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DIVERSITY AND POTENCY MARINE BACTERIA AS SOURCE OF ANTIBIOTIC COMPOUNDS TOWRDS BACTERIA PATHOGEN

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Abstrak

Resistensi antibiotik merupakan salah satu permasalahan global di bidang kesehatan yang dapat disebabkan karena mudahnya masyarakat mendapatkan antibiotik di pasaran, kurangnya pengawasan dari pemerintah terhadap konsumsi antibiotik, penggunaan antibiotik yang tidak tepat, serta adanya konsumsi antibiotik yang berlebihan di masyarakat yang tidak sesuai. Adanya potensi bakteri laut yang menghasilkan senyawa metabolit sekunder khususnya antibiotik, umunya dapat berasal dari berbagai sumber dan substrat yang saling berasosiasi dalam menghasilkan metabolit sekunder. Sumber substrat utama bakteri laut yang diketahui menghasilkan suatu senyawa metabolit sekunder sebagai antibiotik yaitu dapat bersumber dari sedimen, spons, dan seaweed. Beberapa jenis keragaman bakteri laut yang berasosiasi dengan sedimen yang berhasil di identifikasi antara lain *Aeromonas veronii, Arthrobacter* sp*, Bacillus* sp*, Chryseobacterium* sp*, Citrobacter freundii, Enterobacter cloacea, Flavobacterium* sp*, Microbacterium* sp*, Streptomyces tunisiensis, Streptomyces* sp, *Streptomyces microflavus, Stenotrophomonas* sp, *Pristia flexa,* dan *Pseudomonas* sp. Jenis bakteri *Streptomyces* sp memiliki aktivitas yang paling potensial sebagai antibiotik jenis baru. Data menunjukkan adanya keanekaragaman bakteri laut dalam menghasilkan suatu senyawa aktif dari berbagai sumber substrat dapat dijadikan sebagai kandidat antibiotik jenis baru dalam mengatasi tingkat resistensi antibiotik yang ada.
Kata kunci : Sedimen, Spons, *Streptomyces* sp

Abstract

Antibiotic resistance is a global problem in the health sector, which can be caused by the ease with which people can get antibiotics on the market, lack of supervision by the government regarding antibiotic consumption, inappropriate use of antibiotics, and excessive consumption of antibiotics in inappropriate communities. There is the potential for marine bacteria to produce secondary metabolite compounds, especially antibiotics, which generally come from various sources and substrates that associate with each other to produce secondary metabolites. The main substrate source for marine bacteria, known to produce secondary metabolite compounds as antibiotics, can come from sediments, sponges and seaweed. Several types of diversity of marine bacteria associated with sediment that have been identified include *Aeromonas veronii, Arthrobacter* sp, *Bacillus* sp, *Chryseobacterium* sp, *Citrobacter freundii, Enterobacter cloacea, Flavobacterium* sp, *Microbacterium* sp, *Streptomyces tunisiensis*, *Streptomyces* sp, *Streptomyces microflavus*, *Stenotrophomonas* sp, *Pristia flexa*, and *Pseudomonas* sp. This type of bacteria, *Streptomyces* sp, has the most potential activity as a new type of antibiotic. Data shows that the diversity of deep-sea bacteria producing active compounds from various substrate sources can be used as candidates for new types of antibiotics to overcome the existing level of antibiotic resistance.
Keywords: Sediment, Sponge, *Streptomyces* sp

PENDAHULUAN

The problem of antibiotic resistance is a global problem in the health sector and is a new challenge because antibiotic resistance has very high levels of morbidity and mortality (Frieri et al., 2017). In general, antibiotic resistance can occur due to influencing factors, including naturally occurring and congenital factors. Apart from that, antibiotic resistance can occur because it is easy for people to get antibiotics on the market, there is a lack of supervision from the government regarding antibiotic consumption, inappropriate use of antibiotics, and excessive consumption of antibiotics in the community and not by existing recommendations (Kemenkes RI, 2021). The inappropriate use of antibiotics can also cause serious illness because it can cause infection (Noer, 2012). Based on data from the World Health Organization, (2014), there has been an increase in cases of death caused by infectious diseases of around 3.5 million people/year.

Uncontrolled use of antibiotics can give rise to microbial strains resistant to certain types of antibiotics, known as Multi Drugs Resistance (MDR) (Abbanat et al., 2003). Apart from that, antibiotic resistance in several types of microbes can cause the effects of these antibiotics not to be used in optimal doses and according to the recommended doses (Pratiwi, 2017).

