Natural Products from Actinomycetes of Marine Organisms

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The actinomycetes have proven to be a rich source of bioactive secondary metabolites and play a critical role in the development of pharmaceutical researches. With interactions of host organisms and having special ecological status, the actinomycetes associated with marine animals, marine plants, macroalgae, cyanobacteria, and lichens have more potential to produce active metabolites acting as chemical defenses to protect the host from predators as well as microbial infection. This entry focuses on 536 secondary metabolites (SMs) from actinomycetes associated with these marine organisms covering the literature to mid-2021, which will highlight the taxonomic diversity of actinomycetes and the structural classes, biological activities of SMs. Among all the actinomycetes listed, members of *Streptomyces* (68%), *Micromonospora* (6%), and *Nocardiopsis* (3%) are dominant producers of secondary metabolites. Additionally, alkaloids (37%), polyketides (33%), and peptides (15%) comprise the largest proportion of natural products with mostly antimicrobial activity and cytotoxicity. Furthermore, the data analysis and clinical information of SMs have been summarized in this article, suggesting that some of these actinomycetes with multiple host organisms deserve more attention to their special ecological status and genetic factors.

actinomycetes marine animals macroalgae secondary metabolites biological activities

1. Introduction

Actinomycetes are Gram-positive bacteria with a GC-rich linear genome and have proven to be a rich source of secondary metabolites (SMs) of broad structural diversity and biological properties [1]. The ocean has been demonstrated as an ecosystem with many unique forms of actinomycetes [2]. The diversity of marine actinomycetes is determined by the uniqueness of the marine environment: some live freely in seawater, some in the seafloor sediments or sea mud; and some are symbiotic, parasitic, endophytic, or epiphytic with marine organisms [2][3]. Compared with actinomycetes isolated from seawater and sediment samples, recent reports of secondary metabolites from marine actinomycetes associated with a variety of aquatic organisms, including invertebrates such as sponges, corals, ascidians, echinoderms, and vertebrates such as pufferfish, as well as algae and seaweed, have increased significantly [4]. Studies have indicated that multiple active compounds previously isolated from marine invertebrates were possibly produced by their symbiotic microorganisms, especially actinomycetes [5][6][7]. With interactions of the host and having special ecological status, the actinomycetes associated with marine organisms have more potential to produce active metabolites acting as chemical defenses to protect the host from predators and microbial infection.

The objective of this article is to provide an overview of the natural products from actinomycetes associated with marine animals, marine plants, macroalgae, cyanobacteria, and lichens. The present entry was not only summarizing the structural classes and biological activities of SMs but also highlighted the taxonomic diversity of actinomycetes, as well as the data analysis of integrated above information. Some of these metabolites with excellent activity are expected to become new drugs such as antibiotics, antineoplastic drugs, or anticancer drugs. Therefore, actinomycetes with multiple host organisms deserve more attention to their special ecological status and genetic factors.

2. Biology of Actinomycetes Associated with Marine Animals, Marine Plants, Macroalgae, Cyanobacteria and Lichens

Marine actinomycetes are abundant in species and widely inhabit sediments, seawater, and aquatic organisms. At present, these actinomycetes are mainly separated from marine invertebrates especially sponges, ascidians, corals as well as brown algae. It is presently estimated that only 1% of microbes can be separated using traditional culturing techniques, making the potential for this field more compelling [2][6]. However, emerging technologies provide us with the tools to determine overall microbial diversity. As the diversity of metabolites is closely related to biodiversity, the potential for obtaining abundant and novel SMs from actinomyces associated with various marine hosts is relatively high.

The biosynthesis ability of actinomycetes in the production of complex natural products has been known for a long time. Not all actinomycetes, however, are prolific secondary metabolite producers. To assess the diversity and distribution of natural product-producing actinomycetes associated with various marine hosts, it constructed a neighbor-joining phylogenetic tree of 16S rRNA gene sequences. It obtained these associated actinomycetes producing natural products from literature and the antiSMASH database and selected strains with a length of 16S rRNA sequences > 900 bp that were available in the NCBI database to construct the phylogenetic tree. The phylogenetic tree involved 84 strains within nine families, and the family Streptomycetaceae (*Streptomyces*) represents 67% of the actinomycetes, followed by Micromonosporaceae (*Salinispora* and *Micromonospora*), Pseudonocardiaceae (*Saccharopolyspora*) with 18%, 5% of actinomycetes, respectively, indicating the better potential of those three families to produce SMs (**Figure 1**).

