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The natural products discovered in marine sponge-associated microorganisms: structures, activities, and mining strategy

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It is well known that microorganisms are abundant in sponges, which make up 50%-60% of the host biomass. Moreover, mounting evidence suggests that bacteria, fungi, and cyanobacteria, all associated with sponges, are the true creators of the bioactive compounds identified from sponges. The discovery of 774 structurally active compounds from 1998 to 2017 presents a good overview of natural product resources in sponge-associated microorganisms. During the last 5 years, many new molecules, including peptides, polyketides, alkaloids, and terpenes, have been identified from sponge-associated microorganisms through various mining strategies, exhibiting a wide range of biological activities, such as anti-microbial, anti-cancer, enzyme inhibition, and antioxidant properties. In this paper, 140 compounds produced by sponge-associated microorganisms from 2017 to 2022 are systematically discussed in terms of their structures, biological activities, and strain sources, as well as the mining strategies, which not only further updates the natural product library of sponge-associated microorganisms but also provides a new guideline for exploring the "dark matter" in sponges.

KEYWORDS

sponge, sponge-associated microorganism, natural product, biological activity, mining strategy

1 Introduction

Natural products, also known as secondary metabolites, are small molecules produced by living organisms including plants, invertebrates, and microorganisms. They have been frequently utilized in clinical treatment and are crucial for the development of contemporary medicine (Newman and Cragg, 2018; Liu et al., 2020b). The ocean covers

more than 70% of the earth's surface and is the home for a lot of living organisms, making it an excellent target to explore natural products (Martins et al., 2019). The statistics data show that 2659 compounds were identified from sponges between 2010 and 2019, occupying 47.2% of the marine natural products discovered from all invertebrates (Calado et al., 2022). As a result, sponges are regarded as one good source of bioactive compounds and are frequently referred to as “chemical factories” or “gold mines” (Gavriilidou et al., 2021).

The sponges (phylum Porifera) are the simplest and likely the most ancient group of animals with a fossil record dating over 580 million years (Li et al., 1998; Love et al., 2009). They attach to the solid substrate in the sea and feed on bacteria and bacteria-sized particles in the filtered water. Therefore, sponges are also responsible for the purification of water indirectly (Taylor et al., 2007). Sponges are important parts of the benthic zone with a worldwide distribution, from freshwater to marine and from intertidal to the deep sea (Taylor et al., 2007). So far, as many as 15,000 species have been identified, including mainly are Calcarea, Hexactinellida, Homoscleromorpha, and Demospongiae (Kiran et al., 2018), but their diversity may be richer (Abdelmohsen et al., 2014). Another reason for the ongoing interest in sponges is their close association with microorganisms, including bacteria, fungi, and viruses (Buttachon et al., 2018; Kiran et al., 2018). Microorganisms have been known to form a variety of distribution relationships with sponges, including extracellular exosymbiosis, extracellular endo-symbiosis, intracellular symbiosis, and intranuclear symbiosis, accounting for 50%-60% of the host biomass (Lee et al., 2001; Zhang et al., 2017). Indeed, the relationship between sponges and microorganisms is very complicated, because the microbial population can be selectively enriched by sponge-active metabolites (Sathiyarayanan et al., 2017).

Under the ecological pressure of intense competition, overgrowth, poisoning, infection, and predation, sponges have evolved defensively chemical weapons (secondary metabolites) to protect themselves from threats (Proksch, 1994), including amino acids, nucleosides, polyethers, alkaloids, macrolides, porphyrins, terpenes, and sterols. Most of them exhibit anti-cancer, anti-inflammatory, anti-fungal, and anti-viral activities (Shukla, 2016). However, mounting evidence shows that these weapons actually originate from microorganisms rather than sponges themselves. The surface or inner space of the sponge is richer in nutrients than seawater, thus providing a perfect and safe habitat for microorganisms (Lee et al., 2001). In return, microorganisms participate in the construction of the sponge's chemical defense system. For example, Bovio et al. discovered cyclo-L-Trp-L-Ala, echinulin, neocheinulin A, dihydroauroglaucin, and flavoglaucin from the sponge-associated fungus *Eurotium chevalieri* MUT 2316, showing the inhibition on the adhesion and growth of marine bacteria and microalgae (Bovio et al., 2019).

Sponge-associated microorganisms, as important treasures for natural product discovery, have received a lot of attention. Of 774 natural products were identified from sponge-associated microorganisms between 1998 and 2017 (Cheng et al., 2020). Meanwhile, a series of review articles systematically make a

systematic discussion the natural products from sponge-associated microbes (Abdelaleem et al., 2022; Alahmari et al., 2022; Amelia et al., 2022; Esposito et al., 2022; Bibi et al., 2017). Therefore, with the technology being updated, many new research methods have been applied to explore natural products from sponges and their associated microorganisms, which accelerate the discovery of new compounds. To update the knowledge in this field, we summarize the most recent progress on the origins, structures, and bioactivities of active natural products from sponge-associated microorganisms during the last 5 years (2017-2022). Moreover, a thorough discussion of the mining strategy is also included.

