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Review Article

NOVEL BIOACTIVE COMPOUNDS FROM MANGROVE DERIVED ACTINOMYCETES

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ABSTRACT

Mangrove is most productive and unexplored ecosystem that approximately covers one fourth of world coastline with high diversity of thriving organism. Recently the rate of isolation of novel bioactive compounds from microorganism living in mangrove forest has tremendously increased which is reflected in significant hasten for exploration of mangrove actinomycetes. Actinomycetes are group of bacteria which are extremely interesting as active producers of many primary and secondary metabolites. Many survey reports has depicted that the biologically active compounds which have been obtained so far from microbes, 45 percent are produced by actinomycetes, 38 percent by fungi and 17 percent by unicellular bacteria. Actinomycetes from mangrove environment provide diverse and are potential rich source of antibiotics, anticancer, antifungal and antiviral agent, enzyme and enzyme inhibitor. Mangrove actinomycetes are a prolific but underexploited source for the discovery of novel secondary metabolites.

KEYWORDS: Mangrove actinomycetes, bioactive compounds, anticancer agent.

INTRODUCTION

Actinomycetes, characterized by a complex life cycle, are filamentous Gram-positive bacteria belonging to the phylum *Actinobateria* that represents one of the largest taxonomic units among the 18 major lineages currently recognized within the domain bacteria[1]. They are the most economically and biotechnologically valuable prokaryotes and are responsible for the production of about half of the discovered bioactive secondary metabolites, antibiotics, anticancer agents and enzymes. Around 23,000 bioactive secondary metabolites produced by microorganisms have been reported and over 10,000 of these compounds are produced by actinomycetes, representing 45% of all bioactive microbial metabolites discovered. Among actinomycetes, around 7,600 compounds are produced by *Streptomyces* species[2].

This group is majorly distributed in soil population. Soil conditions such as geographical location, pH, temperature, moisture and nutrient influenced the number and type of actinomycetes. Unlikely terrestrial habitat actinomycetes is less understood in the mangrove areas, further, very little information is available in literature related to mangrove actinomycetes and its novel bioactive compounds.Mangroves, unique woody plant communities of intertidal coasts in tropical and subtropical coastal regions, are highly productive ecosystems though surprisingly little is known about the microbial communities living therein[3], although there is evidence that mangrove sediments contain high populations of novel actinomycetes.

Mangrove ecosystems are nutritionally versatile as that of terrestrial ranging from phototrophy to chemolithotrophy and chemohetrotrophy which affect the diversity of mangrove actinomycetes in terms of genetic and metabolic features and therefore new metabolites. Mangrove soil, sediments, swamps, bottom mud and plants are rich source of new species of *Streptomyces*, *Nocardiopsis* and various strain of actinomycetes.The forest is unique for its agroecological condition and soil of this mangrove forest is routinely or occasionally inundated with low, moderate or high saline water. This ecosystem is ideally situated at the interphase between the terrestrial and marine environment and supports a rich and diverse group of microorganisms. The mangrove environment is a potent source for the isolation of antibiotic-producing actinomycetes[4].

This review article report the identified novel secondary metabolites having different type of activities that has been isolated from actinomycetes thriving in mangrove environment.

Distribution of Species

The mangrove forest of the world is approximately 53,190 square miles[5]. The largest percentage of mangrove is found in Asia basically Sunderban and South China Sea from where novel species of actinomycetes has been obtained. In India, the area under mangrove is distributed over 4900 sq. km., which accounts for around 8% of India's coastline[6] and from mangrove forest such as Manakkudi, Kanyakumari district, Parangipettai coastal area, Pichavaram, Tamilnadu and also in west coast of India these actinomycetes have been reported. Other mangrove forests present in Wenchang and Pohoiki, Hawaii has also given evidences for existence of actinomycetes. Diversity of microbial communities inhabiting this unique swampy, saline, anaerobic environment is useful as it provides clue of the microorganism and its adaptability in such environment[7].

BIOACTIVE COMPOUNDS PRODUCED BY MANGROVE ACTINOMYCETES

In literature very few examples are there for exploitation of mangrove actinomycetes for discovery of novel bioactive compounds and many are at early stage of research. Members of the genus *Streptomyces* are a rich source of novel bioactive, commercially significant compounds. Although *Streptomyces* strains were frequently isolated from terrestrial environments, they have also been recovered from aquatic and symbiotic environments[8].Table 1 represents the various secondary metabolites that have been isolated from actinomycetes which are present in diverse source and different environmental condition of mangrove ecosystem.