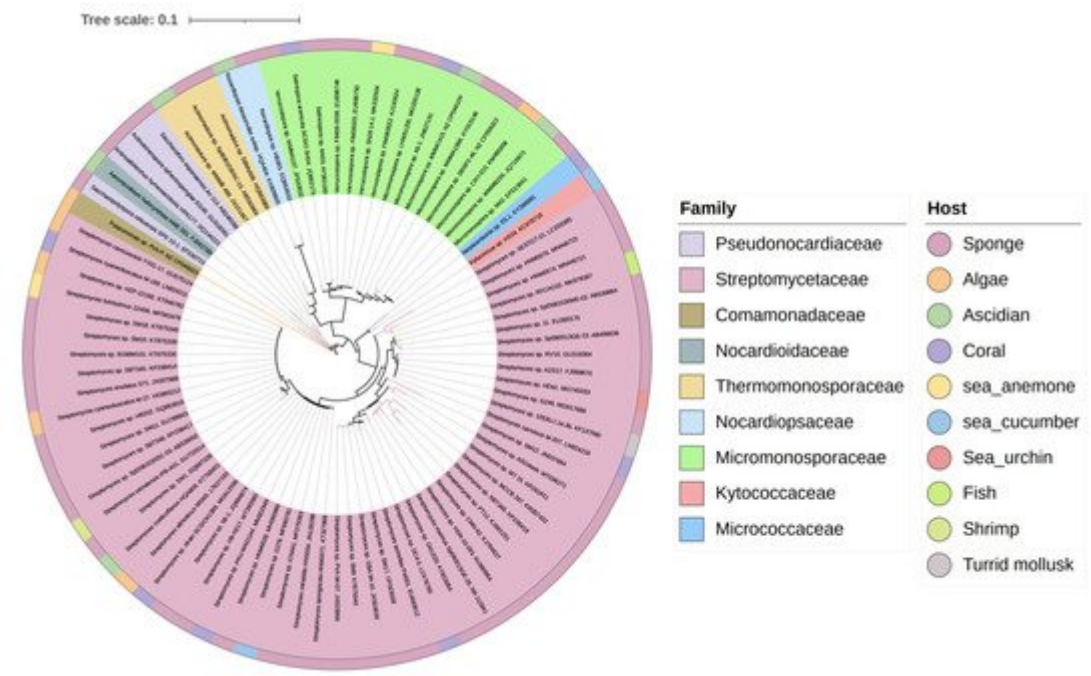

Figure 1. Neighbor-Joining phylogenetic tree based on 16S rRNA gene sequences of natural product-producing actinomycetes. The aligned sequences were analyzed by the bootstrap method with a bootstrap number of 10,000. The colored labels indicate the classification of actinomycetes; the outer color strip shows their host sources.

3. Chemical Structures and Biological Properties of the Actinomycetes Associated with Marine Animals, Marine Plants, Macroalgae, Cyanobacteria, and Lichens

3.1. Natural Products of the Actinomycetes Derived from Marine Animals

Among the 34 animal phyla known on the earth, marine animals account for 33 species, 15 of which are unique to the ocean. Studies have shown that some symbiotic microorganisms are species-specific [8], indicating that marine animals may be rich in microbial resources. And the active substances in marine animals are mostly produced by their associated microorganisms, of which actinomycetes are an important group [5][6][7]. Therefore, actinomycetes associated with marine animals are a flourishing source for novel natural products.

Two novel indolocarbazole alkaloids, 4'-N-methyl-5'-hydroxystaurosporine (**1**) and 5'-hydroxystaurosporine (**2**), as well as the known staurosporine (**3**) (**Figure 2**) were purified from the culture broth of *Micromonospora* sp. L-31-CLCO-002, which was associated with marine sponge *Clathrina coriacea* collected offshore Fuerteventura (Canary Islands). These compounds displayed cytotoxicity against various tumor cell lines[9][10]. The analysis of structure-activity relationships of staurosporine and its derivatives demonstrated that hydroxylation at C-3 of the indolocarbazole moiety led to the increase in anti-proliferative activity, while hydroxylation at C-11 caused a decrease in activity. The results suggested that not only the presence/absence of hydrophilic substitutions but also the position of the alteration within the molecule is significant in the anti-proliferative activities of the various staurosporine analogs [11][12].

