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# Update on Bioactive Molecules of Actinomycetes

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**Marine and terrestrial regions are explored from many years and their bioactive compounds are being exploited. As the use of therapeutic novel compounds increases, researchers from all over the world started exploring oceans for bioactive compounds. Actinomycetes, filamentous bacteria have been extensively studied for their therapeutic compounds. They are found to occur in aquatic environments; freshwater and marine habitats. Mostly the marine actinomycetes have attracted a great attention as they have unique metabolic and physiological capabilities. Aquatic habitats enable them to survive in extremes of pressure, salinity and temperature, with the potential production of novel secondary metabolites not observed in actinomycetes, isolated from terrestrial habitats. Secondary metabolites produced from these actinomycetes viz. amino glycosides (streptomycin and kanamycin), ansamycins (rifampicin), anthracyclines (doxorubicin), β- lactam (cephalosporines), macrolides (erythromycin and tetracycline) and many others are considered to be bioactive. The biological diversity of actinomycetes is enormous in nature with diverse chemical compounds. These diverse chemical compounds have been responsible for great biological activities such as antimicrobial, antimalarial, antidiabetic, antitumor, antioxidant, insecticidal, antitubercular etc. Hence there is a scope of developing these bioactive metabolites as a potent therapeutic drug or lead compounds. However, the potential of actinomycetes is correctly studied though the exact wealth of these is unexplored.**

**Key words:** Actinomycetes, Therapeutic, Pharmacological, Biological diversity.

Actinomycetes, filamentous, high G+C content and a gram positive the prokaryotic, bacteria, are the most promising inexpensively important microorganism. This group of microbes is extensively distributed in the natural ecosystem about all over the world. Actinomycetes are chiefly found in terrestrial habitats, but they are widely dispersed in a variety of other habitats also including compost, lake bottoms and river mud[1]. The growth of beneficial and harmful actinobacteria has been facilitated by the both Marine mangroves and Eastern Ghats of Indian ecosystem. Marine environment and swampy areas have become an important source in the field of discovery for novel bioactive natural products and biological variety. They play a very important role in recycling of biomaterials by decomposing complex mixtures of polymers in dead plant, animal and fungal materials. They help in the biodegradation and humus formation by the recycling of nutrients and recalcitrant polymer such as keratin, lignocelluloses and chitin[2]. In soil, they produce a volatile substance like geosmin responsible of the characteristic "wet earthy aroma"[3]. They also exhibit varied metabolic and physiological properties such as the production of extracellular enzymes[4]. Out of 22,500 bioactive compounds obtained from

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microbes, greater than 50% of the known natural antibiotics are obtained from actinomycetes. Among actinomycetes, about 7,600 compounds are produced by *Streptomyces* species[5]. The isolated compounds from marine actinomycetes has a broad spectrum of biological activities such as antibiotic, antifungal, antiviral, toxic, neurotoxic, cytotoxic, antimitotic, , immunosuppressive agent, enzymes and antineoplastic activities[6,7].

Now a day, progress has been made on the discovery of drug from actinomycetes using, fermentation, molecular characterization, and combinatorial biosynthesis and high throughput screening of new secondary metabolites related to existing pharmacophores[8]. In addition to that, production of new bioactive compounds from marine actinomycetes has become a great source. The actinomycetes isolates are isolated all around the world, from shallow costal sediments to the deepest sediments from the Mariana Trench. This shows that the actinomycetes are omnipresent in marine sediments, but lower in numbers than in soil[9]. The oceans are highly complex environments and house a diverse assemblage of microbes that occur in environments with extreme variations in pressure, salinity, and temperature. About 70% of the Earth's surface is covered by the oceans and as an unexplored area of opportunity. A marine microorganism includes complex and a diverse range of microscopic life forms, out of that only 1% has been cultured or identified[10]. They have been found in symbiosis with other marine invertebrates, especially sponges[11]. As they have unique metabolic and physiological capabilities, marine actinomycetes have attracted a great attention. They also have the great potential to produce compounds with fascinating pharmacological activities that could not be observed in terrestrial microorganisms[12].

