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Sponges-associated marine bacteria as sources of antimicrobial compounds

Amal Nasser Alahmari[1*]; Shahira A. Hassoubah[1]; Bothaina Ali Alaidaroos[1]

[1]Department of Biological Sciences, Faculty of Sciences, P.O. Box 80203, King Abdulaziz University, Jeddah, Saudi Arabia

[*]Corresponding author E-mail: amsfferalahmari@stu.kau.edu.sa

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Abstract

Drug-resistant bacteria are considered to be a substantial risk to the public health. In recent years, a significant number of researches have focused on the marine environment as a promising, and underexplored source of compounds with remarkable bioactivities that might contribute to the battle against superbugs. The Red Sea environment is one of the richest and most interesting sources of natural products, which are widely used either in medicinal and/or nutritional fields. Furthermore, several studies have reported that marine sponges and their associated microorganisms; mostly bacteria, are abundant producers of bioactive compounds such as secondary metabolites. This mini-review aimed to discuss tens of secondary metabolites of various chemical classes that were generated by a variety of bacterial phyla associated with marine sponges, including *Actinobacteria*, *Proteobacteria*, *Firmicutes*, *Bacteroidetes*, and Cyanobacteria. Numerous secondary metabolites with antibacterial or antifungal efficacy have been recovered from marine bacteria derived from sponges; they have been used as potential sources of antimicrobial compounds and might be promising sources that can be exploited in the future for several pharmaceutical purposes.

Keywords: Marine sponges, Bacteria, Antimicrobial compounds, Secondary metabolites, *Actinobacteria*, Pharmaceutical purposes

1. Introduction

Antimicrobial agents are a large class of chemicals that kill or prevent the growth of microorganisms (Asif, 2017). When these antimicrobial agents are being more specific, the antibiotics, antibacterials, antifungals, antivirals, and antiprotozoals become capable of targeting specific microorganisms (Thumar and Singh, 2022). In light of the antimicrobial modes of action, these compounds

can affect the pathogenic microbes (Fig. 1), such as bacteria and fungi in a variety of ways, including interfering with the functions and structure of the cell wall (Chitemerere and Mukanganyama, 2014), inhibiting DNA/RNA synthesis and functions of the nucleic acids (Singh *et al*., 2021), destabilizing the intermediate metabolic steps (Anandhi *et al*., 2014), suppressing protein synthesis in the microbial cells (Kirmusaoglu, 2019), disturbing the normal microbial interactions (Radulovic *et al*., 2013), and coagulating the cytoplasmic components (Mogosanu *et al*., 2015). Moreover, Adedeji, (2016) added that antibiotics that are considered as one of the effective antimicrobial agents, represent one of the most significant scientific discoveries in the recent history, and act as fundamental therapies in modern medicine. According to Serwecińska, (2020), antibiotics are potent antimibacterial agents that are effective against the pathogenic bacteria, as they can kill or suppress the bacterial growth, as shown in Fig. (1).

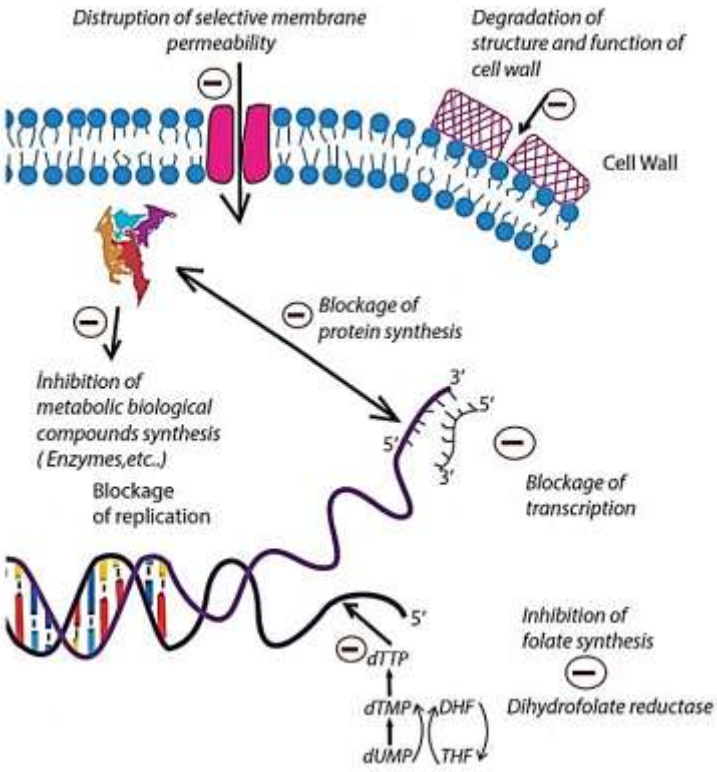

Fig. 1. Mechanisms of action of the antimicrobials against the bacteria, adopted by Kirmusaoglu, (2019)

Misuse of the antibiotics in several fields, including medicine, agriculture and food manufacturing, has resulted in the emergence of antibiotic-resistant bacteria, which pose a serious threat to the public health and cause increased mortality (Al-Amoudi *et al*., 2016). The nature of microorganisms provides them with the molecular tools necessary to develop antibiotic resistance (Brown and Wright, 2016). A previous study conducted by Trianto *et al*., (2019) reported that multidrug-resistant (MDR) microorganisms have emerged as a result of decreased development of new antibiotics for several years, which have been used for treatment of the infectious diseases. According to Sibero *et al*., (2018), methicillin-resistant *Staphylococcus aureus* (MRSA) and several strains of *Escherichia coli*; for instance, represent significant problems that might spark new epidemics. In fact, scientists predicted that if no immediate actions have been taken to develop new antibiotics and/or antimicrobial agents, the annual death tolls due to resistant infections will reach 10 million by 2050 (Stokes *et al*., 2020).

A previous study of Fair and Tor, (2014) highlighted that scientists are diligently searching for new potential sources of bioactive chemicals that might aid in the fight against the MDR strains. Recently, the marine environment has attracted the attention of scientists as a promising source for the discovery of biologically active natural products, due to its diverse environmental conditions and rich biodiversity, in addition to the massive amounts of natural compounds produced by all the living marine organisms and their associated microbial communities (Brinkmann *et al*., 2017). Several previous studies have discovered more than 15,000 natural compounds that have been extracted from the marine organisms, including bioactive compounds with antibacterial potential, which have been obtained from the marine invertebrates (Bibi *et al*., 2020). The marine sponges are one of the most important aquatic invertebrates and one of the richest sources of natural compounds, and are considered as a 'gold mine' for bioactive compounds with several activities, including antibacterial, antifungal, antioxidants, and others (Wu *et al*., 2019). About 5300 compounds have been recovered from 500 species of sponges (Kamaruding *et al*., 2020).

The objectives of the current study were to study the natural bioactive compounds derived from aquatic microorganisms, natural bioactive compounds recovered from marine bacteria, anti-biofilm compounds of microbial origins, and anti-biofilm compounds obtained from marine bacteria.

2. Nature as a source of antimicrobial compounds

Antibiotic-resistant bacteria are becoming increasingly common, posing a serious threat to the public health (Ventola, 2015). This is attributed to abuse of antimicrobial medication, microbial mutation, and antibiotic overuse in livestock and fish production, in addition to poor hygienic procedures (Ali *et al*., 2018). Antibiotic resistance highlights the need for studying and researching for novel antimicrobial compounds to be obtained from the different natural and artificial sources (Luo *et al*., 2019).