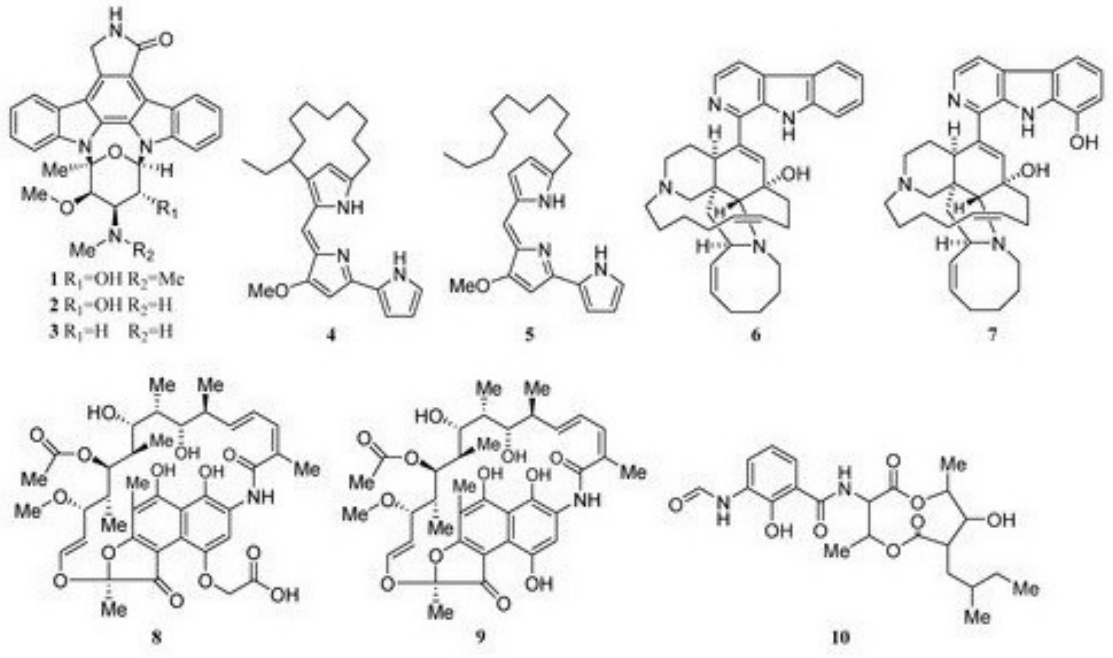

Figure 2. Structures of compounds **1**–**78**.

Isolation of two rifamycins B and SV (**8**, **9**) (**Figure 2**) was reported in 2006 from the *Salinispora* sp. strain M403 associated with sponge *Pseudoceratina clavata*. This is the first recorded source of rifamycins from marine bacteria and *Salinispora* sp. represents a potential new source of rifamycins outside the genus *Amycolatopsis*. Rifamycins are a group of antibiotics that belong to the ansamycin family with pronounced activities against Gram-positive bacteria[9][13]. The structure and activity relationship of rifamycins with many different targets have been extensively studied[14][15] . The rifamycin SV has been successfully widely used in the clinical treatment of tuberculosis, leprosy, and mycobacterial infections.

3.2. Natural Products of the Actinomycetes Derived from Marine Plants, Macroalgae, Cyanobacteria, and Lichens

Streptomyces cyaneofuscatus M-27 and *Streptomyces carnosus* M-40 were associated with diverse intertidal marine brown macroalgae (*Phyllum heterokontophyta*, *Fucus spiralis*, and *Cystoseira baccata*) from the central Cantabrian Sea. *Streptomyces cyaneofuscatus* M-27 produced several antitumor antibiotics of the anthracycline family, of which two antibiotics were identified as daunomycin (**307**) and cosmomycin B (**308**) (**Figure 3**). And it also led to the isolation of an antifungal macrolactam maltophilin (**309**) (**Figure 19**). In addition, lobophorine B (**310**) (**Figure 3**) was separated from *Streptomyces carnosus* M-40 derived from macroalgae *Cystoseira baccata* with anti-inflammatory and antituberculosis properties[16].

