

Review Article

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Decade of synthetic and natural sources of medicine emphasis on Actinobacteria and its anti-microbial properties - Review

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Abstract

Microorganisms have always shown great importance in several aspects of human life. Whether it is in the case of infectious diseases or when a suitable antidote is needed during a serious pandemic. Several measures and studies have been carried out so far to meet the drastic depletion of natural sources of treatments. Bacteria have developed numerous anti-phage systems in response to the ongoing danger posed by viruses. Over the years a remarkable variety of molecular mechanisms have been identified though little is understood about their ecological functions in naturally occurring microbial communities. Medicines and modes of various approaches towards betterment and industrial values have been quite of interest. Present evolving microorganisms have raised serious issues for the modified more effective methods and ways to resolve the upcoming days of unpredictable consequences of manly and natural origin. Actinobacteria have shown light on a very effective class of secondary metabolite-producing sources. It has been found to have a wide range of novel products that can prove to be a boon to living beings. The Actinobacteria from marine sources have been found to be far more beneficial in the long run as they are preserved in such highly stressed conditions of temperature, pressure, and salinity gradient. Most of the antibiotic-producing organisms have been found in this class.

Keywords

Marine,
actinobacteria,
secondary
metabolites,
antiviral,
antibiotics.

Introduction

Diversity is the hallmark of all life forms that inhabit the soil, air and water. All these habitats pose their unique inherent challenges which helps breed the “fittest” creatures. Similarly, the biodiversity from the marine ecosystem has evolved unique properties due to challenging environments. These challenges include permafrost regions to hydrothermal vents, oceanic trenches to abyssal plains, fluctuating saline conditions, pH, temperature, light, atmospheric pressure, and the availability of nutrients (Ward & Bora, 2006). Actinobacteria have been isolated from the huge area of marine organisms including sponges, tunicates, corals, molluscs, crabs, mangroves and seaweeds (Gunjal & Bhagat, 2022). The marine environment where Actinobacteria need to adapt extreme conditions like high atmospheric pressure (with a maximum of ~1100 atmospheres), temperature from 0°C in deep sea floor to 100°C near hydrothermal vents and high acidic condition (Abuhijleh *et al.*, 2021). It may be reflected in genetic and metabolic diversity of marine Actinobacteria (Manivasagan *et al.*, 2013). This makes marine derived compounds as special ones to investigate. Low molecular compounds, the bioactive molecule show various activities that can be used as natural medicines. One of the significant global health concerns include the antiviral resistance caused by influenza virus which has been an issue of global concern thrice as a pandemic in the twentieth century can be a threat again in the future (Smyk, J.M. *et al.*, 2022) (Ramesh *et al.*, 2023). Current and future outbreaks of new influenza virus are and will be more severe than the preceding epidemic outbreaks due to frequent antigenic changes. NA antigen sequence and the viral hemagglutinin (HA) changes by a single amino acid led to antigenic drift which increases the virulence of viruses along with the infectious rate and their parallel (same species) and perpendicular (other species) spread thereby evading the host's immunity.

Genetic reassortment events produce variety of variations that exacerbates the threat. Viral pathogens propagate systematically through the tracheobronchial tree's transmissible aerosols, which ultimately impact the respiratory tract, making lower respiratory infection the deadliest communicable disease. (Yi *et al.*, 2020) Since the creation of efficient vaccines and antiviral medications is time consuming and challenging, viral illnesses are far more difficult to prevent and treat than fungal and bacterial infections. The emerging three viral illnesses in India include respiratory, arboviral and bat borne (Maurya *et al.*, 2019) In present day of newer and faster emergence of infections and resistance towards the medicines there is indeed need for development of antibiotics that can prove to be a better answer to the microworld the actinobacteria present in the mangrove areas have been promising field if study because the Actinobacteria present in mangrove ecosystems with their particular combination of terrestrial and marine influences, have been shown to harbour a wealth of "rare" Actinobacteria that have the potential to produce novel secondary metabolites with potent biological activities, such as compounds that are antifungal, anticancer, and antibiotics (Xu *et al.*, 2014) (Azman *et al.*, 2015). Chemical synthesis has produced nearly all present approved antiviral medications but natural sources have aided more in the creation of antiviral medications offering insights valuable for the synthesis of chemical compounds. (Anestopoulos *et al.*, 2020). The cellular machinery of the hosts used by the viruses to spread as its interaction is known already. The diversity of the natural goods is very high so is their structural complexity. In order to create antiviral medications from the natural compounds the target involving the host and the viral proteins for viral replication should be known (Surya *et al.*, 2016)

