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Endophytic Actinomycetes as Emerging Source for Therapeutic Compounds

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ABSTRACT: Endophytic actinomycetes, which reside within the plant tissues, are reported to have several beneficial effects on the host-plants, such as, inhibition of pathogens, increase in availability of nutrients like nitrogen and phosphorus, increasing plant growth etc. Besides these roles, they are also known to produce secondary metabolites of varied therapeutic significance. Actinomycetes isolated from various sources like soil, water etc. are the well known sources of antibiotics. However, frequent appearance of drug resistance in bacteria, the emergence of life threatening viruses, the problems associated with the recurrence of disease in patients with organ transplants, and significant increase in the incidences of fungal infections in the world's population only underscore our inadequacy to cope with these medical problems. So there is an urgent need to explore the new sources, possibly from the unique niche, which can provide novel organisms with novel metabolites for therapeutic applications. Studies have indicated that the organisms and their biotopes that are subjected to constant metabolic and environmental interactions should produce even more secondary metabolites. Endophytes are microbes that inhabit such biotopes, namely, higher plants, which are why they are currently considered to be a pool of novel secondary metabolites offering the potential for applications in medicine, agriculture, and industry. These microbial resources will be of interest to mankind providing sustainable and environment-friendly solutions. India is a country known for its plant diversity, which could well translate into a unique endophytic microbial diversity as it is considered that nearly every plant is a habitat for one or more endophytes. As evident from the recent literature, endophytic actinomycetes are being increasingly explored for new therapeutic molecules which may effectively address the current human health issues in the areas of infectious diseases and metabolic disorders.

NOTE: Full length manuscript of Singh & Dubey. Endophytic Actinomycetes As Emerging Therapeutic Microrganisms . 2014; 4(3): 140.

INTRODUCTION

The need for new and useful compounds to help prevent or cure human ailments is never ending. The continuously changing environmental conditions and emergence of new complications in human health continue to maintain the pressure on scientific community to develop new and affective solution to these problems. The emergence of drug-resistant and multi-drug resistant pathogens, serious viral pathogens, complication in metabolic disorders like diabetes, recurrence of health complications in patients with organ transplant and increased incidences of fungal infections show our inadequacy to cope up with these medical problems. This situation continues to place challenges before the medical community to discover and develop desirable treatment and therapies.

Natural products have been well known for their contribution in the medicine field. It is also widely accepted that from the ancient time when we were dependent solely on the natural product as the source of medicine till the era of high throughput techniques where we have reached 'nano' to 'pico' drugs, natural sources have been proven as the best source for drug discovery. It is reported that 80% of the drug substances were natural products or inspired by a natural compound **[1].** The natural products were either from plants or microorganisms on a broad classification. Since both of these sources have been extensively explored, it is only obvious that plants and microbes from unexplored unique habitat may be examined in search for novel drug sources to tackle the upcoming challenges of viral and microbial infections and metabolic disorders. As actinobacteria (actinomycetes) have long been known as the excellent source of therapeutic compound, it occurred that such organisms from unique habitat may prove useful for this purpose. One such habitat could be plant cells and tissues, where endophytic actinobacteria may reside. In view of extensive diversity of plants, it could be expected that there would be a vast reservoir of unique actinobacteria, which might turn out to be a goldmine for new therapeutic compounds.

The term: 'Endophyte' was given by de Bary in 1866. According to his definition, "Endophytes are the microorganisms, which reside inside the plant tissues and are significantly different from those found on the plant surface". Since then, many other definitions have been given by different researchers with few modifications. The most appropriate and the collective of most of the definitions says, " Endophytes includes a suite of microorganisms that grow intra or inter-cellularly in the tissues of higher plants as well as small plants without causing any harmful effect on their host, and have proven to be the richest source of bioactive natural products **[2].**

The discovery of endophytes came into sight in middle of the nineteenth century, but due to special ecological niche, i.e. inside plants, it failed to attract the attention of researchers until a large number of livestock was poisoned because of feeding on the grass that had poisonous due to infection by endophyte **[3].** However, work on the endophytes and their occurrence is still scanty **[4].** With increasing exploration of endophytes, it is emerging that these organisms are capable of producing a variety of bioactive compounds which are having great importance in ecology, medicine, pathology as well as industries **[5, 6].** From the past decades it is quite evident that discovery rate of active novel chemical entities are declining **[7].** While plant sources are being extensively explored for new chemical entities for therapeutic purposes, endophytic actinobacteria do constitute one other important source for drug discovery.

