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REVIEW ARTICLE

Endophytic bacteria: a new source of bioactive compounds

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Abstract In recent years, bioactive compounds are in high demand in the pharmaceuticals and naturopathy, due to their health benefits to human and plants. Microorganisms synthesize these compounds and some enzymes either alone or in association with plants. Microbes residing inside the plant tissues, known as endophytes, also produce an array of these compounds. Endophytic actinomycetes act as a promising resource of biotechnologically valuable bioactive compounds and secondary metabolites. Endophytic *Streptomyces* sp. produced some novel antibiotics which are effective against multi-drug-resistant bacteria Antimicrobial agents produced by endophytes are eco-friendly, toxic to pathogens and do not harm the human. Endophytic inoculation of the plants modulates the synthesis of bioactive compounds with high pharmaceutical properties besides promoting growth of the plants. Hydrolases, the extracellular enzymes, produced by endophytic bacteria, help the plants to establish systemic resistance against pathogens invasion. Phytohormones produced by endophytes play an essential role in plant development and drought resistance management. The high diversity of endophytes and their adaptation to various environmental stresses seem to be an untapped source of new secondary metabolites. The present review summarizes the role of endophytic bacteria in synthesis and modulation of bioactive compounds.

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Introduction

The "bioactive" or "biologically active" compounds are extra-nutritional constituents present in small quantities in lipid-rich foods and plant products (Cammack et al. 2006). These compounds are mostly produced by plants and microbes, and have broad pharmaceutical properties including anti-cancer, cardiovascular, anti-lipidemic, anti-hypertensive, anti-glycaemic, antithrombotic, anti-atherogenic and anti-diabetic (Puri et al. 2005; Chang et al. 2013; Atanasov et al. 2015; Villaescusa et al. 2015). Nowadays, bioactive compounds are used as preferred synthetic medicines for various diseases with very few side effects (Chang et al. 2013).

The endophytic fungi, bacteria and actinomycetes play a significant role in the production of bioactive compounds. Bioactive compounds like alkaloids, steroids, terpenoids, peptides, polyketones, flavonoids, quinols and phenols, and the natural insecticide azadirachtin produced by endophytic bacteria (Li et al. 2008; Kusari et al. 2012; Molina et al. 2012) have agricultural, industrial and medical applications (Hallmann et al. 1997; Kobayashi and Palumbo 2000; Zinniel et al. 2002).

Endophytic microbes spend most of their life cycle within the plant tissues without causing any visible damage to the host plant. Many endophytes also secrete specialized metabolites or biologically active compounds (Liarzi et al. 2016). Endophytic bacteria are also having the potential due to their ability to produce plant growth hormones, phosphate solubilization, nutrient acquisition and fixation of N_2 (Glick 2012).

Synthesis of bioactive compounds by endophytic microbes

The bioactive compounds synthesized by endophytes that help the host plant to develop systemic resistance against pathogens are also used in the pharmaceutical industries as antibiotics, anti-cancer, anti-viral, anti-diabetic and other bioactive compounds (Guo et al. 2008).

Endophytic fungi

Endophytic fungi are one of the major potential sources for the production of valuable bioactive compounds (Dreyfuss and Chapela 1994). *Pestalotiopsis neglecta* BAB-5510, an endophytic fungus of *Cupressus torulosa,* is considered to be a promising source of phenols, flavonoids, terpenoids, alkaloids, tannins, carbohydrates and saponin (Sharma et al. 2016), while *Gilmaniella* sp. AL12, an endophytic fungus, can stimulate *Atractylodes lancea* to produce volatile oils such as β-caryophyllene, zingiberene, caryophyllene oxide, β-sesquiphellandrene, hinesol, β-eudesmol and atractylone (Chen et al. 2016). Among the bioactive compounds, the antioxidants are the major compounds, frequently in discussions for good health and preventing diseases (Perucka and Materska 2003; Sanatombi and Sharma 2008; Al Othman et al. 2011). Capsaicin, a bioactive compound, abundantly found in red and chili peppers has been used as a medicine to remedy pain and as anti-cancerous agent for various human cancers. *Alternaria alternata,* an endophytic fungus isolated from *Capsicum annum*, produces capsaicin (Devari et al. 2014; Clark and Lee 2016). The endophytic organisms also produced various enzymes having pharmaceutical potential. *Eurotium* sp. an endophytic fungus, isolated from rhizomes of *Curcuma longa* produced asparaginase, an important anti-cancer enzyme (Jalgaonwala and Mahajan 2014). Endophytic fungus *Huperzia serrata* strains, L10Q37 and LQ2F02, also showed anti-acetylcholinesterase activity (Zhejian et al. 2015). *Talaromyces pinophilus,* an endophytic fungus isolated from strawberry tree (*Arbutus unedo*), produced siderophore ferrirubin, platelet-aggregation inhibitor herquline B and the antibiotic 3-*O*-methylfunicone. This strain also exhibited toxic effects against the pea aphid *Acyrthosiphon pisum* (*Homoptera aphidiidae*) (Vinale et al. 2017). The endophytic fungus *Fusarium oxysporum* 162 produced nematode antagonistic compounds, 4-hydroxybenzoic acid, indole-3-acetic acid (IAA) and gibepyrone D (Liu et al. 2016; Bogner et al. 2017).

Endophytic actinomycetes

Endophytic actinomycetes appear to be the promising source of bioactive agents, which can also be exploited for protection of crops and production of therapeutic agents (Balagurunathan and Radhakrishnan 2010; Prashith-Kekuda 2016). To date, more than 140 actinomycetes genera have been described and only a few of them produced majority of the known essential antibiotics (Jensen et al. 2005; Bull and Stach 2007; Pimentel-Elardo et al. 2010). Actinomycetes produce different types of secondary metabolites; many of these possess biological activities and have the potential to develop as therapeutic agents. Marine actinomycetes are underexploited source of novel secondary metabolites (Lam 2006). *Streptomyces rochei* CH1, an endophytic actinomycete of *Cinnamomum* sp., showed significant antibacterial activity against various test pathogens like *Aeromonas caviae*, *Vibrio parahemolyticus* and *Pseudomonas aeruginosa* (Roy and Banerjee 2015). *Streptomyces cyaneofuscatus* (KY287599) showed broad spectrum antimicrobial activities against *Escherichia coli* MTCC 739, *P. aeruginosa* MTCC 2453, *Micrococcus luteus* NCIM 2170, *Staphylococcus aureus* MTCC and yeast pathogen *Candida albicans* MTCC 3017. *Streptomyces* KX852460 also showed anti-fungal activity against *Rhizoctonia solani* AG-3 KX852461, the causative agent of target spot disease of tobacco leaf (Ahsan et al. 2017; Zothanpuia et al. 2017).

Endophytic bacteria

Majority of the endophytic bacteria showed beneficial effects like enhancement of biological N_2-fixation, production of phytohormones, solubilization of phosphate and inhibition of ethylene (C_2H_2) biosynthesis in response to biotic and abiotic stresses and have bio-control activity. More than 300 endophytic actinobacteria and bacteria belonging to the genera *Streptomyces, Nocardiopsis, Brevibacterium, Microbacterium, Tsukamurella, Arthrobacter, Brachybacterium, Nocardia, Rhodococcus, Kocuria, Nocardioides,* and *Pseudonocardia* were isolated from different tissues of *Dracaena cochinchinensis* Lour. (a traditional Chinese medicine known as dragon's blood). Of these, 17 strains having antimicrobial and anthracyclines-producing activities also showed anti-fungal and cytotoxic activities against two human cancer cell lines, MCF-7 and Hep G2 (Dudeja and Giri 2014; Salam et al. 2017).

Mode of entry and establishment of endophytic bacteria in the plant

Endophytic bacteria were found in various environments which include tropic, temperate, aquatic, xerophytic, deserts, Antarctic, geothermal soils, rainforests, mangrove swamps and also coastal forests (Strobel et al. 2002; Suryanarayanan and Murali 2006). Endophyte–plant interaction is controlled by the genes of both organisms and modulated by the environmental conditions (Battistoni et al. 2005; Rosenblueth and Romero 2006). Obligate bacterial endophytes are strictly dependent on their host plant for their growth while facultative endophytes are biphasic alternating between plants and the soil.

Endophytes are transmitted through the seeds or recruited from the soil rhizosphere. They enter the host plant through the cracks formed in the lateral root junction or wound caused by microbial or nematodes phytopathogens (Chi et al. 2005) and quickly spread to the endorhizosphere. Entry of endophytic bacteria in the plant roots also occurs through root hairs and spaces between epidermal cells (Hardoim et al. 2008). In the invasive process, the degradation of plant cell envelop occurs by enzymatic activity, such as production of endoglucanases, pectinases and cellulases which assist them to colonize endorhizosphere. Endoglucanases loosen larger cellulose fiber and may help in entry to the plant. In addition, exoglucanases may also help in the colonization process (Reinhold-Hurek and Hurek 2011). Some strains of *Streptomyces* have been reported to produce hydrolytic cell wall-degrading enzymes such as chitinases, cellulases, hemicellulases, amylases and glucanases along with lignin-degrading enzymes. Endophytic *Streptosporangium* sp. from maize produced glucoamylase. The cell wall degrading enzymes, endogluconase and polygalacturonase, seem to be required for the infection of *Vitis vinifera* by *Burkholderia* sp. (Compant et al. 2005) (Fig. 1).

Bioactive compounds synthesized by endophytic bacteria

Bacterial endophytes have several potential applications in pharmaceutical and drug discovery (Strobel 2006; Guo et al. 2008). Endophytes associated with ethnomedicinal plants serve as a potential source of natural products for application in oxidative stress and as new bioactive agents (Nongkhlaw and Joshi 2015). The antimicrobial agents counteract the multi-drug resistance (MDR) in pathogenic microbes. Many microorganisms of agricultural concern have also acquired resistance to the commonly used antimicrobial compounds and the interest in natural methods of pathogen control through new, eco-friendly agents has been increasing day by day. Amines and amides are the common metabolites from endophytes that are toxic to insects but not mammals. Endophytes also produce extracellular hydrolyases such as cellulases, proteinase, lipases and esterases to establish resistance against plant invasions (Tan and Zou 2001). Endophytic bacteria associated with *Hypericum perforatum* and *Ziziphora capitata* belong to *Arthrobacter, Achromobacter, Bacillus, Enterobacter, Erwinia, Pseudomonas, Pantoea, Serratia,* and *Stenotrophomonas*. *H. perforatum* with antibacterial activity supported colonization of more bacteria with antagonistic activity, as compared to *Z. capitata*. Theses isolates were able to control tomato root rot caused by *F. oxysporum* (Egamberdieva et al. 2017) (Fig. 2).