The previous study of Dias *et al*., (2012) documented that secondary metabolites are examples of naturally occurring compounds that have shown promise as potential therapeutic agents. Secondary metabolites are substances generated by metabolism of the living organisms, although they are not essential for their survival, growth, and/or reproduction. These compounds have shown potency in the microorganism's defense (Sanchez and Demain, 2011). Furthermore, plants, fungi, and bacteria; where their numbers are in billions, are the primary sources that produce an abundance of chemical compounds with diverse chemical structures, activities, and pharmacological efficacies. However, the vast majority of these compounds are yet unknown to humans (Anand *et al*., 2019).

2.1. Marine environment as a harbor of antimicrobial sources

Recently, El-Hossary *et al*., (2020) revealed that compared to the terrestrial environment, marine habitats have not been extensively studied as sources of antibiotics against those pathogenic microorganisms. The marine environment is the largest habitat on earth, representing more than 70 % of the planet's surface (Stincone and Brandelli, 2020). The oceans possess various and extreme environmental conditions, including temperature, light, salt, pH, and pressure, where diverse organisms survive. The oceanic habitats vary from shallow sun illuminated water bodies to oceanic trenches with pressures of up to 100 MPa at a depth of 11 km. Additionally, the oceanic temperatures can be higher than 350 °C in pressurized fluids of the hydrothermal vents, and may be as low as -35 °C in the different channels of the sea ice (Bertrand and Munoz-Garay, 2019).

Few examples of the many species that make up the marine life include protozoans, anemones, jellyfish, roundworms, flatworms, bryozoans, squid, clams, copepods, annelids, sea cucumbers, sea stars, sponges, corals, and algae, in addition to free-living microorganisms, such as fungi and bacteria (Hughes and Fenical, 2010). The level of success in exploring and finding un-described natural compounds that are chemically active in the marine organisms is 500 times greater than that of the terrestrial species; therefore, the biological marine resources used for biotechnological applications represent promising fields (Dionisi *et al*., 2012).

The first trail to discover antimicrobial potential in the aquatic organisms was initiated around the 1950's (Tortorella *et al*., 2018). A previous study of Hughes and Fenical, (2010) reported that in the open oceans seawater there are more than million different kinds of microorganisms living in these marine habitats, involving about 106 bacterial cells and 103 fungal cells per milliliter. Marine microorganisms, including bacteria, archaea, and eukaryotes have evolved over millions of years to have unique metabolic and physiological capabilities, which allow them to thrive in the aquatic ecosystems and adapt to the most severe zones (Bertrand and Munoz-Garay, 2019). More than forty thousand marine natural products (MNPs); largely secondary metabolites, have been identified and characterized so far from a wide variety of marine microbial species. The chemical classes of these MNPs include polyketides, terpenoids, peptides, alkaloids steroids, phenols, lipids, and lactones. In addition, high concentrations of these MNPs have demonstrated beneficial pharmaceutical activities, including antimicrobial, cytotoxic, hypolipidemic, antimalarial, anti-inflammatory, analgesic, and anti-asthmatic (Liu *et al*., 2019).

A previous study conducted by Schillaci *et al*., (2013) aimed to investigate the antimicrobial and antibiofilm potential of the echinoderm *Holothuria tubulosa* as an uncommon source of these bioactive agents. This study tested the antibacterial efficacy of the peptides fraction of the cytosol obtained from *H. tubulosa* coelomocytes against some Gram-negative and Gram-positive human pathogens. Three different strains of *Staphylococcus aureus*, besides *Enterococcus faecalis*, *Psuedomonas aeruginosa*, and a strain of *Staphylococcus epidermidis* as a biofilm producer were tested. Results have demonstrated that the antimicrobial peptides derived from coelomocytes of *H. tubulosa* are attractive novel candidates that can be used to develop useful antimicrobial agents against the surface adherent staphylococci and *P. aeruginosa*.

A recent research of El-Demerdash *et al*., (2019) has shown that bacteria associated with sponges of the genus *Suberea* produce bromotyrosine derivatives as one of the effective bioactive secondary metabolites, whereas the sponge *Agelas mauritiana* produces many diterpene alkaloids (Hong *et al*., 2017), and the sponge *Aaptos aaptos* has produced alkaloids secondary metabolites named as aaptamine, 9-demethylaaptamine , 4-N-methylaaptamine, and 9-methoxyaaptamine, where all have shown antibacterial potency against *Vibrio* sp. and *V. harveyi* (Khameneh *et al*., 2019).

2.1.1. Marine bacteria as sources of antimicrobial secondary metabolites

Marine bacteria face lots of antagonistic oceanic conditions, and what may help these bacteria to survive are the huge numbers of secondary metabolites they produce, which aid them in self-defence (Barzkar *et al*., 2019). A promising secondary metabolite identified as Bogorol A (Table 1, Fig. 2) has been isolated from *Bacillus* sp.; a free-living marine bacteria. This antibiotic has shown strong antibacterial efficacy detected using minimum inhibitory concentration (MIC) against the methicillin-resistant *Staphylococcus aureus* recording MIC= 2.5 µg/ ml, and the vancomycin-resistant *Enterococcus* spp. (MIC= 9 µg/ ml) (Yamashita *et al*., 2015).

Moreover, the actinomycete *Nocardiopsis dassonville* isolated from shallow water of the island of Kauai, Hawaii, has produced the novel indole nucleosides designated as kahakamides A (Gao *et al*., 2012). The metabolite kahakamides A (Table 1) has been effective against *B. subtilis* (Schumacher *et al*., 2001). Furthermore, *Nocardia dassonville* is another actinomycete recovered from the Arctic Ocean through sediment samples. *N. dassonville* has shown significant antifungal potential against *Candida albicans*, recording MIC of 64 µg/ ml; in addition, the same effect has been caused by N-(2-hydroxyphenyl)-2-phenazinamine, which is a new secondary metabolite produced by *N. dassonville* (Table 1, Fig. 2).

