Asian Journal of Research in Biosciences

Volume 6, Issue 2, Page 172-184, 2024; Article no.AJORIB.1557

Exploration of Actinobacteria for Multifaceted Applications: Lessons to Learn from the Genome, Proteome and Metabolome of Pristine Microbial Majority

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Authors' contributions

This work was carried out in collaboration among all authors. Author SL collected literature and prepared the first draft of the manuscript. Authors ND, RTS and PS assisted planning, preparation of the whole manuscript. Author KV conceived the study, planned and prompted the manuscript. All the authors have read and approved the manuscript.

Article Information

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://prh.globalpresshub.com/review-history/1557

Review Article

Received: 11/02/2024
Accepted: 15/04/2024
Published: 19/04/2024

ABSTRACT

Actinobacteria are a diverse group of bacteria known for their prolific production of bioactive secondary metabolites. These metabolites have garnered significant attention in recent years due to their wide-ranging potential for biomedical applications. This review aims to provide an overview of actinobacterial metabolites and their significance in various aspects of biomedical research and

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applications. Actinobacterial metabolites are known for their diverse chemical structures and biological activities. They encompass a wide array of compounds, including antibiotics, anticancer agents, immunomodulators, and enzyme inhibitors. These metabolites have been instrumental in the development of numerous pharmaceuticals that have transformed the field of medicine. In the context of antibacterial research, actinobacterial metabolites have played a pivotal role in combating multidrug-resistant pathogens. Their potent antimicrobial properties have led to the discovery of antibiotics such as streptomycin, vancomycin, and rifamycin, which have been crucial in treating bacterial infections. This review highlights the diverse biomedical applications of actinobacterial metabolites, emphasizing their role in combating infectious diseases, cancer, drug discovery, and immunotherapy. The exploration of actinobacterial biodiversity and their metabolite diversity holds great promise for addressing current and emerging biomedical challenges. Furthermore, advancements in genomics, synthetic biology, and bioprocessing techniques are expected to enhance the production and utilization of actinobacterial metabolites for future biomedical innovations. Moreover, actinobacterial metabolites have shown potential in immunomodulation, opening avenues for the development of immunotherapies and vaccines. Compounds like teicoplanin and tacrolimus have been employed to modulate the immune system and treat autoimmune diseases and organ transplantation.

Keywords: Actinobacteria; antibiotics; anticancer agents; immunomodulation; biomedical applications; secondary metabolites.

1. INTRODUCTION

Actinobacteria are diversified group of Gram-positive bacteria with high guanine and cytosine content in their DNA, which can be adapted terrestrial or aquatic ecological niche. Though they are unicellular like bacteria, they do not have individual cellular structures with cell wall, rather they produce a mycelium that is aseptate and highly slender. Actinobacteria include some of the most common soil, freshwater, and marine types, playing an important role in decomposition of organic materials, such as cellulose and chitin. Hence, they have pivotal role in organic matter turnover, carbon cycle, replenishing the supply of nutrients in the soil, and is an important part of humus formation. Actinobacterial colonies show powdery consistency, chalky texture and stick firmly to agar surface, producing hypha-like filaments and conidia / sporangia-like bacterial cells forming fungi-like colony on the agar media. Actinobacteria produce a variety of secondary metabolites with high pharmacological and commercial interest. From the discovery of actinomycin, a number of antibiotics have been discovered from Actinobacteria, especially from the genus *Streptomyces*. They are widely distributed in soil with high sensitivity to acid and low pH and grows well between pH 6.0 and 9.0. Actinobacteria have a number of important functions, including degradation/decomposition of all sorts of organic substances such as cellulose, polysaccharides, protein fats, organic acids, and so on. They are also responsible for subsequent decomposition of humus (resistant to microbial decomposition) in soil and for the earthy smell of freshly ploughed soils (due to geosmin from *Streptomyces albidoflavus*), producing a number of antibiotics like streptomycin, terramycin, aureomycin, and so on. This review gives an overview about the types of Actinobacteria, their habitat, systematic classification and various biotechnological applications, and their ill effects on plants and animals." Actinobacteria have been extensively studied for their ability to degrade pesticides. *Streptomyces* and other actinobacteria from *Arthrobacter* and *Frankia* genera have been identified.