Secondary metabolites

Secondary metabolites, though not essential for growth of an organism, play an adaptive role in functioning as the defense compound or the signaling molecule during ecological interactions and environmental stresses. Endophytic microorganisms produce low-molecular weight secondary metabolites that include antimicrobial compounds, phytohormones, or their precursors, vitamins like B12 (Ivanova et al. 2006) and B1 (Mercado and Bakker 2007), bioprotectants (Trotsenko and Khmelenina 2002). Several secondary metabolites are alkaloids, steroids, terpenoids, peptides, polyketones, flavonoids, quinols and phenols. These compounds also have important role in therapeutic applications such as anti-cancer, antioxidant, antimicrobial, anti-inflammatory, and immunosuppressive agents (Korkina 2007).

Secondary metabolites synthesis

Some endophytic bacteria modulate the production of secondary metabolites. Microbial secondary metabolites are synthesized from only a few precursors of primary metabolism with a relatively small number (Demain and Fang 2000). Endophytes synthesize secondary metabolites via a variety of pathways, e.g., polyketide, isoprenoid or amino acid derivation (Jalgaonwala 2013). However, the biosynthetic pathways are responsible for the production of both primary and secondary metabolites (Nicolaou et al. 2011) (Fig. 3).

The high species diversity of endophytes and their adaption to various environments could be considered a rich and almost un-trapped source of new secondary metabolites for pharmaceutical or agricultural applications (Bacon and White 2000). Nature has provided a broad spectrum of structurally diverse secondary metabolites (Verpoorte 1998; Maier et al. 1999). These metabolites act as biofilm, toxins, virulence factors (Raaijmakers and

Fig. 1 Routes of entry of endophytic bacteria

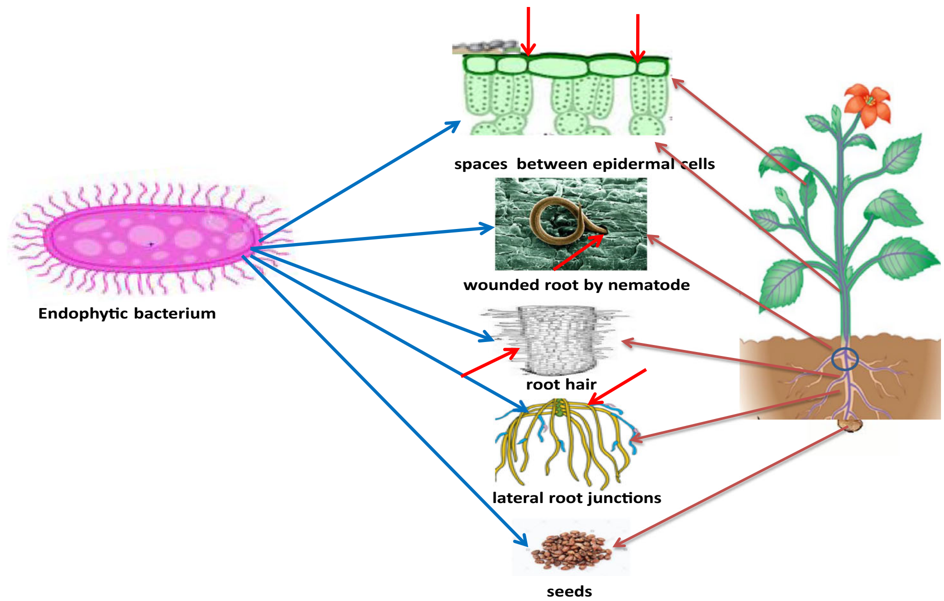
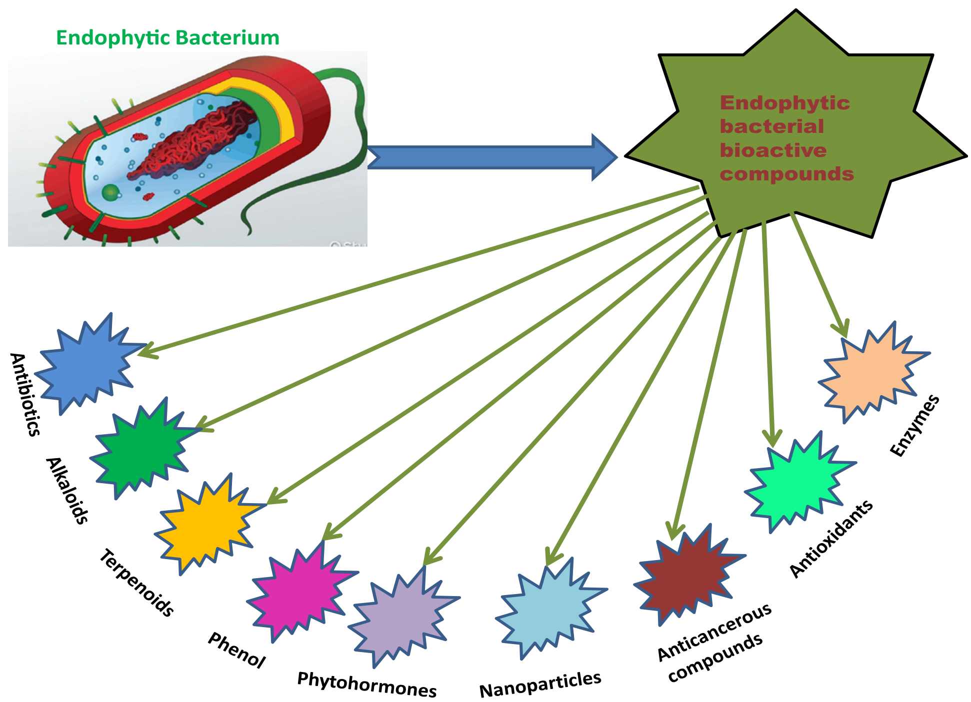


Fig. 2 Bioactive compounds synthesized by endophytic bacteria



Mazzola 2012) and interfering agents with the hormone signaling in plants (Lopez et al. 2008; Glick 2012). The production and modulation of auxins and C_2H_2 by endophytic bacteria–plant interactions play an essential role in plant development and drought stress management (Hardoim et al. 2008; Glick 2012).

Terpenoids

Terpenes are derived biosynthetically from isoprene units. Approximately, 50,000 terpenoid metabolites including monoterpenes, sesquiterpenes, and di-terpenes representing nearly 400 distinct structural families have been isolated from plants, fungi and bacteria. In contrast, a relatively minor fraction of these widely occurring metabolites has been identified in prokaryotes (Yamada et al. 2015). Among the numerous volatiles, the most common *Streptomyces* terpenoids, geosmin, 2-methylisoborneol, tricyclic α, β-unsaturated ketone and albaflavenone are the well-known volatile odoriferous microbial metabolites. The sesquiterpenoid antibiotic, pentalenolactone is the common metabolite isolated from more than 30 species of

