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A review on bioprospecting of actinomycetes isolated from marine soil samples of India concerning their antimicrobial secondary metabolites

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Sixty-three years of research on terrestrial actinomycetes and forty-three years on marine actinomycetes in India yielded several novel actinomycetes species. Those actinomycetes were screened for their biological activities using culture filtrate/ crude solvent extracts. There are few reports on purifying and identifying secondary metabolites and exploring their biological activities. Actinomycetes are known for producing a diverse group of secondary metabolites with multiple biological activities. Omics technology has been currently used for rapid screening of actinomycetes genera to identify novel stains and their biosynthetic gene clusters (BGCs). Only a few reports on using omics technology to explore actinomycetes' genera for novelty, their BGCs, secondary metabolites, and their biological activities in India have been available. Bioactivity-guided extraction, purification, and identification of secondary metabolites and scalable production of the bioactive compounds in the laboratory are time-consuming. Using omics technology to explore the actinomycetes isolated from several niches, including deep-sea sediments, would reduce the time required for screening and identification of novel BCGs and their metabolites. The growing microbial drug resistance to the existing antibiotics has increased the demand for newer antibiotics worldwide. This warranted the researchers to explore actinomycetes genera for novel antibiotics, bioactive compounds, and new chemical entities. Isolation of actinomycetes from unexplored and underexplored regions, screening followed by whole genome sequencing, annotation and identification of BGCs and their selective expression would help us produce a scalable quantity of novel bioactive compounds for biomedical applications.

Keywords: Actinomycetes, Antimicrobial activity, Biosynthetic gene clusters, Omics tools, Secondary metabolites, Whole genome sequencing

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Introduction

Actinomycetes are prolific producers of numerous secondary metabolites and new chemical entities. Natural sources, including phytochemicals from plants and secondary metabolites from microbes are considered to be an alternative to chemically synthesised compounds[1]. Medicinal plants have been extensively studied and explored to a larger extent already for their bioactive phytochemicals. Researchers are now focusing more on actinomycetes; although isolation and identification of novel actinomycetes from terrestrial sources have been exhausted worldwide, their marine counterpart is more promising due to their presence in hostile environments (deep-sea sediments and thermal vents), unexplored and underexplored regions of deep-sea dwelling habitats[2,3]. Even after six decades of research on actinomycetes in India, there are still unexplored and under-explored habitats in the Indian subcontinent which need to be studied for isolation of novel actinomycetes species and their bioactive secondary metabolites[4].

Actinomycetes diversity remains a treasure trove for the discovery of diverse antibiotics, and currently, many of the antibiotics available in the market are derived from the genus *Streptomyces*[5]. These actinomycetes habitats in all types of soils; agricultural, rhizosphere, barren-lands, marine coastal areas, mangroves, volcanoes, ice points, mountains, forests, estuaries, deep sea, lakes, and lagoons[6] as well as marine organisms including sea grass, sponges, corals, molluscs, a fishes etc. Major actinomycetes genera reported in India, include *Streptomyces* (40%), *Micromonospora* (18), *actinopolyspora* (15%), *Sacharopolyspora* (10%), *Actinomudura* (8%) and others (9%)[7]. Secondary metabolites extracted from actinomycetes exhibit

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multiple biological functions, which include antimicrobial, antiparasitic, antifouling and anti-biofilm, anticancer and antitumor, cytotoxic, bioremediation and probiotic activity. It also produced several pigments, biosurfactants, and enzymes of industrial importance[8]. The Indian peninsula is a tropical region with diverse ecosystems; especially the southern part surrounded by the Bay of Bengal and the Arabian Sea serves as a rich source for actinobacterial diversity[9]. In this review, actinomycetes isolated from Indian soil samples, their secondary metabolites and their bioactivity and scope for using omics technology for gene analysis using GO, COG, KEGG, antiSMASH, biosynthetic gene similarity clustering and prospecting engine (BiG-SCAPE)(bioinformatics tool), antibiotic-resistant target seeker (ARTS) 2.0 (for identification of resistance genes among BGCs) and molecular network analysis of secondary metabolites and their scope to speed up the screening process for the isolation of novel strains and their novel secondary metabolites are discussed[10].