Common pesticide-degrading actinobacteria include *Gordonia, Kocuria, Nocardioides*, and *Rhodococcus*. Microorganisms can degrade pesticides such as organophosphorous (chlorpyrifos, dimethoate), organochlorine (endosulfan, lindane, pentachlorophenol, pentachloronitrobenzene, hexachlorobenzene), triazine (atrazine, simazine, terbuthylazine), synthetic pyrethroids (deltamethrin, cypermethrin), and benzimidazole (carbendazim) compounds [1,2].

In recent years, many new antibiotics generated by endophytic actinobacteria collected from medicinal plants have been shown to be effective against bacteria, fungi, and viruses. Furthermore, these antibiotics displayed action at much lower concentrations. This demonstrates the antibiotics' powerful and broad spectrum microbiocidal activity, which is derived from

endophytic actinobacteria, primarily from the *Streptomyces* genus.

Multi-drug resistance potential in pathogens is increasing everyday as a result of excessive antibiotic use. Scientists from all over the world are constantly searching for novel antibiotic molecules to combat this problem. Endophytic microorganisms, particularly actinobacteria, appear to be a source of innovative and effective chemicals to battle the growing number of multidrug-resistant infections. Out of 65 strains of endophytic actinobacteria, 12 strains were able to suppress penicillin-resistant *Staphylococcus aureus*, belonging to the genus *Glycomyces*. The bulk of them were *Streptomyces* obtained from plants *Achyranthes bidentata*, *Paeonia lactiflora, Radix platycodi*, and *Artemisia argyi* [3].

El-Shatoury *et al.,* [4] found larvicidal activity in *Streptomyces* sp. isolated from *Artemisia herba-alba, Echinops spinosus, Balotta undulate*, and *Mentha longifolia*. The authors evaluated the cytotoxic effect on *Artemia salina* larvae and found 27 out of 41 endophytic actinobacteria, with nine isolates, primarily from *Artemisia* and *Echinops*, exhibiting a high mortality rate of 100% after 12 hours. *Streptomyces albovinaceus* and *S. badius* isolated from Asteraceae plants were also discovered to have substantial larvicidal activity against *Culex quinquefasciatus* (mosquito larvae) in the first and fourth instar stages [5]. Six isolates demonstrated high larvicidal activity (80-100% mortality), while four isolates exhibited robust larvicidal activity (100% mortality) at the fourth instar stage.

Natural antioxidants, or phenolic substances, give protection by scavenging damaging free radicals. Endophytic *Streptomyces* sp. isolated from *Alpinia oxyphylla* produced two active chemicals 2,6-dimethoxyterephthalic acid, which displayed high antioxidant potential [6]. Tanvir *et al.,* [5] found that 66.6% of the endophytic actinobacteria isolated from medicinal plants had strong antioxidant activity. Anti-inflammatory medications are used to reduce inflammation, and one of the endophytic actinobacteria demonstrated this property. Taechowisan *et al.,* [7] found that *Streptomyces aureofaciens*-produced 5,7-dimethyloxy-4-p-methoxylphenylcoumarin and 5,7-dimethoxy-4-phenylcoumarin were effective anti-inflammatory drugs.

Overuse of agrochemicals has significantly reduced soil fertility and threatens to deprive a large population of important food supplies. Remedial measures involve the use of natural means to sustain and grow our treasured agricultural lands. Actinobacteria, a naturally occurring microorganism in bulk soil or rhizosphere soil, have attracted the interest of nearly all researchers who work to device toxicity free natural products for agricultural use. Because of their exceptional qualities compared to other microorganisms, they are excellent for increasing soil quality, enhancing plant development, and thereby contributing to the Green Revolution [8].

