Chapter 4
Microbial Endophytes: Progress and Challenges

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4.1 Introduction

Endophytes are microbes (fungi or bacteria) that live within the plant tissues without causing any noticeable symptoms of disease (Tejesvi et al. 2007). Endophytes invade the tissues of living plants and reside between living plant cells (Vanessa and Christopher 2004). Some form a mutually beneficial relationship (symbiosis) with the host plants while others are opportunistic pathogens. Petrini et al. (1992) reported that there may be more than one type of mycoendophytes found within a single plant. For example, 13 taxa of mycoendophyte were isolated from the leaf, stem, and root tissues of *Catharanthus roseus* (Kharwar et al. 2008).

It is reported that fungal metabolites are not only indispensable for medicine but also important for plant protection. The demand for new highly effective agricultural agents to control farm pests and pathogens is huge, and partly arises from the removal of synthetic compounds from the market because of their toxicity toward the environment. Shipunov et al. (2008) tested the co-introduction and host-jumping hypotheses in plant communities by comparing endophytes isolated from the invasive spotted knapweed (*Centaurea stoebe*, Asteraceae) in its

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native and invaded ranges. Shipunov et al. (2008) reported that endophytes can affect the competitiveness of *C. stoebe*. Both co-introduction and host-jumping of endophytes align with hypotheses of plant invasion that are based on enhanced competitiveness. Kharwar et al. (2008) reported 183 mycoendophytes representing 13 fungal taxa isolated from leaf, stem, and root tissues of *C. roseus* from two sites representing two different ecosystems in North India. The leaf tissues showed more diversity of endophytes such as *Drechslera*, *Curvularia*, *Bipolaris*, *Alternaria,* and *Aspergillus* sp. Wei et al. (2009) studied the colonization frequencies of endophytic *Pestalotiopsis* species diverse with host plants, ages, tissues, and sites. Ya-li et al. (2010) reported 49 endophytic fungi which were recovered from *Saussurea involucrata* and identified using morphological and molecular techniques. Among these fungi *Cylindrocarpon* sp. was the dominant species followed by *Phoma* sp. and *Fusarium* species. Li and Shun (2009) reported the recovery of 300 isolates in which 172 isolates were from *Dracaena cambodiana* and 128 from *Aquilaria sinensis*.

4.2 Fungal Endophyte Diversity and Bioactive Compounds

The maximum biological diversity in terrestrial ecosystems is in tropical and temperate rainforests. Interestingly, they also have the greatest number of mycoendophytes. These ecosystems cover only 1.44 % of the land's surface, yet they harbor more than 60 % of the world's terrestrial biodiversity (Strobel and Daisy 2003). Hazalin et al. (2009) isolated 300 endophytes from various parts of plants collected from the National Park, Penang in Malaysia. Some of these endophytes demonstrated cytotoxic activity against the murine leukemic P388 cell line and 1.7 % against a human chronic myeloid leukemic cell line K562 (Hazalin et al. 2009). Survey of the literature provides evidence of increasing research on endophytes and their secondary metabolites. Studies on medicinal plants used by indigenous communities to treat various diseases have resulted in a wealth of scientific discoveries.

Fungal endophytes are being increasingly accepted as an ecological group of microorganisms that may provide sources for new secondary metabolites with useful biological activities. An array of active principles has been isolated and characterized from endophytes and many of these have diverse bioactivities (anticancerous, antioxidants, antifungal, antibacterial, antiviral, anti-insecticidal, and immune suppressants). Isolation of endophytic fungi from coffee plants (*Coffea arabica* and *C. robusta*) was shown to have antimicrobial activity against various human pathogenic bacteria (Sette et al. 2006). At present, there is an urgent need to search for endophytic metabolite that can be developed as safe, effective antifungal agents that are nonpetrochemical, eco-friendly, and easily obtained (Liu et al. 2006). Endophyte *Taxomyces andreanae,* which produces taxol in vitro, was isolated from *Taxus* sp. (Stierle et al. 1993). Vennila et al. (2010) studied the effect of taxol extracted from the endophytic fungus *Pestalotiopsis* *pauciseta* recovered from *Tabebuia pentaphylla* Hems. *T. pentaphylla* (family Bignoniaceae) is distributed in Northern Mexico, Southern Florida, and Cuba.

Zhou et al. (2010) summarized the recent advances in taxol-producing endophytic fungi all over the world. Kajula et al. (2010) studied the extracellular siderophore production as well as production of antibacterial and antioxidant compounds by endophytic fungi of Scots pine (*Pinus sylvestris* L.) and Labrador tea (*Rhododendron tomentosum* Harmaja). The pinolenic acid contained in pine nut oil helps curb appetite. It is used as a pain reliever in arthritis, aches, and sore muscles. Yang et al. (1994) reported that the phenol and phenolic acids detected in culture medium of endophytes often have remarkable biological activities. 2-Hydroxy-6-methylbenzoic acid was isolated from endophytic *Phoma* species which showed noteworthy antibacterial activity. *Phoma medicaginis* exists as a prolonged asymptomatic infection of its host plant (*Medicago* species). Suryanarayanan et al. (2005) studied the cactus *Cylindropuntia fulgida* for its endophytic diversity. The authors reported 900 endophytic isolates belonging to 22 fungal species from 21 cactus sp.

Karsten et al. (2007) reported herbicidal and algaecidal activity in ethyl acetate extract of an endophytic *Phoma* sp. isolated from *Fagonia cretica*, as ethnomedicine, *F. cretica* is used against fever, thirst, vomiting, dysentery, asthma, urinary discharges, liver trouble, dropsy, delirium, typhoid, toothache, stomach troubles, and skin diseases. Randa et al. (2010) isolated a *Botryosphaeria rhodina* from the stem of the medicinal plant *Bidens pilosa* (Asteraceae) that showed anti-inflammatory, antiseptic, and antifungal effects. Borges and Pupo (2006) reported two novel hexahydroanthraquinone derivatives, dendryol E and F isolated from *Phoma sorghina*, which was found as endophyte in association with the medicinal plant *Tithonia diversifolia*.

Schwarz et al. (2004) optimized the culture conditions of *Phoma* species and reported highest nematicidal activity in yeast malt glucose medium. Phomodione, 2,6-diacetyl-7-hydroxy-4a,9-dimethoxy-8,9b-dimethyl-4a.9b-dihydrodibenzo furan-1,3, an usnic acid derivative, was isolated from culture broth of a *Phoma* species which was an endophyte in the Guinea plant (*Saurauia scaberrinae*). Smith et al. (2008) provided direct evidence from bioassays of endophytes isolated from tropical plants and bioinformatic analyses that will give a novel chemistry of potential value. Raviraja (2005) studied 18 species of mycoendophytes, isolated from bark, stem, and leaf segments of five medicinal plant species growing within the Kudremukh range in the Western Ghats of India. The most common endophytic fungi were *Curvularia clavata*, *C. lunata*, *C. pallescens,* and *Fusarium oxysporum*. The greatest species richness and frequency was found in the leaf segments, rather than the stem and bark segments of the host plant species. Thus, if endophytes could produce the same rare and important bioactive compounds as their host plants, this would not only reduce the need to harvest slow-growing and possibly rare plants but also help to preserve the world's ever-diminishing biodiversity.

Large number of eco-friendly drugs produced by fungal endophytes is large as compared to endophytic bacteria and actinomycetes. Natural products from fungal endophytes can be grouped into several categories, including alkaloids, steroids, terpenoids, isocoumarins, quinones, phenylpropanoids and lignans, phenol and phenolic acids, aliphatic metabolites, lactones, etc. Zhen-Liang et al. (2011) reported novel bioactive compounds with spiro-5, 6-lactone ring skeleton isolated from endophyte *Massrison* sp. which is recovered from wild *Rehmannia glutinosa*. Further, they performed the antifungal and cytotoxic activities of the compounds. Debbab et al. (2009) reported secondary metabolites in *Chaetomium* sp. isolated from *Salvia officinalis* and evaluated their cytotoxic activity. Rukachaisirikul et al. (2007) reported endophytic *Phomopsis* species which produces secondary metabolites such as phomoenamide, phomonitroester, and deacetylphomoxanthone, and showed antibacterial activity against *Mycobacterium tuberculosis*. Tuberculosis (TB) infections are continuously increasing. Gordien et al. (2010) studied extracts from Scottish plants, lichens, and mycoendophyte which were screened for activity against *Mycobacterium aurum* and *M. tuberculosis*. The greatest activity against *M. aurum* was shown by extracts of *Juniperus communis* roots of the lichen *Cladonia arbuscula* and of a mycoendophyte isolated from *Vaccinium myrtillus* (Gordien et al. 2010). It is obvious that mycoendophytes serve as a source of potentially useful medicinal compounds. For example, 3-Nitropropionic acid was isolated from *Phomopsis* species which inhibited *Mycobacterium tuberculosis* (Copp and Pearce 2007). Guo et al. (2008) studied the new antimicrobial metabolites isolated and extracted from the culture of *Colletotrichum* species from *Artemisia annua,* which is a traditional Chinese herb. It is well recognized for its synthesis of artemisinin (Antimalarial drug).