2 New bioactive compounds from sponge-associated microorganisms

There are 45 publications released between 2017 and 2022, reporting 140 new structures identified from sponge-associated microorganisms, such as sesquiterpenes, polyketides, peptides, alkaloids, etc. The new compounds exhibit a variety of biological activities, including anti-microbial, anti-cancer, enzyme inhibition, and so on.

2.1 Antimicrobial activity

Antibiotics are a great discovery of modern medicine. The application of antibiotics in clinical treatment has greatly improved the survival rate of human beings (Abdelmohsen et al., 2014). However, many antibiotics no longer have the clinical therapeutic impact as before due to the prevalence of drug resistance. Searching for new antibiotics is therefore an important way to resist the shortage of new medicine. Previous studies have shown that sponge-associated microorganisms contain a variety of antibacterial compounds, showing a good inhibitory effect on *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, and other bacteria. Some compounds could even inhibit drug-resistant bacteria, such as Methicillin-resistant *Staphylococcus aureus* (MRSA), Methicillin-resistant *Streptococcus epidermidis* (MRSE), and vancomycin-resistant *Enterococci* (VRE) (Cheng et al., 2020). Besides, some newly discovered compounds from sponge-associated microorganisms exhibit potent anti-fungal activity (Liang et al., 2023).

To explore new antibiotics, Wang et al. found cymopolyphenols A-F (Figure 1A, 1-6) from sponge-associated *Cymostachys* sp. NBUF082 by using the “One Strain, Many Compounds” (OSMAC) strategy combined with LC-MS/MS-based molecular networking. Antibacterial tests showed that cymopolyphenols A and C-F were effective against several Gram-positive and Gram-negative bacteria (MIC, 16-64 µg/ml), including *Pseudoalteromonas carrageenovora*, *Vibrio shilanii*, *V. scopthalmi*, *V. alginolyticus*, *Salmonella typhi*, *Pseudomonas aeruginosa*, *S. aureus*, and *B. pumilus* (Wang et al., 2021). Persiamycin A (Figure 1A, 7) is a new linear tetracycline compound acquired from sponge-associated *Streptomonospora* sp. PA3. It displayed an inhibitory effect on *S.*

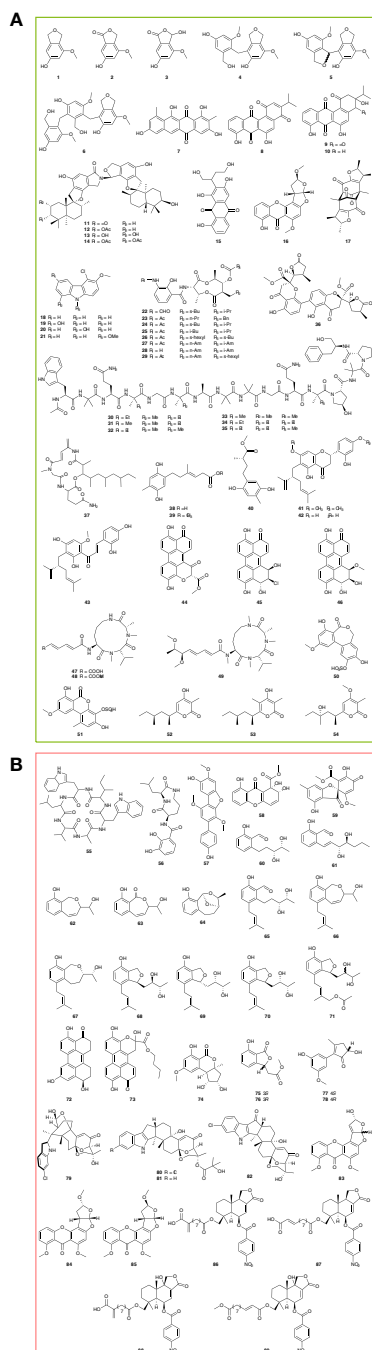


FIGURE 1
The antibiotic compounds (1-54, A) and The cytotoxic compounds (55-89, B).

aureus, *Klebsiella pneumoniae*, and *P. aeruginosa*, and the diameters of the inhibition zone are 9.2-9.7 mm (Matroodi et al., 2020). Different from persiamycin A, nocardiopepsistins A-C (Figure 1A, 8-10) are a group of new angular tetracyclines, which were discovered from the sponge-associated *Nocardiopepsis* sp. HB-J378 and exhibited antibacterial activity against MRSA (MIC, 3.12-12.5 $\mu\text{g}/\text{mL}$) (Xu et al., 2018).