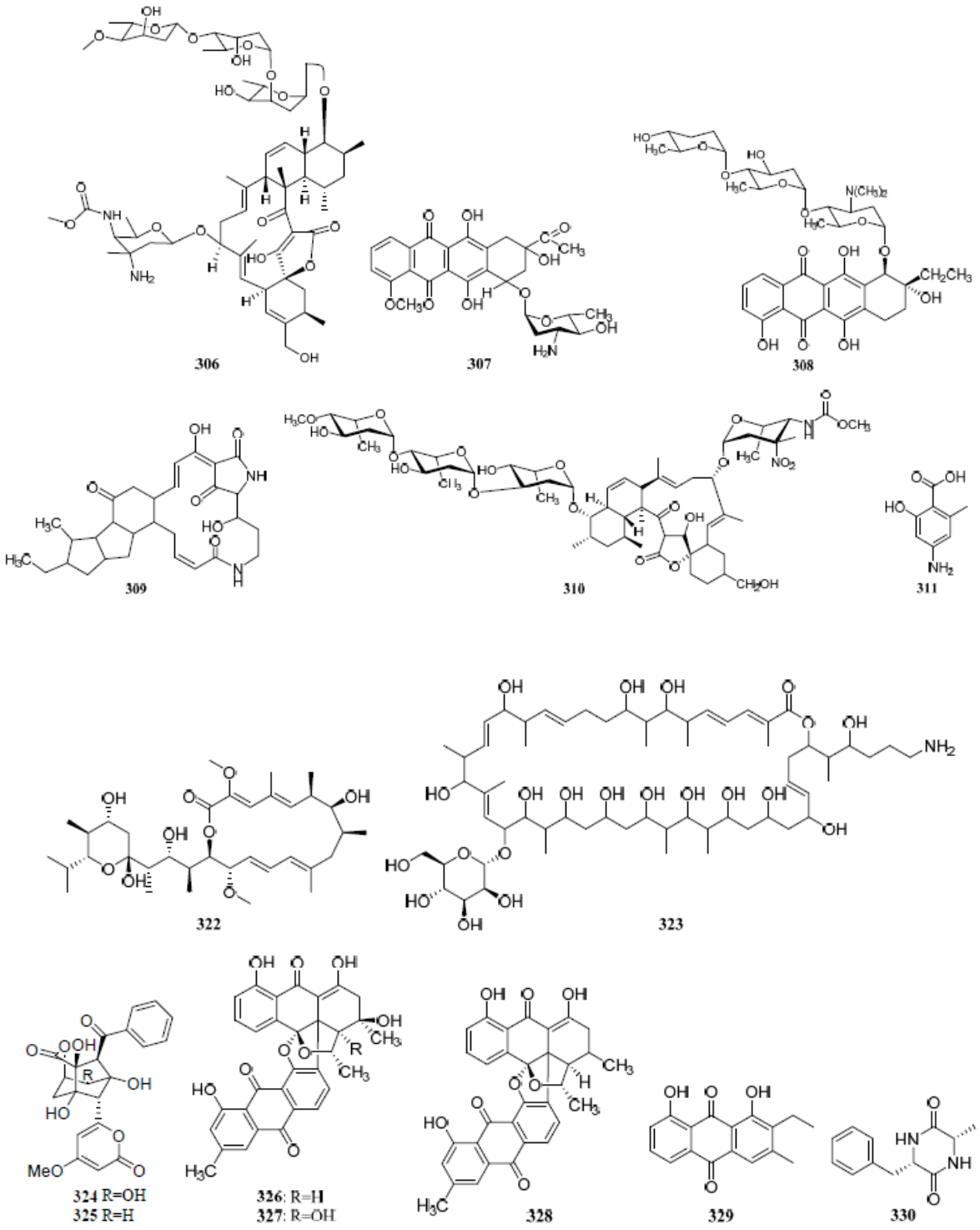

Figure 3. Structures of compounds **306–331**.

Isolation of antibiotic Bisanthraquinones (**326**–**328**) (**Figure 3**) was reported from *Streptomyces* sp. N1-78-1 associated with unicellular cyanobacteria parasitized on the tunic surface of *Ecteinascidia turbinate* collected in La Parguera, Puerto Rico. The metabolites **326** and **327** potently inhibited the growth of MRSA. All compounds were moderately active against HCT-116 human colon tumor cells [17].

3.3. Data Analysis of the Secondary Metabolites from Actinomycetes Associated to Various Hosts

A total of 536 metabolites have been discovered from 155 actinomycetes associated with various marine hosts belonging to 22 genera. Among them, alkaloids (37%), polyketides (33%), and peptides (15%) comprise the largest proportion of secondary metabolites, while *Streptomyces* (68%), *Micromonospora* (6%), and *Nocardiopsis* (3%) are the dominant producers (**Figure 3**). Figure 22 showed the distribution of secondary metabolites currently identified in different host-related actinomycetes. The majority of the secondary metabolites were isolated from the actinomycetes associated with sponges (47%), ascidians (11%), and corals (9%), as well as brown algae (5%). Furthermore, the Sankey diagram and histogram were done to show the distribution of secondary metabolites produced by actinomycetes with various genera derived from different hosts, which is convenient for readers to have an overall understanding of the current secondary metabolites from marine organism-associated actinomycetes (**Figures 6** and **7**).

Approximately 64% of the SMs displayed various biological activities, especially antimicrobial activity and cytotoxicity (**Figure 8**). Interestingly, some of these active metabolites with multiple biological properties deserve more attention (Table S7); for example, metabolites with cytotoxicity usually have antibacterial or antiparasitic activities, and some metabolites showed antibacterial activity can also act as enzyme inhibitors. This study advances the knowledge of these actinomycetes in respect to the metabolic potential of medicinal lead compounds.

3.4. Clinical Information of the Secondary Metabolites

Molecules with excellent activities, which have been in clinical applications or have entered clinical trials, were listed in Table 1. For example, rifamycin SV (**9**) is the earliest rifamycin antibiotic used in clinical application. Tetrodotoxin (**105**) has been widely used as an analgesic, sedative, antispasmodic, and local anesthetic in clinics. And daunomycin (**307**) has a good effect on acute myeloid leukemia. In addition, for these drugs already in clinical use, more clinical trials are underway for new diseases or new usages. (More detailed information can be found on the website ClinicalTrials.gov accessed on 25 October 2021).

