

# Endophytic actinobacteria of medicinal plants: diversity and bioactivity

Patrycja Golinska · Magdalena Wypij · Gauravi Agarkar ·  
Dnyaneshwar Rathod · Hanna Dahm · Mahendra Rai

Received: 17 April 2015 / Accepted: 4 June 2015 / Published online: 21 June 2015  
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**Abstract** Endophytes are the microorganisms that exist inside the plant tissues without having any negative impact on the host plant. Medicinal plants constitute the huge diversity of endophytic actinobacteria of economical importance. These microbes have huge potential to synthesis of numerous novel compounds that can be exploited in pharmaceutical, agricultural and other industries. It is of prime importance to focus the present research on practical utilization of this microbial group in order to find out the solutions to the problems related to health, environment and agriculture. An extensive characterization of diverse population of endophytic actinobacteria associated with medicinal plants can provide a greater insight into the plant-endophyte interactions and evolution of mutualism. In the present review, we have discussed the diversity of endophytic actinobacteria of from medicinal plants their multiple bioactivities.

**Keywords** Actinobacteria · Antimicrobial activity · Bioactive compounds · Endophytes · Medicinal plants

## Introduction

Many types of microbial population such as bacteria and fungi have been found to be associated with the internal tissues of plant as endophytes. The term endophyte was coined by De Bary (1866), which involves the existence of microorganisms inside the infested plant tissues without having negative effects on host plant (Schulz and Boyle 2006). Almost all the plants have been found to be infested with one or more endophytes (Petrini et al. 1992). The microbes are producers of growth promoting metabolites, insect and pest repellents, antimicrobials against plant pathogens, protectors in stress conditions and many more (Rya et al. 2007; Staniek et al. 2008; Rai et al. 2014a, b). They also possess the potential to produce unique secondary metabolites, which can be exploited in pharmaceutical, agricultural and other industries. Thus, there is a growing interest of researchers in bioprospecting of endophytic microbial communities inhabiting the plants from various ecosystems.

*Actinobacteria* are Gram-positive typically filamentous bacteria, and is a major phylum in the domain *Bacteria* (Ludwig and Klenk 2005). Actinobacteria are widely distributed in both terrestrial and aquatic ecosystems. They play important roles in decomposition of complex materials from dead plants, animals, algae and fungi and in recycling of the nutrients resulting in humus formation (Sharma 2014). Actinobacteria are an important and a large group of soil

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P. Golinska (✉) · M. Wypij · D. Rathod · H. Dahm  
Department of Microbiology, Nicolaus Copernicus  
University, 87100 Torun, Poland  
e-mail: golinska@umk.pl

G. Agarkar · D. Rathod · M. Rai  
Department of Biotechnology, SGB Amravati University,  
Amravati 444602, Maharashtra, India

microbes with high potential of producing different bioactive metabolites including antimicrobial, anti-cancer and other pharmaceutical compounds (Fiedler et al. 2008; Schulz et al. 2009). These microbes have been the largest producers of different antibiotics since the discovery of Penicillin in 1928 and provided the vast diversity of antibiotics against many deadly diseases. Total number of bioactive metabolites produced by microorganisms are around 23,000 out of which 10,000 (45 % of all bioactive metabolites) are produced by actinobacteria alone and among this group of bacteria, 7600 (76 %) compounds are reported from a single genus *Streptomyces* (Berdy 2012). This signifies their prime importance in the world of pharmaceuticals.

It is well known that the medicinal plants are the rich sources of precious bioactive compounds. As a consequence of long term association of endophytes with such plants, the former may also participate in metabolic pathways and enhance its own natural bioactivity or may gain some genetic information to produce specific biologically active compound similar to the host plant (Stierle et al. 1993; Eyberger et al. 2006; Mitchell et al. 2010; Kumar et al. 2013; Chithra et al. 2014; Rai et al. 2014a, b). Therefore, the endophytes isolated from medicinal plants are of immense significance.

The beneficial interactions of endophytic actinobacteria with plants are being considered as an important area of research. These endophytic actinobacteria are attractive source of novel bioactive compounds and therefore, many research groups are involved in the study of their bioactivities and industrial applications. The present review is focused on the advances in endophytic actinobacteria isolated from medicinal plants including their diversity and broad-spectrum bioactivities.

### Isolation of endophytic actinobacteria

Different methods have been used by researchers for isolation of endophytic actinobacteria. Takahashi and Omura (2003) emphasized that the diversity of actinobacteria depend mainly on the methods of isolation. The most frequently employed method for their detection and enumeration involves isolation from surface-sterilized host plant tissue. Isolation of endophytic actinobacteria depend on various factors, which include- host plant species, age and type of

tissue, geographical and habitat distribution, sampling season, surface sterilants, selective media and culture conditions (Hallmann 2001; Gaiero et al. 2013).

In general, the isolation protocol involves the collection of plant parts such as leaves, stem, roots that should be processed freshly or stored at 4 °C until isolation within 24 h. These explants are washed in running tap water to remove adhered epiphytes, soil debris or dust particles on the surface, followed by surface sterilization using one or more different surface sterilizing agents. The most commonly used surface sterilants include ethanol and a strong oxidant or general disinfectant like household bleach (NaOCl) with 2–5 % (w/v), available chlorine (for 2–4 min). Qin et al. (2008b) and Dochhil et al. (2013) applied combination of 5 % sodium chlorate (NaClO<sub>3</sub>), 2.5 % sodium thiosulfate (Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>), 75 % ethanol and 10 % sodium bicarbonate (NaHCO<sub>3</sub>) as sterilizing agents to inhibit the growth of fungal endophytes. The strength of sterilizing chemicals depends on permeability of the sample. Otherwise, the internal tissues will be sterilized (Hallmann et al. 2006). All the explants are finally rinsed with sterile distilled water, divided into small fragments (1 cm for stem or roots and 1 cm<sup>2</sup> for leaves) and inoculated on appropriate agar medium. In another method, the surface sterilized plant tissues are macerated and thoroughly homogenized with phosphate buffer or other suitable liquid medium. This suspension is serially diluted as 10<sup>-1</sup> to 10<sup>-5</sup> and spread on agar medium in order to obtain endophytic actinobacteria. The media are supplemented with antifungal antibiotics such as nystatin and cycloheximide (50 or 100 µg/ml) to suppress the fungal growth. After incubation at 26 ± 2 °C for 15–30 days, individual colonies with characteristic actinomycete morphology emerging out from the plant tissue are isolated. The pure cultures of the isolates are obtained by streaking on fresh media plates. The efficacy of the surface sterilization method, resulting from lack of microbial growth, can be authenticated by inoculating the last washing water into the same media plates.

Various types of growth media have been described by the authors for the isolation of endophytic actinobacteria such as starch casein (Küster and Williams 1964), starch casein nitrate (SCNA), actinomycetes isolation, soybean (Williams and Davies 1965), chitin-vitamin B (Hayakawa and Nonomura 1987), tap water-yeast extract (TWYE; Crawford et al. 1993) agars and humic acid vitamin B (HV), yeast

extract casamino acid (YECA), synthetic (Mincer et al. 2002), modified Gause (Ivantiskaya et al. 1978) and glycine–glycerol (Küster 1959) media. Zhao et al. (2011) also underlined the need of using wider range of isolation methods to acquire more knowledge about species diversity of actinobacteria within medicinal plants. A modified method employed by Machavariani et al. (2014) describes the pre-treatment of leaves with solutions of heteroauxin and zircon, which helped to isolate and increase the numbers of rare actinobacteria from medicinal plants.