Hence this paper reviews the present scenario of diversity of actinomycetes and their bioactive compounds.

**Biodiversity of actinomycetes**

Form the last 40 years many terrestrial actinomycetes have been characterized, while marine actinomycetes have received less attention. Early studies with simple approaches indicated that the marine environment was a great attention of discovering new actinomycetes[13]. Recently many scientists encouraged to study the actinomycetes distribution in marine environments. Also, the emergence of new molecular techniques has revealed the presence of actinomycetes in unique marine environments[14]. Many laboratories across the world have isolated and identified many marine actinomycetes. The diversity and secondary metabolite potential of actinomycetes collected from the South China Sea and the Yellow sea and were investigated. Ten families and 13 genera of *Actinomycetales* were found, among which ten isolates are of novel species[15].

Wetlands are considered to be as important ecosystems which are in-between open water and terrestrial ecosystems. They are gifted with specific structural and functional characteristics performing ecological roles in the biosphere[16]. They are considered as a key environment with a varied range of biological resources to initiate ecological research into the habitat of actinomycetes that produces bioactive substances. However, reports on actinomycetes diversity from wetlands are rather sparse, though wetlands acts as nature's kidney and provide great range of natural nutrients and xenobiotics draining from the terrestrial environment, to support wide range of microorganisms. Diversity of 11 soil actinomycetes isolated from various regions of a wetland were analysed and screened for their antibacterial activity. Their study revealed the good diversity of *Nocardioform* actinomycetes and *Streptomyces* in the wetland soils and many of them exhibited good antibacterial potential[17].

39 sediment samples were collected from the Bay of Bengal coast of Puducherry and Marakkanam and from that 164 actinomycetes strains were isolated. The orderly screening of isolates for antimicrobial activity resulted in isolation of actinomycetes strain VITSVK9. The diversity of the collected actinomycetes was identified using morphological and cultural observations of the strains based on ISP manual. Most of the isolated actinomycetes strains were belong to the genera *Streptomyces* (42%). Others include *Micromonospora* (22%), *Actinopolyspora* (8%), *Saccharopolyspora* (6%), *Microbispora* (13%), *Actinoplanes* (9%)[18]. It was already been reported that *Streptomyces* are predominant species in the marine environment among all actinomycetes studied so far and followed by *Micromonospora* species[19].

**Antibiotic compound produced by actinomycetes**

Antibiotics have become crucial in the modern health care system which support and complementing the natural immune system. The emergence of antibiotic-resistant strains, has led to the search for more potent and novel antibiotic agents. During the last decade, interest in antibiotics produced by actinomycetes has increasing greatly. The novel 5,10-dihydrophencomycin methyl ester and the known microbial metabolites (2-hydroxyphenyl)-acetamide , menaquinone MK9 and phencomycin were isolated from *Streptomyces* sp. and their structures were characterize by NMR methods[20]. The new antitrypanosomal antibiotics, spoxazomicins produced by the new actinomycete *Streptosporangium oxazolinicum* sp. isolated from the roots of a variety of orchid collected in the subtropical Okinawa prefecture[21].

Two new antimycin A analogues, antimycin B1 and antimycin B2, were isolated from a spent broth of marine-derived actinomycete *Streptomyces lusitanus*. Their important structural features were characterized by spectroscopic and chemical methods. The compounds were supposed to be artificial products originated during the treatment process[22].

The discovery of novel microbial natural products is encouraged not only by the quality of biological material but also by the novelty of screening models. The marine actinomycetes from the sponges have also proved to be potent sources of novel antibiotic leads[23].

Lam S, extensively reviewed the novel metabolites produced by marine actinomycetes. There is a large diversity and novelty among the marine actinomycetes. Many of these metabolites possess biological activities as well as potential to be developed as therapeutic agents. *A*byssomicins, Aureoverticillactam, Caprolactones, 3,6-disubstituted indoles, Frigocyclinone, Himalomycins, Komodoquinone A, Mechercharmycins, Trioxacarcins, Salinosporamide A (NPI-0052), Lajollamycin, Helquinoline and Trioxacarcins are some novel antibiotics produced by marine actinomycetes[7].