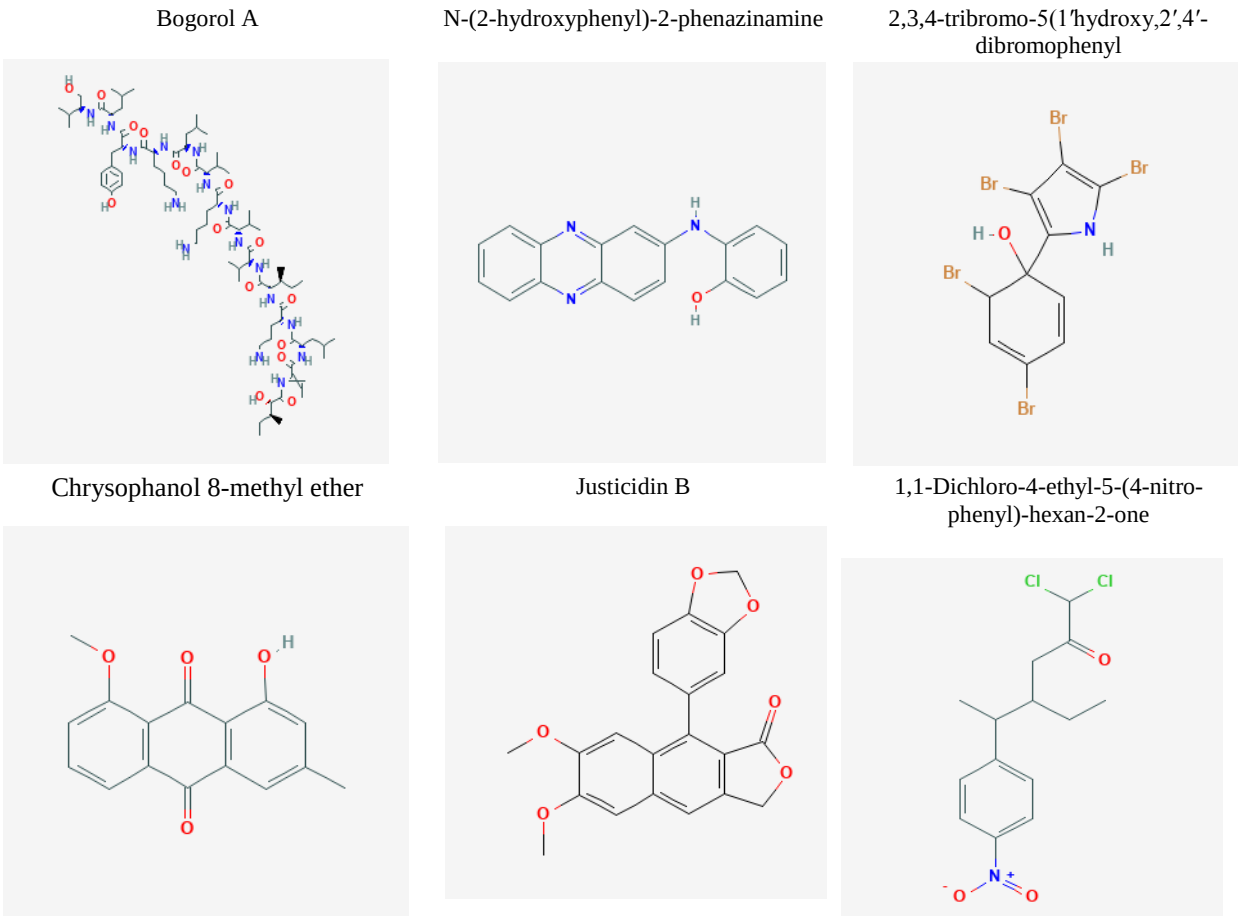

Fig. 2. Chemical structures of the bioactive compounds recovered from several marine bacteria, adopted by Burkholder *et al*., (1966); El-Gendy *et al*., (2008); Gao *et al*., (2012);Yamashita *et al*., (2015)

Table1: Biologically active secondary metabolites recovered from marine bacteria, and their antibacterial potency against several tested bacterial spp.

Marine Bacteria	Secondary Metabolites	Inhibiting	Properties	References
***Bacillus* sp.**	Bogorol A	Methicillin-resistant *Staphylococcus aureus*, and vancomycin-resistant *Enterococcus spp.*	Antibiotic	(Yamashita *et al*., 2015)
Bacillus silvestris	Bacillistatins 1 Bacillistatins 2	*Streptococcus pneumoniae* *Streptococcus pneumoniae*	Antibacterial Antibacterial	(Pettit *et al*., 2009)
Nocardiopsis dassonville	Kahakamides A	*Bacillus subtilis*	Antibacterial	(Schumacher *et al*., 2001)
Nocardia dassonville	N-(2-hydroxyphenyl)-2-phenazinamine	*Candida albicans*	Antifungal	(Gao *et al*., 2012)
Pseudomonas bromoutilis	2,3,4-tribromo-5(1′hydroxy,2′,4′-dibromophenyl) pyrrole	*S. aureus, D. pneumoniae, S. pyogenes,* and *M. tuberculosis*	Antibiotic	(Burkholder *et al*., 1966)
***Nocardia* sp. ALAA 2000**	Chrysophanol 8-methyl ether	Gram-positive, Gram-negative bacteria and Fungi.	Antimicrobial	(El-Gendy *et al*., 2008)
	Asphodelin; 4,7'-bichrysophanol	Gram-positive, Gram-negative bacteria and Fungi.	Antimicrobial	
	Justicidin B		Antimicrobial	
	Ayamycin; 1,1-dichloro-4- ethyl-5-(4-nitro-phenyl)-hexan-2-one	Gram-positive, Gram-negative bacteria and Fungi.	Antimicrobial	
		Gram-positive, Gram-negative bacteria and Fungi.		

The isolated marine bacterium identified as *P. bromoutilis* that is obtained from tropical water in the vicinity of Puerto Rico, has the potency to produce an antibiotic known as pyrrole, which suppresses the bacterial growth of several Gram-positive bacteria (Burkholder *et al*., 1966). The pyrrole antibiotic known as 2,3,4-tribromo-5(1′hydroxy,2′,4′-dibromophenyl) pyrrole (Table 1, Fig. 2), has been effective against *Diplococcus pneumonia*, *Staphylococcus aureus*, and *Streptococcus pyogenes*; recording MIC of 0.0063 µg/ ml, and has been effective also against *Mycobacterium tuberculosis* (MIC= 0.2 µg/ ml).

The symbiont bacteria have produced attractive bioactive antimicrobial compounds. The marine actinomycete *Nocardia* sp. ALAA 2000 symbiont with the red alga *Laurencia spectabilis*, have produced novel secondary metabolites with promising biological activities. These active compounds have been identified as chrysophanol 8-methyl ether (Table 1, Fig. 2), asphodelin; 4,7'- bichrysophanol, and justicidin B. This is in addition to the newly isolated compound, which has been classified as an ayamycin compound known as 1,1-dichloro-4- ethyl-5-(4-nitro-phenyl)-hexan-2-one (Table 1, Fig. 2). All these four compounds have shown antimicrobial activity against the tested Gram-positive and Gram-negative bacteria, and also against eight tested fungi (El-Gendy *et al*., 2008). Moreover, the marine bacterium *B. silvestris* that has been isolated from the Pacific Ocean (Southern Chile) crab produced two novel cyclodepsipeptides with antibacterial potentials. Both of these biologically active compounds named bacillistatins 1 and 2, have demonstrated antibacterial activity against the antibiotic-resistant *Streptococcus pneumonia*e; recording MICs values > 64 µg/ ml (Pettit *et al*., 2009). Table (1) demonstrates several secondary metabolites recovered from some marine bacteria, and their antibacterial activity against several other bacterial spp.

2.1.2. Phylum Porifera as a gold mine of antimicrobial compounds

A previous study conducted by Logashina *et al.* (2017) has investigated the antibacterial potential of 7 different species of sponges, including *Neopetrosia exigua*, *Xestospongia testudinaria*, *Aaptos suberiptoides*, *Cinachyrella australiensis*, *Clathria basilana*, *Clathria reinwardti*, *Stylissa carteri*, and *Pachastrella* sp., which belong to the phylum Porifera. Methanol extracts prepared from each of these species have been tested against 6 bacterial spp., mainly MDR *P. aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA). *X. testudinaria* extract has demonstrated stronger antibacterial potency against all the tested bacterial pathogens, recording inhibition zone (IZ) diameters against *Staphylococcus aureus* (20.10 ± 0.26 mm), *E. coli* (9.5 ± 0.12 mm), *Klebsiella pneumonia* (15.25 ± 0.34 mm), *Salmonella typhi* (15.25 ± 0.26 mm), *P. aeruginosa* (15.25 ± 0.45), and MRSA (17.50 ± 0.23 mm)..