### Diversity of endophytic actinobacteria in medicinal plants

Current identification and classification of actinobacteria are based a polyphasic approach, comprising morphological, physiological and molecular studies (Goodfellow et al. 2012) based on each taxon should be described and differentiated from related taxa. The sequencing of highly conserved macromolecules, notably 16S rRNA genes, has provided valuable data for constructing phylogenies at and above the genus level (Ludwig and Klenk 2005). The DNA: DNA relatedness, molecular fingerprinting and phenotypic techniques are methods of choice for delineating taxa at and below the rank of species (Rosselló-Mora and Amann 2001). Distinguishing phenotypic differences are required for the description of a new species (Wayne et al. 1987). Exploring the diversity of endophytic actinobacteria is indispensable for screening of beneficial strains and understanding their ecological niche.

Endophytic actinobacteria are able to associate with their host at a very early stage of the plant development (Hasegawa et al. 2006). Minamiyama et al. (2003) noticed in SEM studies that mycelia of *Streptomyces galbus*, which was spread on the surface of the tissue-culture medium in which rhododendron seedlings were growing, grew on leaf surfaces and entered into the leaf tissues via stomata. Further, they also observed that the internal mycelia grew out of stomata after internal multiplication within host leaves. Moreover, the authors observed that within host leaves, hyphae of *S. galbus* were present individually or in colonies in intercellular spaces but not inside epidermal or mesophyll cells.

The maximum endophytic actinobacteria have been recovered from roots followed by stems and least in

leaves (Qin et al. 2009; Gangwar et al. 2014). The woody plants conferred far greater diversity of actinobacteria in comparison to herbaceous plants. The high rate of occurrence of actinobacteria in roots as compared to other tissues is very common. This underlines the fact that the actinobacteria are natural dwellers of soil that easily come in contact with the roots of plants and may form the symbiotic association with them by entering the plant tissues. The results obtained by Nimnoi et al. (2010) suggested that different locations within the plant also differ in the diversity of actinomycete flora. Strobel and Daisy (2003) reported that the greater diversity of endophytes is probable to occur in the tropical and temperate regions. Du et al. (2013a) analyzed the endophytic diversity of 37 medicinal plants and reported 600 actinobacteria belonging to 34 genera and 7 unknown taxa. The authors depicted that there was no direct relationship between host plants and their endophytic flora regarding the utilization of sole carbon source, fermentation of carbon sources for production of acids and enzymes, rather the physiological characteristics of endophytic isolates were related to the geographical distribution of their host plants.

The measures of functional biodiversity may be more reliable and powerful than the taxonomic measures in order to recognize mechanistic basis of diversity and its effects on the plant-endophyte interactions (Parrent et al. 2010). Species distribution and biological diversity of endophytic actinobacteria of medicinal plants are extensively influenced by ecological environment (Hou et al. 2009). El-Shatoury et al. (2013) interpreted that the plant species can be separated into three clusters representing high, moderate and low endophytic diversity on the basis of generic diversity analysis of endophytes. The authors also reported that the endophytes represent high functional diversity, based on forty four different traits including catabolic and plant growth promotion traits and such traits may characterize a key criteria for successful habitation of endophytes within the endosphere. Furthermore, the stress-tolerance traits were more predictive measure of functional diversity of endophytic actinobacteria (El-Shatoury et al. 2013).

Hasegawa et al. (1978) reported a new genus of actinobacteria namely *Actinosynnema*, from a grass blade, which was probably the first report of an actinomycete of plant origin. A comprehensive literature survey has revealed the huge diversity of

endophytic actinobacteria isolated from interior tissues of stem, leaves and roots of medicinal plants (Table 1). Taechowisan et al. (2003) studied the diversity of actinobacteria residing in medicinal plants based on their morphology and the amino acid composition of the whole-cell extract and analysed the percentage of endophytic actinobacteria recovered from different explants: 64 % isolates from roots, 29 % from leaves, and 6 % from stems of 36 different plant species.

Janso and Carter (2010) also assessed the diversity of endophytic actinobacteria, including those from medicinal plants, albeit by ribotyping with Pvu II restriction enzyme to digest the genomic DNA. Ribotypes were then compared to each other using appropriate software (Janso and Carter 2010). The authors have found that 85 % of 123 isolates studied were determined to be unique at the strain level. The isolates were classified to six families and 17 different genera. *Streptomyces* accounts for the dominant genus, which is most commonly isolated as endophytic actinomycete (Qin et al. 2009; Zhao et al. 2011; Shutsrirung et al. 2014; Gangwar et al. 2014) while others include genera such as *Micromonospora*, *Actinopolyspora*, *Saccharopolyspora*, *Nocardia*, *Oerskovia*, *Nonomuraea*, *Streptovercillium*, *Microbispora*, *Streptosporangium*, *Promicromonospora* and *Rhodococcus* (Verma et al. 2009; Zhao et al. 2011). Some rare actinobacteria like *Dietzia*, *Blastococcus*, *Dactylosporangium*, *Actinocorallia*, *Jiangella*, *Promicromonospora*, *Oerskovia*, *Microtetraspora* and *Intrasporangium* were also reported as endophytes (Qin et al. 2009; Zhao et al. 2011; Qin et al. 2012b; El-Shatoury et al. 2013). A novel halotolerant actinomycete was isolated from a salt marsh plant *Dendranthema indicum* collected from the coastal region of China (Zhang et al. 2013). New species of endophytic actinobacteria such as *Rhodococcus cercidiphylli* and *Saccharopolyspora endophytica* were isolated from leaf of *Cercidiphyllum japonicum* (Li et al. 2008) and root of *Maytenus austroyunnanensis* (Qin et al. 2008a), respectively. Du et al. (2013b) proposed a new genus and species, *Allonocardiopsis opalescens* gen. nov., sp. nov., based on the polyphasic taxonomic study, within the suborder *Streptosporangineae*. Wang et al. (2008) studied the diversity of uncultured microbes associated with medicinal plant *Mallotus nudiflorus* and concluded that actinobacteria were the most dominant microbes, covering about 37.7 % of whole endophytic isolates.

In 2012b, Qin and co-workers studied the diversity of endophytic actinobacteria recovered from root, stem and leaf tissues of *Maytenus austroyunnanensis* which was collected from tropical rainforest in Xishuangbanna, China. Later the authors concluded the diversity of isolates by combination of cultivation and culture-independent analysis and based on 16S rRNA gene sequencing. Further by using different selective isolation media and methods total of 312 actinobacteria were isolated from above plants which were affiliated with the order *Actinomycetales* (distributed into 21 genera). Based on a protocol for endophytes enrichment, three 16S rRNA gene clone libraries were constructed and 84 distinct operational taxonomic units were identified and they distributed among the orders *Actinomycetales* and *Acidimicrobiales*, including eight suborders and at least 38 genera with a number of rare actinobacteria genera. Moreover, six genera from the order *Actinomycetales* and uncultured clones from *Acidimicrobiales* were found to be unknown and reported as first time endophytes. This study confirms abundant endophytic actinobacterial consortium in tropical rainforest native plant and suggests that this special habitat still represents an underexplored reservoir of diverse and novel actinobacteria of potential interest for bioactive compounds discovery.