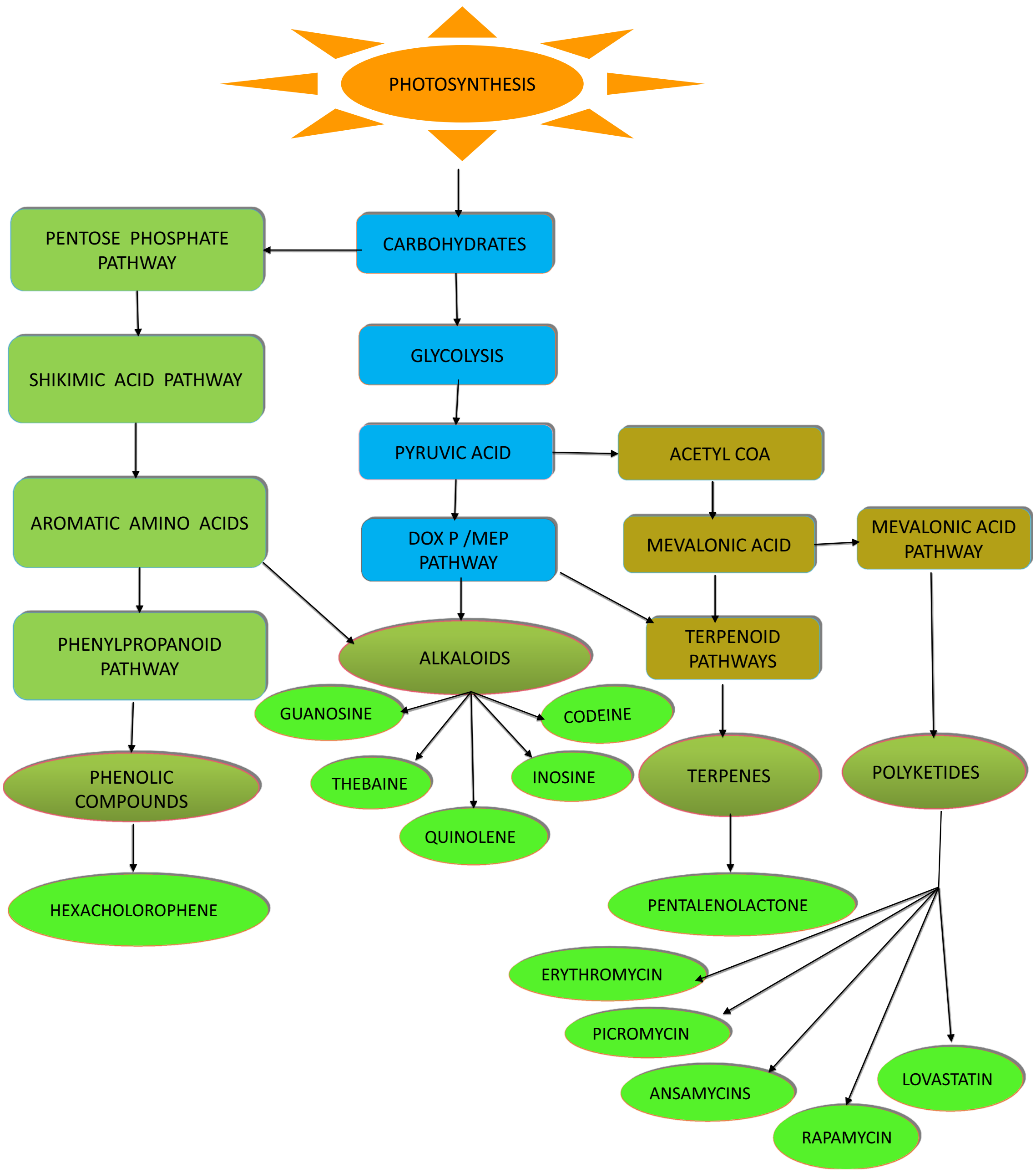


Fig. 3 Pathways for the synthesis of some secondary metabolites

Streptomyces (Takahashi et al. 1983). *Streptomyces exfoliatus* UC5319 produced pentalenene synthase (ADO85594); the first characterized, cloned, and sequenced terpene synthase from *Streptomyces* (Lesburg et al. 1997). The endophytic bacterium *Pseudomonas fluorescens* ALEB7B can switch on the generation of reactive oxygen species (ROS) in *A. lancea* (a Chinese medicinal plant that contains oxygenous sesquiterpenoids) that leads to increased oxygenous sesquiterpenoid content (Zhou et al. 2015).

Alkaloids

Alkaloids, the low-molecular-weight, nitrogen-containing compounds, are important in pharmaceutical industries because of their high biological activities. Most alkaloids are derived from amines produced by the decarboxylation of amino acids, such as histidine, lysine, ornithine, tryptophan and tyrosine. Endophytes produce alkaloids as the secondary metabolites that have diverse biological potential as anti-fungal, anti-cancer, and anti-viral agents (Silva et al. 2007). Endophytic *Bacillus cereus, Aranicola* *proteolyticus, Serratia liquefaciens, Bacillus thuringiensis*, and *Bacillus licheniformis* isolated from *Pinellia ternata* have the ability to produce alkaloids (guanosine and inosine) in fermentation broth similar to their host plant (Liu et al. 2015). The capsular endophyte *Acinetobacter* SB1B in Opium poppy unregulated the expression of key genes for the benzylisoquinoline alkaloid (BIA) biosynthesis except thebaine and codeine. In contrast, *Marmoricola* sp. SM3B, another endophyte, could up-regulate the biosynthesis of both thebaine and codeine. *Acinetobactor* and *Marmoricola* sp. as microbial inoculants modulated the alkaloid producing genes in Opium poppy (Pandey et al. 2016).

Phenols

Among the different dietary bioactive compounds, polyphenols constitute an interesting group as some possess important biological activities including antioxidant, anti-carcinogenic or antimicrobial activities. They have been reported to lower the risks of many chronic diseases, including cancer, cardiovascular diseases, chronic inflammation, and many degenerative diseases. Phenolic compounds may be synthesized by the shikimate pathway (Kyselova 2011; Valdes et al. 2015; Carvalho et al. 2016; Lai Thi Ngoc Ha 2016). Dietary polyphenols may contribute to the maintenance of intestinal health by preserving the gut microbial balance through stimulation of the growth of beneficial bacteria (i.e., lactobacilli and bifidobacteria) and inhibition of pathogenic bacteria, exerting probiotic like effect (Duenas et al. 2015).

Endophytic bacterial isolates *P. fluorescens* Endo2 and Endo35 on inoculation induced systemic resistance against dry root rot of black gram (*Vigna mungo* L.) caused by *Macrophomina phaseolina* under glasshouse conditions. The bacterized black gram plants inoculated with dry root rot pathogen showed increased activities of peroxidase (PO), polyphenol oxidase (PPO), phenylalanine ammonia lyase (PAL) in addition to accumulation of phenolics and lignin (Karthikeyan et al. 2005). Inoculation of Talh tree (*Acacia gerrardii* Benth.) with endophytic bacterium *B. subtilis* (BERA 71) in combination with arbuscular mycorrhizal fungi (AMF) (*Rhizophagus intraradices*; *Claroideoglomus etunicatum and Funneliformis mosseae*) not only induced the acquired systemic resistance in plant but turned out to be potentially beneficial in ameliorating the deleterious impact of salinity on plant metabolism by modulating the osmoregulatory system (glycine, betaine, proline and phenols) and antioxidant enzymes system (Hashem et al. 2016).

Phytohormones and defense enzymes

Phytohormones are signal molecules that coordinate cellular activities and control plant growth and development. They play crucial roles in regulating plant responses to various stresses at extremely low concentrations. Bacterial endophytes and plants interactions result in the production and modulation of plant hormones (Lopez et al. 2008; Glick 2012). IAA is the most common, naturally occurring, plant hormone of the auxins class. The endophytic *B. cereus* (ECL1), *B. thuringiensis* (ECL2), *Bacillus* sp. (ECL3), *Bacillus pumilis* (ECL4), *Pseudomonas putida* (ECL5), and *Clavibacter michiganensis* (ECL6) isolated from *C. longa* L. produced IAA (Javid et al. 2011; Kumar et al. 2016). *Pseudomonas, Agrobacterium* and *Bacillus* isolated from the root of *Cassia tora* produced phytohormones and solubilized tricalcium phosphate (Kumar et al. 2015). Endophytic *Artherobacter* EZB-4 and *Bacillus* EZB-8 isolated from the pepper plant (*Capsicum annum* L.) produced IAA and increased the plant biomass. These endophytic bacteria also caused a significant reduction in up or down-regulation of the stress inducible genes (*CaACCO* and *CaLTPI*) compared to the gene expression in non-inoculated plants. Both the strains reduced osmotic and drought stresses (Sziderics et al. 2007). *Achromobacter piechaudi* E6S facilitated the plant growth by producting IAA, 1-aminocyclopropane-1-carboxylate (ACC) deaminase and solubilizing phosphate (Ma et al. 2016).

Abscisic acid (ABA) is considered as a plant stress hormone and is responsible for many kinds of stresses including water, salt, and cold temperatures. Drought is one of the stresses limiting crop production throughout the world. It is the single most devastating environmental constraint which hampers crop productivity more than any other stress (Farooq et al. 2012; Lambers et al. 2008). ABA and gibberellins (GA) produced by endophyte *Azospirillum lipoferum* alleviated the drought stress in maize (Cohen et al. 2009). Endophytic *B. amyloliquefaciens* SB-9 isolated from grapewine secreted high level of melatonin and produced three intermediates of melatonin biosynthetic pathway namely 5-hydroxytryptophan, serotonin and *N*-acetylserotonin. *Serratia marcescens* UPM39B3, an endophytic strain, induced the production of peroxidase, polyphenol oxidase, phenylalanine and ammonia lyase, besides total soluble phenols and lignothioglycolic acid in banana plantlets. Colonization of *B. amyloliquefaciens* SB-9 was also able to counteract the adverse effect of salt and drought-induced stresses by reducing the production of malondialdehyde (MDA) and reactive oxygen species (ROS) in grapewine roots (Jiao et al. 2016).

Besides phytohormones, salicylic acid (SA) is a critical plant hormone involved in various processes, such as seed germination, root initiation, stomatal closure, floral induction, and thermogenesis, besides the tolerance of plant to biotic and abiotic stresses. Endophytic bacteria enhanced the growth of sunflower seedlings under water stress, through the production of SA which also inhibited the growth of pathogenic fungi (Forchetti et al. 2010; Klessig et al. 2016).

Endophytic bacteria induced modulation of secondary metabolites production

Endophytic bacteria can be applied using different delivery techniques depending on need and growth stages of the plant. The seed treatment and foliar spray with bacterial endophytes seem to be economical because of lower cost. However, our knowledge of how bacterial endophytes enter and colonize plants is limited. Some endophytic plant growth promoting bacteria (PGPB) used as microbial inoculants enhanced the synthesis of biologically active compounds in the host plant. Turmeric rhizome contains a number of phenolic compounds, curcuminoids and sesquiterpenoids. Inoculation of turmeric rhizomes with endophytic *Azotobactor chroococcum* CL13 enhanced the production of curcumin (Kumar et al. 2014). Bacterial prodigiosins and their synthetic derivatives are effective pro-apoptotic agents against various cancer cell lines, with multiple cellular targets including multi-drug resistant cells with little or no toxicity towards normal cell lines. *S. marcescens* KC-1, an endophytic bacterial strain, secretes red pigment prodigiosins (Darshan and Manonmani 2015; Khanam and Chandra 2015).

Endophytic induction of secondary metabolites may be more widespread in aromatic and medicinal plants. The quality and quantity of flavor in strawberries are influenced by plant-associated methylobacteria (Verginer et al. 2010). *Stenotrophomonas maltophilia* (N5-18) delivered through foliar spray significantly enhanced the photosynthetic efficiency, total alkaloid and morphine content coupled with the decrease in thebaine content in Opium poppy (*Pappaver sominiferum*). The increase in capsule biomass and alkaloid content was followed by the consequent increase in productivity of *P. sominiferum* (Bonilla et al. 2014). Inoculation of *Catharanthus roseus* explants with endophytic *Staphylococcus sciuri* and *Micrococcus* sp. significantly enhanced the vindoline, ajmalicine and serpentine production (Tiwari et al. 2013).

