Biotechnological Communication

Antimicrobial Activity of Metabolites Extracted from Marine Actinomycetes

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ABSTRACT

Actinomycetes are free-living bacteria that are widely distributed and found in several habitats. These bacteria are essential organism in soil system, they contribute to agroindustry as the origin of active compounds. Their economical and biotechnological importance lies in the production of bioactive secondary metabolites including anticancer, insecticides, and antibiotic agents, such Actinomycetes-derived agents have been commonly used in both medical and industrial fields. Mainly, different Actinomycetes species isolated from coastal habitats are found to be novel sources of antibiotics. Thus, further investigating Actinomycetes will provide a better understanding of the physiological features and chemical composition of marine Actinomycetes. It also enables to use of large synthetic libraries of derived molecules (e.g., secondary metabolites) to develop biological drugs to combat advanced bacterial infections. Actinomycetes can produce more powerful biological compounds of medicinal and economic importance; moreover, it can provide insight into new antibiotics against different types of pathogens that cause infection to humans and support human health by overcoming complications caused by pathogenic bacteria and drug resistance. In particular, Actinomycetes of marine origin are a promising source of biomedical microbial products and natural products with an interesting microbial activity against many other pathogenic causing microorganisms. They are diverse in nature and have unique chemical compositions. During the past years, many new anti-microbial agents were discovered and deemed powerful therapeutic agents. The discovery of bioactive compounds continues to increase. However, the underlying potential of Actinomycetes has yet to be found. Therefore, this work conducts a review of the antimicrobial activity of metabolites extracted from marine Actinomycetes.

KEY WORDS: ACTINOMYCETES, ANTIBIOTIC, APPLIED MICROBIOLOGY, MARINE ENVIRONMENTS, METABOLITES.

INTRODUCTION

Marine environments contain enormous biological diversity. It is now thought to be a main source of a variety of pharmacologically and bioactive metabolites, among which actinomycetes are the most important source of natural bioactive compounds, which represent the storage pool for bioactive compounds with antibacterial, antiviral, anti-inflammatory, antimalarial, or antitumor activity. The rapid emergence of drug-resistant pathogens has led to the demand for new antimicrobial compounds. Drug-resistance pathogens are considered a threat to public health globally, which poses an urgent need for developing new antibiotics to fight pathogens and help reduce emerging infectious diseases. Although developing new drugs through using combinatorial libraries of molecules, natural compounds and bioactive microbial metabolites are potent sources of bioactive scaffolds that are recognized as the basis for antibiotics development (Elmallah et al. 2020; Ghosh et al. 2020).

There are 30 phyla in the domain bacteria, the largest phylum is Actinobacteria with 6 classes, 16 orders, 14 suborders, 63 families, and more than 370 genera (Barka et al. 2016). It plays an essential role in biotechnology, producing secondary bioactive metabolites for pharmaceutical, medical and agricultural applications, they are being evaluated

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for biofuel production and the compounds used in the development of plastics, detergents, and food preservatives/ additives (Valliappan et al. 2014; Jagannathan et al. 2021). Actinomycetes are a group with filamentous morphology, they are Gram-positive bacteria and characterized by high C+ G genome. They are dominating marine ecosystems such as estuaries, seaweed meadows, and mangrove forests (Chaudhary et al. 2013; Shamikh et al. 2020; Jagannathan et al. 2021).

In recent decades, the antimicrobial activity of metabolites considered one of the hotspot areas in marine environments research. That's due to the diversity of marine ecosystems on microbial, metabolic, and genetic levels (Liu et al. 2010; Jose and Jha 2016). Many factors play a crucial role that affect the variety of living organisms in the marine environment, such as nutrients, temperature, salinity, and tidal movement. Water occupies the majority of the earth's surface (i.e., up to 97% of the) and holds 87% of undiscovered living organisms, making it distinguished by its enormous biodiversity, which attracts scientists and researchers' interest (Bérdy 2012; Duncan et al. 2015). The new discoveries of marine bacteria from ecosystems significantly support identifying new biologically active secondary metabolites, which increase biodiversity importance on how it can provide an extensive reservoir of potentially active compounds (Gozari et al. 2018; Suresh et al. 2020). Actinomycetes are rich sources of several bioactive compounds of biomedical prominence worldwide. They manifest a high physiological diversity and produce various bioactive independent reported compounds, antibiotics, antioxidants, and other critical pharmaceutical products (Mahapatra et al. 2019; Shamikh et al. 2020; Mani et al. 2021).