Chartarlactams are new phenylspirodrimane-type dimers with antibacterial activity. Liu et al. identified chartarlactams Q-T (Figure 1A, 11-14) from a sponge-associated *Stachybotrys*

chartarum WGC-25. The bioassay showed that chartarlactams Q-S inhibited *S. aureus* with MIC values of 8, 16, and 4 $\mu\text{g}/\text{mL}$, respectively. Besides, it was found that chartarlactam T can inhibit the ZIKV virus by blocking virus entry and RNA replication in the antiviral experiment, indicating a multi-target feature (Liu et al., 2020a). In searching for new natural products, versiconol B and oxygensterigmatocystin I (Figure 1A, 15-16) were discovered from sponge-associated *Aspergillus* sp. F40. According to the structures, versiconol B belongs to the anthraquinone family, while oxygensterigmatocystin I is a member of xanthone. The antibacterial test showed that versiconol B inhibited *S. aureus* and *V. parahaemolyticus* with MIC values of 48 and 24 $\mu\text{g}/\text{mL}$, respectively (Tian et al., 2018). Penicitrinone G (Figure 1A, 17), a new citrinin derivative, was identified from the sponge-associated *Penicillium citrinum* WK-P9 through a bioassay-guided strategy. It could inhibit 8 pathogenic bacteria at 64 $\mu\text{g}/\text{mL}$, including *B. megaterium* DSM32, *B. subtilis* JH642, *B. subtilis* DSM10, *Micrococcus luteus* ATCC 4698, *M. smegmatis* ATCC 607, *Listeria monocytogenes* DSM20600, *S. aureus* ATCC25923, and *E. coli* K12 (Sabdaningsih et al., 2020).

Chlorcarbazomycins A-D (Figure 1A, 18-21) are a group of new chlorinated carbazole alkaloids, which were identified from the sponge-associated *Streptomyces diacarni* LHW51701. The bioassay showed chlorcarbazomycin C could inhibit MRSA, *M. smegmatis*, *B. mycoides*, and *C. albicans* with a MIC value of 32 $\mu\text{g}/\text{mL}$, while the other three compounds are against MRSA, *M. smegmatis*, *B. mycoides*, and *C. albicans* at 128 $\mu\text{g}/\text{mL}$ (Cheng et al., 2021). Li et al. found 8 novel antimycins I-P (Figure 1A, 22-29) from the sponge-associated *Streptomyces* sp. NBU3104 by metabolomics and genomics. Among them, antimycin I was effective against phytopathogenic fungi, such as *C. albicans*, *P. expanses*, *P. lemon*, and *Botrytis cinerea*, with MIC values of 2, 4, 4, and 1 $\mu\text{g}/\text{mL}$, respectively. Moreover, antimycin I could effectively inhibit the gray mold of apples *in vivo* (MIC, 8 $\mu\text{g}/\text{mL}$), showing good potential for agricultural applications (Li et al., 2022). In addition, Hao et al. identified 6 novel 16-residue peptaibols, acremo-peptaibols A-F (Figure 1A, 30-35), from sponge-associated *Acremonium* sp. IMB18-086. Compared with other members of the SF3 protein peptide family, acremo-peptaibols A-F lacked the highly conserved Thr6 and Hyp10 residues. Among them, acremo-peptaibols A and E showed antibacterial activity against *S. aureus*, MRSA, *B. subtilis*, and *C. albicans* (MIC, 16-64 $\mu\text{g}/\text{mL}$) (Hao et al., 2021).

Kumla et al. discovered a new dihydrochromone dimer, paeiclin E (Figure 1A, 36), from the sponge-associated *Neosartorya fennelliae* KUFA 0811. It displayed an inhibition activity against *S. aureus* and *Enterococcus faecalis* with MIC values of 32 $\mu\text{g}/\text{mL}$ and 16 $\mu\text{g}/\text{mL}$, respectively (Kumla et al., 2017). Rakicidin F (Figure 1A, 37) was identified from the sponge-associated *Streptomyces* sp. GKU 220 by chromatography, showing inhibition against *B. subtilis* and *E. coli* in the disk diffusion test at a dosage of 25 μg (Kitani et al., 2018). Ketidocillinones A-C (Figure 1A, 38-40) are three new polyketides, which discovered from the sponge-associated fungus *Penicillium* sp. HDN151272, possessing antibacterial activity against *P. aeruginosa*, *M. phlei*, and Methicillin-resistant coagulase-negative staphylococci

(MRCNS) with MIC values ranging from 1.56 to 25 $\mu\text{g}/\text{mL}$ (Shah et al., 2020). Flavonoids are a group of natural substances with variable phenolic structures. Cao et al. discovered three new lavandulylated flavonoids, (2S,2''S)-6-lavandulyl-7,4'-dimethoxy-5,2'-dihydroxyflavanone, (2S,2''S)-6-lavandulyl-5,7,2',4'-tetrahydroxyflavanone, and (2''S)-5'-lavandulyl-2'-methoxy-2,4,4',6'-tetrahydroxychalcone (Figure 1A, 41-43), from sponge-associated *Streptomyces* sp. G248. They displayed inhibitory effects against 5 pathogenic microorganisms, including *E. faecalis*, *S. aureus*, *B. cereus*, *P. aeruginosa*, and *C. albicans*, and their MIC values range is 1-8 $\mu\text{g}/\text{mL}$ (Cao et al., 2019). Three new perylenequinone derivatives, xanalterate A, altertoxin VIII, and IX (Figure 1A, 44-46), were identified from the sponge-associated *Alternaria* sp. HDN19-690. However, only xanalterate A showed inhibition activity against 6 bacterial strains (MRCNS, *B. subtilis*, *Proteus mirabilis*, *Bacillus cereus*, *E. coli*, and *M. phlei*) with MIC values ranging from 3.13 to 12.5 μM (Hou et al., 2022).