Bioactive compounds produced by microbes are more convenient than plants

Bioactive compounds produced by the plants exhibit strong physiological activities. However, their production suffers from various problems including heterogeneous quality and insufficient level of productivity. Microorganisms produce primary and secondary metabolites under controlled environmental conditions assuring their maximum efficiency in uniform and high quality (Sato and Kumagai 2013). The association of plant with endophytic microorganisms has been proved as a source of materials and products with high medicinal potential as compared to the plants alone. Bioactive compounds such as secondary metabolites and enzymes synthesized by microorganisms have been extensively used as food and food supplements (Subbulakshmi et al. 2012; Mitsuhashi 2014; Wendisch 2014), pharmaceuticals (Elander 2003; Endo 2010), biofuels (Geddes et al. 2011), biopesticides (Waldron et al. 2001; Yoon et al. 2004) and detergents (Shaligram and Singhal 2010), as well as in the manufacturing process of these industrial products (Kirk et al. 2002; Merino and Cherry 2007). Metabolites and enzymes production methods have been improved since the time of their first importance was realized. *B. subtilis* and *Lactobacillus plantarum* enhanced the content of bioactive compounds (soluble phenolic compound content and antioxidant activity) in kidney bean extracts after fermentation (Limona et al. 2015).

Antimicrobial compounds

Antimicrobial metabolites produced from the endophytes are the bioactive natural compounds (Guo et al. 2008). Endophytes have developed a resistance mechanism to control pathogenic intrusion by producing secondary metabolites (Tan and Zou 2001). Many antimicrobial compounds produced by endophytes belong to several structural classes such as peptides, alkaloids, steroids, quinines, terpenoids, phenols and flavonoids (Yu et al. 2010). The novel antimicrobial metabolites from endophytes are now becoming the alternative option to overcome the increasing levels of drug resistance (Ferlay et al. 2010; Taechowisan et al. 2012). A large number of endophytic actinomycetes were isolated from 26 medicinal plants from Panxi plateau with the huge spectrum of antimicrobial activity, being the valuable reservoirs of novel bioactive compounds (Zhao et al. 2011). Endophytic *Streptomyces* sp. TQR12-4 isolated from Elite *Citrus nobilis* fruit showed antimicrobial activity and inhibited test pathogens *Colletotrichum truncatum, Geotrichum candidum, F. oxysporum* and *F. udum* (Hong-Thao et al. 2016).

Nanopartcles might play a significant role as antimicrobial agents. Nanoparticles have made a significant impact on the treatment of various types of cancer. Endophytic bacteria synthesize various nanoparticles which emerges as a novel field in the research area of pharmaceutical engineering (Sunkar and Nachiyar 2012). Silver nanoparticles have antibacterial properties and act as antiviral agent against HIV-1, hepatitis B virus, respiratory syncytial virus and herpes simplex virus (Sun et al. 2005; Taylor et al. 2005; Lu et al. 2008; Baram-Pinto et al. 2009). Endophytic strains of *Bacillus* sp. isolated from the medicinal plants *Adhatoda beddomei* (Malabar nut) and *Garcinia xanthochymus* (Egg tree) synthesized silver nanoparticles (AgNPs) by reduction of silver nitrate ($AgNO_3$) (Pissuwan et al. 2006; Kitov et al. 2008; Sunkar and Nachiyar 2012).

Anti-cancerous compounds

Several bioactive compounds produced by endophytes have been identified as anti-cancer agents (Firakova et al. 2007). Endophytic bacterial strain, EML-CAP3 isolated from *C. annuum* L. (red pepper) leaf, showed potent anti-angiogenic activity. This endophytic bacterial strain produced lipophilic peptides which inhibited the proliferation of human umbilical vein endothelial cells and also exhibited anti-angiogenic potential in tumor progression (Jung et al. 2015). Ginseng (*Panax ginseng*) is known for its ginsenosides that have anti-cancerous property. The transformed *Paenibacillus polymyxa*, an endophytic bacterium of Ginseng leaf, showed high ginsenoside concentration. This endophytic bacterial strain on inoculation to Ginseng plants through foliar applications combined with irrigation enhanced plant growth and the concentration of ginsenosides (Gao et al. 2015). Morphological abnormalities in the cells induced by exopolysaccharides (EPS) are the anti-tumoral mechanisms of action associated with the mitochondrial dysfunction of the treated cells. *Bacillus* serves a source of first discovered anti-tumoral EPS, a natural product of high therapeutic value for cancer treatment as a new anti-cancer agent (Chen et al. 2013). L-Asparaginase catalyzes the conversion of L-asparagine necessary for the function of some neoplastic cells, such as lymphoblasts. L-Asparaginase introduced to the multi-drug chemotherapy in children and adults with acute lymphoblastic leukemia resulted in significant improvement and complete remission in majority of the patients (Jakubas et al. 2008). Endophytic *B. licheniformis, B. pseudomycoides* and *Paenibacillus denitriformis* showed efficient production of L-asparaginase (Joshi and Kulkarni 2016).

Antibiotics

Antibiotics are natural compounds produced by microorganisms as secondary metabolites to kill or inhibit other microorganisms. They played an important role in twentieth century for the treatment of infectious diseases. Till now, pharmaceutical industries have primarily targeted the drugs from soil organisms, bacteria or fungi. Among the bacteria, actinobacteria are particularly noteworthy, as they produce antibiotics. *Streptomyces* sp. are fruitful organisms, producing ~80% of the total antibiotics (Sathiyaseelan and Stella 2011; Thenmozhi and Krishnan 2011). At least seven thousand different secondary metabolites have been discovered from *Streptomyces* isolates (Berdy 2005). *Streptomyces* synthesizes antibiotics, fungicides, modulators of the immune response, and effectors of plant growth (Hopwood 2007). Antimicrobial drugs produced by some endophytic bacteria are listed in Table 1. Endophytic *Streptomyces* sp. LJK109 isolated from *Alpinia galangal* root produces 3-methylcarbazoles which is major anti-inflammatory component and also suppresses macrophage production of the inflammatory mediators NO, PGE2, TNF-α, IL-1β, IL-6 and IL-10 in a dose-dependent manner (Taechowisan et al. 2012) (Table 1).

The majority of endophytic bacteria produce different kinds of antibiotics. Ecomycin, pseudomycins and kakadumycins are some of the novel antibiotics produced by endophytic bacteria (Christina et al. 2013). *Pseudomonas viridiflava*, an epiphyte or endophyte of the leaves of many grasses, produced ecomycin, which is used for the treatment of respiratory and urinary tract infections, skin, eye and gut Infections. The structure of ecomycin incorporates some unusual amino acids such as homoserine and beta-hydroxyaspartic acid, besides common amino acids alanine, serine, threonine and glycine (Miller et al. 1998). Naphthomycin K, a chlorine-containing ansamycin, showed cytotoxicity against P388 and A-549 cell lines. Endophytic *Streptomyces* sp. CS synthesized 24-demethylbafilomycin C1, a member of bafilomycin, which targets both autophagy and apoptosis pathways in pediatric B cell acute lymphoblastic leukemia (Li et al. 2010; Qin et al. 2011; Yuan et al. 2015). Endophytic *Streptomyces* sp. isolated from *Aucuba japonica* and *Cryptomeria japonica* produced two new novobiocin analogs and cedarmycins, respectively. A new naphthoquinone antibiotic, alnumycin was also isolated from the endophytic *Streptomyces* sp. from *Alnus glutinosa. Streptomyces* sp. NRRL30562, an endophyte of snake vine plant, produced new peptide antibiotic, munumbicins A-D40 with a broad spectrum activity against several human diseases, phytopathogenic fungi and bacteria. Endophytic *Streptomyces* sp. NRRL30566 isolated from a fern-leaved grevillea (*Grevillea pteridifolia*) tree produced kakadumycin which is chemically related to echinomycin (Castillo et al. 2003).

Future prospective

As our understanding of endophytic bacteria continues to grow, the potential to exploit their unique characteristics of bioactive compound synthesis alone or with plants is also

Table 1 Antibiotics and drugs produced by some endophytic bacteria

Compounds	Endophytic bacteria	Biological activity	References
Ecomycin	*Pseudomonas viridiflava*	Anti-fungal	Miller et al. (1998)
Bacilysocin	*B. subtilis* 168	Anti-fungal	Tamehiro et al. (2002)
Nystatin	*Streptomyces noursei*	Anti-fungal	Fjaervik and Zotchev (2005)
KB425796-A	*Paenibacillus* sp. 530603	Anti-fungal	Kai et al. (2013)
Bacillomycin	*B. subtilis, B.amyloliquefaciens*	Anti-fungal, Hemolytic	Aranda et al. (2005)
Munumbicin	*Streptomyces* NRRL 30562	Antibacterial	Castillo et al. (2002)
Harmaomycin	*Streptomyces* sp.	Antibacterial	Bae et al. (2015)
Subtilin	*B. subtilis*	Antibacterial	Stein (2005)
Tetracyclin	*Streptomyces remosus* and *S. aureofaciens*	Antibacterial	Mark et al. (2001)
Bacteriocins	*B. subtilis*	Antibacterial	Sansinenea and Ortiz (2011)
Amicoumacin	*B. subtilis*	Antibacterial, anti-inflammatory	Pinchuka et al. (2002)
Artemisinin	*Pseudonocardia* sp.	Anti-malarial	Li et al. (2012)
Coronamycin	*Streptomyces* sp.	Anti-malarial	Ezra et al. (2004)
Spectinomycin	*Streptomyces spectabilis*	Anti-tuberculosis	Barry (2014)
Treponemycin	*Streptomyces* Strain MS-6-6	Anti-tuberculous	Mahmoud et al. (2015)
Androprostamines	*Streptomyces* sp. MK932-CF8	Anti-prostate cancer	Yamazaki et al. (2015)
Camptothecine	*Lysinibacillus* sp. and *B. cereus*	Anti-cancer	Singh et al. (2013)
Indolocarbazoles	*Streptomyces* sp.	Anti-cancer	Dong et al. (2014)
Doxorubicin	*Streptomyces* sp.	Treatment of Breast cancers and tumors	Brayfield (2013)
Anthracyclin	*Streptomyces* sp. YIM66403	Antitumor	Wei et al. (2015)
Daptomycin	*Streptomyces roseoporous*	Bacterial infections of skin and underlying tissues	Miao (2005)
Monensin	*Streptomyces cinnamonensis*	Prevent coccidiosis	Lowicki and Nski (2013)
Mytomycin C	*Streptomyces caespitosus and S. lavendulae*	Chemotherapeutic agent	Danshiitsoodol et al. (2006)
Saadamycin	*Streptomyces* sp. Hedaya48,	Anti dermatophyte	Gendy and Bondkly (2010)
Strepturidin	*Streptomyces albus* DSM 40763	Immunotherapy	Pesic et al. (2014)
Thaxtomin A	*Streptomyces scabies*	Cellulose synthesis inhibitor	Francis et al. (2015)
Xiamycin	*Streptomyces* sp.	Anti HIV activity	Ding et al. (2010)
β-exotoxin	*B. thuringiensis*	Insecticidal	Espinasse et al. (2002)
Albaflavenol B	*Streptomyces* sp.	As sesquiterpene	Raju et al. (2015)