Ligninase, Laccase and Manganese peroxiase

Ligninase, Laccase and Manganese peroxiase are lignin degrading enzyme produced by *Streptomyces psammoticus* that has been isolated from west coast of India. Samples were collected from sediments, soil, decaying logs found in intertidal region and swamp. These enzymes can degrade

compounds like syrnigic acid, feruillic acid, vanillic acid, cinnamic acid and guaiacol acid[9].

Benzamides and Quinazolines

One new benzamide, 3-hydroxyl-2-*N*-iso-butyryl-anthranilamide (Fig.1a) together with two known benzamide 3-hydroxyl-anthranilamide , anthranilamide and three known quinazolin 8-hydroxly-4(3*H*)-quinazoline, 8-hydroxyl-2methyl-4(3H)-quinazoline (Fig. 1b) and 8-hydroxyl-2,4-dioxoquinazolin were extracted from *Sterptomyces sp.* (No.061316). The strain was isolated from mangrove soil sample collected at Wenchang. These compounds display inhibiting effect against Caspase-3 catalytic activity *in vitro*. Research on Caspase-3 inhibitors can help to develop drugs against excessive apoptosis-related diseases[10].

Alkaline Protease

Alkaline protease is an enzyme which has been extracted from alkalotolerant *Streptomyces sp.* Actinomycetes were isolated from rhizosphere soil of mangrove species, *Rhizophora annamalayana* Kathir, on the bank of Vellur estuary, Portonovo, South coast of India[11].

L-glutaminase

L-glutaminase is an enzyme produced from *Streptomyces olivochromogenes* that has been isolated from the mangrove *Rhizophora apiculata* of Parangipettai coastal area,Tamil Nadu,India.In food industry this enzyme is used as a flavor enhancer by increasing glutamic acid content in food through hydrolysis of L-glutamine to L-glutamic acid and ammonia. It is also used in enzyme therapy for cancer especially for acute lymphocytic leukemia. Another important application of L-glutaminase is in biosensors for monitoring the glutamine levels in mammalian and hybridoma cells[12].

Chalcomycin B

Chalcomycin B (Fig.2) is a new macrolide antibiotic produced from *Streptomycete isolates* B7064 that has been derived from mangrove sediment near Pohoiki, Hawaii. This compound has antibacterial and antifungal activities against *Bacillus subtilis*, *Streptomyces viridochromogenes*, *Staphylococcus aureus*, *Escherichia coli*, *Candida albicans* and *Mucor miehei*[13].

α- Galactosidase

α-Galactosidase or melibiase (α-D-galactoside galactohydrolase) is an exoglycosidase which has been derived from two actinomycetes cultures, coded AGP-27 and AGP-47. These organisms were isolated from soil sample collected from mangrove regions along the West coast of India. This compound cleaves terminal α-1,6 linked galactose residue from from α-D-galactosides including galactose oligosaccharides, such as melibiose, raffinose and stachyose, and branched polysaccharides, such as galactomannans and galacto (gluco) mannans[14].

L-asparaginase

The oncolytic enzyme L-asparaginase produced by *Streptomycetes parvulus* KUAP106 that has been isolated from sediment sample pichavaram mangrove ecosystem, situated along the South East coast of India[15].

Norcardiatone

Three new 2-pyranone derivatives, namely Norcardiatones (Fig.3) were produced from the strain *Nocardiopsis* sp. A00203, mangrove endophytic actinomycetes from leaves of *Aegiceras corniculatum* collected from Jimei, Fujian Province, China. [16] All derivatives of norcardiatones compounds were extracted as yellow oil. These compounds shows cytotoxic activity against HeLa cells and antimicrobila activity against *Escherichia coli*, *Bacillus subtilis*, *Staphylococcus aureus* and yeasts (*Candida albicaus* and *Aspergillus niger*) [16].

Rifamycin

Rifamycin produces by an actinomycetes strain AM105^T that was extracted from mangrove sediments samples, South China. Phylogenetic analysis showed a close relationship of strain AM105^T with *Micromonospora matsumotoense* DSM 44100^T, *Micromonospora carbonacea* DSM 43168^T, *Micromonospora mirobrigensis* DSM 44830^T and *Micromonospora siamensis* JCM 12729^T. A clear antimicrobial activity was revealed against *Staphylococcus aureus*, *Staphylococcus aureus* OY84 (a meticillin-resistant clinical isolate), *Bacillus subtilis*. Further identification showed that the active compound (purple amorphous powder) consisted of rifamycin S and its isomer while M. carbonacea was reported to produce everninomicin[17].

Anthrone and Lactone

Two anthrones and one lactone (Fig.4) were produced from an actinomycete strain (N2010-37) of bottom mud in Zhanjiang Mangrove, South China Sea. They have cytotoxicity activity against human chronic granulocytic leukemia cell line K562 strain[18].

