



Prospecting potential of endophytes for modulation of biosynthesis of therapeutic bioactive secondary metabolites and plant growth promotion of medicinal and aromatic plants

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Abstract Medicinal and aromatic plants possess pharmacological properties (antidiabetes, anticancer, antihypertension, anticonvulsant, antileprosy, etc.) because of their potential to synthesize a wide range of therapeutic bioactive secondary metabolites. The concentration of bioactive secondary metabolites depends on plant species, local environment, soil type and internal microbiome. The internal microbiome of medicinal plants plays the crucial role in the production of bioactive secondary metabolites, namely alkaloids, steroids, terpenoids, peptides, polyketones, flavonoids, quinols and phenols. In this review, the host specific secondary metabolites produced by

endophytes, their therapeutic properties and host-endophytes interaction in relation to production of bioactive secondary metabolites and the role of endophytes in enhancing the production of bioactive secondary metabolites is discussed. How biological nitrogen fixation, phosphorus solubilization, micro-nutrient uptake, phytohormone production, disease suppression, etc. can play a vital role in enhancing the plant growth and development. The role of endophytes in enhancing the plant growth and content of bioactive secondary metabolites in medicinal and aromatic plants in a sustainable mode is highlighted.

Keywords Antimicrobial compounds · Biological nitrogen fixation · Internal microbiome · Phytochemistry · Quorum sensing

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Introduction

Medicinal and aromatic plants have the capability to synthesize different types of bioactive secondary metabolites (Cushnie et al. 2014) that are significant to endure and prosper in the indigenous habitat, incorporating defensive capacities as for abiotic and biotic stresses (Vardhini and Anjum 2015). The "bioactive" secondary metabolites are derived from intermediates of primary metabolites and are not essential for growth and development of organisms (Tiwari and Rana 2014). There are five main classes of secondary metabolites produced by plants and microbes such as

terpenoids and steroids, fatty acid-derived substances and polyketides, alkaloids, nonribosomal polypeptides, and enzyme cofactors (Erb and Kliebenstein 2020). These biologically active secondary metabolites possess pharmaceutical properties and are used in the treatment of skin disorders, cancer, hypertension, cardiovascular diseases, diabetes, leprosy, thyroid, obesity etc. (Olasehinde et al. 2017; Seca and Pinto 2018; Shayganni et al. 2016). The biologically active secondary metabolites are species and environment specific, therefore, their production and composition depends on plant species, soil types and relationship with microorganisms (Morsy 2014). The communities of plants microbiota and their physiological functions are also affected by bioactive secondary metabolites produced by several medicinal and aromatic plants (Chaparro et al. 2014).

Earlier research focused on bioactive secondary metabolites of medicinal plants only, however, now the focus is shifting towards its microbiome as a large number of bioactive secondary metabolites are actually produced by associated microbes or through their interaction with the host plant. The endophytic microorganisms have crucial role in the production of bioactive secondary metabolites such as- steroids, alkaloids, peptides, polyketones, terpenoids, flavonoids, and phenols (Matsumoto and Takahashi 2017; Pratiwi et al. 2018). Bioactive secondary metabolites also have certain agricultural, industrial and medical applications (Aswani et al. 2020; Daud et al. 2019). It is believed that the phytochemical constituents of plants are related either directly or indirectly to endophytic microbes and their interactions with host plants (Qi et al. 2012). Egamberdieva et al. (2017a) reported that antimicrobial activity of medicinal and aromatic plants correlates with the proportion of antagonistic endophytes.

Apart from producing secondary metabolites on its own, these endophytes may also associate with plants to accelerate the biosynthesis of bioactive compounds secreted by them. The synergistic effect of endophytic microorganisms and medicinal plants have been investigated as a source of crude products with high medicinal potential as compared to plants alone (Hardoim et al. 2015; Heinig et al. 2013). Likewise, Strobel (2003) reported that endophytes associated with medicinal plants produces a wide varieties of secondary metabolites as compared to them alone. Ding et al. (2018) reported that endophytic

fungi- *Aspergillus* sp., *Fusarium* sp. and *Ramularia* sp. of *Rumex gmelini* Turcz increased the production of bioactive compounds in the host plant and showed similarity with them in relation to production pattern of secondary metabolites.

Rapid urbanization and industrialization due to a gradual increase in the world population have put immense pressure on the available cultivated land for accelerated crop production and productivity. To achieve this, excessive and irrational use of agrochemicals such as fertilizers, herbicides, fungicides, and other supplements has been adopted. However, continuous use of these agrochemicals for enhanced soil fertility, productivity and plant production has resulted in adverse impacts on the ecosystem, including pollution of soil, groundwater, and aquifers (Bohlool et al. 1992; Byrnes 1990; Mulongoy et al. 1991; Zhu and Chen 2002). Hence, eco-friendly methods are need of the hour to maintain the quality of soil, water and other habitats of living organisms to keep sustained crop production and ecological stability. Plant growth-promoting substances are produced in huge amounts by these rhizospheric and endophytic microbes that influences the overall growth and development of medicinal and aromatics plants directly or indirectly (Larkin and Tavantzis 2013; Sharma et al. 2020). Endophytes enhances the plant growth and development through different mechanisms like- nutrient acquisition, biological control of phytopathogens and tolerance to abiotic stress (Berg et al. 2014; Egamberdieva et al. 2011; Malfanova et al. 2011). Reports suggest that microbes enhance the survivability of plants by modulating biosynthetic activities involved in accumulation of stress tolerant molecules (proline, glycine betaine, etc.) and antioxidant enzymes (catalase, peroxidase, glutathione reductase, superoxide dismutase, etc.) in plants body under stress conditions (Hussain et al. 2014; Tiwari et al. 2016; Vardharajula et al. 2011).

The objective of this review is (1) to reveal plant- and microbe-derived constituents of medicinal plants; (2) to discuss host endophytic interaction in relation to modulation of biosynthesis of bioactive secondary metabolites in medicinal plants, (3) to highlight possible mechanisms of plant growth promotion of medicinal plants by endophytes.

Bioactive secondary metabolites and endophytes

Endophytic fungi, have the potential to produce similar class and even in some cases exactly the same secondary metabolites that are pharmacologically active as their hosts (Venieraki et al. 2017). This relationship of endophytic fungi with its host is certainly more complex than it appeared initially. It was proposed that the horizontal transfer of genes responsible for the production of these bioactive compounds might have been introduced from the host. However, the genome sequencing showed otherwise, as the corresponding genes differ significantly among the host and endophytic fungi and might have evolved independently (Lu et al. 2019). Inspecting the mechanisms underlying the synthesis of endophyte mediated plant metabolites plays an important role in exploring these endophytes for the production of new bioactive metabolites commercially, especially the ones produced by the plants.

Host plant specific therapeutics bioactive secondary metabolites produced by endophytes

Belonging to the group of natural products with extreme diversity, secondary metabolites are organic compounds synthesized by microorganisms, plants and animals that are not associated with the organism's normal growth and development. These metabolites are often synthesized to their maximum potential mostly during the stationary phase. The organisms producing secondary metabolites can survive in their absence, thus making them non-essential for immediate survival. However, the secondary metabolites are also essential for cellular metabolism of organism and dependent on primary metabolites for synthesis of important enzymes, substrates and other molecules necessary for long term host survival (Roze et al. 2011). Secondary metabolites are often categorized into different classes and among them most are classified on the basis of their biosynthetic origin like alkaloids, steroids, terpenoids, peptides, polyketones, flavonoids, quinols and phenols (Matsumoto et al. 2017; Pratiwi et al. 2018).

Plants being an excellent source of numerous bioactive compounds, especially the medicinal plants, have been used in traditional medicines for treatment of several diseases and are basis for discovery and advancement of modern therapeutics (Pan et al.

2013). For primary healthcare, nearly 80% population is absolutely reliant on herbal drugs in developing countries and in the last four decades, more than 51% of the small molecule therapeutics approved were natural product based, with rest being produced synthetically. This ever-growing demand for herbal medicines and naturally produced healthcare products, emphasizes the rapidly growing use of medicinal plants (Chen et al. 2016).

Earlier studies on medicinal plants were mainly focused on their constituents, however, with advancement in technology the paradigm has been shifted to structural and functional attributes of microbiomes associated with the host medicinal plants. Surprisingly, it was observed that not only the host plants but also their associated microbial population, plant endophytes in particular, were able to produce the plant therapeutic compounds (Table 1). Ever since the report on *Taxomyces andreanae*, an endophyte of *Taxus brevifolia*, producing a bioactive secondary metabolite similar to its host (Stierle et al. 1993), several plant-derived bioactive secondary metabolites have been reported to be synthesized by the host endophytes (Zhao et al. 2011). Recent studies have also shown that microbes or their interaction with host produces several important natural products and in several cases involving medicinal plants it is assumed that microbiome associated with plant, especially endo-microbiome, is significantly involved in bioactive compound production from the plant either directly or indirectly (Miller et al. 2012). The metabolism of associated microbiome and its interaction with host highly influences and regulates the quality, growth and health of medicinal plants. Even the ability of phytotherapeutics to suppress human pathogens can be attributed to these medicinal plant associated microbiome and their metabolites (Miller et al. 2012; Mousa and Raizada 2013).

Endophytic bacteria are the potential source of numerous secondary metabolites that have applications in many plant growth and development aspects like antibiotics, antiparasitics, antioxidants, plant growth promoting compounds and enzymes, etc. There are various reports suggesting the role of host-specific endophytic bacteria in producing the bioactive compounds with antimicrobial activities. The antibacterial activity of endophytic *Bacillus* and *Lysinibacillus* species isolated from African *Combretum molle* was recorded against *Bacillus cereus*,

Table 1 List of host specific secondary metabolites produced by different microorganisms or by their interactions with the host