### Bioactivities of endophytic actinobacteria

The plant endosphere consists of a large variety of microbial endophytes, which constitute a complex micro-ecosystem (El-Shatoury et al. 2013). A vast diversity of secondary metabolites in actinobacteria may occur due to the natural adaptations to environment, as a part of competition for common resources such as plant matter in soil. It has been observed that the genes responsible for the production of individual secondary metabolites were found almost always located as a cluster in the genome and referred to as biosynthetic gene clusters (Doroghazi and Metcalf 2013). Although, there is no data available about full genome sequencing on actinobacteria from medicinal plants it has been known, that whole genomes of *Streptomyces* sp. and non-*Streptomyces* non-endophytic actinobacteria such as *Streptomyces avermitilis* MA-4680 (Ōmura et al. 2001; Ikeda et al. 2003) and *Streptomyces coelicolor* A(3)2 (Bentley et al. 2002) as

**Table 1** Endophytic actinobacteria isolated from medicinal plants

Species of actinomycetes	Host plant	Tissue	Bioactive compounds	Reference
<i>Streptomyces longisporoflavus</i> , <i>Streptomyces</i> sp.	<i>Rauwolfia densiflora</i>	Stem, leaf, inflorescence	ND	Akshatha et al. (2014)
<i>Amycolatopsis</i> sp., <i>Micromonospora</i> sp., <i>Streptomyces</i> sp.	<i>Siparuna crassifolia</i> , <i>Calycophyllum acreanum</i> , <i>Capirona decorticans</i> , <i>Ocotea longifolia</i> , <i>Aspidosperma</i> sp., <i>Palicourea longifolia</i> , <i>Monstera spruceana</i> , <i>Croton lechleri</i> , <i>Cantua buxifolia</i> , <i>Banisteriopsis caapi</i> , <i>Iryanthera laevis</i> , <i>Eucharis cyaneosperma</i>	Stem	ND	Bascom-Slack et al. (2009)
<i>Kineococcus endophytica</i>	<i>Limonium sinensis</i>	ND	ND	Bian et al. (2012b)
<i>Streptomyces phytolobitans</i>	<i>Curcuma phaeocaulis</i>	Root	ND	Bian et al. (2012a)
<i>Kitasatospora</i> sp.	<i>Taxus baccata</i>	Wood/inner cortical tissues	Paclitaxel	Caruso et al. (2000)
<i>Streptomyces</i> sp. NRRL 30562	<i>Kennedia nigriscans</i>	Stem	Munumbicins A, B, C and D	Castillo et al. (2002)
<i>Streptomyces</i> sp. NRRL 30566	<i>Grevillea pteridifolia</i>	Stem	Kakadumycins	Castillo et al. (2003)
<i>Streptomyces</i> sp. NRRL 30562	<i>Kennedia nigriscans</i>	ND	Munumbicins E-4 and E-5	Castillo et al. (2006)
<i>Pseudonocardia endophytica</i>	<i>Lobelia clavatum</i>	Inner tissue	ND	Chen et al. (2009)
<i>Micromonospora</i> sp., <i>Nonomuraea</i> sp., <i>Planotetraspor</i> sp., <i>Pseudonocardia</i> sp., <i>Microbispora</i> sp.	<i>Elaeagnus angustifolia</i>	Root nodules	ND	Chen et al. (2011)
<i>Streptomyces</i> sp.	<i>Spermacoce verticillata</i>	Leaf	ND	Conti et al. (2012)
<i>Allonocardopsis opalescens</i>	<i>Centella asiatica</i>	Root, stem, leaf	Indole acetic acid (IAA)	Dochhil et al. (2013)
<i>Streptomyces</i> sp. Hedaya48	<i>Lonicera maackii</i>	Fruit	ND	Du et al. (2013b)
	<i>Aplysina fistularis</i>	Inner healthy tissue	Vanillin, 5,7-dimethoxy-4- <i>p</i> -methoxyphenylcoumarin, Saadamycin	El-Gendy and EL-Bondkly (2010)

Table 1 continued

Species of actinomycetes	Host plant	Tissue	Bioactive compounds	Reference
<i>Streptomyces</i> sp.	<i>Artemisia herba-alba</i> , <i>Echinops spinosus</i> , <i>Mentha longifolia</i> , <i>Balloia undulate</i>	Green aerial parts	ND	El-Shatoury et al. (2006)
<i>Kibdelosporangium</i> sp., <i>Kitasatosporia</i> sp., <i>Nocardia</i> sp., <i>Nocardioides</i> sp., <i>Promicromonospora</i> sp., <i>Pseudonocardia</i> sp., <i>Streptomyces</i> sp.	<i>Achillea fragrantissima</i>	ND	Siderophores, Chitinase	El-Shatoury et al. (2009)
<i>Streptomyces</i> sp. MSU-2110	<i>Monstera</i> sp.	Stem	Coronamycin	Ezra et al. (2004)
<i>Actinopolyspora</i> sp., <i>Micromonospora</i> sp., <i>Saccharopolyspora</i> sp., <i>Streptomyces</i> sp.	<i>Aloe vera</i> , <i>Mentha</i> , <i>Ocimum sanctum</i>	Root, stem, leaf	ND	Gangwar et al. (2011)
<i>Actinopolyspora</i> sp., <i>Micromonospora</i> sp., <i>Saccharopolyspora</i> sp., <i>Streptomyces</i> sp.	<i>Aloe vera</i> , <i>Mentha arvensis</i> , <i>Ocimum sanctum</i>	Root, stem, leaf	Hydroxamate-type of siderophore, Catechol-type of siderophore, Indole acetic acid (IAA)	Gangwar et al. (2014)
<i>Streptomyces</i> sp. TP-A0569,	<i>Allium fistulosum</i>	Leaf	Fistupyron 7'-Demethylnovobiocin, 5''-demethylnovobiocin, Novobiocin, 6-Prenylindole, Anicemycin Pteridic acids A and B Clethracycin	Igarashi (2004)
<i>Streptomyces hygrosopicus</i> TP-A0451,	<i>Pteridium aquilinum</i>	Stem	Cedarmycins A and B	
<i>Streptomyces hygrosopicus</i> TP-A0326,	ND	ND	Pterocidin	
<i>Streptomyces</i> sp. TP-A0456	<i>Cryptomeria japonica</i>	Twig		
<i>Streptomyces hygrosopicus</i> TP-A0451	ND	ND	Pterocidin	Igarashi et al. (2006)

**Table 1** continued

Species of actinomycetes	Host plant	Tissue	Bioactive compounds	Reference
<i>Micromonospora lupini</i>	ND	ND	Lupinacidins	Igarashi et al. (2007)
<i>Streptomyces cavourensis</i> AB184264.1	<i>Catharanthus roseus</i>	Leaf	ND	Kafur and Khan (2011)
<i>Streptomyces laceyi</i> MS53	<i>Ricinus communis</i>	Stem	6-Alkylsalicylic acids (salicylins A and B)	Kim et al. (2006)
<i>Actinomycetes</i> sp.	<i>Emblica officinalis</i>	Twig, leaf	ND	Kumar et al. (2011)
<i>Streptomyces</i> sp.	<i>Cistanches deserticola</i>	Root	Tyrosol (possible ligand for GPR12)	Lin et al. (2008)
			Phenylethylamine derivatives, Cyclic dipeptides, Nucleosides and their aglycones, <i>N</i> -acetyltryptamine and Pyrrole-2-carboxylic acid	
<i>Streptomyces</i> sp. CS	<i>Maytenus hookeri</i>	ND	24-demethyl-bafilomycin C1 (Naphthomycin A)	Lu and Shen (2003)
<i>Streptomyces</i> sp. CS	<i>Maytenus hookeri</i>	Tissue cultures	Naphthomycin K, A and E	Lu and Shen (2007)
<i>Micromonospora</i> sp., <i>Nocardopsis</i> sp., <i>Streptomyces</i> sp.	<i>Achillea millefolium</i> , <i>Aloe arborescens</i> , <i>Anthoxanthum odoratum</i> , <i>Arcium lappa</i> , <i>Convallaria majalis</i> , <i>Fragaria vesca</i> , <i>Geranium pretense</i> , <i>Hippophae rhamnoides</i> , <i>Lysimachia nummularia</i> , <i>Matricaria matricarioides</i> , <i>Melilotus officinalis</i> , <i>Mentha arvensis</i> , <i>Plantago major</i> , <i>Rosa cinnamomea</i> , <i>Rubus idaeus</i> , <i>Tanacetum vulgare</i> , <i>Taraxacum officinale</i> , <i>Trifolium pretense</i> <i>Urtica dioica</i> , <i>Viola odorata</i>	Leaf	ND	Machavariani et al. (2014)