Furthermore, Actinomycetes are a valuable source of unique chemicals, secondary receptors, and new therapeutic compounds (Longnecker and Kujawinski 2020; Safaei et al. 2021). In a recent work, ninety-seven new species of Actinomycetes were found in the marine environment between (2013) and (2017). The marine Actinomycetes ecological systems are broadly classified, includes genera consisting of Streptomyces, Actinomyces, Arthrobacter, Corynebacterium, Frankia, Micrococcus, and various others. Importantly, almost 1% Actinomyces have been detected, classified, studied, and documented. From the 500,000 of biological source-derived-natural compounds that have been discovered worldwide, only 14% are derived from bacteria and fungi, and about 30% of them are Actinomycetes where 60% of utilized antibiotics are derived from Streptomyces (Rasool and Hemalatha 2017; Subramani and Sipkema 2019; Jagannathan et al. 2021).

The overspread of emerging infectious diseases and human pathogens resistant to many drugs have been an imminent threat to global health (Khan and Khan 2016). As a result, there has been a paramount need to discover biologically effective medicinal drugs and natural products relevant to meet these challenges. This review summarizes the diversity of Actinomycetes and bioactive compounds of marine Actinomycetes and their roles on medical and industrial fields (Elmallah et al. 2020; Safaei et al. 2021).

Characterization of marine metabolites: Marine organisms have received great popularity and attention among scientists for their enormous potential and ability to many bioactive compounds (Mahajan and Balachandran 2012). Actinomycetes have been reported as the leading and determinant producer of bioactive compounds for marine ecosystems. As such, peptides, terpenes, polyketides, and alkaloids (Dalisay et al. 2013; Pimentel-Elardo et al. 2010; Abdelfattah et al. 2019; Khalifa et al. 2019; Mayer et al. 2021).

They have various important bioactivities, such as antibacterial, antioxidants, anticancer, antifungal, and antialgae, antibiotics, anti-oncological agents, and many effective compounds are pharmaceutical with diverse biological activities. With new advances in sequencing technologies, marine organism-associated Actinobacterial 16S rRNA gene sequences are stored in NCBI database (Pimentel-Elardo et al. 2010; Valliappan et al. 2014; Abdelfattah et al. 2019; Khalifa et al. 2019; Elmallah et al. 2020; Guimarães et al. 2020; Mayer et al. 2021).

Bioactive Constituents of Marine Organisms: Polyketides: Recently, novel aromatic polyketides were identified from the aquatic sponges are include strains of Saccharopolyspora and Streptomyces. One major source of aromatic polyketides is the sponge-associated Actinomycetes. Thence, from about 15 South China Sea sponges, a total of 77 Actinomycetes were collected. The isolated Actinomycetes phylogenetic was mainly based on gene sequencing (i.e., 16S rRNA), which facilitated their classification into 12 families and 20 genera. According to that, Marihabitans, Polymorphospora, and Streptomonospora were isolated for the first time from the marine sponges and considered 'rare genera'. Remarkably, the gene β-ketoacyl synthase (KSα) was utilized to assess the possibility of the Actinomycetes strains producing aromatic polyketides (Mani et al. 2021).

Alkaloids: Altemicidin is a monoterpene alkaloid, and it has an antibacterial activity that was isolated from Streptomyces species. Streptomyces and Micromonospora have the main antibacterial activity. Between these, there are five groups of Streptomyces, that are flavus, albosporus, roseosporus, viridis, and hygroscopicus. Almost 65% of all isolated antimicrobial, have an antimicrobial role in inhibition Gram-positive bacteria activity. And 47% were against Gram-negative bacteria, while 32% inhibit both bacteria (Mani et al. 2019; Mani et al. 2021).

Peptides: Bioactive peptides have presently been isolated and characterized from a variety of natural and processed foods. Within the biological process, peptides work as possible physiological modulators during intestinal absorption. Their release is sustained by their structure and their organic compound sequence. Overall, the bioactive peptides are found to own nutraceutical capabilities and promote human health. Properties have got a lot of publicity throughout the human health community, such as Antihypertensive and antimicrobial property. Distinct purified peptides that have been isolated from phyla like Porifera and Craniata have cytotoxic impacts on different

cell lines, such as pancreatic and breast cell lines cell line (Lazcano-Pérez et al. 2012; Pujiastuti et al. 2019). In addition, Apratoxin A, coibamide A, and lyngbyabellin B that have been isolated from Leptolyngbya sp and Lyngbya majuscule, respectively, are also showed cytotoxic impact against human HeLa cervical carcinoma cells (Khalifa et al. 2019; Suresh et al. 2020).