Moreover, another recent study of Kamaruding *et al*., (2020) has screened the antibacterial potential of several sponges, including *Xestospongia muta*, *Xestospongia exigua*, and *Iotrochota baculifera* against *M. luteus*, *Staphylococcus aureus*, *E. coli*, and *S. typhimurium*. All the sponges have been extracted using two organic solvents, i.e., diethyl ether and butanol. The diethyl ether fraction of *X. exigua* has inhibited the growth of *M. luteus* by 18 %, *Staphylococcus aureus* by 7 %, and *E. coli* by 13 %.

During 2021, a recent study has been carried out by Piron *et al*., (2021) on 3 marine sponges; mainly *Agelas clathrodes*, *Verongula rigida*, and *Desmapsamma anchorata*, for the detection of their antibacterial activity against *E. coli*, *B. cereus*, *Staphylococcus aureus*, *P. aeruginosa*, and *Staphylococcus saprophyticus*. Only the ethanoic extract of *A. clathrodes* has demonstrated inhibitory effect against *Staphylococcus aureus* recording IZ diameter of 10.66 mm, *Staphylococcus saprophyticus*

with IZ of 9.5 mm, while the rest of the bacterial strains have shown resistance to ethanolic extracts of all the tested sponges. Water extracts of the 3 sponges have not demonstrated inhibitory effects against the tested bacterial strains.

3. The Red sea as a source of antimicrobial compounds

The Red Sea shows a unique habitat of huge biodiversity of the aquatic microorganisms, and is one of the special planet ecosystems, which makes it one of the richest promising sources of the medicinal and nutritional natural products (Hamed and Hussein, 2020). According to El-Hossary *et al*., (2020), starting from 2015 till the end of 2019, a total of 677 marine natural products have been isolated from the Red Sea marine microorganisms only.

In Egypt, 6 types of hard corals have been collected from the Red Sea, and have been analyzed for their antibacterial and antifungal properties (Hamed and Hussein, 2020). The bioactive substances have been extracted from these corals using both water and organic solvents, and then tested against 5 pathogenic bacterial and 3 fungal sp. However, all the tested extracts have not shown inhibitory effects.

Moreover, El-Samak *et al*., (2018) have studied the bacteria associated with the invertebrates that provide metabolites that can be used as products of Biosynthetic Gene Clusters (BGC), which are defined by Chen *et al*., (2020) as organized cluster groups of genes encoding for a biosynthetic pathway that is responsible for producing secondary metabolites. A total of 50 bacterial spp. isolated from 8 different invertebrate samples have shown antibacterial activity against 4 bacterial strains and a single fungal pathogen. Results have shown that 60 % of the isolated bacteria have BGC [i.e., either polyketides (PKS), or non-ribosomal peptides (NRPS), or both], which produce bioactive metabolites with antimicrobial activity and/or any other biological activity. In the light of detection of 4 novel bioactive natural products from the marine fungus identified as *Penicillium minioluteum*, which have been classified chemically as purpurides E, F and G, in addition to peniisocoumarin H. The two compounds purpurides E and F have effectively acted as antimicrobial agents, inhibiting growth of the microbial pathogens; recording MIC's values of 6 µg/ ml against MRSA, 10 µg/ ml against *E. coli*, and 12 µg/ ml against *C. albicans* for the compound purpurides E. On the other hand, compound purpurides F has recorded MIC's of 3 µg/ ml against MRSA, 6 µg/ ml against *E. coli*, and 6 µg/ ml against *C. albicans* (Ma *et al*., 2020).

Chlorocatechelins are unique siderophores, which is attributed to their acylguanidine structures and chlorinated catecholate complexes (Kishimoto *et al*., 2014). Figure (3) demonstrate Chlorocatechelin A (compound 1), which has been isolated from *Streptomyces* strain MUSC 135T, and has demonstrated efficacy against a wide variety of pathogenic bacteria and fungi. This novel *Streptomyces* strain has been found in the silt of a mangrove forest on the eastern coast of Peninsular Malaysia. Bacitracin A (Compound 2), is a broad-spectrum antibiotic that is produced by this *Streptomyces* strain MUSC 135T that has shown activity against *Staphylococcus aureus* ATCC BAA-44; recording IZ diameter of 10.5 mm (Lee *et al*., 2014; Ser *et al*., 2015). *Streptomyces* CTF9's fermentation broth has been mined for novel bioactive compounds, such indole-3-lactic acid (Compound 3) and phenylacetic acid (Compound 4). These *Streptomyces* extracted bioactive components have shown strong antifungal efficacy in their preliminary testing's against the yeast *C. albicans*; recording IZ diameter of 19.6 ± 0.333 mm, and against *Mucor miehei* (IZ= 13 ± 0.00 mm) (Sajid *et al*., 2011).

4. Novel metabolites with antimicrobial activity recovered from the Red Sea

The Red Sea is one of the most important habitats on the planet that represents a great source of natural bioactive compounds (El-Hossary *et al*., 2020). However, Helber *et al*., (2018) have noticed the ability of diverse marine organisms to defend themselves

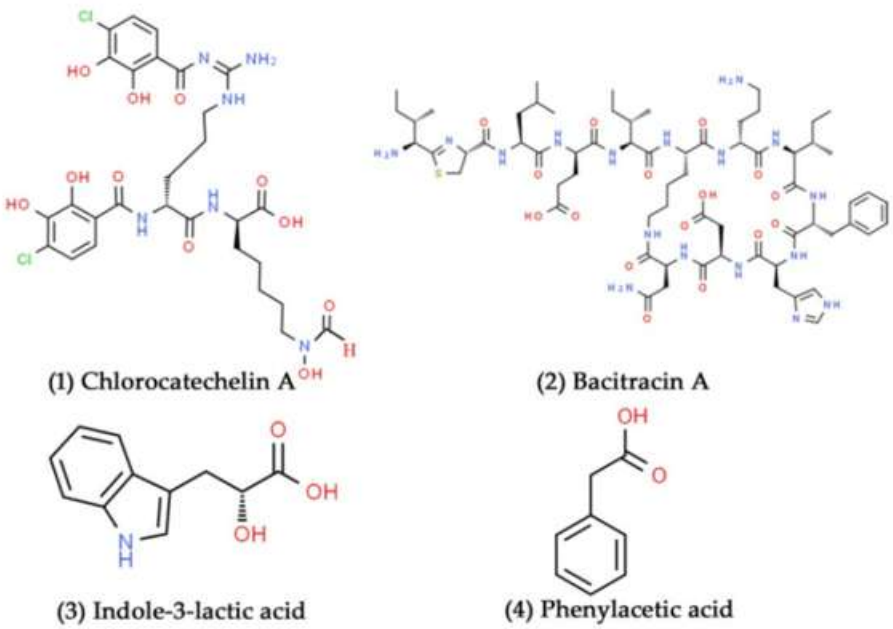

Fig. 3. Chemical structural representation of Chlorocatechelins antimicrobial compounds (1-4) derived from marine Actinobacteria, adopted by Srinivasan *et al*., (2021)

against the predators and cause the inhibition of microbial pathogens, due to their secondary metabolites that are produced as bioactive compounds. In the Red Sea, bioactive compounds obtained from crude extracts prepared *in vitro* from the marine microorganisms have demonstrated several activities, including antibacterial, antifungal, antiviral, anticancer, antimalarial, immunosuppressive, and anti-inflammatory, beside the neuro-suppressive ones, and even more (Amina and Al Musayeib, 2018). These biologically active secondary metabolites have been classified into several chemical classes, such as alkaloids, terpenoids, steroids, sterols, and other classes (Abou El-Ezz *et al*., 2017).