Actinomycetes are the prokaryotic microorganisms that belong to the phylum Actinobacteria and possess mycelium like fungus and forms spores **[8, 9].** They are gram positive, spore forming bacteria characterized with formation of aerial and substrate mycelia **[10]**. They have high G+C content in DNA; more than 55 %. The term 'Actinomycetes' was derived from Greek atkis (a ray) and mykes (fungus), and has features of both bacteria and fungi **[11].** Actinomycetes are clubbed with bacteria in the same class of Schizomycetes but confined to the order Actinomycetales **[12, 13]**. Actinomycetale is the largest group among the 18 major categories in the classification of bacteria **[14, 9].**

About 75% of the drug compounds derived from the natural sources are known to be obtained from this large group of gram positive soil bacteria **[15-17]** i.e. actinobacteria. As per the study of some specific actinomycetes like *Streptomyces coelicolor and S. avermititis,* a milestone has been established in the discovery of bioactive compounds because the whole genome sequence of these two microbes led to identification of astounding numbers of gene clusters entirely dedicated to the production of economically and medically important secondary metabolites. They also found around 23 groups of gene while trying to locate the genes responsible for the secondary metabolism **[18, 19].** This data supports that the Actinomycetes are the gold mines for researchers, which is still not explored to its potential.

On the other hand, we are very well aware of the fact that from the ancient time we are harnessing plants in various forms to get the medical benefits. Plants have been known for the production of active biomolecules. Ayurveda, Unani and other ancient systems of medicine have traditionally been dependent on plants for preparation of medicines. It is presumed that endophytic actinobacteria from such plants might have acquired the ability to produce therapeutic compounds via horizontal gene transfer.

The present demand of new drugs needs novelty, which requires exploration of the sites that are exclusive and unique. One of such relatively unnoticed niche is the inner tissues of the plants **[20].** It is hypothesized that these microorganisms can perform better than the epiphytes or soil microorganism because of the symbiotic relationship with plants. India is known for its diverse flora. Around 20,000 medicinally important plants have been recorded recently **[21]**, but only 800 plant species are being used by more than 500 traditional communities for remediation of several diseases **[22, 23].**

As per today's scenario, most of the world's population depends upon plant-derived medical treatment as the first line of health care because of its negligible side effects. Plants are known to maintain a microbiota **[24, 25],** where several microbes may reside inside the plants as endosymbiont. However, we are having insufficient knowledge about the biodiversity, crosstalk of plants and microbes and the therapeutic and other application of endophytic actinomycetes present inside the wild and native plants **[26].**

The association can be obligate or facultative but usually does not cause any harm to the plant. They show signs of mutualism with their host **[27].** The association between the plants and their endophytes are specific. Plant and the microbe mediated signals, determined by the environment within the plant tissue, may lead to such specificity **[28].** Endophytes have adapted themselves to the niches due to long period of co-evolution with the host plant via gene regulation. The literature revealed that new actinomycetes were being consistently discovered from the tissues of the medicinal plants **[29-32]**. Further, based on the findings reported in literature, it may be safely predicted that endophytic actinomycetes of medicinal plants can produce important compounds and some of them may possess new chemical structures **[33-35].**

Endophytes produce a number of compounds in order to maintain the symbiotic association with plants, to promote plants growth and help them to survive in the plant environment. Use of such metabolites is being explored as potential therapeutic agent, biocontrol agent and for several other applications [**27, 36, 37].**

Various chemical entities with unique structure, including alkaloids, benzopyranones, chinones, flavonoids, phenolic acids, quinones, steroids, terpenoids, tetralones, xanthones, and others have been reported to be produced by endophytes **[38],** which may find application as agrochemicals, antibiotics, immuno-suppressants, anti-parasitics, antioxidants, and anticancer agents **[39].** It is also reported that these microorganism may alter the physiology of host pant conferring upon them resistance to biotic and abiotic stresses by producing bioactive compounds **[40, 41]**. Apart from the interest in unique niche of endophytes, the production of antibiotics and other secondary metabolites have attracted the attention of researchers in search of its novelty and applications **[42-44].**

An overview on current development in this significant area is being provided in this review.