Endophyte	Host plant	Bioactive compounds	Therapeutics properties	Reference
<i>Macrococcus caseolyticus</i> (ALS-1)	Aloe vera	1,1-diphenyl-2-picrylhydrazyl	Free radical scavenging	Akinsanya et al. (2015)
<i>Paenibacillus polymyxa</i>	Ginseng (<i>Panax ginseng</i>)	Ginsenosides	Anticancer	Gao et al. (2015)
<i>Streptomyces</i> sp. LJK109	<i>Alpinia galangal</i>	3-methylcarbazoles	Anti-inflammatory component	Taechowisan et al. (2012)
<i>Eurotium</i> sp.	<i>Curcuma longa</i>	Asparaginase	Anti-cancer enzyme	Jalgaonwala and Mahajan et al. (2014)
Endophytic fungal strains	<i>Salvia miltiorrhizae</i>	Tanshinones and Salvianolic acids	Anti-carcinogenic, anti-atherosclerosis, and anti-hypertensive	Chun-Yan et al. (2015)
<i>Fusarium oxysporum</i> , <i>Talaromyces radicus</i>	<i>Catharanthus roseus</i>	Vinca alkaloids (vincristine, vindesine, vinorelbine, vinblastine)	Anticancer	Palem et al. (2015)
<i>Rhizoctonia bataticola</i>	<i>Coleus forskohlii</i>	Forskolin	Anti-HIV or antitumor, Anti-hypertension	Mir et al. (2015)
Endophytic fungi	<i>Macleaya cordata</i>	Sanguinarine	Antibacterial, antihelminthic, antitumor	Wang et al. (2014)
<i>Phomopsis</i> , <i>Diaporthe</i> , <i>Schizophyllum</i> ,	<i>Cinchona</i>	Quinine alkaloids (cinchonidine and cinchonine),	Antimalarial compounds	Maehara et al. (2013)
<i>Alternaria alternata</i> , <i>Colletotrichum capsici</i> , <i>Colletotrichum taiwanense</i>	<i>Passiflora incarnate</i>	C-glycosyl flavonoids (vitexin, orientin and chrysin) and b-carbolic alkaloids (harmalin, harmalol etc.)	Antibacterial, anti-inflammatory, anti-diabetic, anxiolytic, hepatoprotective	Seetharaman et al. (2017)
<i>Fusarium</i> <i>edolens</i> 6WBY3	<i>Fritillaria cirrhosa</i>	Peimisine, imperialine-3 β -D-glucoside, and peimine	Antitussive and expectorant drugs	Pan et al. (2017) and Chithra et al. (2014)
<i>Colletotrichum gloeosporioides</i>	<i>Piper nigrum</i>	Piperine	Antibacterial, antifungal, antipyretic,	Chithra et al. (2014)
<i>Aspergillus flavus</i>	<i>Solanum nigrum</i>	Solamargine	Antioxidant, diuretic, antimicrobial, anti-cancer	El-Hawary et al. (2016)
Fungal endophytes	<i>Digitalis lanata</i>	Digoxin-Glycosides	Cardiotonic	Kaul et al. (2013)
<i>Alternaria alternata</i>	<i>Capsicum annum</i>	Capsaicin	Cardio protective, anti-lithogenic effect, analgesia	Devari et al. (2014)

Escherichia coli, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* (Diale et al. 2018). Leaf and root endophytes of *Raphanus sativus* and in another study root endophytes of *Zingiber officinale* were shown to exhibit antibacterial activity (Taechowisan et al. 2013). There have been reports where cell-wall degrading enzymes from endophytic *Macrococcus* sp., *Bacillus* sp., and *P. polymyxa* isolated from *Panax ginseng* and *Plectranthus tenuiflorus* have been shown to exhibit antimicrobial activity

(El-Deeb et al. 2013). The other endophytic bacteria such as *Paenibacillus denitriformis*, *Bacillus pseudomycoides* and *B. licheniformis* have been reported to produce L-asparaginase enzyme efficiently (Joshi and Kulkarni 2016). This enzyme has major role in chemotherapy as it catalyses the L-asparagine conversion (Jiang et al. 2018).

Actinomycetes has been well documented for their contribution in antibiotic development and also other bioactive metabolites production. This potential

of actinomycetes to synthesize bioactive secondary metabolites is also being studied for their endophytic forms. The endophytic actinomycetes of Chinese medicinal and mangrove plants reported to exhibit antibacterial activity against *Enterococcus faecalis*, *S. aureus*, *Klebsiella pneumoniae*, *E. coli*, *Acinetobacter baumannii* and *P. aeruginosa*. Among these, some were even resistant to antibiotics like methicillin, carbapenem and vancomycin (Jiang et al. 2018). The characterization of several metabolites isolated from endophytic *Streptomyces* species has been found to exhibit various activities like antibacterial, antimalarial and antifungal (Ek-Ramos et al. 2019). Similarly, endophytic actinomycetes from Iranian medicinal plants, *Kennedia nigricans* and Malaysian plants has been seen to exhibit antimicrobial activity against various bacterial pathogens (Fikri et al. 2018). *Streptomyces* sp. (strain SUK06), an endophyte isolated from *Thottea grandiflora* (Malaysian medicinal plant), has been reported to inhibit the growth of methicillin-resistant *S. aureus* (MRSA) (Ghadin et al. 2008).

The endophytic fungi also produces a wide range of these bioactive secondary metabolites with vital functions, exhibiting valuable medicinal and antibiotic properties. Numerous fungal endophytes has been reported to display host specificity in terms of metabolite synthesis. For example, out of the 27 fungal strains obtained from *Ginkgo biloba* trees bark, only one strain i.e. *Fusarium oxysporum* SY0056 was able to synthesize Ginkgolide B (Cui et al. 2012). Similarly, *Pestalotiopsis uvicola* GZUYX13 from *Ginkgo biloba* leaves, was the only isolate among the 57 strains obtained from different plant parts including root, stem and leaf that was able to produce bilobalide metabolite (Qian et al. 2016). Both these metabolites have been very well documented to have therapeutic roles with the former being involved in cardiovascular or respiratory system disorder while the later having neuroprotective effects (Kiewert et al. 2008; Usai et al. 2011). In another study, out of 11 fungal strains examined for Vincamine indole alkaloids production, isolated from roots and stems of *Nerium indicum*, only one fungal strain (CH1) was able to produce vincamine alkaloids similar to its host. These alkaloids are reported to show therapeutic properties like cerebrovascular prevention, vascular dementia reduction, etc. (Vora et al. 2013). Moreover, the fungal endophytes of *Rheum palmatum* (You et al.

2013) and *Forsythia suspense* (Qu et al. 2008) were reported to produce bioactive compounds like rhein and emodin, and Phillyrin, respectively. These compounds have major applications in alleviating pain and anti-inflammatory properties.

Host-endophytes interaction in relation to production of therapeutic secondary metabolites by medicinal plants

Recently, investigation on the endophytic microorganisms has increased owing to their intimate association with the host. From the conventional point of view, the quantity and quality of the medicinal plant based crude drugs depends largely on the genotypic characters and ecological habitat of the plant and the nutrient status of soil (Dai et al. 2003; Sherameti et al. 2005). Furthermore, this has been recognized gradually in the recent years that endophytic microorganisms have been one of the major drivers in regulating the quantity and quality of crude drugs via host-specific interactions, thus making it indispensable to understand in-depth relationship of endophytic microorganisms with the medicinal plants in order to promote or enhance the production of crude drugs.

Studies revealed that, endophytes do produce secondary metabolites that are either identical or similar to their hosts. Some of these bioactive compounds which are produced by endophyte and host collaboration includes anticancer drugs like podophyllotoxin and camptothecin (Puri et al. 2006) and azadirachtin as natural insecticides (Kusari et al. 2012). There have been numerous mechanisms reported for simultaneous synthesis of biological compounds. However, in some instances, the biosynthetic mechanism completely differs in plants and their endophytes even for the same compound (Bomke et al. 2009). The horizontal gene transfer between the endophytes and their host has been hypothesized as one of the possible mechanisms, though it has been restricted to microorganisms (Taghavi et al. 2005). So, one thing is clear and can be strongly put forward that the interactions between the host and their endophytes significantly regulates the co-production of these bioactive compounds (Heinig et al. 2013).

Recently, significant attention has been given to endophytes by the microbial chemistry community owing to their contribution for the discovery of novel bioactive metabolites. And, it has also been reported

that this intimate association of endophytes with their host was more promising in production of higher number and diversity of the bioactive compounds as compared to non-endophytes like epiphytes of rhizospheric microorganisms (Strobel et al. 2003). The relationship being symbiotic in nature is likely to give compounds with reduced cell toxicity. This particular attribute is of prime importance for medical community as these compounds may not adversely affect the eukaryotic systems.

Taxol, a multibillion-dollar anticancer drug, is one of the major success story of endophytic natural products. Initially, this compound was isolated from a traditional medicinal plant *Taxus brevifolia* (Pacific yew tree) (Wani et al. 1971). After that numerous plants other than this have been reported to produce taxol. The endophytic fungi from *Taxomyces andreanae* has been investigated to produce this compound (Stierle et al. 1995). Considering the mechanism behind its biosynthesis in the host, it has

been suggested that the genome of endophytes has no significant homology with *Taxus* sp. for the production of taxol (Heinig et al. 2013), demonstrating the independent development of taxol biosynthesis in endophytes. Nevertheless, this example supports the rationale that traditional medicinal plants can be used as the starting point to investigate endophytes for their production of biologically active compounds. As stated earlier, approximately 70% of anti-infectives or their derivatives are naturally produced. However, instead of synthesising these derivatives through combinatorial chemistry, their biosynthesis at genetic level has been elucidated. These synthesis of natural products are regulated mostly by single gene clusters, therefore efforts are carried out in the direction to utilize these clusters through genetic engineering for biosynthesis of these natural compounds and also their derivatives. Figure 1 shows host endophytes interaction in relation to modulation of biosynthesis of bioactive secondary metabolites.

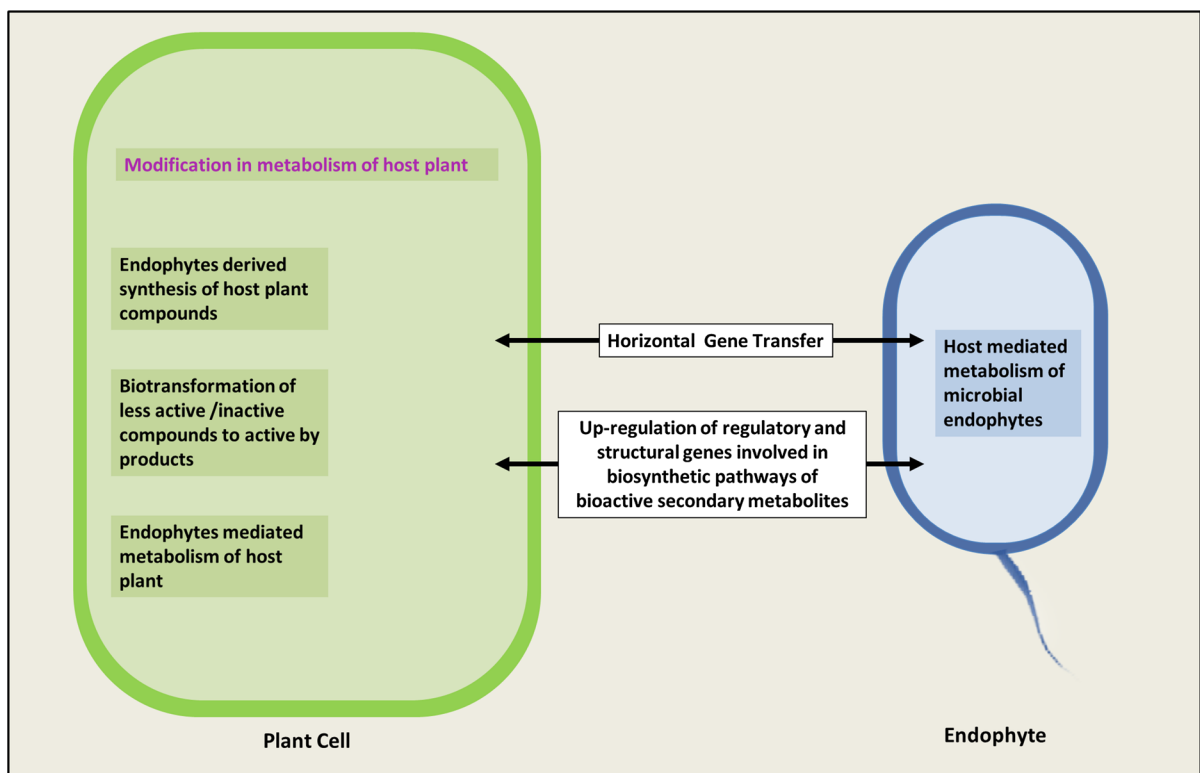


Fig. 1 Host endophytes interaction in relation to modulation of biosynthesis of bioactive secondary metabolites