2. ANTISEPTIC PROPERTIES

One of the major risks to modern development, food security, and global health is microbial antibiotic resistance. According to the World Health Organization's Global Report on the Surveillance of Antimicrobial Resistance [9], bacterial resistance to frequently used antibiotics in the treatment of infections has increased to worrying levels in many regions of the world. In 2017, According to Monciardini *et al.,* [10], powerful actinobacteria that produce antibiotics were isolated from sea sediment which were exposed to physical pre-treatment techniques to promote their development. Similar aseptic techniques were used in the current investigation to stop the formation of undesirable germs. In a study by Norouzi *et al.,* [11] the Kirby-Bauer disc diffusion method was used to compare the antibacterial potential of crude extracts from several actinobacteria against numerous bacterial pathogens with antibacterial activity of Gentamicin. Two powerful marine actinobacteria isolates, MN2 and MN39, were able to synthesize biomolecules with antibacterial activity against multidrug-resistant (MDR) bacteria, according to the disc diffusion analysis.

3. ANTIFUNGAL ACTIVITY

Many actinobacteria especially those from the genus *Streptomyces*, are renowned as antifungal biocontrol agents because they prevent a number of fungal plant infections from growing [12,13]. The synthesis of antifungal substances and extracellular hydrolytic enzymes is often correlated with *Streptomyces* species antagonistic action against fungi infections [14,15]. Major hydrolytic enzymes in the lysis of fungal cell walls include chitinase and -1,3-glucanase, for example, the cell walls of *Fusarium oxysporum*, *Sclerotinia minor*, and *Sclerotium rolfsii* to breakdown the cell wall metabolism many actinobacteria were isolated

[16]. Extracellular metabolites from *Streptomyces* species have been studied for their antifungal properties against various fungi in prior studies. The antagonistic capacity of extracellular metabolites from *Streptomyces* strains to inhibit the growth of fungal infections, such as *Colletotrichum gloeosporioid-es* and *Sclerotinia rolfsii* (with a broad host range), is, however, little understood Errakhi *et al.,* [12] not only human infection and also in agriculture field *Arachis hypogaea* L., or groundnuts, are among the most significant oilseed crops. Thirteenth in the list of most important food crops is groundnut. Around the world, leaf spot disease is nearly always present alongside plants and causes a large loss in output [17]. Identify marine sample from different place were showed various activity later it was found it belong to *Streptomyces*. Short-chain dehydrogenase/reductase enzymes in *Fusarium oxysporum* were shown to be docked with antifungal compounds from marine sediment associated actinobacteria collected from Muthupet mangrove lagoon ecosystem, Tamil Nadu. Compounds were initially discovered by GC-MS/MS analysis and were thought to be the possible candidate ligands for the observed antifungal effects [18]. Similar investigation to identify the potential target in leaf spot disease pathogen *Pithomyces atro-olivaceous* of groundnuts resulted in the mitochondrial ATP synthase subunit 'A' present in the F0 complex. The fungicide leads from marine actinobacterium *Kutzneria* sp. TSII were the promising candidates with antifungal activity as revealed in the investigation utilizing GC–MS/MS and molecular docking analysis. Due to the fact that this subunit is essential for proton channelling across the inner mitochondrial membrane, which permits ATP generation in *Pithomyces atro-olivaceous* mitochondrion, targeting ATP synthesis with potential antimetabolites of marine actinobacteria would be promising ideology [19].