Table 1 continued

Species of actinomycetes	Host plant	Tissue	Bioactive compounds	Reference
<i>Actinomadura</i> sp.	<i>Phyllanthus niruri</i> ,	Root		Mini Priya (2012)
<i>Kibdelosporangium</i> sp.,	<i>Withania somnifera</i> ,		Volatile organic compounds (VOCs),	
<i>Kitatosporia</i> sp.,	<i>Catharanthus roseus</i> ,		Diffusible metabolites	
<i>Nocardioides</i> sp.,	<i>Hemidesmus indicus</i>		Chitinase, Cellulases, CMC-ase,	
<i>Pseudonocardia</i> sp.,				
<i>Streptomyces</i> sp.,				
Undefined actinomycetes				
<i>Actinomadura</i> sp.,	<i>Achillea fragrantissima</i> ,	ND	Volatile organic compounds (VOCs),	Moussa et al. (2011)
<i>Kibdelosporangium</i> sp.,	<i>Catharanthus roseus</i> ,		Diffusible metabolites	
<i>Kitatosporia</i> sp.,	<i>Artemisia herba-alba</i> ,			
<i>Nocardia</i> sp.,	<i>A. judaica</i> ,			
<i>Nocardioides</i> sp.,	<i>Jasania montan</i> ,			
<i>Pseudonocardia</i> sp.,	<i>Launae</i> sp.,			
<i>Streptomyces</i> sp.,	<i>Echinops spinosissimus</i> ,			
Undefined actinomycetes	<i>Pulicaria</i> sp.,			
	<i>Centauria</i> sp.,			
	<i>Nerium oleander</i>			
<i>Actinomycete</i> sp.,	<i>Mirabilis jalapa</i> ,	Leaf, stem, root, flower	ND	Passari et al. (2015)
<i>Brevibacterium</i> sp.,	<i>Clerodendrum</i>			
<i>Leifsonia</i> sp.,	<i>colebrookianu</i> ,			
<i>Microbacterium</i> sp.,	<i>Eupatorium odoratum</i> ,			
<i>Streptomyces</i> sp.	<i>Alstonia scholaris</i>			
	<i>Musa superba</i>			
<i>Streptomyces olivochromogenes</i>	<i>Tinospora crispa</i>	Root, leaf, stem	Inhibitor of alpha-glucosidase	Pujjianto et al. (2012)
	<i>Phaleria macrocarpa</i> ,			
	<i>Curcuma aeruginosa</i> ,			
	<i>Andrographis paniculata</i> ,			
	<i>Caesalpinia sappan</i> ,			
	<i>Curcuma xanthoriza</i> ,			
	<i>Gynura procumbens</i> ,			
	<i>Physalis peruviana</i> ,			
	<i>Hibiscus sabdariffa</i>			



**Table 1** continued

Species of actinomycetes	Host plant	Tissue	Bioactive compounds	Reference
<i>Streptomyces setonii</i> ,	<i>Maytenus saquifolia</i> ,	ND	Celastramycins A and B	Pullen et al. (2002)
<i>Streptomyces sampsonii</i> ,	<i>Putterlickia retrospinosa</i> ,			
<i>Streptomyces</i> sp. Q21,	<i>Putterlickia verrucosa</i>			
<i>Streptomyces</i> sp. MaB- QuH- 8				
<i>Glycomyces endophyticus</i>	<i>Carex baccans</i>	Root	ND	Qin et al. (2008b)
<i>Glycomyces mayteni</i>	<i>Scoparia dulcis</i> ,	Root	ND	Qin et al. (2009)
<i>Glycomyces scopariae</i>	<i>Maytenus austroyunnanensis</i>			
<i>Pseudonocardia sichuanensis</i>	<i>Jatropha curcas</i>	Root	ND	Qin et al. (2011)
<i>Nocardioides panzhihuaensis</i>	<i>Jatropha curcas</i>	Stem	ND	Qin et al. (2012a)
<i>Actinomadura</i> sp.,	<i>Maytenus austroyunnanensis</i>	Root, stem, leaf	ND	Qin et al. (2012b)
<i>Amycolatopsis</i> sp.,				
<i>Cellulosimicrobium</i> sp.,				
<i>Glycomyces</i> sp.,				
<i>Gordonia</i> sp.,				
<i>Janibacter</i> sp.,				
<i>Jiangella</i> sp.,				
<i>Microbacterium</i> sp.,				
<i>Micromonospora</i> sp.,				
<i>Mycobacterium</i> sp.,				
<i>Nocardia</i> sp.,				
<i>Nocardioopsis</i> sp.,				
<i>Nonomuraea</i> sp.,				
<i>Plantactinospora</i> sp.,				
<i>Polymorphospora</i> sp.,				
<i>Promicromonospora</i> sp.,				
<i>Pseudonocardia</i> sp.,				
<i>Saccharopolyspora</i> sp.,				
<i>Streptomyces</i> sp.,				
<i>Streptosporangium</i> sp.,				
<i>Tsukamurella</i> sp.,				

Table 1 continued

Species of actinomycetes	Host plant	Tissue	Bioactive compounds	Reference
<i>Streptomyces</i> sp.	<i>Azadiracta indica</i> , <i>Ocimum sanctum</i> , <i>Phyllanthus amarus</i>	Root, leaf	ND	Shenpagam et al. (2012)
<i>Streptomyces antibioticus</i>	<i>Curcuma domestica</i> , <i>Phaleria macrocarpa</i> , <i>Isotoma longiflora</i> , <i>Symplocos cochinchinensis</i>	Root, stem, leaf	ND	Sunaryanto and Mahsunah (2013)
<i>Streptomyces aureofaciens</i> CMUAc130	<i>Zingiber officinale</i> , <i>Alpinia galanga</i>	Root	ND	Taechowisan and Lumyong, (2003)
<i>Microbispora</i> sp., <i>Micromonospora</i> sp., <i>Nocardia</i> sp., <i>Streptomyces</i> sp., Unidentified isolates	<i>Zingiber officinale</i> , <i>Alpinia galanga</i>	Root, stem, leaf	ND	Taechowisan et al. (2003)
<i>Streptomyces aureofaciens</i> CMUAc130	<i>Zingiber officinale</i>	Root	5,7- dimethox y-4-p-methoxyphenylcoumarin, 5,7-dimethoxy-4-phenylcoumarin	Taechowisan et al. (2005, 2007)
<i>Microbispora</i> sp., <i>Micromonospora</i> sp., <i>Nocardia</i> sp., <i>Streptomyces</i> sp. Tc022, Unidentified isolates	<i>Alpinia galanga</i>	Root	Actinomycin D	Taechowisan et al. (2006)
<i>Microbispora</i> sp., <i>Nocardia</i> sp., <i>Sacchromonospora</i> sp., <i>Streptomyces</i> sp., <i>Streptosporangium</i> sp., <i>Streptoverticillium</i> sp.	<i>Azadiracta indica</i>	Root, stem, leaf,	ND	Verma et al. (2009)
<i>Jishengella endophytica</i> 16111	<i>Xylocarpus granatum</i>	Root	Alkaloids	Wang et al. (2014)
<i>Saccharopolyspora dendranthemae</i>	<i>Dendranthema indicum</i>	Stem	ND	Zhang et al. (2013)