4.3 Endophytic Actinomycetes

The actinomycetes that reside in the tissues of living plants and do not visibly harm the plants are known as endophytic actinomycetes (Strobel et al. 2004). Endophytic actinomycetes exist in the inner tissues of living plants. They have been isolated from the stem, leaf, fruit, root, and interior of other parts of many plants species (Okazaki et al. 1995; de Araújo et al. 2000; Coombs and Franco 2003). These organisms have attracted taxonomists, agronomists, chemists, ecologists, and evolutionary biologists. It has been indicated by numerous studies that these prolific actinomycetes appear to have a capacity to produce an impressive and important array of secondary metabolites. These metabolites exhibit a wide range of biologically active compounds, such as antibiotics, antitumor, anti-infectives, and other important chemical agents, such as plant growth promoters and enzymes. Similarly, actinomycetes also contribute to their host by promoting growth and enhancing their ability of withstanding in unfavorable environmental conditions (Qin et al. 2011a, b). Moreover, it represents under explored reservoir of novel species of potential interest in the discovery of novel lead compounds and for exploitation in pharmaceutical, agriculture, and industry (Qin et al. 2009a, b).

The actinomycetes accounts for a high proportion of soil microbial diversity and contains the most economically significant prokaryotes, producing about half of the known bioactive compounds (Lazzarini et al. 2000), including antibiotics (Bérdy 2005), antitumor agents (Cragg et al. 2005), immunosuppressive agents (Mann 2001), and enzymes (Oldfield, 1998). Endophytic actinomycetes have attracted attention in recent years, with increasing reports of isolates from a range of plant types, including medicinal plants (Taechowisan et al. 2003; Zin et al. 2007) and crop plants (cereals, such as wheat and rice, as well as potatoes, carrots, tomatoes, and citrus) (Nejad and Johnson 2000; Araújo 2002; Coombs and Franco 2003; Surette et al. 2003; Sessitsch et al. 2004; Tian et al. 2007). Endophytic actinomycetes promote the growth of host plants as well as to reduce disease caused by plant pathogens through various mechanisms, including the production of secondary metabolites, which are used in direct antagonism against plant diseases and pests (Cao et al. 2004, 2005; Castillo et al. 2007), also changes in host physiology (Igarashi et al. 2002), and the induction of systemic acquired resistance in plants (Conn et al. 2008). Similarly, other metabolites have antibiotic activity, suggesting that these organisms can be an important source for bioprospecting. Day-by-day the new species of endophytic actinomycetes have been increasingly reported. Thus, these endophytes are expected to be potential sources of new species with new bioactive agents (Gu et al. 2006; Duangmal 2008).

Higher plants contain a promising niche inside their tissues. The studies have demonstrated that some actinomycetes can form important associations with plants and colonize themselves in their inner tissues. For example, *Frankia* species and *Streptomyces scabies* important actinomycetes can penetrate their respective hosts and establish a relation as either endophyte or pathogen (Benson and Silvester 1993; Doumbou et al. 1998). The actinomycetes that live within the tissue of living plants and do not cause any symptom or do not visibly harm the plants are known as endophytic actinomycetes (Stone et al. 2000). It is suggested that there are approximately 300,000 plant species on the Earth, and each plant is considered to be the host for one or more type of microbial endophytes (Strobel and Daisy 2003), which creates an enormous biodiversity of endophytic microorganisms. But, a few of these endophytic actinomycetes associated with plants have been studied, indicating the opportunity to find new species and new related natural products among plants living in different niches and ecosystems. Recent studies revealed that large group of endophytic actinomycetes species and their diverse compounds with different biological functions are present (Araujo et al. 2002; Coombs and Franco 2003; Ryan et al. 2008; Bascom-Slack et al. 2009). But in some cases, actinomycetes act as biological agents (Cao et al. 2005) that enhance the plant growth promotion activity (Igarashi et al. 2002) and promote plant development in adverse environmental conditions (Hasegawa et al. 2006). These organisms are relatively unstudied and are potential sources of novel natural products used in medicine, agriculture, and industry (Strobel et al. 2004). Continuously, new findings in the recent study of the endophytic actinomycetes have an enormous biotechnological potential in the areas of natural products discovery and related applications.

Moreover, the natural products play highly significant role in drug discovery and development process. Cragg (2005) reported that 28 % of the new chemicals were discovered and 42 % of these chemicals were natural products and their derivatives, including anticancerous drugs. More than 22,000 biologically active metabolites were recovered from microorganisms, out off these 45 % compounds were recovered from actinomycetes, such as *Streptomyces* which is an excellent producer (Bérdy 2005). The application of actinomycetes for health and well-being of people throughout the world is a revolution in medicine (Demain and Sanchez 2009).

4.3.1 Diversity of Endophytic Actinomycetes in Medicinal Plants

Medicinal plants play a very important role in medicine to cure different types of diseases. In 1886, the genus *Frankia* was isolated from non-legume root nodules, which indicate the association between actinomycetes and host (Okazaki 2003). In the last two decades, endophytic actinomycetes have been isolated from all examined vascular plants, ranging from woody trees to herbaceous plants. The symbiotic colonization of terrestrial plants by actinomycetes is ubiquitous and common in nature. Therefore, the endophytic actinobacteria are important components of microbial biodiversity because of the frequent plant species. The plants which maintain the ethnobotanic values it is considered as promising sources of endophytes which produce novel bioactive compounds.

Endophytic actinomycetes also reported from crop plants, such as wheat, rice, potato, carrots, tomato, and citrus (Nejad and Johnson 2000; Araujo et al. 2002; Coombs and Franco 2003; Surette et al. 2003; Sessitsch et al. 2004; Tian et al. 2007; Velazquez et al. 2008), woody tree species (Taechowisan et al. 2003; Zin et al. 2007; Yuan et al. 2008; Zhao et al. 2010a, b, c), mosses, and ferns (Janso and Carter 2010). This study reported that the greatest diversity of endophytes is probable to occur in the tropical and temperate regions (Strobel and Daisy 2003). The occurrence of actinomycetes in roots compared to other tissues is common. Taechowisan et al. (2003) screened 5,400 roots, leaves, and stem tissues from 36 species of plants and recovered 212 isolates from roots, 97 from leaves, and 21 from stems. Furthermore, Verma et al. (2009a, b) recovered more than double the number of all isolates from roots than from stems or leaves from 20 different Indian lilac trees and *Azadirachta indica*. Root plays a vital role for water and nutrient uptake for plants, and therefore it is an ideal substrate for actinomycete colonization (Janso and Carter 2010).

Endophytic actinomycetes diversity and antibiotic activity was reported recovered from medicinal plants of tropical regions (Li et al. 2008a, b; Bascom-Slack et al. 2009; Qin et al. 2009a). Qin et al. (2009b) reported 2,174 endophytic actinomycetes isolated from different medicinal plants of tropical rainforest of China. Among these only from one kind of plant, *Maytenus austroyunnanensis*, one new genus, and seven new species of endophytes were isolated. The richness of actinomycetes and their diversity from tropical rainforest are much higher compared to biogeographical regions. Similarly, tropical rainforest has a promising potential as a source of actinomycetes and new endophytes. It is reported that the endophytic actinomycetes are diverse and the diversity may vary between different host plant regions and different plant species.

Taechowisan et al. (2003) isolated 330 endophytes from different medicinal plants belonging to four different genera (*Streptomyces, Microbispora, Nocardia* and *Micromonospora*). Also El-Shatoury et al. (2009) reported endophytic actinomycetes associated with the medicinal plant, *Achillea fragrantissima* (Forssk) Sch. Bip. (Compositae), of Saint Katherine, South Sinai, Egypt. The diversity of endophytic actinomycetes showed no significant differences between different locations of the studied regions. Twenty-five isolates were identified and categorized into seven genera of actinomycetes (viz. *Streptomyces*, *Nocardioides*, *Kitasatosporia*, *Nocardia*, *Kibdelosporangium*, *Pseudonocardia,* and *Promicromonospora).* In addition to these one unidentified isolate was also obtained. Genera *Nocardia* and *Streptomyces* were the most recorded in *A. fragrantissima* internal tissues. An endophytic actinomycete was recovered from four medicinal plants such as *Artemisia herba-alba, Echinops spnosus, Mentha longifolia,* and *Ballota undulata* belonging to different genera. Among these the *Streptomyces* species was dominant as compared to other (El-Shatoury et al. 2006). An endophytic actinomycete novel species *Pseudonocardia endophytica* sp. nov. was isolated from the inner tissues of the traditional Chinese medicinal plant *Lobelia clavata* by Chen et al. (2009). Wang et al. (2008) reported the diversity of uncultured microbes associated with medicinal plant *Mallotus nudiflorus* and found that actinomycetes were the most dominant microbial group, covering about 37.7 % of whole endophytes isolated. *Glycomyces endophyticus* sp. nov. is an endophytic actinomycete, designated strain YIM 56134T, isolated from the root of a Chinese medicinal plant, *Carex baccans* Nees, collected from Yunnan, South West China. This medicinal plant harbors other endophytic actinomycetes in their internal tissues (Qin et al. 2008).

