bacillus amyloliquefaciens | Firmicutes | Unidentified | ND | A. fumigatus | [83] |
| Aplysina fistularis Sharm El-Sheikh, Egypt (ND) | Streptomyces sp. Hedaya48 | Actinobacteria | Saadamycin | MIC (1.0 µg/mL) | Aspergillus niger | [107] |
| Halichondria sp. West Coast of India (10 m) | Bacillus sp. SAB1 | Firmicutes | 3-Phenylpropionic acid | DOI (1–3 mm) at 50 µg/disc | A. niger | [69] |
| Halichondria sp. West Coast of India (10 m) | Bacillus sp. SAB1 | Firmicutes | 4’-Oxybsu(3-phenylpropionic acid) | DOI (4-6 mm) at 50 µg/disc | A. niger | [69] |
| Halichondria sp. West Coast of India (10 m) | Bacillus sp. SAB1 | Firmicutes | 3-Phenylpropionic acid | DOI (4-6 mm) at 50 µg/disc | Rhodotorula sp. | [69] |
Table 3. Cont.

| Halichondria sp. | West Coast of India (10 m) | Bacillus sp. SAB1 | Firmicutes | 4,4′-Oxybis(3-phenylpropionic acid) DOI (7–10 mm) at 50 µg/disc | Rhodotorula sp. [69] |
|------------------|---------------------------|-------------------|------------|---------------------------------------------------------------|----------------------|
| Halichondria japonica | Iriomote island, Japan (ND) | Phoma sp. Q60596 | Ascomycota | YM-202204 IC<sub>50</sub> (1.56 µg/mL) | Saccharomycyes cerevisiae [108] |
| Hymeniacidon perleve | Nanji island, China (ND) | Pseudomonas strain N6-3-1 | Proteobacteria | Norharman (a beta-carboline alkaloid) DOI (3–5 mm) | S. cerevisiae [59] |
| Hymeniacidon perleve | Nanji island, China (ND) | Bacillus megaterium N6-3-2 | Firmicutes | Unidentified DOI (3–5 mm) | S. cerevisiae [59] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio litoralis MANO22P | Proteobacteria | Unidentified | ND | S. cerevisiae [83] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio sp. SC-C1-5 | Proteobacteria | Unidentified | ND | S. cerevisiae [83] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio sp. BSv21697 | Proteobacteria | Unidentified | ND | S. cerevisiae [83] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Vibrio splendidus LGP32 | Proteobacteria | Unidentified | ND | S. cerevisiae [83] |
| Leucosolenia sp. | Lough Hyne, Co. Cork, Ireland (15 m) | Bacillus amyloliquefaciens | Firmicutes | Unidentified | ND | S. cerevisiae [83] |
| Pannonicia sp. | Sdot-Yam, Israel (ND) | Aspergillus insuetus | Ascomycota | Insuetolides A MIC (60.09 µg/mL) | Neurospora crassa [114] |
| Pannonicia sp. | Sdot-Yam, Israel (ND) | Aspergillus insuetus | Ascomycota | (E,E)-6-(60,70-Dihydroxy-20,40-octadienoyl)-strobilactone A MIC (69.97 µg/mL) | N. crassa [114] |
| Pannonicia sp. | Sdot-Yam, Israel (ND) | Aspergillus insuetus | Ascomycota | (E,E)-6-(60,70-Dihydroxy-20,40-octadienoyl)-strobilactone A | MIC (71.79 µg/mL) | N. crassa [114] |
| Myxilla incrustans | The Caribbean Island of Dominica (ND) | Microsphaeropsis sp. | Ascomycota | Microsphaeropsin ND | Eurotium repens [115] |
| Myxilla incrustans | The Caribbean Island of Dominica (ND) | Microsphaeropsis sp. | Ascomycota | (R)-Mellein ND | E. repens [115] |
| Myxilla incrustans | The Caribbean Island of Dominica (ND) | Microsphaeropsis sp. | Ascomycota | (3R,4R)-Hydroxymellein ND | E. repens [115] |
| Myxilla incrustans | The Caribbean Island of Dominica (ND) | Microsphaeropsis sp. | Ascomycota | 4,8-Dihydroxy-3,4-dihydro-2H-naphthalen-1-one ND | E. repens [115] |
| Ectyoplasia ferox | The Caribbean Island of Dominica (ND) | Coniothyrium sp. | Ascomycota | (3R)-6-Methoxymellein ND | E. repens [115] |
| Ectyoplasia ferox | The Caribbean Island of Dominica (ND) | Coniothyrium sp. | Ascomycota | (3R)-6-Methoxy-7-chloromellein ND | E. repens [115] |
| Ectyoplasia ferox | The Caribbean Island of Dominica (ND) | Coniothyrium sp. | Ascomycota | (p-Hydroxyphenyl) ethanol ND | E. repens [115] |
| Ectyoplasia ferox | The Caribbean Island of Dominica (ND) | Coniothyrium sp. | Ascomycota | Phenylenethanol ND | E. repens [115] |
Table 3. Cont.

