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Promising sponge derived marine fungi as antibacterial and biofilm inhibitors

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ABSTRACT

Marine organisms, especially sponges, provide many sources of metabolites with various biological activities. Most sponges associate with microbes such as fungi. To solve the problem of sponge availability, it is necessary to isolate compounds from marine-derived fungi due to their feasibility and advantages. This study, thus, highlights that the most prominent genera to produce metabolites active as antibacterials and antibiofilm were *Aspergillus*, *Penicillium*, *Neosartorya*, and *Trichoderma*. The summarized data of isolated compounds related to antibacterial and antibiofilm activities until 2022 included anthraquinones, sterigmatocystin analogs, hydroxy pyrrolidine alkaloids, helvolic acid derivatives, lactones, prenylated phenylbutyrolactones, citrinin and derivatives, bisthiodiketopiperazine, cyclotetrapeptides, dihydrochromone dimers, amino lipopeptides, furan derivatives, aspiron-derivatives, halogenated metabolites, and alkaloids. Since the biofilm mechanism is very complex, some antibacterial compounds do not necessarily work as antibiofilms. Nevertheless, it can be concluded that compounds produced from sponge-associated fungi have the potential to be developed as new antibacterial and antibiofilm agents although still require further investigation related to the mechanism of actions of the compounds.

INTRODUCTION

Bacterial resistance has become a worldwide problem that endangers the efficacy of existing antibiotics to treat infections, especially with the emergence of multidrug-resistant (MDR) strains of bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA) and MDR strains of *Escherichia coli*. Antimicrobial resistance may be attributed to several factors, including the formation of biofilms. Biofilms are complex communities of microorganisms that produce a polymeric extracellular matrix on the surfaces that can inhibit the penetration of antibiotics, making them more resistant than planktonic cells [1–3]. In addition to modifying existing drugs, researchers are looking for new antibiotics by exploring marine organisms. Since the ocean covers about 70% of the earth, it is undeniable that marine environments have more enormous biodiversity compared to terrestrial creatures and contain very promising bioactive compounds to explore. The life of marine organisms varies depending on their surrounding environmental conditions, such as temperature, light, salinity, pressure, and depth of their habitat. They have different evolutionary systems, metabolic pathways, and ecology from terrestrial creatures [4,5], which leads to distinctive chemical composition, complexity, and biological efficacy [6,7].

Marine sponges are known to serve as a source of food and are commonly found throughout the world's oceans. Sponges are soft, sessile, and able to survive in water with strong currents, since the current provides food and oxygen for its life. They can

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live in various marine habitats, from shallow to deep seas [8,9]. Sponges are immobile and vulnerable to predators, producing metabolite compounds in self-defense [10]. Many studies report that metabolite compounds contained in sponges have therapeutic activities, including cytotoxic activity [11,12], antimicrobial activity [13,14], antiplasmodial activity [15], and other activities. Given the large potential of sponges as food and medical resources, especially by way of isolating their active compounds, which makes it is necessary to pay attention to the survival of organisms and their environment. Interestingly, sponges can associate with various microbes, both fungi and bacteria. These associated microbes produce metabolites similar to their host but may also create novel active metabolites [16–18]. Some metabolites of sponge-associated microbes have chemical structures similar to terrestrial species, making them a great resource for further exploration, especially as antibacterial agents [19–21].

This review aims to examine isolated metabolite compounds from sponge-associated fungi with antibacterial and biofilm inhibitor activity, including the genus that produces the most active compounds, their antibacterial and antibiofilm potential, and to find out the relationship between antibacterial and biofilm inhibitor activity. The original article used various potential values as a way to compare their antibacterial potential by way of changing its μg/ml units based on the molecular weight. However, the difficult conversion forces it to preserve its original value. This review is expected to assist many researchers in exploring compounds with potential development as new antibacterial and antibiofilm to that "supply issues" to avoid sponge exploitation.

MATERIAL AND METHODS

This review highlights metabolite compounds from fungi associated with sponges exhibiting antibacterial and antibiofilm activity. The data presented were derived from primary articles in English related to keywords "marine" OR "sea" AND "sponge-associated fungi" OR "marine-derive fungi" AND "antibacterial" AND "antibiofilm," which was discovered in 2002–2022 from Scopus and Pubmed. Variables discussed include genus/species of fungi associated with sponges, species of sponges, metabolite compounds, their potential value, and the type of bacteria being inhibited. The minimum inhibitory concentration (MIC) (units μg/ml or μM) or the diameter of inhibition/DOI (unit mm) of metabolites indicates their ability to inhibit bacterial growth. The potential of antibiofilms is shown by their ability to inhibit the formation of biofilms (% inhibition of biofilms).

Sponge-associated fungi as a source of antibacterial

Many studies reported the activity of sponges, including antimicrobial, cytotoxic, anti-inflammatory, antidiabetic, and antimalarial [22–26]. Microorganisms are closely related to sponge life because of the nature of sea sponges as feeder fillers; their body tissues are related to these microorganisms. These associated microorganisms provide host advantages regarding nutrient supply, skeletal stabilization, regulating waste, and secondary metabolite production [27–30]. Fungi associated with sponges have shown the ability to produce unique and biologically active structures. On this basis, utilizing appropriate biotechnology to isolate metabolite

compounds from fungi associated with sponges is likely to be developed as new drugs. Until 2022, there had been 55 articles related to fungi associated with sponges with antibacterial and antibiofilm activity. During these two decades (2002–2022), there was a notable increase in the number of publications (Fig. 1).

The highest publication was found in the 2017–2021 period with 27 articles, which constantly escalated in terms of quantity. Countless scientists were found to show a growing interested in studying sponges associated with microbes, thus indicating a trend considering the need to maintain the existence of sponges. We identified that the most frequently studied families were Trichocomaceae, Hypocreaceae, Herpotrichiellaceae, and Pleosporaceae (Fig. 2), and the genus most commonly studied were *Aspergillus*, *Penicillium*, *Trichoderma*, and *Neosartorya* (Fig. 3A and B). Some genus were the most prolific sources of antibiotics [31,32].
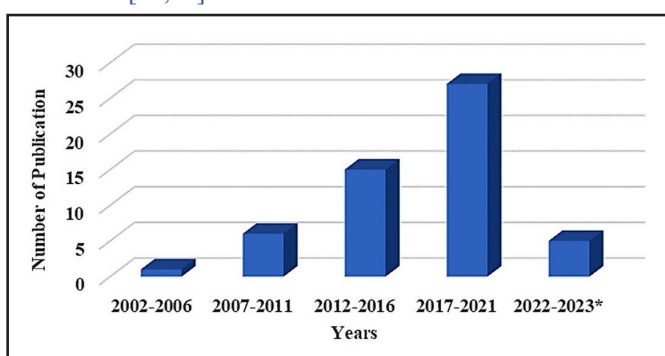

Figure 1. An overview of research related to sponge-associated fungi with antibacterial and anti-biofilm activity. January 2023*.
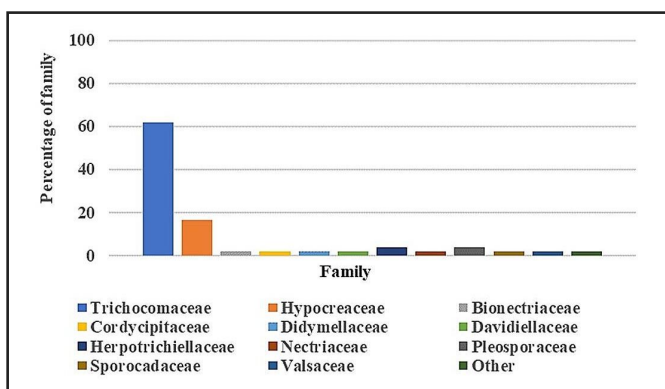

Figure 2. The distribution of the family of sponge-associated fungi with antibacterial and biofilm inhibitors activity ($N = 55$).
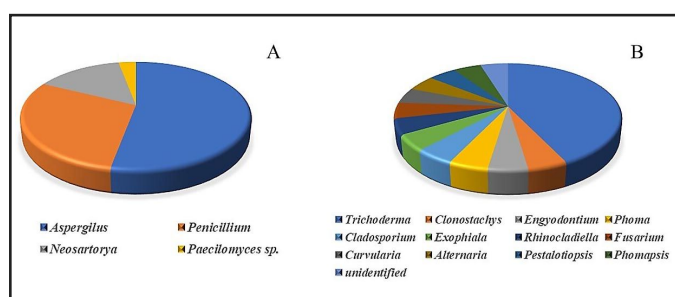

Figure 3. The distribution of the genus sponge-associated fungi with antibacterial and antibiofilm activity. (A) Family Trichocomaceae (B) Other than Trichocomaceae.