CROSS LINKING BETWEEN ENDOPHYTE AND THE PLANTS

Roots are the most favorite part of the plants to be colonized by the microbes. Such interaction between the plants and the microbes may subsequently result in endo-symbiotic relationship between them. In many cases, the endophytic microbes play significant role in protection of plants against pathogenic agents **[45-48].**

Studies have been performed with endophytes by inoculating the host plant with endophyte **[49]** for evaluation of colonization pattern of vegetative tissues and effect of endophytes on host plant. This technique comprehends the plant biology and microbial ecology **[48, 50].**

It is considered that the endophytes contribute in growth stimulation of plants by the production of phytohormone, nitrogen fixation or biocontrol of phytopathogens. Endophytes are the main contributor in the production of antibiotics or siderophores, by nutrient competition or by induced systemic resistance **[41, 51].** Further, it has been reported that many secondary metabolites produced by plants are enhanced by microorganism present inside them as endophytes. Since these reports are confined to fungus, endophytic actinomycetes can offer the opportunity for further research aimed at understanding the correlation between the metabolism of the plants and their endophytes. However, attenuation (loss of) of metabolite production by the endophytes upon sub-culturing presents a problem in advancing our understanding of the subject **[52-54]**. Although the reasons for such attenuation are not studied, it could be due to lack of host stimulus in the culture media and/or silencing of genes in axenic cultures **[55].** Attempts to reverse the attenuation by amending axenic cultures with host tissue extracts have not been successful **[52, 54, 56].** One of the most appropriate reasons behind the relationship of endophytes and plants is genetic recombination of microbe with the host while evolving with the plant. This can lead to the incorporation of pathway genes from host to endophytes **[57].** However there has been no proof for the horizontal transfer of gene encoding secondary metabolite between host and microbe **[54, 58].**

Endophytes are recruited out of a large pool of soil or rhizospheric species and clones. Competition experiments with endophytes have shown that some of them are more aggressive colonizers and displace others. In effect, the mechanism underlying the production of plant secondary metabolites by endophytes remains enigmatic.

APPLICATIONS OF ENDOPHYTES IN THERAPEUTICS

Actinomycetes are known for production of vast range of secondary metabolites. These secondary metabolites are further purified and presently available as many drugs such as antimicrobial, antifungal, antitumour, antidepressant, anti-inflammatory and antidiabetics etc. But the dispersion of drugs and the resistance acquired by the microorganism has challenged the medical field for the development of new drugs. So endophytes could offer a good alternative source for the development of novel drugs. In India, while works have been carried out on endophytic bacteria and fungi, not much is seen in case of endophytic actinomycetes **[59-61].**

Several strains of filamentous fungi, *Streptomycetes* sp. and to a lesser extent several bacterial strains have been found to be important producer of drug molecules exhibiting structural and functional diversity. During 1950s and 1960s, the majority (70%) of antibiotics were discovered from these species. However, a steep decline is seen in discovery of new drugs from the above sources during the recent years; the actinomycetes presently contribute about 30- 35% of total microbial drugs in contrast to the 75-80% share that existed earlier **[62].** Apparently, therefore, endophytic actinobacteria may offer better prospects for novel drug discovery.

ANTIMICROBIAL PROPERTIES

Endophytes have been reported to produce metabolites, which are active at low concentration against other microorganism **[63].** A large number of antimicrobial compounds belonging to the classes like alkaloids, peptides, steroids, terpenoids, phenols, quinines, and flavonoids have been reported from endophytic actinomycetes **[64].** Some of the endophytic actinomycetes showed activity against phytopathogenic fungi **[59].** Another *Streptomycete NRRL* 30562 isolated from the snakevine possessed an activity against many pathogenic fungi and bacteria **[65, 66].** Application of endophytic actinomycetes derived bioactive compounds is very clear from the literature and their diversity is well documented in various environment conditions, normal to extreme. Endophytic actinomycetes also produce industrially important enzymes like cellulase, xylanase, pectinase, amylase, lipase and protease etc.