| Species | Location                  | Genus                | Class           | Compound Name                                      | Concentration | Pathogen                  |
|---------|---------------------------|----------------------|-----------------|---------------------------------------------------|---------------|---------------------------|
| *Myxilla incrustans* | The Caribbean Island of Dominica (ND) | Microsphaeropsis sp. | Ascomycota     | Microsphaeropsin                                  | ND            | *U. violacea*             |
| *Myxilla incrustans* | The Caribbean Island of Dominica (ND) | Microsphaeropsis sp. | Ascomycota     | (R)-Mellein                                       | ND            | *U. violacea*             |
| *Myxilla incrustans* | The Caribbean Island of Dominica (ND) | Microsphaeropsis sp. | Ascomycota     | (3R,4R)-Hydroxymellein                            | ND            | *U. violacea*             |
| *Myxilla incrustans* | The Caribbean Island of Dominica (ND) | Microsphaeropsis sp. | Ascomycota     | 4,8-Dihydroxy-3,4-dihydro-2H-naphthalen-1-one     | ND            | *U. violacea*             |
| *Ectyoplasia ferox*  | The Caribbean Island of Dominica (ND) | Coniothyrium sp.    | Ascomycota     | (3R)-6-Methoxymellein                            | ND            | *U. violacea*             |
| *Ectyoplasia ferox*  | The Caribbean Island of Dominica (ND) | Coniothyrium sp.    | Ascomycota     | (p-Hydroxyphenyl) ethanol                         | ND            | *U. violacea*             |
| *Ectyoplasia ferox*  | The Caribbean Island of Dominica (ND) | Coniothyrium sp.    | Ascomycota     | (3S)-(3',5'-Dihydroxyphenyl)butan-2-one           | ND            | *U. violacea*             |
| *Ectyoplasia ferox*  | The Caribbean Island of Dominica (ND) | Coniothyrium sp.    | Ascomycota     | (3S)-(3',5'-Dihydroxyphenyl)butan-2-one           | ND            | *Mycotypha microspora*    |

Table 3 is organised according to the target fungi. IC_{50}: half maximum inhibitory concentration; IC_{80}: 80% inhibitory concentration; MIC: minimum inhibitory concentration; DOI: diameter of inhibition; ND: not determined.
5. Antiprotozoal Activity

Malaria, caused by *Plasmodium* spp. infections, represents the most devastating protozoal disease worldwide, and results in both mortality and economic loss, mainly in developing countries [116]. Developing drugs with a better therapeutic profile against the parasite is one of the key aims of current malaria research, which includes screening for antimalarial substances from marine organisms [117,118].

Manzamine A (16) (Figure 4), first reported by Sakai and co-workers [119] from the sponge *Haliclona* sp., is a promising substance against *Plasmodium* spp. Initially, its antitumor property was of main interest, but subsequently diverse antimicrobial activities such as: anti-HIV, antibacterial, and antifungal were identified from the compound [120]. Currently the antimalaria properties of manzamine A are considered its most promising bioactivity. Manzamine A was shown to inhibit *P. falciparum* D6 and W3 clonal cell lines that are sensitive and resistant against the antimalarial chloroquine [121], with IC$_{50}$ values of 0.0045 and 0.008 µg/mL, respectively [122]. Furthermore, *in vivo* screening by Ang et al. [116] showed that manzamine A at concentration of 0.008 µg/mL inhibited 90% growth of the parasite *Plasmodium berghei* that causes malaria in rodents. In addition, Rao et al. reported [122] that manzamine A displayed anti-*Leishmania* activity, indicated by IC$_{50}$ and IC$_{90}$ values of 0.9 µg/mL and 1.8 µg/mL, respectively, against *Leishmania donovani*.

Isolation of manzamine A from several other sponge species [120] raised the hypothesis that it was of microbial origin [123,124]. Hill et al. [125] confirmed this hypothesis by isolating *Micromonospora* sp. M42 as the microbial producer of manzamine A from the Indonesian sponge *Acanthostrongylophora ingens*. A series of analyses using molecular-microbial community analysis, and Matrix Assisted Laser Desorption Ionization-Mass Spectrometry (MALDI-MS) corroborated that indeed the strain *Micromonospora* sp. M42 synthesizes manzamine A [126,127]. Considering the therapeutic potential of manzamine A for treating malaria and leishmaniasis, *Micromonospora* sp. M42 could be a sustainable provider of the substance, because the “Sponge Supply Problem” has been overcome [127]. Moreover, identification of several manzamine-derivatives e.g. manzamine E, F, J, and 8-hydroxymanzamine A, from marine sponges which displayed antibacterial, antifungal and antiprotozoal activity [122,124], could also lead to isolation of associated microbial producers in the future.