Sclerotiotides M-O (Figure 1A, 47-49) are a class of aspochracin-type cyclic tripeptides with a side chain. They were identified from sponge-associated *Aspergillus insulicola* HDN151418, and sclerotiotides M and N displayed antimicrobial activity against a panel of pathogenic strains, including *B. cereus*, *Proteus species*, *M. phlei*, *B. subtilis*, *Vibrio parahemolyticus*, *Edwardsiella tarda*, MRCNS, and MRSA, with MIC values ranging from 1.56 to 25.0 μM (Sun et al., 2020). Alterlactone 5'-O-sulfate and 3'-hydroxyalternarior 5-O-methyl ether-3'-O-sulfate are two new dibenzopyrones identified from sponge-associated *Alternaria* sp. SCSIOS02F49 (Figure 1A, 50-51). Among them, alterlactone 5'-O-sulfate was shown to alter the external structure of *S. aureus* and caused the rupture or deformation of the cell membranes (Chen et al., 2022b). In addition, Ding et al. found three new polyketides, nipyrones A-C (Figure 1A, 52-54), from a marine sponge-associated *Aspergillus niger*, but only nipyron C inhibited *S. aureus* and *B. subtilis* with MIC values of 8 $\mu\text{g}/\text{mL}$ and 16 $\mu\text{g}/\text{mL}$, respectively (Ding et al., 2019).

2.2 Cytotoxicity

Natural products are rich resources for anti-cancer compounds. Moreover, some of them or their derivatives have been developed into clinical-used medicines. During the last 5 years, a lot of new compounds with potent anticancer properties have been identified from sponge-associated microorganisms, providing more drug leads for pharmaceutical research. To explore new natural products, Ibrahim et al. identified *Nocardiosis* sp. UR67 strain from the red sea sponge *Callyspongia* sp. and identified a new cyclic hexapeptide, nocardiotide A (Figure 1B, 55). It exhibited cytotoxicity against the murine CT26 colon carcinoma, human HeLa cervix carcinoma, and human MM.1S multiple myeloma cell lines with IC_{50} values of 12, 11, and 8 $\mu\text{M}/\text{mL}$, respectively (Ibrahim et al., 2018). Petrocidin A (Figure 1B, 56) is a new cyclic dipeptide identified in *Streptomyces* sp. SBT348, which was identified from the Mediterranean sponge *Petrosia ficiformis*. It showed antiproliferative activity against human promyelocytic leukemia cells HL-60 and human colon cancer cell

line HT-29 with IC_{50} values of 3.9 and 5.3 $\mu\text{g}/\text{mL}$ (Cheng et al., 2017).

Wang et al. identified a new *p*-terphenyl alcohol, 4-O-methylcandidusin A (Figure 1B, 57), from the sponge-associated *Aspergillus candidus* OUCMDZ-1051. It selectively inhibited cancer cell lines MDA-MB-468, BT474, and A431 with IC_{50} values of 1.84, 6.05, and 0.98 $\mu\text{mol}/\text{L}$, respectively (Wang et al., 2020). Globosuxanthone F and 2'-hydroxy bisdechlorogedin (Figure 1B, 58-59) are two polyketides discovered from the sponge-associated *Pleosporales* sp. NBUF144. Among them, globosuxanthone F was found an antiproliferative effect against CCRF-CEM human acute lymphatic leukemia cells with an IC_{50} value of 0.46 μM , without showing any cytotoxicity at 20 μM (Zhou et al., 2021b). Lei et al. discovered 12 new polyketide derivatives, heterocornols A-L (Figure 1B, 60-71) from the sponge-associated *Pestalotiopsis heterocornis*. The heterocornols A-C and F-H possessed cytotoxicity against 4 human cancer cell lines, including the human gastric carcinoma cell line, human large-cell lung carcinoma cell line, human prostate cancer cell line, and human hepatocellular carcinoma cell line. Their IC_{50} values ranged from 15.0 to 83.5 μM . Interestingly, these polyketide derivatives also exhibited antibacterial activity against *S. aureus* and *B. subtilis* (IC_{50} , 25-100 $\mu\text{g}/\text{mL}$) (Lei et al., 2017).

In addition, Pang et al. identified 7 new compounds from the sponge-associated *Alternaria* sp. SCSIO41014, including altertoxin VII, butyl xanalterate, nordihydroaltenuenes A, (S)-isoochracinate A1, (R)-isoochracinate A2, (S)-alternariphent A1 and (R)-alternariphent A2 (Figure 1B, 72-78). However, only altertoxin VII displayed cytotoxicity against human erythroleukemia, human gastric carcinoma cells, and hepatocellular carcinoma cells with IC_{50} values of 26.58, 8.75, and 13.11 $\mu\text{g}/\text{mL}$, respectively (Pang et al., 2018b). Ascandinines A-D (Figure 1B, 79-82) are classified as a new type of indole diterpenoid, which were identified from sponge-associated *Aspergillus candidus* HDN15-152. Among them, ascandinine D showed cytotoxicity against HL-60 cells with an IC_{50} value of 7.8 μM (Zhou et al., 2021a). *Aspergillus nomius* NC06 was identified from the marine sponge *Neopetrosia chaliniformis* and proved to synthesize three new oxisterigmatocystins J-L (Figure 1B, 83-85). In the bioassay test, oxisterigmatocystins J and K induced apoptosis and cell death in HT 29 colon cancer cells with IC_{50} values of 6.28 and 15.14 μM (Artasasta et al., 2021). Insulicolides D-G (Figure 1B, 86-89) belong to two new nitrobenzoyl sesquiterpenoids, which are identified from a sponge-associated *Aspergillus insulicola* HDN151418. Further studies indicated that insulicolide D could significantly suppress cell proliferation to induce apoptosis and blocked migration and invasion of pancreatic ductal adenocarcinoma (PDAC) cell lines with IC_{50} values of 2.3-22.9 μM (Sun et al., 2022).

