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Review Article

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Therapeutic compounds from medicinal plant endophytes: molecular and metabolic adaptations

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Abstract

During the last few decades, endophytes have attracted increased attention due to their ability to produce a plethora of bioactive secondary metabolites. These compounds not only help the endophytes to outcompete other plant-associated microbes or pathogens through quorum sensing, but also enable them to surmount the plant immune system. However, only a very few studies have described the interlink between various biochemical and molecular factors of host-microbe interactions involved in the production of these pharmacological metabolites. The peculiar mechanisms by which endophytes modulate plant physiology and metabolism through elicitors, as well as how they use transitional compounds of primary and secondary metabolism as nutrients and precursors for the synthesis of new compounds or enhancing existing metabolites, are still less understood. This study thus attempts to address the aspects of synthesis of such metabolites used in therapeutics by the endophytes in the light of their ecological significance, adaptation, and intercommunity interactions. Our study explores how endophytes adapt to the specific host environment, especially in medicinal plants that produce metabolites with pharmacological potential and simultaneously modulate host gene expression for the biosynthesis of these metabolites. We also discuss the differential interactions of fungal and bacterial endophytes with their hosts.

Keywords: pharmacological metabolites, endophyte adaptation, host recognition, elicitor, exopolysaccharide, extracellular enzymes, inter-community interactions

Introduction

Endophytes play a crucial role in plant growth and physiology and yet remain the most overlooked component of the plant ecosystem (Nicoletti and Fiorentino 2015). These microbes have successfully adapted to the specific chemical environment of the plant as their habitat. Simultaneously, they provide advantages to the host by contributing to primary and secondary metabolite production that helps in their growth as well as stress resistance (Strobel and Daisy 2003, Ludwig-Müller 2015). Endophyte community structure varies with plant type, genetic background, age, season, and surrounding environment (Jasim et al. 2014, Sharma et al. 2020). Depending on these factors, their density varies from 10^2 to 10^9 microbes per cm^3 of the plant (Costa et al. 2012). Bacterial endophytes are more diverse in roots than in shoots, whereas fungal density remains comparatively stable (Furtado et al. 2019). However, the understanding of these dynamics of bacteria and fungi, as well as their functional role in the plant, is still limited.

During the last few decades, endophytes have attracted increased attention due to their ability to produce a plethora of bioactive secondary metabolites. These compounds not only help them to outcompete other plant-associated microbes or pathogens through quorum sensing during establishment but also enable them in surmounting the plant immune system (Berg and Hallmann 2006). Metabolites produced by endophytes depend on the type of biotopes to which they are adapted, especially in tropical habitats, where adaptation to the host may involve horizontal gene transfer (HGT) or genetic recombination, leading to the production of similar compounds (Kusari et al. 2009a, Mathur and Ulanova 2022). However, some metabolites are produced specifically in response to various biotic or abiotic factors where the newly established endophytes compete with the existing endophyte or pathogen for space and resources (Lattanzio et al. 2006). This makes contribution to host defence one of the prominent features of plant–endophyte interaction, especially towards pathogenic microbes. Plants induce a defence system against a series of stresses, which constitute cumulative defence compounds from the host and their endophytes (Prado et al. 2012). As a result, endophytes produce compounds with antimicrobial or antioxidative properties, not only to support the host but also to outcompete other microbes in the plant (Ludwig-Müller 2015).

Some plants are known to produce compounds that have antioxidant, antimicrobial, and anti-inflammatory properties. These plants have been used in traditional medicine and are being actively explored in recent years for bioactive compounds with therapeutic potential. In medicinal plants, the quality and quantity of the therapeutic compounds obtained are dependent on factors such as temperature, sunlight, and soil conditions (Namdar et al. 2019). These compounds produced by medicinal plants may be strongly influenced by the endophyte association (Zhai et al. 2018). Thus, an understanding of these plant-microbe interactions can provide valuable insight to not only improve the quantity but also the type