Many endophytic bacteria and fungi have already been reported for their therapeutic uses. Now reports from endophytic actinomycetes have begun to emerge. *Streptomyces sp.* BT01, an endophyte isolated from *Boesenbergia rotunda* (L.*) Mansf* produces anti-bacterial compounds that were active against *E. coli* and *P. aerogenosa* **[66].** Further, several compounds from endophytic actinomycetes with potential antimicrobial properties were isolated from various host plants like tomato, banana, wheat, and maize **[67-70].** Strains of Streptomyces, Microminospora and nocardiopsis with antimicrobial properties against human pathogens, were isolated from medicinal plants of tropical regions. Several of the endophytic actinomycetes isolated from medicinal plants of Moscow (Russia) were active against pathogenic bacteria **[71].** Another report on Endophytic actinomycetes isolated from Banana showed that one of the isolates, BAR1 showed antagonistic activity against both fungal and bacterial pathogens **[72].** Three Actinomycetes isolated from *Citrus aurantifolia* were found to be antibacterial **[73].**

In a study out of twenty endophytes screened**,** majority showed antibacterial activity against *Escherichia coli, Staphylococcus aureus* and *Klebsiella pneumonia* **[74]**. Some of the compounds from endophytic actinomycetes that exhibited anti-microbial properties included munumbicins A-D **[65],** celastramycins A-B **[75],** kakadumycins **[76]** and demethylnovobiocins **[77, 31].** Two novel compounds: cedarmycins A and B isolated from endophytic *Streptomyces sp. TP-A0456,* are active at low MICs against fungal pathogens **[77].** Saadamycin is one of the new compounds isolated from endophyte

Streptomyces sp. Hedaya48, which is active against dermatophytes and other clinical fungi **[78, 79].** Actinomycin D derived from *Streptomyces sp. Tc022* displayed very strong antifungal activity **[80].** Few peptide antibiotics: munumbicins E-4 and E-5 and munumbicins A-D from endophytic *Streptomyces NRRL 30562*, showed activity against broad spectrum of gram positive and negative bacterial pathogens **[65].** Few phenolic compounds like 2-Allyloxyphenol obtained from novel species *Streptomyces* sp. MS1/7 was found to be inhibitor of 21 strains of bacteria and 3 strains of fungi **[81, 82].**

The studies described above, strengthened the assumption that endophytic actinobacteria could be a promising source of antimicrobial substances.

ANTIOXIDANT PROPERTY

There are many diseases due to the effect of reactive oxygen species (ROS). In the prevention and treatment of disease linked to ROS, one of the strategies involves use of antioxidants as supplement. Studies revealed that many endophytic actinomycetes can be the better antioxidant than the synthetic counterparts. In this series a report on isolates SORS64b, SORS124, AGRS16, AGLS2, AGRS19 isolated from plants of asteraceae famiy showed antioxidant property using DPPH assay **[83].** Five more endophytic actinomycetes possessed very good antioxidant property and were reported to be helpful for plants in order to withstand the oxidative stress; they can be useful as antioxidant agent for human being also **[84].** Phenolic compound: 2-Allyloxyphenol obtained from novel species *Streptomyces* sp. MS1/7 was found to be a good antioxidant **[81, 82].** Endophytic actinomycetes isolated from *Catharanthus roseus* were also reported to possess antioxidant property **[85].**

Natural antioxidants are commonly found in medicinal plants, vegetables, and fruits. However, it has been reported that metabolites from endophytes can be a potential source of novel natural antioxidants. Endophytic *Xylaria sp.* isolated from the medicinal plant *Ginkgo biloba* has been evaluated for antioxidant activity **[86].** There are many more chances of getting very good active antioxidant compounds from endophytic actinomycetes based upon their occurrence in the plants having antioxidant property.