2.3 Enzyme inhibitors

Enzyme inhibitors are an important type of medicine, which have been widely used in clinical treatment against various diseases. For example, the well-known antivirus drugs (Paxlovid and Molnupiravir), which belong to protease inhibitors, saved millions

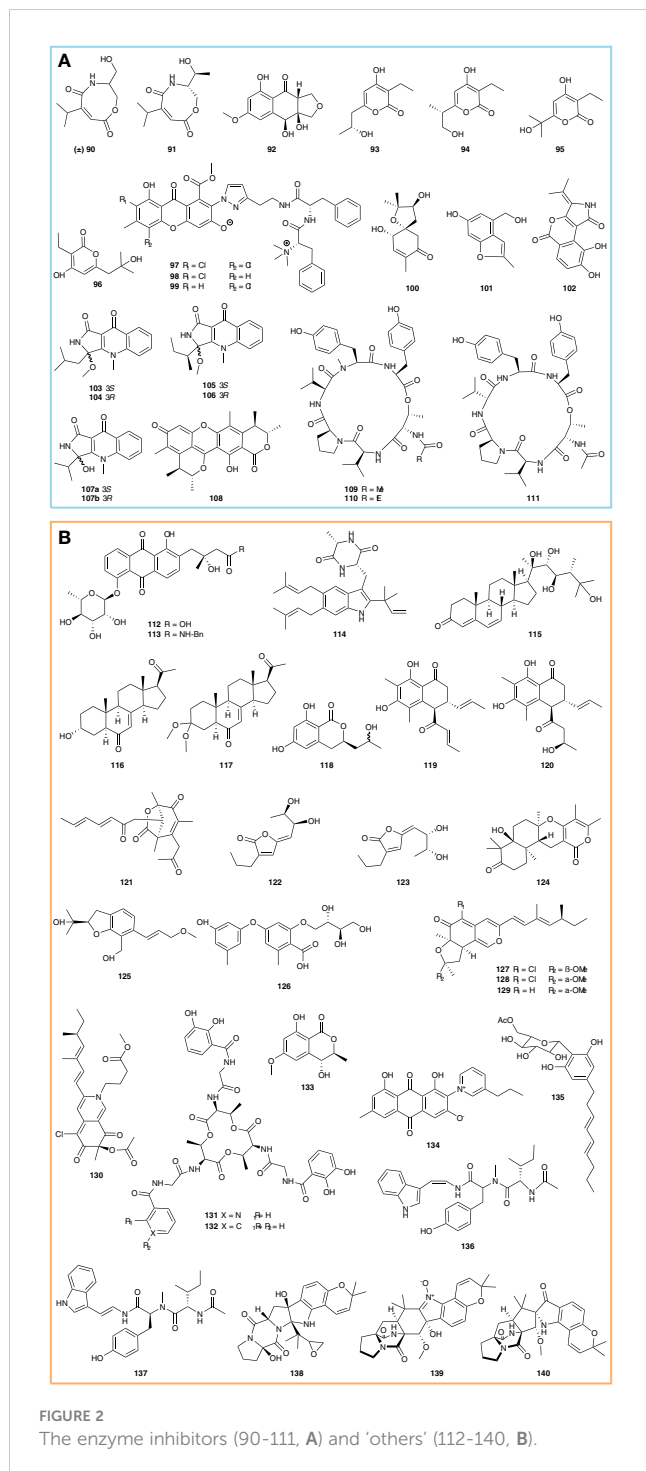
of lives in the battle against Coronavirus (COVID-19) (Wen et al., 2022). It is known that many new compounds with enzyme inhibition activity have been found in sponge-associated microorganisms during the past 5 years. For example, two new carboxamides ((±)-vochysiamide C and (+)-vochysiamide B) and a new polyketide (4S,3aS,9aR-3a,9a-deoxy-3a hydroxy-1-dehydroxyarthrinone) (Figure 2A, 90-92) were identified from the sponge-associated *Arthrinium* sp. SCSIO 41421 using chromatography. The (±)-vochysiamide C and (+)-vochysiamide B showed inhibition on 79.38% and 84.22% acetylcholinesterase,