Genus *Aspergillus*

  Aspergillus contains various chemical metabolites likely to be developed into new drugs, including antimicrobial properties. Marine life contains abundant resources, which thus caught the attention of many researchers. Studies on antibacterial chemicals generated by *Aspergillus* fungi associated with sponges are presented in Table 1. The compounds of averantine (**1**) and nidurufin (**2**) are anthraquinones isolated from the fungus *Aspergillus versicolor* associated with the sponge *Petrosia* sp. in the Jeju Sea, Korea. Both of them showed antibacterial activity against gram-positive clinical isolate bacteria, including *Staphylococcus aureus* SG511, *S. aureus* 285, *S. aureus* 503,

Table 1. Collected data from sponge-associated fungi with antibacterial activity.

Fungi species	Sponge source	Compound	Against bacteria	Potency	Refs
Aspergillus					
Aspergillus versicolor	*Petrosia* sp.	Averantin	*Staphylococcus aureus* SG511	(MIC) 3.13 µg/ml	[33]
		Nidurufin	*Staphylococcus aureus* SG511	(MIC) 6.25 µg/ml	
		Averantin	*Staphylococcus aureus* 285	(MIC) 3.13 µg/ml	
		Nidurufin	*Staphylococcus aureus* 285	(MIC) 3.13 µg/ml	
		Averantin	*Staphylococcus aureus* 503	(MIC) 1.56 µg/ml	
		Nidurufin	*Staphylococcus aureus* 503	(MIC) 3.13 µg/ml	
		Averantin	*Streptococcus pyogenes* 308A	(MIC) 0.78 µg/ml	
		Nidurufin	*Streptococcus pyogenes* 308A	(MIC) 3.13 µg/ml	
Aspergilus flavus GU815344	*Callyspongia* spp.	Desmethylnomifensine	*Staphyloccocus aureus*	DOI (27.0 mm)	[35]
		Unidentified	*Escherichia coli*	DOI (42.9 mm)	
Aspergillus clavatus MFD15	Unidentified	1H-1,2,4 Triazole 3-carboxaldehyde 5- methyl	*Escherichia coli*	(MIC) 800 ± 10 µg/ml	[47]
			Staphyloccocus epidermidis	(MIC) 1,600 ± 6 µg/ml	
Aspergillus sp.	*Xestospongia testudinaria*	Aspergiterpenoid A	*Staphylococcus albus*	(MIC) 1.24 µg/ml	[45]
		(Z)-5-(Hydroxymethyl)-2-(6′-methylhept-2′-en-2′-yl)-phenol	*Bacillus cereus*	(MIC) 2.33 µg/ml	
		(−)-Sydonic acid		(MIC) 0.66 µg/ml	
		(−)-5-(Hydroxymethyl)-2-(2′,6′,6′-trimethyltetrahydro-2H-pyran-2-yl)-phenol		(MIC) 0.62 µg/ml	
		(−)-Sydonic acid	*Escherichia coli*	(MIC) 1.33 µg/ml	
		(Z)-5-(Hydroxymethyl)-2-(6′-methylhept-2′-en-2′-yl)-phenol		(MIC) 2.33 µg/ml	
		Aspergiterpenoid A		(MIC) 4.72 µg/ml	
		(−)-Sydonol		(MIC) 5.04 µg/ml	
		(−)-Sydonic acid	*Micrococcus tetragenus*	(MIC) 5.33 µg/ml	
		(Z)-5-(Hydroxymethyl)-2-(6′-methylhept-2′-en-2′-yl)-phenol		(MIC) 2.33 µg/ml	
		Aspergiterpenoid A		(MIC) 2.36 µg/ml	
		(−)-Sydonol		(MIC) 0.32 µg/ml	
		(−)-Sydonic acid	*Vibrio parahaemolyticus*	(MIC) 2.66 µg/ml	
		(−)-Sydonic acid	*Vibrio anguillarum*	(MIC) 1.33 µg/ml	
Aspergillus versicolor MF359	*Hymeniacidon perleve*	5-methoxydihydro sterigmatocystin	*Staphylococcus aureus* (ATCC 6538)	(MIC) 12.6 µg/ml	[34]
			Bacillus subtilis (ATCC 6633)	(MIC) 3.125 µg/ml	

(Continued)

Fungi species	Sponge source	Compound	Against bacteria	Potency	Refs
Aspergillus sydowii ZSDS1-F6	Unidentified	Aspergillusene A	*Klebsiella pneumonia*	(MIC) 21.4 μM	[44]
		Z)-5-(Hydroxymenthyl)-2-(6′-methylhept-2′-en-2′-yl)-phenol		(MIC) 10.7 μM	
		diorcinol		(MIC) 21.7 μM	
		Aspergillusene A	*Aeromonas hydrophila*	(MIC) 4.3 μM	
		sydonic acid	*Enterococcus faecalis*	(MIC) 18.8 μM	
Aspergillus sp. SCSIO XWS03F03	Unidentified	Secalonic acid D	*Staphyloccocus aureus* ATCC 29213	(MIC) 7.19 μM	[122]
			Mycobacterium tuberculosis	(MIC) 1.26 μM	
Aspergillus flavus	*Acanthostrongylophora ingens*	Unidentified	*Bacillus subtilis*	(DOI) 14.4 mm	[37]
			Staphylococcus epidemidis	(DOI) 11.5 mm	
			Salmonella typosa	(DOI) 10.23 mm	
			Escherichia coli	(DOI) 14.75 mm	
Aspergillus candidus KUFA0062	*Epipolasis* sp.	Preussin	*Staphylococcus aureus* ATCC 29213	(MIC) 32.0 μg/ml	[39]
			Enterococcus faecalis ATCC29212	(MIC) 32.0 μg/ml	
			MRSA	(MIC) 32.0 μg/ml	
			vancomycin-resistant enterococci (VRE) strains	(MIC) 32.0 μg/ml	
Aspergillus fumigatus HNMF0047	Unidentified	16-O-propionyl-16-O-deacetylhelvolicaci	*Streptococcus agalactiae*	(MIC) 16.0 μg/ml	[43]
		6-O-propionyl-6-O-deacetylhelvolic acid		(MIC) 2.0 μg/ml	
		helvolic acid		(MIC) 8.0 μg/ml	
Aspergillus oryzae	*Chelonaplysilla sp*	Unidentified	*Staphylococcus aureus*	(DOI) 8.83 ± 1.01 mm	[46]
			Escherichia coli	(DOI) 8.54 ± 1.00 mm	
Aspergillus mellinus		Unidentified	*Staphylococcus aureus*	(DOI) 16.69 ± 0.51 mm	[46]
			Escherichia coli	(DOI) 16.88 ± 0.57 mm	
Aspergillus candidus OUCMDZ-1051	Unidentified marine sponge (XS-3)	4-*O*-methylcandidusin A	*Escherichia coli* ATCC 11775	(MIC) 10.0 μg/ml	[40]
			Enterobacter aerogenes ATCC 13408	(MIC) 73.28 μg/ml	
			Pseudomonas aeruginosa ATCC 10145	(MIC) 73.28 μg/ml	
			Staphylococcus aureus	(MIC) 73.28 μg/ml	
Aspergillus flavus strain MC-10-L	*Stylissa flabelliformis*	Unidentified	*Staphylococcus aureus* ATCC 25923	(MIC) 942.0.0 μg/ml	[38]
			Escherichia coli ATCC 25922	(MIC) 557.0 μg/ml	
			Enterococcus faecalis ATCC 29212	(MIC) 363.0 μg/ml	
			Bacillus subtilis ATCC 6633	(MIC) 1,169.0 μg/ml	
Aspergillus fumigatus	*Stylissa flabelliformis*	Unidentified	*Staphylococcus aureus* ATCC 25923	(MIC) 856.0 μg/ml	[38]
			Escherichia coli ATCC 25922	(MIC) 1,203.0 μg/ml	
			Enterococcus faecalis ATCC 29212	(MIC) 339.0 μg/ml	
			Bacillus subtilis ATCC 6633	(MIC) 1,137.0 μg/ml	

(Continued)