Induction of metabolic activities of host plant

Induction of host secondary metabolism by the endophytes has been dealt less when compared to the endophyte metabolism induction, however, phenolic compounds related to defense in roots infected with endophytes have been studied long ago and are very well reported (Schulz et al. 1999). Induction of phenolic compound by infection of endophytes in *Lolium perenne* has been reported. Some of the major compounds that induced the antioxidant potential of plant extracts upon colonization of endophytes include chlorogenic acids, hydroxycinnamic acids and glycosylated flavonoids (Qawasmeh et al. 2012). Although these metabolic changes can be reduced or even remain unaltered upon infection, but scenario changes when the host interacts with endophytic toxic compounds. The toxicity to plants can be attributed to the herbicidal activity of endophytes. In a study, it was shown that leucinostatin A, a peptide derived from endophyte, was glycosylated in *Taxus* species, whereas it was still toxic to the non-host plants (Strobel et al. 1997). These toxic compounds may be used to regulate the selectivity of plant–microbe interrelationship.

Effect of host plant on metabolic pattern of endophytes

As discussed earlier, host plant metabolism is influenced by their endophytes, and vice versa. It can also be speculated that alteration of secondary metabolite patterns in endophytes is influenced by their host range. The regulation of pathogenic fungi metabolite patterns by the host plant has also been reported. *Heterobasidium* species showed different metabolic pattern for infecting and non-infecting pine species (Hansson et al. 2014).

Modification of metabolisms of endophytes inside the host plant

Metabolism of bioactive metabolites from host and their biosynthesis by endophytes are the most fascinating areas, however, meagre information is available. In recent times, the ability to synthesize bioactive metabolites by endophytes has gained momentum, corresponding to the constant discovery of these endophytic fungi capable of producing

plant compounds. As mentioned earlier also, so far synthesis of Taxol (paclitaxel) by endophytes is the most notable example for synthesis of plant metabolite partially. Owing to its important medical use as anti-cancer drug, its production on large scale in cell cultures has been optimized, however, one has to look for alternative sources other than plants to meet the ever growing demands for this drug (Cusido et al. 2014; Heinig et al. 2013; Malik et al. 2011).

The discovery of Taxol production in *T. andreanae*, an endophytic fungus of *Taxus brevifolia* was succeeded by the isolation of other endophytic fungus from a variety of *Taxus* sp. (Yuan et al. 2006; Zhang et al. 2009). After that, several other fungi, isolated from *Taxus baccata* and non-*Taxus* plants, were reported for the production of microbial taxane including *Aspergillus*, *Alternaria*, *Fusarium*, *Cladosporium*, *Monochaetia*, *Pestalotia*, *Pestalotiopsis*, *Pithomyces*, *Penicillium* and *Xylaria*. However, upon re-examination of taxane biosynthesis by fungi and host plant revealed no independent biosynthesis of taxane in the endophytes (Heinig et al. 2013). On the other hand, different bioactive metabolites including torreyanic acid also having anticarcinogenic properties were found in an endophyte, *Pestalotiopsis microspora*, isolated from other species of Taxaceae (Lee et al. 1996). In similar findings, endophytes were reported to produce different compounds in hosts from unrelated families like podophyllotoxin from Berberidaceae and rohitukine from Meliaceae, as precursor for another cancer drug (Müller et al. 2015). In some cases, like podophyllotoxin from *Podophyllum*, the sustainable production of such valuable bioactive compounds has not yet been achieved, though *Trametes hirsute*, a novel fungal endophyte, has shown promising approach for synthesis of this compound (Puri et al. 2006). Synthesis of insecticidal compounds like azadirachtin A and B from *Eupenicillium parvum* of *Azadirachta indica* has also been reported (Kusari et al. 2012). These examples, of course doesn't rule out the endophytes existence on respective host plants.

So, far the examples involved fungi as endophytes, however, the bacterial endophytes also share similar interactions with their host. Bioactive metabolites of oxylipin family with antimicrobial properties have been reported from stem extracts of *Alternanthera brasiliana* (Trapp et al. 2015). Several among these metabolites were also found in the genus *Bacillus*

isolated from *Alternanthera* plants and it was speculated that these compounds of oxylipin family obtained by the host from their bacterial endophytic counterparts shared some similarity (Trapp et al. 2015).

Biotransformation of host compounds by endophytes

Paraconiothyrium variable, a leaf endophyte isolated from a medicinal plant *Cephalotaxus harringtonia*, has been reported to metabolize the metabolites of its host plant. In-depth analysis and monitoring of these compounds and structural characterization revealed beneficial effects of the fungal endophyte. The endophyte could transform the glycosylated flavonoids, leading to aglycone compound production in the host which significantly induced the hyphal growth from spores (Tian et al. 2014). This study strongly depicts an underlying chemical co-operation between the host and the endophyte. In another study the symbiotic fungi *Colletotrichum tropicale* in cucumber plant changed the leaf chemistry by altering the host metabolism such that the leaf cutting by ants was reduced to almost half in the colonized plants as compared to non-colonized plants. Thus, the endophytes could even alter the plant–insect interaction (Estrada et al. 2013). Besides this, endophytes has also been reported to show the detoxification of host defense compounds. A toxic compound called benzoxazinoids is synthesized by maize plants for its protection from other pests. However, the enzymes synthesized by endophyte metabolizes this compound via deglycosylation resulting in a non-toxic product (Saunders and Kohn, 2008). Not only this, the detoxification of benzoxazinoids also leads to enhanced colonization by other non-tolerant fungal endophytes. The other mechanisms applied by endophytes to detoxify certain toxic plant compounds includes nitration, hydrolysis, acylation, reduction and oxidation (Zikmundova et al. 2002).

Modulation of phytochemistry of medicinal plants by endophytes

Apart from the biosynthetic mechanisms and interactions mentioned above regarding the bioactive metabolites, endophytes have also been observed to play a major role in improving the biosynthesis of host metabolites (Table 2). In a study, when *Catharanthus*

roseus plants were inoculated with *Choanephora infundibulifera* and *Curvularia* sp., it was observed that the content of a terpenoids indole alkaloid (TIA) was increased by 229–403%. There was a significant upregulation in regulatory and structural genes involving biosynthetic pathway of TIA in endophyte inoculated plants, as evident from real-time PCR results (Pandey et al. 2016). In a similar study, biosynthesis of tanshinones was enhanced and related genes were upregulated by application of polysaccharide fraction from an endophyte *Trichoderma atroviride* in host plant *Salvia miltiorrhiza* (Ming et al. 2013). From correlative transcriptome and metabolome analysis, this can be further suggested that endophytes can even reprogram the host metabolism by favouring secondary metabolism over the primary one (Dupont et al. 2015).

Like the fungal partners, bacterial endophytes have also been reported to exhibit potential for producing several bioactive metabolites with profound effect on both primary and secondary metabolism of the host. Upon inoculation of poplar plants with *Paenibacillus* sp., levels of urea, threitol and asparagine increased significantly whereas several organic acids, sugar phosphates and amino acids were reduced (Schering et al. 2009). Likewise, inoculation of grapevine with an endophyte *Enterobacter ludwigii* significantly increased the level of vanillic acid while reducing several others including ampelopsin, catechin, isohopeaphenol, esculin, etc. (López-Fernández et al. 2016).

Several studies involving medicinal plants, *Arabidopsis thaliana*, food crops, trees/shrubs and ornamentals were conducted to understand the effect of bacteria on its phytochemistry. Among them, medicinal and crop plants were investigated in detail, and comprehensive information has been reviewed to know the mechanism behind the bacteria-mediated alterations or regulations in host plants. Next comes the herbs in which the families Lamiaceae, Asteraceae and Fabaceae were the dominating ones studied in which Bacillales and Pseudomonadales were the most investigated bacterial orders followed by Actinomycetales.

The main purpose of study with the medicinal plants was to explore the potential of endophytic bacteria to regulate the level of bioactive or specific medicinal metabolite(s). Upregulation of cytochrome P450 oxidoreductase and monooxygenase genes was

Table 2 Role of endophytes in modulation of phytochemistry of medicinal and aromatic plants

Sl.N	Endophytes	Host plant	Bioactive Compounds	Function of inoculated endophytes	References
1	<i>Choanephora infundibulifera</i> and <i>Curvularia</i> sp.	<i>Catharanthus roseus</i>	Terpenoids Indole Alkaloid (TIA)	Expression of terpenoid indole alkaloid (TIA) pathway genes, geraniol 10-hydroxylase (<i>G10H</i>), tryptophan decarboxylase (<i>IDC</i>), strictosidine synthase (<i>STR</i>), 16-hydroxytabersonine-Omethyltransferase (<i>16OMT</i>), desacetoxylindoline-4-hydroxylase (<i>D4H</i>), deacetylindoline-4-Oacetyltransferase (<i>DAT</i>) were upregulated in endophyte-inoculated plants	Pandey et al. (2016)
	<i>Choanephora infundibulifera</i> and <i>Curvularia</i> sp.		Vindoline and catharanthine	The gene for the vacuolar class III peroxidase (PRX1), responsible for coupling vindoline and catharanthine, was upregulated in endophyte-inoculated plants These endophytes may enhance vindoline production by modulating the expression of key structural and regulatory genes of vindoline biosynthesis without affecting the primary metabolism of the host plant	Pandey et al. (2016)
2	<i>Trichoderma atroviride</i>	<i>Salvia miltiorrhiza</i>	Tanshinones	Polysaccharide fraction of <i>Trichoderma atroviride</i> stimulates many of the genes (<i>HMGCR</i> , <i>DXR</i> , <i>GGPPS</i> , <i>CPS</i> , and <i>KSL</i>) involved in the biosynthesis of tanshinones and then promotes the accumulation of tanshinones in <i>Salvia miltiorrhiza</i> hairy roots	Ming et al. (2013)
3	<i>Pseudonocardia</i> sp.	<i>Artemisia annua</i>	Artemisinin	Endophytes inoculation upregulate the cytochrome P450 oxidoreductase and monooxygenase genes involve in artemisinin biosynthesis, resulting enhance the production of artemisinin in <i>Artemisia annua</i>	Li et al. (2012)
4	<i>Staphylococcus sciuri</i> and <i>Micrococcus</i> sp.	<i>Catharanthus roseus</i>	Terpenoid indole alkaloids like vindoline, serpentine and ajmalicine	<i>Staphylococcus sciuri</i> and <i>Micrococcus</i> sp. significantly enhanced the Vindoline content by 38.36%, and 68.51%, respectively Significant increase in the content of serpentine (54.74%) and ajmalicine (46.34%) due to inoculation of <i>Micrococcus</i> sp.	Tiwari et al. (2013)