In 2015, about 3 metabolites out of 5 novel bioactive compounds have been recovered from the Egyptian Red Sea sponge *Phyllospongia lamellose* that belong to terpenes, and have shown antimicrobial activity. These compounds include Phyllospongin D, phyllospongin E, and 12α-acetoxy-13β,18β-cyclobutan-20,24-dimethyl-24oxoscalar-16-en-25β-ol, which have shown significant antibacterial potential against *Staphylococcus aureus*, *V. parahaemolyticus*, and *B. subtilis*; recording MIC values= ~ 1.7-3.3 µg/ml (Hassan *et al*., 2015). Moreover, Ashour *et al*., (2007) isolated a deoxyhyrtiosine A compound for the first time from the marine sponge *Hertios erectus*, which has recorded moderate antimicrobial efficacy against *B. subtilis* and *Saccharomyces cerevisiae*.

About 4 novel compounds have been obtained from *Suberea mollis* sponge, mainly Subereamollines A, subereamollines B, subereaphenols B, and C, which have been regarded as new compounds. These compounds have exhibited uneven antibacterial potential against *Staphylococcus aureus*; recording IZ diameter of 3-5 mm, *P. aeruginosa* (IZ diameter= 3-7 mm), and *K. pneumoniae* (IZ diameter= 7-9 mm), in addition to the Aeroplysinin-1 compound that has displayed significant antibacterial potency against the tested bacteria (Abou-Shoer *et al*., 2008). Further bio-

prospecting to isolate more biologically active marine secondary metabolites has led to the recovery of 2 sterols for the first time from *Heteroxenia fuscescens*; mainly, gorgosten-5(E)-3β-ol and sarcoaldosterol A. These 2 metabolites have expressed potential antibacterial efficacy against *B. subtilis*; recording IZ diameters of 13.7± 0.03 mm, 12.2± 0.02 mm; *Staphylococcus aureus* (IZ diameters of 12.3± 0.03 mm, 13.5± 0.01 mm), and *E. coli* (14.5± 0.03 mm, 14.2± 0.01 mm), respectively (Mohammed *et al*., 2011). However, in 2006, a novel compound designated as latrunculin T has been obtained from the marine sponge *Negombata magnifica* found in the Red sea. Latrunculin compounds have exhibited strong antimicrobial activity against *Staphylococcus aureus*, *B. cereus*, *C. albicans*, and *S. cerevisiae*, recording MIC values in the range of 2.5-19 μM (El Sayed *et al*., 2006).

5. Description of the marine sponges

Sponges, which belong to the phylum Porifera, have been recorded among the earliest multicellular animals, and are considered as the progenitor of virtually all forms of life on Earth (Borisenko *et al*., 2019). Sponges have no tissues, which mean that they have no organs, muscles, and/or a nervous system. Despite of the fact that these organisms' have simple anatomy; however recent studies have revealed unexpected genomic complexity in these sponges (Pita *et al*., 2016). Sponges are benthic organisms that include more than 8000 species in marine water, and around 150 species in the freshwater, which have ecological functions in the aquatic environment (Folkers and Rombouts, 2020). Clearly, these aquatic organisms perform key functional roles in their ecosystems, where their filter feeds act actively and efficiently in pumping and cleaning large amounts of water in almost all oceans and continental water from the surface to higher depths. Moreover, sponges have been grouped into 4 taxonomic classes, including *Hexactinellida*, *Demospongiae*, *Calcarea*, and the recently added *Homoscleromorpha* (Manconi and Pronzato, 2016). The class *Calcarea* of sponges has shown a limited growth only in the shallow environments, where it is least demanding to produce calcium carbonate. While *Demospongiae* accounts for 90 % of all the sponge spp., and obviously lives in broad habitats from the epipelagic till the bathypelagic zone. *Demospongiae* thrives in both of freshwater and marine environments; under various shapes and sizes. Finally, *Hexactinellida* that are known also as glass sponges, represent the least adaptable species (Folkers and Rombouts, 2020).

Sponges provide living shelters for diverse organisms and exhibit a symbiotic relationship with the autotrophic microorganisms, which are needed for primary production of nutrients (Taylor *et al*., 2007). Scientists working in the field of natural products chemistry and research have suggested that these sponges and the associated microorganisms represent promising potentials, which will provide future drugs that can serve in the treatment of various diseases.

6. Marine sponges and the symbiotic microbes

Sponges are sessile that date back to about 600 million years, and successful survival of these organisms' in the various and extreme environments refers to several types defences including evolution, in addition to roles of the associated microorganisms (Brinkmann *et al*., 2017). Sponge-associated microorganisms may be symbiotic that come across food sources, and/or may be pathogenic. Sponges can recognize the food bacteria and bacterial symbionts; and act as filter feeders; where they adsorb a variety of microorganisms that probably hold within the sponge either extracellularly or intracellularly (Thiel *et al*., 2007). For example, the sponge *Aplysina aerophoba* has been used in a previous study conducted by Taylor *et al*., (2007) to test its uptake rates of the bacterial isolates, and experimental evidences have demonstrated that this sponge could distinguish between the food bacteria that have been phagocytized and the bacterial symbionts. Moreover, sponge-associated microorganisms contribute to 35-60 % of the sponge biomass, which include cyanobacteria, heterotrophic bacteria, and fungi, in addition to

unicellular algae (Thomas *et al*., 2010). Several sponge species contain diverse microbial consortia within their mesophyll matrix, which can reach densities of up to 109 microbial cells/cm3 of a sponge (Pita *et al*., 2016).

The symbiotic relationships between the sponges' hosts and their microbiota provide the essentials required for the sponges' life, such as sponge nutrition, health, chemical defenses, and removal of contaminants and/or metabolic waste products. Furthermore, in other cases, the symbionts fix nitrogen that helps the sponges to survive in nutrient-limited reef environments, while the symbionts have gained nutrients (i.e., oxygen and inorganic compounds); in addition to protection provided by the sponge host (Keren *et al*., 2017). Moreover, there are anaerobic conditions provided by the sponge's host to the anaerobic/ microaerophilic microorganisms, which could be attributed to the localized active respiration and minimal water circulation (Brinkmann *et al*., 2017).

Microorganisms living within the sponge hosts may be sponge specific, and this has been evidenced by the fact that distantly related sponges from different geographical locations harbor similar microbial groups, which have not been detected in the surrounding seawater and/or the other marine habitats (Taylor *et al*., 2007).