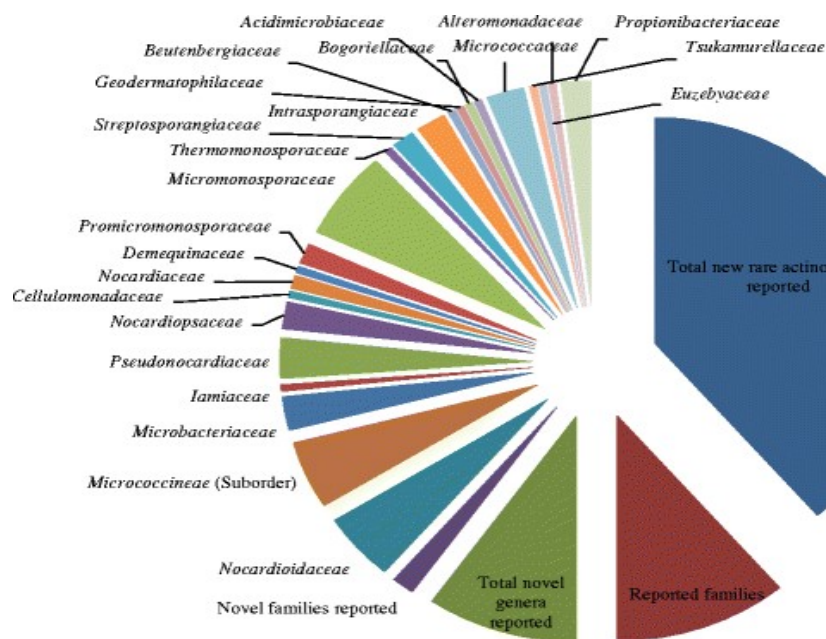


Fig.1 Alternative sources of antibiotics other than conventional treatment are necessary to address the rising growth of multi resistant diseases (Quinn *et al.*, 2020)

Significance of Actinobacteria over virus

Bacteria in general is found to have a certain feature of its own whether be the self defense mechanism or the responses that they give to the external environment where they are to survive. They may have even some compounds that they produce which can be used by humans for various purposes. The main light is shown on the secondary metabolites that can prove to be highly beneficial in various fields like antibiotics, pesticides and other industrially important products. Actinobacteria when compared have greater affinity towards several infections and other potentially active microorganisms as shown in Fig.1. The secondary metabolites from Actinobacteria are being used in the fields of pharmaceuticals, cosmetics, pesticides, enzymes, some of which even has anti cancerous and anti-tumor activities. In the viral research field, leupeptin an inhibitor of *Streptomyces roseus*'s cysteine and serine proteases prevent the entry of Marburg virus through the glycoprotein suggesting unidentified play of host proteins as a part of glycoprotein activation. Cysteine, serine proteases inhibited by antipain and elastatinal from Actinomycetes were used to inhibit Polio 2A protease.

Another significant contribution was the in the discovery of crucial class of anti-HIV drugs that are highly active in antiretroviral therapy aided by pepstatin an aspartic proteinase inhibitor isolated from several *Streptomyces* species (Takizawa, N., Yamasaki, M. 2017). The discovery of antiviral compounds from marine actinomycete is a promising avenue for the development of new therapeutic agents. Actinomycetes derived compounds such as Musacin C, Cyclomarin A, Fattiviracin A1, FK 506, Antimycin, MM461156, Resistomycin and Benzastatin C have shown potential against various viruses including VZV(Varicella Zoster Virus), HIV(Human Immunodeficiency Virus), HSV-1(Herpes Simplex Virus type 1), White Spot Syndrome virus in shrimp, Hepatitis C, Western Equine Encephalitis virus and Orthopox viruses. The antiviral mechanisms of the compounds go like the inactivation of the viral particles neutralizing the ability to infect the host cell by binding to the viral protein or altering the viral structure rendering it non-infectious. Some compounds prevent the virus entry to host cell by blocking critical receptors or pathways necessary for viral entry which halts the infection process before its process begins. The compounds disrupt the

process of relying onto the host cell machinery for its replication, inhibiting the synthesis of viral proteins or genetic material limiting the spread of virus within the host.

The potential of these drug leads light to the importance of marine actinomycetes as source of antiviral therapies. Isolation of additional metabolites, mechanistic investigations, structure activity relationship(SAR) studies is essential for understanding the efficacy, potential for clinical applications and safety is to be further considered in the continued research.

Recent developments in marine Actinobacterial compounds

Even though many microbial sources producing therapeutic valued product, Actinobacteria gain a special importance, as they are already proven for its antagonistic ability. It has been estimated that approximately one-third of the thousands of naturally occurring antibiotics have been obtained from Actinobacteria are playing a major role in global pharmaceutical industries against the rise of drug-resistant bacteria due to inappropriate usage of antibiotics (Sunil *et al.*, 2012). It increases the demand for new antibiotics, thus the research for the novel antimicrobial compounds is extensive. Recently many researchers started to investigate the marine organisms for bioactive compounds Natural products investigation from the marine actinobacteria revealed that they can synthesize numerous natural products including alkaloids, polyketides, peptides, isoprenoids, phenazines, sterols, and others.(Barka *et al.*, 2016)These compounds are highly different compared with terrestrial compounds in physio-chemical and stability aspects. These natural products have a potential to provide future drugs against crucial pathogens like medically important superbugs (MRSA, VRSA, ESBL and NDM1), cancer, protozoal infections and lethal viruses. Notably, Streptomyces were highly targeted because of its ability to produce more than 80% of the antimicrobials with variety of chemical diversities (Mayer *et al.*, 2024). Streptomyces a potent genus produces about 75% of the commercially and medically useful antibiotics.