Actinomycetes (Phylum: Actinobacteria) are capable of producing many complex chemical compounds/natural products/ new chemical entities with diverse biological activities[11]. Actinomycetes isolated from marine soil samples collected from the coastal regions of India are extensively studied for antibacterial activity. Only very few reports are available on the antibacterial activity of extracted/ derived secondary metabolites from actinomycetes genera. Few recent reports have mainly focused on isolating actinomycetes from unexplored and underexplored sites capable of producing novel secondary metabolites/chemical compounds. The evolution of multidrug drug-resistant bacterial strains and the infectious diseases caused by them remains a significant threat to the effective control and treatment of bacterial diseases. The alarming increase in antibiotic resistance strains is more prevalent in almost all parts of the world, which poses a considerable challenge for healthcare workers to control these superbugs[12]. Hence, a great demand exists for developing new drug molecules to target the superbugs. Actinomycetesgenera have been proven to be more effective in producing novel secondary metabolites capable of inhibiting drug-resistant superbugs[13]. Multiple biological functions of actinomycetes and their secondary metabolites are shown in Fig. 1.

Recently reported antibacterial secondary metabolites from actinomycetes

Presence of antibacterial compounds (1-Tetradecanol, Phenol, 2,5-bis(1,1-dimethylethyl)-, 1-Nonadecene, n-Pentadecanol, and Pyrrolo[1,2-a]pyrazine-1,4-dione hexahydro-3-(phenylmethyl)- from *Streptomyces* sp. PBR11 and their antibacterial activity have been reported recently[10]. Isolation of phenol, 2,4-bis(1,1-dimethyl ethyl), and propanoic acid, 2-Hydroxy-, ethyl ester having antibacterial activity against fish pathogens have been reported[14]. Isolation of 3-octanone, neopentylisothiocyanate and 2-methyl butyl isothiocyanate from *S. malachitospinus* (ITD-35) and their antibacterial activity against human pathogens has been reported[15]. Diketopiperazine having anti-MRSA activity derived from *Nocardiopsis*sp. SCA30 has been reported[16]. Novel antibiotic picolinamycin produced by *Streptomyces* sp. SM01 has been reported to be very effective against multidrug-resistant bacterial pathogens[17]. *Streptomyces bacillaris* RAM25C4 derived 1,4-benzenediol, 2,6-ditert- butylphenol, and 1 H, 5 H, pyrrolo (10 20:3, 4) imidazo compound have been reported to be active against bacterial pathogens [18]. A bioactive secondary metabolite N-(4- aminocyclooctyl)-3, 5-dinitrobenzamide isolated from *Pseudonocardiaendophytica* (VUK-10) has been shown to inhibit *Streptococcus mutans* with the MIC value of 4 μg/mL[19]. Antibacterial compounds reported from different genera of marine actinomycetes in the last ten years are given in Table 1.

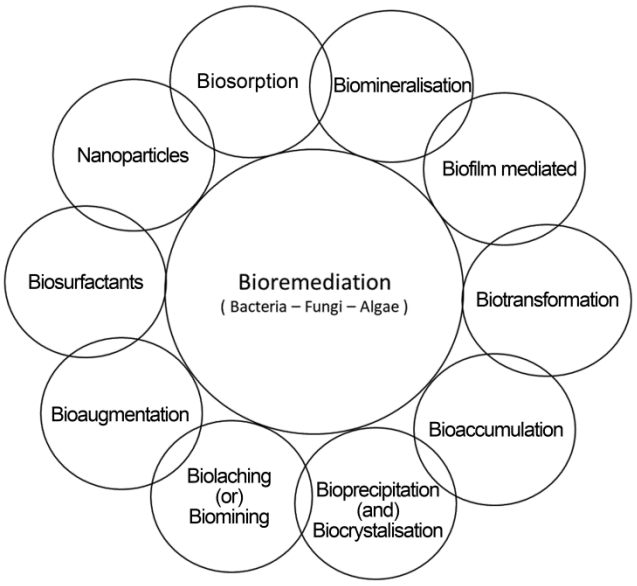

Fig. 1 — Biological functions of actinomycetes-derived secondary metabolites.