Table 2 (continued)

SLN	Endophytes	Host plant	Bioactive Compounds	Function of inoculated endophytes	References
5	<i>Burkholderia</i> sp.	<i>Panax ginseng</i>	Ginsenoside	Biotransformation of ginsenoside Rb1 to potent antitumor form ginsenoside Rg3 by endophytic bacterium <i>Burkholderia</i> sp. GE 17-7 isolated from <i>Panax ginseng</i>	Fu et al. (2017)
6	Endophytic bacterial community	<i>Putterlickia retropinosa</i> and <i>P. verrucosa</i> plants	Maytansine	Endophytic bacterial community harbored within the roots of <i>Putterlickia verrucosa</i> and <i>P. retropinosa</i> plants were responsible for the biosynthesis of the important anticancer and cytotoxic compound maytansine	Kusari et al. (2014)
7	<i>Azotobacter chroococcum</i> CL13	Turmeric	Phenolic compounds, sesquiterpenoids and curcuminoids	Inoculation of plant growth promoting strain <i>Azotobacter chroococcum</i> also boost up phenolic compounds and sesquiterpenoids and curcuminoids synthesis in host	Kumar et al. (2014)
8	<i>Stenotrophomonas maltophilia</i> (N5-18)	<i>Pappaver somniferum</i>	Morphine and total alkaloid	The content of morphine and total alkaloid increased significantly in <i>Pappaver somniferum</i> when <i>Stenotrophomonas maltophilia</i> (N5-18) was applied through foliar spray	Bonilla et al. (2014)
9	<i>Gilmaniella</i> sp. AL12	<i>Atractylodes lancea</i>	Volatile content	The endophyte, <i>Gilmaniella</i> sp. AL12, reported to increase the herb medicines quality of <i>Atractylodes lancea</i> as they interfere with the characteristic metabolites by altering the accumulation of volatile content in host	Wang et al. (2012)

observed in *Artemisia annua* induced by the endophyte *Pseudonocardia* sp.. These genes were responsible for biosynthesis of artemisinin, an antimalarial agent (Li et al. 2012). In another study, two endophytic bacteria, *Micrococcus* sp. and *Staphylococcus sciuri* have reported to boost the production of metabolites like serpentine, ajmalicine and vindoline, having therapeutic applications, in *Catharanthus roseus* (Tiwari et al. 2013). Similarly, many other major endophytic bacteria including *Azospirillum brasiliense*, *Bacillus subtilis*, *Pseudomonas fluorescens*, *Paenibacillus polymyxa*, etc. have been reported to enhance the production and accumulation of important secondary metabolites in the host (Del Giudice et al. 2008; Gao et al. 2015).

Additionally, the root endophytes have also been suggested to play an important role in transformation of plant metabolites to various other derivatives depending on the interaction. For example, root-associated bacteria was found in the essential oil producing parenchymatous cells of *Vetiver* plant where they metabolized the oil sesquiterpenes to other new compounds that were either absent or present in least amounts in raw oil (Del Giudice et al. 2008). Similarly, the vetiver plantlets inoculated *in-vitro* with root-associated bacteria produced oils with marked differences in composition as compared to the plantlets *in-vivo*. It was further reported that these group of bacteria significantly induced the plant terpene synthase gene expression (Del Giudice et al. 2008). Besides this the bacterial endophyte, *Burkholderia* sp., from ginseng roots transforms ginsenoside Rb1 to potent antitumor form Rg3 (Fu et al. 2017). Accordingly, it can be further suggested from these studies that the endophytic bacteria besides enhancing the amount of particular bioactive metabolites in their host, also executed the biotransformation of less active compounds to active by-products. Interestingly, it was observed that an important metabolite maytansine, an antitumor agent, is biologically synthesized by community of root endophytic bacteria in *Putterlickia retrospinosa* and *P. verrucosa* plants, which was initially presumed to be of plant origin (Kusari et al. 2014).

The research conducted to explore, analyse and understand the underlying mechanism of bacteria-mediated phytochemical alterations are expanding due to the development in next generation sequencing and advance mass spectroscopy technologies. Future

investigations on reprogramming of plant metabolome by beneficial microorganisms can henceforth be put beyond their roles as plant growth regulators or as plant protectants only. Keeping in view, their close association with the hosts than their free-living counterparts along with their promising applications, the endophytes are drawing notable attention in the present dynamics of research. It can now be established that the bioactive metabolites discovered in crude plant extracts can have various origin viz. plants, endophytes, or from synergistic effort of plant and endophytes, from endophyte mediated modification of plant metabolites and vice-versa (Etalo et al. 2018). Moreover, besides plant–microbe interaction, microbe-microbe interactions like bacterial endosymbionts in the fungal hyphae or endophyte-endophyte interactions adds to the complexity of plant metabolome, suggesting how the interplay of chemistry and genetics regulates the interactional outcomes.

Talking about the application part of endophytic bacteria, they are applied using various approaches based on the host plant growth stage and need. Among the many available methods, foliar spray and seed coating were proven more economical. There are several other endophytes that have been applied for plant growth promotions as microbial inoculants to boost up the bioactive compound synthesis in host. For example, *Azotobacter chroococcum* CL13 when applied to the turmeric rhizomes, saw an increase in the production of several phenolic compounds and sesquiterpenoids and curcuminoids (Kumar et al. 2014). This induction of secondary metabolites by the endophytes could be more efficient in medicinal and aromatic plants. In a related study, inoculation of two endophytic bacteria *P. aeruginosa* and *P. pseudoalcaligenes* in a medicinal plant *Hyptis suaveolens* increased the content of essential oils (Jha 2019). Similarly, the content of morphine and total alkaloid increased significantly in *Pappaver somniferum* when *Stenotrophomonas maltophilia* (N5-18) was applied through foliar spray, which ultimately lead to increased productivity (Bonilla et al. 2014). The endophyte, *Gilmaniella* sp. AL12, have been reported to increase the herb medicinal quality of *Atractylodes lancea* as they interfere with the characteristic metabolites by altering the accumulation of volatile content in host (Wang et al. 2012). Synthesis of these bioactive compounds in medicinal plants, as mentioned earlier, are a reflection of genetic and biochemical

alterations taking place between the endophyte and the host plant.

To date, most of the investigations involved an effect of single microbial strain on the plant metabolome. Future studies that debriefs the inter-relationships of microbiome composition and functions with dynamics of plant metabolome will greatly assist in understanding the ecological importance of microbe-derived alteration of the plant metabolome.

Plant growth promotion and endophytes

Endophytic bacteria colonise and multiply in the internal tissue of plants but do not cause disease symptoms in their hosts (Alori et al. 2017). Endophytes can promote the growth and development of medicinal plants through a variety of mechanisms (Fig. 2), including: (1) biological nitrogen fixation (BNF); (2) phosphate mobilization and solubilization; (3) siderophore production; (4) K and Zn solubilization; (5) phytohormone production; (6) production of volatile organic compounds (VOCs); (7) induction of systemic acquired resistance (SAR) and induced systemic resistance (ISR); (8) stimulating beneficial plant–microbe interaction; (9) interference with pathogen toxin production and (10) modulating the expression of stress-responsive genes in the plant biological system.

Endophytes play a significant role in plant growth promotion and biological control of plant pathogens in medicinal and aromatic plants, as shown in Tables 3 and 4. There is growing interest in using these beneficial endophytic microbes as biofertilizers and biopesticides under various abiotic and biotic stresses (Mohamad et al. 2018). The symbiotic association between endophytic microbes and plants helps each other in nutrient acquisition, water uptake and other nutrients supplements (Malfanova et al. 2011). Furthermore, many recent studies have begun to look into the importance of endophytic bacteria to medicinal plants, particularly those that grow in unusual or stressed environments (Egamberdieva et al. 2017b; Sharma et al. 2020; Vejan et al. 2016; Yan et al. 2019).

Biological nitrogen fixation

Nearly 78 percent of nitrogen is found in the atmosphere, but it is inactive, and plants cannot use it. The plant can only absorb nitrogen in its reduced form, such as ammonia or nitrate. Nitrogen is an essential primary nutrient for plants in agricultural production systems and one of the most important yield-limiting factors worldwide (Dojima and Craker 2016). Biological nitrogen fixing diazotrophs are alternative source of nitrogenous chemical fertilizers and protect

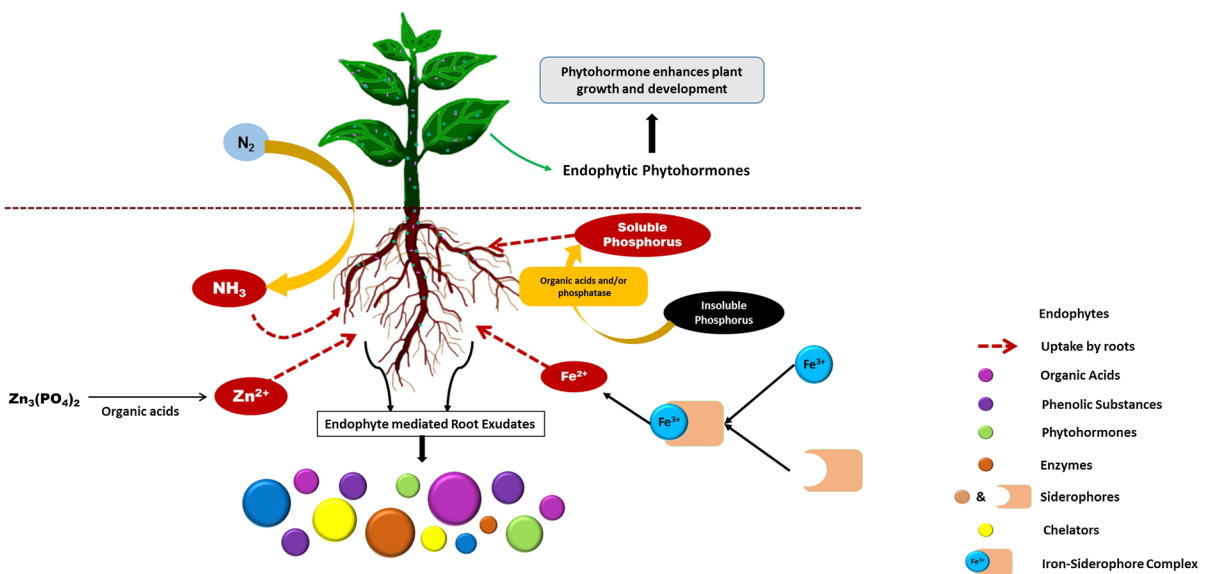


Fig. 2 Mechanisms employed by endophytes for plant growth and promotion

Table 3 Role of endophytes in plant growth promotion of medicinal and aromatic plants