Fungi species	Sponge source	Compound	Against bacteria	Potency	Refs
Aspergillus flavipes KUFA1152	*Mycale sp*	Aspulvinones B'	*Enterococcus faecalis* ATCC 29212	(MIC) 16.0–32.0 µg/ml	[48]
			Staphylococcus aureus ATCC 29213	(MIC) 16.0 µg/ml	
		Aspulvinones H	*Enterococcus faecalis* ATCC 29212	(MIC) 32.0 µg/ml	
			Staphylococcus aureus ATCC 29213	(MIC) 16.0 µg/ml	
		Aspulvinones R	*Enterococcus faecalis* ATCC 29212	(MIC) 8.0 µg/ml	
			Staphylococcus aureus ATCC 29213	(MIC) 8.0 µg/ml	
		Aspulvinones S	*Enterococcus faecalis* ATCC 29212	(MIC) 8.0 µg/ml	
			Staphylococcus aureus ATCC 29213	(MIC) 4.0 µg/ml	
		Aspulvinones T	*Enterococcus faecalis* ATCC 29212	(MIC) >64.0 µg/ml	
			Staphylococcus aureus ATCC 29213	(MIC) >64.0 µg/ml	
Aspergillus nomius	Unidentified	Unidentified	*Staphylococcus aureus*	(MIC) 6.25 µg/ml	[123]
Aspergillus stellatus KUFA 2017	*Mycale* sp.	5[(3E,5E)-nona-3,5-dien-1-yl]-benzene	*Staphylococcus aureus* ATCC 29213	(MIC) 32.0 µg/ml	[49]
			Enterococcus faecalisB3/101 (VRE)	(MIC) 16.0 µg/ml	
			Staphylococcus aureus 74/24 (MRSA)	(MIC) 16.0 µg/ml	
			Enterococcus faecalis ATCC 29212	(MIC) 16.0 µg/ml	
Penicillium					
Eupenicillium sp.	*Axinella* sp.	Alphabeta-dehydrocurvularin	*Staphyloccocus aureus*	(MIC) 375.0 µg/ml	[124]
Penicillium sp. FF001	*Melophus* sp.	citrinin	MRSA ATCC10537	(MIC) 1.95 µg/ml	[52]
			rifampicin-resistant	(MIC) 0.97 µg/ml	
			Staphylococcus aureus		
			Vancomycin-resistant *Enterococcus faecium*	(MIC) 1.95 µg/ml	
Penicillium adametzioides AS-53	Unidentified	Lapatins B	*Vibrio harveyi*	(MIC) 16.0 µg/ml	[56]
		Glyantrypine		(MIC) 32.0 µg/ml	
		verruculogen		(MIC) 32.0 µg/ml	
Penicillium. adametzioides AS-53	Unidentified	Adametizines A	*Staphyloccocus aureus*	(MIC) 8.0 µg/ml	[55]
			Aeromonas hydrophilia	(MIC) 8.0 µg/ml	
			Vibrio harveyi	(MIC) 32.0 µg/ml	
			Vibrio parahaemolyticus	(MIC) 8.0 µg/ml	
			Gaeumannomyces graminis	(MIC) 16.0 µg/ml	
		adametizines B	*Staphyloccocus aureus*	(MIC) 64.0 µg/ml	
Penicillium erubescens KUFA0220.	*Neopetrosia* sp.	GKK1032B	*Enterococcus faecalis* ATCC29212	(MIC) 8.0 µg/ml	[58,59]

(Continued)

Fungi species	Sponge source	Compound	Against bacteria	Potency	Refs
			Enterococcus faecium ATCC19434	(MIC) 16.0 µg/ml	
			Staphylococcus aureus ATCC29213	(MIC) 32.0 µg/ml	
			vancomycin-resistant *Enterococcus faecalis* (VRE) B3/101	(MIC) 8.0 µg/ml	
			Enterococcus faecium 1/6/63 (VRE)	(MIC) 32.0 µg/ml	
			MRSA 66/1	(MIC) >64.0 µg/ml	
		Erubescensoic acid	Gram-negative	NA	
			Gram-positive	NA	
			MDR strains	NA	
Penicillium simplicissimum	*Chelonaplysilla* sp.	Unidentified	*Staphylococus aureus*	(DOI) 11.96 ± 0.79 mm	[46]
			Escherichia coli	(DOI) 12.29 ± 0.72 mm	
Penicillium citrinum MN859968	*Dactylospongia* sp.	Unidentified	*Escherichia coli*	(DOI) 15.50 ± 0.30 mm	[125]
			Staphylococcus aureus	(DOI) 16.14 ± 0.75 mm	
Penicillium citrinumstrain WK-P9	*Suberea* sp.	Penicitrinone A	*Mycobacterium smegmatis* ATCC607	(MIC) 32.0 µg/ml	[57]
		Penicitrinol J	*Bacillus subtilis JH642,*	(MIC) 16.0 µg/ml	
			Bacillus megaterium DSM32,	(MIC) 16.0 µg/ml	
			Mycobacterium smegmatis ATCC607	(MIC) 32.0 µg/ml	
Penicillium sp.	*Stylissa flabelliformis*	Unidentified	*Staphylococcus aureus* ATCC 25923	(MIC) 1,343.0 µg/ml	[38]
			Escherichia coli ATCC 25922	(MIC) 719.0 µg/ml	
			Enterococcus faecalis ATCC 29212	(MIC) 800.0 µg/ml	
			Bacillus subtilis ATCC 6633	(MIC) 1,333.0 µg/ml	
Penicillium chrysogenum	*Cliona* sp.	Unidentified	*Staphyloccocus aureus* ATCC 5368	(MIC) 250.0 ± 0.82 µg/ml	[126]
			Escherichia coli ATCC 10536	NA	
Neosartorya					
Neosartorya paulistensis (KUFC 7897)	*Chondrilla australiensis*	Sartorypyrone C	*Staphylococcus aureus* ATCC 25923	(MIC) 128.0 µg/ml	[127]
			Bacillus subtilis ATCC 6633	(MIC) 128.0 µg/ml	
			Pseudomonas aeruginosa ATCC 27853	(MIC) 128.0 µg/ml	
			Escherichia coli ATCC 25922	(MIC) 128.0 µg/ml	
		Tryptoquivalines L	*Staphylococcus aureus* ATCC 25923	(MIC) 128.0 µg/ml	
			Bacillus subtilis ATCC 6633	(MIC) 128.0 µg/ml	
			Pseudomonas aeruginosa ATCC 27853	(MIC) 128.0 µg/ml	
			Escherichia coli ATCC 25922	(MIC) 128.0 µg/ml	
		Tryptoquivalines H	*Staphylococcus aureus* ATCC 25923	(MIC) 128.0 µg/ml	
			Bacillus subtilis ATCC 6633	(MIC) 128.0 µg/ml	

Fungi species	Sponge source	Compound	Against bacteria	Potency	Refs
		Tryptoquivalines F	*Pseudomonas aeruginosa* ATCC 27853	(MIC) 128.0 µg/ml	
			Escherichia coli ATCC 25922	(MIC) 128.0 µg/ml	
			Staphylococcus aureus ATCC 25923	(MIC) 128.0 µg/ml	
			Bacillus subtilis ATCC 6633	(MIC) 128.0 µg/ml	
			Pseudomonas aeruginosa ATCC 27853	(MIC) 128.0 µg/ml	
			Escherichia coli ATCC 25922	(MIC) 128.0 µg/ml	
Neosartorya glabra KUFA 0702	*Mycale* sp.	Sartoryglabramide A	*Escherichia coli* ATCC 25922	(MIC) >256.0 µg/ml	[63]
		Sartoryglabramide B	*Escherichia coli* ATCC 25922	(MIC) >256.0 µg/ml	
		fellutanine A	*Escherichia coli* ATCC 25922	(MIC) >256.0 µg/ml	
		sartoryglabramide A	*Staphylococcus aureus* ATCC 25923	(MIC) >256.0 µg/ml	
		Sartoryglabramide B	*Staphylococcus aureus* ATCC 25923	(MIC) >256.0 µg/ml	
		Fellutanine A	*Staphylococcus aureus* ATCC 25923	(MIC) >256.0 µg/ml	
Neosartorya quadricincta KUFA 0081	*Clathria reinwardti*	Polyketide derivates Benzoic acid derivates	Gram positive and negative bacteria	(MIC) >256.0 µg/ml	[128]
Neosartorya fennelliae KUFA 0811	*Clathria reinwardtii*	paecilin E	*Staphylococcus aureus* ATCC 29213	(MIC) 32.0 µg/ml	[65]
		Dankasterone A	*Enterococcus faecalis* ATCC 29212	(MIC) 16.0 µg/ml	
		Dankasterone A	*Staphylococcus aureus* ATCC 29213	(MIC) >64.0 µg/ml	
		Dankasterone A	*Enterococcus faecalis* ATCC 29212	(MIC) 32.0 µg/ml	
Neosartorya spinosa KUFA 1047	*Mycale* sp.	Penipurdin A	*Enterococcus faecalis* ATCC 29212	(MIC) >64.0 µg/ml	[65]
		Tenellic acid C		(MIC) >64.0 µg/ml	
		neospinosic acid		(MIC) >64.0 µg/ml	
		spinolactone		(MIC) >64.0 µg/ml	
		vermixocin A		(MIC) >64.0 µg/ml	
		Penipurdin A	*Enterococcus faecalis* B3/101 (VRE)	(MIC) >64.0 µg/ml	
		Tenellic acid C		(MIC) >64.0 µg/ml	
		neospinosic acid		(MIC) >64.0 µg/ml	
		Spinolactone		(MIC) >64.0 µg/ml	
		vermixocin A		(MIC) >64.0 µg/ml	
		Penipurdin A	*Staphylococcus aureus* ATCC 29213	(MIC) >64.0 µg/ml	
		Tenellic acid C		(MIC) >64.0 µg/ml	
		neospinosic acid		(MIC) >64.0 µg/ml	
		spinolactone		(MIC) >64.0 µg/ml	
		vermixocin A		(MIC) >64.0 µg/ml	
		Penipurdin A	*Staphylococcus aureus* 66/1 (MRSA)	(MIC) >64.0 µg/ml	
		Tenellic acid C		(MIC) >64.0 µg/ml	
		neospinosic acid		(MIC) >64.0 µg/ml	

(Continued)