Data from the Menteri Kesehatan RI (2011) shows that Indonesia is in 8th place out of 27 countries with the level of drug resistance to Multi Drugs Resistance (MDR) bacteria in the world based on data from the World Health Organization (WHO). Over the last few years, there has been an increase in cases of Multi-Drug Resistance (MDR), especially in the group of Gram-negative bacteria (Zarb et al., 2012). WHO (World Health Organization) data shows approximately 30 types of diseases caused by bacterial infections, and several strains of these bacteria have developed resistance to certain antibiotics. So, WHO has regulated the use of antibiotics wisely and evaluated antibiotic use so that it is not excessive (World Health Organization, 2017). As concerns arise regarding antibiotic resistance produced by MDR strains, it is necessary to explore sources of new antibiotic diversity to overcome existing resistance. One potential source for new types of antibiotics is the ocean.

The sea is the largest ecosystem, which is a potential source of diversity for new types of antibiotics because almost 71% of the earth's surface is covered by the sea, and the sea is also known to have a high diversity of bacteria. Over the last few decades, there has been much research focusing on marine bioactive compounds from various sources, including the presence of marine microorganisms(Spellberg & Shlaes, 2014). It is estimated that the sea has a high diversity of types of microorganisms, one of which is bacteria, namely around $10^4 – 10^6$ bacteria/ml (Pedrós-Alió, 2006).

Marine bacteria also have a lot of potential, such as dyes, food, and sources of medicine, especially new types of antibiotics. Marine bacteria can produce secondary metabolite compounds which have a unique structure according to complex environmental conditions and strong bioactivity. Exploring the potential of marine bacteria as a potential source of new types of antibiotics can be carried out by isolating bacteria which can be sourced from seawater, marine invertebrates, sediments and marine plants, both from the coast and parts of the deep sea. It is known that several species of marine bacteria have been identified and have antibacterial, antibiotic, antifungal and antiviral activity, including the Genus *Microccus, Vibrio, Alcaligenes, Pseudomonas, Xanthomonas, Flavobacterium,* and *Achromobacteria* (Das et al., 2006).

The presence of secondary metabolite compounds produced by several types of marine bacteria as a form of defence mechanism against extreme environmental conditions such as limited oxygen, high pressure and low light intensity (Debbab et al., 2012). It is known that secondary metabolite compounds produced by several types of marine bacteria include Bogorol A, Halobacillin, and Moja vensis A (Muhammad Abdul Mojid Mondol, Shin, & Islam, 2013).

Apart from that, other bioactive compounds are often produced by marine bacteria, including alkaloids, terpenoids, peptides, steroids and polyketides (Piggott & Karuso, 2005). These secondary metabolite compounds are known to have antibacterial, antibiotic, antifungal and antiviral activity(Andryukov et al., 2019) . The results of other studies also show that around 10 - 20% of bacteria isolated from marine waters have potential in the fields of biotechnology, therapeutic therapy and pharmaceutical development (Grandgirard et al., 2002). Apart from that, secondary metabolite compounds produced by several types of marine bacteria can be used as antimicrobial, antioxidant, anti-angiogenesis, diabetes and cytotoxic agents (Debbab et al., 2010).

This review article discusses a general overview of the diversity of marine bacteria that are used as a source of antibiotics, including sources of isolation as well as sources of isolation for the production of antibiotic compounds produced by these bacteria. Although many journals discuss the diversity of marine bacteria as a source of antibiotics, there are not many articles that discuss in detail and comprehensively the diversity and potential of marine bacteria as a source of active antibiotic compounds against pathogenic bacteria originating from various isolated sources and compounds produced by bacteria. The sea, It is hoped that this article can provide a detailed, comprehensive and in-depth general overview of the antibiotic compounds contained in marine bacteria from various sources. It is also hoped that the results of this study can become further reference material regarding the diversity of marine bacteria as a source of diversity for new types of antibiotics and their potential to inhibit the growth of pathogenic bacteria that have developed resistance to certain types of drugs.

METODE

This research uses the *Systematic Literature Review* (SLR) method, the data collection used in this journal refers to the database sources Scopus, NCBI, Sprinter Link, PubMed and Science Direct, which discuss the distribution of marine bacteria as a source of antibiotics. The keywords used are "*Marine bacteria*", "*Antibiotic*", "*Multi drug resistance* (MDR)", and "*Bacteria pathogen*" in the database search. The publication data used in the systematic review method ranges from 2013 - 2023, with data that is considered still relevant to the data needed. The analysis data obtained is then explored and reviewed based on the subsection of findings obtained during the search.