**Table 1** continued

Species of actinomycetes	Host plant	Tissue	Bioactive compounds	Reference
<i>Streptomyces</i> sp. neu-D50	Soybean	Root	3-acetyliden-7-prenylindolin-2-one (isoprenoids, 7-isoprenylindole-3-carboxylic acid, 3-cyanomethyl-6-prenylindole, 6-isoprenylindole-3-carboxylic acid and 7,40 -dihydroxy-5-methoxy-8-(g,g-dimethylallyl)-flavanone)	Zhang et al. (2014)
<i>Micromonospora</i> sp., <i>Nonomuracea</i> sp., <i>Oerskovia</i> sp., <i>Promicromonospora</i> sp., <i>Rhodococcus</i> sp., <i>Streptomyces</i> sp.	<i>Potentilla discolor</i> , <i>Ainsliaea henryi</i> , <i>Impatiens chinensis</i> , <i>Rhizoma Arisaematis</i> , <i>Dioscorea opposita</i> , <i>Stellera chamaejasme</i> , <i>Salvia miltiorrhiza</i> , <i>Drosera peltata</i> , var. <i>multiseptata</i> , <i>Artemisia annua</i> , <i>Achyranthes aspera</i> , <i>Cynanchum auriculatum</i> , <i>Gnaphalium hypoleucum</i> , <i>Mosla dianthera</i> , <i>Cassytha filiformis</i> , <i>Vaccinium bracteatum</i>	Root, stem, leaf	ND	Zhao et al. (2011)
<i>Streptomyces</i> sp. YIM66017	<i>Alpinia oxyphylla</i>	ND	2,6-dimethoxy terephthalic acid, yangjinhualine A, $\alpha$ -hydroxyacetovanillone and cyclo(Gly-Trp)	Zhou et al. (2014)

ND no data

well as *Saccharopolyspora erythraea* NRRL 23338 (Oliynyk et al. 2007), *Salinispora tropica* CNB-440 (Udwary et al. 2007) contain around 20 or more natural product biosynthetic gene clusters for the production of known or predicted secondary metabolites (Goodfellow and Fiedler 2010). The potential of actinobacteria isolated from medicinal plants, especially of non-productive non-streptomycete ones to produce secondary metabolites can be estimated by detection of polyketide synthase (PKS) (both I and II type) and nonribosomal peptide synthetase (NRPS) genes (Janso and Carter 2010). The authors studied 29 strains and all of them produced bands of the expected size for NRPS and majority of them possessed PKS (66 % of PKS I and 79 % of PKS II type) genes. However, some of the pathways encoded by these genes may not be functional. The above study suggests that the non-productive actinobacteria possess the genetic capacity to produce secondary metabolites, if cultivated under proper growth conditions (Janso and Carter 2010).

Amongst prokaryotes, members of Actinobacteria, notably the genus *Streptomyces*, remains the richest source of valuable natural products (Pandey et al. 2004; Newman and Cragg 2007; Lu and Shen 2007; Olano et al. 2009; Berdy 2012). The diverse arrays of bioactivities of endophytic actinobacteria are further classified into pharmaceutical and agricultural applications and are illustrated below in detail.

## Pharmaceutical applications

### Antimicrobial and antiviral activity

In recent years, many of novel antibiotics synthesized by endophytic actinobacteria recovered from medicinal plants found to be active against bacteria, fungi and viruses. Moreover, these antibiotics demonstrated their activity at significantly lower concentrations (Table 2). This indicates the strong and broad spectrum microbiocidal potential of the antibiotics originating from endophytic actinobacteria, mainly of the genus *Streptomyces*.

Day by day due to excessive use of antibiotics, the multi-drug resistance capacity of pathogens is becoming more and more severe. The scientists all over the world are endeavouring continuously to search new antibiotic compounds in order to tackle this problem.

Here endophytic microbes, especially actinobacteria appear as a source of novel and active compounds to combat the increasing number of multidrug-resistant pathogens. Out of 65 strains of endophytic actinobacteria 12 strains were able to suppress penicillin-resistant *Staphylococcus aureus*, belonging to the genus *Glycomyces* and majority of them were *Streptomyces* isolated from plants *Achyranthes bidentata*, *Paeonia lactiflora*, *Radix platycodi* and *Artemisia argyi* (Zhang et al. 2012). Wang et al. (2014) displayed moderate antiviral activity against influenza virus type A subtype H1N1 of peroloyrine, 1-hydroxy- $\beta$ -carboline, lumichrome, 1*H*-indole-3-carboxaldehyde from *Jishengella endophytica* with IC<sub>50</sub> value of 38.3, 25.0, 39.7, and 45.9  $\mu\text{g ml}^{-1}$ , respectively. Further, they also suggested that 1-hydroxy- $\beta$ -carboline could be a promising new hit for anti-H1N1 drugs.

### Larvicidal and antimalarial activity

Larvicidal activity of *Streptomyces* sp. isolated from *Artemisia herba-alba*, *Echinops spinosus*, *Balotta undulate* and *Mentha longifolia* was observed by El-Shatoury et al. (2006). The authors studied cytotoxic effect against larvae of *Artemia salina* was positive for 27 out of 41 endophytic actinobacteria and of these, nine isolates, mainly from *Artemisia* and *Echinops* exhibited high mortality rate reaching to 100 % death after 12 h. Similarly, *Streptomyces albobovineus* and *S. badius* isolated from plants of family *Asteraceae* were also found to have significant larvicidal potential against first and fourth instar stages of *Culex quinquefasciatus* (mosquito larvae) (Tanvir et al. 2014). They illustrated strong larvicidal activity (80–100 % mortality) of six isolates while four isolates showed potent larvicidal activity (100 % mortality) at the fourth instar stage.

Castillo et al. (2002) have found that one of the tested munumbicins type D was considerably active against the parasite *Plasmodium falciparum*, the most pathogenic plasmodium causing malaria, with IC<sub>50</sub> of 4.5  $\text{ng ml}^{-1}$ . They also described that outstanding activity of each of the munumbicins against *P. falciparum* were within the range to be pharmacologically interesting with IC<sub>50</sub> of 175, 130, 6.5 and 4.5  $\text{ng ml}^{-1}$  in munumbicin A–D, respectively. Authors emphasized special interest of the munumbicins C and D because of their extremely low IC<sub>50</sub> values. Furthermore, they also reported that munumbicins B, C and D