Fungi species	Sponge source	Compound	Against bacteria	Potency	Refs
		spinolactone		(MIC) >64.0 µg/ml	
		vermixocin A		(MIC) >64.0 µg/ml	
Trichoderma					
Trichoderma sp 05FI48	Unidentified	Trichoderins A	*Mycobacterium smegmatis*	(MIC) 0.1 µg/ml	[70]
		Trichoderins A1	*Mycobacterium smegmatis*	(MIC) 1.56 µg/ml	
		Trichoderins B	*Mycobacterium smegmatis*	(MIC) 0.63 µg/ml	
		Trichoderins A	*Mycobacterium bovis BCG*	(MIC) 0.02 µg/ml	
		Trichoderins A1	*Mycobacterium bovis BCG*	(MIC) 0.16 µg/ml	
		Trichoderins B	*Mycobacterium bovis BCG*	(MIC) 0.02 µg/ml	
		Trichoderins A	*Mycobacterium tuberculosis H37Rv*	(MIC) 0.12 µg/ml	
		Trichoderins A1	*Mycobacterium tuberculosis H37Rv*	(MIC) 2.0 µg/ml	
		Trichoderins B	*Mycobacterium tuberculosis H37Rv*	(MIC) 0.13 µg/ml	
Trichoderma atroviride NF16	*Axinella* sp.	Trichorzianines (1-12)	*Staphylococcus albus* *Bacillus subtilis*	(MIC) 50.0–200.0 µg/ml	[73]
Trichoderma koningii PF04	*Phakellia fusca*	Hypofurans A	*Staphylococcus aureus* ATCC25923	(MIC) 32.0 µg/ml	[76]
		N-isobutyl-2 phenylacetamide		(MIC) 32.0 µg/ml	
		Citrantifidiol		(MIC) 32.0 µg/ml	
Trichoderma asperellum BK261A	*Cinachyrella* sp.	Unidentified	MDR *Escherichia coli*	NA	[78]
Trichoderma reesei MG547722.1	*Cinachyrella* sp.	Unidentified	Extended-spectrum β-lactamase (ESBL) *Escherichia coli*	(DOI) 9.09 ± 0.14 mm	[78]
			Salmonella enterica ser. Typhi	(DOI) 14.78 ± 0.0 mm	
			MRSA	(DOI) 7.40 ± 0.14 mm	
			Staphylococcus haemolyticus	(DOI) 6.81 ± 0.11 mm	
Trichoderma reesei (HN-2016-018)	Unidentified	Gliocladinin D	*Staphylococcus aureus* ATCC 25922	NA	[129]
			Escherichia coli ATCC 25923	NA	
			Pseudomonas aeruginosa ATCC 27853	NA	
		2-(2′-hydroxypropyl)-5-methyl-7 hydroxychromone	*Staphylococcus aureus* ATCC 25922	NA	
			Escherichia coli ATCC 25923	NA	
			Pseudomonas aeruginosa ATCC 27853	NA	
		Pachybasin	*Staphylococcus aureus* ATCC 25922	NA	
			Escherichia coli ATCC 25923	NA	
			Pseudomonas aeruginosa ATCC 27853	NA	

(Continued)

Fungi species	Sponge source	Compound	Against bacteria	Potency	Refs
		Emodin	*Staphylococcus aureus* ATCC 25922	NA	
			Escherichia coli ATCC 25923	NA	
			Pseudomonas aeruginosa ATCC 27853	NA	
		Vertinolide	*Staphylococcus aureus* ATCC 25922	NA	
			Escherichia coli ATCC 25923	NA	
			Pseudomonas aeruginosa ATCC 27853	NA	
Trichoderma reesei TV221	*Stylissa flabelliformis*	Unidentified	*Escherichia coli* ATCC 25922	(DOI) 14.37 mm	[79]
			Staphylococcus aureus ATCC 25923	(DOI) 17.67 mm	
Trichoderma reesei JCM 2267	*Stylissa flabelliformis*	Unidentified	*Staphylococcus aureus* ATCC 25923	(MIC) 344.0 µg/ml	[38]
			Escherichia coli ATCC 25922	(MIC) 144.0 µg/ml	
			Enterococcus faecalis ATCC 29212	(MIC) 63.0 µg/ml	
			Bacillus subtilis ATCC 6633	(MIC) 516.0 µg/ml	
Other genus					
Curvularia lunata	*Niphates olemda*	1,3,8-Trihydroxy-6-methoxyanthraquinone (lunatin)	*Escherichia coli*	(DOI) 11.0 mm	[80]
			Escherichia coli HBI-101	(DOI) 10.5 mm	
		Bisanthraquinone cytoskyrin A	*Escherichia coli*	(DOI) 11.0 mm	
			Escherichia coli HBI-101	(DOI) 9.0 mm	
Exophiala sp.	*Halichondria panicea*	Chlorohydroaspyrones A	*Staphyloccocus aureus*	(MIC) 62.5 µg/ml	[81]
		Chlorohydroaspyrones B	*Staphyloccocus aureus*	(MIC) 62.5 µg/ml	
		Chlorohydroaspyrones A	MRSA	(MIC) 125.0 µg/ml	
		Chlorohydroaspyrones B	MRSA	(MIC) 125.0 µg/ml	
Paecilomyces sp.	Unidentified	cholesteryl linoleate stigmasterol 2,5-furandimethanol	MRSA	(DOI) 18 ±0.2 mm	[130]
Engyodontium album (IVB1b)	*Ircinia variabilis*	1-(4-hydroxybenzoyl) indole-3-carbaldehyde (6)	*Vibrio parahaemolyticus*	NA	[84]
Rhinocladiella sp. (IO2)	*Ircinia oros*	2-hydroxymethyl-3-methyl-7-methoxychromone (1)	*Escherichia coli*	NA	[84]
		2-hydroxymethyl-3-tert-butyl-7-methoxychromone (2)	*Staphylococcus aureus*	NA	
		2,3-dimethyl-7-methoxychromone (3)	*Vibrio alginolyticus*	NA	
		3-(3-chloro-2-hydroxypropyl)-8-hydroxy-6-methoxy-isochromen-1-one (4)	*Vibrio. anguillarum*	NA	

(Continued)

Fungi species	Sponge source	Compound	Against bacteria	Potency	Refs
Pestalotiopsis heterocornis	*Phakellia fusca*	pestaloisocoumarins A	*Bacillus subtilis*	(MIC) 50.0 µg/ml	[16]
		Pestaloisocoumarins B		(MIC) 25.0 µg/ml	
		gamahorin		(MIC) 100.0 µg/ml	
		Pestalachloride B		(MIC) 3.0 µg/ml	
		pestalachloride E		(MIC) 50.0 µg/ml	
		pestalalactone atropisomers		(MIC) 50.0 µg/ml	
		pestaloisocoumarins A	*Staphylococcus aureus*	(MIC) 25.0 µg/ml	
		pestaloisocoumarins B		(MIC) 25.0 µg/ml	
		gamahorin		(MIC) 100.0 µg/ml	
		Pestalachloride B		(MIC) 3.0 µg/ml	
		pestalachloride E		(MIC) 25.0 µg/ml	
		pestalalactone atropisomers		(MIC) 50.0 µg/ml	
Fungal strain L14J	*Reniera japonica* MNP-2016	Unidentified	*Staphyloccocus aureus*	(DOI) 18–28 mm	[131]
Phoma sp.135	*Ectiplasia perox*	Cryptophomic acid	*Escherichia coli*	(MIC) 28 ± 0.4 µg/ml	[83]
			Bacillus subtilis	(MIC) 32 ± 0.2 µg/ml	
			Staphylococcus aureus	(MIC) 30 ± 0.4 µg/ml	
		Cryptotriol	*Escherichia coli*	(MIC) 17 ± 0.3 µg/ml	
			Bacillus subtilis	(MIC) 20 ± 0.2 µg/ml	
			Staphylococcus aureus	(MIC) 27 ± 0.2 µg/ml	
		Cryptodiol	*Escherichia coli*	(MIC) 20 ± 0.3 µg/ml	
			Bacillus subtilis	(MIC) 30 ± 0.2 µg/ml	
			Staphylococcus aureus	(MIC) 35 ± 0.3 µg/ml	
Cladosporium halotolerans MN859971	*Dactylospongia sp*	Unidentified	*Escherichia coli*	(DOI) 12.74 ± 0.45 mm	[125]
Phomapsis sp.	*Chelonaplysilla* sp.	Unidentified	*Staphylococcus aureus*	(DOI) 15.92 ± 0.52 mm	[46]
		Pestaloisocoumarins B	*Escherichia coli*	(DOI) 16.33 ± 0.51 mm	
Fusarium sp. LY019	*Suberea mollis*	Fusaripyridines A	*Escherichia coli*	(MIC) 13. 61 µg/ml	[82]
			Staphylococcus aureus	(MIC) 13. 61 µg/ml	
		Fusaripyridines B	*Escherichia coli*	(MIC) 14.73 µg/ml	
			Staphylococcus aureus	(MIC) 14.73 µg/ml	

This table organized in order of the most reported genus with antibacterial activity. MIC = Minimum Inhibitory Concentration. DOI = Diameter of Inhibition. NA = no activity.

and most sensitive to *Streptococcus pyogenes* 308A. Other compounds, including sterigmatocystin, which is a xantone, and methyl-averantin showed potential as potent antitumors against human tumor cells A-549, SK-OV-3, SK-MEL-2, XF-498, HCT-15 indicated by IC_{50} values ranging from 0.41 to 4.61 µg/ml [33]. The cytotoxic activity of the averantin compound is likely due to the presence of free hydroxyl derivatives, which affect its polarity.