increasing day by day. The plant benefits enhanced by combined application of beneficial microorganisms in the form of bio-fertilizer have become an alternative tool for organic farming. Exploitation of endophytic bacteria as a plant growth-promoting agent further necessitates our ability to understand and utilize bacterial endophytes in agriculture under integrated bio-fertilizer technology programme. How endophytes modulate the physiology of plant and its metabolism and how they use the intermediary substances of primary and secondary metabolism as nutrition and precursor to produce either novel compounds or enhance the existing important secondary metabolites are still largely unknown.

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Compliance with ethical standards

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References

Ahsan T, Chen J, Zhao X, Irfan M, Wu Y (2017) Extraction and identification of bioactive compounds (eicosane and dibutyl phthalate) produced by Streptomyces strain KX852460 for the biological control of *Rhizoctonia solani* AG-3 strain KX852461 to control target spot disease in tobacco leaf. AMB Expr 7:54. doi:10.1186/s13568-017-0351-z

Al Othman ZA, Ahmed YB, Habila MA, Ghafar AA (2011) Determination of capsaicin and dihydrocapsaicin in capsicum fruit samples using high performance liquid chromatography. Molecules 16:8919–8929. doi:10.3390/molecules16108919

Aranda FJ, Teruel JA, Ortiz A (2005) Further aspects on the haemolytic activity of the antibiotic lipopeptide iturin A. Biochim Biophys Acta 1713:51–56. doi:10.1016/j.bbamem.2005.05.003

Atanasov AG, Waltenberger B, Pferschy-Wenzig EM, Linder T, Wawrosch C, Uhrin P et al (2015) Discovery and resupply of pharmacologically active plant-derived natural products: a review. Biotechnol Adv 33:1582–1614. doi:10.1016/j.biotechadv.2015.08.001

Bacon CW, White JF (2000) Microbial endophytes. Marcel Dekker Inc., New York

Bae M, Chung B, Oh KB, Shin J, Oh DC (2015) Hormaomycins B and C: new antibiotic cyclic depsipeptides from a marine mudflat-derived *Streptomyces* sp. Mar Drugs 13:5187–5200. doi:10.3390/md13085187

Balagurunathan R, Radhakrishnan M (2010) Biotechnological, genetic engineering and nanotechnological potential of actinomycetes. In: Maheshwari DK, Dubey RC, Saravanamurthu R (eds) Industrial exploitation of microorganisms, 1st edn. I.K. International Publishing House Pvt. Ltd, New Delhi, pp 302–436

Baram-Pinto D, Shukla S, Perkas N, Gedanken A, Sarid R (2009) Inhibition of herpes simplex virus type 1 infection by silver nanoparticles capped with mercaptoethane sulfonate. Bioconjug Chem 20:1497–1502

Barry CE (2014) Tuberculosis drug discovery goes au naturel. Nature 27:436–437. doi:10.1038/506436a

Battistoni F, Bartels D, Kaiser O, Reamon-Buettner MS, Hurek T, Reinhold Hurek B (2005) Physical map of the *Azoarcus* sp. strain BH72 genome based on a bacterial artificial chromosome library as a platform for genome sequencing and functional analysis. FEMS Microbiol Lett 249:233–240

Berdy J (2005) Bioactive microbial metabolites. J Antibiot (Tokyo) 58:1–26. doi:10.1038/ja.2005.1

Bogner CW, Kamdem RST, Sichtermann G, Mattheaus C, Heolscher D, Popp J, Proksch P, Grundler FMW, Schouten A (2017) Bioactive secondary metabolites with multiple activities from a fungal endophyte. Microb Biotechnol 10:175–188. doi:10.1111/1751-7915.12467

Bonilla A, Sarria ALF, Algar E, Munoz Ledesma FJ, Solano BR, Fernandes JB, Gutierrez Manero FJ (2014) Microbe associated molecular patterns from rhizosphere bacteria trigger germination and *Papaver somniferum* metabolism under greenhouse conditions. Plant Physiol Biochem 74:133–140. doi:10.1016/j.plaphy.2013.11.012

Brayfield A (ed) (2013) Doxorubicin. *Martindale: the complete drug reference*. Pharmaceut Press. Retrieved 15 April 2014

Bull AT, Stach JE (2007) Marine actinobacteria: new opportunities for natural product search and discovery. Trends Microbiol 15:491–499

Cammack R, Atwood T, Campell P, Parish H, Smith A, Vella F, Stirling J (2006) Oxford dictionary of biochemistry and molecular biology, 2nd edn. Oxford University Press, Oxford, pp 74–75

Carvalho PLN, Silva EO, Paula DAC, Luiz JHH, Ikegaki M (2016) Importance and implications of the production of phenolic secondary metabolites by endophytic fungi: a mini-review. Mini Rev Med Chem 16:259–271

Castillo UF, Strobel GA, Ford EJ, Hess WM, Porter H, Jensen JB, Albert H, Robinson R, Condron MA, Teplow DB et al (2002) Munumbicins, wide-spectrum antibiotics produced by *Streptomyces* NRRL 30562, endophytic on *Kennedia nigriscans*. Microbiol 148:2675–2685. doi:10.1099/00221287-148-9-2675

Castillo U, Harper JK, Strobel GA, Sears J, Alesi K, Ford E, Lin J, Hunter M, Maranta M, Ge H et al (2003) Kakadumycins, novel antibiotics from *Streptomyces* sp. NRRL 30566 an endophyte of *Grevillea pteridifolia*. FEMS Microbiol Lett 224:183–190. doi:10.1016/S0378-1097(03)00426-9

Chang CL, Lin Y, Bartolome AP, Chen YC, Chiu SC, Yang WC (2013) Herbal therapies for type 2 diabetes mellitus: chemistry, biology, and potential application of selected plants and compounds. Evid Base Complement Altern Med 2013:378657

Chen F, Ren CG, Zhou T, Wei YJ, Dai CC (2016) A novel exopolysaccharide elicitor from endophytic fungus *Gilmaniella* sp. AL12 on volatile oils accumulation in *Atractylodes lancea*. Sci Rep 6:34735. doi:10.1038/srep34735

Chen YT, Yuan Q, Shan LT, Lin MA, Cheng DQ, Li CY (2013) Antitumor activity of bacterial exopolysaccharides from the endophyte *Bacillus amyloliquefaciens* sp. isolated from *Ophiopogon japonicas*. Oncol Lett 5:1787–1792. doi:10.3892/ol.2013.1284

Chi F, Shen S, Cheng H, Jing Y, Yanni Y, Dazzo F (2005) Ascending migration of endophytic rhizobia, from roots to leaves, inside rice plants and assessment of benefits to rice growth physiology. Appl Environ Microbiol 71:7271–7278

Christina A, Christapher V, Bhore SJ (2013) Endophytic bacteria as a source of novel antibiotics: an overview. Pharmacogn Rev 7:11–16. doi:10.4103/0973-7847.112833

Clark R, Lee S (2016) Anti-cancer properties of capsaicin against human cancer. Anticancer Res 36:837–844

Cohen AC, Travaglia CN, Bottini R, Piccoli PN (2009) Participation of abscisic acid and gibberellins produced by endophytic *Azospirillum* in the alleviation of drought effects in maize. Botany 87:455–462. doi:10.1139/B09-023

Compant S, Reiter B, Sessitsch A, Nowak J, Clement C, Aitbarka E (2005) Endophytic colonization of *Vitis vinifera* L. by plant growth-promoting bacterium *Burkholderia* sp. Strain PsJN. Appl Environ Microbiol 71:1685–1693

Danshiitsoodol N, Pinho CA, Matoba Y, Kumagai T, Sugiyama M (2006) The mitomycin C (MMC)-binding protein from MMC-producing microorganisms protects from the lethal effect of bleomycin: crystallographic analysis to elucidate the binding mode of the antibiotic to the protein. J Mol Biol 360:398–408. doi:10.1016/j.jmb.2006.05.017

Darshan N, Manonmani HK (2015) Prodigiosin and its potential applications. J Food Sci Technol 52:5393–5407. doi:10.1007/s13197-015-1740-4

Demain AL, Fang A (2000) The natural functions of secondary metabolites. Adv Biochem Eng 69:1–39

Devari S, Jaglan S, Kumar M, Deshidi R, Guru S, Bhushan S et al (2014) Capsaicin production by *Alternaria alternata*, an endophytic fungus from *Capsicum annum*, LC–ESI–MS/MS analysis. Phytochemistry 98:183–189

Ding L, Munch J, Goerls H, Maier A, Fiebig HH, Line WH et al (2010) Xiamycin, a pentacyclic indolo sesquiterpene with selective anti-HIV activity from a bacterial mangrove endophyte. Bioorg Med Chem Lett 20:6685–6687. doi:10.1016/j.bmcl.2010.09.010

Dong BX, Ye WW, Han Y, Deng ZX, Hong K (2014) Natural products from mangrove actinomycetes. Mar Drugs 12:2590–2613. doi:10.3390/md12052590