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of compound produced. However, only a limited number of studies have described the interlink between various biochemical and molecular mechanisms involved in the production of these metabolites during host-microbe interactions. This study thus elucidates the aspects of synthesis of such metabolites used in therapeutics by the endophytes of medicinal plants in light of their ecological significance. Our study addressed the following questions: (i) Do endophytes modulate gene expression for the production of pharmacologically active metabolites in medicinal plants? (ii) How do endophytes adapt to the specific host environment? (iii) How does the host interaction of fungal endophytes differ from that of bacterial endophytes in terms of metabolite production? To answer these questions, this study reviews the molecular and metabolic interaction of medicinal plants with their endophytes as well as explored the potential of these endophytes for use in therapeutics.

Plant–endophyte symbiosis: ecological aspect

According to the trait-specific endophytic infallibility hypothesis, endophytes are independent organisms that have acquired the capability to produce bioactive compounds due to evolutionary pressures (Kusari et al. 2009a). This led to the development of a core microbiota associated with different hosts i.e. transmitted vertically to seeds. Evidence from predictive functional analysis of the medicinal plant, *Salvia miltiorrhiza*, shows that the metabolic profile of the seed microbiome remains similar irrespective of its geographical origins (Chen et al. 2018a). However, the establishment and maintenance of both obligate as well as facultative microbiota, especially in medicinal plants, can be explained based on three types of biotic interactions: (i) selective pressure exerted due to host secondary metabolites; (ii) their own metabolic abilities; and (iii) selective pressure due to antimicrobial compounds derived from microbes present in the same ecological niche (Castronovo et al. 2021). This selective pressure not only influences endophyte type but also their density. For example, the low recovery of endophytes from the leaf of the medicinal plant *Pseudowintera colorata* is predicted due to the presence of high levels of antimicrobial sesquiterpene dialdehyde polygodial in the leaf (Purushotham et al. 2020).

Root colonization is the initial and critical step involved in the establishment of symbiosis between plants and microbes. This process involves exudation, plant-microbe, and microbe-microbe interactions via chemical signalling at each step in the rhizosphere (Chagas et al. 2018). The endophyte thus adapts its metabolism by regulating its gene expression according to the physiological state of the host to maximize its nutrient acquisition and competition with microbes in the same niche (Yi et al. 2017). For example, *Bacillus amyloliquefaciens* helps in enhancing nutrient uptake, plant growth, production of hormones and siderophores, and extracellular fungal cell wall degrading enzymes for restricting pathogen growth (Kushwaha et al. 2020).

Several studies indicate that plants themselves mediate plant-microbiome interactions by controlling the expression of specific genes for metabolite synthesis. It is also observed that under nutrient-deficient or stress conditions, the host plant upregulates the production of metabolites for recruitment of the nutrient-delivering endophytic partners (López-Ráez et al. 2011). For example, suppression of the root-specific gene CYP71A27, involved in camalexin (phytoalexin) production, affects the colonization and density of the rhizosphere microbiome by decreasing plant sulfatase activity (Koprivova et al. 2019). An important aspect of this selective and promoting effect of plant compounds (such as root exudates and volatiles) is to attract specific microbial populations that respond to chemotaxis and are fast-growing strains, which enables only a small subset of microbes to colonize (Hartmann et al. 2009).

Recruitment of endophytes during pathogen attack plays an important role in the defence and growth of the host plant. In *Theobroma cacao*, known for its cardiovascular and blood pressure medicinal uses, 40% of the leaf endophytes show antagonistic behaviour against one of its three major pathogens, indicating enhanced defensive potential during direct pathogen encounters (Arnold et al. 2003). The cross-talk between the host and endophyte suggests that plants recognize and differentially recruit endophytes to accordingly augment their resistance against both abiotic and biotic stress (Mattoo and Nonzom 2021). However, endophyte transmission and colonization may not depend solely on their role in metabolite production, and a stable symbiosis can also occur even after the knock-out of the bioactive metabolite gene (Panaccione et al. 2001).