Another strain from *A. versicolor* is MF359, derived from the sponge *Hymeniacidon perleve* in the Bohai Sea, China, isolated 5-methoxydihydrosterigmatocystin (**3**) and showed antibacterial activity against *S. aureus* ATCC 6538 and *Bacillus subtilis* ATCC 6633, which are better than the extract by the Minimum Inhibitory Concentration (MIC) values. In terms of its ability as an antibacterial against MRSA (clinical isolate) and *Pseudomonas aeruginosa* ATCC 15692, the MIC value was >100 µg/ml. This study also has been able to isolate hemiacetal sterigmatocystin, acyl-hemiacetal sterigmatocystin, and aversin [34]. The fungus *Aspergilus flavus* GU815344 derived from the sponge *Callyspongia* spp. in the sea of Kovalam, India, generates desmethylnomifensine (GC-MS verified) to serve as an antibacterial against *S. aureus* and *E. coli*. The inhibitory power of extracts derived from biomass is smaller than extracts from supernatants based on the diameter clear zone against *E. coli* and *S. aureus* bacteria [35]. Similar to the research by Samirana *et al*. [36], the supernatant extract from *Trichoderma reesei* TV 221 associated sponge *Stylissa flabelliformis* showed antibacterial activity better than the biomass extract. *Aspergillus flavus* IBI 141 and *Aspergillus* sp IBI 151 associated with the sponge *Acanthostrongylophora ingens* from Mendeh Island, south coast of West Sumatra, Indonesia, showed antibacterial

activity against bacteria *B. subtilis, Staphylococcus epidemidis, Salmonella typosa,* and *E. coli*. It also has cytotoxic activity against shrimp larvae, with an LC_{50} value of 58.56 ppm. The compound class of the fungus *A. flavus* IBI 141 is phenolics and terpenoids [37].

Several fungi were isolated from the sponge *S. flabelliformis,* including *T. reesei* strain JCM 2267, *A. flavus* strain MC-10-L, *Penicillium sp*, and *Aspergillus fumigatus* [38]. Extracts from the fungus were tested for antibacterial ability against *S. aureus* ATCC 25923, *E. coli* ATCC 25922, *Enterococcus faecalis* ATCC 29212, and *B. subtilis* ATCC 6633. The MIC values of *A. flavus* fungal extract strain MC-10-L and *A. fumigatus* are presented in Table 1. The antibacterial activity of *A. flavus* and *A. fumigatus* fungi is found to be moderate. The cytotoxic ability of *A. flavus* strain MC-10-L extract against T47D tumor cells was shown with an IC_{50} value of 550 (mg/ml). Based on analysis with GC-MS, ethyl acetate extract from the fungus contains cyclohexanone, which requires further research.

The compound preussin (**4**), as a class of hydroxy pyrrolidine alkaloids, was isolated from the fungus *Aspergillus candidus* KUFA 0062 associated with the sponge *Epipolasis* sp. originates from coral reefs in Similan Island National Park in Phang-Nga province, Southern Thailand. This preussin showed better inhibitory activity than its analogues, namely preussin C against bacteria *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, MRSA, and vancomycin-resistant enterococci (VRE). Another activity shown by preussin was inhibited by almost 50% biofilm formation from *E. coli* ATCC 25922 (42.8% ± 32.7% control), *S. aureus* ATCC 29213, and *E. faecalis* ATCC 29212 at concentrations equal to above MIC (Table 2), when preussin was combined with vancomycin antibiotics, oxacillin, and colistin showed a relatively strong synergistic effect. The cytotoxic effect of preussin can reduce the viability of colon cancer cells (6.4% and 8.6% in HCT116 and HT29). The presence of the N-methyl group on the pyrrolidine ring in preussin provides an antibacterial effect and cytotoxic activity. It can serve as a candidate for new antibiotics and anticancers. Other compounds isolated from this fungus are chrysophanic acid and petromurin C [39].

The *p*-terphenyl alcohol group, 4-*O*-methylcandidusin A, which was isolated from the fungus *A. candidus* OUCMDZ-1051, showed a potent and selective cytotoxic effect against MDA-MB-468, BT474, and A431 cancer cells. Its ability to inhibit the growth of *E. coli* bacteria is demonstrated by the MIC value of 10.0 μg/ml using the dilution method. Hence, it can potentially be developed as an anticancer and antibacterial [40]. Natural *p*-terphenyls have been widely reported, where the structural diversity is due to variations in ring B, position, and number of hydroxy groups [41,42]. The 16-*O*-propionyl-16-*O*-deacetylhelvolic acid (**5**), 6-*O*-propionyl-6-*O*-deacetylhelvolic acid (**6**), and helvolic acid (**7**) isolated from the fungus *A. fumigatus* HNMF0047 effective against *Streptococcus agalactiae* even though the MIC value was lower than tobramycin as a control. The 6-O-propionyl-6-*O*-deacetylhelvolic acid has more potent antimicrobial effects than helvolic acid because propionyloxy replaces the acetoxy group at C-6 in helvolic acid [43]. Ethyl acetate extract from the fungus *Aspergillus sydowii* ZSDS1-F6 fermented using oligotropic

medium reported contain sesquiterpenes of bisabolen groups including aspergillusene A, (Z)-5-(Hydroxymenthyl)-2-(6′-methylhept-2′-en-2′-yl)-phenol, diorcinol, and sydonic acid [44]. Aspergillusene A, (Z)-5-(Hydroxymenthyl)-2-(6′-methylhept-2′-en-2′-yl)-phenol, and diorcinol inhibit the bacterial growth of *Klebsiella pneumonia* and *Aeromonas hydrophila*. Except for aspergillusene, both compounds were against H3N2 with IC50 of 57.4 and 66.5 μM. Compounds (Z)-5-(Hydroxymethyl)-2-(6′-methylhept-2′-en-2′-yl)-phenol and (+)-sydonic acid were also found in the fungus *Aspergillus* sp. associated with the sponge *Xestospongia testudinaria* in the South China Sea [45]. Based on the identification and elucidation structure, the fungus also contains (−)5-(hydroxymethyl)-2-(2′,6′,6′-trimethyltetrahydro-2H-pyran-2-yl)-phenol, Aspergiterpenoid A, and (+)-sydonol. These compounds show antibacterial activity with MIC values ranging from 1.25 to >20 μM against some bacteria (Table 1). All compounds showed weak cytotoxic effects (IC50 >50 μg/ml) against human promyelocytic leukemia HL-60 and human lung carcinoma cell A-549. None of the compounds showed cholinesterase inhibitory activity.

Sponge *Chelonaplysilla* sp., which was isolated from 12 fungi-associated were *Aspergillus oryzae, Phomompsis* sp., *Penicillium simplicissimum, Beauveria bassiana,* and *Aspergillus mellinus* [46]. The extracts of *A. oryzae* and *A. mellinus* were more sensitive to *S. aureus* and *E. coli,* demonstrated by a diameter clear zone ranging from 8.54 to 16.88 mm. The cytotoxic effect is shown by extracts from the fungus *Phomompsis* sp. with an IC_{50} value of 83.69 μg/ml. It was concluded that the fungus associated with the sponge *Chelonaplysilla* sp. can be utilized as a novel antibacterial and anticancer therapeutic agent. The fungal strain *Aspergillus clavatus* MFD15 yielded the compound 1H-1,2,4 Triazole 3-carboxaldehyde 5-methyl, which exhibited antibacterial properties against *Staphylococcus epidermidis* and *E. coli* [47] with the MIC values of more than 500 μg/ml The strains showing MIC values exceeding 500 μg/ml indicated low efficacy.

Prenylated phenylbutyrolactone group compounds, namely aspulvinone R, S, T, isolated from the fungus *Aspergillus flavipes* KUFA1152 associated with the sponge *Mycale* sp. from Samasean Island, Gulf of Thailand, Chonburi Province. Aspulvinone R (**8**) and aspulvinone S (**9**) exhibit potential as novel drugs for their antibacterial activity against *E. faecalis* ATCC 29212, *S. aureus* ATCC 29213, *E. faecalis* B3/101 (VRE), and *S. aureus* 66/1 (MRSA) evidenced by their MIC values ranging from 4.0 to 16.0 μg/ml [48]. *Aspergillus stellatus* KUFA 2017 was also reported to be associated with the *Mycale* sp. The presence of 5[(3E,5E)-nona-3,5-dien-1-yl]-benzene (**10**) in the fungal extract has antibacterial activity against *E. faecalis* ATCC 29212, *E. faecalis* B3/101 (VRE), *S. aureus* ATCC 29213, and *S. aureus* 74/24 (MRSA) with MIC values ranging from 16.0 to 64.0 μg/ml. It also significantly inhibited nitric oxide production in lipopolysaccharide-induced raurine macrophage RAW264.7 cells and was found to contain antibiofilm activity [49].