Dreyfuss MM, Chapela IH (1994) Potential of fungi in the diversity of novel, low molecular weight pharmaceuticals. In: Gullo VP (ed) The discovery of Natural Products with therapeutic Potential. Butterworth- Heinemann, Boston, pp 49–80

Dudeja SS, Giri R (2014) Beneficial properties, colonization, establishment and molecular diversity of endophytic bacteria in legumes and non leglumes. Afr J Micrbiol Res 8:1562–1572

Duenas M, Gonzalez IM, Cueva C, Giron AJ, Patán FS, Buelga CS et al (2015) A survey of modulation of gut microbiota by dietary polyphenols. Biomed Res Int. doi:10.1155/2015/850902 **(Article ID 850902)**

Egamberdieva D, Wirth S, Behrendt U, Ahmad P, Berg G (2017) Antimicrobial activity of medicinal plants correlates with the proportion of antagonistic endophytes. Front Microbiol 8:199. doi:10.3389/fmicb.2017.00199

Elander RP (2003) Industrial production of betalactam antibiotics. Appl Microbiol Biotechnol 61:385–392. doi:10.1007/s00253-003-1274-y

Endo A (2010) A historical perspective on the discovery of statins. Proc Jpn Acad Ser B Phys Biol Sci 86:484–493. doi:10.2183/pjab.86.484

Espinasse S, Gohar M, Lereclus D, Sanchis V (2002) An ABC transporter from *Bacillus thuringiensis* is essential for beta-exotoxin I production. J Bacteriol 184:5848–5854. doi:10.1128/JB.184.21.5848-5854

Ezra D, Castillo UF, Strobel GA, Hess WM, Porter H, Jensen JM et al (2004) Coronamycins, peptide antibiotics produced by a verticillate *Streptomyces* sp. (MSU-2110) endophytic on *Monstera* sp. Microbiol 150:785–793. doi:10.1099/mic.0.26645-0

Farooq M, Hussain M, Wahid A, Siddique KHM (2012) Drought stress in plants: an overview. In: Aroca R (ed) Plant responses to drought stress. Springer, Berlin, pp 1–5. doi:10.1007/978-3-642-32653-0

Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM (2010) Cancer incidence and mortality worldwide: IARC cancer base No. 10 Lyon, France: International Agency for Research on Cancer. Globocan 2008 v2.0

Firakova S, Sturdikova M, Muckova M (2007) Bioactive secondary metabolites produced by microorganisms associated with plants. Biologia 62:251–257. doi:10.2478/s11756-007-0044-1

Fjaervik E, Zotchev SB (2005) Biosynthesis of the polyene macrolide antibiotic nystatin in *Streptomyces noursei*. Appl Microbiol Biotechnol 67:436–443. doi:10.1007/s00253-004-1802-4

Forchetti G, Masciarelli O, Izaguirre MJ, Alemano S, Alvarez D, Abdala G (2010) Endophytic bacteria improve seedling growth of sunflower under water stress, produce salicylic acid, and inhibit growth of pathogenic fungi. Curr Microbiol 61:485–493. doi:10.1007/s00284-010-9642-1

Francis IM, Jourdan S, Fanara S, Loria R, Rigali S (2015) The cellobiose sensor CebR is the gatekeeper of *Streptomyces scabies* pathogenicity. mBio 6:02018-14. doi:10.1128/mBio.02018-14

Gao Y, Lu Q, Pu Zang P, Li X, Ji Q, He Z et al (2015) An endophytic bacterium isolated from *Panax ginseng* CA Meyer enhances growth, reduces morbidity, and stimulates ginsenoside biosynthesis. Phytochem Lett 11:132–138. doi:10.1016/j.phytol.2014.12.007

Geddes CC, Nieves IU, Ingram LO (2011) Advances in ethanol production. Curr Opin Biotechnol 22:312–319. doi:10.1016/j.copbio.2011.04.012

Gendy MM, Bondkly AM (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 37:831–841

Glick BR (2012) Plant growth-promoting bacteria: mechanisms and applications. Scientifica. doi:10.6064/2012/963401 **(Article ID 963401)**

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

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

Hardoim PR, Overbeek LS, Elsas JD (2008) Properties of bacterial endophytes and their proposed role in plant growth. Trends Microbiol 16:463–471. doi:10.1016/j.tim.2008.07.008

Hashem A, Abd-Allah EF, Alqarawi AA, Al-Huqail AA, Shah MA (2016) Induction of osmoregulation and modulation of salt stress in *Acacia gerrardii* Benth. by arbuscular mycorrhizal fungi and *Bacillus subtilis* (BERA 71). BioMed Res Int. doi:10.1155/2016/6294098 **(Article ID 6294098)**

Hong-Thao PH, Mai-Linh NV, Hong-Lien NT, Hieu NV (2016) Biological characteristics and antimicrobial activity of endophytic *Streptomyces* sp. TQR12-4 isolated from elite *Citrus nobilis* cultivar Ham Yen of Vietnam. Int J Microbiol. doi:10.1155/2016/7207818 **(Article ID 7207818)**

Hopwood DA (2007) Streptomyces in nature and medicine. The antibiotic makers. Oxford University Press Inc, New York

Ivanova EG, Fedorov DN, Doronina NV, Trotsenko YA (2006) Production of vitamin B12 in aerobic methylotrophic bacteria. Microbiology 75:494–496

Jakubas BP, Kulis MK, Giebel S, Cioch M, Czyż A, Maranda EL et al (2008) Use of L-asparaginase in acute lymphoblastic leukemia: recommendations of the Polish Adult Leukemia Group. Pol Arch Med Wewn 118:664–669

Jalgaonwala RE (2013) Bioprospecting for microbial endophytes and their natural products (Ph.D Thesis). North Maharastra University, Jalgaon, Maharastra, India

Jalgaonwala RE, Mahajan RT (2014) Production of anticancer enzyme asparaginase from endophytic *Eurotium* sp. isolated from rhizomes of *Curcuma longa*. Eur J Exp Biol 4:36–43

Javid MG, Sorooshzadeh A, Moradi F, Sanavy SAM, Allahdadi I (2011) The role of phytohormones in alleviating salt stress in crop plants. AJCS 5:726–734

Jensen PR, Mincer TJ, Williams PG, Fenical W (2005) Marine actinomycete diversity and natural product discovery. Antonie Leeuwenhoek 87:43–48

Jiao J, Ma Y, Chen S, Liu C, Song Y, Qin Y et al (2016) Melatonin producing endophytic bacteria from grapevine roots promote the abiotic stress-induced production of endogenous melatonin in their hosts. Front Plant Sci 7:1387. doi:10.3389/fpls.2016.01387

Joshi RD, Kulkarni NS (2016) Optimization studies on L-asparaginase production from endophytic bacteria. Int J Appl Res 2:624–629

Jung HJ, Yonghyo K, Hyang BL, Kwon HJ (2015) Antiangiogenic activity of the lipophilic antimicrobial peptides from an endophytic bacterial strain isolated from Red Pepper leaf. Mol Cells 38:273–278

Kai H, Yamashita M, Takase S, Hashimoto M, Muramatsu H, Nakamura I et al (2013) KB425796-A, a novel antifungal antibiotic produced by *Paenibacillus* sp. 530603. J Antibiot 66:465–471. doi:10.1038/ja.2013.63

Karthikeyan M, Bhaskaran R, Radhika K, Mathiyazhagan S, Jayakumar V, Sandosskumar R et al (2005) Endophytic *Pseudomonas fluorescens* Endo2 and Endo35 induce resistance in black gram (*Vigna mungo* L. *Hepper*) to the pathogen *Macrophomina phaseolina*. J Plant Interact 1:135–143. doi:10.1080/17429140600997309

Khanam B, Chandra R (2015) Isolation and identification of endophytic bacteria producing bright red pigment from the dye yielding plant *Beta vulgaris* L. Int J Pharm Pharm Sci 7:220–224

Kirk O, Borchert TV, Fuglsang CC (2002) Industrial enzyme applications. Curr Opin Biotechnol 13:345–351. doi:10.1016/S0958-1669(02)00328-2

Kitov PI, Mulvey GL, Griener TP, Lipinski T, Solomon D, Paszkiewicz E et al (2008) In vivo supra molecular templating enhances the activity of multivalent ligands: a potential therapeutic against the *Escherichia coli* O157 AB5 toxins. Proc Natl Acad Sci USA 105:16837–16842

Klessig DF, Tian M, Choi HW (2016) Multiple targets of salicylic acid and its derivatives in plants and animals. Front Immunol 7:206. doi:10.3389/fimmu.2016.00206

Kobayashi DY, Palumbo JD (2000) Bacterial endophytes and their effects on plants and uses in agriculture. In: Bacon CW, White JF (eds) Microbial endophytes. Marcel Dekker, NY, pp 199–233

Korkina LG (2007) Phenylpropanoids as naturally occurring antioxidants: from plant defense to human health. Cell Mol Biol 53:15–25. doi:10.1170/T772

Kumar A, Singh R, Giri DD, Singh PK, Pandey KD (2014) Effect of *Azotobacter chroococcum* CL13 inoculation on growth and curcumin content of turmeric (*Curcuma longa* L.). Int J Curr Microbiol Appl Sci 3:275–283

Kumar V, Kumar A, Pandey KD, Roy BK (2015) Isolation and characterization of bacterial endophytes from the roots of *Cassia tora* L. Ann Microbiol 65:1391–1399. doi:10.1007/s13213-014-0977-x

Kumar A, Singh R, Yadav A, Giri DD, Singh PK, Pandey KD (2016) Isolation and characterization of bacterial endophytes of *Curcuma longa* L. 3 Biotech 6:60. doi:10.1007/s13205-016-0393-y

Kusari S, Verma VC, Lamshoeft M, Spiteller M (2012) An endophytic fungus from *Azadirachta indica* A. Juss. that produces azadirachtin. World J Microbiol Biotechnol 28:1287–1294

Kyselova Z (2011) Toxicological aspects of the use of phenolic compounds in disease prevention. Interdiscip Toxicol 4:173–183. doi:10.2478/v10102-011-0027-5

