

Review Article

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Endophytic Actinomycetes: A Novel Antibiotic Source

Ravi Ranjan Kumar^{1*} and Vasantba J. Jadeja²

¹Department of Biotechnology, Shree M. & N. Virani Science Collage,
Kalawad Road, Rajkot, Gujarat-360005

²Department of Microbiology, Shree M. & N. Virani Science Collage,
Kalawad Road, Rajkot, Gujarat-360005

*Corresponding author

ABSTRACT

Actinomycetes are one of the most attractive sources of antibiotics and other biologically active substances of high commercial value. In the search of novel source of actinomycetes, endophytes have been demonstrated to improve and promote growth of host plants as well as to reduce disease symptoms caused by plant pathogens and various environmental stresses. Endophytic actinomycetes are ubiquitous in most plants and colonise plants without exhibiting pathogenicity. The culturable diversity of endophytic actinomycetes associated with tropical, native plants is not well explored. Endophytic actinomycetes were untouched area for microbiologist, but in recent years it was found to be efficient producer of novel antibiotic and lead compounds to develop new medicines. A large amount of secondary metabolites especially antibiotics was produced by them not only are useful for plants but also are of economical importance to humans. Although the results of basic research concerning these organisms have not sufficiently been realized, it is important to review the present knowledge of antibiotic production capacity for further exploration in future. In the present paper habitat, diversity, interaction, antimicrobial activity, antifungal activity and effects of endophytic actinomycetes have been reviewed.

Keywords

Endophytic actinomycetes, Anticancer, antibiotic, pathogenicity.

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Introduction

Antibiotics are secondary metabolites produced by some microorganisms to inhibit or kill many other microorganisms including different bacteria, viruses and eukaryotic cells. Antibiotics are secondary metabolites and these have also been termed “idiolites” (Walker, 1974). Subsequent and widespread use of antibiotics for therapeutic purposes regularly in human, veterinary and agricultural purposes were favoring the

survival and spread of resistant pathogens. Search for new natural antibiotics and new therapeutic agents by continuous screening of secondary microbial products produced from potential bacterial taxa which overcome drug resistance of pathogenic micro flora are the viable solution to this problem (Gebreselema *et al.*, 2013). Such research necessitates the systematic screening of producers of antibacterial antibiotic from unexplored sources.

Actinomycetes are one of the most attractive sources of novel antibiotics responsible for production of more than 70% of the naturally derived antibiotics which are in clinical use (Atta *et al.*, 2011). Actinomycetes with potential antibiotics is still a thrust area of research and it is suggested that the explorations of materials from new habitats have a pivotal role to play in the search for new microbes and novel metabolites and is urgent to counter the threats posed by the fast emerging phenomenon of antibiotic resistance. Soil, which contains the greatest density and diversity of actinomycetes, has been the predominant and conventional source of actinomycetes strains (Takizawa *et al.*, 1993). Exhaustible exploration of soil based actinomycetes leads to decreased chances of finding any novel antibiotics, hence a new source must be requiring in antibiotic discovery program. More recently, however, researcher have found that other actinomycetes which can be recovered from healthy, surface-disinfected plant tissues, are known to produce a variety of bioactive metabolites with antibiotic, enzymatic and plant growth promoting or inhibiting activities are known as Endophytic actinomycetes (Jeffery *et al.*, 2010).

An endophyte is an endosymbiont, often a bacterium or fungus that lives within a plant for at least part of its life without causing apparent disease. Endophytes are ubiquitous and have been found in all the species of plants studied to date but relationship between endophytes and most of the plants are not well understood. Their association can be obligate or facultative and causes no harm to the host plants. The term “endophytes” includes a group of microorganisms that, for the whole part of their life history, live inside plant tissues without causing immediate overt negative effects and have proven to be rich source of

bioactive natural products (Sachiko *et al.*, 2006). They exhibit complex interactions with their hosts which involves mutualism and antagonism (Carroll *et al.*, 1988 and Parker *et al.*, 1999). Plants strictly limit the growth of endophytes, and these endophytes use many mechanisms to gradually adapt to their living environments (Dudeja *et al.*, 2012). In order to maintain stable symbiosis, endophytes produce several compounds that promote growth of plants and help them adapt better to the environment (Das *et al.*, 2009). Endophytic actinomycetes, which can be recovered from healthy, surface-disinfected plant tissues, are known to produce a variety of bioactive metabolites with antibiotic, enzymatic, and plant growth-promoting or -inhibiting activities (Hasegawa *et al.*, 2006). This review aims to provide an overview about endophytic actinomycetes, their habitat, isolation and role in production of antibiotics.