Table 1 — Antibacterial compounds reported in the last decade (2014 to 2023) from actinomycetes isolated from Indian soil samples

Molecule	Organism	Activity	References
Ethambutol	*Streptomyces* sp. PBR11	Antibacterial	10
Phenol,2,4-bis(1,1-dimethylethyl), and propanoic acid, 2-Hydroxy-, Ethyl Ester,	*Bacillus licheniformis* VIT02	Antibacterial	14
3-octanone, neopentylisothiocyanate and 2-methyl butyl isothiocyanate	*S.malachitospinus* (ITD-35)	Antibacterial	15
Diketopiperazine	*Nocardiopsis*sp. SCA30	Anti-MRSA	16
Picolinamycin	*Streptomyces* sp. SM01	Anti-MRSA	17
1,4-benzenediol, 2,6-ditert- butylphenol, and 1 H, 5 H, pyrrolo (10 20:3, 4) imidazo	*Streptomyces bacillaris* RAM25C4	Antibacterial	18
N-(4-aminocyclooctyl)-3, 5-dinitrobenzamide	*Pseudonocardiaendophytica* (VUK-10)	Antibacterial	19
2, 4-dichloro-5-sulfamoylbenzoic acid	*Streptomyces* sp. VITBRK3	Anti-MRSA &anti-VRE	20
Mithramycin	*Streptomyces* sp. PM1129877	Anti-MRSA & anti-VRE	13
[Coumarin-6ol,3,4-Dihydro-4,4,5,7-TetraMethyl]	*Streptomyces* sp. VITAK1	Antibacterial	21
Z-1-((1-hydroxypenta -2,4-dien-oxy)anthracene-9,10-dione	*Nocardiopsis alba*	Antibacterial	22
1, 2-Benzenedicarboxylic Acid, Mono(2-Ethylhexyl) Ester	*Streptomyces* sp. strain VITSJK8	Antibacterial – ESBL pathogens	23
Actinomycin D	*Streptomyces parvulus*	Antibacterial	24
2,4-bis (1,1-dimethyl ethyl) phenol	Actinomycetes strain SCA 7	Antibacterial	25
Ethyl substituted β-lactum compound	*Streptomyces noursei* DPTD21	Antibacterial	26

Anti-MRSA anti-VRE compound 2, 4-dichloro-5-sulfamoylbenzoic acid (DSBA) extracted from *Streptomyces* sp. VITBRK3 was reported to be very effective against MRSA and VRE pathogens. It showed significant anti-MRSA (MIC 0.5 µg/mL) and anti-VRE (160 µg/mL) activity[20]. Mithramycin was reported to be active against drug-resistant pathogens such as methicillin-sensitive *Staphylococcus aureus* (MSSA), methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-sensitive *Enterococci* (VSE) and vancomycin-resistant *Enterococci* (VRE) pathogens. It was extracted from *Streptomyces* sp. PM1129877 isolated from the Playa region of Rajasthan, India[13]. Abirami *et al.*[21] have reported the extraction of antibacterial secondary metabolite coumarin-6-ol, 3,4-dihydro-4,4,5,7-tetramethyl (CDTM) from *Streptomyces* sp. VITAK1 isolated from marine soil samples of Andaman & Nicobar Islands. The lead compound demonstrated a significant antibacterial activity with an IC_{50} value of 2.5-40 µg/mL against the studied bacterial pathogens. Janardhan *et al.*[22] have reported the extraction of antibacterial secondary metabolite, (Z)-1-((1-hydroxypenta-2,4-dien-1-yl)oxy) anthracene-9,10-dione from *Nocardiopsis alba* isolated from mangrove soils samples of Nellur, Andhra Pradesh, India. Subhashini and Kannabiran[23] have reported the extraction of anti-ESBL compound 1, 2-benzenedicarboxylic acid, mono (2-ethylhexyl) ester (DMEHE) from *Streptomyces* sp. VITSJK8. DMEHE showed high antagonistic activity against *Klebsiella pneumoniae* (VITEB8) with a MIC value of 0.125 µg mL^{-1}, *Klebsiella pneumoniae* (VITEB6) with an MIC value of 0.25 µg mL^{-1} and *Klebsiella pneumonia* (VITEB1) with the MIC value of 2.0µg mL^{-1}. Antibacterial activity of Actinomycin D isolated from *Streptomyces parvulus* has been reported earlier[24]. Few antibacterial compounds were also reported from actinomycetes which include 2,4-bis (1,1-dimethyl ethyl) phenol from terrestrial actinomycetes strain SCA 7[25] and ethyl substituted β-lactum compound from *Streptomyces noursei* DPTD21[26].