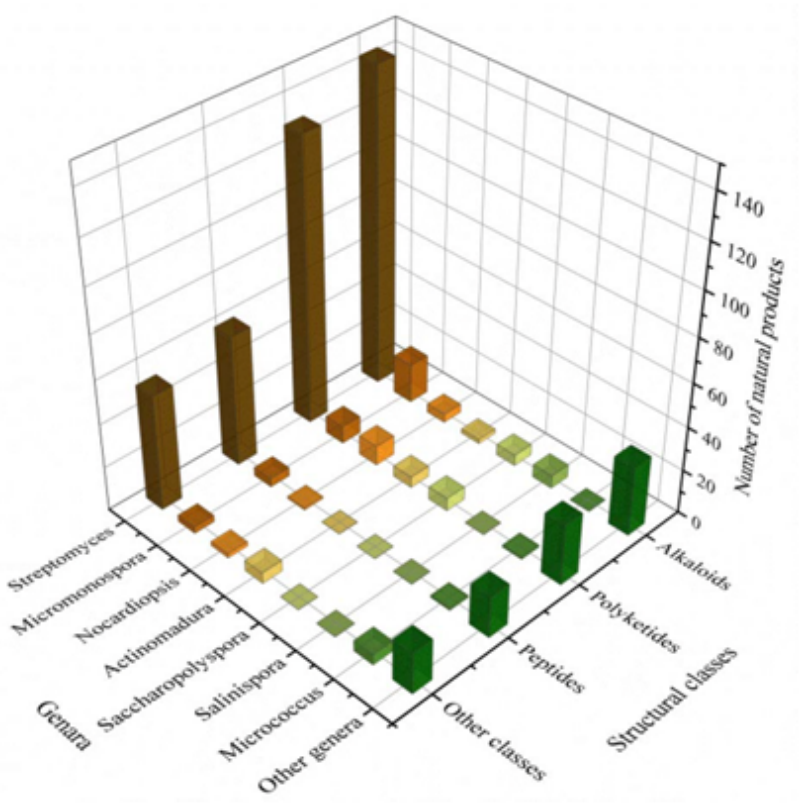

Figure 4. The structural distribution of metabolites from the actinomycete is divided by genera.