S.N	Endophytes	Host plant	Plant growth promoting mechanisms	References
1	<i>Pseudomonas fluorescence</i> PICF7	Olive trees (<i>Olea europaea</i>)	Enhancement of plant growth (symptom delaying) and induced systemic resistance against wilt disease	Mercado-Blanco and Bakker (2007) and Schilirò et al. (2012)
2	<i>Serratia phymathica</i> HRO-C48	Oilseed rape (<i>Verticillium longisporum</i>)	Quorum sensing (signal interference)	Müller et al. (2015)
3	<i>Bacillus subtilis</i> Lu 144	Mulberry (<i>Morus alba</i> L.)	Bacterial wilt of mulberry	Ji et al. (2008)
4	<i>Bacillus sphaericus</i> , <i>Pseudoclavibacter helvolicus</i> , <i>Pantoeaananatis</i>	<i>Panax ginseng</i>	The antifungal activity against phytopathogenic microorganisms	Cho et al. (2007)
5	<i>Pseudomonas Thiruvallensis</i> , <i>Pseudomonas Fred-eriksbergensis</i> , <i>Pseudomonas brassicacearum</i> subsp. <i>neourantitaca</i>	<i>Salvia miltiorrhiza</i>	Showing the plant growth promoting traits	Vendan et al. (2010)
6	<i>Hoefleusaetaeae</i> sp.	<i>Suaeda maritima</i>	These strain inhibited mycelial growth of <i>Pythium litium</i> and <i>Phytophthora capsici</i>	Chung et al. (2013)
7	<i>Bacillus subtilis</i> , <i>Agrobacterium Tumefaciens</i> , <i>Pseudomonas putida</i>	<i>Cassia tora</i>	Showing plant growth promoting traits, antibacterial activity, antifungal activity, antibiotic sensitivity, and salinity tolerance	Kumar et al. (2015)
8	<i>Leclecteria</i> sp., <i>Pseudomonas</i> sp., <i>Stenotrophomonas</i> sp.	<i>Origanum vulgare</i>	These microbes are characterized for various metabolic, PGPR and other biotechnologically useful activities	Bafana et al. (2013)
9	<i>Bacillus pumilus</i>	<i>Chenopodium album</i>	Antifungal activities	Beiranvand et al. (2017)
10	<i>Planomicrobium</i> sp.	<i>Mentha pulegium</i>	Antifungal activities	Jasim et al. (2014)
11	<i>Bacillus aryabhattai</i>	<i>Allium schoenoprasum</i>	Antifungal activities	Beiranvand et al. (2017)
12	<i>Staphylococcus</i> sp.	<i>Achillea millefolium</i>	Antifungal activities	Beiranvand et al. (2017)
13	<i>Planomicrobium chinense</i>	<i>Lavandula angustifolia</i>	Antifungal activities	Beiranvand et al. (2017)
14	<i>Bacillus</i> sp., <i>Stenotrophomonas</i> sp.	<i>Zingiber officinale</i>	Produce IAA, ACC deaminase and siderophore	Jasim et al. (2014)
15	<i>Staphylococcus Epidermidis</i> , <i>Pectobacterium Carotovorum</i> , <i>Bacillus megaterium</i> , <i>Lysinibacillus sphaericus</i>	<i>Panax ginseng</i>	PGPR activities	Liu et al. (2016a, b)
16	<i>Stenotrophomonas Rhizophila</i> , <i>Brevibacterium frigoritolerans</i> , <i>Achromobacterspanius</i>	<i>Glycyrrhiza uralensis</i>	Important source of biofertilizers to promote enhanced survival and growth of licorice and other valuable crops in arid environments	Li et al. (2018a, b, c)
17	<i>Rhizobium</i> sp., <i>Acinetobacter</i> sp., <i>Achromobacter</i> sp., <i>Pseudonocardia</i> sp.	<i>Ferula songorica</i>	They contain growth promoting factors and biologically active compounds including enzymes	Liu et al. (2016a, b)
18	<i>Streptomyces dioscori</i> sp. nov	<i>Dioscorea bulbifera</i> L	Antimicrobial activities	Wang et al. (2018)
19	<i>Bacillus amyloliquefaciens</i> subsp. <i>plantarum</i>	<i>Panax notoginseng</i>	They have antagonistic activity against <i>Fusarium oxysporum</i> , <i>Ralstonia</i> sp. and <i>Meloidogyne hapla</i>	Ma et al. (2013)

Table 3 (continued)

S.N	Endophytes	Host plant	Plant growth promoting mechanisms	References
20	<i>Micrococcus dloeverae</i> , <i>Actinobacteria</i>	<i>Aloe vera</i>	Plant growth promoting activities	Beiranvand et al. (2017), Ma et al. (2013), Prakash et al. (2014)
21	<i>Sphingobium endophyticu</i>	<i>Hylomecon japonica</i>	Plant growth promoting activities	Zhu et al. (2015)
22	<i>Paenibacillus Dendritiformis</i> , <i>Bacillus firmus</i>	<i>Piper nigrum</i>	Produce IAA, ACC deaminase and siderophore	Jasim et al. (2014)
23	<i>Dierzia cercidiphylli</i>	<i>Alcea aucheri</i>	Antimicrobial activities	Beiranvand et al. (2017)
24	<i>Rahmella aquatilis</i> , <i>Rhodanobacter terrae</i>	<i>Ipomoea batatas</i>	IAA producer	Khan and Doty (2009)
25	<i>Pestalotiopsis</i> sp. FT172	<i>Myrsine sandwicensis</i> A	Production of anti-proliferative, Polyketide	Li et al. (2018a, b, c)

the agricultural ecosystem from hazardous effects of chemiclas (Mulongoy et al. 1991).

The endophytic bacteria are ubiquitously associated with medicinal plant species and they have unique functions. Only a few studies on medicinal plants have been conducted to explore the potential of endophytes. However, recently, some studies reported that the medicinal plant *Ferula songorica* has been associated with huge numbers of endophytic bacteria and among them about 88% of the strains related to the BNF (Liu et al. 2017). The medicinal plant *Glycyrrhiza uralensis* F. has been shown to be capable of nitrogen fixation by the majority of endophytic bacterial isolates (76%) (Li et al. 2018a, b, c). Some endophytic diazotrophs, such as *Azospirillum* and *Azotobacter* have the advantage of colonising the interior plant tissue rather than the plant's surface, enabling them to better utilise the carbon source supplied by the plant (Aloo et al. 2020). Besides, endophytic diazotrophs efficiently work in the absence or low amount of oxygen in the internal biological system (stem nodes and xylem vessels) of the plant because the BNF gene- nitrogenase is sensitive to oxygen (Yan et al. 2019).

Solubilization of phosphorus

Phosphorus (P) is an essential element for plant growth and development. Phosphorus is found in soil in a huge amount but mostly inaccessible to plants because soluble phosphorus easily precipitates with calcium in alkaline soils and with iron and aluminium in acidic soils. Plants uptake less than 1% of the total phosphorus in the form of orthophosphate anions (mainly as HPO_4^{2-} and H_2PO_4^-) (Achal et al. 2007; Zhu et al. 2011). Therefore, it is necessary to provide an unavailable form of P to the plant by using different mechanisms. The most feasible approach is to use microbes to solubilize these insolubilized P compounds. The microbes can solubilize phosphorus by secreting phosphatases enzymes or releasing organic acids and protons (Sharma et al. 2020). Plant growth and development are enhanced by the increased availability of phosphorus (Gouda et al. 2016).

The *Bacillus* and *Pseudomonas* are the most efficient phosphate-solubilizing microorganisms (El-Deeb et al. 2013). Li et al (2018a, b, c) reported that endophytic bacterial genera such as *Bacillus* and *Microbacterium* isolated from medicinal plant

Table 4 Role of endophytes in biological control of plant pathogens in relation to medicinal and aromatic plants

S.N	Endophytes	Host plant	Targeted plant pathogen	Mechanisms to control plant pathogens	References
1	<i>Bacillus amyloliquefaciens</i> , <i>Pseudomonas fluorescens</i> <i>Aspergillus terreus</i> , <i>Penicillium oxalicum</i> , <i>Sarocladium kiliense</i>	<i>Withania somnifera</i>	<i>Alternaria alternata</i> , <i>Sclerotium rolfsii</i>	Withanolide modulation	Mishra et al. (2018)
2	<i>Pseudomonas</i> sp. and <i>Burkholderia</i> sp.	<i>Echinacea purpurea</i> and <i>Lonicera japonica</i>	<i>Fusarium</i> sp., <i>Rhizoctonia</i> sp., <i>Pythium</i> sp. and <i>Alternaria</i> sp.	Non ribosomal peptides, polyketides	Kushwaha et al. (2019)
3	<i>Bacillus subtilis</i>	<i>Ocimum sanctum</i>	<i>Alternaria solani</i>	Improving plant growth and resistance ability	Gupta et al. (2016)
4	<i>Bacillus</i> sp.	<i>Ocimum tenuiflorum</i>	<i>Rhizoctonia solani</i> , <i>Sclerotium rolfsii</i> , <i>Alternaria alternata</i> , <i>Microphomina phaseolina</i> , and <i>Bipolaris sorokiniana</i>	Antimicrobials and VOCs	Tiwari et al. (2010)
5	<i>Chaetomium globosum</i> , <i>Trichoderma harzianum</i>	<i>Aloe vera</i>	<i>Sclerotinia sclerotiorum</i>	Antifungal fatty acids	Song et al. (2014)
6	<i>Brevibacillus</i> <i>Burkholderia stabilis</i>	<i>Panax ginseng</i>	<i>Cylindrocarpon destructans</i> , <i>Pythium</i> sp.	Ethyl paraben, chitinases Pyrrolnitrin	Chowdhary and Sharma (2020)
7	<i>Alternaria alternata</i> and <i>Neocosmospora</i> sp.	<i>Euphorbia larica</i>	<i>Fusarium</i> sp.	Fatty acids, fatty acid methyl esters, hydrocarbons and alkanes	Silva et al. (2020) Kim et al. (2020)
8	<i>Bacillus subtilis</i> and <i>Bacillus amyloliquefaciens</i>	<i>Duranta plumieri</i> , <i>Ocimum gratissimum</i> , <i>Terminalia abohera</i> , <i>Manihot esculenta</i>	<i>Sclerotinia sclerotiorum</i>	Morphological alterations in hyphae and reduction of mycelial dry weight	Al-Rashdi et al. (2020)
9	<i>Streptomyces</i> , <i>Brevibacterium</i> , <i>Microbacterium</i> , and <i>Leifsonia</i>	<i>Mirabilis jalapa</i> and <i>Clerodendrum Colebrookianum</i>	<i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , <i>Escherichia coli</i> , and <i>Candida albicans</i>	Antibiotic production	Rahman et al. (2018)
10	<i>Bacillus atrophaeus</i> and <i>Bacillus mojavensis</i>	<i>Glycyrrhiza uralensis</i>	<i>Alternaria solani</i> , <i>Colletotrichum gloeosporioides</i> , <i>Verticillium dahliae</i> , <i>Fusarium oxysporum</i> f. sp., <i>Fulviafulva</i> , <i>Pestalotiopsis microspora</i> , <i>Fusarium oxysporum</i> f. sp. vasinfectum, <i>Fusarium graminearum</i> and <i>Ceratocystis fimbriata</i>	Non ribosomal peptides, polyketides, lytic enzymes	Passari et al. (2015) Mohamad et al. (2018)