4. ANTIVIRULENCE PROPERTIES

AMR is one of the major dangers to global public health that needs to be addressed right away. AMR poses a challenge to the successful prevention and treatment of diseases caused by infection-causing microbes, including viruses, fungi, and bacteria, by leading them to develop novel resistance mechanisms. Actinobacteria produce secondary metabolites as part of their life cycle and apoptosis process, which are necessary for the organisms to defend themselves against environmental infections [20]. Bacteria can develop a genetic resistance to antibiotics after being exposed to them frequently. The production of biofilms, which are homogeneous or heterogeneous microbial populations living in a self-produced matrix of extracellular polymeric molecules, is one of the numerous ways that bacteria avoid exposure to antibiotics. Because biofilms enable its microbial cells to momentarily enter a metabolically dormant state, antibiotics are rendered ineffective and disease recurs because latent bacterial infections persist within the host [21]. Antifungal and antibacterial medications have reportedly lost their effectiveness due to pathogen resistance. Treatment of systemic mycosis is a difficulty due to the evolution of azole resistance against *Candida* and *Aspergillus sp.* Fluconazole is resistant to a variety of *Candida sps. Candida krusei, Candida glabrata, Candida tropicalis, Candida parapsilosis*, and *Candida albicans* are the species with the greatest worldwide resistance rates, with 78.3%, 15.7%, 4.1%, 3.6%, and 1.4%, respectively [22]. The prevalence of antifungal resistance varies throughout several nations. *C. glabrata* resistance to fluconazole reached 36% in the US [23]. Fluconazole resistance in *C. albicans* is quite prevalent in Mexico, reaching 94.9% [24]. It is still a very difficult challenge to control infections caused by methicillin-resistant *S. aureus* (MRSA). Hospital isolates of multi-drug resistant (MDR) bacteria frequently have methicillin resistance. 90% of Americans are now resistant to methicillin, followed by levofloxacin (78.6%), ciprofloxacin (68%) and clindamycin (48.5%) [25]. We urgently need new approaches to identify novel antifungal and antibacterial Candidates that are risk-free, non-toxic, and more potent. In the environment, actinobacteria are widely distributed and have a wide range of taxa [22].

5. ANTIBIOFILM ACTIVITY

In the natural world, bacteria may create biofilms, multi-layered structures that use proteins, nucleic acids, and exopolysaccharides to bind microbial populations to solid surfaces [26]. Worldwide, a wide range of public health issues are raised by foodborne microorganisms. Foodborne illnesses have emerged as a significant issue in a number of food businesses and are frequently linked to consumer and worker microbial infections. It is believed that biofilm causes 80% of all bacterial illnesses [27]. To enter a habitat that protects them from hostile environmental factors and encourages the buildup of vital nutrients, bacteria create a biofilm [28]. They also pose a serious

threat to marine aquaculture [29,30]. Because bacteria are rapidly developing resistance to all antibiotic classes, antibiotics are useless in treating biofilm-associated illnesses. The type and structure of the biofilm, the availability of nutrients and oxygen for bacterial cells, and innate and acquired bacterial resistance are other variables that affect resistance. Known for producing bioactive chemicals, actinobacteria are used extensively in the pharmaceutical, agricultural, and food sectors. This bacterial group has shown the capacity to generate effective antibiofilm compounds. *Streptomyces albus* and *S. akiyosheinsis*, which, respectively, prevent *Vibrio harveyi* and *Staphylococcus aureus* biofilms, are two instances of this [31]. Microbial cells make up less than 10% of the dry mass of the biofilm, with the EPS making up approximately 90% of the overall biofilm. The interactions between the components of the EPS determine the physiological activity of the bacteria in the biofilm, which in turn drives the EPS's self-organization in the matrix. The biofilm's matrix shields the microbes from host immune systems in addition to environmental stressors such desiccation, UV light, metals, antibiotics, and oxidizing chemicals [32]. The Biofilms are, therefore, communities of aggregated bacterial cells embedded in an extracellular polymeric matrix [33].