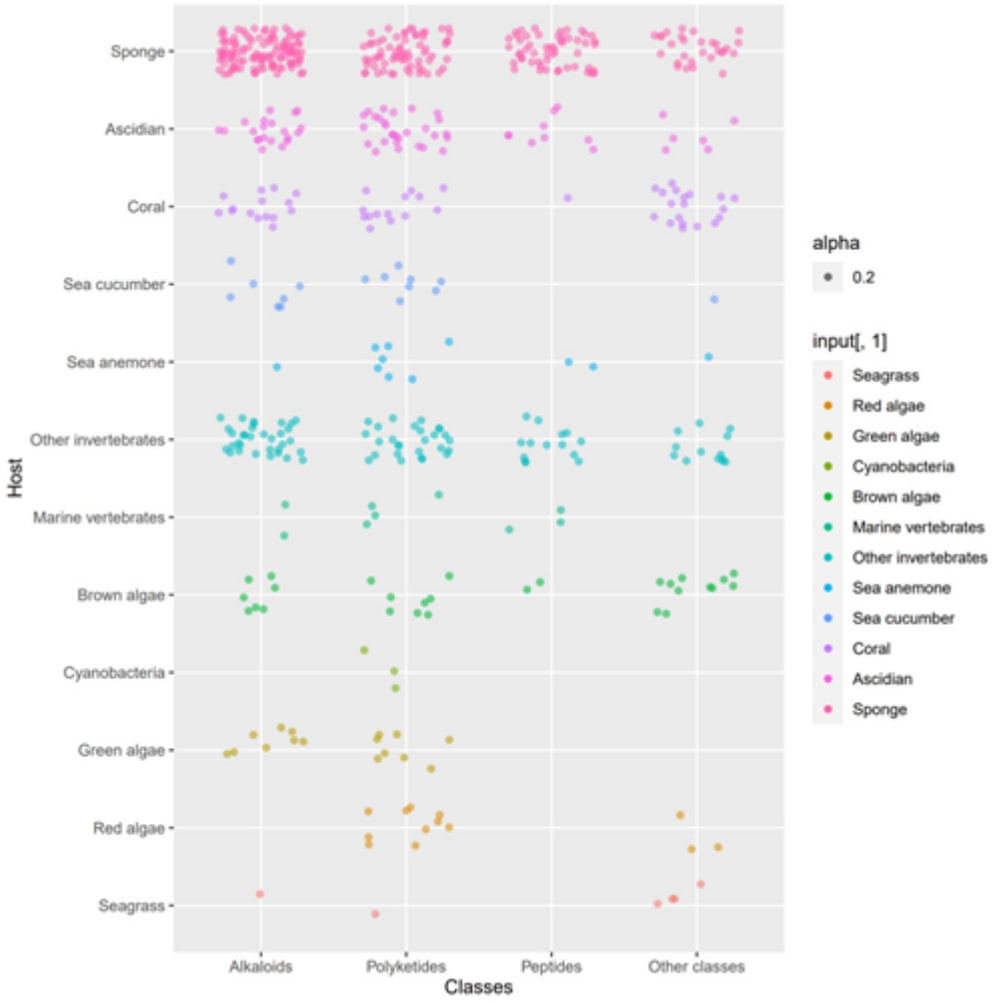

Figure 5. The structural distribution of metabolites from actinomycetes associated with various hosts. The dots in that figure represent the number of compounds and the color darkens when the dots overlap.

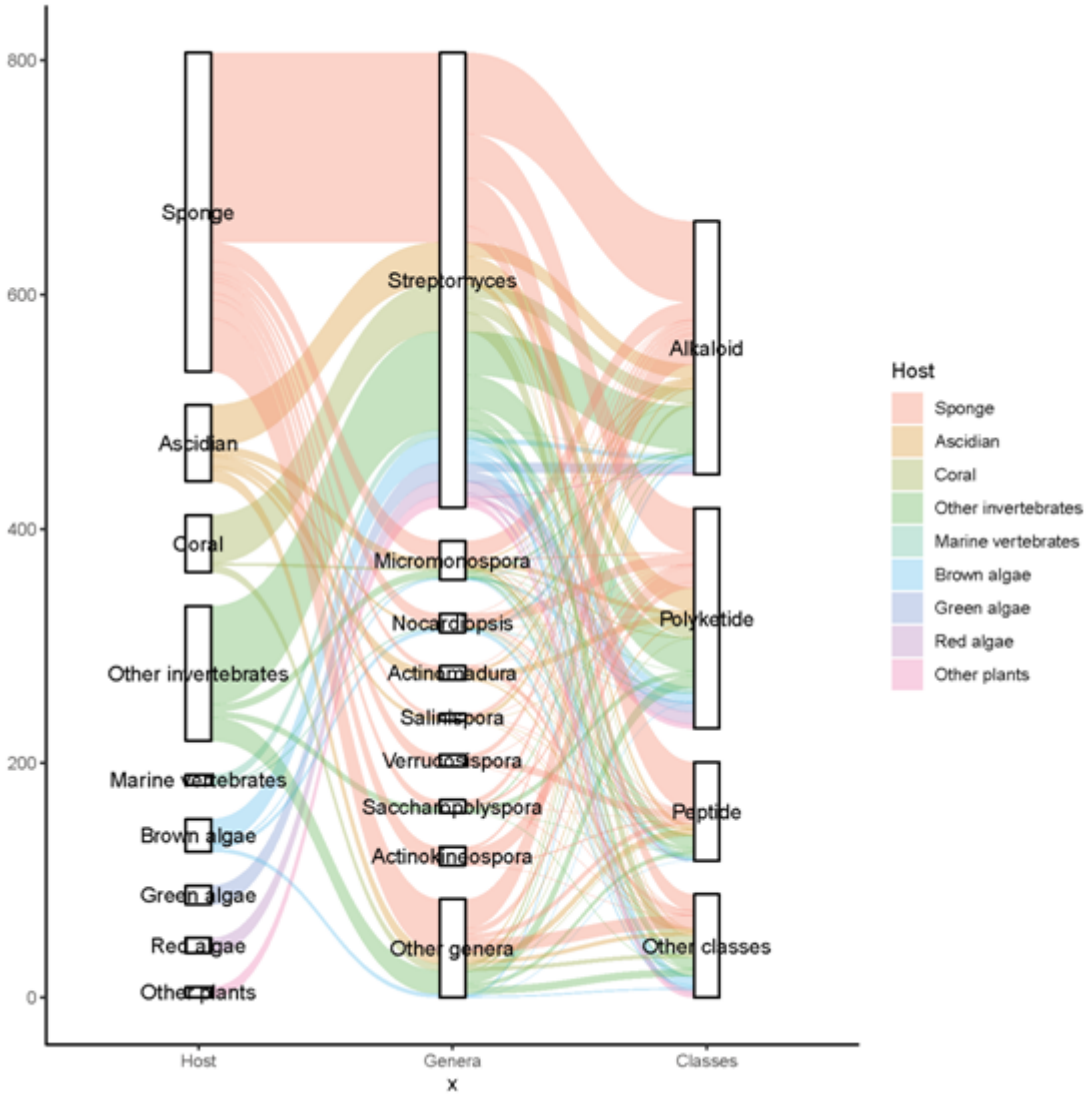

Figure 6. The distribution of secondary metabolites produced by actinomycetes with various genera derived from different hosts. The width of the extended branches in the figure corresponds to the number of secondary metabolites.