Pimentel-Elardo et al. [128] identified three compounds with anti-*Leishmania* and anti-*Trypanosoma* activity from a sponge-associated *Streptomyces* sp, namely the cyclic depsipeptide valinomycin (17), the indolocarbazole alkaloid staurosporine (18) and butenolide (19) (Table 4). Valinomycin and staurosporine inhibited the growth of *L. major* with IC$_{50}$ values of 0.12 µg/mL and 1.24 µg/mL, respectively. In addition, the three compounds displayed bioactivity against *Trypanosoma brucei* with IC$_{50}$ values of 0.0036 µg/mL for valinomycin, 0.0051 µg/mL for staurosporine and 7.92 µg/mL for butenolide.

Scopel et al. [129] isolated two sponge-associated fungi, namely *Hypocrea lixii* F02 and *Penicillium citrinum* F40 (Table 4) that were active against the protozoal parasite *Trichomonas vaginalis*, which causes trichomoniasis, a sexually transmitted disease [130]. Culture filtrates of both isolates inhibited *T. vaginalis* ATCC 30236 and fresh clinical isolates, including the metronidazole-resistant TV-LACM2, with MIC values of 2.5 mg/mL. Further observation indicated that culture filtrates of these two fungi had no haemolytic effect against mammalian cells, which is one of the important criteria to further develop anti-protozoal drugs [129].
### Table 4. Bioactive compounds with antiprotozoal activity from sponge-associated microbes.