Antibiotic resistance

Problems related to human health such as the development of antibiotic resistance in human pathogenic bacteria, fungal infections, and life threatening virus claim for new therapeutic agents for effective treatment of diseases in human, plants, and animals that are currently unmet. Recent review by Newman and Cragg presented a list of all approved agents from 1981 to 2006, from which a significant number of natural drugs are produced by microbes or endophytes (Newman *et al.*, 2007). Endophytes provide a broad variety of bioactive secondary metabolites with unique structure, including alkaloids, benzopyranones, chinones, flavonoids, phenolic acids, quinones, steroids, terpenoids, tetralones, xanthenes, and others (Tan *et al.*, 2001). Such bioactive metabolites find wide-ranging application as agrochemicals, antibiotics, immune

suppressants, antiparasitics, antioxidants, and anticancer agents (Mariana *et al.*, 2010).

Endophytic Actinomycete

Approximately 300 000 plant species growing in unexplored area on the earth are host to one or more endophytes and the presence of biodiverse endophytes in huge number plays an important role on ecosystems with greatest biodiversity, for instance, the tropical and temperate rainforests which are extensively found in Brazil and possess almost 20% of its biotechnological source (Mariana *et al.*, 2010). It has been found also that some endophytic microorganisms can produce valuable pharmaceutical substances of biotechnological interest (Strobel *et al.*, 1998). The endophytes may provide protection and survival conditions to their host plant by producing a plethora of substances which, once isolated and characterized, may also have potential for use in industry, agriculture, and medicines (Strobel *et al.*, 2004). The production of bioactive substances by endophytes is directly related to the independent evolution of these microorganisms, which may have incorporated genetic information from higher plants, allowing them to better adapt to plant host and carry out some functions such as protection from pathogens, insects, and grazing animals.

Endophytes are chemical synthesizer inside plants, in other words, they play a role as a selection system for microbes to produce bioactive substances with low toxicity toward higher organisms (Owen *et al.*, 2004). Considering that only a small amount of endophytes have been studied, recently, several research groups have been motivated to evaluate and elucidate the potential of these microorganisms applied on biotechnological processes focusing on the production of bioactive compounds.

Endophytic actinomycetes which associated with plants also play important role in protecting their host from phytopathogenic invasions. Various endophytic actinomycetes have been isolated from crop, woody and medicinal plants showing product of interests (Table 1). Previous investigations proved that the endophytic actinomycetes are having high ability to inhibit phytopathogenic fungi is mainly by production of bioactive compounds, such as antibiotics and cell wall degrading enzymes and highlighted their importance as candidates for further investigation in the biocontrol of phytopathogens. Endophytic actinomycetes were also reported to hold the ability of triggering plant induced systemic resistance (Moussa *et al.*, 2011). Bioactive natural compounds produced by endophytic actinomycetes have been promising potential usefulness in safety and human health concerns, although there is still a significant demand of drug industry for synthetic products due to economic and time-consuming reasons.

Antimicrobial compound

The discovery of novel antimicrobial metabolites from endophytes is an important alternative to overcome the increasing levels of drug resistance by plant and human pathogens (Mariana *et al.*, 2010). Endophytes are believed to carry out a resistance mechanism to overcome pathogenic invasion by producing secondary metabolites. So far, studies reported a large number of antimicrobial compounds isolated from endophytes, belonging to several structural classes like alkaloids, peptides, steroids, terpenoids, phenols, quinines, and flavonoids (Yu *et al.*, 2010). Metabolite from endophytic actinomycetes bearing antibiotic activity belongs to various structural groups (Table 2) has been reported.

Fistupyron, a microbial metabolite acts as antifungal agent has been isolated from the culture broth of a plant-associated *Streptomyces* sp. TP-A0569. Fistupyron inhibited the in vivo infection of the seedlings of Chinese cabbage by necrotrophic plant pathogen *Alternaria brassicicola* TP-F0423, the cause of Alternaria leaf spot, without any in vitro fungicidal activity (Igarashi *et al.*, 2000).

Cedarmycins A and B is broad spectrum antibiotic were isolated from the cultured broth of actinomycetes *Streptomyces* sp. TP-A0456. The structure of cedarmycin was determined by spectroscopic methods as an alpha, beta-unsaturated butyrolactone with a fatty acid side chain. These compounds showed broad spectrum antibiotic activity against Gram positive, gram negative bacteria and yeasts. Cedarmycins is found to be potently inhibiting the growth of *Candida glabrata* (Sasaki *et al.*, 2001).