The remarkable ability of genus streptomyces to produce a diverse array of secondary metabolites, which possess potent biological activities with significant applications in various fields, including medicine, agriculture, and biotechnology (Passari *et al.*, 2018).

The exploration of marine microbial compounds has opened new avenues in drug development due to their unique biosynthetic pathways (Ezeobiora *et al.*, 2022). A significant potential of marine organisms in clinical setting is exemplified by Marizomib an optimised derivative of actinobacterial compound Salinosporamide A (Feling *et al.*, 2003).Progression through clinical trials highlights the increasing interest in marine derived compounds as therapeutic agents. Saxitoxin and it related congeners derived from marine dinoflagellates, are efficient as potent nerve-blocking pain medications. These have strong pharmacological activities that offer promising alternatives for pain management (Dai *et al.*, 2024).Though majority of the microbial drugs have been emerged from the terrestrial species, the distinct chemical scaffolds and action mechanisms identified in marine microbes exhibit valuable reservoir for novel therapeutic agents as reported by Harvey *et al.*, 2015. In the studies as indicated by Harrison *et al.*, 2016 and Lobo *et al.*, 2015 the marine natural product significantly contributes to addressing unmet medical needs in the fields such as oncology and pain management. These unique properties of the compounds need continued exploration in marine pharmacology to uncover their full therapeutic potential.

Research conducted by (Mayer *et al.*, 2024) highlighted the significant therapeutic potential of the marine compounds focusing on their antibacterial and antiviral properties. In the realm of tuberculosis treatment, Fucoxanthin a marine brown algae carotenoid was found to be bacteriostatic against the Mycobacterium tuberculosis strains it operates through the potent and competitive binding of critical enzyme involving UDP-galactopyranose mutase and arylamine-N-acetyltransferase in the cell-wall biosynthesis which can be a promising avenue for tuberculosis therapy. The period from 2019 to

2021 have shown the publications of five notable antiviral studies that feature marine derived compounds which demonstrate diverse action mechanisms against viruses including hepatitis C virus (HCV), HIV-1, Zika virus, eastern and Venezuelan equine encephalitis viruses. A new phenylspirodimane-type dimer alkaloid isolated from marine sponge derived *Stachybotrys chartarum* inhibit Zika virus (MR766 strain) by influencing the in vitro accumulation of viral proteins NS5 and E in a dose-dependent manner.

The research done by Kim *et al.*, 2019 focused on the secondary bioactive metabolites from marine derived actinomycetes *Streptomyces* sp. MBTG13 strain which demonstrated weak antibacterial properties against *Salmonella enterica* and *Staphylococcus aureus* lead to isolation of 2-alkyl-4-hydroxyquinoline derivatives exhibiting unique ability to inhibit filamentous growth of dimorphic fungus *Candida albicans* marking novel discovery marking a way to understand its effect on fungal morphogenesis. The study evidence of the two compounds shows the effective inhibition of the filament formation and cell adhesion is regulated through gene expression including HWP1, TEC1, ALS1, IFD6 and CSH1. These highlights the potential of the compounds against candidiasis suggesting substantial efficacy in combating the pathogenicity of *C. albicans*. Novel sesquiterpene analogues identified as Harzianoic acids A and B derived from *Trichoderma harzianum* inhibit the life cycle of HCV by binding to the glycoprotein CD81, indicating them as HCV inhibitors. A polyketide Homoseongomycin from marine *Actinomycete* K3-1 demonstrated potent inhibitory effect on eastern and Venezuelan equine encephalitis viruses, while exhibiting low toxicity and impacting both the budding and assembly stages of the viral life cycles.

Actinobacterial plasmids as vectors

Covalently closed circular (CCC)-DNA was abundantly found than linear elements in large number of *Streptomyces* sp. Late 1990's, a great interest among the scientist was found to unveil the genetic significance by their small or gigantic plasmids. To date, several investigations on

various species of actinomycetes, especially on *Streptomyces* in translation process for the production of quite a lot economically important compounds like antibiotics has been done. Conversely, the studies revealed the genetic information for antibiotic production exist generally on chromosomes.

A study conducted using the marine sediments collected from various parts of South India by Ponmurugan *et al.*, 2008 has exposed the presence of CCC-DNA in all the *Streptomyces sannanensis* strains. Out of 4 strains investigated, KN-2 and KL-3 enclosed two plasmids, whereas AP-1 and TN-4 had only one plasmid. In another investigation carried by Nithya *et al.*, 2012) in two different geographical topography viz Manakudi mangrove forest and Yercard hills, Tamil Nadu exhibited the presence of similar plasmid DNA profile ranging between 60 and 15.2 MDa .