ANTITUMOR AND ANTI-INFLAMMATORY AGENTS FROM ENDOPHYTIC ACTINOBACTERIA

The studies on natural compounds shows that bioactive compounds derived from endophytes could be good anti-cancer agents and may prove useful in other disorders like inflammations. This area has drawn considerable attention of the scientific community as reports on anti-inflammatory and anticancer agents from endophytic actinomycetes have appeared. The maytansinoids (19-membered macrocyclic lactams related to ansamycin antibiotics), an extraordinarily potent antitumor agents isolated from higher plant families **[87, 88]** as well as from mosses **[89]** and also from the endophytic actinomycetes *Actinosynnema pretiosum* **[90].** The most interesting fact is that ansacarbamitocins, a new family of maytansinoids, were reported from a soil actinomycete strain *Amycolatopsis CP2808* which belongs to the family Pseudonocardiaceae, the same family as the ansamitocin-producing strain *A. pretiosum* **[90].** Naphthomycin K a novel chlorine containing ansamycin exibited cytotoxicity against P388 and A-549 cell lines and no antimicrobial activity, 24-demethylbafilomycin C1, a member of bafilomycin sub-family, was isolated from the endophytic strain, *Streptomyces sp. CS* **[91, 79].** At the same time, a new 16 membered macrolides belonging to the bafilomycin subfamily showed cytotoxic activity against MDA-MB- 435 cell line in vitro **[91].** *Streptomyces sp. ls9131* an endophyte isolated from *M. hookeri* produced two novel macrolides having anticancer activities **[92].** Dinactin derived from an endophytic actinomycete **[93],** was reported as having antitumor activity. Lupinacidins isolated from endophyte *Micromonospora lupine* **[94]** showed inhibitory activity against murine colon 26-L5 carcinoma cells. Lupinacidins was active against murine colon 26-L5 carcinoma cells **[94],** 6-alkylsalicylic acids, Salaceyins A and B was active against human breast cancer **[95].** These are some of the potent compounds derived from the endophytic actinomycetes mainly *streptomyces sp.* **[96].** Pterocidin isolated from *Streptomyces hygroscopicus TP-A0451* [**97**], 5, 7-dimethoxy-4-phenylcoumarin and 5, 7-dimethoxy-4-p-methoxylphenylcoumarin, isolated from Endophytic *Streptomyces aureofaciens CMUAc130* **[97], [98]** are the novel compounds from endophytic actinomycetes, which possessed antitumor and antifungal activities. As these compounds were originally isolated from plants and subsequently from endophytic actinomycetes, this may well be an example of horizontal gene transfer.

The endophytic actinomycetes showing anticancer activity were also tested for their effect on the formation of nitric oxide (NO), prostaglandin E2 (PGE2) and tumour necrosis factor (TNF-α) as well as on the inducible nitric oxide synthase and cyclooxygenase-2, that is, for their anti-inflammatory effect. And the references support the application of endophytic actinomycetes as potential anti-inflammatory agent **[98, 96].** *Streptomyces sp. SUC1* an endophyte, produced four novel anti-inflammatory secondary metabolites, lensai A-D **[97].** Indolocarbazoles, a novel compound identified with anticancer activity was obtained from an endophytic streptomycetes isolated from mangrove **[98, 99].** In summary, it can be said that endophytic actinomycetes are still unexploited source of novel anti-inflammatory and anti-tumor drugs.

ANTIVIRAL COMPOUNDS

In view of existing and emerging viral infections, which are often fatal, the search for effective anti-viral compounds assumes significance. It constitutes an area of urgent attention. An endophytic fungus, *Cytonaema* sp. was reported to produce cytonic acids A and B, whch were characterized to be novel inhibitors of human cytomegalovirus protease **[100, 101].** Recently, an endophytic actinomycetes, *Streptomyces sp. GT2002/1503*, isolated from *Bruguiera gymnorrhiza* was reported to possess anti-HIV activity, which specifically blocked R5 tropic HIV infection **[102].** It is evident from the literature that there are some promising anti-viral compounds isolated from endophytic actinomycetes, extensive research needs to be undertaken to achieve desirable outcomes.