Antibiotics actinomycin X2, D and Xobeta has been produced by *Streptomyces NRRL 30562*. *Streptomyces NRRL 30562* was originally isolated as an endophyte from *Kennedia nigriscans*, Snakevine, in the Northern Territory of Australia. Actinomycins X2 and D had been previously designated as munumbicins A and B, respectively. These antibiotics are broad spectrum antibiotics showing activity against both human and plant pathogenic bacteria and fungi (Castillo *et al.*, 2006).

Kakadumycin A is broad spectrum peptide antibiotics especially active against Gram positive bacteria and shows impressive activity against the malaria parasite *Plasmodium falciparum*. Endophytic *Streptomyces* sp. (NRRL 30566) from a fern-leaved grevillea (*Grevillea pteridifolia*) in Australia was described as a promising producer of novel antibiotics, "kakadumycin

A". Kakadumycin A is structurally related to echinomycin, a quinoxaline antibiotic, and presents better bioactivity than echinomycin. Each contains, by virtue of their amino acid compositions, alanine, serine and an unknown amino acid (Castillo *et al.*, 2003).

Lansai A–D is a secondary metabolites shows antifungal and anticancerous activity isolated from endophytic actinomycetes *Streptomyces* sp. SUC1. *Streptomyces* sp. SUC1 was isolated from aerial roots of *Ficus benjamina* (Pittaya *et al.*, 2008).

Actinomycin D is potent antifungal antibiotics and a popular antitumor agent has been isolated from endophytic *Streptomyces* sp. Tc022. *Streptomyces* sp. Tc022 was isolated from the roots of *Alpinia galangal*. Actinomycin D strongly inhibited Banana plant pathogen *Colletotrichum musae* and common plant pathogen *Candida albicans* (Thongchai *et al.*, 2006).

Clethramycin, an antifungal antibiotic is produced by actinomycete strain *Streptomyces hygrosopicus* TP-A0623. *Streptomyces hygrosopicus* TP-A0623 was isolated from the root of *Clethra barbinervis* collected in Toyama, Japan. Clethramycin is structurally similar to linearmycin, an inhibitor of spheroplast regeneration in *Candida albicans* (Furumai *et al.*, 2003).

Demethylnovobiocin is broad spectrum antibiotics showed antibiotic activity against gram positive and gram negative bacteria. Actinomycetes strain *Streptomyces* sp. TP-A0556 is an endophytic strain isolated from the plant *Aucuba japonica*. These organisms produces two novel antibiotics, TPU-0031-A and B which was later termed as 7'-demethylnovobiocin and 5"-demethyl novobiocin, respectively (Sasaki *et al.*, 2001).

Saadamycin is an antimycotic compound isolated from endophytic actinomycetes *Streptomyces sp. Hedaya48*. This strain exhibited significant antimycotic activity against dermatophytes and other clinical fungi (El-Gendy *et al.*, 2010).

Anticancer compound

Cancer is a group of diseases characterized by unregulated growth and spread of abnormal cells, which can result in death if not controlled. It has been considered one of the major causes of death worldwide. Anticancer drugs show nonspecific toxicity to proliferating normal cells, possess enormous side effects, and are not effective against many forms of cancer. Thus, the cure of cancer has been enhanced mainly due to diagnosis improvements which allow earlier and more precise treatments. Anticancer properties of several secondary metabolites from endophytes have been investigated recently. There are some evidences that bioactive compounds produced by endophytic actinomycetes could be alternative approaches for discovery of novel drugs, since many natural products from plants, microorganisms, and marine sources were identified as anticancer agents. Some examples of the potential of endophytic actinomycetes on the production of anticancer agents are reviewed.

Paclitaxel and other Taxanes” have generated more attention and interest than any other new drug since its discovery, possibly due to its unique mode of action compared to other anticancer agents. The *Kitasatospora sp.* strain P&U 22869 produces paclitaxel and related taxanes has been isolated from endophytic actinomycetes during screening on *Taxus baccata* plants.

Paclitaxel is an antimicrotubule drug used for the treatment of ovarian and metastatic breast cancer. Food and Drug Administration has approved Taxol for the treatment of advanced breast cancer, lung cancer, and refractory ovarian cancer (Caruso *et al.*, 2000).

Pterocidin is a cytotoxic compound isolated from the endophytic actinomycetes *Streptomyces hygrosopicus* TP-A0451, and the structure was determined on the basis of spectroscopic data. Pterocidin showed cytotoxicity against some human cancer (Yasuhiro *et al.*, 2006).

lupinacidin C is a new anthraquinone derivative antibiotics isolated from the endophytic actinomycete *Micromonospora lupini*. Lupinacidin C exhibited the most potent inhibitory effects among the congeners on the invasion of murine colon carcinoma cells into the reconstituted basement membrane (Igarashi *et al.*, 2011).