The journal data obtained is then re-selected based on the suitability of the title, abstract and research results used during the data search. Then, the journals are selected again by considering the exclusion and inclusion criteria according to the data. The data obtained was then developed in tabular form based on author, journal year, antibiotic bacteria, target microorganisms and research results. The data analysis was carried out descriptively based on research journals that had been collected and met the criteria for analysis with narratives and tables based on existing data.

HASIL DAN PEMBAHASAN

Based on the results of a review of several articles used as sources in searching for data on marine bacteria as antibiotics, 212 data were found that matched the predetermined inclusion characteristics. The results of the comprehensive study found 12 journals which were analyzed because they were in accordance with the data to be developed, such as table form based on author, journal year, antibiotic bacteria, target microorganisms and research results. The data used in this literature review process is antibiotic activity data for several types of marine bacteria ranging from 2013 - 2023, and the sources of antibiotics obtained are sediment, sponge, marine sediment, seaweed, sedimentary mud and river water. Types of antibiotic-producing bacteria found include *Bacillus* sp, C*itrobacter freundii, Aeromonas veronii, Enterobacter cloacae, Pristia flexa, Vibrio diabolicus, Streptomyces tunisiensis, Bacillus tequilensis, Streptomyces* sp, *Steptomyces microflavus, Streptomyces althioticus, Arthrobacter* sp, *Chryseobacterium* sp, *Flavobacterium* sp,

Microbacterium sp, *Pseudomonas* sp, and *Stenotrophomonas* sp. The selected journals that have appropriate data are then extracted and summarized data. Publication data for the last ten years from various countries is presented in Figure 1. Based on research data over the last 10 years, research on antibiotic compounds sourced from marine bacteria has increased from year to year (Figure 1). Based on the diagram displayed, it can also be seen that there has been an increase in research related to antibiotic compounds produced by marine bacteria, dominated by China and India.

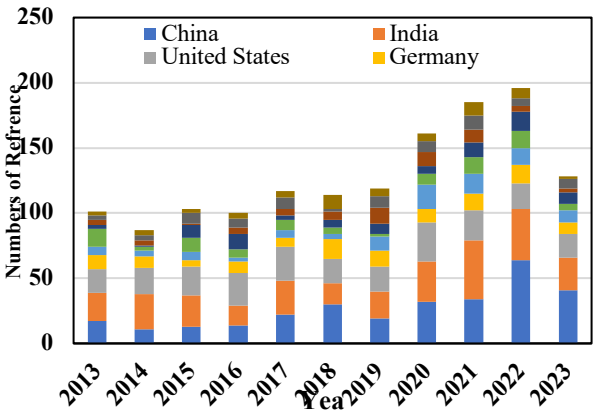

Figure 1. Publication data over the last decade using the keywords "Marine bacteria", "Antibiotic", "Multi Drugs Resistance (MDR)", and "Bacteria pathogen" in database searches and data distribution based on the top fifteen country data. The data source was taken from the Scopus database (www.scopus.com).

DISCUSSION

The diversity of marine bacteria that are sources of antibiotic candidates can come from various types of existing substrates, such as abiotic or biotic substrates. Research shows that the antibiotic activity produced by marine bacteria falls within a broad spectrum of microbial activity. An explanation of the diversity of types of marine bacteria and the main sources of marine bacteria as antibiotic candidates is presented in Table 1 sequentially. Marine bacteria that produce secondary metabolite compounds, especially antibiotics, generally come from various sources and substrates in association with other living creatures. These bacteria can live in marine sediments and are associated with various types of organisms, one of which is the invertebrate group; bacteria can also be associated with algae. The symbiotic relationship between microorganisms and several groups of invertebrates in producing secondary metabolites is used by marine invertebrates as a form of self-defence against other organisms by producing secondary metabolite compounds (Romano et al., 2022).

Exploration of bacteria-producing antibiotic compounds has been carried out from several different sources, including exploration of the transition from soil to new sources, such as the development of exploration in marine sediments. Marine sediments are known to be a major source of antibiotic compounds produced by several types of marine bacteria. The research results show that various types of marine sediment produce different strains of marine bacteria. The differences in the strains produced are due to differences in the distance from the source of isolation and the area where the isolated substrate was taken from marine sediments, whether the collection point is deep or not, or whether the distance is close or far to the edge of the coast, will produce a difference in the strains of marine bacteria. The results of previous research show that marine sediment samples located close to the shoreline surface will produce strains that have almost the same level of relationship as strains located on land (Subramani & Aalbersberg, 2012).