Actinobacteria as host cell for recombinant product production

In early ages of recombinant protein production, *E. coli*, *Bacillus* spp. and *Lactobacillus lactis* was used as host cell to produce the chimeric proteins into the culture media. Later, few fungal species were also used as host cell for the production recombinant protein in order to overcome the issues related to failure of eukaryotic protein folding process in prokaryotic host cells. Recently, few actinobacterial strains viz *Streptomyces*, *Rhodococcus*, *Corynebacterium* and *Mycobacterium* are gaining significance to be host cell for chimeric protein production. The actinobacteria has some advantages over other microbial cell factories as they have unique metabolic diversity and enzymatic potential which may influence the protein synthesis. Also, the intracellular environment of actinobacteria is different from other regular microbial hosts such as *E. coli*, *Bacillus* spp, etc.,

Streptomyces lividans, an Actinobacteria with two important features which facilitate the production recombinant products. Firstly, it has no restriction system which allows effortless gene manipulation

and secondly the cytoplasm has less proteolytic activity which ensure the safety of produced recombinant protein until it gets extracted. The psychotropic ability of another Actinobacteria, *Rhodococcus* which made it as a successful host for the production of temperature sensitive protein. Also, *Corynebacterium glutamicum* was already in the mainstream for the industrial production of L-glutamate.

Rare Marine Actinobacterial Community

The unmapped and under explored environments such as marine, deep sea, and hallow bodies were recognized as rich source for rare actinobacterial community with incredible potent to synthesis novel metabolites. Unlike other sample collections, much efforts are needed to collect deep-sea sediments. Modern sampling practices using advanced equipment, remotely operated underwater vehicle (ROV), and human can provide the access to explore the rare actinomycetes from the marine environment. However, culturing and screening of microbes using the samples collected from such environments are typically difficult due to distinct physical and nutrient requirement or unknown culture conditions. Microorganisms have several competitive intra and inter specific peptides of 20-40 amino acids that have the ability to quickly inhibit and kill broad variety of different bacteria. These amino acids bind to particular target and alter the structure or the functionality of the cell walls of the microorganisms (Boris *et al.*, 2019)

Actinobacteria as bioremediating agent in marine environment

One of the major crises in marine environment is accidental release of hydrocarbons including petroleum and petroleum derived products. These hydrocarbons are known as carcinogenic and neurotoxin since 1940's. Half a decade since 1940, Claude E. ZoBell pulled the attention of research people through his work on application of microbes as a mediate to utilize the hydrocarbons as nutrient and regain the ecology in marine environment. Starting from ZoBell, various research communities around the world

started to focus on discovery of efficient microbial genera to utilize the hydrocarbons. The efficient degradation of hydrocarbons varied in a broad way between 0.003% (soil bacteria) to 100% (marine bacteria). Advancement of genetic engineering, aided the research people to develop a genetically modified microbe for bioremediation, which is trusted for effective clean-up at reduced cost.

In the recent decades, actinobacterial genera got into interest which can enhance the cell surface hydrophobicity serving increased biofilm formation and utilize the lipophilic compounds into it. A study on marine actinomycete *Rhodococcus* sp isolated from inveterately oil polluted region near Bombay has shown to better degradation of hydrocarbons. *Gordonia amicalis* isolated from diesel contaminated marine environment were capable to produce surface active compounds. These surface-active compounds could be associated to biodegradation of hydrophobic compounds spilled over the marine system.

Synthetic actinobacterial antibiotics

More than 40% of antibiotics exhibit in the present era were produced using terrestrial and marine actinomycetes microbes, expressly from *Streptomyces* species. In recent years, researchers have proved that marine actinomycetes were potent resource for the uncovering new natural products. Actinobacteria can be engaged to produce higher quantities of natural products with the aid of advanced metabolic engineering. Such studies could support in stepping down the energy usage, waste emission during the large-scale production. Despite the fact, inadequate data regarding the metabolic profiles on targeted synthetic pathways create quite difficulties.

Two marine actinomycetes producing Thiocoraline antitumor compound belonging to *Micromonospora* sp. isolated from coast of Mozambique were decoded to unveil their biosynthetic pathway for the production of the respective compound. And their heterologous expression in *Streptomyces albus* and

Streptomyces lividans comprises of more non ribosomal peptide synthetase (NRPS) sequence. NRPS modules such as TioR and TioS may constitute as backbone for Thiocoraline synthesis. Also, two other NRPS modules TioY and TioZ could involve in the biosynthesis of further small peptide molecules required in the regulation of Thiocoraline synthesis in *Micromonospora* sp. ML1. Similar studies on sequencing the rare marine *Actinomycetes* sp producing potential bioactive compounds revealing the biosynthetic gene clusters (BGC) could support to overcome the scarce in data supporting the metabolic profile in producing synthetic actinobacterial antibiotic compounds. According to a study done by Hirota-Takahata *et al.*, Vestaines A1 and B1 produced from *Streptomyces* sp. SANK 63697, have antipermeability and pro-angiogenic properties. These substances seem to have important effects on the controlling of the integrity of blood vessels and angiogenesis, indicating possible therapeutic uses involving disorders of blood vessel creation.