Ansamitocin is a group of ansamycin antibiotics show potent antitumour activity. Ansamitocin was isolated from endophytic actinomycetes *Nocardiasp.* No. C-15003 (N-1). Structures of ansamitocin were found to be similar to maytansine and related maytansinoids which shows strong cytotoxic and antineoplastic activities (Eiji *et al.*, 1977).

Naphthomycin K, together with two known naphthomycins A and E were isolated from the commensal strain *Streptomyces sp.* CS of the medicinal plant *Maytenus hookeri*. Naphthomycin is chlorine containing ansamycin group of antibiotics showed evident cytotoxicity against P388 and A-549 cell lines (Lu *et al.*, 2007).

Table.1 Endophytic actinomycete genera within past 15 years

Plant species	Actinomycete taxa	References
Crop plants		
Aarzu Triticum aestivum	<i>Streptomyces, Microbispora, Micromonospora, Nocardioides</i>	Coombs and Franco (2003a)
Cucumis sativus	<i>Streptomyces</i>	Shimizu <i>et al.</i> (2009)
Lupinus termis	<i>Actinoplanes</i>	El-Tarabily (2003)
Zea mays	<i>Microbispora, Streptomyces, Streptosporangium</i>	de Araujo <i>et al.</i> (2000)
Lycopersicon Esculentum	<i>Streptomyces, Streptovorticillium, Nocardia</i>	Cao <i>et al.</i> (2004b)
Oryza sativa	<i>Streptomyces, Nocardioides</i>	Tian <i>et al.</i> (2007)
Brassica campestris	<i>Microbispora, Streptomyces, Micromonospora</i>	Lee <i>et al.</i> (2008)
Musa acuminata	<i>Streptomyces, Actinomadura, Streptovorticillium, Streptosporangium, Nocardia</i>	Cao <i>et al.</i> (2004a)
Woody plants		
Taxus spp.	<i>Streptomyces, Micromonospora, Nocardioforme, Actinoplanes, Actinomadura, Kitasatospora</i>	Caruso <i>et al.</i> (2000)
Acacia auriculiformis	<i>Actinoallomurus</i>	Thamchaipenet <i>et al.</i> (2010)
Rhododendron sp.G	<i>Streptomyces</i>	Shimizu <i>et al.</i> (2000)
Kalmia latifolia	<i>Streptomyces</i>	Nishimura <i>et al.</i> (2002)
Aquilaria crassna	<i>Streptomyces, Nonomuraea, Actinomadura, Pseudonocardia, Nocardia</i>	Nimnoi <i>et al.</i> (2010)
Medicinal plants		
Sambucus adnata	<i>Glycomyces</i>	Gu <i>et al.</i> (2007)
Alpinia galangal	<i>Streptomyces, Nocardia, Microbispora, Micromonospora</i>	Taechowisan <i>et al.</i> (2008)
Kennedia nigricans	<i>Streptomyces</i>	Castillo <i>et al.</i> (2002)
Maytenus Austroyunnanensis	<i>Saccharopolyspora, Actinomadura</i>	Qin <i>et al.</i> (2008, 2009)
Azadirachta indica	<i>Streptomyces, Streptosporangium, Microbispora, Streptovorticillium, Saccharomonospora, Nocardia</i>	Verma <i>et al.</i> (2009)
Thottea grandiflora	<i>Streptomyces</i>	Ghadin <i>et al.</i> (2008)
Rauwolfia densiflora	<i>Streptomyces longisporoflavus,</i>	Akshatha <i>et al.</i> (2014)
Calycophyllum acreanum	<i>Amycolatopsis sp.,</i>	Bascom-Slack <i>et al.</i> (2009)
Limonium sinensis	<i>Kineococcus endophytica</i>	Bian <i>et al.</i> (2012b)
Curcuma phaeocaulis	<i>Streptomyces phytohabitans</i>	Bian <i>et al.</i> (2012a)
Lobelia clavatum	<i>Pseudonocardia endophytica</i>	Chen <i>et al.</i> (2009)
Elaeagnus angustifolia	<i>Micromonospora sp.</i>	Chen <i>et al.</i> (2011)
Others		
Monstera sp.	<i>Monstera sp.</i>	Ezra <i>et al.</i> (2004)
Paphiopedilum Appletonianum	<i>Streptomyces</i>	Tsavkelova <i>et al.</i> (2007)