Recently, a total of 4 cyclic peptides- ogipeptins of secondary metabolites were isolated from Pseudoalteromonas with hydrophobic patterns and recognized as acylated cyclic peptides. Four ogipeptins showed potent antibacterial activity against Escherichia coli and slightly weaker activity against Staphylococcus aureus. It was also found that ogipeptins could block binding of cell surface receptor CD14 and lipopolysaccharide (LPS) and inhibit the discharge of tumor necrosis factor-alpha (TNF-α) caused by LPS (Wang et al. 2018; Suresh et al. 2020).

Terpenes: Terpenes are hydrocarbons that belong to a comprehensive broad family of natural compounds that include primary and secondary metabolites biosynthesized metaphorically from five-carbon isoprene units. Also, auxarthonoside, which consider a novel triterpene glycoside with a rare sugar moiety in nature, it has been discovered in the marine sponge-derived fungus *Auxarthron reticulatum* (Jiang et al. 2019; Núñez- Pons et al. 2020).

Terpenes are one of the most researched classes of molecules found in natural products. In addition to Terpenoids derivatives terpenes (MOU1). Depending on how many isoprene units they produce, they have sometimes named isoprenoids, also known as hemi-, mono-, etc. Antiviral, antibacterial, anticancer and anti-inflammatory activity are among the properties of marine diterpenoids, a diverse and promising class of terpenes (Ciaglia et al. 2017). Sesquiterpenoids have the molecular formula C15H24 and are made up of three isoprene units. They can be acyclic or contain rings, and they appear in several different configurations. Due to a longer chain and an extra binary link in sesquiterpene precursors, cyclic sesquiterpenes are more common than cyclic monoterpenes. Monoterpenes are made up of two isoprene units formed by a single condensation process (Avila et al. 2020). Red algae that live in the shallow waters of the polar regions produce polyhalogenated monoterpenes. These multi-faceted metabolites are frequently found in high concentrations and can be linear or cyclic in most common assumptions. They serve as a defense mechanism herbivory and providing resistance to fouling species. These compounds could also be used offensively, providing producers with allelopathic competitive advantages while harming potential competitors for space and resources (Núñez- Pons et al. 2020).

Antimicrobial activity of metabolites extracted from marine Actinomycetes: The increase in health problems worldwide has increased the demand for treatments that could rapidly solve these problems. Conventional treatments are an undesirable choice due to cytotoxicity, side effects, the long-term effect of use. There has been a new shift for researchers to focus on natural resources to discover biologically active molecules that deem effective and safer for human use. Actinomycetes are a natural mine for many new secondary metabolites of new chemical compounds. They are found in many aquatic environments, including marine sediments and coral reefs (Xu et al. 2014; Avila et al. 2020).

Marine environments and swampy areas have become a crucial source in discovering novel bioactive natural products and biological variety. Consequently, as the use of therapeutic novel compounds increases, researchers started exploring oceans for bioactive compounds (Jadon et al. 2014). Currently, the antibiotic resistance is considered one of the largest public health issues to worldwide; therefore, the development and designing of unique antimicrobial is tremendously subject to the exploration of novel natural products (Jakubiec-Krzesniak et al. 2018; Avila et al. 2020).

Resistance to existing drugs is constantly being reported from all over the world. It creates a significant demand for the identification of new drug molecules that target these resistant pathogens. Actinomycetes have proven their ability to produce novel secondary metabolites with a pent anti-bacterial activity against these drug-resistant pathogens (Ravi and Kannabiran 2018). Despite that, Biosynthetic gene clusters (BGCs) play a crucial role in producing microbial natural products through utilizing metabolic pathways encoded by adjacent chromosomal genes. Furthermore, essential proteins and transporters for produce a metabolite are regulated by encoding the responsible enzymes by BGCs (Jakubiec-Krzesniak et al. 2018; Núñez- Pons et al. 2020).

Antitumor compounds: Chemotherapy is one of the most treatments to fight cancer. Natural products or their derivatives, primarily microorganism products, constitute a considerable number of antitumor compounds. Actinomycetes, mainly are derivatives of many natural products with various biological activities (Olano et al. 2009). Antitumor antibiotics, antibiotics include anthracycline and actinomycin, are among the foremost effective cancer chemotherapeutic agents. Also, Actinobacteria are consider rich of natural products bioactive that proved scientifically in Ontario Institute for Cancer Research (OICR) Drug Discovery as effective. Considerable amount of the marine antitumor compounds is derived from metabolites of the marine Actinobacteria (Degirmenci et al. 2020).