7. Diversity of the sponge associated microorganisms

According to the cultivation-dependent and independent techniques that have been used in several research laboratories, there are 28 listed bacterial phyla associated with the aquatic sponges (Hentschel *et al*., 2012). Really, this does prevent the existence of untapped bacteria, which have not been detected due to limitation of the cultivation techniques that are not helpful to discover all bacterial strains (Bibi *et al*., 2020). In their review, Brinkmann *et al*., (2017) reported that the phyla of *Proteobacteria* are the most dominant bacterial groups associated with sponges, which are followed by several other phyla, such as *Planctomycetes*, *Nitrospira*, *Gemmatimonadetes*, *Bacteroidetes*, *Actinobacteria*, Cyanobacteria, *Chloroflexi*, *Verrucomicrobia*, and *Acidobacteria*. Furthermore, Wichels *et al*., (2006) study discovered a bacterial phylum, which is considered as sponge-specific known as '*Poribacteria*'. These phylum members cannot be cultured under laboratory conditions; however, they can be detected by other molecular tools using specific primers, and not even by using the existing 16S rDNA primers. Knobloch *et al*., (2018) conducted a study on bacterial diversity of the marine sponge *Halichondria panicea* that has been sampled from 4 different geographical locations. Using molecular techniques, results have shown the dominance of a bacterial taxon; for which they have proposed a candidate status '*Candidatus Halichondribacter symbioticus*'. This bacterial taxon has been recorded as a low abundant opportunist in the other sponge species. A recent study has been conducted by Bibi and Azhar, (2021) on six sponges isolated from the Red sea to analyse their bacterial communities, where *Haliclona caerulea* and *Stylissa carteri* have shown significant records. The dominant bacterial phylum is *Proteobacteria* (88-95 %); however, a good microbial abundance of *Bacteroidetes* and *Planctomycetes* (5 %), Cyanobacteria (<1 %), *Firmicutes* (4 %), and *Nitrospirae* (2 %) have been also recorded. Moreover, according to the operational taxonomic units (OTU), there have been 17 identified diverse bacterial genera, where the genus *Pseudoalteromonas* has dominated all the studied sponge samples.

A recent study conducted by Sibero *et al*., (2019) has presented the first report of sponge-associated fungi that have been recovered from Indonesia's mangrove ecosystem, where the fungal diversity has been studied as one of the purposes of this study. A total of 8 fungi have been isolated from the sponge *Amorphinopsis* sp., where 3 fungi out of 8 have shown different antibacterial efficacy, and have been identified as *Eutypella* sp., *Lasiodiplodia theobromae*, and *Fusarium solani*. These 3 fungal strains have demonstrated inhibitory activity against either ESBL

extended spectrum β-lactamase *E. coli*, MRSA, *Salmonella enterica*, and *S. typhi*; recording IZ diameters that ranged from 4.13 ± 0.06 mm to 14.72 ± 0.07 mm.

8. Antimicrobial metabolites recovered from different sponges-associated marine bacterial genera

The scientists have exerted too much efforts on working in bio-prospecting, aiming to obtain natural compounds from all the available sources to help in development of therapeutic and biological applications (Ashforth *et al*., 2010). Furthermore, the bacteria-sponge association offers a great source of antimicrobial substances, such as antibacterial, antifungal, antiviral, and antiprotozoal compounds (Indraningrat *et al*., 2016).

8.1. *Actinobacteria* associated with sponges as sources of antimicrobials

Actinobacteria is a phylum typically composed of Gram-positive bacteria with high amounts of GC content that reaches up to 80 % of the bacterial DNA. Naturally, they exist in several habitats (Stincone and Brandelli, 2020). This phylum is considered as a superior source for production of biologically active compounds, and has demonstrated potency to produce novel secondary metabolites (Amarendra *et al*., 2013).

Actinobacteria that live symbiotically with sponges produce compounds that could act as antibiotics and/or significantly have therapeutics properties (Manivasagan and Kim, 2016). A recent study has been carried out by Alkhalifah, (2021) on the effect of N-acetylglucosamine on the production of biologically active compounds by the sponge-associated *Streptomyces*. The isolated *Streptomyces* sp. RM66 strain has shown antibacterial and antifungal effects against *Staphylococcus aureus* (MIC= 2.3 µg/ ml) and *C. albicans* (MIC= 3.2 µg/ ml). Results have indicated the appearance of several metabolites, including phencomycin, surfactins, and tubermycin B, in addition to more metabolites with promising antimicrobial features (Table 2). The bacterium *Streptomyces* sp. SBT348 isolated from a marine sponge has produced an active compound named (SKC3) (Table 2). This compound has shown good results in causing inhibition of *Staphylococcus epidermidis* (MIC= 31.25 µg/ ml), and also in suppressing biofilm formation by the same strain (Balasubramanian *et al*., 2018b).

In addition, the secondary metabolite ageloline-A that belongs to the chlorinated quinolone class has been isolated from the sponge-derived bacterium *Streptomyces* sp. SBT345. Ageloline A (Table 2) compound has shown a notable inhibition of the formation and growth of *Chlamydia trachomatis*. Moreover, this compound has no cytotoxicity beside its antioxidant potential, which supports its future potential use in the medicinal applications (Cheng *et al*., 2016).

Nocardiopsis dassonvillei MAD08 is an actinomycete isolated from the sponge *Dendrilla nigra* that has been collected from the Indian water. Among 11 different actinomycetes isolated from the sponges, *N. dassonvillei* MAD08 has shown 100 % antimicrobial activity against the tested multidrug-resistant pathogens. Moreover, according to GC-MS analysis, there are several antimicrobial compounds that have been recovered from the *Actinobacteria* and are illustrated in Table (2), including Oxalic acid, Acetic acid, butyl ester, Ethanol, 2-(octyloxy), 2-Isopropyl-5-methyl-1-heptanol, allyl nonyl ester, Butylated Hydroxytoluene, hexyl ester, Cyclohexanecarboxylic acid, Diethyl phthalate, Pentadecanal, 9-Octadecenamide, and 1-Tridecanol, 9-Octadecenal (Selvin *et al*., 2009).

As reported by Kim *et al*. (2006), the polyketide synthase (PKS) gene sequence of the *Salinispora* spp. recovered from the sponge *Pseudoceratina clavata* is most closely related to the known actinobacterial strains, which have generated the antibiotic rifamycin B. In other study conducted by Liu *et al*., (2019), about 49 marine sponge species have been collected from Beibu Gulf, the South China Sea.