The diversity of endophytic actinomycetes associated with tropical, native plants is essentially unexplored. Janso and Carter (2010) isolated 123 endophytic actinomycetes from tropical plants collected from several locations in Papua New Guinea, Mborokua Island, and Solomon Islands. These isolates were found to be prevalent in roots but uncommon in leaves. Characterization of 105 isolates of unique strains by 16S rRNA gene sequence analysis revealed that 17 different genera were represented and rare genera also, such as *Sphaerisporangium* and *Planotetraspora*, which have never been previously reported to be endophytic. Phylogenetic analyses grouped many of the strains into clades distinct from known genera within Thermomonosporaceae and Micromonosporaceae, indicating that they may be unique genera. Although *Streptomyces* was the most frequently isolated genus, the Streptosporangiaceae was also well-represented family, which consisted of five different genera: *Sphaerisporangium*, *Planotetraspora*, *Nonomuraea*, *Streptosporangium*, and *Microbispora*. *Planotetraspora* and *Sphaerisporangium* were common among rare genera of actinomycetes and were consistently represented in plants from each sampling location.

Also *Microbispora*, which belongs to Streptosporangiaceae, is common in a variety of plants. They gave new report on the occurrence of *Planotetraspora* and *Sphaerisporangium* in plants as endophytes. Also three *Kibdelosporangium* strains, from the roots of a *Heterospathe* sp. and *Pandanus* sp., are the first report of endophytes isolated from these genera (Janso and Carter 2010).

Zhu et al. (2009) isolated more than 160 endophytic actinomycetes from multiple tissues of both wild and cultured specimens of the native, tropical tree *Trewia nudiflora*. They reported the presence of actinomycetes from each tissue, provided relatively little information on the biodiversity of these isolated actinomycetes, and characterized only *Streptomyces* sp. Castillo et al. (2007) isolated endophytic actinomycetes from plant species growing in Southern Patagonia, but they only recovered *Streptomyces* sp. from the stems. *Pseudonocardia sichuanensis* sp. nov., a novel endophytic actinomycetes has been isolated from the root of *Jatropha curcas* L. (Qin et al. 2011a, b). Three novel endophytic *Streptomyces* have been isolated from plants with ethnobotanical properties on the Malay Peninsula including *Thottea grandiflora* (Aristolochiaceae), *Polyalthia* sp. (Annonaceae), and *Mapania* sp. (Cyperaceae) (Zhao et al. 2007; Zin et al. 2007). Traditional Chinese medicinal plants are large sources of biologically active compounds, providing raw material for agriculture, pharmaceutical, cosmetics, and fragrance industries. The endophytes of these medicinal plants take part in biochemical pathways and produce analogous or novel bioactive compounds. In a study, 560 endophytic actinomycetes were isolated from 26 medicinal plant species in Panxi plateau. According to the phyllogenetic analysis, seven isolates were *Streptomyces* sp., while the remainder belonged to genera *Micromonospora, Oerskovia, Nonomuraea, Promicromonospora,* and *Rhodococcus* (Zhao et al. 2011).

4.3.2 Bioactive Compounds from Actinomycetes

Endophytic Actinomycetes of medicinal plants participate in metabolic pathways of medicinal plants and produce analogous or novel bioactive compounds, for example taxol (Strobel et al. 1999). Endophytic actinomycetes are considered as rich and potential sources of novel bioactive compounds and various bioactive compounds are continuously isolated from them until now (Taechowisan et al. 2005; Castillo et al. 2006; Igarashi et al. 2007a, b). Endophytic actinomycetes associated with medicinal plants could be a rich source of functional metabolites (Strobel et al. 2004). Natural products from endophytes is evident from the number of review articles that have appeared in the recent literatures (Hasegawa et al. 2006; Zhang et al. 2006; Gunatilaka 2006; Guo et al. 2008; Staniek et al. 2008; Ryan et al. 2008; Verma et al. 2009a, b). Study of the endophytic actinomycetes has resulted in the identification of many new natural products with wide range of biological activities.

Endophytic actinomycetes, mainly from medicinal plants, show the ability to inhibit or kill a wide variety of harmful microorganisms such as pathogenic bacteria, fungi, and viruses. Thus, there is great application value to develop antimicrobial drugs from endophytic actinobacteria. Till now, number of new antibiotics have been isolated, such as kakadumycins (Castillo et al. 2003), celastramycins A-B (Pullen et al. 2002), munumbicins A-D (Castillo et al. 2002), and demethylnovobiocins (Igarashi 2004). This was observed from the culture broth of some endophytic *Streptomyces sp.* a simple compound 6-prenylindole was isolated. This chemical exhibited a significant antifungal activity against plant pathogen *Fusarium oxysporum*. The chemical was originally isolated from the plant liverwort (*Hepaticae*). This compound is isolated from both plant and endophyte (Igarashi 2004). From the strain *Streptomyces* sp. TP-A0456 two novel compounds cedarmycins A and B were isolated, which were also isolated from a twig of cedar. The Cedarmycins A showed antifungal activity against *Candida glabrata* in vitro (Igarashi 2004). Another endophytic *Streptomyces* sp. Tc022 isolated from *Alpinia galanga* strongly inhibited the fungi *Colletotrichum musae* and *Candida albicans*. The metabolites extracted from *Streptomyces* sp. Tc 022 in the broth culture medium showed the presence of a major component actinomycin D, which displayed strong antifungal activity (Taechowisan et al. 2006). Two new chromophoric peptides antibiotics designated as munumbicins E-4 and E-5 were isolated from endophytic *Streptomyces* NRRL 30562 which produces broadspectrum antibiotics such as munumbicins A-D. These compounds showed broadspectrum activity against both Gram-positive and Gram-negative bacteria (Castillo et al. 2006). Recently, a new antifungal compound saadamycin was isolated from endophytic *Streptomyces* sp. Hedaya48, it confers potent antifungal activity against clinical fungi such as dermophytes, etc. (El-Gendy and EL-Bondkly 2010). These studies suggest that actinomycetes possess strong microbial compounds, which are utilized as drugs and can be modified to combat the future challenges by use of biotechnological approaches.

Nowadays, there has been an increasing interest in discovering antitumor agents from endophytes. Endophytic actinomycetes live in close association with their host plants and close relationship with them, then it becomes a real possibility that genes involved in natural products biosynthesis could be exchanged via horizontal gene transfer between endophytic actinomycetes and plants, resulting in synthesis of plant-derived compounds by a microbial endophyte such as the paclitaxel-producing *Kitasatospora* sp. isolated from *Taxus baccata* in Italy (Caruso et al. 2000; Janso and Carter 2010). This is the first report on synthesis of taxol from endophytic actinomycetes. Also, maytansinoids (19-membered macrocyclic lactams ansamycin antibiotics), a potent antitumor agent related to antitumor chemical compounds that were originally isolated from members of the higher plant families Celastraceae, Rhamnaceae, and Euphorbiaceae (Kupchan et al. 1972; Powel et al. 1982) and some mosses (Suwanborirux et al. 1990), were also produced by plant-associated actinomycete *Actinosynnema pretiosum* (Higashide et al. 1977). One novel chlorine-containing ansamycin, namely naphthomycin K, was obtained from the endophytic strain of *Streptomyces* sp. CS was isolated from *Maytenus hookeri* a medicinal plant producing maytansinoids. This compound showed cytotoxic activity against P388 and A-549 cell lines (Lu and Shen 2007). It was quite interesting that the ansacarbamitocins, a new family of maytansinoids, were isolated from an actinomycete strain *Amycolatopsis* CP2808 that belongs to the family Pseudonocardiaceae; also, the ansamitocin-producing strain *A. pretiosum* belongs to the same family (Snipes et al. 2007). The 24-demethylbafilomycin C1, newly added member of the afilomycin subfamily, and two more new bafilomycin derivatives were isolated from the strain *Streptomyces* sp. (Lu and Shen 2003, 2004).