Quorum sensing inhibitors and quorum quenching compounds from actinomycetes

Quorum sensing is a communication system among microorganisms that is needed for their survival. Bacterial virulence is regulated by quorum sensing (QS), and hence, it serves as a target for antivirulence therapy. As a whole, there are three types of quorum sensing systems in bacteria: N-acyl homoserine lactones (AHL) (AI-1), oligopeptide, and universal autoinducer (AI-2). AHL signal molecules are used by the gram-negative bacteria quorum-sensing system, and LuxI/LuxRsignalling molecules are used by the gram-positive organism. Biofilm formation is the key event in the microbial quorum sensing process, and it is responsible for exhibiting resistance by virulent pathogens[27]. Quorum sensing inhibitors, quorum quenching (QQ) compounds and QQ enzymes are responsible for the inactivation of the quorum sensing system. Many natural compounds have been reported as QQ agents. Quorum quenchers exhibit their function by enzymatic inactivation of the signal molecule or inhibition of signal biosynthesis, or inhibition of signal

detection system[28]. Diverse marine environments serve as a rich source for microorganisms capable of producing a variety of QQ agents. Actinomycetes remain as a reliable source for producing QQ agents or Quorum sensing inhibitors (QSI)[29].

Few QQ compounds extracted from actinomycetes (*Streptomyces*) isolated from soil samples collected from different parts of India have been reported earlier. Anitbiofilm activity of QQ compound N-(2-hydroxyphenyl)-2-phenazinamine derived from *Nocardiopsisexhalans* has already been reported[30]. *Streptomyces variabilis* derived 1-hydroxy-1-norresistomycin was an effective biofilm inhibitor[31]. A fatty acyl compound 13Z-Octadecenal extracted from marine *Streptomyces griseoincarnatus* strain HK12 has been shown to exhibit antibiofilm activity[32]. Pyrrolo [1,2-a] pyrazine-1,4-dione, hexahydro-3-(2-methylpropyl) derived from *Nocardiopsis* sp. GRG 1 was an effective inhibitor of bacterial biofilm formation[33]. Similarly, 2,4-bis (1,1-dimethylethyl) was extracted from *Nocardiopsis* sp. ZoA1 has been reported to inhibit the formation of biofilm[34]. A lipopeptide MSA31 derived from *Fasciospongiosumcavernosa* and their antibiofilm activity has been reported earlier[35]. *Streptomyces* sp. D25-derived pigment has also been shown to be an effective inhibitor of biofilm formation[36]. A list of compounds derived from actinomycetes in the last decade capable of inhibiting bacterial biofilm formation is given in Table 2.

Antifungal compounds from actinomycetes

Fungi, being a eukaryotic organism, are always challenging to selectively target with a suitable drug. Several antifungal secondary metabolites have been isolated from actinomycetes worldwide[37]. Even though there are many reports on the antifungal activity of cell-free supernatant and crude solvent extracts prepared from actinomycetes, but only a few reports on secondary metabolites mediated antifungal activity in India. Therefore, it is more important to record the antifungal compounds reported from actinomycetes isolated from Indian soil samples. Dermatophytic fungal infections are constantly increasing throughout the world[38]; Dermatophytosis is considered to be a major threat to the human race globally; many researchers are targeting actinomycetes for the isolation of anti dermatophytic compounds.

Antifungal activity of 1-Nonadecene extracted from *Streptomyces* sp. PBR11 has been reported recently[10]. *Streptomyces chrestomyceticus* ADP4 derived compound phenyl 2′α, 2′β, 6′β-trimethylcyclohexyl ketone phenyl nonanyl ether was reported to be fungicidal in nature[39]. Antifungal activity of phenyl acetic acid extracted from *Streptomyces* sp. has already been reported[40]. Pyrrolidinyl-hexadeca-heptaenone extracted from *Streptomyces* sp. VITAK1 was active against fungal pathogens[41]. Methoxy ethyl cinnamate (ethyl(E)-3-(4-methoxyphenyl) acrylate) extracted from *Saccharomonosporaoceani* VJDS-3 was reported to be very effective against fungal pathogens[42]. A secondary metabolite N-(4-aminocyclooctyl)-3, 5-dinitrobenzamide isolated from *Pseudonocardiaendophytica* (VUK-10) has been shown to inhibit *Candida albicans* with the MIC value of 16 µg/mL[18].

Caerulomycin A from *Actinoalloteichus* sp. extracted from marine invertebrates from Anjuna Beach, Goa, India, showed a very low MIC value of 0.39 to 1.56 µg/mL against human pathogenic fungi[43]. Anticandidal activity of secondary metabolite pyrrolo[1,2-a] pyrazine-1,4-dione,hexahydro-3-(phenylmethyl) extracted from *Streptomyces* sp. VITPK9 was reported earlier[44]. The active secondary metabolite showed a MIC value of 0.78 to 2.0 µg/mL against pathogenic *Candida* species. A list of antifungal compounds extracted from marine actinomycetes in the last decade is given in Table 3.