6. ANTIFOULING PROPERTIES

Marine biofouling is a dynamic process that starts as soon as anything is submerged in water and can take hours to months to develop. It is the unwanted buildup of micro and macroorganisms on submerged surfaces, including bacteria, algae, larvae, and adults of many phyla, as well as their by-products [34]. The process of biofouling is divided into four distinct phases: the physical adherence of macromolecules is followed by the microfouling phase, which is characterized by a biological component. A bacterial biofilm is responsible for creating the proper surface for the subsequent macrofouling organisms to settle on, first as spores and larvae, which then mature into adults [35]. It's interesting to note that marine actinobacteria secrete a variety of safe and effective antifouling chemicals. These metabolites are classified chemically as peptides, polyketides, isoprenoids, sterols, and phenazines, among other groups. It is known that *Streptomyces* sp. produces fatty acids, quorum-sensing inhibitor as antifouling compounds, terpenoids, and steroids [32]. Several businesses, including aquaculture, power plants, and shipping, are at danger due to marine biofouling [34]. Settlement on the vessel's hull results in damage to the rudder and propulsion systems, an increase in drag of up to 60%, and an increase in fuel consumption of up to 40%, as well as an increase in CO_2 and SO_2 emissions. In addition, hull biofouling and ballast water transfer are the primary mechanisms by which alien marine organisms are introduced and spread across the world's ecosystems, resulting in environmental imbalances [36].

7. ANTIOXIDANT POTENTIAL

Antioxidants (AA) slow down the degradative process so that the environment's energetic action can result in greater sustainability. They engage with FR, which enables their oxidation of oxygen. Synthesis antioxidants and natural antioxidants are the two groups of antioxidants that may be distinguished. The majority of synthetic antioxidants produce compounds that cause cancer or other disorders, which is how the two groups vary from one another. Antioxidants can be categorized based on their nature or their function [37]. Ascorbic acid and its derivatives, tocopherols, gallic acid esters, erythorbic acid and its sodium salt, BHA, BHT, and further chemicals THBP and TBHQ are examples of compounds that include ascorbic acid. Secondary antioxidants are compounds that have antioxidant properties but also serve other purposes. Secondary antioxidants include lecithin, sulphur dioxide, and sulphites. In addition to the aforementioned compounds, there are other substances that can enhance the effects of primary antioxidants. These include substances like lactic acid and lactates, citric acid and citrates, tartric acid and tartrates, etc. that either work synergistically or through the catalysis of metal complexes in self-oxidation reactions [38]. The common pathway for cancer, aging, and many other illnesses is cellular damage, which antioxidants play a crucial role in preventing. Antioxidants stop the electron-"stealing" process and destroy free radicals by contributing one of their own electrons. Because they are stable in both forms, the antioxidant nutrients themselves do not turn into free radicals by accepting an electron [39]. They take on the role of scavengers, assisting in preventing cellular damage and disease-causing tissue and cell damage. The body's largest fat-soluble antioxidant is vitamin E. It is one of the best chain-breaking antioxidants on the market, the main protector against oxidation, and the main protector against lipid per oxidation the formation

of unstable molecules with an excess of oxygen) [37]. The primary objective is to evaluate the bioactive compound-producing actinobacteria with efficient radical scavenging capacity by screening the isolated actinobacteria obtained from Chennai, Tamil Nadu [39].