The presence of various environmental factors will also influence the diversity of types of marine bacteria in producing existing secondary metabolite compounds. Environmental factors such as lower environmental temperatures, hydrostatic pressure, pH, aeration and abiotic stress factors will greatly influence the survival, production of secondary metabolites, physiology and motility of marine bacteria. Various types of marine organisms, which are the source of life for marine bacteria, will interact with each other to form secondary metabolite compounds, one of which is antibiotic compounds. The main

substrate source for marine bacteria, which is known to produce secondary metabolite compounds as antibiotics, can be sediments, sponges and seaweed (Table 1).

Marine bacteria that interact with certain substrates and bind to certain particles will produce secondary metabolites in greater quantities compared to free-living bacteria. Marine bacteria that associate with living substrates such as sediment are known to produce secondary metabolites, one of which is antimicrobial. Sediment is a product of the disintegration and decomposition of rocks that have gone through a process of breaking down various types of organic materials carried out by biological agents into organic and mineral materials, which are very useful in the process of producing metabolite compounds produced by marine bacteria (Andriyanto et al., 2019).

Based on data from the literature review, it also shows that there are marine bacteria associated with sediment showing various types of bacterial diversity such as *Aeromonas veronii, Arthrobacter* sp, *Bacillus* sp, *Chryseobacterium* sp, *Citrobacter freundii, Enterobacter cloacea, Flavobacterium* sp, *Microbacterium* sp, *Streptomyces tunisiensis, Streptomyces* sp, *Streptomyces microflavus, Stenotrophomonas* sp, *Pristia flexa*, and *Pseudomonas* sp. Apart from that, it is also known that several marine bacteria have various activities. The research results show that several types of marine bacteria have diverse activities. It is known that the marine bacteria *Bacillus* sp, *Citrobacter freundii, Aeromonas veronii, Enterobacter cloacea*, and *Pristia flexa* isolated from wetland sediments contain antibiotic compounds that can inhibit the growth of *Ralstonia* sp and *Burkholderia cepacian* microorganisms (Kumar et al., 2023). The green pigment produced by the bacteria *Streptomyces tunisiensis* is known to have antimicrobial, antioxidant, antiviral and anticancer activity. The green pigment produced by this bacteria also has antagonistic capabilities against the Gram-negative bacteria *Enterococcus faelicalis* (Ibrahim et al., 2023). Antibiotic-producing marine bacteria from the genus Streptomyces isolated from the sediments of Bangladesh waters are known to have antibiotic capabilities against several bacteria tested, such as *Shigella brodie, Escherichia coli, Pseudomonas* sp, *Proteus* sp, *Staphylococcus aureus* and *Bacillus cereus* (Arefa et al., 2021). Marine bacteria from the genus *Steptomyces* sp isolated from the coastal sediments of the northern part of Egypt (Mediterranean Sea) are known to produce the antibiotic compounds resistoflavin and resistomycin against the methicillin-resistant bacteria *Staphylococcus aureus* and *Escherichia coli* (Kim et al., 2021).

The results of the research show that several types of marine bacteria isolated from various types of aquatic sediment produce compounds that have activity as existing antibiotic candidates. Among them is the marine bacteria *Streptomyces* sp, which was isolated from the sediment of the waters of the west coast of the Philippines and has antibiotic activity against the bacteria *Staphylococcus* sp*, Pseudomonas aeruginosa* and *Escherichia coli* (Tenebro et al., 2021). *Steptomyces microflavus* bacteria isolated from marine sediments are known to contain the compound Chromoycin A9 as an antibiotic against the pathogenic bacteria Methicillin-resistant *Staphylococcus aureus* (MRSA) (Cho et al., 2020). It is known that *Streptomyces* sp bacteria isolated from marine sediments in the coastal waters of Islas de Gigantes Iloilo, Philippines, are known to produce the antibiotic compound two polyketide angucycline glycosides from polycyclic aromatic groups, namely fridamycin A and fridamycin D which are products of type II polyketide synthase biosynthesis, these compounds have antibacterial activity against the pathogenic bacteria *Staphylococcus aureus* (Sabido et al., 2020). Marine bacteria isolated from sediment samples in Polish nature reserves have different levels of resistance to several types of antibiotics. The most common isolates found in the sediment section were isolates from the genera *Pseudomonas* sp and *Bacillus* sp. The tet(X), tet(H), tet(M), and tet(BP) genes are the genes most commonly

found in isolates originating from sediments (Piotrowska et al., 2017).