respectively, at a concentration of 50 µg/mL, while 86% of acetylcholinesterase was blocked by 4S,3aS,9aR-3a,9a-deoxy-3a hydroxy-1-dehydroxyarthrinone at 50 µg/mL (She et al., 2022). Bai et al. discovered 4 new α-pyrone derivatives, germicidins P-S from *Streptomyces* sp. 18A01 (Figure 2A, 93-96), through a combination of the Global Natural Products Social Molecular Networking (GNPS), the LC-DAD-MS profile, and hexokinase II (HK2) inhibitory activity screening. The bioassay showed that germicidins P-S inhibit HK2 with IC₅₀ values ranging from 5.1 to 11.0 µM. Moreover, the molecular docking simulations indicated that the ligand has a strong affinity to Arg91 of HK2 instead of Asn89, resulting in higher hexokinase inhibitory action (Bai et al., 2021). Pancreatic lipase is the most important enzyme for hydrolyzing dietary fat, which can promote digestion and appetite. With the pancreatic lipase as the screening model, Jiao et al. identified 3 new chlorinated PKS-NRPS hybrid metabolites, flavipesides A-C (Figure 2A, 97-99), from the sponge-associated *A. flavipes* 164013. They exhibited a strong inhibition on pancreatic lipase at IC₅₀ values of 0.23, 0.07, and 0.14 µM, respectively (Jiao et al., 2020).

In addition, two new compounds, acremine S and acremine T (Figure 2A, 100-101) were identified from sponge-associated *Acremonium persicinum* KUF1007. The bioassay showed that acremine S and acremine T exhibited inhibition on 10.42% and 14.08% of acetylcholinesterase at 6.6 µM, respectively, while 30.71% and 10.53% of butyrylcholinesterase were blocked by acremine S and acremine T at the concentration 6.25 µM (Alves et al., 2019). Rotinsulu et al. discovered a new protein tyrosine phosphatase (PTP) 1B inhibitor, cladosporamide A (Figure 2A, 102), from sponge-associated *Cladosporium* sp. TPU1507. It displayed inhibition activity against PTP1B and T-cell PTP with IC₅₀ values of 48 and 54 µM, respectively (Rotinsulu et al., 2018). Five new *N*-methyl-4-quinolones, including quinolactacins E1 and E2, quinolactacins F1 and F2, quinolactacin G, and one new citrinin dimer derivative, dicitrinol D (Figure 2A, 103-108) were identified from the sponge-associated *Penicillium* sp. SCSIO41303. The enzyme inhibition test showed that quinolactacin F1 inhibited pancreatic lipase with an IC₅₀ value of 24.6 µg/mL (Guo et al., 2021). Tang et al. discovered three new cyclohexapeptides, petrosamides A-C (Figure 2A, 109-111), from the sponge-associated fungus *Aspergillus* sp. 151304. These peptides displayed significant and dose-dependent pancreatic lipase inhibition activities with IC₅₀ values of 7.6, 1.8, and 0.5 µM, respectively (Tang et al., 2020).

2.4 Others

Besides the anti-microbial, cytotoxic, and enzyme inhibition, some compounds from sponge-associated microorganisms display other types of bioactivities or no activities. In this study, we group them into 'others' for the compound discussion at a convenience. For example, fridamycins H and fridamycins I (Figure 2B, 112-113) are two new types II polyketides synthesized by the sponge-associated bacteria *Actinokineospora spheciospongiae* sp. DSM 45935T. In the experiment against *Trypanosoma brucei* TC221,



fridamycin H showed anti-trypansomal activity at 48 and 72 h (IC_{50} , 7.18 and 3.35 μ M) (Tawfike et al., 2019). Fintiamin (Figure 2B, 114) is a diketopiperazine-indole alkaloid identified from the *Eurotium* sp. identified from the marine sponge *Ircinia variabilis*. As one terpenoid-dipeptide derivative, fintiamin was made up of amino acids and terpenoid moieties and showed an affinity to the cannabinoid CB_1 receptor (Elsebai et al., 2021). Cladosporisteroids A-C and (3*R*)-3-(2-hydroxypropyl)-6,8-dihydroxy-3,4-dihydroiso-coumarin (Figure 2B, 115-118) were identified from sponge-associated *Cladosporium* sp. SCSIO41007, but only cladosporisteroid B exhibited inhibition activity against H3N2 with the IC_{50} value of 16.2 μ M (Pang et al., 2018a). Chen et al. discovered 3 new sorbicillinoid pigments, stasorbicillinoids A-C (Figure 2B, 119-121), from the sponge-associated *Stagonospora* sp. SYSU-MS7888 through phenotype combined with metabolomic and genomic (PMG) strategies. These compounds showed potent anti-inflammatory activity (IC_{50} , 7.1-14.0 μ M) (Chen et al., 2022a). Two new γ -lactones, aspergilactones A-B (Figure 2B, 122-123), were discovered from sponge-associated *Aspergillus* sp. LS45 and inhibited root growth of *Arabidopsis thaliana* Columbia-0 at a concentration of 100 μ M (Huang et al., 2019).