8. ANTIPROTOZOAL ACTIVITY

An intracellular protozoan parasite belonging to the class *Leishmania* causes the vector-borne illness leishmaniasis. Additionally, a contaminated female phlebotomine sandfly's nibbling might disseminate. it between the more than 20 *Leishmania* species that have been found or recognized, three main kinds of the illness have been recorded in humans. They include visceral leishmaniasis (VL), often known as kala-azar or black fever, and cutaneous leishmaniasis (CL), the more common and less severe variant with typically self-healing ulcers. The disease's most severe stage, later, which presents as a systemic sickness. In more than 95% of instances, it is fatal if left untreated. The third condition, known as mucocutaneous leishmaniasis, is a rare form of the disease brought on by the cutaneous form of the parasite. It is characterized by the partial or full obliteration of the mucous layers of the mouth, throat, and nose [40]. Due to the widespread antibiotic-resistant bacteria that cause deadly illnesses like leishmaniasis, the demand for innovative antibiotics is currently rising. Furthermore, the generation of secondary metabolites, which operate as survival strategies for these strains in an uncommon and harsh marine environment, has been linked to the diverse bioactivities displayed by marine actinobacteria [41]. Over 95% of the biosphere's total organic diversity may be found in the ocean, which covers more than 70% of the planet's surface [42]. Researchers who switched to new environments for marine fungi and bacteria that appear to be the most significant sources for novel antibiotic discovery because of their diversity and potential to grow very quickly with high yield in bioreactors found that combating human pathogens was challenging. The sea floor has been created as a habitat for unusual actinobacteria strains of microbes [43].

9. ANTICANCER POTENTIALS

The incidence of cancer is predicted to increase to 26.4 million annual cases worldwide with 17 million fatalities connected to the disease by 2030, from an estimated 12 million new cases and 7.6 million cancer-related deaths in 2008. The majority of these additional cancer cases are anticipated to arise in African nations with low incomes [44]. Cancer undoubtedly remains one of the most serious human health problems and breast cancer is the second most universal cause of cancer deaths in women [45]. Global warming, dietary changes, and changing lifestyles contribute to the terrible human disease known as cancer. There are no effective cancer therapies because some of the medications that are currently in the market have alarming negative side effects. In this regard, natural compounds made from therapeutic plants have become more important for the treatment of cancer. The WHO estimates that 80% of the world's population, mostly those in underdeveloped nations, depends on plant-derived medications for their medicinal needs [46]. Some antioxidants, especially β-carotene, may be helpful in treating precancerous disorders like oral leukoplakia, which may be a sign of oral cancer, according to preliminary research [47]. Streptopyrrolidine, cyclo-(l-Pro-l-Met), streptochlorin, lynamicins, marizomib, and thiocoraline are important secondary metabolites from marine actinobacteria having anticancer potential. ULDF4 and ULDF5, chemical extracts produced from *Streptomyces* strains discovered in Lagos, Nigeria, are the two examples of new anticancer metabolites [48]. ULDF4 and ULDF5 are cytotoxic to human acute myelocytic leukaemia, cervical cancer, stomach carcinoma, breast adenocarcinoma, and acute promyelocytic leukaemia. ULDF4 and ULDF5 are structurally related to staurosporine and kigamicin, which are known to cause apoptosis and necrosis, respectively. Ketomycin is another promising anticancer chemical. Ketomycin lowered breast cancer cell migration and invasion, inhibited NF-κB activity in upstream signalling by limiting the autophosphorylation of inhibitory-κB kinases alpha (IKK-α) and beta (IKK-β), and minimized 3D invasion of breast cancer cells [49]. These hybrid BGCs and CGCs are promising sources of new secondary metabolites and chemotherapeutic agents for medicines. *Streptomyces* substances such as staurosporine, kigamicin, and ketomycin, as well as BGCs/CGCs, should be studied further in order to discover new anticancer therapies. *Streptomyces* was shown to contain the most current anticancer metabolites. In addition, the genera *Actinoalloteichus, Actinokineospora, Actinomadura, Actinosynnema, Amycolatopsis, Catenuloplanes, Dietzia, Microbacterium, Micromonospora, Nocardiopsis*, *Nonomuraea,*

Saccharomonospora, Tsukamurella, Umezawaea, and *Verrucosispor* were also studied to explore anticancer metabolites of interest.