Endophytes produce a variety of metabolites in order to compete with each other as well as with rhizosphere microorganisms (Schulz et al. 1999). As a result, based on the requirement, the same microbe produces, qualitatively or quantitatively, different bioactive compounds in different hosts. A study demonstrated that small-molecule epigenetic modifiers such as suberoylanilide hydroxamic acid and 5-azacytidine influence *Muscodor yucatanensis*, a brefeldin-A producing endophyte of the medicinal plant *Elleanthus* sp., to produce a new set of metabolites (ergosterol and xylaguaianol C) by over-expression of the polyketide synthase (PKS) gene (Qadri et al. 2017).

An endophyte may also switch from a mutualistic to a pathogenic lifestyle, as observed in the case of *Lolium perenne*and its endophyte, *Epichloe festucae*. Crucial mechanisms such as the mitogen-activated protein kinase pathway and production of reactive oxygen species (ROS) maintain the fine balance of mutualistic association with endophytes instead of pathogenesis (Eaton et al. 2011). The symbiotic to pathogenic transition also leads to the 'shut-down' of bioactive metabolite expression in these plants. Selective production of these metabolites is also observed during different modes of reproduction. For example, the biosynthesis of Indole-diterpenes in *Epichloe* fungi has been observed only in asexually reproducing isolates due to the lack of functional alkaloid gene clusters in their sexually reproducing relatives (Young et al. 2009). This ensures rapid endophyte growth and thus enhances the capability of the endophyte for host protection.

However, the understanding of colonization and establishment of the endophytes remains incomplete due to a lack of information on unculturable microbes, despite some recent studies that prepared functional libraries of this microbial set (Bilal et al. 2018, Hong et al. 2019). Metagenomic analysis of the ethylene regulation operon (ACC deaminase gene; acdS) revealed the presence of the upstream transcriptional regulator (acdR) in unculturable *Pseudomonas* strains only; this indicates an either cooperative or alternate regulation mechanism for the ACC in the culturable endophytes (Nikolic et al. 2011). Several studies on medicinal plants have reported the presence of unculturable *Actinobacteria* belonging to the genera *Streptomyces*, which are known to produce a variety