**Table 2** Bioactivity of compounds from endophytic actinobacteria isolated from medicinal plants

Compound	Target cells/microorganism	MIC ( $\mu\text{g ml}^{-1}$ )	Reference
Munumbicins A, B, C and D from <i>Streptomyces</i> sp. NRRL 30562	<i>Pseudomonas aeruginosa</i>	–	Castillo et al. (2002)
	<i>Vibrio fischeri</i>	–	
	<i>Enterococcus faecalis</i>	–	
	<i>Staphylococcus aureus</i>	–	
	<i>Acinetobacter</i> sp.	–	
	<i>Neisseria gonorrhoeae</i>	–	
	<i>Streptococcus pneumoniae</i>	–	
	<i>Bacillus anthracis</i>	–	
	<i>Escherichia coli</i>	–	
	<i>Pythium ultimum</i>	0.2–4.0	
	<i>Rhizoctonia solani</i>	1.5–15.6	
	<i>Phytophthora cinnamomi</i>	1.5–15.6	
	<i>Geotrichum candidum</i>	15.5–31.2	
	<i>Sclerotinia sclerotiorum</i>	0.2–8.0	
	<i>Pseudomonas syringe</i>	0.2–15.6	
	<i>Cryptococcus neoformans</i>	10	
	<i>Candida albicans</i>	10	
	<i>Aspergillus fumigates</i>	20	
	<i>Staphylococcus aureus</i> ATCC 33591 (methicillin resistant)	No activity–2.5	
	<i>Staphylococcus aureus</i> MH II (vancomycin sensitive)	0.4	
<i>Enterococcus faecalis</i> ATCC 51299	No activity–16		
<i>Mycobacterium tuberculosis</i> MDR-P (drug resistant)	10–125		
<i>Mycobacterium tuberculosis</i> H37Rv (ATCC 25618) (drug sensitive)	46–150		
Kakadumycin A from <i>Streptomyces</i> sp. NRRL 30566	<i>Bacillus anthracis</i> 40/BA 100	0.3	Castillo et al. (2003)
	<i>Bacillus anthracis</i> 14578	0.55	
	<i>Bacillus anthracis</i> 28	0.43	
	<i>Bacillus anthracis</i> 62-8	0.41	
	<i>Staphylococcus simulans</i> ATCC 11631	0.25	
	<i>Enterococcus faecalis</i> ATCC 29212	0.062	
	<i>Enterococcus faecalis</i> VRE, ATCC 51299	0.062	
	<i>Enterococcus faecium</i> ATCC 49624	0.062	
	<i>Listeria monocytogenes</i> ATCC 19114	0.25	
	<i>Listeria monocytogenes</i> ATCC 19115	0.25	
	<i>Shigella dysenteriae</i> ATCC 11835	4.0	
	<i>Staphylococcus epidermidis</i> ATCC 12228	0.125	
	<i>Staphylococcus aureus</i> ATCC 29213	0.125	
	<i>Staphylococcus aureus</i> MRSA, ATCC 33591	0.5	
	<i>Staphylococcus aureus</i> GISA, ATCC 700787	0.5	

**Table 2** continued

Compound	Target cells/microorganism	MIC ( $\mu\text{g ml}^{-1}$ )	Reference
	<i>Staphylococcus aureus</i> ATCC 27734	0.125	
	<i>Streptococcus pneumoniae</i> ATCC 49619	<0.0325	
	<i>Streptococcus pneumoniae</i> ATCC 70674	<0.0325	
	<i>Streptococcus pneumoniae</i> ATCC 70676	<0.0325	
	Inhibitor of human breast cancer cell line BT20	n/a	
Munumbicins E-4 and E-5 from <i>Streptomyces</i> sp. NRRL 30562	<i>Burkholderia thailandensis</i>	192–256	Castillo et al. (2006)
	<i>Escherichia coli</i>	16	
	<i>Staphylococcus aureus</i> ATCC 29213	4–8	
	<i>Staphylococcus aureus</i> 43000 (MRSA)	8–16	
	<i>Staphylococcus aureus</i>	32	
	<i>Pythium ultimum</i>	5	
	<i>Bacillus subtilis</i>	5	
	<i>Rhizoctonia solani</i>	80	
	Cytotoxic activity against <i>Plasmodium falciparum</i>	n/a	
Saadamycin/5,7-Dimethoxy-4-p-methoxyphenyl coumarin from <i>Streptomyces</i> sp. Hedaya48	<i>Trichophyton rubrum</i>	5.0/7.5	El-Gendy and EL-Bondkly (2010)
	<i>Trichophyton mentagrophytes</i>	1.5/90	
	<i>Microsporum gypseum</i>	1.25/100	
	<i>Epidermophyton floccosum</i>	1.0/50	
	<i>Aspergillus niger</i>	1.0/20	
	<i>Aspergillus fumigates</i>	1.6/10	
	<i>Fusarium oxysporum</i>	1.2/22	
	<i>Candida albicans</i> ,	2.22/15	
	<i>Cryptococcus humicolus</i>	5.15/10	
Coronamycin from <i>Streptomyces</i> sp. MSU-2110	<i>Pythium ultimum</i>	2	Ezra et al. (2004)
	<i>Phytophthora cinnamomi</i>	16	
	<i>Aphanomyces cochlioides</i>	4	
	<i>Geotrichum candidum</i>	>500	
	<i>Aspergillus fumigates</i>	>500	
	<i>Aspergillus ochraceus</i>	>500	
	<i>Fusarium solani</i>	>500	
	<i>Rhizoctonia solani</i>	>500	
	<i>Cryptococcus neoformans</i> (ATCC 32045)	4	
	<i>Candida parapsilosis</i> (ATCC 90018)	>32	
	<i>Candida albicans</i> (ATCC 90028)	16–32	
	<i>Saccharomyces cerevisiae</i> (ATCC 9763)	>32	
	<i>Candida parapsilosis</i> (ATCC 22019)	>32	
	<i>Candida albicans</i> (ATCC 24433)	>32	
	<i>Candida krusei</i> (ATCC 6258)	>32	
	<i>Candida tropicalis</i> (ATCC 750)	>32	
6-prenylindole from <i>Streptomyces</i> sp. TP-A0595	<i>Alternaria brassicola</i>	Data not given	Igarashi (2004)

**Table 2** continued

Compound	Target cells/microorganism	MIC ( $\mu\text{g ml}^{-1}$ )	Reference
Fistupyrene from <i>Streptomyces</i> sp. TP-A0569	Suppressing spore germination of <i>Alternaria brassicicola</i>	n/a	
Clethramycin from <i>Streptomyces hygroscopicus</i> TP-A0326	<i>Candida albicans</i>	1.0	
	<i>Cryptococcus neoformans</i>	1.0	
Cedarmycin from <i>Streptomyces</i> sp. TP-A0456	<i>Candida glabrata</i>	0.4	
Anicemycin from <i>Streptomyces thermoviolaceus</i> TP-A0648	Cytocidal activity against tumor cell lines	n/a	
Pterocidin from <i>Streptomyces hygroscopicus</i> TP-A0451	Cytotoxicity against human cancer cell lines NCI-H522, OVCAR-3, SF539, and LOX-IMVI	n/a	Igarashi et al. (2006)
Lupinacidins A and B from <i>Micromonospora lupini</i> sp.	Inhibitor of in vitro invasion of colon 26-L5 cells	n/a	Igarashi et al. (2007)
6-Alkylsalicylic acids (Salaceyins A and B) from <i>Streptomyces laceyi</i> MS53	Cytotoxicity against human breast cancer cell line SKBR3	n/a	Kim et al. (2006)
Naphthomycin K from <i>Streptomyces</i> sp. CS	<i>Penicillium avellaneum</i> UC-4376	–	Lu and Shen (2003, 2007)
	<i>Staphylococcus aureus</i>		
	<i>Mycobacterium tuberculosis</i>		
	Cytotoxicity against P388 and A-549 human tumor cells	n/a	
Celastramycins A/B from <i>Streptomyces</i> MaB-QuH- 8	<i>Staphylococcus aureus</i> MRSA 134/93	0.1/no activity	Pullen et al. (2002)
	<i>Staphylococcus aureus</i> MR 994/93	0.2/no activity	
	<i>Enterococcus faecalis</i> V-r 1528	0.8/no activity	
	<i>Mycobacterium smegmatis</i> SG 987	1.6/no activity	
	<i>Mycobacterium aurum</i> SB 66	0.4/no activity	
	<i>Mycobacterium vaccae</i> IMET 10670	0.05/no activity	
	<i>Mycobacterium fortuitum</i>	3.1/no activity	
	<i>Bacillus subtilis</i> ATCC 6633	0.05/no activity	
5,7-dimethoxy-4-pmethoxyphenylcoumarin; 5,7-dimethoxy-4-phenylcoumarin from <i>Streptomyces aureofaciens</i> CMUAc130	<i>Colletotrichum musae</i>	120	Taechowisan et al. (2005)
		150	
Actinomycin D from <i>Streptomyces</i> sp. Tc022	<i>Colletotrichum musae</i>	10	Taechowisan et al. (2006)
	<i>Candida albicans</i>	20	
5,7-Dimethoxy-4-pmethoxyphenylcoumarin; 5,7-dimethoxy-4-phenylcoumarin from <i>Streptomyces aureofaciens</i> CMUAc130	Antitumor activity	n/a	Taechowisan et al. (2007)
Perlolryne, 1-hydroxy- $\beta$ -carboline, lumichrome, 1H-indole-3-carboxaldehyde from <i>Jishengella endophytica</i> 161111	Antiviral activity	n/a	Wang et al. (2014)