| Sponge | Origin (Depth)               | Microorganism          | Phylum          | Compound                          | Property             | Target                | References |
|--------|------------------------------|------------------------|-----------------|-----------------------------------|----------------------|-----------------------|------------|
| *Homophymia* sp. | Toudho, New Caledonia (ND) | *Pseudomonas* sp. 1531-E7 | Proteobacteria | 2-Undecyl-4-quinolone             | IC₅₀ (1 μg/mL)        | *Plasmodium falciparum* | [25]       |
| *Acanthostrengylophora ingens* | Manado, Indonesia (ND) | *Micrococcus* sp. M42 | Actinobacteria | Manzamine A                        | IC₅₀ (0.0045 μg/mL)  | *P. falciparum*       | [124–127] |
| *Hyattella intestinalis* | Palk strait, Tamil Nadu, India (ND) | unidentified bacterial isolate THB20 | Unidentified | Unidentified                        | IC₅₀ (41.88 μg/mL)   | *P. falciparum*       | [131]      |
| *Redia intestinalis* | Palk strait, Tamil Nadu, India (ND) | unidentified bacterial isolate THB23 | Unidentified | Unidentified                        | IC₅₀ (28.80 μg/mL)   | *P. falciparum*       | [133]      |
| *Stylissa carteri* | Palk strait, Tamil Nadu, India (ND) | unidentified bacterial isolate THB14 | Unidentified | Unidentified                        | IC₅₀ (20.73 μg/mL)   | *P. falciparum*       | [134]      |
| *Clathria indica* | Palk strait, Tamil Nadu, India (ND) | unidentified bacterial isolate THB1 | Unidentified | Unidentified                        | IC₅₀ (11.98 μg/mL)   | *P. falciparum*       | [135]      |
| *Acanthostrongylophora ingens* | Manado, Indonesia | *Micromonospora* sp. M42 | Actinobacteria | Manzamine A                        | IC₅₀ (6.29 μg/mL)    | *Trypanosoma brucei*  | [82]       |
| *Aplysina aerophoba* | Rovinj, Croatia (3–20 m) | *Micromonospora* sp. RV115 | Actinobacteria | Diazepinomicin                       | Percentage of growth inhibition (48%) | *T. brucei* | [82]       |
| *Spheciospongia vagabunda* | Rovinj, Croatia (3–20 m) | *Actinomycetes* sp. EG49 | Actinobacteria | Unidentified                        | Percentage of growth inhibition (30%) | *T. brucei* | [82]       |
| unidentified | Rovinj, Croatia (3–20 m) | Brevibacterium sp. EG10 | Actinobacteria | Unidentified                        | Percentage of growth inhibition (28%) | *T. brucei* | [82]       |
| unidentified | Rovinj, Croatia (3–20 m) | *Gordonia* sp. EG50 | Actinobacteria | Unidentified                        | Percentage of growth inhibition (19%) | *T. brucei* | [82]       |
| *Dysidea tupha* | Rovinj, Croatia (3–20 m) | *Kocuria* sp. RV89 | Actinobacteria | Unidentified                        | Percentage of growth inhibition (19%) | *T. brucei* | [82]       |
| *Dysidea avus* | Mediterranean sea (ND) | *Nicardipsis* sp. RV763 | Actinobacteria | 1,6-Dihydroxyxyprenazine (produced from co-culture) | IC₅₀ (4.03 μg/mL)    | *T. brucei* | [98]       |
| *Spheciospongia vagabunda* | Red Sea (ND) | *Actinomycetes* sp. EG49 | Actinobacteria | Actinosporin A                      | IC₅₀ (19.19 μg/mL)   | *T. brucei* | [137]      |
| *Aplysina aerophoba* | Rovinj, Croatia (3–20 m) | *Streptomyces* sp. 34 | Actinobacteria | Valinomycin                         | IC₅₀ (0.0036 μg/mL)  | *T. brucei* | [128]      |
| *Axinella aerophoba* | Rovinj, Croatia (3–20 m) | *Streptomyces* sp. 22 | Actinobacteria | Valinomycin                         | IC₅₀ (0.0036 μg/mL)  | *T. brucei* | [128]      |
| *Todarion sp.* | Rovinj, Croatia (3–20 m) | *Streptomyces* sp. 11 | Actinobacteria | Staurosporine                       | IC₅₀ (0.0051 μg/mL)  | *T. brucei* | [128]      |
| *Tethya sp.* | Rovinj, Croatia (3–20 m) | *Streptomyces* sp. T03 | Actinobacteria | Butenolide                          | IC₅₀ (7.92 μg/mL)    | *T. brucei* | [128]      |
| *Petrosia ficiformis* | Milos, Greece (ND) | *Streptomyces* sp. SBT344 | Actinobacteria | Unidentified                        | IC₅₀ (<10 μg/mL)     | *T. brucei* | [138]      |
| *Sarcotragus foetidus* | Milos, Greece (ND) | *Modestobacter* sp. SBT694 | Actinobacteria | Unidentified                        | IC₅₀ (<10 μg/mL)     | *T. brucei* | [138]      |
| *Phorbas tenacior* | Crete, Greece (ND) | *Micromonospora* sp. SBT697 | Actinobacteria | Unidentified                        | IC₅₀ (14.87 μg/mL)   | *T. brucei* | [138]      |
| Family                  | Species                             | Location                        | Microorganism               | Unidentified | IC_{50} (µg/mL) | T. brucei brucei |
|------------------------|-------------------------------------|---------------------------------|-----------------------------|--------------|-----------------|------------------|
| Petrosia ficiformis    | Milos, Greece (ND)                  | Streptomyces sp. SBT348         | Actinobacteria              | Unidentified | 16.52           | [138]            |
| Ircinia variabilis     | Milos, Greece (ND)                  | Geodermatophilus sp. SBT361     | Actinobacteria              | Unidentified | 18.60           | [138]            |
| Spiritastrella cunctatrix | Milos, Greece (ND)                  | Rhodococcus sp. SBT367          | Actinobacteria              | Unidentified | 19.97           | [138]            |
| Axinella polyoides     | Banyuls-sur-Mer, France (ND)        | Streptomyces axinellae Pol001T  | Actinobacteria              | Tetracycin 1 | 26.02           | [139]            |
| Axinella polyoides     | Banyuls-sur-Mer, France (ND)        | Streptomyces axinellae Pol001T  | Actinobacteria              | Tetracycin 2 | 40.35           | [139]            |
| Axinella polyoides     | Banyuls-sur-Mer, France (ND)        | Streptomyces axinellae Pol001T  | Actinobacteria              | Tetracycin 3 | 23.18           | [139]            |
| Axinella polyoides     | Banyuls-sur-Mer, France (ND)        | Streptomyces axinellae Pol001T  | Actinobacteria              | Tetracycin 4 | 32.17           | [139]            |
| Axinella polyoides     | Banyuls-sur-Mer, France (ND)        | Streptomyces axinellae Pol001T  | Actinobacteria              | Tetracycin B | 17.20           | [139]            |
| Axinella aerea          | Croatia (3–20 m)                    | Streptomyces sp. 34             | Actinobacteria              | Valinomycin  | 0.12            | Leishmania major |
| Axinella aerea          | Croatia (3–20 m)                    | Streptomyces sp. 22             | Actinobacteria              | Valinomycin  | 0.12            | L. major         |
| Tedarum sp.            | Croatia (3–20 m)                    | Streptomyces sp. 11             | Actinobacteria              | Staurosporine| 1.24            | L. major         |
| Axinella polyoides     | Banyuls-sur-Mer, France (ND)        | Streptomyces axinellae Pol001T  | Actinobacteria              | Tetracycin 3 | 31.72           | L. major         |
| Spheciospongia vagabunda | Croatia (3–20 m)                    | Actinomycetopsis sp. EG49       | Actinobacteria              | growth inhibition (48%) | L. major | [82] |