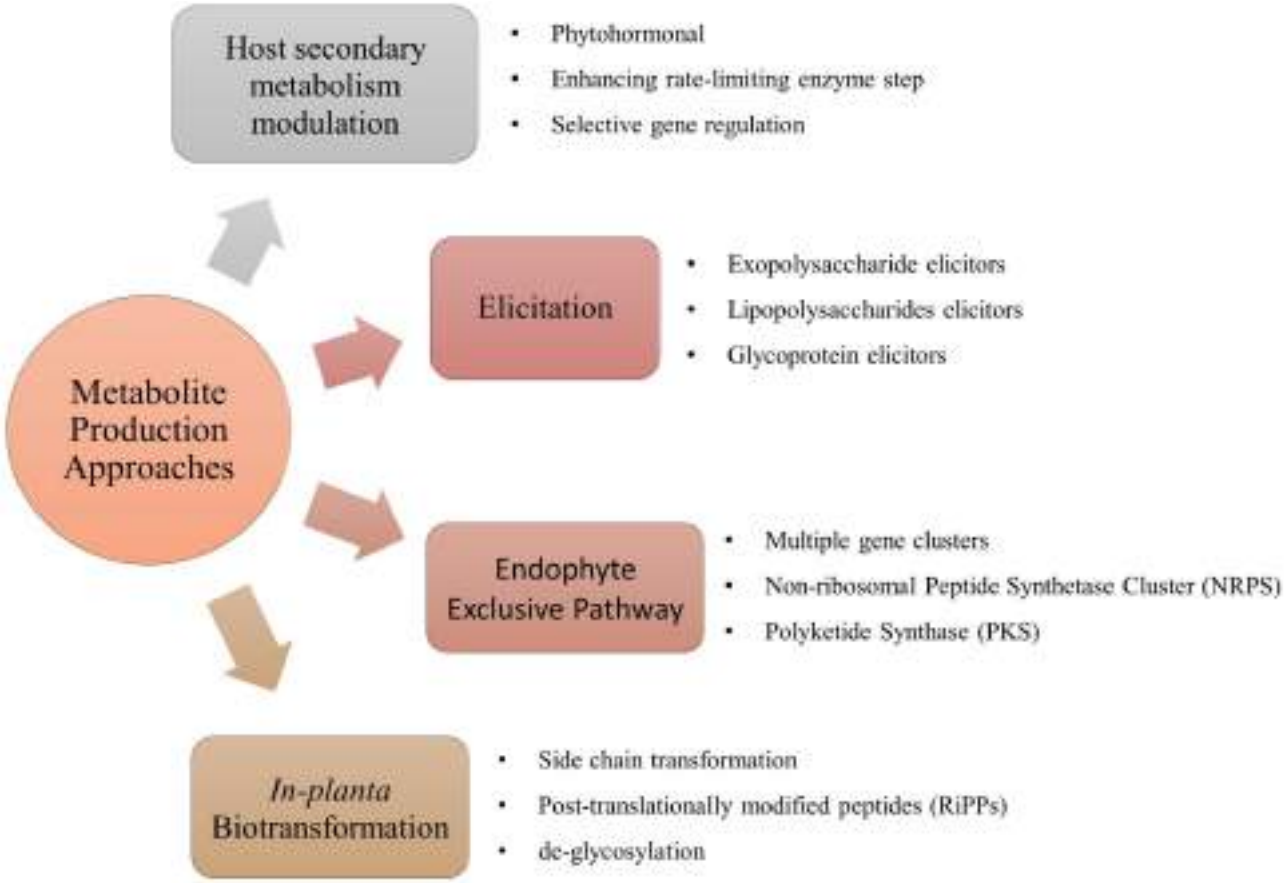

Figure 1. Approaches in metabolite production during endophyte–plant interactions.

of bioactive metabolites and antibiotics (Purushotham et al. 2018, Oberhofer et al. 2019). Furthermore, un-culturable endophytes also produce enzymes such as pectinase for defence against pathogens (Singh et al. 2022). These studies indicate a potential for novel and/or potent compound discovery, which currently remains unexplored.

Plant–endophyte: metabolic symbiosis in bioactive compound production

In medicinal plants, the presence of either PKS or non-ribosomal peptide synthetases (NRPS) gene clusters has been correlated with the production of bioactive natural compounds (Alvin et al. 2014). Bioactive compounds resulting from plant–endophyte interaction can be majorly categorized into four approaches, i.e. (i) produced by the endophyte exclusively; (ii) produced by the host through direct endophyte elicitation; (iii) indirectly produced through modulation of the host secondary metabolism pathway by the endophyte; and (iv) *in-planta* endophyte assisted biotransformation of the metabolite (Fig. 1).

A majority of endophyte-based studies have described the microbial symbiont to produce metabolites similar to those of their host; however, there are reports of the symbiont synthesizing the compound exclusively. For example, a bioactive compound called 3-nitropropionic acid, which was initially thought to be produced from *Astragalus falcatus* (family Fabaceae) and *Coronilla viminalis* (family Leguminosae), was later reported to be produced by their respective endophytic fungi (Chomcheon et al. 2005). In a more recent study, the fungal endophyte *Cyanodermella asteris* from the traditional Chinese medicinal plant *Aster tataricus* produced host-exclusive Astin variants through a NRPS-based symbiotic cross-species pathway (Schafhauser et al. 2019).