In addition, a series of new compounds identified from sponge-associated microorganisms exhibit no bioactivities. For example, Shin et al. identified a new α -pyrone sesquiterpene with an angular tetracycline, ochraceopone F (Figure 2B, 124), from sponge-associated *A. flocculosus*. Ochraceopone F had no antiproliferative effect on human cancer cell lines HCT 15, NUGC-3, NCI-H23, ACHN, PC-3, and MDA-MB-231 at a concentration of 30 μ g/mL (Shin et al., 2018). Asperspin A and asperther A (Figure 2B, 125-126) are two new molecules discovered from the sponge-associated *Aspergillus* sp. LS34 through the OSMAC culture strategy (Li et al., 2019). Sclerotiorins A-D (Figure 2B, 127-130) belong to one group of azaphilone compounds, which were identified from the sponge-associated *P. sclerotiorum* OUCMDZ-3839 (Jia et al., 2019). Wu et al. identified two siderophores, bacillibactins E-F (Figure 2B, 131-132) from the sponge-associated *Bacillus* sp., which are characterized by nicotinic and benzoic acid moieties in their structures (Wu et al., 2020). (3*S*,4*R*)-4-hydroxy-6-methoxymellein, anthraquinone, and acetyl carnemycin E (Figure 2B, 133-135) were identified from sponge-associated *Aspergillus stellatus* KUFA 2017 (Machado et al., 2022). Luo et al. discovered 2 new isomeric-modified tripeptides, aspergillamides C-D (Figure 2B, 136-137) from the sponge-associated fungus *Aspergillus terreus* SCSIO 41008 (Luo et al., 2019). Speramide C, 3,21-*epi*-taichunamide F, and 2-*epi*-amoenamamide C (Figure 2B, 138-140) are three new 2,5-diketopiperazines identified from the sponge-associated *Aspergillus sclerotiorum* GDST-2013-0501. Speramide C represents the first prenylated indole alkaloid with an ethylene oxide ring at the isopentenyl side chain (Wang et al., 2022). Even though these compounds failed to exhibit biological activity, their new structures still enrich the natural product library of sponge-associated microorganisms.

During the last 5 years (2017-2022), 140 new compounds were identified from sponge-associated microorganisms (Supplementary, Table S1). The statistical data show that most of them come from actinomycetes (bacteria) and ascomycota (fungi). However, it is

found that 76% of compounds are of fungal origin. Among those different natural product categories, polyketides occupy 47.85% followed by peptides (12.14%) and alkaloids (4.28%). Even though newly discovered compounds exhibit a variety of biological activities, the antimicrobial and anti-cancer compounds occupy 38.57% and 25%, respectively, providing a lot of lead compounds for drug development.

3 Methodological options for target natural products

3.1 Genome mining

Natural product discovery is developing at a faster speed than before due to technological developments. Genome mining is a technology that uses computer programs to extract useful information from genome data, including gene structure, sequence, quantity, and other molecular features. It examines the conserved regions of enzymes and gene clusters on the genome to guide the discovery of new enzymes and the identification of novel natural products (Zhao and Yang, 2011). This approach has been widely applied in natural product discovery due to a large amount of sequencing data in the database (Blin et al., 2019; Russell and Truman, 2020), and many new compounds have been discovered (Albarano et al., 2020; Kenshole et al., 2021).

Because of the update in sequencing technology, the cost and time consumed to generate genome sequences have significantly decreased over the past decade, providing a good basis for the application of genome mining strategy. Meanwhile, the bioinformatics software for biosynthetic gene cluster (BGC) prediction with high accuracy makes it possible to mine BGCs from massive sequence data. Anti-SMASH (antibiotics & Secondary Metabolite Analysis Shell) is currently the most widely used tool for predicting biosynthetic gene clusters (Medema et al., 2011). The new version (antiSMASH 6.0) could effectively detect splicing enzymes in ribosomally synthesized and post-translationally modified peptides (RiPPs) clusters and support the prediction of 71 types of gene cluster types. Moreover, it could highlight the modular structure of multi-module BGC and integrate the BGC comparison function. PRISM (Prediction Informatics for Secondary Metabolomes) is another commonly used biosynthetic gene cluster prediction tool, and it was updated for the fourth iteration in 2020. The latest version, PRISM 4, can not only generate accurate structure predictions for known BGCs but also perform structural predictions for cryptic BGCs. It could even predict chemical structures from metagenomic data and structure-activity relationships of compounds (Skinnider et al., 2020). Nowadays, it is not a time-costing mission to obtain ten thousand BGC in a limited time with the aid of large genome data and powerful tools. However, it does matter to group BGC into gene cluster families to decrease the analytical difficulty and increase the data process capacity. To this end, Navarro-Muñoz et al. developed the BiG-SCAPE (Biosynthetic Gene Similarity Clustering and Prospecting Engine) and CORASON (core analysis of syntenic orthologues to prioritize natural product gene clusters) automatically construct

BGC similarity network and analyze the BGC phylogeny, realizing the high-throughput analysis of BGC (Navarro-Muñoz et al., 2020). Overall, the development and use of increasingly sophisticated bioinformatics tools make a great advance in the mining of natural products.

Numerous studies have demonstrated the advantages of genome mining in discovering novel compounds from sponge-associated microorganisms. In search of the natural products from sponge-associated microorganisms, Matsuda et al. used genome mining to select the terpene synthase bifunctional terpene synthases gene from *Emericella varicolor* NBRC 32302 for heterologous expression. Finally, a new terpene hydrocarbon, astellifadiene, was identified and identified (Matsuda et al., 2016). Besides, Alex and Antunes detected the presence of several biosynthetic gene clusters-polyketide synthases, nonribosomal peptide synthetase, and siderophore from sponge-associated *Pseudovibrio* sp. POLY-S9 with genome mining (Alex and Antunes, 2015). Overall, the development and use of increasingly sophisticated bioinformatics tools make a great advance in the mining of natural products.