Genus *Penicillium*

Penicillium has been widely acknowledged and proven as an antibiotic since its discovery by Fleming [50]. Research on this genus has continued to expand the understanding of its

Table 2. Summary of research on sponge-associated fungi and their antibiofilm activity.

Fungi species	Sponge source	Compound	Against bacteria	Concentration (μg/ml)	Inhibition biofilm formation (%)	Refs
Penicillium sp. F37	*Axinella corrugata*	Dipeptide *cis-cyclo* (Leucyl-Tyrosyl	*Staphylococcus epidermidis* ATCC 3598	0.25	60.0	[108]
				0.5	65.0	
				1.0	85.0	
Penicillium sp. SCSGAF 0023	Unidentified	Eemodin	*Staphylococcus aureus* ATCC 6538	12.5	91.00 ± 6.12	[111]
		Citrinin			59.67 ± 8.05	
		Secalonic acids B			96.27 ± 0.96	
		Secalonic acids D			98.07 ± 1.12	
		Citreorosein			71.95 ± 1.45	
		Penicillixanthone A			91.25 ± 1.43	
Aspergillus candidus KUFA0062	*Epipolasis sp*	Preussin	*Staphylococcus aureus* ATCC 29213	32.0	42.8 ± 32.7	[39]
			Enterococcus faecalis ATCC 29212			
Penicillium erubescens KUFA0220.	*Neopetrosia* sp.	GKK1032B	*Enterococcus faecalis* ATCC 29212	NA	NA	[58,59]
		Erubescenoic acid	*Pseudomonas aeruginosa* ATCC 27853	NA	NA	
			Staphyllococus aureus ATCC 29213	NA	NA	
			Enterococcus faecalis ATCC 29212	NA	NA	
Neosartorya spinosa KUFA 1047	*Mycale* sp.	Tenellic acid C	*Escherichia coli* ATCC 25922	64.0	16.11	[65]
			Enterococcus faecalis ATCC 29212	64.0	24.11	
			Staphylococcus aureus ATCC 29213	64.0	15.54	
		Neospinosic acid	*Escherichia coli* ATCC 25922	64.0	16.11	
			Staphylococcus aureus ATCC 29213	64.0	44.0	
Aspergillus flavipes KUFA1152	*Mycale sp*	Aspulvinones B'	*Enterococcus faecalis ATCC 29212*	64.0	93.36	[48]
			Staphylococcus aureus ATCC 29213	64.0	100.0	
		Aspulvinones H	*Enterococcus faecalis* ATCC 29212	64.0	96.6	
			Staphylococcus aureus ATCC 29213	64.0	100.0	
		Aspulvinones R	*Enterococcus faecalis* ATCC 29212	16.0	94.51	
			Staphylococcus aureus ATCC 29213	16.0	96.77	
		Aspulvinones S	*Enterococcus faecalis* ATCC 29212	16.0	87.87	
			Staphylococcus aureus ATCC 29213	16.0	100.0	
Aspergillus stellatus KUFA 2017	*Mycale* sp.	5[(3E,5E)-nona-3,5-dien-1-yl]benzene	*Enterococcus faecalis* ATCC 29212	32.0	>90	[49]
			Staphylococcus aureus ATCC 2921	32.0	>90	

This table arrangement by the earliest year. NA = no activity.

potential benefits on medication. *Penicillium* species provide a wide range of metabolite compounds and their biological activities either from terrestrial or marine environments [51]. Several publications regarding the antibacterial activity of the genus *Penicillium* fungi associated with sponges are listed in Table 1. Some studies summarized in this review did not isolate and identify the structure. Hence, which chemicals are involved in the pharmacological activity is still unclear, and additional investigation is required.

The citrinin (**11**) was isolated from the fungus *Penicillium* sp. FF001 association with sponge *Melophus* sp., showing potent antibacterial activity against antibiotic-resistant bacteria, such as MRSA ATCC 10537, rifampicin-resistant *S. aureus,* and Vancomycin-resistant *Enterococcus faecium* [52]. Another potential of citrinin is antifungal activity against *Cryptococcus neoformans* (MIC 3.90 μg/ml) and cytotoxic to shrimp larvae (LD50 96 μg/ml) [52]. *Penicillium crysogenum* also produces citrinin and shows potent antibacterial against gram-positive and Gram-negative bacteria, and antifungal activity [53,54]. The fungal strain *Penicillium adametzioides* AS-53 was cultivated using Potato Dextrose Agar, resulting in two novel bisthiodiketopiperazine compounds, namely adametizines A (**12**) and B (**13**). Concurrently, the metabolites isolated from cultivation in rice media showed novel acorane sesquiterpenes, namely adametacorenols A and B. Adametizines A potential were developed as a novel antibacterial activity based on the MIC values, which were less than 16 μg/ml against bacteria *S. aureus, Aeromonas hydrophilia, Vibrio harveyi, Vibrio parahaemolyticus*, and *Gaeumannomyces graminis*. Cl substitution in C-7 enhances the cytotoxic effect on shrimp larvae and their antimicrobial activity [55]. Quinazolin group compounds, including Lapatins B, glyantrypine, and verruculogen were also isolated from these fungi [56].

Two citrinin-derived compounds, namely Penicitrinone A (**14**), were isolated and identified from *Suberea* sp. and found to be inhibited by *Mycobacterium smegmatic* ATCC607 bacteria (MIC 32 μg/ml). In contrast, Penicitrinol J (**15**) indicated the MIC values 16, 16, and 32 μg/ml for *B. subtilis* JH642, *Bacillus megaterium* DSM32, *M. smegmatic* ATCC607 [57]. Based on the MIC values, all compounds were classified as moderate. The presence of phenolics in the structure of penicitrinol increases its potential as an antibacterial. *Penicillium erubescens* KUFA0220 associated with sponge *Neopetrosia* sp. contains several metabolites including GKK1032B, citromycin, 12-methoxycitromycin, myxotrichin D, 12-methoxycitromycetin, anhydrofulvic acid, myxotrichin C, penialidin D, penialidin F, SPF-3059-30, and secalonic acid A. Only the GKK1032B demonstrated the potential to serve as bacteriostatic against *E. faecalis* ATCC 29212 vancomycin-resistant *E. faecalis* (VRE) B3/101, *E. faecium* ATCC 19434, and *E. faecium* 1/6/63 (VRE) with the MIC values between 8 and 16 mg/ml. A novel polyketide, namely erubescensoic acid, was also isolated from this fungus. The compound was also tested for inhibiting bacterial growth against Gram-negative, Gram-positive, and MDR strains from the environment. The results showed that this compound had no activity. This compound

was also unable to inhibit biofilm formation against *P. aeruginosa* ATCC 27853, *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212 (Table 2) [58,59].

Genus *Neosartorya*

Fungi belonging to the *Neosartorya* genus contain numerous metabolites, such as indole alkaloids, peptides, meroterpenes, and polyketides, with various biological activities, such as antimicrobial, anticancer, and so on [60,61]. Below is an overview of a study on the *Neosartorya* fungus and its antibacterial effect (Table 1). *Mycale* sp. sponge-associated with the fungus *Neosartorya glabra* KUFA 0702 originating from Samasean Island, Gulf of Thailand, contains cyclotetrapeptides group compounds, namely sartoryglabramides A (**16**), sartoryglabramides B (**17**), and new fellutanine A. In addition, this research reported that the compounds have never been isolated before from the genus *Neosartorya* associated with a sponge. Despite the lack of antibacterial activity against *E. coli* and *S. aureus* (MIC >256.0 μg/ml), it is important to note that these compounds may possess other significant biological properties. Several cyclopeptides have been shown to have antifungal and antibacterial activities. However, their potencies depend on the stereochemical configurations of the amino acid constituents [62,63].

Another fungus associated with *Mycale* sp. is *Neosartorya spinosa* KUFA1047 reported by de Sá [64] contains penipurdin A, tenellic acid C, neospinosic acid, spinolactone (**18**), vermixocin (the anthraquinones group). However, only spinolactone showed a bacteriostatic effect against *E. faecalis* B3/101, although lower than ceftazidime antibiotics. Paecilin E (**19**) and dankasterone A (**20**) compounds were isolated from supernatant extracts of the fungus *Neosartorya fennelliae* KUFA 0811 in association with the sponge *Clathria reinwardtii*. Both showed antibacterial activity against *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212, although the antibacterial effect of paecilin E was better than dankasterone A based on the MIC values. This study also assessed the impact of these two compounds on biofilm formation. The findings indicated that neither of these compounds exhibited an inhibitory effect on biomass production in the tested bacterial strains. In the future, it is necessary to test other biological activities to determine the pharmacological effects of these two compounds [65].