Production of similar bioactive compounds from the host plant and microbes can be a possible indication towards horizontal gene transfer, which is also evident from the similarity of the metabolite backbone structure in plants and their fungal endophytes. The taxol biosynthesis gene, 10-deacetylbaccatin-III-10-O-acetyl transferase, from the endophyte *Clasdosporium cladosporiodes*, showed a 97–99% identity with the corresponding host gene (Jennewein et al. 2001). However, metabolite synthesis may follow different biosynthetic pathways regulated by distinct genes in endophytes and their host plants (Aly et al. 2013). For example, the enzymatic conversion of emodin to hypericin (an anti-viral compound) is regulated by the *hyp-1* gene in its host *Hypericum perforatum* (a traditional medicinal plant). However, there is a noticeable disparity in the nucleotide sequence of this gene between the endophyte and its host (Bais et al. 2003, Kusari et al. 2009b). Similarly, the *epoA* gene for Epothilone B biosynthesis in *Aspergillus fumigatus* (an endophyte of *Catharanthus roseus*, a plant with anticancer properties) shows only 40% similarity with its host plant (El-Sayed et al. 2021). This is likely due to independent adaptation processes during the co-evolution of the host and the corresponding endophyte (Kusari et al. 2009a, Aly et al. 2013). In the case of the therapeutic compound Huperzine A, its biosynthesis in the host plant involves

two lysine decarboxylases (LDCs), one copper amine oxidase, and three PKS, whereas knock-out of both LDCs from the endophyte *Colletotrichum gloeosporioides* increases its production (Kang et al. 2019). Co-evolution is also evident in cases where the production of analogues or precursor compounds have been reported by the endophyte independent of the host (Chen et al. 2009, Yang et al. 2017). The antitumour compound maytansinoid ansamitocin was earlier reported to be obtained from the higher plant *Actinosynnema pretiosum*. Interestingly, the maytansinoid backbone is similar to ansamycin antibiotics such as rifamycin B and geldanamycin, which are mainly of microbial origin (Yu et al. 2002). Many endophytes show the capacity to produce multiple analogous or novel bioactive compounds. However, the diversity of bioactive compounds may depend on the microbial type (Shweta et al. 2013). *Serratia marcescens* MSRBB2 (an isolated anti-inflammatory plant called *Maytenus serrata* in traditional medicine) is reported to produce prodiginines via the well-studied monopyrrole and bipyrrole condensation pathways; however, it is able to produce several different analogues of prodiginine (Eckelmann et al. 2018).

Endophytes, in some cases, produce elicitor compounds through a chemical recognition system that activates the signal transduction network for related gene activity, thus increasing bioactive compound accumulation in the host (Tidke et al. 2018). Alternatively, it is suggested that colonization of endophytes triggers plant hydrolases that fragment the endophytes, producing elicitors such as lipopolysaccharides, polysaccharides, and glycoproteins that stimulate plant defense responses and the production of secondary metabolites (Gao et al. 2010). For example, mycelium extract and a fraction of polysaccharide from the endophyte *Trichoderma atroviride* act as elicitors for the production of an anticancer compound tanshinone in the plant *Salvia miltiorrhiza* (Ming et al. 2012). This takes place through upregulation of genes for the rate-limiting enzymes of the biosynthesis pathway, thereby enhancing *in-planta* production of the secondary metabolites (Zhai et al. 2018). Moreover, endophytes can regulate different genes of the same metabolic pathway to produce distinct compounds (Pandey et al. 2016b). For example, the introduction of different endophytic fungi combinations in a dual *in-vitro* culture of plant callus results in strain-specific metabolic profiles with novel metabolite production (Huang et al. 2019). These studies indicate that multiple endophytes may provide enzyme-specific elicitors for one or more steps that help in the upregulation of the secondary metabolite pathway. Song et al. (2017) demonstrated increased production of the therapeutic compound ginsenoside in ginseng plants due to the endophyte *Bacillus stratosphericus*, which is decreased if the bacterial inoculum exceeded the optimum levels due to the utilization of the ginsenoside as a nutrient by the symbiont. This shows the production of the metabolites is not just for defence but also for their own consumption. However, these studies do indicate that the plant–endophyte system also has a feedback regulation on the production of secondary metabolism that maintains a threshold for the synthesis of bioactive compounds.