The six potent antibiotic producing actinomycetes isolates was isolated from the marine sediments of Andaman and nicobar marine islands. Among that, one of the isolates showed potent activity against all tested bacteria and fungi. The potent Actinomycetes were characterized by morphological methods consist of macroscopic and microscopic methods.

All the results were compared with the Bergey's manual of Determinative Bacteriology and the organisms were identified. All the isolates were belonging to the genus *Streptomyces*[24].

Exploring of new habitats is one of the most promising ways to isolate new strains of actinomycetes endowed with antimicrobial activity[25,26]. Isolates of *Streptomyces* strain also isolated from deteriorated wood. The activity of the isolate H2 against *S. aureus*, *Mycobacteria* and *P. aeruginosa* made the study more interested[27].

**Antimalarial compound produced by actinomycetes**

Malaria is a highly infectious disease caused by a protozoan parasite of the genus *Plasmodium*. The transmission of this parasite is by the bite of infectious female Anopheles sp mosquitoes. Five species of Plasmodium are associated with malarial fever viz, P. *falciparum, P. vivax, P. Malariae, P. ovale* and *P. knowlesi.* Among which, *P. falciparum* is extremely virulent. While, *P. vivax* is relatively less virulent and is more common in all over the world and remain three species are linked to the slight outbreak in several parts of the world. For the control of more virulent malarial parasite *Plasmodium falciparum*, three approaches were considered. It includes the step up of effective vaccines, vector control and development of new drugs. Due to the exhibition of multiple antigenicity, the development of a vaccine becomes difficult. The vector control shows limited success. On the other hand, malarial parasites show increasing resistance to the existing drug hence, there is an urgent need for new antimalarial agents[28,29]. There is a need of new drug that ideally directed against new targets such as heme and malarial proteases. However, the isolation of novel enzyme inhibitor from terrestrial sources is uncommon hence marine actinobacteria will provide new potential inhibitors.

The protease inhibitor activity and anti- Pf activity of actinobacterial extracts were screened under *in vitro* and *in vivo* conditions. Among 100 isolates, only 3 isolates exhibited modest to high protease inhibitor activities on trypsin proteinase K and chymotrypsin. The lead compound peptide from *Streptomyces* sp LK3 extract showed

significant anti plasmodial activity (IC50: 25.78 mg/ml). In the *in vivo* model, the highest level of parasitemia suppression (<45%) was observed in 600 mg/kg of the peptide. The result confirmed the up-regulation of TGF-b and down regulation of TNF-a in tissue and serum level in PbA infected peptide treated mice compared to PbA infection. The results obtained inferred that the peptide possesses anti- Pf activity activity which suggests that the extracts have novel metabolites and could be considered as a potential source for drug development[30].

Trioxacarcins are the complex compounds which showed higher anti-malarial activity against the malarial pathogens and some of them possess high antitumor and antibacterial activities. Trioxacarcin A, B and C (55) obtained from *Streptomyces ochraceus* and *Streptomyces bottropensis*[31]. Some of these compounds possess extremely high antiplasmodial activity, which is comparable to that shown by artemisinin, the most active compound against the pathogen of malaria.

New secondary metabolites salinos poramide A screened from marine actinomycetes tropica, is a highly potent inhibitor of the human malaria parasite *in vitro* and *in vivo*. Moderately conserved sequences of the proteasome subunits across species and exponential growth of the parasite in red blood cells, suggests proteasome as the probable target of salinosporamide A in the malaria parasite. The inhibitory effect of salinosporamide with an IC50 of 11.4 nM is as competent as the majority of conventional antimalarials such as artemisinin or chloroquine. The pure compound, salinosporamide A, was tested for its inhibitory effect against parasite development *in vitro* (*P. falciparum*) and *in vivo* (*P. yoelli*). The biochemical and structural-based analyses are reliable with the parasite 20S proteasome being the molecular target. The divergence at the structural level facilitates the discovery of an increased specificity of *Plasmodium* proteasome inhibitors[32].