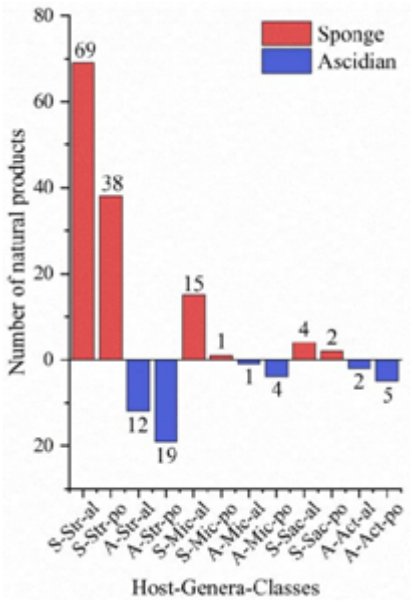

Figure 7. The structural distribution of metabolites from three dominant actinomycetes in the main host's sponge and ascidian. The x-axis labels represent the host-genus-structure classes of actinomycetes: (A) Ascidian; (S) Sponge; (Str) *Streptomyces*; (Mic) *Micromonospora*; (Sac) *Saccharopolyspora*; (Act) *Actinomadura*; (al) alkaloid; (po) polyketide.

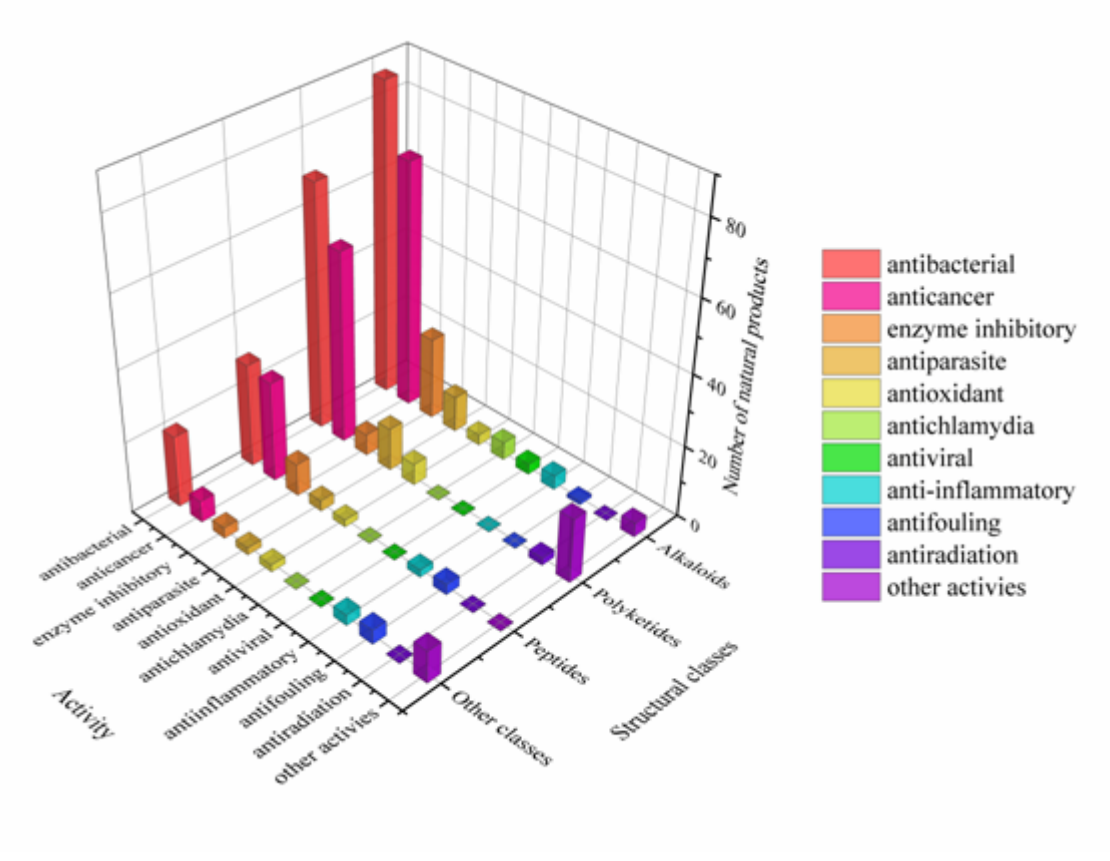

Figure 8. The diversity distribution of biological activity with different structures.

Table 1. Clinical information of the secondary metabolites.