Lai Thi Ngoc Ha (2016) Phenolic compounds and human health benefits. Vietnam J Agri Sci 14:1107–1118

Lam KS (2006) Discovery of novel metabolites from marine actinomycetes. Curr Opin Microbiol 9:245–251. doi:10.1016/j.mib.2006.03.004

Lambers H, Chapin FS, Pons TL (2008) Plant physiological ecology. Springer, New York

Lesburg CA, Zhai G, Cane DE, Christianson DW (1997) Crystal structure of pentalenene synthase: mechanistic insights on terpenoid cyclization reactions in biology. Science 277:1820–1824. doi:10.1126/science.277.5333.1820

Li J, Zhao GZ, Chen HH, Wang HB, Qin S et al (2008) Anti-tumour and antimicrobial activities of endophytic streptomycetes from pharmaceutical plants in rainforest. Lett Appl Microbiol 47:574–580

Li J, Lu C, Shen Y (2010) Macrolides of the bafilomycin family produced by *Streptomyces* sp. C S J Antibiot 63:595–599. doi:10.1038/ja.2010.95

Li J, Zhao GZ, Varma A, Qin S, Xiong Z, Huang HY et al (2012) An endophytic *Pseudonocardia* species induces the production of artemisinin in *Artemisia annua*. PLoS One 7:e51410. doi:10.1371/journal.pone.0051410

Liarzi O, Bucki P, Braun Miyara S, Ezra D (2016) Bioactive volatiles from an endophytic *Daldinia cf. concentrica* isolate affect the viability of the plant parasitic nematode *Meloidogyne javanica*. PLoS One 11:e0168437. doi:10.1371/journal.pone.0168437

Limona RI, Penas E, Torino MI, Villaluengaa CM, Duenas M, Frias J (2015) Fermentation enhances the content of bioactive compounds in kidney bean extracts. Food Chem 172:343–352

Liu Y, Liu W, Liang Z (2015) Endophytic bacteria from *Pinellia ternata,* a new source of purine alkaloids and bacterial manure. Pharm Biol 5:1545–1548. doi:10.3109/13880209.1016580

Liu G, Lai D, Liu ZQ, Zhou L, Liu LZ (2016) Identification of nematicidal constituents of *Notopterygium incisum* rhizomes against *Bursaphelenchus xylophilus* and *Meloidogyne incognita*. Molecules 21:1276. doi:10.3390/molecules21101276

Lopez MA, Bannenberg G, Castresana C (2008) Controlling hormone signaling is a plant and pathogen challenge for growth and survival. Curr Opin Plant Biol 11:420–427. doi:10.1016/j.pbi.2008.05.002

Lowicki D, Nski AH (2013) Structure and antimicrobial properties of Monensin A and its derivatives: summary of the achievements. Bio Med Res Int. doi:10.1155/2013/742149 **(Article ID 742149)**

Lu L, Sun RW, Chen R, Hui HK, Ho CM, Luk JM, Lau GK, Che CM (2008) Silver nanoparticles inhibit hepatitis B virus replication. Antivir Ther 13:253–262

Ma Y, Zhang C, Oliveira RS, Freitas H, Luo Y (2016) Bioaugmentation with endophytic bacterium E6S homologous to *Achromobacter piechaudii* enhances metal rhizoaccumulation in host *Sedum plumbizincicola*. Front Plant Sci 4:75. doi:10.3389/fpls.2016.00075

Mahmoud AY, Abdallah HM, El-Halawani MA, Jiman-Fatani AAM (2015) Anti-tuberculous activity of Treponemycin produced by a *Streptomyces* strain MS-6-6 isolated from Saudi Arabia. Molecules 20:2576–2590. doi:10.3390/molecules20022576

Maier A, Maul C, Zerlin M, Grabley S, Thiericke R (1999) Biomolecular chemical screening: a novel screening approach for the discovery of biologically active secondary metabolites. II. Application studies with pure metabolite. J Antibiot (Tokyo) 52:952–959

Mark N, Greenwald RA, Hillen W, Nelson ML (2001) Tetracyclin in biology, chemistry and medicine. Birkhauser, Basel, p 8

Mercado BJ, Bakker PA (2007) Interaction between plants and beneficial *Pseudomonas* sp., exploiting bacterial traits for crop protection. Antonie Leeuwenhok 92:367–389. doi:10.1007/s10482-007-9167-1

Merino ST, Cherry J (2007) Progress and challenges in enzyme development for biomass utilization. Adv Biochem Eng Biotechnol 108:95–120. doi:10.1007/10_2007_066

Miao V (2005) Daptomycin biosynthesis in *Streptomyces roseosporus*: cloning and analysis of the gene cluster and revision of peptide stereochemistry. Microbiology 151:1507–1523. doi:10.1099/mic.0.27757-0

Miller RV, Miller CM, Kinney DG, Redgrave B, Sears J, Condron M et al (1998) Ecomycins, unique antimycotics from *Pseudomonas viridiflava*. J Appl Microbiol 84:937–944. doi:10.1046/j.1365-2672.1998.00415.x

Mitsuhashi S (2014) Current topics in the biotechnological production of essential amino acids, functional amino acids, and dipeptides. Curr Opin Biotechnol 26:38–44. doi:10.1016/j.copbio.2013.08.020

Molina G, Pimentel MR, Bertucci TCP, Pastore GM (2012) Application of fungal endophytes in biotechnological processes. Chem Eng Trans 27:289–294

Nicolaou KC, Chen JS, Corey EJ (2011) Classics in total synthesis, further targets, strategies, methods III. Wiley, Weinheim, pp 1–770

Nongkhlaw FMW, Joshi SR (2015) Investigation on the bioactivity of culturable endophytic and epiphytic bacteria associated with ethnomedicinal plants. J Infect Dev Ctries 9:954–961. doi:10.3855/jidc.4967

Pandey SS, Singh S, Babu CSV, Shanker K, Shrivastava NK, Kalra A (2016) Endophytes of opium poppy differentially modulate host plant productivity and genes for the biosynthetic pathway of benzylisoquinoline alkaloids. Planta 243:1097–1114. doi:10.1007/s00425-016-2467-9

Perucka I, Materska M (2003) Antioxidant activity and content of capsaicinoids isolated from paprika fruits. Polish J Food Nutr Sci 12:15–18

Pesic A, Steinhaus B, Kemper S, Nachtigall J, Kutzner HJ, Höfle G, Sussmuth RD (2014) Isolation and structure elucidation of the