Today, there is an urgent need for discovering the new small and inexpensive antimalarials molecules. Using a [3H] hypoxanthine incorporation assay on the parasite's erythrocytic stages, it was determined that secondary metabolites produced by marine actinomycetes have significant antimalarial activities. These findings displays that the natural products are the most important sources of medicines against the parasite. The crude extract was obtained from marine actinomycetes isolated from the mangrove and sea grass sediments of Dar es Salaam, Tanzania. The hypoxanthine incorporation assay was used to determine parasite inhibition profiles and 50% inhibitory concentration values of the Actinomycetes crude extracts. The three crude extracts showed strong growth inhibition with an $IC_{50}$ in the low microgram range (0.44 – 7.98 μg/ml)[33].

**Antitumor compounds produced by actinomycetes**

Although, recent advances have been done in the field of the molecular biology of cancer stimulation and progression in its different forms, it is still one of the most threatening illnesses which affect human health and quality of life[34].

One of foremost problem in treatment of various infectious diseases and cancer is the multidrug resistance. There is a need to develop a drug with high great novelty, potency and less toxicity. Marine microbes especially *Streptomyces* sp., is the major source of the antitumor antibiotics. When these antitumor antibiotics interact with DNA it results to cause cell death[35]. Anthracyclines are a special class of antitumor antibiotics which act via topoisomerase II inhibition[36]. An extracellular alkaloid, Pimprinine has been isolated from the culture filtrate of *Streptomyces* CDRIL-312[37].

The novel aporphine alkaloid SSV isolated from bioactive *streptomyces* sp. KS1908, is an antitumor antibiotic obtained from fraction of fermented broth and chemically characterized with advanced spectroscopic data. Hence, aporphine alkaloid SSV has been act as a promising agent for treatment of cancer and microbial infections[38].

Olano et al. reviewed the antitumor compounds from marine actinomycetes, which contain the natural products and the derivative of antitumor compounds, mainly produced by actinomycetes. These antitumor compounds belong to numerous structural classes such as anthracyclines, isoprenoides, macrolides, enediynes, indolocarbazoles, non-ribosomal peptides and others, which exert the antitumor activity mediated by topoisomerase I or II inhibition that induces cell-death through DNA cleavage, mitochondria permeabilization, and inhibition of key enzymes like proteases, involved in signal transduction, or cellular metabolism

and in some cases by inhibiting tumor-induced angiogenesis.

Several Screening methods are used to reduce the cost and time of drug discovery. These approaches are successful in finding the novel anticancer inhibitors from marine actinomycetes. Epidermal growth factor receptor (EGFR) express in many human tumors in lung, head, breast, ovary, bladder, kidneys neck, colon, pancreas, and in gliomas. Investigation of Expression and role of EGFR in cancer prognosis have been takes place in many human cancers[39]. The epidermal growth factor (EGF) is the peptide ligands that bind to cell membrane receptors EGFR and activate intracellular signalling pathways to control tumor cell growth, metastasis, proliferation, survival and angiogenesis. Therefore EGFR act as a target for the development of novel anticancer therapies[40]. Hence a docking was carried out to investigate the anti-cancer activity of the compounds from S. tropica targeting the EGFR. Virtual screening and extra precision (XP) docking of compounds were carried out using Schrödinger protocol. The compounds, arenicolide A, arenamycin A and arenamycin B exhibited good binding interaction to EGFR. The study indicates the importance of small molecules from *Salinispora* species and their use as bioactive molecules[41].

Cancer is supposed to be the public health problem, among which breast cancer is the second highest cancer cause result death in woman. Infect, more effort has been done for the treatment, effective agents are still inadequate. In this regard, natural compounds produced from marine actinomycetes have supposed to be the most promising source of new drug for cancer. Actinomycetes isolated ACT 01 and ACT 02 showed $IC_{50}$ values less than 30µl in both cell lines of breast cancer MCF 7 and MDA-MB-231[42].