**Table 2** continued

Compound	Target cells/microorganism	MIC ( $\mu\text{g ml}^{-1}$ )	Reference
3-Acetyliden-7-prenylindolin-2-one (isoprenoids, 7-isoprenylindole-3-carboxylic acid, 3-cyanomethyl-6-prenylindole, 6-isoprenylindole-3-carboxylic acid and 7,40-dihydroxy-5-methoxy-8-(g.g-dimethylallyl)-flavanone) from <i>Streptomyces</i> sp. neau-D50	Cytotoxic activity against human lung adenocarcinoma cell line A549 <i>Colletotrichum orbiculare</i> , <i>Phytophthora capsici</i> , <i>Corynespora cassiicola</i> , <i>Fusarium oxysporum</i>	n/a	Zhang et al. (2014)
2,6-Dimethoxy terephthalic acid, yangjinhualine A, a-hydroxyacetovanillone, cyclo(Gly-Trp) from <i>Streptomyces</i> sp. YIM66017	Antioxidant activity	n/a	Zhou et al. (2014)

(–) not tested, n/a not applicable

did not cause any detectable lysis of human red blood cells up to a concentration of  $80 \mu\text{g ml}^{-1}$ . Therefore, they suggested that the ultimate development of these compounds as antimalarial or anti-infectious drugs may have to depend upon the synthesis of munumbicin derivatives that have reduced toxicity (Castillo et al. 2002, 2006).

### Cytotoxicity

Among the range of bioactive compounds from endophytic actinobacteria of medicinal plants those with anticancer activity were also found. Castillo et al. (2003) extracted kakadumicin A, which inhibited the human breast cancer cell line BT20 with  $\text{IC}_{50}$  of  $4.5 \text{ ng ml}^{-1}$ . Similarly, Igarashi et al. (2006) reported that human cancer cell lines NCI-H522, OVCAR-3, SF539, and LOX-IMVI were inhibited with  $\text{IC}_{50}$  in the presence of 2.9, 3.9, 5.0 and 7.1 mM of pterocidin extracted from *Streptomyces hygroscopicus* TP-A0451 isolated from *Pteridium aquilinum*. Lu and Shen (2003; 2007) reported cytotoxic activity of naphptomycin A from *Streptomyces* sp. CS isolated from *Maytenus hookeri* against P388 and A549 human tumor cells with  $\text{IC}_{50}$  0.07 and 3.17 mM, respectively. The cytotoxicity against A549 human tumor cells was also studied by Zhang et al. (2014). The cell line was inhibited with value of 3.3 and  $5.1 \text{ mg ml}^{-1}$  in presence of 3-acetyliden-7-prenylindolin-2-one and 7-isoprenylindole-3-carboxylic acid, respectively. Cytotoxic activity of 6-alkalysalicilic acids, salaceyins A and B from *Streptomyces laceyi* MS53 against

human breast cancer cell line, SKBR3 with  $\text{IC}_{50}$  values of 3.0 and  $5.5 \text{ mg ml}^{-1}$  was noticed by Kim et al. (2006). Anthraquinones named lupinacidins from *Micromonospora lupine* sp. were reported to inhibit growth of colon 26-L5 carcinoma cells in mice (Igarashi et al. 2007). Furthermore, anti-invasive effects of lupinacidins were also examined at non-cytotoxic concentrations. The authors reported lupinacidin A as more potent both in cytotoxic and anti-invasive activities than lupinacidin B, suggesting that the alkyl substituent present in lupinacidin A was involved in these activities (Igarashi et al. 2007).

Caruso et al. (2000) reported an anticancerous drug paclitaxel from endophytic actinomycete *Kittatospora* sp. isolated from inner cortical tissues of *Taxus baccata*. Another novel anticancer compound named brartemicin, a trehalose-derived metabolite, was extracted from the actinomycete *Nonomuraea* sp. isolated from *Artemisia vulgaris*. This new compound was capable of inhibiting the invasion of murine colon carcinoma 26-L5 cells with an  $\text{IC}_{50}$  value of  $0.39 \mu\text{M}$  without any cytotoxicity (Igarashi et al. 2009). Taechowisan et al. (2007) evaluated 4-phenylcoumarins on human lung cancer cell lines, which was extracted from *Streptomyces aureofaciens* and found that 5,7-dimethoxy-4-phenylcoumarin can inhibit cell proliferations more actively when compared with 5,7-dimethoxy-4-p-methoxyphenylcoumarin. Moreover, the screening of 4-arylcoumarins for inhibitory effect on transplanted Lewis lung carcinoma (LLC) by intraperitoneal administration has showed antitumor activity with T/C values of 80.08 and 50.0 % at doses



of 1 and 10 mg kg<sup>-1</sup> of 5,7-dimethoxy-4-*p*-methoxyphenylcoumarin and 81.5 and 44.9 % at doses of 1 and 10 mg kg<sup>-1</sup> of 5,7-dimethoxy-4-phenylcoumarin. Authors have concluded that 5,7-dimethoxy-4-phenylcoumarin might be preventing or delaying formation of metastases and both 4-arylcoumarins by their low cytotoxicity to normal cells and effect in malignant cells could be recommended as chemopreventatives and in combined antitumor treatment (Taechowisan et al. 2007).

#### Antidiabetics

Another important group of compounds, which were found in endophytic actinobacteria from medicinal plants were alpha-glucosidase inhibitors (Pujiyanto et al. 2012). Twelve out of 65 isolates obtained from *Tinospora crispa*, *Caesalpinia sappans* and *Curcuma aeruginosa* were able to produce it. This inhibitor showed antidiabetic property by which it can retard the release of glucose from dietary complex carbohydrates and also delay absorption of glucose. Interestingly, it was observed that endophytic actinomycete BWA65 produced these inhibitors which showed doubled activity than its host plant (*Tinospora crispa*). Furthermore, the tissue cultured plants that were devoid of any endophyte had very low capability to produce inhibitor compounds (Pujiyanto et al. 2012). This indicates that the production of alpha-glucosidase inhibitors by this plant is largely due to the contribution of its endophytic actinobacteria. It also strengthens the hypothesis that there may be a phenomenon of inter-kingdom genetic transfer of some specific traits between the host plant and its endophytic counterpart.

Similarly, Akshatha et al. (2014) isolated alpha-amylase inhibitor secreting endophytic actinobacteria *S. longisporoflavus* and *Streptomyces* sp. from well-known antidiabetic medicinal plants *Leucas ciliata* and *Rauwolfia densiflora*. Alpha-amylase inhibitors demonstrated antidiabetic activity similar to alpha-glucosidase inhibitors. The extracts obtained from these actinobacteria did not show insulin-releasing ability, instead it improved the ability of available insulin to pass glucose into muscles.