Xiamycin

Xiamycin (Fig.5) is a pentacyclic indolosesquiterpene that have been obtained from an endophyte *Streptomyces sp* from a mangrove plant *Bruguiera gymnorrhiza* which is one the most important and widespread species in Pacific. Another compound xiamycin methyl ester has also isolated from same strain. Xiamycin exhibits selective anti-HIV activity; it specifically blocks R5 but has no effects on X4 tropic HIV-1 infection and also shows cytotoxic activity. Xiamycin represents one of the first examples of indolosesquiterpenes isolated from prokaryotes[19].

Alkaloids and Quinine

Alkaloids and Quinine were extracted from ACT01 (*Streptomyces sp.*GQ478246) and ACT02 (*Streptomyces sp*. HQ340165). Soil sample was collected from Manakkudi mangrove ecosystem, Kanyakumari district, Tamilnadu, India. These compounds exhibit anticancer activity against breast cancer cell lines (MCF-7 and MDA-MB-231). Alkaloids are nitrogenous compound and are microtubule interfering agent, hence avoid spindle formation during cell division, inhibiting topoisomerase, mitochondrial damage and induce release of Cytochrome c and apoptosis inducing factor. Quinine derivatives (driamycin, daunorubicin, mitomycin C, streptonigrin and lapachol) interfere in DNA and RNA replication and mitochondrial oxidative pathway or the formation of superoxide, peroxide and hydroxide radicals as toxic products in cell line[20].

Azalomycin

Azalomycin F_{4a} 2-ethylpentyl ester and azalomycin F_{5a} 2-ethylpentyl ester, two new macrocyclic lactones, along with three known compounds of azalomycins F_{3a} , F_{4a} and F_{5a} , were identified from metabolites of *Streptomyces* sp. 211726 isolated from mangrove rhizosphere soil. Azalomycin F_{4a} 2-ethylpentyl ester is a new 36-membered macrocyclic lactone antibiotic which showed broad-spectrum antifungal activity and moderate cytotoxicity against human colon tumor cell HCT-116[21, 22].

2- allyloxyphenol

2-allyloxyphenol (Fig.6) is a synthetic drug and intermediate that has been naturally produced from new species of genus *Streptomyces* (strain MS1/7) from the sediments of Sundarbans, Bay of Bengal. Many analogues can be synthesize from 2- alloxyphenol (2- propenoxy-4-nitro

phenol, 2-propenoxy-4-methyl phenol, 2-propenoxy-4-methoxy phenol, 2-propenoxy-4-tertiary butyl phenol, 1, 2-diallyloxybenzene, allyloxy benzene and 2-allyloxynaphthalene. 2-Allyloxyphenol was found to be inhibitory to 21 bacteria and three fungi. It possess strong antioxidant property determine by 1, 1-diphenyl-2-picryl hydrazyl scavenging activity. Absence of hemolytic toxicity, potential carcinogenicity, cytotoxicity and reports of toxic reactions in literature suggest possible application of 2-allyloxyphenol as a food preservative and an oral disinfectant[23, 24].

Cyclopentenone

Four new cyclopentenone derivatives were derived from endophytic *Streptomyces* sp. (GT-20026114) from mangrove plant *Aegiceras* comiculatum collected in South China[25].The cyclopentenone showed a cell growth suppressing action and anticancer action to cancer cells such as human promyelocytic leukemia cells HL-60, human acute lymphoblastic leukemia cells MOLT-3, pulmonary cancercells A-549, SV40-transformed pulmonary cancer cells WI-38VA13, hepatoma cells Hep G2, colic cancer cells HCT 116, human colic cancer cells SW 480, human colic cancer cells WiDr, stomach cancer cells AGS and myeloma cells. They also act as apoptosis and anticancer agent. Antibacterial property of cyclopentenone may be used as an antiseptic agent for improving preserveability of food and beverages[29].

CONCLUSION

Several studies have been conducted to estimate the medicinal and economic value of mangrove ecosystems to compare the valuation of the mangrove ecosystem all of which differ in a number of ways. The actinomycetes obtained from the mangrove are the potent source of novel bioactive compounds. They are the source of various antibiotics, antimicrobial, antifungal, anticancer, enzymes and other bioactive compounds. Isolation, characterization and study of these actinomycetes from mangrove source can be useful in discovery of novel bioactive compounds.