Antiviral compounds from actinomycetes

In India only a few reports are available till date on the antiviral activity of actinomycetes and their secondary metabolites . A novel chemical compound 9(10H)-Acridanone isolated from marine isolate, *Streptomyces fradiae* sp. VITMK2 was reported to be

Table 2 — Antibiofilm compounds reported in the last decade (2014 to 2023) from actinomycetes isolated from Indian soil samples

Molecule	Organism	Activity	References
N-(2-hydroxyphenyl)-2-phenazinamine	*Nocardiopsis exhalans*	Antibiofilm	30
1-hydroxy-1-norresistomycin	*Streptomyces variabilis*	Antibiofilm	31
13Z-Octadecenal	*Streptomyces griseoincarnatus* HK12	Antibioflim	32
Pyrrolo [1,2-a] pyrazine-1,4-dione,hexahydro-3-(2-methylpropyl)	*Nocardiopsis*sp. GRG 1	Antibiofilm	33
2,4-bis (1,1-dimethylethyl)	*Nocardiopsis* sp. ZoA1	Antibiofilm	34
Lipopeptide MSA31	*Fasciospongiacavernosa*	Antibiofilm activity	35
Pigment	*Streptomyces* sp.D25	Antibiofilm activity	36

Table 3 — List of antifungal compounds reported from actinomycetes isolated from Indian Peninsula

Molecule	Organism	Activity	References
1-Nonadecene	*Streptomyces* sp. PBR11	Antifungal	10
Phenyl 2′α, 2′β, 6′β-trimethylcyclohexyl ketone Phenyl nonanyl ether	*Streptomyces chrestomyceticus* ADP4	Antifungal	39
Phenyl acetic acid	*Streptomyces* species	Antifungal	40
Pyrrolidinyl-hexadeca-heptaenone	*Streptomyces* sp. VITAK1	Antifungal	41
Methoxy ethyl cinnamate (ethyl(E)-3-(4-methoxyphenyl)acrylate)	*Saccharomonospora oceani* VJDS-3	Antifungal	42
N-(4-aminocyclooctyl)-3, 5-dinitrobenzamide	*Pseudonocardia endophytica* (VUK-10)	Antifungal	18
Caerulomycin A	*Actinoalloteichus* species	Antifungal	43
Pyrrolo[1,2-a]Pyrazine-1,4-dione,hexahydro-3-(phenylmethyl)	*Streptomyces* sp. VITPK9	Anticandidal	44

Table 4 — Antiparasitic compounds reported in the last decade (2014 to 2023) from actinomcetes isolated from Indian soil samples

Molecule	Organism	Activity	References
Crustecdysone (20-hydroxyecdysone)	*Streptomyces* sp. PBR11	Antiparasitic	10
4-Dodecene	*Streptomyces* sp. VITVSK1	Antiparasitic	46
Protease inhibitor	*Streptomyces* sp.VITBVK2	Antiparasitic	47
Protease inhibitor peptide	*Streptomyces* sp. LK3	Antiviral	48

very effective against fish white spot syndrome virus (WSSV)[45]. The compound 9(10H)-Acridanone at the concentration of 500 µg/animal protected the WSSV-infected shrimp (88.89%), showing the efficacy of the compound against the fish virus.

Antiparasitic compounds from actinomycetes

Antiparasitic compound crustecdysone (20-hydroxyecdysone) isolated from *Streptomyces* sp. PBR11 was reported recently[10]. The compound 20-hydroxyecdysone (20E) (10 µM) induces microfilarial release and immature abortion in the human parasite *Brugia malayi*[46]. Marine isolate *Streptomyces* sp. VITVSK1-derived 4-dodecene and their antiparasitic activity against *Haemaphysalisbispinosa* and *Rhipicephalus* (*Boophilus) microplus*; *Anopheles subpictus* and *Culexquinquefasciatus* larvae have been reported earlier[47]. The compound 4-dodecene showed the LC_{50} and r^2 values against the larvae of *A. subpictus* (82.65 ppm; 0.688), *R. microplus* (173.48 ppm; 0.857), *C. quinquefasciatus* (78.32 ppm; 0.769) and against *H. bispinosa* (126.59 ppm; 0.840) respectively. A protease inhibitor isolated from *Streptomyces* sp.VITBVK2 was reported to be very effective against *Leishmania donovani*[48]. *Streptomyces* sp. LK3-derived protease inhibitor peptide has been reported to be an effective inhibitor of *plasmodium falciparum*[49]. Marine actinomycetes are a good source of protease inhibitors for targeting GP63 protease (Zinc metalloprotease) of leishmanial parasites[50]. A list of antiparasitic compounds reported from actinomycetes isolated from Indian soil samples in the last decade (2014 to 2023) is given in Table 4.