10. PUPICIDAL (OR) LARVICIDAL PROPERTIES

In many respects, arthropods are the most significant organisms in terms of humans and the environment. While most insects are good for the environment, people, and other creatures, others can be harmful to mammals and people. Vector-borne insects can infect humans and other mammals with a number of deadly diseases. Among hematophagous insects, mosquitoes are the most dangerous carriers [50]. They spread dangerous infections that kill millions of people year and have a significant negative influence on public health, labor productivity, and the economy [51]. Diseases like Japanese encephalitis, filariasis, dengue, malaria, dengue hemorrhagic fever, yellow fever, Zika, and chikungunya are primarily spread by mosquitoes [52,53,54]. In 1996, the World Health Organization designated mosquitoes as the "number one public enemy [55]. Diseases spread by mosquitoes claim millions of lives each year. Mosquitoes can thrive in a variety of aquatic environments, including paddy fields, ponds, overhead tanks, brackish water, sewage waters, freshwater pools, and even small containers filled with stagnant rainfall [55]. Not only are mosquito's significant etiological agents for humans, but also for other indigenous wildlife [56]. The increasing severity and spread of mosquito-borne illnesses can be attributed to changes in the environment and ecology, such as urbanization [57].

11. BIOCONTROL PROPERTIES

The following intrinsic benefits of using actinobacteria as biocontrol agents explain their significance: (1) they are not hazardous to plants, (2) they are not dangerous to humans or animals, (3) they increase plant yield, and (4) they reduce the need for synthetic fungicides [58]. Since *Streptomyces* is the easiest to isolate, it is one of the genera that has been investigated the most [59]. The growth of actinobacteria is slower than that of bacteria. To acquire desired actinobacteria in culture media, growth enhancement approaches should be used. These methods are predicated on the use of selected isolation medium and sample pre-treatments, including wet, chemical, and drying pre-treatments of soil containing calcium carbonate, among other methods [60] Furthermore, the addition of leaf residues from Brassica napus and Brassica rapa to the soil encouraged the growth of actinobacteria populations. The suppression of the *R. solani* wilt disease was strongly correlated with the growth in the actinobacteria population [61].

Actinobacteria create a class of antibiotics called macrolides, which prevent the synthesis of fungal proteins [58]. Amphotericin B specifically binds to ergosterol in the fungal cell membrane, altering its permeability and triggering lysis of the cells [59]. Furthermore, *Streptomyces sp*. strains' production of actinomycin D inhibits microbial growth and RNA synthesis [60]. The mitochondrial electron transport chain connecting cytochromes b and c is inhibited by antimycin [62]. When natamycin attaches itself to the ergosterol in the fungal cell membrane, it prevents fungal growth antimycin [62]. Neopeptine is an enzymatic inhibitor of microbial cell wall production [63]. Symbiosis between actinobacteria and plants is another significant mechanism involving the manufacture of antibiotics, as the antibiotic shields the plant against phytopathogenic fungi and the plant exudates promote actinobacterial development [64].

12. PLANT GROWTH PROMOTING POTENTIALS

Actinobacteria that promote plant growth employ a combination of direct (such as hormone production) and indirect (such as pathogen inhibition) strategies to impact plant growth and defense [70]. The most often utilized microorganisms in inoculant compositions are plant growth-promoting bacteria (PGPB), particularly those that colonize the rhizospheric portion of the plant (also known as plant growth-promoting rhizobacteria, or (PGPR) [71]. Plant-growth-promoting actinobacteria (PGPA) and plants have been investigated in great detail throughout the years. Generally speaking, the PGPA that has the ability to form microbial inoculants can help the host plant in two ways: by increasing the bioavailability of nutrients (via biological nitrogen fixation, phosphate solubilization, and siderophore production) and by modulating phytohormones (via the synthesis of auxins, gibberellins, cytokines, and 1-aminocyclopropane-1-carboxylate (ACC) deaminase) [72]. Nitrogen is a well-known and essential component of proteins and nucleic

Table 1. Gene clusters, proteome and metabolome of actinobacteria for biomedical applications