Genus *Trichoderma*

Many species of *Trichoderma* produce metabolite compounds with various activities depending on the strain. This genus is widely recognized as a biological control agent against microorganisms either directly or indirectly. The volatile compounds, such as 1,2-Benzenedicarboxylic acid dibutyl ester, 2H-Pyran-2-one, and palmitic acid produced by *Trichoderma asperellum* are known to serve as effective pesticides [66]. Another potential of *Trichoderma* species is for enhanced growth of plants, which is commonly used for agricultural purposes [67–69]. Trichoderin A (**21**), A1 (**22**), and B (**23**) (new amino lipopeptide) isolated from *Trichoderma* sp. 05FI48 exhibited potent antimycobacterial against *Mycobacterium smegmatis, Mycobacterium bovis* BCG, and *Mycobacterium tuberculosis* H37Rv according to the MIC values (under aerobic and hypoxic

conditions). The mechanism of trichoderin A inhibits Adenosine triphosphate (ATP) production of bacteria [70,71], which may serve as a promising antidormant mycobacterial drug. The study conducted on *Trichoderma atroviride NF16* associated with the sponge *Axinella* sp. from the eastern Mediterranean coast, Israel, showed the antibacterial potential of Trichorzianines (peptaibol group) against *Staphylococcus albus* and *B. subtilis*. Peptaibol is a linear peptide consisting of 5–20 amino acids, such as alpha-aminoisobutyric acid. A large amount of peptide is found in the genus of *Trichoderma* and plays an essential role in the activity of *Trichoderma* spp as a biocontrol agent [72–75]. The furan derivatives, namely hypofurans A (**24**) and B, together with cyclopentanon derivatives, namely *N*-isobutyl-2-phenylacetamide (**25**), citrantifidiol (**26**) were extracted and isolated from the fungus *Trichoderma koningii* PF04 associated with the sponge *Phakellia fusca* originating Yongxing Island in the South China. Except for hypofurans B, all substances showed antibacterial activity with moderate potential against *S. aureus* ATCC25923 [76].

Sponge *Cinachyrella* sp. from the Panjang island, Central Java, Indonesia, was found to be associated with the fungus *T. asperellum* BK261A and *T. reesei* KU377472.1 showed antibacterial activity against MDR *E. coli* based on the diameter inhibition zone. Another sponge *Cinachyrella* sp., collected from Pandang Island, North Sumatra, Indonesia, associated with nine fungi, one of which is *T. reesei* MG547722.1 showed its potential in inhibiting clinical isolate bacteria, including ESBL *E. coli*, *Staphylococcus haemolyticus* strain MDR, MRSA and the highest antibacterial potential against *Salmonella enterica* ser. Typhi [77,78]. Some fungi from the genus of *Trichoderma*, such as *T. reesei* TV221 and *T. reesei* JCM 2267, associated with sponge *S. flabelliformis* showed antibacterial activity with various categories from moderate to weak based on MIC and DOI values [38,79] (Table 1). Unfortunately, all the above-mentioned research did not report the isolated compounds responsible for the antibacterial activities.

Another genus

The screening articles related to sponge-associated fungi reported that fungi from genera other than those mentioned above showed antibacterial activity (Table 1). Ethyl acetate extract from *Curvularia lunata* associated with *Niphates olemda* sponge from Bali Bata National Park, Indonesia, produced a potent antrakinon, namely lunatin (**32**) and cytoskyrin A (bisanthraquinone) to serve as antibacterial activity against *S. aureus*, *E. coli*, and *B. subtilis* although it may not show potential antifungal activity against *Candida albicans* [80]. The aspiron-derived compounds known as Chlorohydroaspyrones A (**27**) and B (**28**) were proven to inhibit the growth of *S. aureus* and MRSA bacteria with MIC values of 62.5 and 125 µg/ml [81]. This fungal organism also produces polyketide substances such as aspirin, asperlactone, and penicillin acid, although their activity is not well reported. Fusaripyridines A and B (dimeric alkaloids) isolated from *Fusarium* sp. LY019 denoted antifungal activity against *C. albicans* at MIC 8.0 µM, but their antibacterial activity was classified as moderate which could serve as a guide for finding new drugs [82].

Other compounds that develop potential as antibacterial agents are cryptophomic acid (**29**), crytotriol (**30**), and cryptodiol

(**31**) isolated from *Phoma* sp.135 [83]. The indole alkaloid compound, namely 1-(4-hydroxybenzoyl)indole-3-carbaldehyde isolated from the fungus *Engyodontium album* (IVB1b) associated with the sponge *Ircinia variabilis* [84]. The isocoumarin derivative, known as 3-(3-chloro-2-hydroxypropyl)-8-hydroxy-6-methoxy-isochromen-1-one was also isolated from the fungus *Rhinocladiella* sp. (IO2) with association with the sponge *Ircinia oros*. However, none of above mentioned showed antibacterial activity against *E. coli*, *S. aureus*, *Vibrio alginolyticus*, *Vibrio anguillarum*, *V. harveyi*, *V. parahaemolyticus*, *Alternaria brassicae*, and *Fusarium graminearum*. Inactive compounds against certain bacteria may have a different effect on other bacteria, which could be attributed to the compound's ability to provide antibacterial effects due to many factors, such as genetic differences between every bacteria, concentration, and polarity of the compound tested [85,86].

Data from Table 1 indicates that the bacteria used in this study to determine the antibacterial effect of sponge-associated fungi were Gram-positive and negative bacteria, both from reference strains and clinical isolates. *Staphylococcus aureus* (Gram-positive bacteria) and *E. coli* (Gram-negative) were the most common bacteria, which mainly caused nosocomial and many infectious diseases [87,88]. Antibiotic-resistant microorganisms, such as MRSA, multidrug-resistant *E. coli*, and vancomycin-resistant *enteroccocus* (VRE) are known to increase the incidence of infections. This condition encourages researchers to look for new antibiotic agents using these bacterial species to solve the resistance problem.

Some methods are commonly used to examine antibacterial agent potential, such as dilution, diffusion, or others [89,90]. Each method has its own advantages and limitations, thus making it necessary to determine the most appropriate to use, depending on various factors, such as the availability of equipment and facilities, amount, and characteristics of the samples. The data on the diameter of the inhibition zone obtained from the diffusion method may not be able to determine the bactericidal and bacteriostatic effects compared to the microdilution method. However, it is revealed to be more convenient, more affordable, more applicable to many different microorganisms, and more easily interpreted [91,92]. It is necessary to recognize that different types of bacteria in bacterial testing can affect antibacterial potential, which is normally categorized based on the MIC value or inhibition diameter marked by the appearance of a clear zone. MIC is the lowest concentration that may inhibit any growth of microorganisms. On the basis of these values, the antibacterial activity is categorized as, i.e., 50–500 µg/ml is vigorous; 600–1,500 µg/ml is moderate; and >1,500 µg/ml indicates weak or inactivity [93,94]. Based on diameter inhibition, there are several categories of antibacterial strength. If the diameter is less than 8 mm, the organism is resistant. The diameter zone between 9 and 14 mm is classified as sensitive, 15 to 19 mm is very sensitive, and more than 20 mm is deemed as extremely sensitive [95,96]. The compounds showed potent antibacterial activity from marine sponges associated with fungi shown in Figure 4. Figure 4 shows that marine derive-fungi contain various compounds and have potential as antibacterial agents.

Sponge-associated fungi as a source of antibiofilm

Superbugs have become a global health issue and contribute to morbidity and mortality rates. Superbugs are described by the increased immunity of microbes to several types of antibiotics. It may occur naturally in bacteria when their genes evolve. Another reason for increasing resistance is biofilm formation, which makes treating infectious diseases more difficult, and thus makes it necessary to develop strategies to eradicate superbugs effectively [97–100]. Biofilm is microorganism communities that adhere to the surface and form an extracellular matrix known as extracellular polymeric substance (EPS) consisting of polysaccharides, various proteins, lipids, and DNA [101–103, 1]. Biofilm morphology depends on its constituent bacteria and conditions for biofilm formation.