Some bioactive compounds are neither exclusively produced by the plant nor the endophyte and likely originate when the plant or endophyte contribute to different steps of the biosynthesis pathway. For example, hydroxylation and chlorination of the anti-tumour compound Astin, which is produced by the endophyte *Cyanodermella asteris*, occur only when it is present in association with its host *Aster tataricus* (Schafhauser et al. 2019). Moreover, some endophytes modify metabolites, such as the de-glycosylation of flavonoids that are produced by plants. These de-glycosylated flavonoids help in the mycelium growth of endophytic fungi, making these specific transformations part of the adaptation strategy of the endophyte on the host (Tian et al. 2014). *Penicillium oxalicum* (a fungal endophyte from *Artemisia annua*) mediates the biotransformation of artemisinic acid (the precursor of artemisinin, the antimalarial drug) and produces some potent metabolites against human promyelocytic leukaemia and colon carcinoma cell lines (Tian et al. 2021). Thus, endophytes can be utilized to produce more potent pharmacological compounds, as in the case of the β-glucosidase-producing endophyte that converts ginsenoside Rb1 into ginsenoside Rg3 (Fu 2019).

Host metabolism during endophyte establishment

Endophytes are well known to regulate plant growth by enhancing phytohormone production and acquiring nutrition from soil (Hardoim et al. 2008). Several studies have reported alterations in the levels of secondary metabolism during endophyte establishment and defence (Yuan et al. 2019). Endophyte stimulates plant metabolic activities as early as after the sixth day of establishment (Hewitt et al. 2020). Increased secondary metabolism is known to cause an upsurge in plant energy requirements, resulting in elevated carbon assimilation efficiency and photosynthesis (Ghaffari et al. 2019, Yuan et al. 2019). Elevated carbohydrate metabolism due to protein elicitors secreted by the endophyte *Pseudomonas fluorescens* is directly correlated with the increased production of sesquiterpenoids such as atractylone and zingiberene in the Chinese medicinal plant *Atractylodes lancea* (Zhou et al. 2018). Another important feature observed during the establishment of endophytes is the regulation of genes for micronutrient uptake responses. One such example is the activation of the *MYB72* gene, which regulates iron mobilization and phenolic compounds in roots (Martínez-Medina et al. 2017). Contrary to this, some reports suggest that endophyte colonization induces metabolic reprogramming in the host plant such that secondary metabolism is favoured over primary metabolism (Dupont et al. 2015, Ghaffari et al. 2019).

Elevated synthesis of antioxidant compounds is a combined response against reactive oxygen species (ROS) produced by the colonizing endophyte as well as an oxidative burst generated as a defence against the microbe effectors by the plant itself (Torres et al. 2012). Endophyte establishment also leads to the downregulation of genes directly involved in host defence, such as PR proteins, a component of salicylic acid, that increase the production of antioxidants (phenylpropanoid, phenolic) and cell-wall synthesis (Dupont et al. 2015). In addition to the overall enhancement of secondary metabolism, there is an observed augmentation in the production of host-specific bioactive compounds (Kumar et al. 2014). For example, the establishment of bacterial endophytic populations in the aerial parts of the medicinal plant *Echinacea purpurea* upregulates valine decarboxylase production for synthesis in amine moieties of the host alkamides (Maggini et al. 2017). Studies have also shown a temporal correlation of endophyte inoculation with significant upregulation of the rate-limiting steps in secondary metabolite synthesis (Ming et al. 2012, Zhai et al. 2018). This correlation may be significant in activating

induced defences to pathogens quicker than non-symbiotic plants or plants that are not inoculated artificially. These studies indicate that endophytes influence plant metabolism by altering metabolite quantity, supporting the co-evolution of plant–endophyte interaction even when the association increases the overall energy requirement of the host.