Table 2: Bioactive metabolites produced by the marine sponge's associated bacteria

Sponge name	Bacterial symbiont	Bioactive compound	Properties	References
***Amphimedon* sp.**	Streptomyces sp. RM66	Surfactins Phencomycin Tubermycin B	Antimicrobials	(Alkhalifah, 2021)
Petrosia ficiformis	Streptomyces sp. SBT348	SKC3	Aantibacterial	(Balasubramanian *et al*., 2018a)
Agelas oroides	*Streptomyces sp*. SBT345	Ageloline A	Antibacterial	(Cheng *et al*., 2016)
Dendrilla nigra	*Nocardiopsis dassonvillei* MAD08	Acetic acid, butyl ester Ethanol, 2-(octyloxy)- Oxalic acid, allyl nonyl ester 2-Isopropyl-5-methyl-1-heptanol Butylated Hydroxytoluene Cyclohexanecarboxylic acid, hexyl ester Diethyl phthalate Pentadecanal- 1-Tridecanol 9-Octadecenal 9-Octadecenamide, (Z)-	Antimicrobials	(Selvin *et al*., 2009)
***Theonella* sp.**	*Nocardiopsis sp.* HB-J378	Nocardiopsistins A Nocardiopsistins B Nocardiopsistins C	Aantibacterial	(Xu *et al*., 2018)
Unidentified sponge	*Actinokineospora spheciospongiae*	Actinokineosin	Aantibacterial	(Takasaka *et al*., 2017)
Haliclona simulans	*Micromonospora* sp.	Quinocycline	Antibacterial	(Flemer, 2013)
Homophymia sp.	*Pseudomonas sp. 1537-E7*	2-nonyl-4-hydroxyquinoline n-oxide	Antibacterial	(Bultel-Poncé *et al*., 1999)
***Hymeniacidon perleve*.**	*Pseudomonas* sp. NJ6-3-1	3,6-diisopropylpiperazin-2, 5-dione	Antimicrobial	(Zheng *et al*., 2005)
Unidentified sponge	*Pseudomonas* sp. F92S91	Pyrone-I	Antibacterial	(Singh *et al*., 2003)
Suberites domuncula	*Pseudomonas* sp.	Unidentified	Antimicrobial	(Thakur *et al*., 2005)
Phorbas tenacior	*Pseudovibrio* P1Ma4 *Vibrio*- P1MaNal1	Unidentified	Antibacterial	(Mitova *et al*., 2004)
***Dysidea* sp.**	*Vibrio* sp.	Brominated diphenyl ethers	Antibacterial	(Elyakov *et al*., 1991)
Halichondria okadai	*Alteromonas* sp.	Alteramide A	Antibacterial	(Shigemori *et al*., 1992)

***Haliclona* sp.**	Eight proteobacteria isolates	Unidentified	Antibacterial	(Radjasa *et al*., 2007)
Stylotella sp.	*Serratia marcescens NBRC 102204*		Antibacterial	(Yoghiapiscessa *et al*., 2016)
	Catenococcus thiocycli TG 5-3	Unidentified		
	Vibrio natriegens ATCC 14048			
Theonella swinhoei	*Pseudoalteromonas flavipulchra- NCIMB 2033* *Candidatus*- Entotheonella palauensis	Theopalauamide	Antifungal	(Bewley and Faulkner, 1998; Schmidt *et al*., 2000)
Unidentified sponge	*Bacillus sp.* M1_CRV_171	Cyclo(L-Pro-L-Tyr) Macrolactin A Macrolactin H 15,17-epoxy-16-hydroxy macrolactin A	Antimicrobial	(Dat *et al*., 2021)
Halichondria japonica	*Bacillus cereus*- QN03323	YM-266183 YM-266184	Antibacterial	(Ken-Ichi *et al*., 2003; Suzumura *et al*., 2003)
Aplysina aerophoba	*Bacillus* sp.	Surfactin Iturin Fengycins	Antimicrobial	(Pabel *et al*., 2003)
Dysidea avara	*Bacillus atrophaeus*	Bacillamide C Neobacillamide A	Antimicrobial	(Liu *et al*., 2012)
Lamellodysidea- herbacea	*Oscillatoria- spongeliae*	2-(2',4'-dibromo- phenyl)-4,6-dibromophenol	Antibacterial	(Hinde *et al*., 1994; Unson *et al*., 1994)
Ptilocaulis trachys	*Lyngbya majuscula*	Majusculamide C	Antifungal	(Williams *et al*., 1993)
Spongia officinalis	*Bacillus sp*	A diketopiperazine compound	Antibacterial	(Bhattacharya *et al*., 2021)

Approximately, 363 bacterial isolates of six different phyla have been obtained, where 123 bacterial spp. belong to *Actinobacteria* strains with high abundance of *Microbacterium* spp. and *Pseudonocardia* group. However, according to the antibacterial assays and genomic screening for bioactive potential, the genus *Microbacterium* has emerged as the most active; despite the fact that it has very few copies of either the PKS or NRPS genes.

Three new metabolites have been isolated from *Nocardiopsis* sp. HB-J378 that is associated with *Theonella* sp. sponge. These metabolites have been identified as nocardiopsistins A-C (Table 2), and have shown antimicrobial activity especially when the bacterial media have been supplemented with Lanthanum chloride ($LaCl_3$), which have remarkably affected the MRSA. Nocardiopsistins A-C compounds have been grouped into angucycline, which is a distinct class of the biologically active aromatic polyketides (Xu *et al*., 2018). Moreover, using mining genomes techniques, a previous study has reached to identify the new peptide that has been cited as actinokineosin. Actinokineosin (Table 2) has demonstrated notable antibacterial activity against *Micrococcus luteus* bacterium recording IZ of 8 mm. This novel peptide has been isolated from the uncommon actinomycete *Actinokineospora spheciospongiae* (Takasaka *et al*., 2017). Moreover, the mining genomes techniques have been used to identify the novel bioactive compounds through the organism's genome databases (Corre and Challis, 2010).

8.2. *Proteobacteria*-associated with sponges as sources of antimicrobial metabolites

The second dominant bacterial phyla in sponges are the *Proteobacteria*, which have been subdivided into six classes; mainly, α-proteobacteria, -β-proteobacteria, γ-proteobacteria, δ-proteobacteria, ε-proteobacteria, and zetaproteobacteria (Bibi *et al*., 2017). Previously, Bultel-Poncé *et al*. (1999) reported the presence of a metabolite named 2-nonyl-4-hydroxyquinoline n-oxide, which has been produced by *Pseudomonas* sp. 1537-E7 associated with the sponge *Homophymia* sp. This compound has shown antibacterial efficacy against *Staphylococcus aureus* bacterium, recording IZ of 20 mm (Table 2). In another study, Zheng *et al*., (2005) examined for the first time the bacteria associated with the sponge *Hymeniacidon perleve*. Results have shown that *Pseudomonas* sp. NJ6-3-1 strain produced the metabolite 3,6-diisopropylpiperazin-2,5-dione with a great antimicrobial activity against the tested bacteria and fungi, including *B. subtilis* (IZ of >5), *Agrobacterium tumefaciens*, *Staphylococcus aureus*, and *S. cerevisiae* (IZ of 3-5 mm).

A novel promising compound that belongs to α-pyrones named pyrone-I (Table 2), which has been isolated from *Pseudomonas* sp. F92S91. Pyrone-I has presented a strong inhibitory activity against all the tested bacteria in the study conducted by Singh *et al*., (2003), including MRSA and vancomycin-resistant *Enterococci* (VRE). In addition, pyrone-I has a selective characteristic action, as it targets the bacterial cell membrane and isn't hemolytic to the human RBCs.

Among about 11 isolates of *Phorbas tenacior* associated bacteria, two bacterial strains have demonstrated antimicrobial activity. *Pseudovibrio* P1Ma4 and *Vibrio* P1MaNal1 have shown characteristic inhibition against *V. parahaemolyticus* CIP 75.2 and *P. atlantica* CIP 104721; recording IZ of 3-6 mm, by using the agar double-layer diffusion assay (Dupont *et al*., 2014). Likewise, two novel secondary metabolites that belong to the cyclic peptides have been isolated from *Ruegeria* sp.; derived from the marine sponge *Suberites domuncula*. These compounds have been identified as Cyclo-(glycyl-L-seryl-L-prolyl-L-glutamyl) and cyclo-(glycyl-L-prolyl-L-glutamyl), where both have

inhibited the growth of *B. subtilis*; recording MIC values of 25 µg/ ml and 50 µg/ ml, respectively (Mitova *et al*., 2004).