**Table 4 is organised according to the target protozoa. IC_{50}: half maximum inhibitory concentrations; MIC: minimum inhibitory concentration; ND: not determined.**
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Figure 4. Chemical structures of the antiprotozoal compounds manzamine A (16), valinomycin (17), staurosporine (18) and butenolide (19).

6. Discussion

6.1. Antimicrobial Compounds from Sponge-Associated Microbes: What We Learned So Far

Bioprospecting is the effort to discover natural compounds with therapeutic and biological applications [140]. In line with this definition, sponge-associated microbes offer a huge potential as the source of antimicrobial substances as shown by many microbial isolates being reported to inhibit pathogenic reference strains in vitro and to synthesize active substances against one or several groups of infectious agents. Based on our review, antimicrobial compounds produced by sponge-associated microbes with the most pronounced bioactivity include: 2-undecyl-4-quinolone, sorbicillactone A, stachybotrin D and chartarutine B against HIV-1; truncateol M against H1N1 M; YM-266183, YM-266184, kocurin, mayamycin, sydonic acid, naphthacene glycoside SF2446A2 and trichoderin A against a variety of bacterial strains; saadamycin and YM-202204 against fungi; manzamine-A against malaria; and valinomycin against Trypanosoma. In this case the most pronounced activity is solely based on reported inhibition data and does not yet take potential side effects into account. Therefore the most promising compounds may be ones that have higher IC$_{50}$ values, but cause less side effects. As these data are not available for the majority of the reported compounds, we have focused on the most potent compounds.

Sponge-associated bacteria and fungi are the two groups of microorganisms that have been found to produce antimicrobial compounds (Figure 5). The large majority of the antimicrobial compounds found in sponge-associated microbiota is produced by bacteria (90%), while fungi account for approximately 10% of the compounds reported. Sponge-associated bacteria derived antimicrobial compounds were found from 35 genera (Figure 5B). At a higher taxonomic level, these 35 bacterial genera can be classified into the four phyla Actinobacteria, Proteobacteria, Firmicutes and Cyanobacteria with percentages of 48.8%, 36.6%, 11.4% and 0.4% respectively. In contrast,
sponge-associated fungi that have been found to produce antimicrobials are affiliated solely to the phylum Ascomycota.

Figure 5. Distribution of sponge-associated microorganisms found to produce antimicrobial compounds: (A) Bacteria and Fungi; (B) Bacterial genera; and (C) Fungal genera. Figure 5 was made based on the summary of the taxonomic affiliations of sponge-associated microbes (N = 272) that were found to produce antimicrobials.
Streptomyces is the most prominent genus as indicated by 30% of sponge bacteria-derived compounds. Streptomyces has become a main target for screening for bioactive compounds both from terrestrial and marine environments due to the high diversity of secondary metabolites they produce [141,142]. Of the many sponge-associated Streptomyces isolates reported, Streptomyces sp. HB202 and Streptomyces sp. RV15 are of particular interest in term of producing antibacterial compounds. Streptomyces sp. HB202, isolated from the sponge Halichondria panicea has been documented to produce three antibacterial substances: mayamycin, streptophenazine G and K, which are mainly active against Gram positive pathogenic bacteria (Table 2). Streptomyces sp. RV15, on the other hand, produces the compound naphthacene glycoside which up to now is the only anti-Chlamydia reported from sponge-associated microbes [46]. In addition, the report on crude extract inhibition of Streptomyces sp. RV15 against S. aureus and E. faecalis [82] may give a hint to discover other antibacterial substances from this strain. Streptomyces sp. Hedaya48 is currently the most potent sponge-associated bacterial isolate for antifungal activities with the production of saadamycin and 5,7-dimethoxy-4-p-methoxylphenylcoumarin [107]. In addition, isolation of the anti-Trypanosoma and anti-Leishmania compounds valinomycin, staurosporine and butenolide from Streptomyces sp. 43, 21 and 11 [128], affirms Streptomyces as the currently most prominent producer of antimicrobial substances from sponges.