In the subsequent research in the field of antitumor by researchers all over found new bioactive chemical compounds including five 16-membered macrolides, belonging to the bafilomycin subfamily were isolated from *Streptomyces* sp. CS. was isolated from *M. hookeri* and showed cytotoxic activity against MDA-MB-435 cell line in vitro (Li et al. 2010). Another strain Streptomyces sp. ls9131, which was also isolated from *M. hookeri*, produced novel macrolides. This compound dimeric dinactin had strong antineoplastic activity and antibacterial activity (Zhao et al. 2005). Two novel compounds anthraquinones and lupinacidins A and B were isolated from the fermented broth of newly identified endophytic actinomycetes, *Micromonospora lupine*. The lupinacidins showed considerable inhibitory effects on the invasion of murine colon 26-L5 carcinoma cells (Igarashi et al. 2007a, b). Kim et al. (2006) isolated two new 6-alkylsalicylic acids, salaceyins A and B from another strain *Streptomyces laceyi* MS53. Salaceyins A and B showed cell toxicity against human breast cancer cell line SKBR3. Pterocidin is a new antitumor cytotoxic chemical compound, isolated from the endophytic *Streptomyces hygroscopicus* TP-A0451 exhibited cytotoxicity against cancer cell lines (Igarashi et al. 2006). Two compounds 5, 7-dimethoxy-4-phenylcoumarin and 5, 7-dimethoxy-4-p-methoxyl-phenylcoumarin isolated from endophytic Streptomyces aureofaciens CMUAc130 were originally produced by numerous species of plants. These bioactive compounds showed high and strong antifungal and antitumor activity (Taechowisan et al. 2005, 2007a). These findings support the application of them as anti-inflammatory agent (Taechowisan et al. 2007b). From the endophytic strain *Streptomyces* sp. SUC1, four novel secondary metabolites, lansai A to D were isolated. Tuntiwachwuttikul et al. (2008) reported lansai B which showed weak activity against the BC cell line, lansai C also showed significant anti-inflammatory activity in LPS-induced RAW 264.7 cells. In a word, endophytic actinobacteria still remain a relatively untapped source of novel natural products, presumed to push forward the frontiers of drug discovery against deadly cancers.

Endophytic actinomycetes also produced various other different bioactive compounds with a large magnitude of functioning. An endophytic *Streptomyces* sp. isolated from a Chinese traditional medicine plant *Cistanche deserticola* produced tyrosol. This compound acts as a new possible ligand for GPR12 (Lin et al. 2008). Coronamycin is a complex of novel peptide antibiotics extracted from verticillate *Streptomyces* sp. isolated from an *Epiphytic vine*, *Monstera* sp., which shows activity against pythiaceous fungi and the human fungal pathogen *Cryptococcus neoformans*. It also shows activity against the malarial parasite *Plasmodium falciparum*. It also showed antifungal activity against human fungal pathogen *Cryptococcus neoformans* (Ezra et al. 2004). Endophytic actinomycetes associated with higher plants, particularly with medicinal plants (used traditional medicines), are harboring bioactive compounds with medicinal properties; it is supported by the examples of taxol and maytansinoids discussed above. Endophytic actinomycetes as a key player of biocontrol agents have been partly discussed (Hasegawa et al. 2006). Studies are continuously conducted to unravel the mechanisms of action of these endophytes for production of bioactive compounds, such as antibiotics and cell wall degrading enzyme (El-Tarabily and Sivasithamparam 2006).

4.4 Bacterial Endophytes

The survival of endophytic bacteria inside different plant tissues is a well-predictable phenomenon (Sharrock et al. 1991; Fisher et al. 1992; McInroy and Kloepper 1995a, b). In general, endophytic bacteria are described as bacteria that are able to colonize the living plant tissues without harming a plant (Kado 1992). Endophytic bacteria isolated from the internal plant tissue of healthy plants comprises over 129 species representing over 54 genera, with *Pseudomonas, Bacillus, Enterobacter,* and *Agrobacterium* being the most commonly isolated bacterial genera (Mundt and Hinkle 1976; Gardener et al. 1982; Sturz 1995; McInroy and Kloepper 1995a; Hallmann et al. 1997a, b; Mahafee and Kloepper 1997).

Endophytic bacteria are usually isolated from the rhizosphere (roots), seeds, or plant material (leaf, branch, and other parts of plant) (Hallmann et al. 1997a, b). A division of rhizobacteria may enter the interior of the root by hydrolyzing cell wall cellulose, through tumors, along water flow, through wounds, or through lateral branching sites (Hallmann et al. 1997a, b; Siciliano et al. 1998). Evidences of plant-associated microbes has been discovered in the fossilized tissues of stems and leaves and these endophytic relationships may have begun from the time that higher plants first have appeared on the Earth, hundreds of millions of years ago to establish these types of relationships (Taylor and Taylor 2000). As a result of these associations between bacteria and plants, there is possibility to happen that some of these endophytic bacteria modified their genetic systems allowing for the transfer of information between themselves and the higher plant and vice versa (Stierle et al. 1993). The endophytic bacteria are known to contribute to the host plants growth and development by producing plant growth regulators. The bacterial endophytes are also known to increase host plants resistance to plant pathogens and parasites to promote biological nitrogen fixation and to produce antibiotics. The major group of endophytic bacteria comes under the category of actinomycetes, which are mostly studied and established group of endophytic bacteria. In the next section we will be confined to the endophytic bacteria other than Endophytic actinomycetes, which have already been discussed above.

4.4.1 Diversity of Endophytic Bacteria in Medicinal Plants

Various researchers reported endophytic microbes from various plants either medicinally useful or not. Nearly 300,000 plant species that exists on the earth and each individual plant is host to one or more endophytes. Only a few these plants have ever been completely studied for their endophytic nature. Consequently, the opportunity to find new and interesting microorganism among myriads of plants in different ecosystems is great (Strobel and Daisy 2003). Endophytic bacteria are commonly associated with medicinal plants.

Based on the visible morphological differences totally 20 bacterial isolates were isolated from *Andrographis paniculata* plant samples in India. Among all these 20 endophytic bacterial isolates, 11 were Gram-positive cocci and nine Gram-positive rods. Total seven isolates showed positive result for endospore staining and they were suspected as *Bacillus* species. The other isolates could not be identified (Arunachalam and Gayathri 2010). Cho et al. (2002) reported a strain of Bacillus CY22 from the roots of Balloon flower *Platycodon grandiflorum* in Republic of Korea. This was the endophytic bacterium capable of secreting various biologically active compounds showing activity against various pathogenic bacteria and fungi. A total of 98 isolates of bacterial endophytes were obtained from 27 medicinal plants by Berde et al. (2010). Among these isolates 58.43 % were Gram-positive rods, 19.10 % were Gram-negative rods, 10 % Gram-positive, and 10 % Gram-negative cocci. Bhore et al. (2010) screened three bacterial endophytes *Pseudomonas resinovorans, Paenibacillus polymaxa*, and *Acenitobacter calcoaceticus* from the leaves of Sambung Nyawa [*Gynura procumbens* (Lour.) Merr.].

The species *Jacaranda decurrens* Cham. is a shrub present in diverse physiognomies of the Brazilian Cerrado, popularly described as a medicinal plant that acts in gynecological infections, Giardia and amoeba's diseases, and as an antisyphilitic. A total of 18 isolates of endophytic bacteria were isolated from *Jacaranda decurrens* Cham. with predomination of the bacteria of the genera *Bacillus* (39 %), *Pseudomonas* (27.6 %), *Corynebacterium* (16.7 %), *Actinomyces* (11.1 %) and *Staphylococcus* (5.6 %) (Carrim et al. 2006). In a study, Laorpaksa et al. (2008) screened 106 isolates of endophytic bacteria from 35 Thai medicinal plants. These endophytic bacteria belong to the diverse genera of bacteria, most of these endophytic bacteria showed antimicrobial properties against bacterial and fungal human pathogens.

The diversity of endophytic bacteria associated with ginseng (*Panax ginseng* C.A. Meyer) plants of varying age levels in Korea was investigated. A total of 51 colonies of endophytic bacteria were isolated from the interior of ginseng stems. These endophyte communities recovered from ginseng plant based on the results of 16S rDNA analysis, *Bacillus* and *Staphylococcus,* were dominant in age group 1–4-year-old plants. Other bacteria such as *Pseudomonas, Agrobacterium,* and *Stenotrophomonas, Mycobacterium Paenibacillus,* and *Staphylococcus* also being predominant genera (Vendan et al. 2010).

Echinacea is one of the most popular herbal supplements and the popularity of this remedy is due to its use for the treatment of infections and its immune-stimulatory and anti-inflammatory effects (Giles et al. 2000). Thirty-nine isolates of endophytic bacteria were isolated and selected based on colony morphology from four different micropropagated species of *Echinacea* (20 isolates from *E. pallida* var. *angustifolia*, four from *E. pallida* var. pallida, seven from

E. purpurea, and eight isolates from *E. pallida* var. *tenneseensis*). These isolates mainly include *Bacillus pumilus* (from *E. purpurea*), *Acinetobacter lwofii* and *Stenotrophomonas maltophila* (from *E. pallida* var. *angustifolia*), *Bacillus pumilus* (from *E. pallida* var. *pallida*), *Pseudomonas stutzeri,* and *Wautersia paucula* (from *E. pallida* var. *tenneseensis*). *W. paucula* was previously known as *Ralstonia paculua* (Lata et al. 2006).