Table1. List of Bioactive Compounds produced from various species of mangrove actinomycetes

Compound	Source	Activity	Reference
Ligninase, Laccase and Manganese Peroxidase.	*Streptomyces psammoticus*	Lignin degrading enzyme	9
Benzamides and Quinazolines	*Streptomyces sp.*	Inhibit Caspase –3 activity	10
Alkaline Protease	*Streptomyces sp.*	Enzymatic activity	11
L-glutaminase	*Streptomyces olivochromogenes* (P2).	Enzymatic activity	12
Chalcomycin B	*Streptomyces* sp.	Antibiotic	13
α- galactoside galactohydrolase	Actinomycetes strain AGP-42 and AGP-47	Cleave terminal α- 1 – 6 linked galactosr residue from glycoconjugates.	14
L-asparagine aminohydrolase	*Streptomycetes parvulus* KUAP106	Antitumor and anti neo plastic agent.	15
Norcardiatones A , B and C	*Nocardiopsis* sp. A00203	Antimicrobial and Cytotoxic	16
Rifamycin	Actinomycetes strain, AM105^T	Antibiotic	17
Anthrone and lactones	Actinomycete Strain (N2010-37)	Antitumor and cytotoxic	18
Xiamycin	*Streptomyces sp.* GT2002/1503	Anti-HIV activity	19
Alkaloids and Quinine	Actinomycetes isolates ACT01 and ACT02	Anticancer	20
Azalomycin	*Streptomyces* sp. 211726	Antifungal and cytotoxic	21,22
2- allyloxyphenol	*Streptomyces* strain MS1/7^T	Antibacterial	23,24
Cyclopentenone	*Streptomyces* sp. (GT-20026114)	Anticancer, apoptosis and antibacterial	25

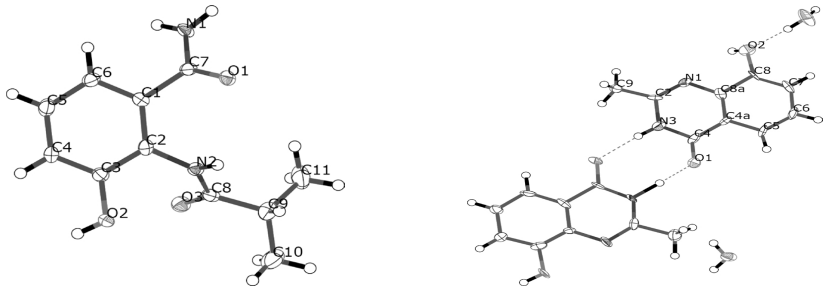
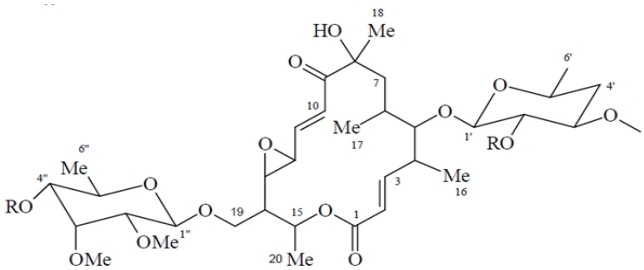


Fig1. (a) 3-Hydroxyl-2-*N*-iso-butyryl-anthranilamide (b) 8-Hydroxyl-2-methyl-4(3*H*)-quinazoline.



1a: R = H

1b:R = EtCO

Fig. 2. Chalcomycin B

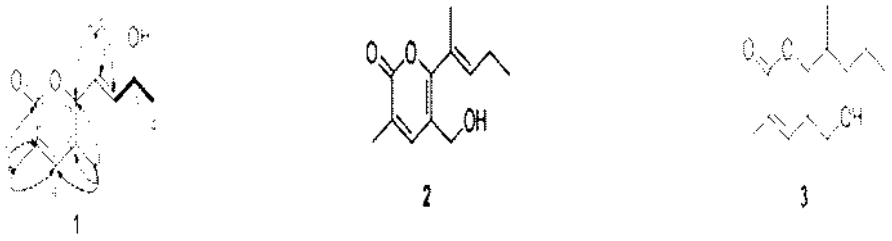


Fig. 3. Norcardiatone derivatives

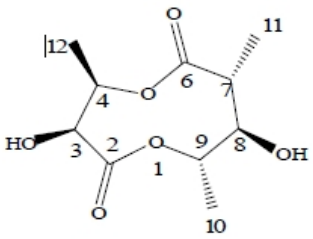


Fig 4. Lactone

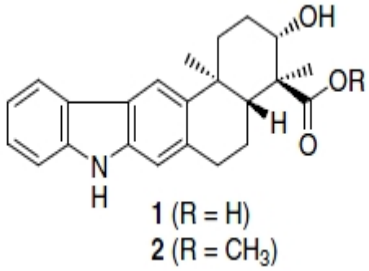


Fig 5. Xiamycin

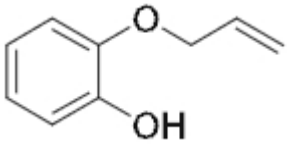


Fig 6. 2-alloxyphenol

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