Alteramide A (Table 2) is a novel secondary metabolite with antibacterial potential, which has been isolated from *Alteromonas* sp. associated with the sponge *Halichondria okadai* (Shigemori *et al*., 1992). Furthermore, about 56 bacterial isolates recovered from the sponge *Haliclona* sp. have been tested. Among them, 8 bacterial strains that belong to the phylum *Proteobacteria* have demonstrated biological activity. Using the paper disk assay, the active strains have shown remarkable in vitro IZ diameters of 9 mm against *V. parahaemolyticus*, *Aeromonas hydrophila*, and *Staphylococcus aureus* (Radjasa *et al*., 2007).

Four bacterial isolates have been recovered from the marine sponge *Stylotella* sp. that belong to *Proteobacteria*, and have demonstrated significant antimicrobial and antioxidant activity. In this study, *Serratia marcescens* NBRC 102204, *Catenococcus thiocycli* TG 5-3, and *V. natriegens* ATCC 14048 have inhibited the growth of *P. aeruginosa* and *Staphylococcus aureus*; recording IZ diameters of 6-10 mm. On the other hand, *Pseudoalteromonas flavipulchra*- NCIMB 2033 inhibited growth of all the tested bacteria; recording IZ diameters between 6-10 mm against *P. aeruginosa*, *B. subtilis*, and *E. coli*, in addition to *C. albicans* with IZ diameter of 11-15 mm (Yoghiapiscessa *et al*., 2016).

A previous study conducted by Schmidt *et al*., (2000) has isolated the antifungal secondary metabolite theopalauamide (Table 2). This metabolite is a bicyclic glycopeptide that has been isolated from the bacterium *Candidatus Entotheonella palauensis* associated with *Theonella swinhoei* marine sponge.

8.3. *Firmicutes*-associated sponges bacteria as antimicrobial metabolite sources

Although the majority of bacteria in the phylum *Firmicutes* are Gram-positive; however, there are a few exceptions, such as the Gram-negative bacteria with pseudo-outer membrane (Stincone and Brandelli, 2020). Meanwhile, *Firmicutes* contain low GC nucleotides in their genome compared to *Actinobacteria* (Amarendra *et al*., 2013).

Recently, Dat *et al*., (2021) have carried a study on Vietnamese sponge-associated bacteria, where they have isolated more than 450 bacterial strains. *Bacillus* sp. M1-CRV-171 is a strain that has shown promising bioactivity. Moreover, 4 active secondary metabolites have been isolated from this strain, which have been identified as: cyclo (L-Pro-L-Tyr), macrolactin A, macrolactin H, and 15,17-epoxy-16-hydroxy macrolactin A (Table 2). These compounds have demonstrated antimicrobial effects against several bacteria and fungi. Likewise, *B. cereus* QN03323 has produced two novel metabolites with antibacterial properties. These compounds have been named as YM-266183 and YM-266184 (Table 2), and are classified as thiopeptides. They have acted as antibiotics against the MRSA, methicillin-Resistant *Staphylococcus epidermidis* (MRSE), and VRE. This strain of *Bacillus cereus* QN03323 has been associated with the marine sponge *Halichondria japonica* (Suzumura *et al*., 2003).

The diketopiperazine compound recently reported by Bhattacharya *et al*., (2021) is a (3S, 6S)-3,6-diisobutylpiperazine-2,5-dione, which has shown antibacterial potential against *E. coli* (MIC= of 16 µg/ ml) and *Staphylococcus aureus* (MIC= 22 µg/ ml). This secondary metabolite has been isolated from *Bacillus* sp. associated with the marine sponge *Spongia officinalis*. In the previous study of Pabel *et al*., (2003), about 5 *Bacillus* spp. have been isolated from the Mediterranean sponge *Aplysina aerophoba*. Individually, these bacteria have produced different types of cyclic lipopeptides that have antimicrobial properties, and have been identified as surfactin, iturin, and fengycins. These cyclic lipopeptides have demonstrated antifungal efficacy against *C. albicans*, beside antibacterial potentials against *Staphylococcus aureus*, *E. coli*, and *Vibrio* sp. Furthermore, bacillamide C and a new compound

known as neobacillamide A have been isolated from *B. atrophaeus* that lives as a symbiont with the marine sponge *Dysidea avara*. These two compounds have demonstrated antimicrobial properties (Liu *et al*., 2012).

8.4. Cyanobacteria -associated with sponges as sources of antimicrobial compounds

The photosynthetic prokaryotes that are distributed in all types of the aquatic environments belong to the phylum Cyanobacteria (Konstantinou *et al*., 2020). These bacteria live freely and/or as symbionts with the fresh and marine water organisms (Amarendra *et al*., 2013). Cyanobacteria provide nutrition to the marine sponges through several biological interactions, support the host's metabolic pathways, and are also capable of fixing nitrogen (Thomas *et al*., 2010). A previous study of Unson *et al*., (1994) has described 2-(2',4'-dibromo-phenyl)-4,6- dibromophenol metabolite with antibacterial potency (Table 2). This compound has been isolated from the cyanobacterium *Oscillatoria spongeliae* associated with *Lamellodysidea herbacea*. Majusculamide C is a secondary metabolite classified as a cyclic depsipeptide, which has shown an antifungal characteristic (Table 2). This compound has been isolated from *Lyngbya majuscula* that is associated with the marine sponge *Ptilocaulis trachys* (Williams *et al*., 1993).

8.5. *Bacteroidetes*-associated sponges bacteria as sources of antimicrobials

One of the major bacterial phyla is the *Bacteroidetes*, where most of their members are Gram-negative, and exist in biotic and abiotic environments, such as the human guts and skins and/or in the terrestrial and marine environments (Stincone and Brandelli, 2020). In a previous study conducted by Kennedy *et al*., (2009), *Salegentibacter* sp. bacterium has been isolated from the marine sponge *Haliclona simulans*, and demonstrated inhibitory activity against the MRSA. This isolated strain has been confirmed to possess at least one NRPS gene that enables it to produce a biologically active secondary metabolite. In another study, a total of 114 bacterial isolates have been recovered from two marine sponges, mainly *Hymeniacidon perlevis* and *Halichondria panicea*. The isolated *Dokdonia* sp. and *Aquimarina* sp. bacteria have shown antibacterial activity against *Staphylococcus aureus* ATCC 29213 beside 70.2 % of the marine isolates, which may be attributed to the production of secondary metabolites with antimicrobial potentials (Rodriguez Jimenez *et al*., 2021).

Conclusion

The marine environment provides an unlimited source for bioactive compounds with antimicrobial activity. Moreover, the global serious issue against MDR bacteria caught the scientists' attention to discover novel compounds from the marine organisms and their associated microorganisms. In fact, secondary metabolites production by the marine organisms has been confirmed to be one of the organism's defenses against the predators and pathogenic microbes. Finally, the sponge-microbial associations provide one of the richest sources of these bioactive secondary metabolites.

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