4.4.2 Chemical Diversity of Endophytic Bacteria

The need for new and useful compounds to provide resistance and relief in all aspects of human conditions is continuously over growing. Natural products have been the traditional pathfinder compounds offering an untold diversity of chemical structures (Strobel and Daisy 2003). The word *Bioprospecting* is today most commonly used to express the collection and screening of biological material for commercial purposes (Synnes 2007). Molecules derived from natural products, particularly those products by plant and microbes, have an excellent record of providing novel chemical structural compounds for development of new pharmaceutical products. It was not until Pasteur discovered that fermentation is caused by living cells that people seriously began to investigate microorganisms as a source of high value metabolites. Since then people have been engaged in the discovery and application of microbial metabolites with the activity against both plant and human pathogens. Further, most of the discovery of plethora of microbes for application that span a broad spectrum of utility in medicine, agriculture, and industry is now practical (Balagurunathan and Radhakrishnan 2007).

Bacterial endophytes are mostly responsible for the production of the chemical metabolites which are used by the plants for their growth and development, against pathogens, etc. Apart from these functional metabolites which are utilized by plants, these endophytic bacteria also produce chemicals which are having pharmaceutical functions such as antibacterial, antifungal, anticancer, and many more biological activities. Bhore et al. (2010) screened cytokinin and cytokinin-like compounds from the endophytic bacteria (*Pseudomonas resinovorans, Paenibacillus polymaxa,* and *Acenitobacter calcoaceticus*) isolated from the medicinal plant *Gynura procumbens* (Lour.) Merr. resulted in growth and development of the host plant. In a study, Carrim et al. (2006) reported proteolytic, amilolytic, lipolytic, and esterasic activity showing enzymes from isolates of endophytic bacteria isolated from the *Jacaranda decurrens* Cham. a medicinal plant. All these enzymes are of biotechnological and pharmaceutical interest used for various purposes. The amylolytic activity was shown by isolates *B. coagulans* CAR3, *B. licheniformis* CAR4, *B. megaterium* CAR5, *Act. pyogenes* CAR1, and *P. stutzeri* CAR8. Esterases and lipases were produced by *Coryne. renale* CAR 7, *Bacillus, Ps. stutzeri,* and *Corynebacterium.* The presence of proteolytic activity was observed in *B. circulans* CAR 2, *B. coagulans*

CAR3*, B. licheniformis* CAR4*, B. megaterium* CAR5, *Coryne. renale* CAR7, and *Corynebacterium*.

In another study, Vendan et al. (2010) studied 18 isolates of endophytic bacteria isolated from Ginseng (*Panax ginseng* C.A. Meyer) medicinal plants. Among these 18 isolates 14 isolates of endophytic bacteria were producing Indole Acetic Acid in nutrient broth. The ability to produce IAA is considered for the development of plant growth. Also, IAA-producing endophytic bacterial screening was studied for the isolates from micropropagated plantlets of *Echinacea*. These bacteria include *Acinetobacter, Bacillus, Pseudomonas, Wautersia (Ralstonia),* and *Stenotrophomonas*. *Pseudomonas stutzeri* P3 strain which have been extensively exploited for the production of IAA plant growth regulator (Lata et al. 2006).

4.5 Conclusion

The need for new bioactive compounds to overcome the growing problems of drug resistance in microorganisms and the appearance of new diseases is of increasing importance. The capability of fungi to produce bioactive metabolites has encouraged researchers to isolate and screen fungi from diverse habitat and environments to search for novel bioactive metabolites. Therefore, endophytes have been proved as an outstanding source of both novel and bioactive natural products, which have an enormous potential for the development of new drugs and agricultural products. Consequently, endophytes are known to be a rich and reliable source of biologically active compounds with potential benefits in medicinal, industrial, and agricultural application. In contrast, the development of techniques such as combinatorial chemistry and equipment such as peptide synthesizers gives rise to exciting opportunities and expectations for the synthesis of biological active compounds. Additionally, as most endophyte research has been conducted on cultivated species, the diversity of studied endophytes has been further restricted by limitations in the ability to cultivate endophytes in the laboratory.

In spite of the increased number of reports in the last decade, endophytes are still a relatively poorly investigated group of microorganisms. Therefore, the research focusing on endophytes is a promising field in the chemistry and biological properties of natural products. To overcome the infectious disease, there is need for a variety of novel antimicrobial compounds of biological origin. The endophytes hold enormous potential as sources of antimicrobials. These endophytes may open new vistas for the development of new drugs and agricultural products. The multi-drug resistance problem in microbes underscores the need for further research on novel metabolites obtained from endophytes.

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References

Araujo WL, Marcon J, Maccheroni W Jr, Van Elsas JD, Van Vuurde JW, Azevedo JL (2002) Diversity of endophytic bacterial populations and their interaction with *Xylella fastidiosa* in citrus plants. Appl Environ Microbiol 68:4906–4914

Arunachalam C, Gayathri P (2010) Studies on bioprospecting of endophytic bacteria from the medicinal plant of *Andrographis paniculata* for their antimicrobial activity and antibiotic susceptibility pattern. Int J Curr Pharm Res 2(4):63–68

Balagurunathan R, Radhakrishnan M (2007) Exploiting the less explored microbiol endophytes. Adv Biotech 6(2):20–23

Bascom-Slack CA, Ma C, Moore E, Babbs B, Fenn K, Greene JS, Hann BD, Keehner J, Kelley-Swift EG, Kembaiyan V, Lee SJ, Li P, Light DY, Lin EH, Schorn MA, Vekhter D, Boulanger LA, Hess WM, Vargas PN, Strobel GA, Strobel SA (2009) Multiple novel biologically active endophytic actinomycetes isolated from upper Amazonian rainforests. Microb Ecol 58(2):374–383

Be′rdy J (2005) Bioactive microbial metabolites. J Antibiot 58:1–26

Benson DR, Silvester WB (1993) Biology of Frankia strain actinomycetes symbionts of actinorrhizal plants. Microbiol Rev 57:293–319

Berde CV, Bhosale PP, Chaphalkar SR (2010) Plasmid of endophytic bacteria as vectors for transformation in plants. Int J Interg Biol 9(3):113–118

Bhore SJ, Nithya R, Loh CY (2010) Screening of endophytic bacteria isolated from leaves of Sambung Nyawa [*Gynura procumbens* (Lour)] for cytokinin-like compounds. Bioinformation 5(5):191–197

Borges WS, Pupo MT (2006) Novel anthraquinone derivatives produced by *Phoma sorghina* an endophyte found in association with the medicinal llant *Tithonia diversifolia* (Asteraceae). J Braz Chem Soc 17:929–934

Cao LX, Qiu ZQ, You JL, Tan HM, Zhou S (2004) Isolation and characterization of endophytic *Streptomyces* strains from surface-sterilized tomato (*Lycopersicon esculentum*) roots. Lett Appl Microbiol 39:425–430

Cao LX, Qiu ZQ, You JL, Tan HM, Zhou S (2005) Isolation and characterization of endophytic streptomycete antagonists of fusarium wilt pathogen from surface-sterilized banana roots. FEMS Microbiol Lett 247:147–152

Carrim AJI, Barbosa EC, Vieira JDG (2006) Enzymatic activity of endophytic bacterial isolates of *Jacaranda decurrens* cham (Carobinha-do-campo). Braz Arch Biol Technol 49(3):353–359

Caruso M, Colombo AL, Crespi-Perellino N, Fedeli L, Malyszko J, Pavesi A, Quaroni S, Saracchi M, Ventrella G (2000) Studies on a strain of Kitasatospora sp paclitaxel producer. Ann Microbiol 50:89–102

Castillo UF, Strobel GA, Ford EJ, Hess WM, Porter H, Jensen JB, Albert H, Robison R, Condron MAM, Teplow DB, Stevens D, Yaver D (2002) Munumbicins wide-spectrum antibiotics produced by Streptomyces NRRL 30562 endophytic on *Kennedia nigriscans*. Microbiology 148:2675–2685

Castillo P, Navas-Cortés JA, Gomar-Tinoco D, Di Vito M, Jiménez-Díaz RM (2003) Interactions between *Meloidogyne artiellia*, the cereal and legume root-knot nematode, and *Fusarium oxysporum* f. sp. ciceris race 5 in chickpea. Phytopathology 93(12):1513–1523

Castillo UF, Strobel GA, Mullenberg K, Condron MM, Teplow DB, Folgiano V, Gallo M, Ferracane R, Mannina L, Viel S, Codde M, Robison R, Porter H, Jense J (2006) Munumbicins E-4 and E-5: novel broad-spectrum antibiotics from Streptomyces NRRL 3052. FEMS Microbiol Lett 255:296–300

Castillo UFL, Browne G, Strobel WM, Hess S, Ezra G, Pacheco Ezra D (2007) Biologically active endophytic streptomycetes from *Nothofagus* spp and other plants in Patagonia. Microb Ecol 53:12–19

Chen HH, Qin S, Li J, Zhang YQ, Xu LH, Jiang CL, Kim CJ, Li WJ (2009) *Pseudonocardia endophytica* sp nov isolated from the pharmaceutical plant *Lobelia clavata*. Int J Syst Evol Microbiol 59:559–563

