Review Article

Pharmaceutical and Biotechnological Importance of Actinobacterial Products

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ABSTRACT

Many compounds produced by marine microbes possess significant pharmaceutical applications. Actinobacteria are one among the microbes producing a variety of antibiotics. Apart from antibiotics, it also produces many novel enzymes and important pharmaceutical products. Actinobacteria serves as a reservoir of antibiotics and novel chemical compounds and it contributes 80% of antibiotics available in the market. It was continuously been explored for novel bioactive compounds and new chemical entities. Many of them are more promising against microbial pathogens and even drug resistant pathogens. Apart from antibiotics, many enzymes are also produced by actinobacteria. The usage of enzymes in diverse pharmaceutical and biotechnological industries is gaining momentum and moreover, there is a growing demand for the discovery of novel metabolites and enzymes to fulfill the requirement of pharmaceutical industry. Apart from all these products actinobacteria also produces biosurfactants. Members of actinobactaerial genera have been extensively used in the removal of toxic dyes and other toxic pollutants. In this review, the up to date information available on the pharmaceutical and biotechnological uses of actinobacterial products and the scope for screening of actinobacterial genome for production of novel compounds for pharmaceutical applications have been discussed.

Key words: Actinobacteria, Metabolites, Antibiotics, Enzymes, Biosurfactants, Dye degradation.

INTRODUCTION

Actinobacteria are Gram-positive bacteria with high G+C content, produces various compounds such as antibiotics, biosurfactants,immunemodifiers,probiotics, enzymes and enzyme inhibitors (Figure 1) which are useful in pharmaceutical, textile, paper, food, leather and detergent industries.[1] Actinobacteria are found in various natural habitats like soil, water, freshwater, ponds, lakes, industrial effluents, waste water and in marine environment[2] Actinobacteria grow on adverse environments are useful in decomposition of organic matter.[3] Actinobacteria derived from both marine and terrestrial environments are known to produce several bioactive compounds with potential pharmaceutical applications. Actinobacteria derived secondary metabolites are proved to be very effective in inhibiting bacterial biofilm formation.[4] Bacterial biofilm confers protection to antibiotic treatment. Few of them are rare strains due to their poor growth rate, they are *Actinoplanes, Microbispora, Micromonospora, Dactylosporangiu* and *Kineospora*.[5]

Actinobacteria are valuable prokaryotes considered as the richest source for several natural products of commercial interest and nearly half of the compounds available in the market are from actinobacteria.[6] Marine microorganisms especially actinobacteria are involved in the degradation of dead plankton, plants and animals which helps in cleaning of the environment clean for the survival of other macroorganisms. Several new compound of pharmacological and industrially importance was reported from actinobacteria isolated from

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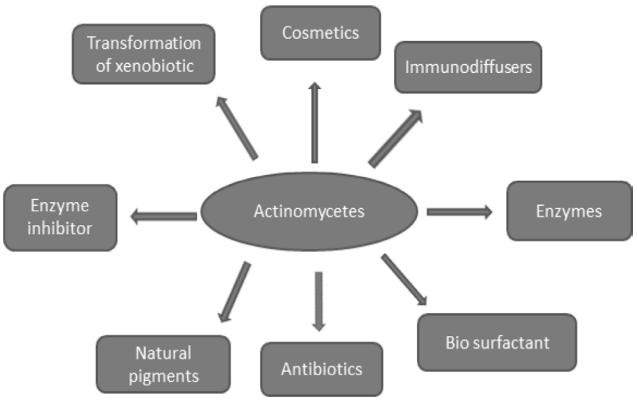

Figure 1: Pharmaceutical and biotechnological applications of actinobacteria.

marine, unexplored regions and wet land. Many actinomycetes produce several enzymes like peptidase, xylanase, lignilase, amylase, pectinase, hemicellulase and keratinase.[7] Production of these enzymes by actinobacteria enables them to degrade the organic matter found in the marine environment.[8] This paper mainly focuses the pharmaceutical value of actinobacterial derived secondary metabolites.