The signaling pathway with potent antineoplastic activity (RRME: a series of amino acids inside the cell that carries an indication assisted by the cell's surface receptor towards DNA within the nucleus of the cells). RRME pathway components were discovered in cancer cells (Liu et al. 1989). Drugs that reverse the 'on' or 'off' function are being tested as cancer therapies. Diazepinomicin binds and performs RAS kinase inhibition, thus preventing protein phosphorylation and activation downstream of the RAS signal transduction pathway (Abdelmohsen et al. 2012). This agent binds to a highly expressed receptor in the cells of some tumor cell types known as peripheral benzodiazepine receptor (PBR) triggering cell cycle arrest and apoptosis in

cells that express PBR. The barrier (BBB) may be crossed by Diazepinomicin (Degirmenci et al. 2020).

Diazepinomicin has also demonstrated antioxidant and antiparasitic activity against Trypanosoma with an IC_{50} of 70–90 mM (Hassan et al. 2017). Furan 2-ylacetate, a cytotoxic secondary metabolite formed by marine Streptomyces sp., and rhodomycin B, a cytotoxic secondary metabolite produced by Streptomyces purpurascens, has been documented by Suthindhiran and Kannabiran (F2A has demonstrated cytotoxic activity against different cancer cells). Anticancer activity against the HeLa cell, Streptomyces sp. KS190, KS190 was have anticancer effect on Hep2, HeLa, HL-60, and MCF7 (Ravi and Kannabiran 2018; Degirmenci et al. 2020).

Anti-inflammatory compounds: Actinomycetes secondary bioactive metabolites, including ozenoxacin is a powerful anti-microbial agent that is essential versus sensitive and Gram-positive-resistance strains (i.e., Staphylococci and Streptococci). Also, ozenoxacin exhibits efficacy against certain Gram-negative isolates (Morrissey et al. 2019; Tabara et al. 2020). Nevertheless, ozenoxacin'a anti-inflammatory properties have not been fully investigated. Taking together that anti-inflammatory effects of ozenoxacin were studied both *In vitro* and in vivo. Inhibitory effects of ozenoxacin were proved to inhibit the releasing of interleukin (IL)-6 and IL-8 that induced by *Cutibacterium acnes*. That result on ozenoxacin recognition as a potential therapeutic agent on inflammatory acne. Actinomycetes are widely distributed in marine living organisms. They produce 80% of known antibiotics and exhibit numerous bioactivities in their other metabolites such as anti-inflammatory, and anticancer activities (Tabara et al. 2020).

Antiviral compounds: Viruses are organisms that are associated with disease in living organisms such as animals and plants. Recently, viruses frequently show their roles in the world's ocean (Bhatnagar et al. 2010). They comprise a huge portion of microorganisms inducing diverse infectious diseases. The presence of various viral diseases, such as human immunodeficiency virus (HIV) and viral hepatitis encourage the development of new immense efficacy therapeutic agents. Carboxyl has proven to inhibit virus replication in critical cells such as cells expressing CD4 receptor. Furthermore, carboxyl polyethers have pivotal role in fighting both acute and chronic infections (Kevin et al. 2009; Hassan et al. 2017; Tabara et al. 2020).

Antibacterial compounds: The major cause of turbidity and mortality around the world is the bacterial infections. To overcome such a challenge, the antibiotic-resistance bacterium has been generated very expeditiously, resulting in causing severe problems while both Staphylococcus aureus and other pathogens are mainly associated with infection (Hassan et al. 2017). According to World Health Organization (WHO) statistics, about 50,000 lives got lost every year in the USA and Europe due to antibiotic-resistance. The current developed antimicrobial agents cannot sufficiently address the Grams-negative bacteria's problem of large resistance (Tabara et al. 2020).

21 Actinomycetes are isolated from the sediment Caspian Sea sediment; 14 stains showed antibacterial activities against multidrug-resistance (MDR) indicator bacteria. According to the isolated Actinomycetes, they can produce bioactive compounds that can inhibit the growth of Methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant Enterococci (VRE), and the *P. Aeruginosa*, which have more than MDR bacteria (Norouzi et al. 2018). From the marine soil Actinomycetes, the first two bagremycins A and B, were extracted have showed antimicrobial activity against both *Arthrobacter aurescens* and *Streptomyces viridochomogenes* (Zhang et al. 2018; Tabara et al. 2020).