Moreover, quinine derivative like, driamycin, daunorubicin, mitomycin C, streptonigrin and laprochol; anthroquinone families parimycin, trioxacarcins and gutingimycin showed antitumor activity.

**Antitubercular compounds produced by actinomycetes**

Tuberculosis (TB) is a highly infectious disease caused by *Mycobacterium tuberculosis,* is one among the leading cause of infectious disease worldwide. One of the world population suffered with *M. tuberculosis* and hence at a risk of active TB[43]. In the late of 1940s and 1950s, a number of effective antitubercular agents were discovered, with rifampicin getting introduced in 1960s[44]. In 1940s, Streptomycin was the first drug to be introduced for the treatment of TB but immediately after its introduction many of the patients started showing resistance against this antibiotic[45]. Multidrug resistance (combined isoniazid and rifampicin) strongly impacts on control program of TB. However, there is an urgent to discover novel antibiotics against drug resistance *M. tuberculosis*.

The two natural antibiotics, Lasalocid and Monensin isolated mainly from fungal mycelium of *Streptomyces cinnamonensis* (Actinomycetes). These antibiotics belong to the family of the polycyclic carboxylic polyethers[46]. Monensin and lasalocid and their metal complexes with Tl(I), La(III) and Gd(III) are active against *Mycobacterium tuberculosis*. These ionophores could be considered as potential antitubercular agents for the future discovery of new drug design[47].

Plant endophytes represent the rare and previously undiscovered microbial taxa to reduce the rediscovery of known compounds. 50 strains and 300 crude extracts in total were isolated from traditional Chinese medicines (TCMs) for growth inhibitory activity against Bacillus Calmette-Guérin (BCG)[48], an attenuated strain of the bovine tuberculosis bacillus *Mycobacterium bovis*. The crude extract of *Streptomyces* sp. strain Y3111 associated with the stems of Heracleum souliei, showed good anti-BCG activity with an MIC value of 12.5µg/mL. The Bioassay-guided fractionations yield the structurally diverse heraclemycins A–D. The structures were determined by different spectroscopic techniques including HRMSESI, 1D NMR, and 2D NMR. Heraclemycin C showed strong anti-BCG activity with a MIC value of 6.25µg/mL. This inferred that the endophytic microbes associated with TCMs can facilitate the discovery of new natural products and potentially new and novel molecular scaffolds for drug discovery[49].

**Antidiabetic compound produced by actinomycetes**

Diabetes mellitus is a metabolic disorder characterized by hyperglycaemia, negative nitrogen balance sometime ketonemia and glycosuria.

Resulting either from inadequate secretion of insulin, an inadequate response of target cells to insulin, or combination of these factors. Insulin deficiency is due to functional disorder of the pancreas.

Diabetes mellitus is the highest cause of death among other chronic diseases. More than 95% of diabetes is type 2 diabetes or often called non-insulin dependent diabetes[50]. This cannot be cured, but can be controlled. Hence major efforts have been directed towards the development of oral hypoglycaemic drugs, to identify compounds able to enhance insulin action in target tissues. Attention has been focused on searching from terrestrial microorganism to look for new sources of drug and many new families of antibiotics are found from these microorganism.

For the treatment of type-2 diabetes; Voglibose, Acarbose, valienamine, adiposin-1, and trestatin-B were reported from *Streptomyces hygroscopicus-limoneus*[51,52], *Actinoplanes utahensis*[53], *S. calvus*[54,55] and *S. dimorphogenes*[56] respectively. Voglibose is an alpha-glucosidase inhibitor that lowers the post prandial blood glucose levels in people with diabetes mellitus. It is produced and marketed in India by trade name Volix® and Vocarb®.[51]. Acarbose is an oral alpha-glucosidase and alpha-amylase inhibitor, first launched by Bayer in Switzerland in 1989 for the oral treatment of type-2 diabetes mellitus[53]. Valielamine, a precursor of voglibose and a new aminocyclitol, isolated from the fermentation broth of *Streptomyces hygroscopicus* subspecies *limoneus*. It has more potent a-glucosidase inhibitory activity against porcine intestinal sucrase, maltase and isomaltase than valienamine, validamine and hydroxylvalidamine which were reported as building blocks of validamycins and microbial oligosaccharide a-glucosidase inhibitors[57].