nucleoside antibiotic strepturidin from *Streptomyces albus* DSM 40763. J Antibiot 67:471–477. doi:10.1038/ja.2014.16
Pimentel-Elardo SM, Kozytska S, Bugni TS, Ireland CM, Moll H, Hentschel U (2010) Anti-parastic compounds from *Streptomyces* sp. strains isolated from Mediterranean Sponges. Mar Drugs 23:373–380. doi:10.3390/md8020373
Pinchuka IV, Bressollier P, Sorokulova IB, Verneuil B, Urdaci MC (2002) Amicoumacin antibiotic production and genetic diversity of *Bacillus subtilis* strains isolated from different habitats. Res Microbiol 153:269–276. doi:10.1016/S0923-2508(02)01320-7
Pissuwan D, Valenzuela SM, Cortie MB (2006) Therapeutic possibilities of plasmonically heated gold nanoparticles. Trends Biotechnol 24:62–67. doi:10.1016/j.tibtech.2005.12.004
Prashith-Kekuda TR (2016) Isolation, characterization and antimicrobial potential of endophytic actinomycetes. Int J Curr Microbiol Appl Sci 5:100–116. doi:10.20546/ijcmas.2016.507.008
Puri SC, Verma V, Amna T, Qazi GN, Spiteller M (2005) An endophytic fungus from *Nothapodytes foetida* that produces camptothecin. J Nat Prod 68:1717–1719
Qin S, Xing K, Hong JJ, Xu LL, Li WJ (2011) Biodiversity, bioactive natural products and biotechnological potential of plant-associated endophytic actinobacteria. Appl Microbiol Biotechnol 89:457–473. doi:10.1007/s00253-010-2923-6
Raaijmakers JM, Mazzola M (2012) Diversity and natural functions of antibiotics produced by beneficial and plant pathogenic bacteria. Annu Rev Phytopathol 50:403–424. doi:10.1146/annurev-phyto-081211-172908
Raju R, Gromyko O, Fedorenko V, Luzketsky A, Muller R, Albaflavenol B (2015) Albaflavenol B, a new sesquiterpene isolated from the terrestrial actinomycete, *Streptomyces* sp. J Antibiot 68:286–288. doi:10.1038/ja.2014.138
Reinhold-Hurek B, Hurek T (2011) Living inside plants: bacterial endophytes. Curr Opin Plant Biol 14:435–443
Rosenblueth M, Romero EM (2006) Bacterial endophytes and their interactions with hosts. APS 19:827–837
Roy S, Banerjee D (2015) Bioactive endophytic actinomycetes of *Cinnamomum* sp. isolation, identification, activity guided purification and process optimization of active metabolite. Am J Microbiol 6:4–13. doi:10.3844/ajmsp.2015.4.13
Salam N, Khieu T, Liu M, Vu T, Chu-Ky S, Quach N, Phi Q, Rao MPN, Fontana A et al (2017) Endophytic actinobacteria associated with *Dracaena cochinchinensis* Lour.: Isolation, diversity, and their cytotoxic activities. BioMed Res Int. doi:10.1155/2017/1308563 **(Article ID 1308563)**
Sanatombi K, Sharma GJ (2008) Capsaicin content and pungency of different capsicum sp. cultivars. Not Bot Hortic Agrobot Cluj 36:89–90
Sansinenea E, Ortiz A (2011) Secondary metabolites of soil *Bacillus* spp. Biotechnol Lett 33:1523–1538. doi:10.1007/s10529-011-0617-5
Sathiyaseelan K, Stella D (2011) Isolation, identification and antimicrobial activity of marine actinomycetes isolated from Parangipettai. Recent Res Sci Technol 3:74–77
Sato F, Kumagai H (2013) Microbial production of isoquinoline alkaloids as plant secondary metabolites based on metabolic engineering research. Proc Jpn Acad Ser B 89:165–181
Shaligram NS, Singhal RS (2010) Surfactin—a review on biosynthesis, fermentation, purification and applications. Food Technol Biotechnol 48:119–134
Sharma D, Pramanik A, Agrawal PK (2016) Evaluation of bioactive secondary metabolites from endophytic fungus *Pestalotiopsis neglecta* BAB-5510 isolated from leaves of *Cupressus torulosa* D.Don. 3 Biotech 6:210. doi:10.1007/s13205-016-0518-3
Silva GH, Teles LH, Zanardi LM, Young MC, Eberlin MN, Hadad R et al (2007) Cadinane sesquiterpenoids of *Phomopsis cassiae* an endophytic fungus associated with *Cassia spectabilis* (Leguminosae). Phytochemistry 67:1964–1969. doi:10.1016/j.phytochem.2006.06.004
Singh S, Bindu H, Raghu J, Suma HK, Manjunatha BL, Kumara PM et al (2013) Isolation of endophytic bacteria producing the anticancer alkaloid camptothecine from *Miqueliadentata Bedd*. (Icacinaceae). Phytomedicine 20:913–917. doi:10.1016/j.phymed.2013.04.004
Stein T (2005) Bacillus subtilis antibiotics: structures, syntheses and specific functions. Mol Microbiol 56:845–857. doi:10.1111/j.1365-2958.2005.04587.x
Strobel G (2006) Harnessing endophytes for industrial microbiology. Curr Opin Microbiol 9:240–244. doi:10.1016/j.mib.2006.04.001
Strobel G, Ford WJ, Harper JK, Arif AM, Grant DM, Peter F, Chau RM (2002) Isopestacin, an isobenzofuranone from *Pestalotiopsis microspora* possessing antifungal and antioxidant activities. Phytochemistry 60:179–183
Subbulakshmi GK, Thalavaipandian A, Bagyalakshmi RV, Rajendran A (2012) Bioactive endophytic fungal isolates of *Biota orientalis* (L) Endl., *Pinus excelsaWall*. and *Thuja occidentalis* L. Int J Adv Life Sci 4:9–15
Sun RW, Chen R, Chung NP, Ho CM, Lin CL, Che CM (2005) Silver nanoparticles fabricated in Hepes buffer exhibit cytoprotective activities toward HIV-1 infected cells. Chem Commun (Camb) 40:5059–5061
Sunkar S, Nachiyar CV (2012) Biogenesis of antibacterial silver nanoparticles using the endophytic bacterium *Bacillus cereus* isolated from *Garcinia xanthochymus*. Asian Pac J Trop Biomed 2:953–959. doi:10.1016/S2221-1691(13)60006-4
Suryanarayanan TS, Murali TS (2006) Incidence of *Leptosphaerulina crassiasca* in symptomless leaves of peanut in southern India. J Basic Microbiol 46:1003–1006
Sziderics AH, Rasche F, Trognitz F, Sessitch A, Wilhelem E (2007) Bacterial endophyte contribute to abiotic stress adaptation in pepper plants (*Capsicum annum* L.). Can J Microbiol 53:1195–1202. doi:10.1139/W07-082
Taechowisan T, Chanaphat S, Ruensamran W, Phutdhawong WS (2012) Anti-inflammatory effect of 3-methylcarbazoles on RAW 2647 cells stimulated with LPS, polyinosinic-polycytidylic acid and Pam3CSK. Adv Microbiol 2:98–103
Takahashi S, Takeuchi M, Arai M, Seto H, Otake N (1983) Studies on biosynthesis of pentalenolactone. V isolation of deoxypentalenylglucuron. J Antibiot (Tokyo) 36:226–228. doi:10.7164/antibiotics.36.226
Tamehiro N, Okamot-Hosova Y, Okamoto S, Ubukata M, Hamada M, Naganawa H et al (2002) Bacilysocin, a novel phospholipid antibiotic produced by *Bacillus subtilis* 168. Antimicrob Agents Chemother 46:315–320. doi:10.1128/AAC.46.2.315-320.2002
Tan RX, Zou WX (2001) Endophytes: a rich source of functional metabolites. Nat Prod Rep 18:448–459. doi:10.1039/B100918O
Taylor PL, Omotoso O, Wiskel JB, Mitlin D, Burrell RE (2005) Impact of heat on nanocrystalline silver dressings. Part II: physical properties. Biomaterials 26:7230–7240
Thenmozhi M, Krishnan K (2011) Anti-Aspergillus activity of Streptmyces sp. VITSTK7 isolated from bay of Bengal coast of Puducherry, India. J Nat Environ Sci 2:1–8
Tiwari R, Awasthi A, Mall M, Shukla AK, Srinivas KS, Syamasundar KV, Kalra A (2013) Bacterial endophyte mediated enhancement of in planta content of key terpenoid indole alkaloids and growth parameters of *Catharanthus roseus*. Ind Crops Prod 43:306–310. doi:10.1016/j.indcrop.2012.07.045
Trotsenko YA, Khmelenina VN (2002) Biology of extremophilic and extremotolerant methanotrophs. Arch Microbiol 177:123–131. doi:10.1007/s00203-001-0368-0
Valdes L, Cuervo A, Salazar N, Ruas-Madiedo P, Gueimonde M, Gonzalez S (2015) The relationship between phenolic

compounds from diet and microbiota: impact on human health. Food Funct 6:2424–2439. doi:10.1039/c5fo00322a
Verginer M, Siegmund B, Cardinale M, Muller H, Choi Y, Maıguez CB et al (2010) Monitoring the plant epiphyte *Methylobacterium extorquens* DSM 21961 by real-time PCR and its influence on the strawberry flavor. FEMS Microbiol Ecol 74:136–145. doi:10.1111/j.1574-6941.2010.00942.x
Verpoorte R (1998) Exploration of nature's chemo diversity: the role of secondary metabolites as leads in drug development. Drug Discov Today 3:232–238
Villaescusa BP, Rangel-Huerta OD, Aguilera CM, Gil A (2015) A systematic review of the efficacy of bioactive compounds in cardiovascular disease: carbohydrates, active lipids and nitrogen compounds. Ann Nutr Metab 66:168–181. doi:10.1159/000430960
Vinale F, Nicoletti R, Lacatena F, Marra R, Sacco A, Lombardi N, D'Errico G, Digilio MC, Lorito M, Woo SL (2017) Secondary metabolites from the endophytic fungus *Talaromyces pinophilus*. Nat Prod Res 31:1778–1785
Waldron C, Matsushima P, Rosteck PR, Broughton MC, Turner J, Madduri K (2001) Cloning and analysis of the spinosad biosynthetic gene cluster of *Saccharopolyspora* spinosa. Chem Biol 8:487–499. doi:10.1016/S1074-5521(01)00029-1
Wei L, Xueqiong Y, Yabin Y, Lixing Z, Lihua X, Zhongtao D (2015) A new anthracycline from endophytic *Streptomyces* sp. YIM66403. J Antibiot 68:216–219. doi:10.1038/ja.2014.128
Wendisch VF (2014) Microbial production of amino acids and derived chemicals: synthetic biology approaches to strain development. Curr Opin Biotechnol 30:51–58. doi:10.1016/j.copbio.2014.05.004
Yamada Y, Kuzuyama T, Komatsu M, Shinya K, Omura S, Cane DE et al (2015) Terpene synthases are widely distributed in bacteria. Proc Natl Acad Sci USA 112:857–862. doi:10.1073/pnas.1422108112
Yamazaki Y, Someno T, Igarashi M, Kinoshita N, Hatano M, Kawada M et al (2015) Androprostamines A and B, the new anti-prostate cancer agents produced by *Streptomyces* sp. MK932-CF8. J Antibiot 68:279–285. doi:10.1038/ja.2014.135
Yoon YJ, Kim ES, Hwang YS, Choi CY (2004) Avermectin: biochemical and molecular basis of its biosynthesis and regulation. Appl Microbiol Biotechnol 63:626–634. doi:10.1007/s00253-003-1491-4
Yu H, Zhang L, Li L, Zheng C, Guo L, Li W et al (2010) Recent developments and future prospects of antimicrobial metabolites produced by endophytes. Microbiol Res 165:437–449. doi:10.1016/j.micres.2009.11.009
Yuan N, Song L, Zhang S, Lin W, Cao Y, Xu F, Fang Y, Wang Z, Zhang H, Li X (2015) Bafilomycin A1 targets both autophagy and apoptosis pathways in pediatric B-cell acute lymphoblastic leukemia. Haematologica 100:345–356
Zhao K, Penttinen P, Guan T, Xiao J, Chen Q, Xu J et al (2011) The diversity and anti-microbial activity of endophytic actinomycetes isolated from medicinal plants in Panxi Plateau, China. Curr Microbiol 62:182–190. doi:10.1007/s00284-010-9685-3
Zhejian W, Zhao M, Lili W, Chengchen T, Zhibi H, GuiXin C, Wankui L (2015) Active anti-acetylcholinesterase component of secondary metabolites produced by the endophytic fungi of *Huperzia serrata*. Electron J Biotechnol 18:399–405
Zhou JY, Yuan J, Li X, Ning YF, Dai CC (2015) Endophytic bacterium triggered reactive oxygen species directly increase oxygenous sesquiterpenoid content and diversity in *Atractylodes lancea*. Appl Environ Microbiol 82:1577–1585
Zinniel DK, Lambrecht P, Harris NB, Feng Z, Kuczmarski D, Higley P (2002) Isolation and characterization of endophytic colonizing bacteria from agronomic crops and prairie plants. Appl Environ Microbiol 68:2198–2208. doi:10.1128/AEM.68.5.2198-2208.2002
Zothanpuia Passari AK, Chandra P, Leo VV, Mishra VK, Kumar B, Singh BP (2017) Production of potent antimicrobial compounds from *Streptomyces cyaneofuscatus* associated with fresh water sediment. Front Microbiol 8:68. doi:10.3389/fmicb.2017.00068