As noted by Nakashima *et al.* 2017, the compounds Trehangelins, Mangromicins, Nanaomycins F&G, Iminimycins A&B and Sagamilactam, isolated from different actinobacteria species like *Streptomyces* and *Lechevaleria aerocolonigenes* have important biological activities, such as antibiotic capabilities, antioxidant qualities, antitrypanosomal effects and photo oxidative inhibition. As reported by Yixizhuoma *et al.* in 2017, angucycline derivatives derived from *Streptomyces* sp. IFM 11490 have been found as a potential antitumor agent. These compounds exhibit significant cytotoxic activity against tumor cells highlighting them as a major source of naturally available product in the treatment of cancer. Though further research is needed to understand their mechanism of action and efficacy in clinical purposes. Another product Elaiophylin derived from *Streptomyces hygroscopicus* ACTMS-9H showed potential against cancer which is being explored for their various cancer therapeutic properties highlighted in the study by Lima *et al.*, 2017. *Streptomyces* sp. SUE01 produces Granaticins an antibiotic known

for their efficacy against various microorganisms is detailed in the study by Vela Guroic and Olivera in 2017 for its rich diversity of secondary metabolites. Ahsan *et al.*, has reported in 2017 that Eicosane and dibutyl phthalate derived from the *Streptomyces* KX852460 have been recognized for their antifungal properties. The study highlights the potential of these compounds in developing natural antifungal agents contributing to better understanding of microbial metabolites in fighting against fungal infections.

Another compound 1,19-bis(-hydroxyazetidin-1-yl) nonadeca- 5 14-diene-1,8,12,19-tetrone, derived from *Streptomyces roche* M32, has been identified for its cytotoxic activity offering implications in drug development for cancer as reported by Pazhanimurugan *et al.* in 2016. *Pseudonocardia endophytica* (VUK) derived compound N-(4-aminocyclooctyl)-3,3-(1H-indol-6-yl)methyl hexahydropyrrolo(1,2-a)pyrazine-1,4-dione has shown promising anticancer and antimicrobial activities that indicate its potential in development of therapeutic agents against infections as reported by Mangamuri *et al.*, in 2016. Naphthalenepropanoic acid a compound produced by *Micromonospora* sp. HS-HM-36, has been studied for its significance in microbial secondary metabolite research for its antitumor and antibacterial properties as noted by Gao *et al.*, in 2016. Khalil *et al.*, in 2015 has reported that Aranciamycin produced by *Streptomyces* sp. CBM-M0150 demonstrated potential in combating microbial infection offering promising avenue as agents against various antibacterial resistant strains.

Actinobacterial metagenomics

Metagenomics is a study of microbial community where it can uncover the potential of several microbial species by retrieving its nucleic acid sequence and without culturing in an optimized laboratory condition. One of the largest and productive environments for the microbes in the present biosphere is the ocean. Aquatic (ocean) ecosystem is a heterologous habitat and frequently affected by the varying environmental

conditions at every water column. Metagenomics studies from ocean environment reveals the presence of actinobacterial community in those locations. Studies reveals that the aquatic actinobacteria possess low GC content (40-50%) than soil actinobacteria in their genomic DNA.

Stromatolites from Shark Bay, Australia validate the ubiquity of actinobacteria in the oceanic environment. Studies to understand the microbial community on these living fossils provided a poor data and comprehended as being cyanobacteria. Molecular characterization of three sediments revealed three different mat communities with high range of diversity and low abundance of actinobacterial community. A study discovered a novel heterotrophic actinobacterial community Rhodopsin and it is assessed that, it occupies almost 4% of the total cells studied in the Mediterranean, tropical and temperate zone. It also assigned a new microbial subclass *Candidatus actinomarinidae*. The work correspondingly suggests the genome reconstruction coupled with single cell genomics to the recovery in pure culture representatives may resolve the present technical hitches and could provide a better understanding on involvement of microbes in global carbon cycle. Certain *Streptomyces* species have genome sized up to 12Mb, the production of specialized metabolites takes up 0.8-3Mb of their entire actinomycete genome resulting in 20-50 Biosynthetic Gene Clusters(BGC) per strain.

Symbiotic relationship of Actinobacteria in Marine Environment

Marine sponges are the primogenital multicellular organisms and evolving as a better source for secondary metabolite producing creature from marine environment. Scientific reports evident the evolutionary symbiotic relationship between the marine sponges and several bacterial communities in the form of mutualistic and parasitic. Symbiotic bacteria associated with marine sponges may assist as food source or as disease causing agent. But some articles show the symbiotic association between the antibiotic producing actinobacteria, which may protect them from several diseases. With regards to microbiota, marine sponges are

classified into high and low microbial abundance sponges. Interesting evidence was, actinobacteria together with *Streptomyces* sp. associate with both the marine sponge category.

A study on *Haliclona* sp isolated from coastal water of Japan provided the evidence of 162 actinobacterial strains (of which nearly 81% strains belonging to *Streptomyces* sp.). The current study screened 6 phylogenetically novel strains producing secondary metabolites and quite a lot NRPS (Non-Ribosomal Peptide Synthetase) generated antibiotics fitting into the familiar class of antibiotics. JBIR-43 compound exhibited an excellent cytotoxic activity and JBIR 34, 35 reported as interesting compounds due to its unique chemical structure. A similar study on *Haliclona* sp collected from shallow waters of South China sea revealed the presence of 54 actinobacteria.(Yang & Song, 2018) Of which 24 selected isolates taken for 16s rRNA gene studies exposed the genera to which they belong to and majority of isolated belongs to the genus *Streptomyces*. Interestingly PKS-I-PKS-II-NRPS combinations were found in the different isolates of same species indicating their probable of natural product diversity and divergent genetic evolution among the microbes. A study has found the presence of actinobacteria association with 28 recognized marine sponges and several other studies describe the leading association of *Streptomyces* spp and *Mycobacterium* spp with marine sponges.