Cho SJ, Park SR, Kim MK, Lim WJ, Ryu SK, An CL, Hong SY, Lee YH, Jeong SG, Cho YU, Yun HD (2002) Endophytic *Bacillus* sp. isolated from the interior of balloon flower root. Biosci Biotechnol Biochem 66:1270–1275

Conn VM, Walker AR, Franco CMM (2008) Endophytic actinobacteria induce defense pathways in *Arabidopsis thaliana*. Mol Plant-Microbe Interact 21:208–218

Coombs JT, Franco CMM (2003) Isolation and identification of actinobacteria isolated from surface-sterilized wheat roots. Appl Environ Microbiol 69:5603–5608

Copp BR, Pearce AN (2007) Natural product growth inhibitors of *Mycobacterium tuberculosis*. Nat Prod Rep 2:278–297

Cragg GM, Kingston DGI, Newman DJ (2005) Anticancer agents from natural products. Brunner-Routledge Psychology Press, Taylor and Francis Group, Boca Raton, pp 47–70

de Araújo JM, da Silva AC, Azevedo JL (2000) Isolation of endophytic actinomycetes from roots and leaves of maize (Zea ays L). Braz Arch Biol Technol 43:1516–1591

Debbab A, Aly AH, Edrada-Ebel R, Mueller WEG, Mosaddak M, Hakikj A, Ebel R, Proksch P (2009) Bioactive secondary metabolites from the endophytic fungus *Chaetomium* sp isolated from *Salvia officinalis* growing in Morocco. Biotech Agro Soc Environ 13(2):229–234

Demain AL, Sanchez S (2009) Microbial drug discovery: 80 years of progress. J Antibiot 62:5–16

Doumbou CL, Akimov V, Beaulieu C (1998) Selection and characterization of microorganisms utilizing Thaxtomin A a phytotoxin produced by *Streptomyces scabies*. Appl Environ Microbiol 64:4313–4316

Duangmal K, Thamchaipenet A, Ara I, Matsumoto A, Takahashi Y (2008) *Kineococcus gynurae* sp nov isolated from a Thai medicinal plant. Int J Syst Evol Microbiol 58:2439–2442

El-Gendy MMA, El-Bondkly AMA (2010) Production and genetic improvement of a novel antimycotic agent saadamycin against dermatophytes and other clinical fungi from endophytic *Streptomyces* sp Hedaya 48. J Ind Microbiol Biotechnol 37(8):831–841

El-Shatoury S, Abdullah H, El-Kraly O, El-Kazzaz W, Dewedar A (2006) Bioactivities of endophytic actinomycetes from selected medicinal plants in the World Heritage Site of Saint Katherine Egypt. Int J Bot 2(3):307–312

El-Shatoury S, El-Kraly O, El-Kazzaz W, Dewedar A (2009) Antimicrobial activities of actinomycetes inhabiting *Achillea Fragrantissima* (Family: Compositae). Egyptian J Nat Tox 6(2):1–15

El-Tarabily KA, Sivasithamparam K (2006) Potential of yeasts as biocontrol agents of soil-borne fungal plant pathogens and as plant growth promoters. Mycoscience 47:25–35

Ezra D, Castillo UF, Strobel GA, Hess WM, Porter H, Jensen JB, Condron MAM, Teplow DB, Sears J, Maranta M, Hunter M, Weber B, Yaver D (2004) Coronamycins peptide antibiotics produced by a verticillate *Streptomyces* sp (MSU-2110) endophytic on *Monstera* sp. Microbiology 150:785–793

Fisher PJ, Petrini O, Scott HML (1992) The distribution of some fungal and bacterial endophytesin maize (*Zea mays* L). New Phytol 122:299–305

Gardener JM, Feldman AW, Zablotowicz RM (1982) Identity and behavior of xylem-residing bacteria in rough lemon roots of Florida citrus tree. Appl Environ Microbiol 43:1335–1342

Giles JR, Palat CT, Chien SH, Chang ZG, Kennedy DT (2000) Evaluation of echinacea for treatment of common colds. Pharmacotherapy 20:690–697

Gordien AY, Gray AI, Ingleby K, Franzblau SG, Seidel V (2010) Activity of Scottish plant, lichen and fungal endophyte extracts against *Mycobacterium aurum* and *Mycobacterium tuberculosis*. Phytother Res 24(5):692–698

Gu QHL, Luo W, Zheng ZH, Liu Y, Huang H (2006) *Pseudonocardia oroxyli* sp nov isolated from *Oroxylum indicum* root. Int J Syst Evol Microbiol 56:2193–2197

Gunatilaka AAL (2006) Natural products from plant-associated microorganisms: distribution structural diversity bioactivity and implications of their occurrence. J Nat Prod 69:509–526

Guo B, Wang Y, Sun X, Tang K (2008) Bioactive natural products from endophytes: a review. Appl Biochem Microbiol 44:153–158

Hallmann J, Rodriguez-Kabana R, Kloepper JW, Quadt-Hallmann A, Mahaffee WF (1997a) Bacterial endophytes in agricultural crops. Can J Microbiol 43:895–914

Hallmann QA, Hallmann J, Kloepper JW (1997b) Bacterial endophytes in cotton: location and interaction with other plant associated bacteria. Can J Microbiol 43:254–259

Hasegawa S, Meguro A, Shimizu M, Nishimura T, Kunoh H (2006) Endophytic actinomycetes and their interactions with host plants. Actinomycetologica 20:72–81

Hazalin NAMN, Ramasamy K, Lim SM, Wahab IA, Cole ALJ, Majeed AB (2009) Cytotoxic and antibacterial activities of endophytic fungi isolated from plants at the National Park Pahang Malaysia. Complem Alt Med 9:46

Higashide E, Asai M, Ootsu KTS, Kozay Y, Hasegawa T, Kishi T, Sugino Y, Yoneda M (1977) Ansamitocins a group of novel maytansinoid antibiotics with antitumour properties from *Nocardia*. Nature 270:721–722

Igarashi Y (2004) Screening of novel bioactive compounds from plant-associated actinomycetes. Actinomycetologica 18:63–66

Igarashi Y, Iida T, Yoshida R, Furumai T (2002) Pteridic acids A and B novel plant growth promoters with auxin-like activity from *Streptomyces hygroscopicus* TP-A0451. J Antibiot 55:764–767

Igarashi Y, Miura S, Fujita T, Furumai T (2006) Pterocidin a cytotoxic compound from the endophytic *Streptomyces hygroscopicus*. J Antibiot 59:193–195

Igarashi Y, Rujillo ME, Martínez-Molina E, Miyanaga S, Obata T, Sakurai H, Saiki I, Fujita T, Furumai T (2007a) Antitumor anthraquinones from an endophytic actinomycete *Micromonospora lupini* sp nov. Bioorg Med Chem Lett 17:3702–3705

Igarashi Y, Trujillo ME, Martínez-Molina E, Yanase S, Miyanaga S, Obata T, Sakurai H, Saiki I, Fujita T, Furumai T (2007b) Antitumor anthraquinones from an endophytic actinomycete *Micromonospora lupini* sp. nov. Bioorg Med Chem Lett 17(13):3702–3705

Janso JE, Carter GT (2010) Biosynthetic potential of phylogenetically unique endophytic actinomycetes from tropical plants. Appl Environ Microbiol 76:4377–4386

Kado CI (1992) Plant pathogenic bacteria. In: Balows A, Truper HG, Dworkin M, Harder W, Schleifer KH (eds) Prokaryotes. Springer, New York

Kajula M, Tejesvi MV, Kolehmainen S, Mäkinen A, Hokkanen V, Mattila S, Pirttilä AM (2010) The siderophore ferricrocin produced by specific foliar endophytic fungi in vitro. Fungal Biol 114(2–3):248–254

Karsten K, Umar F, Ulrich F, Barbara S, Siegfried D, Gennaro P, Piero S, Sándor A, Tibor K (2007) Secondary metabolites isolated from an Endophytic *Phoma* sp absolute configuration of tetrahydropyrenophorol using the solid-state TDDFT CD methodology. Eur J Org Chem 19:3206–3211

Kharwar RN, Verma VC, Strobel G, Ezra D (2008) The endophytic fungal complex of *Catharanthus roseus* (L) G Don. Curr Sci 95(2):228–233

Kim N, Shin JC, Kim W, Hwang BY, Kim BS, Hong YS, Lee D (2006) Cytotoxic 6-alkylsalicylic acids from the endophytic *Streptomyces laceyi*. J Antibiot 59:797–800

Kupchan SM, Komoda Y, Court WA, Thomas GJ, Smith RM, Karim A, Gilmore CJ, Haltiwanger RC, Bryan RF (1972) Maytansine a novel antileukaemic ansa macrolide from *Maytenus ovatus*. J Am Chem Soc 94:1355–1356

Laorpaksa A, Jianmongkol S, Pothiwong W (2008) Antimicrobial activity of endophytic bacteria isolated from Thai medicinal plant. Thai J Pharm Sci 32:21–32

Lata H, Li XC, Silva B, Moraes RM, Halda-Alija L (2006) Identification of IAA-producing endophytic bacteria from micropropagated *Echinacea* plants using 16S rRNA sequencing. Plant Cell Tissue Org Cul 85:353–359