Pharmaceutical applications of actinobacteria

Actinobacteria is considered as a major producer of antibiotics[1] (Table 1). Most of the commercially available antibiotics are derived from the group *Streptomyces*. It also produces a variety of secondary metabolites of pharmaceutical importance.[9,10] Actinobacteria also synthesize various enzyme inhibitors of low molecular weight compounds used in cancer treatment. Rrevistin, an enzyme derived from *Streptomyces* species plays a significant role in inhibiting reverse transcriptase and alistragin from *Streptomyces roseoviridis* found a role in inhibiting carboxypeptidase.[11] *Streptomyces tsukubaensis* sp. produces immunomodifiers FR-900506 showed inhibitory activity against interleukin-2 production, mixed lymphocyte reaction, interferon and cytotoxic-T cells.[12] Actinomycetes derived antimicrobial, anti-insecticide; anticancer, anti-parasitic compounds have wide range of applications in numerous pharmaceutical industries.

Enzymes from actinobacteria

Actinobacteria produces several enzymes with diverse activities which help in the process of mineralization of organic matter and also help in canalization of various biochemical reactions. Production of various enzymes such as L-glutaminase, α-galactosidase, amylase, cellulase, protease, L-asparaginase was reported from marine actinobacteria.[13] Amylases hydrolyze starch molecule to give various products like dextrins and

Table 1: Natural product antibiotics from actinobacteria.

Antibiotic Name	Actinobacteria	References
Streptomycin	*Streptomyces griseus*	49
Neomycin, Tylosin A	*Streptomyces fradiae*	50
Kanamycin	*Streptomyces kanamyceticus*	51
Erythromycin A	*Streptomyces erythraea*	52
Oleandomycin	*Streptomyces antibioticus*	53
Spiramycin	*Streptomyces ambofaciens*	54
Monensin A	*Streptomyces cinnamonensis*	55
Tiacumicin B	*Dactylosporangium aurantiacum* sub sp. *hamdenensis*	56
Rifamycin SV	*Amycolatopsis mediterranei*	57
Kanglemycin A	*Nocardia mediterranei* var. *kanglensis*	58
Oxytetracycline	*Streptomyces rimosus*	59
Chlortetracycline	*Streptomyces aureofaciens*	60
Pristinamycin IA/IIA (PIA and PIIA)	*Streptomyces pristinaespiralis*	61
Fattiviracins	*Streptomyces microflavus*	62
Lomofungin	*Streptomyces lomondensis*	63
Actinomycin D	*Streptomyces chrysomallus*	64
Oxanosine	*Streptomyces capreolus MG265-CF3*	65
Nanchangmycin	*Streptomyces nanchangensis*	66
Kenalactams A-E	*Nocardiopsis* CG3	67
Nystatin A1	*Streptomyces noursei*	68
Nystatin-BSG005	*Streptomyces noursei GG5073SP*	69
Amphotericin B	*Streptomyces nodosus*	70
Natamycin	*Streptomyces natalensis*	71

smaller polymers consist of glucose unit. Several thermo stable actinobacteria including *Thermomonospora* and *Thermoactinomycetes* are the biggest producers of amylases. Cellulase is another group of hydrolytic enzymes used in detergents, color extraction from juices, biostoning of jeans, pretreatment of biomass containing cellulose to improve the nutritional quality of forage.[14] Two groups of extracellular amylases namely α-amylase and glucoamylase are reported from actinobacteria.[15] These amylase containing detergents were used for washing clothes at a lower temperature.[16] Production of α-amylase by *Streptomyces* sp. SBU3 has already been reported.[17]

Organisms like *Thermobifida fusca* and *Acidothermophillus cellulolyticus* are useful in biofuel industry.[18] The enzyme lipase has several applications in food, chemical,

Table 2: Industrially important enzymes from actinobacteria.			
Microbes	**Enzymes**	**Applications**	**References**
Streptomyces	Amylase	Food and beverage industries	35
Streptomyces	Protease	Leather, photographic and detergent industries	28
Nocardiopsis albus sub sp. *prasina* OPC-131	Chitinase	Sea food industry	36
Streptomyces	Pectinase	Fruit and vegetable processing industry	36
Streptomyces purpeofuscus *Streptomyces albidoflavus*	Xylanase	Pulp and paper industry	37
Streptomyces griseorubens	Cellulase	Biofuel industry	38