ANTIDIABETIC PROPERTY OF ACTINOMYCETES

Till now, most of the antidiabetic activities have been reported in the extracts of medicinal plants. In the recent years some of the microorganisms have also been reported to produce anti-diabetic agents. But endophytic actinomycetes have not been properly explored for anti-diabetic drugs.

β-Carbolines and Indoles isolated from endophytic actinomycetes *Microbiospora sp.* LGMB259 showed promising activity against α-glucosidase, which is one of the targets for antidiabetic drugs **[103, 104].** Extract of *Streptomyces sp.* JQ92617 from *R. densiflora* was reported as the first compound from endophytic *Streptomycetes* with antidiabetic activity as confirmed by glucose uptake assay. *Streptomyces longisporoflavus* JX96594 was active as inhibitor of α amylase and α glucosidase activities **[105].** Endophytic actinomycetes BWA 15, BWA 35, BWA 36, BWA 3A,, BWA 4 and BWA 4A isolated from the roots of Indonesian medicinal plants, *Caesalpinia sappan,* has been reported as potential α glucosidase inhibitor. However *Streptomyces olivochromogenes* was found to be the best endophytes, which produced α glucosidase inhibitor among the isolates from Indonesian medicinal plant [**106].** *Streptomyces sp.* Loyola UGC, isolated from *Dhatura stramomium* L showed remarkable alpha glucosidase inhibition [**107].**

This was also given in some literature that *Micromonospora* and *Streptomyces* strains, among seven genera of Actinomycetes, showed anti-PTP1B activity along with cytotoxicity **[108].** *In vivo* studies showed that NFAT-133 worked effectively as anti-diabetic by way of reducing systemic glucose levels in the experimental animals **[109]**. Acarbose, voglibose, valienamine, adiposin-1, and trestatin-B, the standard drugs to be reported as antidiabetic, were isolated from *Actinoplanes utahensis* **[110],** *Streptomyces hygroscopicus-limoneus* **[111, 112]** *S. calvus* **[113, 114],** and *S. dimorphogenes* **[116]** respectively. So it is predicted that the endophytic actinomycetes can be the better agents against diabetes. One experimental study showed that EEA isolate from the roots of *Catharantus roseus. (l.) G. Don* exhibited very potential radical scavenging activity as well as marked α glucosidase inhibitory activity **[115].**

Since most of the rhizospheric actinomycetes colonise to become endophytes and show enhanced and modified property so we can look forward for such new and novel microorganism. Recently, bioactivity studies of secondary metabolites from mangrove actinomycetes have become a hot spot. Various screening studies on endophytic actinomycetes proved that they are not only antimicrobial, antineoplastic **[108]** but also very good PTP1B inhibitor and glucosidase inhibitor **[117],** at the same time these microbes have been successfully used for production of protease, cellulase, amylase, esterase, L-asparaginase production **[81, 99, 118, 119].**

CONCLUSION

Scientific community has shown keen interest in exploring endophytic microorganisms for biotechnological applications for the past few decades. Currently, there are several bioactive compounds which could prove to be useful in development of drugs for significant diseases. Due to the great economic and scientific importance of endophytes, scientists have already started their exploration for unique compounds and their applications. It is very important to review and highlight the previous achievements in endophytic research in order to draw the attention of research community towards this emerging field.

Endophytes can be bacteria, fungi or actinomycetes. But in this review we have focused upon the applications of endophytic actinomycetes as they are least explored and are widely regarded as an excellent source for drug discovery.

From this review, we have highlighted that endophytic actinomycetes isolated from unique habitats like the intracellular and intercellular space of plant tissues and especially from the unexplored plants have high probability of providing novel compounds which can be effective against multidrug resistant bacteria, pathogenic fungi, and complications of metabolic disorders. Secondly there are very few natural compounds available against the viruses so it could be a pioneer in the treatment of viral infections. Thus, in view of the accounts provided above, it can be safely concluded that bioactive compounds isolated from endophytic actinomycetes envisages being the most promising source of novel drugs for therapeutic applications.

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