Lazzarini A, Cavaletti L, Toppo G, Marinelli F (2000) Rare genera of actinomycetes as potential producers of new antibiotics. Antonie Van Leeuwenhoek 78:399–405

Li JG, Shun XG (2009) Endophytic fungi from *Dracaena cambodiana* and *Aquilaria sinensis* and their antimicrobial activity. Afr J Biotechnol 8(5):731–736

Li J, Zhao GZ, Chen HH, Wang HB, Qin S, Zhu WY, Xu LH, Jiang CL, Li WJ (2008a) Antitumour and antimicrobial activities of endophytic *Streptomycetes* from pharmaceutical plants in rainforest. Lett Appl Microbiol 47:574–580

Li J, Zhao GZ, Chen HH, Qin S, Xu LH, Jiang CL, Li WJ (2008b) Rhodococcus cercidiphylli sp nov a new endophytic actinobacterium isolated from leaf of *Cercidiphyllum japonicum*. Syst Appl Microbiol 31:1108–1113

Li J, Lu CH, Shen YM (2010) Macrolides of the bafilomycin family produced by *Streptomyces* sp CS. J Antibiot. doi:10.1038/ja.2010.95

Lin ZJ, Lu XM, Zhu TJ, Fang YC, Gu QQ, Zhu WM (2008) GPR12 Selections of the metabolites from an endophytic *Streptomyces* sp. asociated with *Cistanches deserticola*. Arch Pharm Res 31:1108–1114

Liu JY, Huang LL, Ye YH, Zou WX, Guo ZJ, Tan RX (2006) Antifungal and new metabolites of *Myrothecium* sp Z16 a fungus associated with white croaker *Argyrosomus argentatus*. J Appl Microbiol 100:195–202

Lu CH, Shen YM (2003) A new macrolide antibiotics with antitumor activity produced by *Streptomyces* sp CS a commensal microbe of Maytenus hookeri. J Antibiot 56:415–418

Lu CH, Shen YM (2004) Two new macrolides produced by *Streptomyces* sp. CS. J Antibiot 57:597–600

Lu CH, Shen YM (2007) A novel ansamycin naphthomycin K from *Streptomyces* sp. J Antibiot 60:649–653

Mahafee WF, Kloepper JW (1997) Changes in the bacterial communities of soil rhizosphere and endorhiza associated with field grown cucumber (*Cucumis sativus* L). Microb Ecol 34:210–223

Mann J (2001) Natural products as immunosuppressive agents. Nat Prod Rep 18:417–430

McInroy JA, Kloepper JW (1995a) Population dynamics of endophytic bacteria in field-grown sweet corn and cotton. Can J Microbiol 41:95–901

McInroy JA, Kloepper JW (1995b) Survey of indigenous bacterial endophytes from cotton and sweet corn. Plant Soil 173:337–342

Mundt JO, Hinkle NF (1976) Bacteria with in ovules and seeds. Appl Environ Microbiol 32:694–698

Nejad P, Johnson PA (2000) Endophytic bacteria induce growth promotion and wilt disease suppression in oilseed rape and tomato. Biol Control 18:208–215

Okazaki T (2003) Studies on actinomycetes isolated from plant leaves In: Kurtböke DI (ed) Selective isolation of rare actinomycetes. Queensland Complete Printing Service, Australia

Okazaki T, Takahashi K, Kizuka M, Enokita R (1995) Studies on actinomycetes isolated from plant leaves. Annu Rev Sankyo Res Lab 47:97–106

Oldfield C, Wood NT, Gilbert SC, Murray FD, Faure FR (1998) Desulphurisation of benzothiophene and dibenzothiophene by actinomycete organisms belonging to the genus *Rhodococcus* and related taxa. Antonie Van Leeuwenhoek 74:119–132

Petrini OTN, Sieber LT, Viret O (1992) Ecology metabolite production and substrate utilization in edophytic fungi. Natl Toxin 1:185–196

Powel RG, Weisleder D, Smith CR, Kozlowski J, Rohwedder WK (1982) Treflorine, trenudine, and Nmethyltrenudone: novel maytansinoids tumour inhibitors containing two fused macrocyclic rings. J Am Chem Soc 104:4929–4934

Pullen C, Schmitz P, Meurer K, Bamberg DD, Lohmann S, Franc SDC, Groth I, Schlegel B, Möllmann U, Gollmick F, Gräfe U, Leistner E (2002) New and bioactive compounds from streptomyces strains residing in the wood of Celastraceae. Planta 216:162–167

Qin S, Wang HB, Chen HH, Zhang YQ, Jiang CL, Xu LH, Li WJ (2008) *Glycomyces* endophytic sp nov an endophytic actinomycete isolated from the root of *Carex baccans* Nees. Int J Syst Evol Microbiol 58:2525–2528

Qin S, Chen HH, Klenk HP, Zhao GZ, Li J, Xu LH, Li WJ (2009a) Glycomyces scopariae sp nov and Glycomyces mayteni sp nov isolated from two medicinal plants in China. Int J Syst Evol Microbiol 59:1023–1027

Qin S, Jie L, Hua-Hong C, Guo-Zhen Z, Wen-Yong Z, Cheng-Lin J, Li-Hua X, Wen-Jun L (2009b) Isolation diversity and antimicrobial activity of rare actinobacteria from medicinal plants of tropical rain forests in xishuangbanna China. App Environ Microbiol 75:6176–6186

Qin S, Xing K, Jiang J, Xu L, Li W (2011a) Biodiversity bioactive natural products and biotechnological potential of plant-associated endophytic actinobacteria. Appl Microbiol Biotechnol 89:457–473

Qin S, Xing K, Fei S, Lin Q, Chen X, Cao C, Sun Y, Wang Y, Li W, Jiang J (2011b) *Pseudonocardia sichuanensis* sp nov a novel endophytic actinomycete isolated from the root of *Jatropha curcas* L. Antonie Van Leeuwenhoek 99:395–401

Randa A, Kirstin S, Hans-Martin D, Isabel S, Christian H (2010) Botryorhodines A–D antifungal and cytotoxic depsidones from Botryosphaeria rhodina an endophyte of the medicinal plant Bidens pilosa. Photochemistry 71(1):110–116
Raviraja NS (2005) Fungal endophytes in five medicinal plant species from Kudremukh Range Western Ghats of India. J Bas Microbiol 45(3):230–235
Rukachaisirikul T, Saekee A, Tharibun C, Watkuolham S, Suksamrarn A (2007) Biological activities of the chemical constituents of *Erythrina stricta* and *Erythrina subumbrans*. Arch Pharm Res 30(11):1398–1403
Ryan RP, Germaine K, Franks A, Ryan DJ, Dowling DN (2008) Bacterial endophytes: recent development and applications. FEMS Micribiol Lett 278:1–9
Schwarz M, Köpcke B, Weber RWS, Sterner O, Anke H (2004) 3-Hydroxypropionic acid as a nematicidal principle in endophytic fungi. Phytochemistry 65:2239–2245
Sessitsch A, Reiter B, Berg G (2004) Endophytic bacterial communities of field-grown potato plants and their plant-growth promoting and antagonistic abilities. Can J Microbiol 50:239–249
Sette LD, Passarini MRZ, Delarmelina C, Salati F, Duarte MCT (2006) Molecular characterization and antimicrobial activity of endophytic fungi from coffee plants. J Microbiol Biotech 22:1185–1195
Sharrock KR, Parkes SL, Jack HK, Rees-George J, Hawatthorne BT (1991) Involvement of bacterial endophytes in storage roots of buttercup squash (*Cucurbita maxima* D hybrid 'Delica'). NSJ Crop Hortic Sci 19:157–165
Shipunov A, Newcombe G, Raghavendra AKH, Anderson CL (2008) Hidden diversity of endophytic fungi in an invasive plant. Am J Bot 95(9):1096–1108
Siciliano SD, Thoreat CM, de Freitas JR, Huci PJ, Germida JJ (1998) Differences in the microbial communities associated with the roots of different cultivars of canola and wheat. Can J Microbiol 44:844–851
Smith SA, Tank DC, Boulanger LA, Bascom-Slack CA, Eisenman K, Kingery D, Babbs B, Fenn K, Greene JS, Hann BD, Keehner J, Kelley-Swift EG, Kembaiyan V, Lee SJ, Li P, Light DY, Lin EH, Ma C, Moore E, Schorn MA, Vekhter D, Nunez PV, Strobel GA, Donoghue MJ, Strobel SA (2008) Bioactive endophytes warrant intensified exploration and conservation. PLoS ONE 3(8):e3052. doi:10.1371/journal.pone.0003052
Snipes CE, Duebelbeis DO, Olson M, Hahn DR, Dent WH, Gilbert JR, Werk TL, Davis GE, Lee-Lu R, Graupner PR (2007) The ansacarbamitocins: polar ansamitocin derivatives. J Nat Prod 70(10):1578–1581
Staniek A, Woerdenbag HJ, Kayser O (2008) Endophytes: exploiting biodiversity for the improvement of natural product-based drug discovery. J Plant Interact 3:75–93
Stierle A, Strobel G, Stierle D (1993) Taxol and taxane production by *Taxomyces andreanae* an endophytic fungus of Pacific yew. Science 260:214–216
Stone JK, Bacon CW, White JF (2000) An overview of endophytic microbes: endophytism defined. In: Bacon CW, White JF (eds) Microbial endophytes. Marcel Dekker Inc, New York, pp 3–29
Strobel G, Daisy B (2003) Bioprospecting for microbial endophytes and their natural products. Microbiol Mol Biol Rev 67:491–502
Strobel GA, Miller RV, Martinez-Miller C, Condron MM, Teplow DB, Hess WM (1999) Cryptocandin a potent antimycotic from the endophytic fungus *Cryptosporiopsis quercina*. Microbiology 145:1919–1926
Strobel G, Daisy B, Castillo U, Harper J (2004) Natural products from endophytic microorganisms. J Nat Prod 67:257–268
Sturz AV (1995) The role of endophytic bacteria during seed piece decayan and potato tuberisation. Plant Soil 175:257–263
Surette MA, Sturz AV, Lada RR, Nowak J (2003) Bacterial endophytes in processing carrots (*Daucus carota* L var sativus): their localization population density biodiversity and their effects on plant growth. Plant Soil 253:381–390
Suryanarayanan TS, Wittlinger SK, Faeth SH (2005) Endophytic fungi associated with cacti in Arizona. Mycol Res 109(5):635–639