Table 3: Other products from actinobacteria.			
Actinomycetes	**Product**	**Applications**	**References**
Streptomyces sp.VITDDK3	Biosurfactant	Textile industry	72
Streptomyces sp.	Probitotic	Aquaculture industry	60
Streptomyces sp. NK458	Enzyme (Dextranase)	Food industry	73
Thermobifida fusca BCRC 19214	Enzyme (Laccase)	Hair coloring agent	74
Kocuriarosea HN01	Compound	Agriculture	75
Actinomadura keratinilytica strain Cpt29	Enzyme (Keratinase)	Leather industry	76
Pseudonocardia thermophila JCM3095	Enzyme (Nitrile hydratase)	Acrylamide production	34
Streptomyces sp. strain AH4	Enzyme	Detergent industries	47
Actinomycetes nocardiopsis A17	Biosurfactant	Pharmaceutical and cosmetics industry	77
Streptomyces griseoaurantiacus	Enzyme (cellulase)	Biodegradation	78

pharmaceutical and detergent industries. Microbial lipases are well known for its stability, selectivity and broad spectrum specificity which play a vital role in several biotechnological industries for the synthesis of biopolymers and biodiesel.[19] Protease is another group of enzyme produced from micro-organisms for industrial use.[20] More than 60% of the proteases are produced from micro-organisms and used for commercial applications, which include toothpastes for its antiplaque activity and antitartar cosmetics and recovery of silver from the used X-ray films.[21] Enzymes produced by actinomycetes are used in lignocellulose degradation in the pulp and paper industries and textile industries. Alkaline protease production by *Thermoactinomyces* sp. RS1 has already been reported.[22] Potential cellulolytic acidothermophilic actinobacterium DSK59 isolated from banyan tree finds potential application in bio refinery processes and the cellulase from the isolate hydrolyze sorghum biomass.[23] Other industrially important enzymes such as dextran's, nitrile hydrates, lactase and carbon monoxide dehydrogenasemes are also isolated from *Streptomyces* sp, *Pseudonocardia thermophila* and *Thermobifida fusca.* The enzyme laccase produced by *Thermobifida fusca* are used as a hair coloring agent.[24] Martinez and his coworkers immobilized thermo stable nitrile hydrates produced by *Pseudonocardia thermophila* in the gel matrix for acrylamide production.[25] Fibrinolytic protease activity (blood clot lysis) by *Streptomyces radiopugnans* VITSD8 has been reported recently.[26] Important enzymes produced by actinobcteria are given in Table 2.

Biosurfactants from actinobacteria

Products derived from actinobacteria are given in Table 3. Surfactants are important chemical products used in soaps and detergents. Production of bio surfactants from microbial sources like yeast, actinobacteria and bacteria[27] and its applications in a wide variety of fields like agriculture, cosmetics, pharmaceuticals, detergents, food processing, textile manufacture and paint industries[28,29] have been reported. Bio surfactants produced from actinobacteria serves as an alternatives for synthetic surfactants used in many industries, for environmental applications like enhanced oil recovery, lubrication, bioremediation, crude oil drilling, foaming, wetting, dispersion and solubilisation.[30] Marine sponge derived micro-organism have gained an intense importance for the production of bio surfactants and metabolites for their high stability and biochemical accessibility.[31] It was reported that bio surfactants display important biological activities including antimicrobial, insecticidal, immune modulation and antitumor activities.[32] Production of lipopeptide bio surfactant from marine sponge, *Dendrilla nigra* derived actinobacteria, *Brevibacterium aureum*

MSA 13 has been reported.[33,34] Recently extraction of lipid based bio surfactant produced by *Actinomycetes nocardiopsis* (strain A17) has been reported. It serves as a chemical surfactant source for use in pharmaceutics and cosmetics.[35] Trehalose, a lipid biosurfactant produced by rare actinobacteria, *Rhodococcus* species and *Mycobacteria* species.[36]