Effort has been made to identify the extracts that stimulate the uptake of glucose, similar to insulin. Novel Antidiabetic compounds from a *Streptomyces* strain PM0324667 was identified which expressed a secondary metabolite that induced glucose uptake in L6 skeletal muscle cells. A tri-substituted simple aromatic compound with anti-diabetic potential was isolated by fractionation techniques. It was characterized by MS and 2D NMR spectral data and identified as NFAT-133, a immunosuppressive agent that inhibits NFAT-dependent transcription in vitro. The compound induced glucose uptake in differentiated L6 myotubes with an EC50 of 6.3 ± 1.8 μM without activating the peroxisome proliferator-activated receptor-g. Further, NFAT-133 was also efficacious *in vivo* in diabetic animals and reduced systemic glucose level[58].

An alpha glucosidase inhibitor can retard the liberation of glucose from dietary complex carbohydrates and delay glucose absorption, resulting in reduced postprandial plasma glucose levels and suppress postprandial hyperglycaemia. Hence it is one of the compounds for the treatment of diabetes. Attempt had been made to select alpha glucosidase inhibitor-producing endophytic actinomycetes from various diabetic medicinal plants. Endophytic actinomycetes isolate BWA65 (*Streptomyces olivochromogenes*) from *Tinospora crispa* has great ability to inhibit the alpha glucosidase activity. Actinomycetes have largely contributed towards the production of alpha-glucosidase inhibitor compounds in this plant[59].

**Insecticidal activity of actinomycetes**

As the environmental contamination increases by toxic chemicals, for this alternative approaches for controlling pest populations have become research priorities. For limiting the destructive impacts of pest populations, ecological or biological control methods has evolved[60,61].

Actinomycetes play an significant role in the biological control against insect together with the house fly *Musca domestica*[62], *Culex quinquefasciatus*[63], cotton leaf worm *spodopetra liltoralis*[64], *Drosophila melanogaster*[65], *Helicoverpa armigera*[66], *Anopheles mosquito* larvae[67] and *Culex pippins*[68].

The biological activity of secondary metabolites of some actinomycetes isolates had been investigated against the last instar larvae of the cotton leaf worm *Spodoptera littoralis* through the food plant (Castor leaves). *Streptomyces* and *Streptoverticillum* were the most potent actinomycetes, which cause larval and pupal mortality[64]. The biological activities of actinomycetes secondary metabolites against some phytopathogenic fungi as well as cotton leaf worm (*S. littoralis*) were investigated. They showed that the pellets of some *Streptomyces* isolates were more active against cotton leaf worm than

culture filtrates. Generally, isolates S05, S08, S10 and S15 showed 80, 100, 70 and 80% mortality against cotton leaf worm, respectively. The result demonstrated the ability to use such *Streptomyces* isolates as effective biopesticide agents[66]. The purified compound, aminoglycosidic antibiotic produced from *Streptomyces bikiniensis* is also effective against 2nd instar larvae of cotton leaf worm *Spodoptera littoralis*[69].

It was found that the actinomycete isolates showed strong larvicidal activity against *Anopheles* mosquito larvae[67]. However, actinomycetes were effective against *Culex quinquefasciatus*[63]. The insecticidal efficacy of different concentrations of extract was evaluated against 3rd instar larvae of *A. aegypti* and it was found that the extract caused mortality of larvae in a dose dependent manner[70].

## CONCLUSION

As the scope of naturally found bioactive compounds increases day by day, search for novel active biomolecules increases. From the last many decades research on bioactive molecules produced from marine microorganism has geared up. Among all actinomycetes has proved to be the best. These are diverse in nature having various chemical entities responsible for the activity against many other disease causing microorganisms. Hence these bioactive compounds are considered to be as potent therapeutic agents. However, actual potential of actinomycetes is yet to be discovered. In future we will discover the new activities of microbial metabolites and expand their practical utilization.

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