Suwanborirux K, Chang CJ, Spjut RW, Cassady JM (1990) Ansamitocin P-3 a maytansinoid from *Claopodium crispifolium* and *Anomodon attenuatus* or associated actinomycetes. Experientia 46:117–120

Synnes M (2007) Bioprospecting of organisms from the deep sea: Scientific and environmental aspects. Clean Tech Environ Policy 9:53–59

Taechowisan T, Peberdy JF, Lumyong S (2003) Isolation of endophytic actinomycetes from selected plants and their antifungal activity. World J Microbiol Biotechnol 19:381–385

Taechowisan T, Lu C, Shen Y, Lumyong S (2005) Secondary metabolites from endophytic *Streptomyces aureofaciens* CMUAc130 and their antifungal activity. Microbiology 151:1691–1695

Taechowisan T, Wanbanjob A, Tuntiwachwuttikul P, Taylor WC (2006) Identification of *Streptomyces* sp. Tc022 an endophyte in *Alpinia galangal* and the isolation of actinomycin D. Ann Microbiol 56(2):113–117

Taechowisan T, Lu CH, Shen YM, Lumyong S (2007a) 4-arylcoumarin inhibits immediate-type allergy. Food Agric Immunol 18:203–211

Taechowisan T, Lu CH, Shen YM, Lumyong S (2007b) Antitumor activity of 4-arylcoumarins from endophytic *Streptomyces aureofaciens* CMUAc130. J Cancer Res Trer 3:86–91

Taylor TN, Taylor EL (2000) The rhynie chert ecosystem: a model for understanding fungal interactions In: Bacon CW, White JF (eds). Microbial endophytes. Marcel Decker Inc, New York, pp 31–48

Tejesvi MV, Nalini MS, Mahesh B, Prakash HS, Kini KR, Shetty HS, Ven S (2007) New hopes from endophytic fungal secondary metabolites. Bol Soc Quím Méx 1(1):19–26

Tian XL, Cao LX, Tan HM, Han WQ, Chen M, Liu YH, Zhou SN (2007) Diversity of cultivated and uncultivated actinobacterial endophytes in the stems and roots of rice. Microb Ecol 53:700–707

Tuntiwachwuttikul P, Taechowisan T, Wanbanjob A, Thadaniti S, Taylor WC (2008) Lansai A–D secondary metabolites from Streptomyces sp SUC1. Tetrahedron 64:7583–7586

Vanessa MC, Christopher MMF (2004) Analysis of the endophytic actinobacterial population in the roots of wheat (*Triticum aestivum* L) by terminal restriction fragment length polymorphism and sequencing of 16S rRNA Clones. Appl Environ Microbiol 70:31787–31794

Velazquez E, Rojas M, Lorite MJ, Rivas R, Zurdo-Pineiro JL, Heydrich M, Bedmar EJ (2008) Genetic diversity of endophytic bacteria which could be find in the apoplastic sap of medullary parenchym of the stem of healthy sugarcane plants. J Basic Microbiol 48:118–124

Vendan RT, Yu YJ, Lee SH, Rhee YH (2010) Diversity of endophytic bacteria in ginseng and their potential for plant growth promotion. J Microbiol 48(5):559–565

Vennila R, Thirunavukkarasu SV, Muthumary J (2010) Evaluation of fungal taxol isolated from an endophytic fungus *Pestalotiopsis pauciset* AVM1 against experimentally induced breast cancer in sprague dawley rats. Res J Pharmacol 4(2):38–44

Verma VC, Gond SK, Kumar A, Mishra A, Kharwar RN, Gange AC (2009a) Endophytic actinomycetes from *Azadirachta indica* A Juss: isolation diversity and anti-microbial activity. Microb Ecol 57:749–756

Verma VC, Kharwar RN, Strobel GA (2009b) Chemical and functional diversity of natural products from plant associated endophytic fungi. Nat Prod Commun 11:1511–1532

Wang HX, Geng ZL, Zeng Y, Shen YM (2008) Enrichment plant microbiota for a metagenomic library construction. Environ Microbiol 10:2684–2691

Wei J, Xu T, Guo L, Liu A, Zhang Y, Pan X (2009) Endophytic *Pestalotiopsis* species associated with plants of *Podocarpaceae Theaceae* and *Taxaceae* in southern China. Fun Div 24:55–74

Ya-li LV, Fu-sheng Z, Juan C, Jin-long C, Yong-mei X, Xiang-dong L, Shun-xing G (2010) Diversity and antimicrobial activity of endophytic fungi associated with the *Alpine* plant *Saussurea involucrate*. Biol Pharm Bull 33(8):1300–1306

Yang X, Strobel G, Stierle A, Hess WM, Lee J, Clardy J (1994) A fugal endophyte-tree relationship: *Phoma* sp in *Taxus wallachiana*. Plant Sci 102:1–9

Yuan HM, Zhang XP, Zhao K, Zhong K, Gu YF, Lindstrom K (2008) Genetic characterization of endophytic actinobacteria isolated from the medicinal plants in Sichuan. Ann Microbiol 58(4):597–604

Zhang HW, Song YC, Tan RX (2006) Biology and chemistry of endophytes. Prod Rep 23:753–771

Zhao PJ, Fan LM, Li GH, Zhu N, Shen YM (2005) Antibacterial and antitumor macrolides from isp ls9131. Arch Pharm Res 28:1228–1232

Zhao GZ, Li J, Huang HY, Zhu WY, Zhao LX, Tang SK, Xu LH, Li WJ (2010a) Pseudonocardia artemisiae sp anovel actinobacterium isolated from surface-sterilized *Artemisia annua* L. Int J Syst Evol Microbiol. doi:10.1099/ijs0021931-0

Zhao J, Mou Y, Shan T, Li Y, Zhou L, Wang M, Wang J (2010b) Antimicrobial metabolites from the endophytic fungus *Pichia guilliermondii* isolated from *Paris polyphylla* var. *yunnanensis*. Molecules 15:7961–7970

Zhao J, Zhou L, Wub J (2010c) Promotion of *Salvia miltiorrhiza* hairy root growth and tanshinone production by polysaccharide–protein fractions of plant growth-promoting rhizobacterium *Bacillus cereus*. Pro Biochem 45:1517–1522

Zhao K, Penttinen P, Guan T, Xiao J, Chen Q, Xu J, Lindstrom K, Zhang L, Zhang X, Strobel GA (2011) The diversity and anti-microbial activity of endophytic actinomycetes isolated from medicinal plants in Panxi Plateau China. Curr Microbiol 62:182–190

Zhen-Liang S, Ming Z, Ji-Fa Z, Jing F (2011) Antifungal and cytotoxic activities of the secondary metabolites from endophytic fungus *Massrison* sp. Phytomedicine 18(15):859–862

Zhou X, Zhu H, Liu L, Lin J, Tang K (2010) A review: recent advances and future prospects of taxol-producing endophytic fungi. Chem Mater Sci 86(6):1707–1717

Zhu N, Zhao P, Shen Y (2009) Selective isolation and ansamycintargeted screenings of commensal actinomycetes from the “maytansinoids-producing” arboreal *Trewia nudiflora*. Curr Microbiol 58:87–94

Zin NM, Sarmin NIM, Ghadin N, Basri DF, Sidik NM, Hess WM, Strobel GA (2007) Bioactive endophytic *Streptomycetes* from the Malay Peninsula. FEMS Microbiol Lett 274:83–88