Future aspects of Actinobacteria

Discovery of novel chemical compounds synthesized by microbial community present in the oceanic environment has become as a thought-provoking clue for the prevailing complications in microbial drug resistance and several other hitches. Predominantly, marine actinomycetes got additional attention due to its great genomic and metabolic diversity. Newer efficient techniques can aid in isolating effective secondary metabolite producing organism and understanding its taxonomic evolution culture independent studies upon the marine environment have exposed the presence and distribution of several rare

actinobacterial community. With the development of in silico technologies, chemical and genetic modification techniques along with understanding the rapidly growing protein structure medications developed from natural sources like Actinobacteria can help eradicate future infectious viral outbreaks. The less availability of specialized antiviral drugs the prospect of facing the threat of emerging and resurfacing of the viral infections is presently confronted. As answer to such rise of antiviral pandemic a broad-spectrum antiviral medication have to be developed and the best available option will be that molecules, synthesized from the Actinobacteria a lead source for several of the biomolecules that are bet natural sources.

Numerous different BGCs were unveiled in 21 unusual marine actinomycetes isolated from sub-tropical and temperate marine environments. Species of *Nocardia* and *Actinomadura* had 38BGCs and 44BGCs per strain which is a considerable feature of actinobacteria (Gohel & Singh, 2012). Remarkably 3% of the BGCs had similarities between unusual actinomycetes and *Streptomyces* strains which indicates promising source for novel biosynthetic innovations. A potential source of novel metabolite analysis suggested the discovery of 24 of 176 BGCs were found in the 119 genomes of rare actinomycete *Salinospora* which were isolated from various sub tropical and tropical regions (Letzel *et al.*, 2017). *Actinomadura* sp. K13-0306 derived Sagamilactam has been studied for its anti-trypanosomal activity combating against trypanosomiasis a disease caused by trypanosoma parasite highlighting *Actinomadura* species as an important source for the discovery of new antimicrobial agents as reported by (Kimura *et al.*, 2016) *Streptomyces griseus* RSH0407 study as highlighted by Huang *et al.*, 2015 has revealed Nonactic acid derivatives has potential applications in cancer research or therapeutic development warranting further investigation into their efficacy and their mechanism of action. 2-Methyl butyl propyl phthalate and Diethyl phthalate from *Streptomyces cheonanensis* VUK-A strain has been investigated and studied for its potential application in developing effective

antimicrobial and cytotoxic therapeutics has been investigated by (Mangamuri *et al.*, 2016).

The benzothioate glycoside compounds Sucheonosides A-D derived from the *Streptomyces* strain SSC21, possess anti diabetic properties according to Shin *et al.* 2015 these offer potential therapeutic properties that benefit for diabetes management through their unique biochemical interactions. (Manimaran *et al.*, 2017) has reported that compound Pyrroo(1,2-A) pyrazine-1,4-dione, hexahydro-3-(2-methylpropyl) demonstrated antibacterial properties. Deferoxamine and pyrrolizidine related compounds derived from *Streptomyces pluripotens* MUSC137 possess potential as therapeutic agents in targeting cancer cells and addressing oxidative stress-related conditions is shown in the study done by Ser *et al.*, 2015. Chromomycin SA and 1-(1H-indol-3-yl) propane-1,2,3-triol derived from *Streptomyces* KML-2 have been identified for its highlighting potential as antitumor agents thereby can be used in cancer treatment research as noted by Aftab *et al.*, in 2015. *Streptomyces* sp. VITJS8 derived sesquiterpenes have shown promising anti-cancer properties which underscores them as natural compounds in cancer treatment is highlighted in the study by (Naine *et al.*, 2016). The compounds Daunomycin, Maltophilin and Cosmomycin derived from *S. carnosus* M-40 and *S. cyaneofuscatus* M-27 exhibit biological activities particularly anti-tumor, anti-inflammatory and anti-fungal properties is highlighted in the study by (Braña *et al.*, 2015). (Khieu *et al.*, 2015) has reported the therapeutic applications of (z)-tridec-7-ene-1,2,13-tricarboxylic acid derived from *Streptomyces* sp. HUST012 for its cytotoxic effects and antimicrobial properties indicating its potential as bioactive compounds.