Table.2 Antibiotics which are isolated from endophytic Actinomycetes

ANTIBIOTICS	PRODUCERS	Reference
Fistupyrone	<i>Streptomyces</i> sp. TP-A0569	Igarashi <i>et al.</i> , (2000)
Cedarmycin A	<i>Streptomyces</i> sp. TP- A0456	Sasaki <i>et al.</i> , (2001)
Munumbicins A & B	<i>Streptomyces</i> NRRL 30562	Castillo <i>et al</i> (2006)
Kakadumycin	<i>Streptomyces</i> sp. NRRL 30566	Castillo <i>et al</i> (2003)
lansai A-D	<i>Streptomyces</i> sp. SUC1	Pittaya <i>et al.</i> (2008)
Actinomycin D	<i>Streptomyces</i> sp. Tc022	Thongchai <i>et al.</i> (2006)
Clethramycin	<i>S.hygroscopicus</i> TP-A0623	Furumai <i>et al.</i> (2003)
Demethylnovobiocin	<i>Streptomyces</i> sp. TP-A0556	Sasaki <i>et al.</i> (2001)
Saadamycin	<i>Streptomyces</i> sp. Hedaya48	El-Gendy <i>at al.</i> (2010)

Table.3 Anticancer compounds which are isolated from endophytic Actinomycetes

Anticancer compounds	Producers	Reference
Paclitaxel	Kitasatospora sp. strain P&U 22869	Caruso <i>et al</i> (2000)
Pterocidin	<i>Streptomyces hygroscopicus</i> TP-A0451	Yasuhiro <i>et al.</i> (2006)
lupinacidin C	<i>Micromonospora lupini</i>	Igarashi <i>et al.</i> (2011)
Ansamitocin	<i>Nocardiasp.</i> No. C-15003	Eiji <i>et al.</i> (1977)
Naphthomycin K	<i>Streptomyces</i> sp. CS	Lu <i>et al.</i> (2007)
Ansacarbamitocins	<i>Amycolatopsis</i> CP2808	Snipes <i>et al.</i> (2007)
24-demethyl-bafilomycin C1	<i>Streptomyces</i> sp. CS	Jian <i>et al.</i> (2010)
Salaceyins A and B	<i>Streptomyces laceyi</i> MS53	Kim <i>et al.</i> (2006)
5,7-dimethoxy-4-p-	<i>Streptomyces aureofaciens</i> CMUac130	Taechowisan <i>et al.</i> (2005)
5,7-dimethoxy-4-phenylcoumarin	<i>Streptomyces aureofaciens</i> CMUac130	Taechowisan <i>et al.</i> (2005)

Ansacarbamitocins belongs to family of maytansinoids that are unusually substituted with a glucose subunit and two carbamate functional groups and exhibit potent antitumor and antifungal activity. Ansacarbamitocins were isolated from actinomycetes strain *Amycolatopsis* CP2808 which belongs to family *Pseudonocardiaceae* (Snipes *et al.*, 2007).

24-demethyl-bafilomycin C1 antibiotics were isolated from the strain *Streptomyces* sp. CS, a commensal microbe of *Maytenus*

hookeri, as a new member of the bafilomycin subfamily. Bafilomycin form a family of 16-membered ring macrolide antibiotics shows toxicity on the MDA-MB-435 cell line (Jian *et al.*, 2010).

Salaceyins A and B exhibited modest cytotoxicity against a human breast cancer cell line (SKBR3). Salaceyins A and B are 6-alkylsalicylic acids isolated by bioassay-guided fractionation from the culture of the endophytic *Streptomyces laceyi* MS53 (Kim *et al.*, 2006).

5,7-dimethoxy-4-pmethoxylphenylcoumarin and 5,7-dimethoxy-4-phenylcoumarin isolated from endophytic actinomycetes *Streptomyces aureofaciens* CMUac130 shows strong antitumor and antifungal activity. 4-arylcoumarins isolated from endophytic *Streptomyces aureofaciens* CMUac130, also shows inhibitory activity against lung carcinoma (Taechowisan *et al.*, 2005; Thongchai *et al.*, 2007).

In conclusion, endophytic microorganisms are to be found in virtually every plant on earth. These organisms reside in the living tissues of the host plant and do so in a variety of relationships, ranging from symbiotic to slightly pathogenic. These organisms have been overlooked for their potential metabolites, but in past decades, research on endophytic actinomycetes shown to be promising antibiotics and anticancer agent. Endophytic actinomycete produces a plethora of substances like antibiotics, antimycotics, immune suppressants, and anticancer compounds of potential use to modern medicine, agriculture, and industry. Endophytic actinomycetes are now considered for the potential prospects of finding new drugs that may be effective candidates for treating newly developing diseases in humans, plants, and animals are great.

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