Pseudovibrio follows as the second most prolific bacterial genus isolated from sponges (20%) with respect to antimicrobial activities. Reports on Pseudovibrio ssp. are concentrated on antibacterial activity and are mainly based on screening of crude extracts. Up to now, tropidithetic acid is the only antibacterial compound that has been identified from Pseudovibrio [72]. Although representing a lower percentage of the sponge-associated bacteria found to produce antimicrobials than Streptomyces and Pseudovibrio, 9% of the currently known bioactives was found to be produced by sponge-associated Bacillus ssp., with activities against viruses, bacteria and fungi. Bacillus cereus QNO3323 is currently the most prominent antimicrobial producer from this genus with the very potent thioproteptides YM-266183 and YM-266184 that are active against Gram positive bacteria.

Sponge-associated Ascomycota found to produce antimicrobials can be further classified into 12 genera. Of these 12 fungal genera, Aspergillus (30%) and Penicillium (23%) are currently the two most prominent groups of sponge-associated fungi reported as antimicrobial producers. This finding is not surprising since both Aspergillus and Penicillium are known prolific producers of secondary metabolites from other sources [143]. Aspergillus versicolor [58] and an unidentified Aspergillus sp. isolated from the sponge Xestospongia testudinaria [48] showed a strong antibacterial activity as indicated by potent inhibition of pathogenic bacteria. The antimicrobial activities found from sponge-associated Penicillium ssp. are particular remarkable as it is the only fungal genus that is found to produce antivirals, antibacterials antifungals and antiprotozoals. Penicillium chrysogenum [26] and Penicillium sp. FF01 [57] are to the most promising sponge-associated Penicillium isolates for which anti-HIV activity (sorbicillactone) and antibacterial activity (citrinin) were reported, respectively. Sponge-derived Stachybotrys ssp. are only known for antiviral activity, particularly against HIV and enterovirus 71 (EV71), and there are no reports of other antimicrobial activities. Generally, although the number of produced antimicrobials is outnumbered by those of sponge-associated bacteria, sponge-associated fungi should be considered as an important reservoir of antimicrobial compounds.

When the chemical structures of sponge-microbe-derived compounds are considered, a rather diverse array of structures is observed, including peptides, terpenoids, phenazines, indoles, phenoles and polyketides. Sixty percent of the antivirals from sponge-associated microbes are ketone derivatives (quinolone, sorbicillactone, isoindolinone, butyrolactone, furanone, xanthone, methanone, phenone). Peptide derivatives constitute 19% of the total identified antibacterial substances and roughly 12.5% from the total antimicrobial compounds reviewed here. Phenazine derivatives are the second most frequently isolated class of antibacterial compounds from sponge-associated microbes (15%) as exemplified in this review by the antibacterial compounds streptophenazine [89], phenazine alkaloid antibiotics [55], 6-hydroxymethyl-1-phenazine-carboxamide and 1,6-phenazinedimethanol [94].
Phenazine is a nitrogen-containing heterocyclic compound with a wide range of biological activities [67,144], and several studies from terrestrial environments and chemically synthesized phenazines have been reported as antiviral [145], antibacterial [146], and antimalaria [147]. Moreover, this group of compounds is attractive for therapeutic application since their structures are relatively small and hence can easily reach tissues and organs [67,148].

6.2. Discovering Antimicrobial Compounds from Sponge-Associated Microbes: From Culture-Dependent to Culture-Independent Methods

Isolation of antimicrobial producers provides a valuable basis for assessing the biotechnological potential of sponge-associated microbes. In a wider perspective, however, only a small fraction of this sponge-microbial community has been isolated under laboratory conditions leaving the majority resistant to in vitro growth with current cultivation approaches [15,149,150]. Several studies have focused on improving cultivability of sponge-associated microbes. Some of the approaches include using low nutrient media [151], floating filter cultures [152], employing different carbon sources, e.g., lectin [153], sponge extracts [152], and in situ cultivation using a diffusion growth chamber [154]. Furthermore, flow-cytometry and density gradient centrifugation have been applied to separate sponge cells from their associated bacteria to enrich the inoculum [155,156]. Additionally, co-cultivation through mixing of two or more microbial isolates in vitro [157] is an approach proposed to discover more natural compounds from sponge-associated microbes. The idea behind co-culture lies in the fact that many biosynthetic gene clusters found in microorganisms remain cryptic under standard laboratory conditions, and co-cultivation might provide a possibility to activate these silent genes [158,159]. As an example, the co-culture by Dashti et al. [98] of the sponge-associated Actinobacteria, Actinokinespora sp. EG49 and Nocardiopsis sp. RV163, resulted in isolation of the antibacterial compound 1,6-dihydroxyphenazine, which was not found from the individual isolates. However, even if the cultivability of sponge-associated microbes is improved, there is a long way ahead to reach a point that we will be able to isolate and routinely cultivate 50% of the microbes that are found in sponges. At the same time, the advance of genetic and molecular studies has resulted in the development of tools to study genes, transcripts and proteins by directly analyzing environmental DNA, RNA and proteins, thus bypassing cultivation procedures [157]. In relation to screening for antimicrobial activity, metagenomics has been applied to identify antimicrobials of uncultivated microorganisms from terrestrial environments, such as the antimycobacterial nocardamine, the putative antibacterial activity of terragines A–E [160], violacein that is active against S. aureus, Bacillus sp. and Streptococcus sp. [161] and a polyketide with activity against the yeast Saccharomyces cerevisiae [162].