Sponges are one source of isolation of antibiotic-producing bacteria where sponges produce metabolites as a source of self-defence. The results of the research that has been carried out show that several types of sponges contain metabolite compounds such as antibiotics. It is known to produce secondary metabolite compounds, namely perforin and tachylecin. It is known that these types of compounds can suppress the growth of various pathogenic bacteria. The compound produced due to the interaction between marine bacteria and sponges will produce a defence molecule in the defence system. Apart from that, it is also known that several types of marine bacteria produce okadaic acid, which plays a role in fighting foreign particles and increases the immune response in host cells. The presence of marine bacteria that live and are associated with sponges is also known to produce specific secondary metabolites, such as antifouling and tribromophenol compounds, which function as specific defences against pathogenic bacteria (Chen et al., 2021).

Based on data from a literature review, it also shows that the marine bacteria *Vibrio diabolicus*, which is associated with sponges on the coast of Torosiaje, Gorontalo, is known to have antibiotic activity against several types of pathogenic bacteria such as *Escherichia coli* and *Staphylococcus aureus* (Retnowati & Katili, 2023). *Streptomyces* sp bacteria isolated from marine sponges on Bakki Island, Barru Regency, Sulawesi, are also known to have antibiotic activity and contain alkaloid compounds against *Staphylococcus aureus* and *Escherichia* coli bacteria (Fauziah & Djide, 2022). The marine bacterium *Bacillus* tequilensis isolated from the Lithistida sponge in the Seribu Islands is known to have activity in producing new antibiotic compounds such as terpenoids, alkaloids, peptides and polyketides against the pathogenic bacteria *Saccharomyces aureus* (Mardiana et al., 2020).

Table 1. Antibiotic Activity of Marine Bacterial Species from Various Sources

Source	Bacteria Strain	Target Microorganism	References
Sediment	*Bacillus* sp, *Citrobacter freundii, Aeromonas veronii, Enterobacter cloacea,* and *Pristia flexa*	*Ralstonia* sp, *Burkholderia cepacian.*	(Kumar et al., 2023)
Sediment	*Streptomyces tunisiensis*	*Enterococcus faelicalis*	(Ibrahim et al., 2023)
Sediment	*Streptomyces* sp	*Shigella brodie, Escherichia coli, Pseudomonas* sp*., Proteus* sp*., Staphylococcus aureus,* and *Bacillus cereus*	(Arefa et al., 2021)
Sediment	*Streptomyces* sp	Methicillin-Resistant *Staphylococcus aureus* and *Escherichia coli*	(Kim et al., 2021)
Sediment	*Streptomyces* sp	*Staphylococcus* sp, *Pseudomonas aeruginosa* dan *Escherichia coli.*	(Tenebro et al., 2021)
Sediment	*Streptomyces* sp	*Shigella brodie, Escherichia coli, Pseudomonas* sp*., Proteus* sp*., Staphylococcus aureus,* and *Bacillus cereus.*	(Arefa et al., 2021)
Sediment	*Steptomyces microflavus*	Methicillin-resistant *Staphylococcus aureus* (MRSA)	(Cho et al., 2020).
Sediment	*Streptomyces* sp	*Staphylococcus aures* (MRSA)	(Sabido et al., 2020)
Sediment	*Arthrobacter* sp*, Bacillus* sp*, Chryseobacterium* sp*, Flavobacterium* sp*, Microbacterium* sp*, Pseudomonas* sp*, and Stenotrophomonas* sp	*Aeromonas* sp, *Vibro* sp	(Piotrowska et al., 2017)
Sediment	*Bacillus* sp	*Staphylococcus aureus*, and *Bacillus substilis*	(Mondol et al., 2013)

Sponge	*Vibrio diabolicus*	*Escherichia coli* dan *Staphylococcus aureus*	(Retnowati & Katili, 2023)
Sponge	*Streptomyces* sp	*Staphylococcus aureus* dan *Escherichia coli*	(Fauziah & Djide, 2022)
Sponge	*Bacillus tequilensis*	*Saccharomyces aureus*	(Mardiana et al., 2020)
Seaweed	*Streptomyces althioticus*	*Bacteroides fragilis, Haemophilus influenza,* dan *Neisseria meningitidis*	(Brana et al., 2019)