- **Anthraquinones** from *Micromonospora* spp. Are colourful organic compounds that has notable biological activities that are anthraquinone derivatives and some related polyketides. These hold potential for pharmaceutical, anticancer and antimicrobial therapies also facilitate the drug development

and production. These compounds disrupt replication intercalating into DNA

- **Asterobactine** from *Nocardia asteroides*: is a hydroxamate siderophore that chelates iron depriving cancer cells of nutrients. It is a low molecular weight hydrophilic molecule that binds iron ions to facilitate iron uptake aiding bacterial survival and pathogenicity which helps in the microbial iron acquisition, medicinal chemistry and bioremediation.
- **Borrelidine** from *Streptomyces* spp.: It has a complex heterocyclic structure with indole ring. They are derived from tryptophan pathway that helps in the drug development and helps in understanding cytotoxic effects of the alkaloid inhibiting protein synthesis.
- **IB-00208** from *Actinomadura* spp.: it is a compound that has potential of antimicrobial and anticancer effects.
- **Diazepinomicin** from *Micromonospora* spp.: is an antibiotic that has a unique macrocyclic diazepine structure which has potential immunomodulatory and antitumor effects. It inhibits topoisomerases which block DNA replication.
- **LL-E33288 complex** from *Micromonospora* spp.: is a complex group of macrolide antibiotics with large cyclic ester molecules that inhibit protein synthesis. It has antibacterial and anti-tumor activities.
- **Lomaiviticins** from *Micromonospora* spp.: they are potent antibiotics that induce DNA double strand breakage and generate reactive oxygen species causing cell death. They are complex dimeric anthraquinone derivative attached with sugars. They are highly promising candidates for anticancer and synthetic analogs.
- **Lupinacidins** from *Micromonospora* spp.: are bioactive polyketide metabolites exhibiting antimicrobial and anticancer effects. The complex lactone structures disrupt cell membranes or enzymes interfering with cell division and induce apoptosis.
- **Abyssomycin** derived from the marine *Verrucospora* spp is presumed to interfere with the bacterial DNA or protein synthesis

based on the structural similarities to the other antibiotics.

- **Actinomycins** derived from the *Streptomyces anulatus* bind with the DNA and inhibit the RNA synthesis.
- **Amphotycin** from *Streptomyces canus* is a glycopeptide antibiotic effective in inhibiting the cell wall synthesis.
- **Anthracycline** from *Micromonospora* spp. Are potent antibiotic that intercalate into the DNA disrupting bacterial DNA replication by inhibiting the topoisomerase II.
- **Fluorometabolites** from *Streptomyces cattley* are rare fluorinated compounds involving fluorine substitution in natural products enhancing the biological activity or stability.
- **Aspartocins** are peptide antibiotics from soil derived *Streptomyces canus* mainly target the gram-positive bacteria by disrupting cell wall synthesis or interfering with the essential enzymes.
- **Avermectin** derived from *Streptomyces avermitilis* is known primarily for its antiparasitic activity.
- **Chloramphenicol** derived from *Streptomyces venezuelae* is a broad-spectrum antibiotic that inhibits the bacterial protein synthesis by binding to the 50s ribosomal subunit.
- **Clostromicins** from *Micromonospora* spp. Inhibits bacterial protein synthesis by targeting ribosomes and disrupting membrane integrity of the bacteria.
- **Cycloheximide** derived from *Streptomyces griseus* inhibits protein synthesis in eukaryotes by blocking the ribosomal translational elongation without affecting the prokaryote ribosomes helping studies like cell cycle, apoptosis and protein production.
- **Cycloserine** from *Streptomyces orchidaceus* is an analog of cyclic amino acid D-alanine that target the bacterial cell wall synthesizing enzymes involved in peptidoglycan crosslinking like D-alanine-D-alanine ligase and is used as an antitubercular agent.
- **Daptomycin** produced by *Streptomyces roseosporus* disrupts bacterial cell membrane similar to calcium dependent lipid insertion causing the depolarization thereby cell death.

It is used to treat serious infections such as bacteremia, endocarditis and skin infections.

- **Erythromycin** macrolide antibiotic from *Saccharopolyspora erythraea* works by reversibly binding to bacterial 50s ribosomal subunit which then stop the bacterial growth by inhibiting protein synthesis. It is used to treat respiratory, STDs and skin infections.
- **Gentamycin** produced by the bacterium *Micromonospora purpurea* is an aminoglycoside antibiotic which works by binding to the 30s ribosomal unit irreversibly leading to cell death by misreading of mRNA. It is used to treat severe infections like respiratory infections, urinary infections and septicemia or in combination with other antibiotics.
- **Hygromycin** from *Streptomyces hygroscopicus* is an aminoglycoside antibiotic consisting of hygromycin A and B. It binds to the 30s ribosomal unit inhibiting the protein synthesis in bacteria and eukaryotic cells

misleading mRNA and inhibiting translocation leading to cell death. Used in genetic engineering as selective agent.

- **Kanamycin** produced from *Streptomyces kanamyceticus* is an aminoglycoside antibiotic that binds to the 30s ribosomal subunit that misleads mRNA and inhibits protein synthesis. It is a selective agent in molecular biology and is used to treat bacterial infections.
- **Leucomycin** from *Streptomyces kitasoensis* is a macrolide precursor which inhibits bacterial protein synthesis and is mainly used to treat respiratory infections. intermediate in erythromycin biosynthesis and for research on macrolide pathways.
- **Lincomycin** produced by *Streptomyces lincolnensis* is a lincosamide antibiotic that binds to the 50s ribosomal unit inhibiting protein synthesis. It is effective against infections in penicillin allergic patients and valuable in bacterial mechanism research.