OMICS tools for genome mining of actinomycetes

The large actinomycetes genome usually contains many biosynthetic gene clusters (BGCs) and can produce diverse compounds with multiple biological activities[51]. A detailed scheme for screening of actinomycetes using OMICS tools is shown in Fig. 2. Scientists used OMICS tools to identify new gene clusters and gene cluster families (GCFs)using antiSMASH prediction and characterisation tool for the identification of potential compounds; antiSMASH 7.0 is the latest tool used for

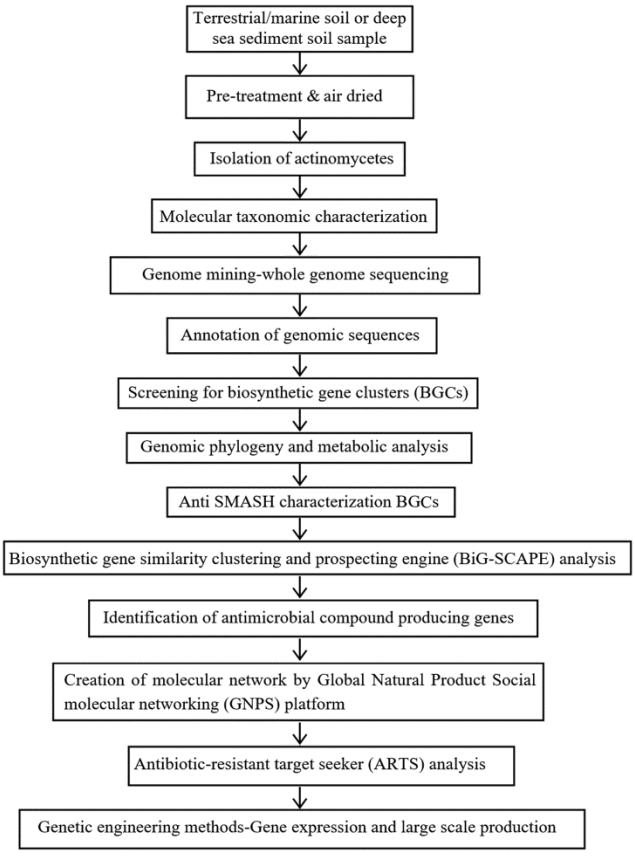

Fig. 2 — Omics tools for exploring actinomycetes genera for identification of antimicrobial compounds producing genes.

predections[52]. The identified BGCs were analysed using biosynthetic gene similarity clustering and prospecting engine (BiG-SCAPE) tool for gene cluster similarity. Antibiotic-resistant target seeker (ARTS) was also used to check the presence of antibiotic-resistance genes. Once identified, the BGC has been modified by genetic engineering methods to improve the efficacy, yield, and better analogues of the bioactive compound[53].

Conclusion

This review summarises the research updates on actinomycetes-derived antimicrobial compounds and their biological applications in India from 2014 to till date. Genome mining studies for identifying BGCs and novel secondary metabolites have yet to be carried out extensively on potential actinomycetes isolated and reported from Indian soil samples. Most of the studies reported were used only cell-free supernatants or crude solvent extracts prepared from potential strains. The secondary metabolite responsible for the bioactivity was reported only in very few studies. Moreover, most of these studies followed the conventional bioactivity-guided extraction and purification of secondary metabolites. These studies are more time-consuming and very tedious processes of purification of complex biomolecules and often ending up with a poor yield of the active compound. Hence, marine actinomycetes research in India has to be focused more towards the use of whole genome sequencing, annotation, identification of BGCs and OMICS tools for the isolation of potential/novel actinomycetes species containing bioactive compounds and new chemical entities to be used as drugs to control superbugs, deadly pathogens and other biological applications from unexplored and under-explored regions.

Conflict of interest

The author declared no conflict of interest.

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