Table 4 (continued)

S.N	Endophytes	Host plant	Targeted plant pathogen	Mechanisms to control plant pathogens	References
11	<i>Arthrobacter</i> , <i>Achromobacter</i> , <i>Bacillus</i> , <i>Enterobacter</i> , <i>Erwinia</i> , <i>Pseudomonas</i> , <i>Pantoea</i> , <i>Serratia</i> , and <i>Stenotrophomonas</i>	<i>Hypericum perforatum</i> and <i>Ziziphora capitata</i>	<i>Fusarium oxysporum</i>	HCN and Cell wall degrading enzymes	Egamberdieva et al. (2017a)
12	<i>Bacillus</i> , <i>Serratia</i> and <i>Enterobacter</i>	24 different Medicinal plant species from Western Ghats, India	<i>Pectobacterium carotovorum</i>	Bioactive secondary metabolites (NRP5, lantipeptide, bacteriocins)	Webster et al. (2020)
13	<i>Bacillus</i> and <i>Enterobacter</i> species	<i>Thymus vulgaris</i>	<i>F. oxysporum</i>	Bioactive metabolites (benzene, 1,3-dimethyl-, p-xylene, dibutyl phthalate, bis (2-ethylhexyl) phthalate, and tetracosane)	Mohamad et al. (2020)
14	<i>Streptomyces</i>	<i>Thymus roseus</i>	<i>Alternaria solani</i> , <i>Valsamalicola</i> , and <i>Valsamali</i>	Non ribosomal peptides, polyketides	Musa et al. (2009)
15	<i>Trichoderma citrinoviride</i>	<i>Panax ginseng</i>	<i>Botrytis cinerea</i> and <i>Cylindrocarpon destructans</i>	high endo-1,4-b-D-glucanase activity, ginsenoside	Park et al. (2019)
16	<i>Alternaria</i> sp.	<i>Nothapodytes nimmoniana</i>	<i>Sclerotium rolfii</i>	mycotoxin (tenazonic acid)	Rajani et al. 2019
17	<i>Streptomyces</i> , <i>Bacillus</i> , <i>Pseudomonas</i> , <i>Microbacterium</i> , <i>Stenotrophomonas</i> , <i>Lysinibacillus</i> , <i>Ochrobactrum</i> , <i>Rhizobium</i> , <i>Brevibacterium</i> , <i>Achromobacter</i>	13 medicinal plants, Beijing Botanical garden China	<i>Dothiorella gregaria</i> , <i>Sclerotinia sclerotiorum</i> and <i>Botryosphaeria dothidea</i>	Polyketides, polyene, chitinases, siderophores	Liu et al. (2010a, b)
18	<i>Pseudomonas</i> sp.	<i>Leptospermum scoparium</i>	<i>Pseudomonas syringae</i> pv. <i>Actinidiae</i>	phenazine, 2,4-DAPG, and hydrogen cyanide	Wicaksono et al. (2018)

Glycyrrhiza uralensis were able to phosphate solubilization. Additionally, the medicinal plant *Ferula sinkiangensis* had almost 19% of the endophytic bacteria related to phosphate solubilization (Liu et al. 2017). Moreover, many researchers reported that medicinal plants like *Vitis vinifera*, *Capsicum annuum*, *Trigonella foenum*, *Trigonella foenum-graecum* and *Lactuca sativa* were associated with endophytic microbes which can solubilize phosphate for the growth and development of medicinal plants (Li et al. 2018a, b, c; Radhakrishnan et al. 2017).

Enhancement of uptake and translocation of micronutrients

Micronutrients play a crucial role in plant metabolism, photosynthesis, respiration and biosynthetic reactions. These are also important constituents of cytochromes, ribosomes and co-factors of different enzymes such as catalase, peroxidase, DNA polymerase and RNAPolymerase (Kerkeb and Connolly 2006; Mahender et al. 2019; Rout and Sahoo 2015). Micronutrient use efficiency is only 2–5% (Tian et al. 2008). Rhizospheric or endophytic microorganisms have a significant contribution to the enhancement of uptake and translocation of micronutrients through different mechanisms (Singh et al. 2018; Singh et al. 2017a; Singh et al. 2017b; Singh and Prasanna, 2020) such as: (1) siderophore production; (2) organic acid secretion in root exudates; (3) secretion of phytase enzyme; (4) secretion of metal chelating substances; (5) upregulation of micronutrient transporter or genes; (6) modification of root morphology and anatomy.

Siderophores are iron-binding chelating compounds that are produced by endophytic or rhizospheric microbes to improve plant growth and development by providing iron to plants and by inhibiting the growth of plant pathogenic microorganisms in the root zone or plant biological system (Mohamad et al. 2020; Niessen and Soppa, 2020). Siderophores convert insoluble ferric ions or $\text{Fe}(\text{OH})_3$ into the soluble ferric complex compound that can be uptake by plants (Solanki et al. 2014). Li et al. (2018a, b, c) found that around 23 and 57% of the endophytes related to the medicinal plant's *Glycyrrhiza uralensis* Fisch. and *Ferula sinkiangensis* secreted siderophores, respectively, and these microbes belongs to different group of microbe genera such as *Bacillus*,

Achromobacter, and *Janibacter*. The endophytic bacteria associated with medicinal plants such as *Capsicum annuum*, *Launaea nudicaulis*, *Jatropha curcas*, *Arachis Hypogaea*, *Brassica oxryrhina*, and *Brassica napus* were showed siderophore production ability (Egamberdieva and Tiezzi 2019; Ma et al. 2010; Mohamad et al. 2019; Radhakrishnan and Lee 2016). Besides iron, endophytes also enhance Zn availability to plants through organic acids secretion in root exudates (Singh et al. 2017b). The most effective Zn solubilizing Gram-positive microscopic organisms have to belong to the genus *Bacillus*. Furthermore, it has been reported that *Bacillus amyloliquefasciens*, *Bacillus megaterium*, and *Bacillus* sp., show phosphorus, potassium, and zinc solubilization (Verma et al. 2015).

Production of phytohormones

Phytohormones are signal molecules that coordinate cellular activities and management of medicinal plant growth, development and vigor. The best-known example of phytohormones that are produced by endophytic microbiota is indole-3-acetic acid (IAA), which is synthesised via the indole-3-pyruvate pathway. Like rhizospheric microbes, endophytic microbes have been shown to have plant growth promoting activities that can be due to the production of phytohormones and enzymes involved in growth regulation, such as ethylene, 1-aminocyclopropane-1-carboxylic acid (ACC) deaminase, 2,3-butanediol, cytokinins, auxins, indole-3-acetic acid (IAA), acetoin, or combinations of these plant growth hormones (Asaf et al. 2017; Egamberdieva et al. 2017c; Li et al. 2018a, b, c). Indole-3-acetic acid (IAA) is the phytohormone responsible for stimulating cell division, cell elongation, differentiation, and gene regulation to promote plant growth and development (Sharma et al. 2020). Recently, many IAA producing endophytic bacteria (*Arthrobacter* sp., *Enterobacter* sp., *Pantoea* sp., *Bacillus* sp., *Brevibacterium* sp., *Achromobacter* sp., and *Stenotrophomonas* sp.) have been reported to be associated with the medicinal plants *Hypericum perforatum*, *Ferula sinkiangensis*, *Ziziphora capitata* *Ajuga bracteosa* (Egamberdieva et al. 2017b; Li et al. 2018a, b, c; Liu et al. 2017; Naragani et al. 2016). The endophytic fungus *Fusarium* sp. impacts on the growth and development of *Euphorbia pekinensis* (E5 and E4) by producing IAA and GA (Dai et al. 2003).

The fungi *Fusarium* sp. DL26 and *Pyrenochaeta* sp. DL351 could improve the growth and development of the orchid *Dendrobium loddigesii* Rolfe by root elongation by secreting IAA and NH_3 . (Chen et al. 2010).

El-Deeb et al. (2013) reported that *Plectranthus tenuiflorus* medicinal plant was inhabited by *Bacillus* sp., *Bacillus megaterium*, *Bacillus pumilus*, *Bacillus licheniformis*, *Micrococcus luteus*, *Paenibacillus* sp., *Pseudomonas* sp., and *Acinetobacter calcoaceticus* endophytes. These endophytic isolates effectively produce gibberellic acid (GA) and cytokinin. GA has biologically important functions such as plant growth-promoting factors, i.e., stem and root elongation, flowering, and/or helping to overcome dormancy in seeds. Cytokinins are a category of plant hormones that play an important role during the cell cycle, i.e., induce the plant cellular division process and, consequently, influence the formation and relative growth of roots and shoots (Arkhipova et al. 2007). Abscisic acid (ABA), which is considered a plant stress hormone, is responsible for many types of stress, including water, salt, and low temperatures (Fahad et al. 2015). Salicylic acid (SA) is also known as a critical phytohormone that is involved in various processes, like seed germination, root initiation, floral induction, and thermogenesis, besides plant tolerance to biotic and abiotic stresses (Yan et al. 2019; Fahad et al. 2015).

Resistance toward abiotic stresses

Plants are exposed to a number of factors which are detrimental to their growth, productivity, and survival in the environment, known as stress. It can be both biotic and abiotic in nature. Abiotic stresses include salinity, pH, temperature fluctuations, excess or low water, irradiance, nutrient deficiency or excess, and even mechanical injury and wounding. Whereas, biotic stress can include various pathogens (bacteria, fungi, and viruses) and herbivores. Endophytic bacteria often produce various compounds that can alleviate these stresses and confer protection to the plant. According to various reports, plants on inoculation with these endophytes often accumulate compounds mainly, carbohydrates, proline, various lytic enzymes, and antibiotics that can inhibit various pathogens (Brader et al. 2014). Moreover, it causes the plant to develop resistance against pathogens

by complementing the induced systemic resistance mechanisms (Pieterse et al. 2014).

Endophytes are known to provide various plant-growth promoting nutrients as well as assist in coping with various environmental stresses, which ultimately improves plants yield and productivity. It is therefore of great concern in having knowledge about endophytes, their role in promoting plant growth and their biocontrol, defence and resistance to disease and environment. *Acremonium strictum* AL16 an endophytic fungus in association with a Chinese medicinal herb, *Atractylodes lancea* improved the plant growth traits and also alleviated drought conditions by increasing soluble sugars, proteins, proline and antioxidant enzyme activity. It also increased the abscisic acid levels in the host as well as decreased the degree of plasmalemma oxidation, thereby conferring protection to the host plant (Yang et al. 2014).