#### Other bioactive compounds

Phenolic compounds are known as natural antioxidants, which provide protection by scavenging

harmful free radicals. Endophytic *Streptomyces* sp. isolated from *Alpinia oxyphylla* produced two active compounds 2,6-dimethoxy terephthalic acid and yangjinhualine A, which demonstrated considerable antioxidant activity (Zhou et al. 2013; 2014). Out of the total endophytic actinobacteria isolated from medicinal plants, 66.6 % isolates demonstrated potent antioxidant activity (Tanvir et al. 2014). Antiinflammatory drugs are used to reduce the inflammations and this property was also shown by one of the endophytic actinomycete. Taechowisan et al. (2006) demonstrated the successful application of 5,7-dimethoxy-4-*p*-methoxyphenylcoumarin and 5,7-dimethoxy-4-phenylcoumarin produced by *Streptomyces aureofaciens* as an antiinflammatory agents.

#### Agricultural applications

##### Plant growth promoters

The endophytic actinomycetes can also be a source of metabolites, which promote or improve host plant growth as well as reduce disease symptoms caused by plant pathogens or various environmental stresses (Shimizu 2011). Several scientific investigations evidenced the plant growth promotion activity and secretion of plant growth hormones from endophytic actinobacteria. Dochhil et al. (2013) demonstrated the plant growth enhancement and higher seed germination percentage by the application of two *Streptomyces* sp. isolated from *Centella asiatica*. These strains were also evaluated for production of a plant growth promoter, indole acetic acid (IAA) which was found in much higher concentration as 71 g/ml and 197 g/ml. The isolates of the genus *Nocardioopsis* presented highest IAA production ability among all other actinomycete genera (Shutsrirung et al. 2014). In the field trials conducted by El-Tarabily et al. (2010), *Actinoplanes campanulatus*, *Micromonospora chalicea* and *Streptomyces spiralis* were applied individually and in combination to cucumber seedlings, which enhanced plant growth and yield.

Igarashi (2004) and Igarashi et al. (2002) isolated pteridic acids A and B from *Streptomyces hygroscopicus* isolated from a stem of bracken (*Pteridium aquilinum*) as plant growth promoters with auxin-like activity. They found that pteridic acids induced the formation of adventitious roots in hypocotyl of kidney

beans at 1 mM as effectively as auxin (indole acetic acid; IAA), a natural plant growth hormone. Additionally, authors noticed that pteridic acid A promotes the root elongation at 20 ppm. However, the rice germination was inhibited at 100 ppm of IAA. Gangwar et al. (2014) also found actinobacteria, mostly *Streptomyces* sp, capable of producing IAA. Plant growth promoters were produced within the range of 9.0–38.8  $\mu\text{g ml}^{-1}$ .

Endophytic actinobacteria are able to employ additional means of fungal antagonism such as chitin enzymes and siderophores. Chitin is the most characteristic polysaccharide of the fungal cell wall. Endophytic actinobacteria are able to produce fungal cell wall degrading enzymes especially by the production of chitinase (El-Tarabily and Sivasithamparam 2006). The role of siderophores produced by endophytic microorganisms has been paid more attention because these metabolites are suggested to be involved in promoting the growth of host plants as well as antagonism to phytopathogen (Cao et al. 2005; Tan et al. 2006; Rungin et al. 2012). El-Shatoury et al. (2009) reported actinobacteria from *Achillea fragrantissima* which were either capable of producing chitinases or siderophores and also showed remarkable inhibitory activity against phytopathogenic fungi. Chitinases produced by the endophytic actinomycete *Actinoplanes missouriensis* (El-Tarabily 2003; El-Tarabily and Sivasithamparam 2006) were reported to cause hyphal lysis and reduction in conidial germination. The studies by El-Shatoury et al. (2009) were supported by Gangwar et al. (2014) where authors recorded production of hydroxamate-type of siderophore ranging between 5.9 and 64.9  $\mu\text{g ml}^{-1}$  and catechol-type of siderophore in the range of 11.2–23.1  $\mu\text{g ml}^{-1}$  by actinobacteria from *Aloe vera*, *Mentha arvensis* and *Ocimum sanctum*. In another investigation, El-Tarabily et al. (2010) applied endophytic *Actinoplanes campanulatus*, *Micromonospora chalcea* and *Streptomyces spiralis* to cucumber seedlings. As it reduced seedling damping-off as well as root- and crown- rot of mature cucumber plants caused by *Pythium aphanidermatum* successfully, authors suggested that these strains of endophytic actinobacteria can be employed as biological control agents.

The 6-prenylindole, a new bioactive compound from *Streptomyces* sp. was studied by Igarashi (2004). This simple molecule showed significant antifungal

activity against plant pathogens, *Alternaria brassicicola* and *Fusarium oxysporum*. 6-prenylindole was first reported as a component of the liverwort (*Hepaticae*). This is an interesting example of the isolation of the same compound from plant and microorganism (Igarashi 2004). Similarly, Zhang et al. (2014) showed antifungal activity of one new prenylated indole derivative and tree known hybrid isoprenoids with  $\text{IC}_{50}$  values in range of 30.55–89.62 against phytopathogenic fungi *Colletotrichum orbiculare*, *Phytophthora capsici*, *Corynespora cassiicola* and *Fusarium oxysporum*. Lu and Shen (2003; 2007) reported antifungal activity of naphthomycins A and K extracted from *Streptomyces* sp. CS against *Penicillium avellaneum* UC-4376. Igarashi (2004) reported the compound fistupyron from *Streptomyces* sp. isolated from a leaf of spring onion (*Allium fistulosum*) and determined as an inhibitor of spore germination of *Alternaria brassicicola*. The latter is the cause of black leaf-spot, a major disease of cultivated *Brassica* plant. Although fistupyron did not show in vitro antifungal activity against *A. brassicicola*, it completely inhibited the infection of *A. brassicicola* by pretreating the seedlings with 100 ppm of the compound. Studies by Igarashi et al. (2002) revealed that fistupyron did not give any effect on the growing hyphae but specifically suppresses the spore germination at 0.1 ppm.

Thus, the metabolites obtained from these actinobacteria inhibit the phytopathogenic fungi and can be better and safer alternatives to the chemical fungicides, which pose potential environmental threat and mammalian toxicities. In terms of the availability, the endophytic actinobacteria are the rich and cost-effective source of numerous agro-based biological agents. So, it is desirable to evaluate more such compounds that might have different modes of action to protect the crops than the existing chemical fungicides and will also avoid the problems of cross-resistance.

## Conclusion and future perspectives

There is a pressing need to search for new therapeutic drugs, particularly anti-infective compounds due to the rapid increase of resistance in major known pathogens to front line antibiotics. Therefore, screening and isolation of promising strains of endophytic actinobacteria with antimicrobial properties which are

relatively poorly investigated has increased the interest of researchers in both basic and applied fields. Clearly, more research on the formulation, development of novel technologies and methodologies is needed for employing them in the agricultural, medical and pharmaceutical fields.

An extensive characterization and identification of the diverse population of endophytic actinobacteria associated with medicinal plants may also provide greater insight into the plant-endophyte interaction and evolution of mutualism. It is also important to understand the mechanism that enables these microbes to interact with their host plants may be of biotechnological potential. Several questions are yet to be answered. Is there any combination between the metabolic pathways of plants and endophytes, which together constitutes for particular bioactivity? What genetic control exists for synthesis of secondary metabolites similar to the host plants? In order to address this research area in depth, it is necessary to understand the physiology and biochemistry of endophytic actinobacteria as well as their defensive role and secondary metabolite producing ability inside the plants.

**Acknowledgments** Support from The National Science Centre (NCN)-“Grant Symphony 1” No. 2013/08/W/NZ8/00701 and from the project of “Enhancing Educational Potential of Nicolaus Copernicus University in the Disciplines of Mathematical and Natural Sciences-visiting professors for Professor Mahendra Rai from Amravati University, India” conducted under Sub-measure 4.1.1 Human Capital Operational Programme—Task 7 (Project No. POKL.04.01.01-00-081/10) are acknowledged.

**Conflict of interest** The authors declare that they have no conflict of interest.

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