3.2 Metabolomics analysis

Metabolomics is a discipline that studies the chemical process of metabolites. Its basic goal is to conduct a comprehensive qualitative and/or quantitative analysis of all metabolites present in living systems to reflect changes in their metabolites after stimulation with the characteristics of the simple operation (Liu and Locasale, 2017; Zhao et al., 2018). At present, metabolomics is widely used in natural product mining research, and the most common-used technology is liquid chromatography-mass spectrometry (LC-MS) (Salem et al., 2020). The liquid chromatography separation system can greatly reduce the complexity of the sample entering the mass spectrometer. Meanwhile, mass spectrometry is very sensitive to capturing a lot of ions from trace amounts of samples (Zhang et al., 2018). Therefore, the emergence of LC-MS/MS provides a powerful tool for compound structure elucidation.

In terms of metabolomics data analysis, the emergence of many new tools has made it possible to realize the automation and high throughput of data analysis (Perez De Souza et al., 2020). Yang et al. demonstrated that molecular networking, an approach that organizes MS/MS data based on chemical similarity, is a powerful complement to traditional dereplication strategies. It visualizes the output data in the network and dereplicates new chemical entities by comparing it to the MS/MS data of known compounds (Yang et al., 2013). In addition, Principal Component Analysis (PCA) is another common-used option for metabolomics analysis, which is used to analyze multivariate data by transforming many correlated variables into smaller linear data sets to define a data set (Kemsley et al., 2007). The PCA analysis could simplify the complexity of high-dimensional data while preserving trends and patterns (Lever et al., 2017).

The PCA and molecular networks are widely used as powerful tools in separating metabolites, avoiding tedious separation work for compounds. Based on the chemical uniqueness of PCA, Cheng et al. used liquid chromatography/high-resolution mass

spectrometry (LC-HRMS) and nuclear magnetic resonance (NMR) to analyze the bacteria identified from the Mediterranean sponge *Petrosia ficiformis*. Finally, a new compound, named petrocidin A (Cheng et al., 2017), was identified from *Streptomyces* sp. SBT348. In addition, Li et al. discovered 8 new antibacterial compounds (antimycins I-P) by analyzing the secondary metabolites of the sponge-associated actinomycete *Streptomyces* sp. NBU3104 through integrating genome mining and molecular networking (Li et al., 2022), indicating a potent application of metabolomics in natural product discovery from sponge-associated microorganisms.

3.3 Bioactivity-guided approaches

Bioassay is one traditional strategy for bioactive compound discovery. The bioassay on crude extract not only confirmed the existence of bioactive compounds but also track the functional molecule in the crude extracts. However, if some biological activity is due to a mixture or synergistic effects from more components, it is not easy to find real clues. Although this strategy is believed to lead to the repeated discovery of known compounds, it still plays an important role in exploring new natural products from a variety of organisms, such as sponge-associated microorganisms. Devi et al. screened the crude extracts of marine bacteria identified from the surface of the sponge *Halichondria* sp. against 16 clinical pathogenic bacteria. With the bioassay guiding, three compounds, including indole, 3-phenylpropionic acid, and a dimer 4,4'-oxybis[3-phenylpropionic acid] were identified with a combination of ESI-MS and NMR (Devi et al., 2010). Gavriilidou et al. screened the extracts of 21 sponge-associated bacteria for antibacterial and anticancer compounds. Finally, one extract was found against MRSA, and more than 70% of extracts exhibited cytotoxicity (Gavriilidou et al., 2021).

4 Discussion and prospect

Sponges have been proven a rich reservoir of bioactive compounds. With a lot of new natural products being identified from sponge-associated microorganisms, it is believed that the real producers of bioactive compounds from sponges might be the microorganisms rather than the sponges themselves. Therefore, discovering natural products from sponge-associated microorganisms not only provides more leading compounds for drug development but also is of great significance to understand the interaction between sponges and their associated microorganisms (Pita et al., 2018). In the past 5 years, 140 new compounds were identified from sponge-associated microorganisms, exhibiting great chemical diversity. Although most of them exhibit bioactivity in the *in vitro* tests, their biological targets and mechanism of action are still elusive, which needs further study in the future.

Nowadays, the discovery of new natural products is much faster than ever due to technological development. However, there are still a lot of new challenges that deserved to pay more attention. For example, the study of the biological function and ecological roles of microbial secondary metabolites usually requires the combination of multiple

technologies to resolve the research difficulties, such as genomics, metabolomics, synthetic biology, and so on. With the technology being updated at a high frequency, we believe more compounds will be uncovered from sponge-associated microorganisms, and their diverse biological functions will provide us with a new perspective on drug development and ecological protection.

Author contributions

PL, HL, YZ, MW, and LWL conceived, designed, and wrote this manuscript. XZ and LLL improved the quality of the manuscript by compiling information in the form of tables and figures. All authors read and approved the manuscript. All authors contributed to the article.

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Conflict of interest

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Supplementary material

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