Unfavourable environmental conditions, viz. temperature extremes, heavy metal toxicity, salinity, drought, and floods can negatively impact plant growth, development and yield (Farooq et al. 2009; Wang et al. 2003; Zhu 2002). Endophytes can help medicinal plants in alleviating these stresses and promoting their growth (Nadeem et al. 2014; Shahzad et al. 2015) For instance, *Pseudomonas fluorescens* when inoculated in Madagascar periwinkle (*Catharanthus roseus*) improved its growth attributes as compared to control uninoculated plants under water deficit stress conditions (Jaleel et al. 2007). Furthermore, *Pseudomonas fluorescens* along with *Piriformospora indica* in a dual inoculation improved the transplanting shock in musli (*Chlorophytum* sp.) (Gosal et al. 2010). Also, when an autochthonous isolate was tested along with native mycorrhizal fungi (alone and in consortium), plant growth was stimulated along with improved nutrient and drought tolerance responses (Armada et al. 2016).

Gagné-Bourque et al. (2016) reported the increase of total soluble carbohydrates along with glucose, fructose and starch in drought induced *Brachypodium distachyon* grass associated with *Bacillus subtilis* strain B26. However, well-known stress related metabolites (raffinose-related carbohydrate) were not proliferated. Pepper plants (*Capsicum annum* L.) in association with *Bacillus* and *Arthrobacter* endophytes showed significant proline accumulation in relation to osmotic stress responses (Sziderics et al. 2007). Moreover, endophytes associated with plants

can also modulate enzymatic activity causing mitigation of abiotic stress. Damodaran et al. (Damodaran et al. 2014) reported an increase in defence enzymes like Phenylalanine lyase, peroxidase, catalase and superoxide dismutase on inoculation with endophytes like *Bacillus subtilis*, *Bacillus cereus*, *Bacillus thuringiensis*, *Bacillus saffensis*, *Bacillus pumilus*, and *Bacillus marisflavi* in response to high sodium concentrations in gladiolus plants. Association with endophytes have also resulted in plant growth promotion as well as tolerance to low temperature. *Bacillus* and other derived genus have been associated with *Triticum aestivum* cultivated in northern hills zone of India, showing its temperature flexibility (Verma et al. 2015).

Resistance toward biotic stresses (biological control of plant pathogens)

Interest in worldwide food production is expanding so as to take care of the teeming millions. However, plant diseases are turning into an obstacle as to how to accomplish these objectives. Symptoms of different plant diseases can range from rusts, blights, scabs, cankers, spots, mildews, wilts and many more as they affect the quality and quantity of the produce. A number of approaches can be followed to control the disease progression, mainly cultural, chemical and biological. Cultural practices are time consuming and does not guarantee complete protection whereas chemical control strategies are not environmentally friendly and cause resistance in pathogens. Biological control, which involves the use of microorganisms to inhibit or reduce disease incidences, provides a practical solution to the problem (Maloy, 1993) (Table 4).

Endophytes show biocontrol activities in two ways- direct or indirect. Direct biocontrol is shown by the endophyte either through production of antagonist metabolites like lytic enzymes (Strobel 2003), antibiotics (Berg and Hallmann 2006), siderophores, and insecticidal compounds (Azevedo et al. 2000; Hallmann et al. 1998) or by competing with pathogen for space and nutrients. Indirect biocontrol is shown by priming the plant defence mechanism through callose deposition, hydrolysing enzymes production or activating the plant defense proteins (PRPs) in a process known as induced systemic resistance (Kloepper and Ryu 2006). Furthermore, endophytes can trigger plant growth through plant growth promotion (PGP)

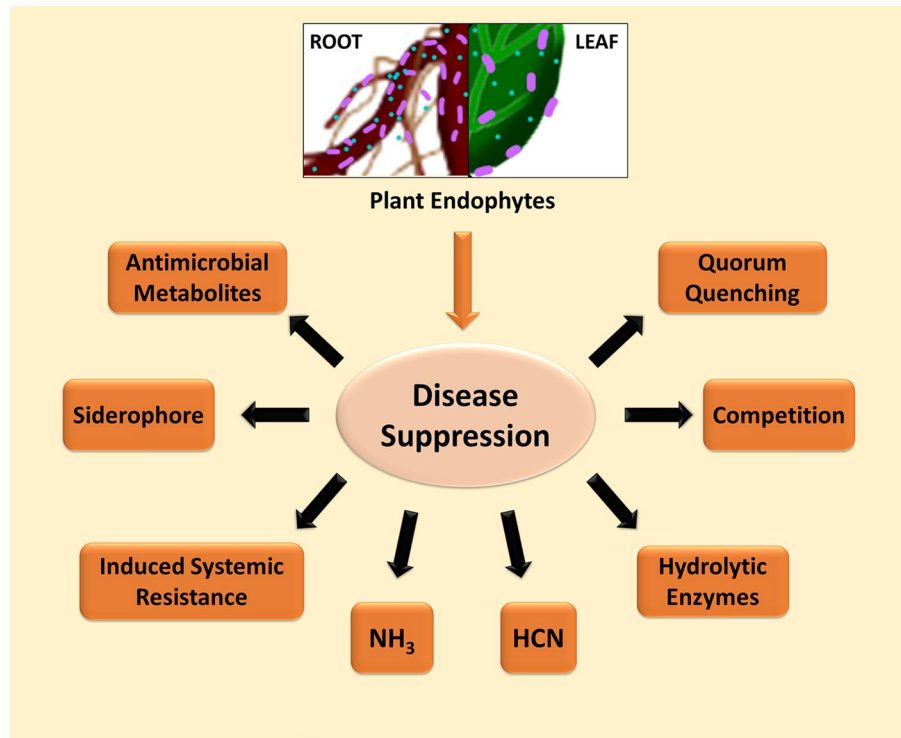
activities and can outcompete cell death caused by pathogen (Berg and Hallmann 2006). Moreover, endophytes associated with medicinal plants have received special interest as they are the producers of important bioactive secondary metabolites. As such plant microbe interaction involving endophytes and medicinal plants have been extensively reviewed (Sekar and Kandavel 2010; Singh 2013). Figure 3 show the mechanisms employed by endophytes for biological control of plant pathogens.

The use of microbial endophytes as biocontrol agents against several phytopathogenic fungi have been advocated by a number of researchers (Egamberdieva et al. 2017b; Erdogan and Benlioglu 2010; Lacava et al. 2007). They have been used on a number of crops like *Nicotiana attenuata* (Santhanam et al. 2014), *Solanum torvum* and *Solanum melongena* (Achari and Ramesh 2014), *Solanum trilobatum* (Bhuvaneswari et al. 2013) and have shown biological control due to a number of bioactive metabolites. Egamberdieva et al. (2017a) reported antagonistic activity against the phytopathogens *Alternaria alternata*, *Pythium ultimum*, *Fusarium oxysporum*, *Fusarium culmorum*, *Fusarium solani*, *Botrytis cinerea*, *Gaeumannomyces graminis* because of the endophytes *Bacillus*, *Pseudomonas*, *Arthrobacter*, *Stenotrophomonas* and *Serratia*, isolated from medicinal plants *Ziziphora capitata* and *Hypericum perforatum*.

Endophytic microorganisms from medicinal plants also demonstrated antimicrobial activity against human pathogens in addition to phytopathogens. In an investigation by Passari et al. (2015) almost half of the endophytes isolated showed antagonistic activity against at least two out of the four pathogens tested, namely: *Candida albicans*, *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Further, El-Deeb et al. (2013) isolated endophytic microbes from different parts of the medicinal plant *Plectranthus tenuiflorus* which demonstrated antimicrobial activity against at least one out of the six human pathogens like *Klebsiella pneumonia*, *Proteus mirabilis*, *Escherichia coli*, *Streptococcus agalactiae*, *Staphylococcus aureus* and *Candida albicans*.

Mohamad et al. (2018) isolated 114 endophytes from *Glycyrrhiza uralensis*, wild ethnomedicinal plant in Xinjiang desert, and estimated their antifungal activity against different phytopathogens namely *Alternaria solani*, *Colletotrichum gloeosporioides*, *Verticillium dahliae*, *Fusarium oxysporum* f. sp.,

Fig. 3 Mechanisms employed by endophytes for biological control of plant pathogens



Fulvia fulva, *Pestalotiopsis microspora*, *Fusarium oxysporum* f. sp. *vasinfectum*, *Fusarium graminearum* and *Ceratocystis fimbriata*. The results indicated that endophytes belonged to various genera including *Bacillus atrophaeus*, *Bacillus mojavensis*, *Bacillus halotolerans*, *Brevibacterium frigoritolerans*, and *Nocardioides alkalitolerans*. They also inhibited various human pathogens like *Bacillus cereus*, *Salmonella enteritidis*, *Staphylococcus aureus*, and *Escherichia coli*. Endophytic isolates exhibiting antagonism against a variety of fungal phytopathogens in vitro also had the ability to suppress *Fusarium oxysporum* f. sp. *radicis-lycopersici* in vivo (Egamberdieva et al. 2017b). Moreover endophytic fungi were also influenced by insect's attack, so they also produced bioactive insecticidal compounds.

Production of antimicrobial metabolites

Pathogens in nature have acquired resistance to commonly used synthetic chemicals; therefore, the search for alternate antimicrobial compounds is the need of the hour. Endophytes offer these eco-friendly metabolites, mainly amides and amines, which are not only natural but also nontoxic to mammals. These

antimicrobial agents are perhaps secondary metabolites produced by the endophytes. It includes polyketides, which are amino acid derived compounds or terpenes and low molecular weight compounds with varied structures (Keller et al. 2005). Synthesis of these polyketides is carried out by large multimodular complexes known as polyketide synthases (PKS) and they are basically carboxylic acids derived via condensation of acetyl coenzyme A (acetyl CoA) and malonyl CoA forming carbon chains of β -ketone groups (Keller et al. 2005).

Pseudomonas fluorescens Q2-87 an endophytic bacteria whose PKSs synthesise 2,4-diacetylphloroglucinol and has been antagonistic to a number of phytopathogens (Alvin et al. 2014), whereas PKS from *Aspergillus nidulans* produces the cholesterol lowering compound, lovastatin (Keller et al. 2005). Moreover, along with PKSs, endophytes also synthesize non-ribosomal peptides produced in non-ribosomal peptide synthetases (NRPS), which aids in the condensation of non-proteinogenic and proteinogenic amino acids. Penicillin and cephalosporin, β -lactam antibiotics, are produced by the first identified fungal NRPS (Keller et al. 2005).

Many investigators reported various NRPs namely spoxazomicins, siderophores, and serobactin produced from endophytic microbes of orchids and grasses namely, *Streptosporangium oxazolinicum*, *Pseudomonas aeruginosa*, and *Herbaspirillum seropedicae* respectively (Inahashi et al. 2011; Miller et al. 2012; Rosconi et al. 2013). Moreover, the presence of genes related to NRPS or PKS should be a primary step in characterization of endophytes producing bioactive metabolites as they contain conserved regions critical for their functioning (Miller et al. 2012). The β -ketoacyl synthase (KS) domain of PKS and adenylation (A) domain of NRPS are conserved, which promotes condensation of acetyl CoA and malonyl CoA and which identifies growing peptide chain respectively (Keller et al. 2005).