Dye degradation by actinobacteria

Biodegradation of azo dyes is economical and highly environment friendly which is applicable for the control of environment pollution caused by growth of industries leading to adverse effect on human health and ecology.[37] Effluents from the textile industries include dyes, heavy metals, detergents, grease, oil and other inorganic salts. The textile dye effluents are very hard to degrade due to its color, pH, high temperature, high Chemical Oxygen Demand (COD).[38] Azo dyes are the most used dyes in textile industries compared to natural dyes due to its variety in color.[39] Physical and chemical methods of removing dyes will eventually lead to large amount of sludge's causing environmental pollution. Microorganisms play a significant role in converting toxic compounds into normal harmless products such as carbon dioxide and water. Bioremediation through microorganisms is a cost effective and environmental friendly.[40] Actinobacteria degrades chemical dyes easily in 8 to 10 days. Combination of two organisms will be highly effective in dye degradation rather than using one organism.[41] The microbial discoloration of azo dyes leads to formation of colorless aromatic amines by reductive cleavage of azo linkage under anaerobic conditions. Under aerobic condition biodegradation of simple sulfonated amino-benzane and amino-naphthalene compounds is very simple and effective.[42] However, the genus *Streptomyces* was considered as the best source for degradation of several azo dyes in textile as well as in detergent industries. Actinobacteria A and B degrade reactive yellow dye by using lignolytic enzymes such as lignin peroxidase, laccase and tyrosinase produced at static condition.[43] A novel lignin peroxidase from *Streptomyces griseosporeus* SN9 can be useful in various biotechnological processes like detergent formulations and textile dye-distaining.[44] Touioui *et al.* 2015 reported two alkaline serine proteases (SAPS-P1 and SAPS-P2) produced by *Streptomyces* sp. strain AH4 and suggested it can be a good source for application in laundry as detergents for its high stability and compatibility with commercial liquid and solid laundry detergents.[45] Extracellular alkaline protease from *Streptomyces kayangensis* strain TN650 (STAP) showed high stability and compatibility with a variety of commercialized detergents and laundry detergent formulations.[46] Effluents from tanneries and fertilizer industries enter into nearby river and streams causing health hazards to the humans. Azo dyes are the predominant dye which is been highly used in textile, food, paper and leather industries which is highly toxic and carcinogenic in nature. Actinobacterial species are extensively used to degrade the azo dyes from industries.[47] *Nocardia* strains are involved in the transformation of xenobiotics. It plays a key role in degradation of organic pollutants present in soil and water. *Nocardia* degrade aromatic hydrocarbons by hydroxylation. Degradation of dalapon 2, 2-dichloropropionic acid (herbicide) by *Nocardia* species was already been reported.[48]

CONCLUSION

Actinobacteria serves as a 'treasure trove' of new natural product antibiotics. Actinobacteria and members of its genera play a very important role in not only production antimicrobial metabolites and antibiotics but also produces several industrially important products like enzymes, drugs, natural pigments, bio surfactants, bio remediating agents. Actinobacteria being the efficient producers of bioactive metabolites and enzymes could be exploited further for the production of new anti biotics, pharmaceutical and biotechnological products. Although, a great work has been carried out on actino bacterial genera, more comprehensive studies are still needed to exploit the potential of actinomycetes. Genome mining of actinobacteria would certainly help to identify the potential stains based on polyketide synthase (PKS) and non-ribosomal polyketide synthases (NRPSs) genes encoded for novel compounds of pharmaceutical value. This not only fulfills the needs of the pharmaceutical industry in making new drugs but also help in human health and well being.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

ABBREVIATIONS

G+C: Guanine+ Cytosine; **COD:** Chemical Oxygen Demand; **PKS:** Polyketide synthase; **NRPSs:** Non-ribosomal polyketide synthases.

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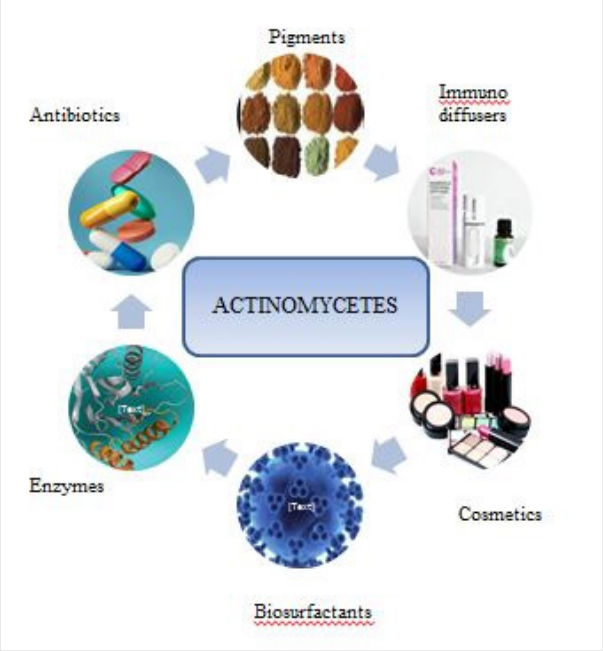
PICTORIAL ABSTRACT



SUMMARY

- Actinobacteria plays a vital role in pharmaceutical and biotechnological industries by producing many natural compounds such as antibiotics, enzymes, natural pigments, biosurfactants and enzyme inhibitors.
- Dye degradation by these actinobacteria was found to be more effective when compared to the other degradation techniques.
- Metabolites derived from actinomycetes play a significant role in various cosmetic industries.
- This review briefly discusses the pharmaceutical as well as biotechnological importance of actinobacterial products.

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