Seaweed is one source of isolation of antibiotic-producing marine bacteria where seaweed produces metabolite compounds as a source of self-defence. Besides that, it is also known that seaweed contains various bioactive compounds which function as candidates, antibacterial, antibiotic, anticoagulant and antioxidant (Bansemir., 2006). It is known that types of seaweed such as *Eucheuma cottonii* produce various types of flavonoid, alkaloid and steroid compounds, which can suppress the growth of pathogenic bacteria by damaging the permeability of bacterial walls, lysosomes and microsomes due to the interaction of flavonoid compounds which interact with bacterial DNA (Siregar et al., 2012). The presence of several types of flavonoid derivative compounds produced by several types of marine bacteria will damage the cytoplasmic walls. The presence of ions involved in the form of H+ from phenol will cause the cell wall to break down, causing the cell to leak because the phospholipids cannot maintain the cytoplasmic membrane.

It is known that the extract of the marine bacterium *Streptomyces althioticus* isolated from seaweed Cantabrian Sea (Northeastern Atlantic Ocean) shows strong antibiotic activity against Gram-negative pathogenic bacteria such as *Bacteroides fragilis, Haemophilus influenza*, and *Neisseria meningitidis* (Brana et al., 2019). The activity of antibiotic compounds produced by bacteria, especially marine bacteria, shows that these marine bacteria can be used as potential candidates for the development of potential secondary metabolites of marine bacteria, especially antibiotics. Marine bacteria that associate with other living creatures produce the secretion of secondary metabolites in the form of antibiotic compounds, indicating that these bacteria have great potential to produce new types of antibiotic compounds. In general, the content of secondary metabolites produced by marine bacteria will depend on the habitat and living environment of the bacteria themselves, especially antibiotic compounds. The relationship between environmental factors and the types of antibiotic compounds produced is because seawater contains various active substances that play a role in biological processes. Sea water also contains inhibitor agent factors, where these inhibitor agents are useful in the growth of microorganisms.

Many studies have been carried out regarding the activity of marine bacteria from various sources, which are used as potential candidates for antibiotics to overcome the existing problem of antibiotic resistance. This shows that there are scientific studies that have been carried out regarding the antibiotic activity of marine bacteria, from the most basic level of isolation to the content of bioactive compounds that are used as antibiotic candidates. Apart from that, the results of the literature review data show that there is a trend in several countries which have carried out many scientific publications regarding marine bacterial antibiotic compounds from various sources over the last decade. The data results also show that countries such as China, India and the United States are the countries with the highest level of research on the diversity and activity of marine bacterial antibiotic compounds over the last decade. The diversity of deep-sea bacteria produces an active compound which is used as a candidate for a new type of antibiotic to overcome the existing level of antibiotic resistance.

CONCLUSION

Research articles published over the last decade regarding the diversity and

potential of marine bacteria as antibiotic candidates against pathogenic bacteria show that marine ecosystems include enormous biodiversity and are a source of potential candidates for exploration in the search for new bioactive compounds. Marine bacteria that produce secondary metabolite compounds, especially antibiotics, generally come from various sources and substrates that associate with each other to produce secondary metabolites, one of which is a candidate for a new type of antibiotic. The main substrate source for marine bacteria, known to have secondary metabolite compounds as antibiotics, can come from sediments, sponges and seaweed.

Several types of diversity of marine bacteria associated with sediment that have been identified include *Aeromonas veronii, Arthrobacter* sp, *Bacillus* sp, *Chryseobacterium* sp, *Citrobacter freundii, Enterobacter cloacea, Flavobacterium* sp, *Microbacterium* sp, *Streptomyces tunisiensis, Streptomyces* sp, *Streptomyces microflavus, Stenotrophomonas* sp, *Pristia flexa*, and *Pseudomonas* sp. This type of bacteria, *Streptomyces* sp, has the most potential activity as a new type of antibiotic. Research on the diversity and antibiotic activity of marine bacteria shows that China, India and the United States have the highest levels of research on the diversity and training of marine bacterial antibiotic compounds over the last decade. Data shows a variety of deep-sea bacteria that produce active compounds that can be used as candidates for new types of antibiotics to overcome existing levels of antibiotic resistance.

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