Two main metagenomic approaches, functional screening and sequence homology-based methods, are generally distinguished [163]. Functional screening relies on detection of the metabolic activities of metagenomic library clones without requiring any prior sequence information [163–165]. Gillespie et al. [9] applied function-based metagenomics with E. coli as expression host, to identify the antibiotics turmoyycin A and B from a soil sample. MacNeil et al. [166] identified the antimicrobial indirubin by constructing a BAC (bacterial artificial chromosome) library in E.coli. Yung et al. [167] reported two hydrolytic enzymes from fosmid clones CcAb1 and CcAb2, which were derived from a metagenome of the sponge Cymbastela concentrica using E. coli as the host. Both fosmid clones inhibited the growth of Bacillus sp. with an inhibition diameter of 20 mm, and clone CcAb1 showed additional inhibition of S. aureus and an Alteromonas sp. with diameters of inhibition of 50 mm and 60 mm, respectively. Further phylogenetic analysis showed that active genes encoding for these enzymes were of microbial origin [167]. He et al. [168] constructed a fosmid library of the sponge Discoderma calyx using E. coli as the host and identified antimicrobial activity of the enzyme 3-hydroxypalmitic acid against B. cereus and C. albicans. In addition, using the same approach He et al. [169] observed an active clone, pDC113, that displayed a clear inhibition zone against B. cereus. Subsequently, 11 cyclodipeptides were identified from this clone. Generally, it can be stated that although a number of antimicrobials have been discovered through functional screening of metagenomic libraries from
sponges, the expression of large gene clusters such as those encoding (polyketide synthase (PKS) and (non-ribosomal peptide synthetase (NRPS) is still a difficult hurdle to take. Several key elements need to be considered to achieve successful expression of biosynthetic gene clusters; namely mobilizing the biosynthetic pathway into a suitable vector, selecting an appropriate heterologous host and stably maintaining the gene clusters in the host [170]. The size of many of these gene clusters requires the use of cloning vectors that can accept large inserts, such as fosmids, or BACs if the required insert size is over 100 kb [171]. Selection of heterologous expression systems in particular is a crucial factor before applying functional metagenomics to identify antimicrobials, because expression hosts are microbes as well and especially clones that express genes encoding for enzymes involved in production of antimicrobials may therefore be non-viable. Ongley et al. [170] pointed out some considerations in selecting an expression host such as relatedness to the native producer, availability of genetic tools and precursors, a high growth rate, and suitability for fermentation at a large scale. *E. coli*, the most commonly used expression host, has limitations for expressing parts of metagenomes because, e.g., of the sheer size of some gene clusters, genes with deviating codon usage, incompatible regulatory elements, lack of biosynthesis precursors or unavailability of posttranslational modifications [165,172]. Therefore, in order to make screening for antimicrobials through metagenomic libraries more efficient, it is of utmost importance to diversify the suite of expression hosts used. Several non-*E. coli* hosts, such as Agrobacterium tumefaciens, Bacillus subtilis, Burkholderia graminis, Caulobacter vibrioides, Pseudoalteromonas haloplanktis, Pseudomonas putida,Ralstonia metallidurans, Rhizobium leguminosarum, Streptomyces avermitilis, S. albus, Pseudomonas putida, Sulfolobus solfataricus, Thermus thermophilus, Thioacapsa roseopersicina and Saccharopolyspora sp. have been developed and should be more seriously considered as expression hosts when performing metagenomic screenings for antimicrobials [165,172,173].