The cycle growth of biofilm formation begins with the initial attachment phases. Planktonic bacteria attached to a surface or devices initiate reversible or irreversible attachment. Microorganisms have specific signals to start biofilm formation. They prefer hydrophobic surfaces because they reduce the repulsive force between the bacteria and the surface, resulting in stronger adhesion. The next phase is microcolony formation, characterized by bacteria multiplying and biofilm EPSs production [2,104–106]. In the mature phase, biofilms develop entirely and, eventually multilayers. The cell density reaches a peak and forms a typical 3-D biofilm structure. After the biofilm reaches complete maturity, the dispersal step begins by releasing bacteria into the environment. The dispersal stage is essential in the biofilm life cycle because it promotes new biofilm initiation at other sites [1,107]. The biofilm life cycle is presented in Figure 5. In recent years, biofilm-related research has attracted many researchers, although studies on exploring marine-associated fungi and their potential as antibiofilm are still rare. The summarized data of sponge-derived fungi and their potential to serve as antibiofilm is shown in Table 2. A *cis-cyclo* (Leucyl-Tyro-syl) dipeptide was successfully isolated from *Penicillium* sp. associated with the sponge *Axinella corrugata*. The compound effectively inhibited biofilm formation of *S. epidermidis* ATCC 35984 up to 85% at a concentration of 1 mg/ml and fully inhibited at 2 mg/ml. Observation of the biofilm structure by Scanning Electron Microscope (SEM) showed that the sample group treated with 1.0 mg ml dipeptide showed less intense EPS formation [108]. Diketopiperazines have many biological activities, such as antitumor and antiviral. Bacterial signaling systems, including quorum-sensing (QS), can be influenced by diketopiperazine [109,110]. Secalonic acid D (SAD) and B isolated from *Penicillium* sp. SCSGAF 0023 effectively inhibits biofilm formation >90% at 6.25 µg/ml against *S. aureus* ATCC 6538, although there is no effect on the *P. aeruginosa* PAO1 on the concentration up 100%. SAD showed a biofilm eradication effect at level 12.5 µg/ml. The biofilm architecture of *S. aureus,* also influenced by SAD, showed a decrease in biofilm biomass and thickness by the dose-dependent. SAD can regulate the transcription level of biofilm-related genes. Nonetheless, other genetic studies are needed to clarify the mechanism of SAD inhibition of *S. aureus* biofilm formation [111], which concludes that SAD has the potential to develop as an antibiofilm agent.
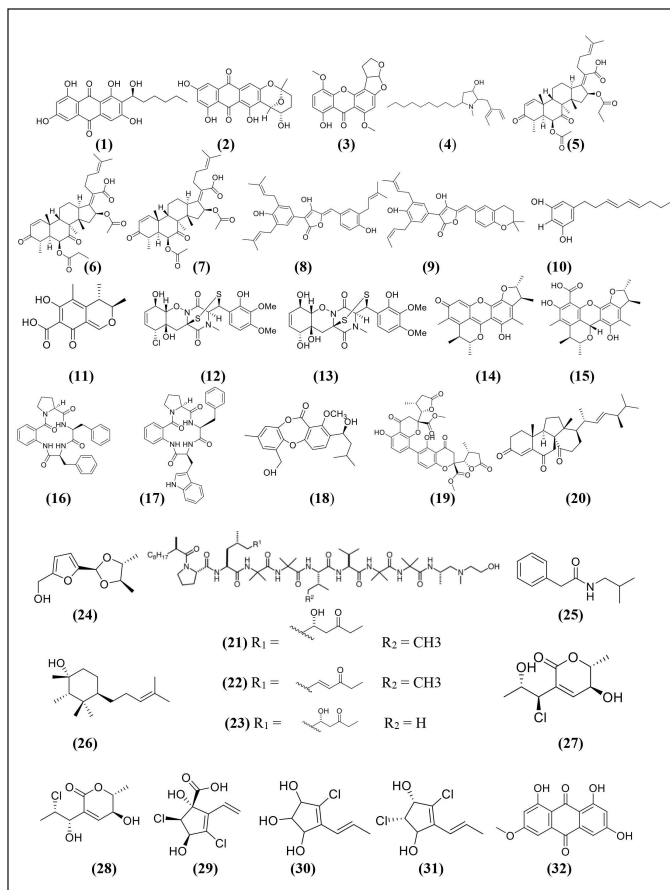

Figure 4. Structure compounds from marine sponge derived-fungi with potent antibacterial activity [33,34,70,76,80,81,83,65,72,39,43,49,52,55,57,62,65].

Tenellic acid C and neospinosic acid, both isolated from *N. spinosa* KUFA 1047, are potentially developed as antibiofilm agents due to their ability to suppress biofilm production of *E. coli* ATCC 25922 and *S. aureus* ATCC 29213. Neospinosic acid particularly showed the most potent inhibition, up to 44% for *S. aureus* ATCC 29213 biofilm formation (Table 2), and the viability of biofilm decreased by 98% after 8 hours of incubation, even though after 24 hours, the decrease in viability was only 10%. This phenomenon may occur because bacteria adapt genetically and phenotypically [65]. The prenylated phenylbutyrolactones, identified as Aspulvinones B', Aspulvinones H, Aspulvinones R, Aspulvinones S, and Aspulvinones T isolated from *A. flavipes* KUFA1152 showed antibiofilm activity to *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213 bacteria (Table 2). The presence of prenyl substituents in ring A of compounds Aspulvinones R and Aspulvinones S may be responsible for antibacterial activity and inhibition of biofilm formation. Nevertheless, none of the compounds exhibited synergistic effects with antibiotics against multidrug-resistant bacteria.

Another strain was isolated from *Mycale sp*, *A. stellatus* KUFA 2017, contains 5[(3E,5E)-nona-3,5-dien-1-yl] benzene can inhibit biofilm formation almost 99% on *E. faecalis* ATCC 29212 and *S. aureus* ATCC 2921 [48,49] (Table 2). These compounds may develop as new drugs for antibacterial
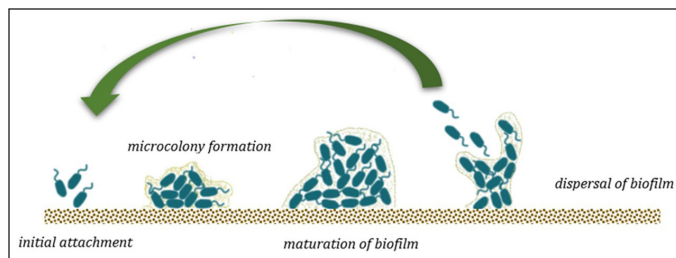
Figure 5. Biofilm life cycle.

and biofilm inhibitors. Several compounds isolated from fungi associated with marine sponges may not show antibiofilm activities, such as erubescenoic acid (Table 2), which was isolated from *P. erubescens* KUFA0220 [58,59]. However, it does not mean they have no biological effects, thus making it crucial to conduct further investigation in other bioassays to examine what these compounds can potentially accomplish. Biofilms are formed not only of monospecies but also of polymicrobial (including Gram-positive and Gram-negative bacteria) or biofilm complexes of bacteria and fungi. Each Gram-positive or Gram-negative bacteria has its mechanism for biofilm formation [112], but generally, the stages of biofilm formation are illustrated in Figure 5. *Staphylococcus aureus* is a Gram-positive bacteria contributing to most biofilm-associated infections, including biofilm on medical devices. *Escherichia coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 are Gram-negative bacteria that produce strong biofilms [113–115].

Biofilm formation is a complicated process, and improving our understanding of biofilms molecular composition and function will greatly assist in identifying and developing effective strategies for preventing and treating infections caused by these complex multicellular communities. Several feasible strategies are applicable for biofilm prevention and therapy, including biofilm formation inhibition and eradicating existing biofilms. Inhibition of biofilm formation by preventing bacteria from attaching to a surface and inhibiting the formation of EPS [101] inhibits cell-to-cell communication by anti-QS [116], modify surfaces to make it harder for bacteria to attach and grow on surfaces, especially on medical devices [117,118]. Physical and chemical methods also can eradicate biofilm [119–121].

This review highlighted that some compounds isolated from sponge-associated fungi showed antibacterial and antibiofilm activity, but some were only active as antibacterial or antibiofilm. This phenomenon may occur because the mechanism of action of antibiofilm may differ from that of antibacterials, especially if polymicrobials cause biofilms. Some studies did not report the compound mechanism as antibacterial or antibiofilm. Future research is expected to observe the compound mechanism thoroughly and may lead to the development of antibiofilm agents for specific targets.

CONCLUSION

Currently, the efficacy of conventional antibiotics is especially limited to biofilm-related infections. The marine environment offers a rich opportunity to discover novel, highly effective antibacterial, and antibiofilm chemicals. This review summarized the isolated compounds from marine derive-

fungi with promising potential to develop as antibacterial or antibiofilm, including anthraquinones, sterigmatocystin analog, hydroxy pyrrolidine alkaloids, helvolic acid derivatives, lactones, prenylated phenylbutyrolactones, citrinin and derivatives, bisthiodiketopiperazine, cyclotetrapeptides, dihydrochromone dimer, amino lipopeptide, furan derivatives, aspiron-derivatives, halogenated metabolites, and alkaloids. Thorough research is required to determine the reliable mechanism of bioactive compounds, considering that the interaction between bacteria in biofilms is challenging to treat. Hence, exploring new antibacterial and antibiofilm agents derived from marine natural products has considerable value to drug development as a way to solve problems related to sponge availability.

AUTHOR CONTRIBUTION

All authors contributed to the conception and design, acquisition of data, analysis, and interpretation of data, drafting the article, or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the published version; and agreed to be accountable for all aspects of the work. According to the guidelines defined by the International Committee of Medical Journal Editors (ICMJEs), all authors are eligible to be authors.

CONFLICTS OF INTEREST

The authors declared that there are no conflicts of interest.

ETHICAL APPROVALS

This study does not involve animal or human subjects for experimental purposes.

DATA AVAILABILITY

All data generated and analyzed are included in this research article.

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