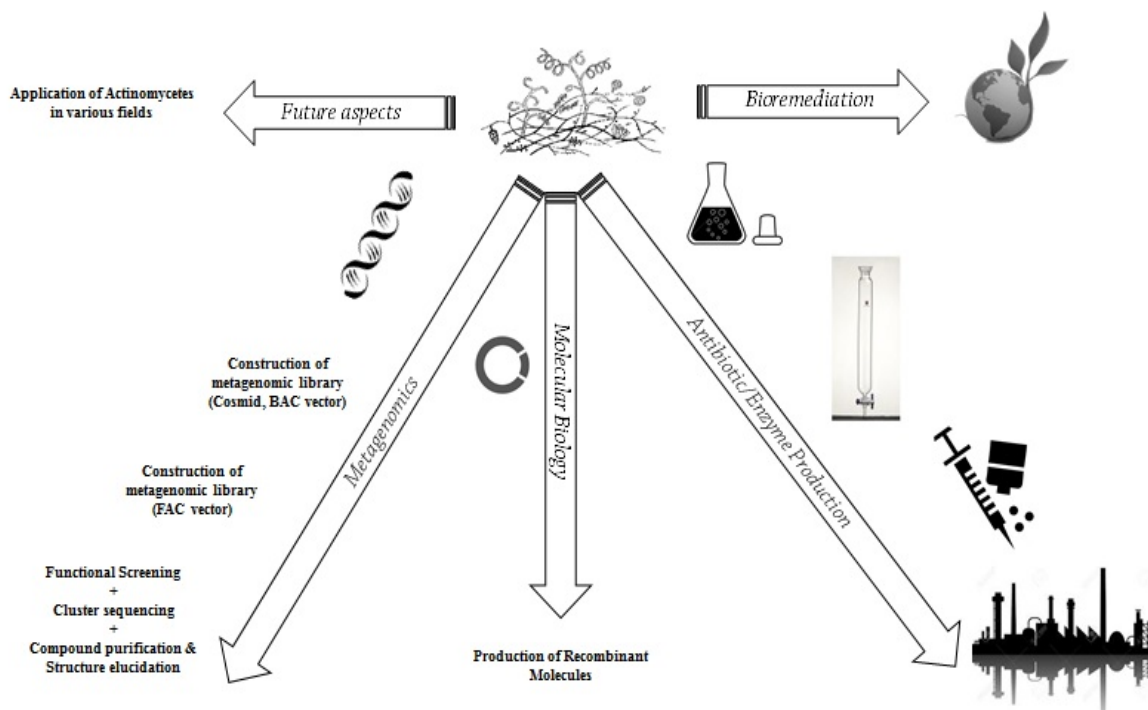


Fig.2 An overview of the possibilities of Actinobacteria in various fields.

Conclusion

Recent research has demonstrated the tremendous metabolic potential of marine Actinobacteria and the diversity of their bioactive secondary metabolites, underscoring the significance of these microbes. These microorganisms have the traits of fungus and bacteria in common (Abuhijleh *et al.*, 2021). Many of the actinomycetes undergo dramatic morphological changes while living as mycelial organisms. They are responsible for more than 45% of the bioactive secondary metabolites production. Because of their significant saprophytic traits, they are able to efficiently breakdown animal and plant waste products through decomposition. (Parmar & Singh, 2018). Actinobacteria of marine origin have greater significance as they have wider and more complex secondary metabolic system. They have found to have wider range of chemical compounds that have industrial or medicinal uses. The exploration of marine derived actinomycetes not only offers a hope in combating viral infections currently posed as healthcare challenges but also enriches the existing drug repertoire (Valan *et al.*, 2012). The uniqueness of these microorganisms could lead to discovery of novel antiviral agents with distinct capabilities in the mechanism of action. The study done on marine actinomycete *Streptomyces kaviengensis* a novel compound Antimycin A was discovered, this compound demonstrated significant anti-viral activity against the Western Equine Encephalitis Virus (WEEV), with half-maximal inhibitory concentrations (IC₅₀) below 4nM and high selectivity index (>550), indicating its safety and potency (Siddharth *et al.*, 2020). Further investigations revealed several analogues of Antimycin A exhibit antiviral properties. The mode of action involves the inhibition of the mitochondrial electron transport chain, which leads to de novo pyrimidine synthesis crucial for viral replication. The compound was found to have broad-spectrum antiviral activity, affecting RNA viruses across multiple families like *Flaviviridae*, *Togaviridae*, *Picornaviridae*, *Paramyxoviridae* and *Bunyaviridae*. The studies on Antimycin A (in vivo) revealed that the compound not only

lowered viral titre in the central nervous system but also improved clinical outcomes and increased survival rates in mice infected with WEEV. These findings underscore the potential source for antiviral drug development from marine derived natural products as a promising target for future therapeutic strategies highlighting mitochondrial electron transport as was reported in the research done by (Raveh *et al.*, 2013)

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Conflict of interest

The authors declare that they have no competing interests.

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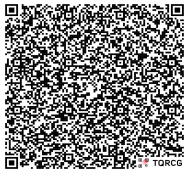
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