Sequence-based screening, on the other hand, requires information on the sequence of genes involved in the production of a natural product as guidance to search for similar sequences in a sequenced metagenomic library or scaffolds reconstructed from direct metagenomic sequencing [165]. Homology-based screening is suitable to identify a compound with highly conserved biosynthesis pathways, e.g., those mediated by PKS and NRPS [174]. Piel and colleagues [175–179] applied this method, and identified the antitumor polyketide onnamide from uncultivated bacteria of the sponge *T. swinhoei*. Sequence-based screening was applied by Fisch [180] to unravel the complete pathway of the polyketide psymberin that was found to possess a potent antitumor activity, from uncultivated sponge-associated microbes. By sequence-based screening of metagenomic libraries, Schirmer et al. [181] reported diverse polyketide gene clusters in microorganisms from the sponge Discodermia dissoluta. The development of techniques that yield longer read lengths, such as Pacific Biosciences (PacBio) RS II SMRT (Single Molecule Real-Time) sequencing technology, in which a single read can be extended over 10 kbp [182], can be instrumental in increasing the accuracy in assembling large gene clusters. Application of PacBio for secondary metabolite gene clusters has been reported by Alt and Wilkinson [183], who identified the 53,253 bp genomic fragment encoding the transacyltransferase (trans-AT) polyketide synthase (PKS) from a marine *Streptomyces* sp responsible for the production of the antibiotic anthracimycin (atc). Furthermore, using *Streptomyces coelicolor* as heterologous expression host, the authors confirmed production of anthracimycin [183]. Furthermore, single-cell analysis by combining cell separation and fluorescence-assisted cell sorting (FACS) could be a strategy to overcome the complexity of the microbial community in sponges since this method can be used to select for genomes from microbes that are present in low abundance in the sponge leading to a simplified reconstruction of secondary metabolite gene clusters present in these bacteria [184]. This strategy has been applied by Wilson et al. [185] for resolving the gene clusters encoding the machinery needed for the production of the polytheonamides produced by the candidate genus *Entotheonella* from the sponge *Theonella swinhoei*.

Inspired by these examples, homology-based screening could be further exploited to identify biosynthesis gene sequences that could lead to the identification of novel antimicrobial substances from
Nature’s excessive diversity. Moreover, application of homology-based screening can benefit from publicly available metagenomic sequencing data and prediction tools for analyzing biosynthesis gene clusters, e.g., AntiSMASH (Antibiotics and Secondary Metabolite Analysis Shell) [186,187]. Application of sequence-based screening, however, is limited by the fact that the found sequences need to be related to known compounds, inherently limiting the potential for novelty. Furthermore, information on gene sequences is no guarantee that the acquisition of a complete gene pathway has been obtained [188]. Therefore, sequence-based methagenomics should ideally be complemented by chemical analysis to confirm whether the predicted compound exists and is fully functional (Figure 6).

Figure 6. General overview of the strategies used to discover antimicrobial compounds from sponge-associated microorganisms.

7. Conclusions and Outlook

Sponge-associated microbes already offer a rich source of potent antimicrobial compounds against viruses, bacteria, protozoa and fungi, and currently available compounds are predominantly active against HIV-1, H1N1, nosocomial Gram positive bacteria, Escherichia coli, Plasmodium spp, Leishmania donovani, Trypanosoma brucei, Candida albicans and dermatophytic fungi. Streptomyces, Pseudovibrio, Bacillus, Aspergillus and Penicillium are the microbial genera associated with sponges from which potent antimicrobial compounds are most frequently isolated. However, none of the antimicrobial compounds highlighted in this review have been successfully marketed as pharmaceuticals. To clearly translate bioactivity of these important compounds it is crucial to further unravel their mode of actions and measure their level of toxicity, since the majority of these studies has been focused on in vitro bioassays and elucidation of the chemical structures only.

The known versatility of antimicrobial activities found in sponge-associated microorganisms could easily be expanded even without considering additional sponge sampling campaigns. Bioactivity screens of identified compounds or undefined sponge extracts is often restricted to a specific antimicrobial activity. The selection, for instance, relies on the specific research activities of the
groups involved in isolating the microbes [117]. Consequently, it is probably safe to assume that other potent antimicrobial properties from many sponge isolates and their bioactive compounds remain undetected. Therefore, known antimicrobial compounds and producer strains are a valuable source for additional antimicrobial activities screenings using different target types (viruses, bacteria, fungi, protozoa and beyond). In addition, sponge-derived strain collections that comprise isolates that tested negative for antimicrobial activity at first may have done so, because the compound of interest is not produced under standard laboratory conditions. Exposure of these strains to potential microbial targets may lead to recovery of bioactivity that would otherwise go unnoticed.

Ideally, researchers who isolate microbes from sponges will deposit them to publicly available culture collections so that laboratories with complementary expertise and interests could benefit and screen the deposited isolates for different antimicrobial activities. This will make exchange of materials and knowledge that can be obtained much more efficient. Importantly, a fair agreement on intellectual property rights needs to be established for translating this into reality. Lastly, the revolutionary advance of next generation sequencing technologies combined with more diversified heterologous expression systems (Figure 6) are expected to open up the large unexplored reservoir of antimicrobials produced by yet uncultivated sponge-associated microbes.

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