Chowdhary and Sharma (2020) reported that endophytic fungi (*Chaetomium globosum* and *Trichoderma harzanium*) of *Aloe vera* showed antagonistic activity against *Sclerotinia sclerotiorum* by the production of various antifungal compounds like hexadecanoic acid, 2, 3-bis[(trimethylsilyl) oxy] propyl ester and other unsaturated fatty acids (palmitic and linoleic acid). A variety of other metabolites like fatty acids, fatty acid methyl ester, alkanes and hydrocarbons have also been reported to suppress fungal pathogens like *Fusarium* (Al-Rashdi et al. 2020). Morphological changes have been elicited because of these metabolites like loss of turgidity, disintegration and shrinkage of hyphae in the fungal pathogen. *Bacillus* and *Streptomyces* species constitutes the most diverse and cosmopolitan gram positive bacterial endophytes present, producing secondary metabolites having antimicrobial property against phytopathogens (Reinhold-Hurek and Hurek, 2011; Frank et al. 2017).

Streptomyces sp. is source of a number of antibiotics, hence is known for its antagonistic activity against different phytopathogens. *Streptomyces* sp. strain NRRL 30,562 associated with *Kennedia nigricans* was reported to be antagonistic against various plant pathogenic bacteria and fungi due to the presence of antibiotics, namely munumbicins A, B, C, and D (Castillo et al. 2006). Also *Streptomyces caeruleatus* endophyte in leguminous plants was effective against *Xanthomonas campestris* pv glycine (Mingma et al. 2014). Moreover, endophytic actinobacteria from *Azadirachta indica* and *Nothofagus* sp. have been evaluated for their antimicrobial activities against various phytopathogenic fungi

such as- *Sclerotinia sclerotiorum*, *Mycosphaerella fijiensis*, *Pythium*, *Phytophthora* sp. and *Rhizoctonia solani* (Castillo et al. 2007; Verma et al. 2009). *Streptomyces seoulensis* characterized from two different plant species in southern Patagonia by Castillo et al. (2007) suggested the plants survival strategy against phytopathogens in that particular area due to production of metabolites. Matsumoto and Takahashi (2017) reported the antagonistic activity of endophytic actinobacteria against *Xanthomonas campestris* pv. *Oryzae* strain KB-88, *Kocuria rhizophila* strain KB-212, and *Mucor racemosus* strain KF-223.

The genus *Bacillus* has been reported in several instances to have antimicrobial activity. More often, they have been proposed for crop management (Aloo et al. 2018). Gond et al. (2015) described lipopeptides producing *Bacillus subtilis* and *Bacillus amyloliquefaciens* as endophytes in maize seeds and inhibiting *Fusarium moniliforme*. Similarly, *Bacillus amyloliquefaciens* endophytic in *Bruguiera gymnorhiza* (L.) showed antagonism against a variety of fungal and bacterial pathogens particularly *Capsicum* wilt in pots as well as field trials (Hu et al. 2010). Moreover, *Bacillus cereus* and *Bacillus mojavensis* endophytes in rice exhibited antagonism against a variety of fungal pathogens in rice, namely, *Magnaporthe grisea*, *Magnaporthe salvinii*, *Fusarium verticillioides*, *Fusarium fujikuroi*, and *Fusarium proliferum* (Etesami and Alikhani, 2017).

Endophytes isolated from radish mainly *Brachybacterium*, *Paenibacillus* and *Bacillus subtilis* possessed antifungal activity against *Rhizoctonia solani*, *Pythium ultimum*, *Fusarium oxysporum* and *Phytophthora capsici* (Seo et al. 2010). Furthermore, *B. subtilis* strain EDR4 endophyte in wheat reported an antifungal protein which inhibited growth of *Fusarium graminearum*, *Gaeumannomyces graminis* var *tritici* *Bacillus cinerea*, *Fusarium oxysporum* f.sp. *vasinfectum*, *Rhizoctonia cerealis*, and *Macrophoma kuwatsukai* (Liu et al. 2010a, b).

Egamberdieva et al. (2017a) reported endophytic bacteria of various genera, namely, *Bacillus*, *Arthrobacter*, *Stenotrophomonas*, *Erwinia*, *Serratia*, *Achromobacter*, *Pseudomonas*, *Enterobacter*, and *Pantoea* from *Ziziphora capitata* and *Hypericum perforatum*. Latter supported the growth of various bacteria having antagonistic activity against *F. oxysporum* than the former. On the contrary, *Fusarium oxysporum* as an endophyte can produce antagonistic compounds

against nematode such as gibberpyrone D, 4-hydroxybenzoic acid and indole-3-acetic acid (IAA) (Bogner et al. 2017).

Another significant class of antimicrobial secondary metabolites are the lipopeptides, which are known for their antimicrobial activity as well as activator of plant defence machinery (Stein, 2005; Raaijmakers et al. 2010). There are several isoforms of lipopeptides which can be produced by the same bacterial species. The most investigated ones are related to *Bacillus* and *Paenibacillus* lipopeptides (Villarreal-Delgado et al. 2018). Moreover, many *Bacillus amyloliquefaciens* strains are known to produce higher lipopeptides (Ongena and Jacques, 2008).

Production of hydrolytic enzymes

The antagonistic activity of endophytes against various pathogens can also be due to their ability to produce a number of lytic enzymes. These enzymes can degrade the cell wall polymer complexes of different pathogens and make it susceptible to lysis. Lipases and chitinases are enzymes which degrade the chitinous cell wall of fungus making it a potent biocontrol agent against phytopathogens (Suresh et al. 2010; Wahyudi et al. 2011). *Pseudomonas* sp. endophytically associated with a number of medicinal plants like *Coleus forskohlii*, *Launaea nudicaulis*, and *Cupressus sempervirens* produced chitinolytic enzymes and exhibited control against phytopathogens, namely, *Fusarium chlamydosporum*, *Fusarium solani*, *Fusarium oxysporum*, *Seiridium cardinal*, *Ralstonia solanacearum*, and *Macrophomina phaseolina* (Mansoor et al. 2007; Raio et al. 2011; Singh et al. 2013). Furthermore, *Bacillus* sp. as endophyte in association with some medicinal plants like *Glycyrrhiza uralensi*, *Panax quinquefolius*, and *Arachis hypogaea* controlled plant diseases because of their ability to produce chitinolytic enzymes (Mohamad et al. 2018; Nautiyal et al. 2013; Song et al. 2014). Sahu et al. (2020) reported different strains of Bacilli isolated from *Ocimum tenuiflorum* showing antagonism against sheath blight of rice by inducing defense enzymes mainly phenyl ammonia lyase, peroxidase, and polyphenol oxidase. In similar study endophytes in association with *Ziziphora capitata*, a medicinal plant, also produced chitinolytic enzymes (Egamberdieva et al. 2017a). Moreover, different lytic enzymes like cellulases, lipases and proteases were produced

by endophytes associated with plants like *Ferula sinkiangensis*, *Ferula songorica*, *Glycyrrhiza uralensis*, and *Hypericum perforatum* (Egamberdieva et al. 2017a; Li et al. 2018a, b, c; Liu et al. 2017; Liu et al. 2016a, b).

Disrupting quorum sensing signals in pathogens

Pathogens communicate with each other via signalling molecules such as N-acyl homoserine lactones (AHLs), often called as quorum sensing (Waters and Bassler 2005). This cell to cell communication is responsible for regulating the expression of various virulence factors contributing in the pathogenicity (Fuqua et al. 2001). Endophytes can degrade these QS signals, called as Quorum quenching, which can ultimately reduce the virulence of the pathogen (Helman and Chemin, 2015). For example, many *Bacillus* species can produce AHL lactonases which can degrade these signalling molecules, thereby diminishing the virulence (Zhou et al. 2008). Rajesh and Rai (2014) investigated the potential of endophytic *Bacillus firmus* and *Enterobacter asburiae* associated with *Pterocarpus santalinus* in degrading the AHLs and preventing *Pseudomonas aeruginosa* biofilm formation. Moreover, these enzymes have also been reported in various other endophytic microbes like *Pseudomonas*, thus, contributing in better disease control and improved plant health.

Inducing overproduction of antimicrobial or immunological compounds by plants

Notwithstanding the previously mentioned approaches, endophytic microbes can also stimulate the immunological or antimicrobial responses in plants through the production of varied compounds. In a study done by Siddaiah et al. (2017), *Trichoderma hamatum* UoM 13, an endophytic fungus can lead to the overproduction of various defence enzymes, salicylic acid and pathogenesis related proteins (PRP) which complements systemic immunity against downy mildew in pearl millet. Moreover, there has been an upregulation of host defence genes (Tc00g04254) in *Theobroma cacao* leaves because of endophytic fungus *Colletotrichum tropicale* on pathogen damage (Mejía et al. 2014). Kushwaha et al. (2019) studied the compatibility of fungal endophytes (*Aspergillus*, *Sarocladium* and *Penicillium*) of

Withania somnifera with biological control (*Trichoderma viridae*) and reported that the co-inoculation significantly increased the withanolide A content by expressing its biosynthetic genes.

Space competition with pathogens

Endophytes can often compete with the pathogen for space, thereby limiting its ability to grow and cause disease. Fungal endophytes, in particular, proliferate rapidly, thereby exhausting the nutrients for the pathogen to grow. It has been suggested that colonization by *Beauveria bassiana* endophytically can control the damping off and root rot of tomato and cotton, competition for space being the likely mechanism for biological control against *Rhizoctonia solani* and other pathogens (Ownley et al. 2008). Moreover, in response to endophyte, the plant produces lignin and other cell wall components, thereby limiting the growth of the endophyte and maintaining its avirulence (Harman et al. 2004).

Conclusions and future prospects

For medicinal and aromatic plants, endophytes have more valuable functions, such as controlling phytopathogens, promoting plant growth and modulating the phyto-chemistry. Endophytes of medicinal and aromatic plants are more efficient in producing bioactive secondary metabolites that can be used as antimicrobial agents against human, animal, and plant pathogens. Application of endophytes as a substitute for pesticides or chemical fertilisers is more fascinating because it prompts use of medicinal plants by the consumer and the pharmacology industry without any residue of synthetic chemicals. Thus, endophytes may be more prominent agents in scavenging synthetic chemical compounds and enhancing the production of bioactive secondary metabolites in medicinal plants. Therefore, there is a further need to isolate endophytes from medicinal plants to explore as a plant growth promoting agent and detect the bioactive compounds to utilise instead of synthetic chemicals to save the environment. Endophytes of medicinal and aromatic plants could produce some important bioactive secondary metabolites freely, which enables the pharmacological industry to conduct large-scale

fermentation of bioactive secondary metabolites, independent of the cultivation of medicinal plants.

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Consent for publication Consent was obtained from all the individual participants included in the study. All the authors have read and approved the manuscript.

Ethical approval The publications does not include results of studies involving humans.

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