Another antimicrobial potential substance is the buanmycin which is isolated from the Streptomyces strain from a tidal mudflat in Busan, Korea. It is a new pentacyclic xanthone. However, buanmycin doesn't only show strong effect on inhibiting Gram-positive *S. aureus, B. subtilis, K. rhizophila*. And Gram-negative bacteria *Salmonella enterica*, and *P. hauseri*. It can also inhibit *S. aureus* sortase A enzyme; this enzyme can play an essential role in facilitating Gram-positive bacteria adhesion to the host (Jakubiec-Krzesniak et al. 2018). Moreover, *Streptomyces* sp. strain Al-Dabhi 90 from Saudi Arabian marine exhibited an important antimicrobial activity against the drug resistant pathogens such as *Klebsiella pneumonia, S. aureus, E. coli, Pseudomonas aeruginosa, Enterococcus faecium*, and *Proteus mirabilis*. From Andaman and Nicobar Islands soil, 12 Actinomycetes were isolated depending on different morphological appearances. All of the isolates are subjected to antibacterial activity, and among the 12 isolates *Streptomyces* sp. Strain VITAK1 showed an antibacterial activity (Mani et al. 2021).

Novel metabolites produced by marine Actinomycetes: During the last two decades, scientific studies of marine microbes and their ability to produce vital metabolites were tremendously increased. Many bioactive compounds have been derived from Actinomycetes, representing the largest diversity of populations of the identified species. 45% of the bioactive microbial metabolites are produced by Actinomycetes, and Streptomyces are the most important sources of secondary metabolites of higher clinical importance, producing 70% of the antibiotics (Khadayat et al. 2020). Tanking together that more than 20,000 bioactive compounds have been obtained from microorganisms (Subramani et al. 2013). Many essential drugs such as rapamycin belongs to immunosuppressive group, while mitomycin, and leomycin belongs to the anticancer drugs and antimicrobial drugs as medications of that are vancomycin and erythromycin. The increasing demand for antibiotics proves their effectiveness in fighting important bacterial pathogens (Tommasi et al. 2015). For this purpose, researchers have become oriented towards discovering new discovering and focus on natural products from underexplored habitats, especially in marine environments that contain rare genera of Actinomycetes (Subramani et al. 2013; Jackson et al. 2018; Safaei et al. 2021).

Actinomycetes have demonstrated their tremendous ability to produce new secondary or therapeutic metabolites,

including antibiotics, anticancer, growth factors, enzymes, and herbicides (Luzhetskyy et al. 2007). This confirms that Actinomycetes remain a promising source for drug discovery. A recent literature review survey done by Subramani and Sipkema (2019) showed that 167 new biological compounds were obtained from 58 different Actinomycetes species. Most of these compounds provided a diverse antimicrobial activity. *Nocardiopsis, Micromonospora, Salinispora* and *Pseudonocardia* are the largest genera from which compounds were extracted. The genus Micromonospora exhibited unique and chemically diverse bioactive compounds. Safaei et al. (2021) carried out a study on freshwater snail Physa acuta and discovered novel Streptomyces species (Subramani and Sipkema 2019; Safaei et al. 2021).

The antimicrobial activity was isolated, and then the extracts were tested against bacteria and fungi, where 7NS3 represented a new species of Streptomyces and was given the name Streptomyces sp. DSM 110735 at the Leibniz Institute-German Collection of Microorganisms and Cell Cultures (DSMZ). Al-Dhabi et al. (2019) studied Actinomycetes in the Persian Gulf regions and found marine Streptomyces sp. Al-Dhabi-90 had a good biological action (anti-bacterial) against clinical pathogens and a MDR (Al-Dhabi et al. 2019). In another field, Streptomyces isolates were tested against dermatophytes fungi, found that Streptomyces sp. ACT2 (GQ478247) achieved high efficiency anti-dermatophytid, and it is an essential source of bioactive compounds listed four novels bioactive obtained from marine Streptomyces sp. shell-016. They showed activity against different lines of cancer cells lines (Shamikh et al. 2020; Suresh et al. 2020; Han et al. 2020).

CONCLUSION

The findings of the present study has found that recent studies have moved from discovering bioactive molecules, specifically Actinomycetes in the soil, to new marine environments that sound like large extensive compounds awaiting discovery. Improving strategies of bioactivity-guided, cultivation variation centered and metabolome- and genome-based approaches for identifying and isolating bioactive molecules form the basis for the characterization of novel compounds from Actinobacteria. Likewise, approaches to genome sequencing, bioinformatics, and the partnership of molecular genetics that lead to an understanding of the principles of biogenesis should be developed to produce new secondary metabolites of practical value.

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