Compounds	Study Title	Conditions	Related Compounds for Interventions	Phase	NCT Number
Rifamycin SV (**9**)	Rifamycin SV-MMX® 400 mg b.i.d. vs. Rifamycin SV-MMX® 600 mg t.i.d. vs. Placebo in Acute Uncomplicated Diverticulitis	Uncomplicated Diverticulitis	Rifamycin SV-MMX®	Phase 2	NCT01847664
	Rifamycin SV-MMX® 600 mg Tablets Administered Three or Two Times Daily to Patients With IBS-D	Diarrhea-predominant Irritable Bowel Syndrome	Rifamycin SV	Phase 2	NCT03099785
	Study to Evaluate Safety and Efficacy of Rifamycin SV Multi-Matrix System (MMX) for the Treatment of Traveler's Diarrhea (TD)	Traveler's Diarrhea	Rifamycin SV MMX	Phase 3	NCT01142089
	Rifamycin SV-MMX® Tablets Versus Ciprofloxacin Capsules in Acute Traveller's Diarrhoea	Traveler's Diarrhea	Rifamycin SV-MMX®	Phase 3	NCT01208922
Diazepinomicin (**28**)	A Phase I Study of ECO-4601 in Patients With Advanced Cancer	Tumors Glioma Colorectal Cancer	ECO-4601	Phase 1	NCT00338026
	Efficacy Study of TLN-4601 in Patients With Recurring Glioblastoma Multiforme	Glioblastoma Multiforme	TLN-4601	Phase 2	NCT00730262

Table 1. *Cont.*

Compounds	Study Title	Conditions	Related Compounds for Interventions	Phase	NCT Number
Staurosporine (**3**)	A Phase I Trial of Continuous Infusion UCN-01 in Patients With Refractory Neoplasms	Breast Cancer Lymphoma Neoplasm Prostatic Neoplasm	7-hydroxystaurosporine (UCN-01)	Phase 1	NCT00001444
	PK and Safety of Midostaurin in Subjects With Impaired Hepatic Function and Subjects With Normal Hepatic Function	Hepatic Impairment	Midostaurin	Phase 1	NCT01429337
	Phase I Combination of Midostaurin, Bortezomib, and Chemo in Relapsed/Refractory Acute Myeloid Leukemia	Acute Myeloid Leukemia AML With Multilineage Dysplasia Following Myelodysplastic Syndrome	Midostaurin	Phase 1	NCT01174888
	Azacitidine With or Without Nivolumab or Midostaurin, or Decitabine and Cytarabine Alone in Treating Older Patients With Newly Diagnosed Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome	Acute Myeloid Leukemia Myelodysplastic Syndrome Myelodysplastic Syndrome With Excess Blasts-2	Midostaurin	Phase 2 Phase 3	NCT03092674
Tetrodotoxin (**105**)	Tetrodotoxin Open-label Efficacy and Safety Continuation Study	Pain Cancer	Tetrodotoxin	Phase 3	NCT00726011
	Safety & Efficacy Study of Subcutaneous Tetrodotoxin for Moderate to Severe Inadequately Controlled Cancer-related Pain	Pain Cancer	Tetrodotoxin	Phase 3	NCT00725114
Daunomycin (**307**)	Pilot Study Efficacy and Tolerance Fish Oil Emulsion Daunorubicin and Cytarabine Treatment of AML Younger Patients	Acute Myeloid Leukemia (AML)	Daunorubicin	Phase 2	NCT01999413
	A Randomized Study of Gemtuzumab Ozogamicin (GO) With Daunorubicine and Cytarabine in Untreated Acute Myeloid Leukemia (AML) Aged of 50–70 Years Old	Acute Myeloid Leukemia	Daunorubicin	Phase 3	NCT00927498
Linoleic acid (**340**)	Proof of Principle Trial to Determine if Nutritional Supplement Conjugated Linoleic Acid (CLA) Can Modulate the Lipogenic Pathway in Breast Cancer Tissue	Breast Cancer	Conjugated Linoleic Acid (CLA)	Early Phase 1	NCT00908791
	Conjugated Linoleic Acid / Leucine Versus Metformin on Visceral Fat in Metabolic Syndrome	Metabolic Syndrome	Conjugated linoleic acid/Leucine	Phase 2	NCT02629627
	Conjugated Linoleic Acid and Atherosclerosis	Atherosclerosis	Cis9, trans11 conjugated linoleic acid	Phase 3	NCT00706745
Actinomycin D (**251**)	Dactinomycin in Treating Patients With Persistent or Recurrent Gestational Trophoblastic Neoplasia	Gestational Trophoblastic Tumor	Dactinomycin	Phase 2	NCT00003688
	Addition of Ipilimumab (MDX-010) To Isolated Limb Infusion (ILI) With Standard Melphalan and Dactinomycin In The Treatment of Advanced Unresectable Melanoma of The Extremity	Melanoma	Dactinomycin	Phase 2	NCT01323517
	Methotrexate Compared With Dactinomycin in Treating Patients With Gestational Trophoblastic Neoplasia	Gestational Trophoblastic Neoplasia	Dactinomycin	Phase 3	NCT00003702

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