S. No.	Name of actinobacteria	Gene clusters / Proteome of actinobacteria	Metabolites from actinobacteria	Biological function	References
1.	*Micromonospora sp. TP-A0468*	Polyketide synthase (PKS Type II)	Kosinostatin	Antitumor / Anticancer	[65]
2.	*Streptomyces halstedii*	PKS (Type I) / HLS cluster	Halstoctacosanolide	Polyketide Antibiotics	[66]
3.	*Streptomyces atroolivaceus*	Transat PKS-NRPS Hybrid	Leinamycin	Antitumor / Antimicrobial	[67]
4.	*Streptomyces verticillus*	Type I PKS-NRPS Hybrid	Bleomycin	Cancer chemotherapy as antineoplastic agent	[68]
5.	*Salinispora tropica CNB-440*	Terpene biosynthetic cluster	Sioxanthin	Antioxidant Carotenoids	[69]

acids. It is also a nutrient that is necessary for plant growth. Although 78% of the atmosphere is made up of nitrogen gas, which is widely present in the air, plants cannot absorb it directly until it is transformed into its soluble form [73]. The nitrogenase enzyme system, which is employed by the biological nitrogen fixer (BNF) transforms atmospheric nitrogen into ammonium and nitrates, which are needed by plants [74]. In order to counteract the limited availability of nitrogen provided by biological nitrogen fixers, synthetic nitrogen fertilizers are also supplied. However, the sustainability of agriculture and public health may be compromised by these fertilizers. Actinobacteria are hence an excellent alternative to be used as BNF to enhance plant growth for sustainable agriculture. *Frankia* is a flexible actinobacterium that can fix nitrogen in nonlegume plants both freely and in symbiotic relationships. It can enter the root cell by a variety of routes, including intracellular root-hair invasion and intercellular root invasion [75]. The effects of *Streptomyces*–plant interactions that promote plant growth can be categorized into three categories: biofertilization, biostimulation, and bioprotection, as stated for other advantageous interactions [76]. Certain critical mineral nutrients are present in insoluble forms in many soils due to their mineralogical and electrochemical characteristics, making them unavailable to plants [8].

13. MULTI-OMICS TO EXPLORE ACTINOBACTERIAL METABOLITES FOR BIOLOGICAL APPLICATIONS

In the recent decades, advent of multi-omics approaches has updated the mechanistic role played by genomes, transcriptomes, proteomes and metabolomes of actinobacteria in constructing the useful biomolecules for the above-described properties for humankind. The following Table 1 shall explain well in detail about the participative gene clusters for the biosynthesis of suitable metabolites for diversified biomedical applications and explore the promising multifarious potential of actinobacteria which are pristine microbial majority. Biomining of this treasure would guide the future researchers to find all possible solution to the arising problems of mankind.

14. CONCLUSION

In conclusion, actinobacterial metabolites offer a treasure trove of bioactive compounds with vast potential for biomedical applications. These versatile bacteria have proven to be prolific producers of antibiotics, anticancer agents, immunomodulators, and other therapeutically valuable compounds. Their unique metabolic pathways and diverse ecological niches continue to inspire researchers to discover novel compounds with promising pharmaceutical properties. However, while actinobacteria have yielded numerous valuable metabolites, challenges remain in optimizing production, scaling up, and ensuring sustainability. Additionally, the ongoing issue of antibiotic resistance highlights the need for continuous exploration of new actinobacterial metabolites and their mechanisms of action. As we delve deeper into understanding actinobacterial genetics, metabolic pathways, and ecological interactions, we can harness the potential of these microorganisms to address pressing biomedical challenges and improve human health. Collaborations between microbiologists, synthetic biologists, and pharmaceutical researchers will be crucial in unlocking the full potential of actinobacterial metabolites for the benefit of mankind.

ACKNOWLEDGEMENT

All the authors thank Sacred Heart College (Autonomous), Tirupattur for providing necessary facilities for the preparation of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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