Host-specific symbiotic reprogramming in endophytes

According to the xenohormesis hypothesis stated by Howitz and Sinclair (2008), as a part of selective pressure, endophytes have evolved to perceive chemical cues from the host plant environment and produce a pre-emptive defence response to increase their survival. The recruitment of endophytes is based on a coevolutionary selection process based on the intergenomic interaction of the two symbiotic partners (Wani et al. 2015). Therefore, endophytic microbes also show certain distinct characteristics from their non-symbiotic relatives. During establishment, endophytes may undergo modifications or adaptations to overcome plant defences. Thus, in order to establish a sustainable endophytic association with the host, the microbe undergoes genetic as well as transcriptomic reprogramming. For example, endophytes synchronize with their host and initiate the production of jacalin-containing proteins that bind to the extracellular microbial mannose to avoid microbe-associated molecular patterns (MAMP) that would otherwise trigger plant defence (Levy et al. 2018). However, endophytes not only circumvent the plant's innate immune response but also adapt to specialized host metabolites. For example, the foliar endophyte *Fusarium solani* from *Camptotheca acuminata* is protected from the defence compound camptothecin produced by itself and the host plant due to an alteration in the amino acid residues in the catalytic domain of its topoisomerase I (Kusari et al. 2011). Interestingly, the topoisomerase I isolated from a different endophyte associated with the plant roots also encodes the same alteration to prevent camptothecin action (Kusari et al. 2012).

A study comparing rhizospheric *Burkholderia* strains reported 40 'endophytic genes' that facilitate endophyte lifestyle adaptation through encoding transporter proteins family, stress responses, virulence management, cell wall degradation, protein secretion, and delivery systems (Ali et al. 2014). These genes are required for the colonization and establishment of endophytes without provoking the plant defence response. *Kitasatospora* SUK42, the endophyte of the traditional herb *Antidesma neurocarpum,* showed over-expression of genes related to capsule formation, dormancy, sporulation, cell signalling regulation, and isoprenoid synthesis during adaptation (Zin et al. 2021). However, in the same study, an overall decrease in the size of the microbe's genomic material was observed due to a reduction in gene subsets for iron acquisition, transposable elements, carbohydrates, RNA, protein, and sulphur metabolism compared to their non-endophytic relatives. These changes in microbial metabolism may be a result of the endophyte being a metabolic sink of host nutrients (carbohydrate and protein) due to their high energy requirement (Ahlholm et al. 2002). Quantitative domain analysis revealed that the presence of asparaginase, oligopeptide transporters, and adenosine deaminase used in the endophyte nitrogen metabolism functionally differentiates them from the rhizoplane microbes (Bünger et al. 2020). A successful endophytic lifestyle is also dependent on an efficient membrane transport system to facilitate the uptake of host nutrients. A genomic study of the endophyte *Micromonospora lupini* reported 631 CDSs coding for transporters related to ATP-binding, ABC transporters, the major facilitator superfamily, ion channels, and secondary transporters, which together constituted ~8.9% of the genome (Trujillo et al. 2014). Transcriptome analysis of *Phomopsis liquidambari* reported <8% unigenes involved in transport activity, which is important for their host adaptation (Zhou et al. 2017). These changes in the transport system help the endophytes for better adjustment to the host environment as well as improved nutrient absorption from the host. Various cell surface motifs involved in host recognition, attachment, and metabolic exchange during endophyte–plant interactions have been described in Fig. 2.

Host recognition

An important requirement for recognition and communication in endophyte–plant interaction is the cell surface components. The strain of bacterium *Staphylococcus epidermidis* (which is majorly described as a human-associated pathogen) adapted to the endophytic lifestyle and exclusively expressed unique genes for cell surface lipoproteins, LPXTG protein (protein with conserved cell wall-sorting motif), intercellular adhesion protein C, and membrane protein (Chaudhry and Patil 2016). Increased expression of these components ensures microbial attachment to the host tissue, especially in the rhizosphere microbiota. Many microbes may be attracted to plant chemical cues but fail to thrive inside the plant endosphere due to a lack of adhesion ability (Reinhold-Hurek et al. 2015). In general, genes related to chemotaxis, adhesion, and quorum sensing are upregulated in endophytes to facilitate interaction with the host.

Host attachment and metabolic exchange

Studies have reported the role of flagellum and pilli in the mediation of endophytic competence as well as quorum sensing rather than induction of plant defence (Shastry et al. 2020, Fernández-Llamosas et al. 2021). Pilli (such as types I and IV) and flagella drive chemotaxis towards root exudates that provide a competitive advantage to the colonizing endophyte by facilitating mobility and/or adhesion (Taghavi et al. 2010). A comparative study of soil microbes and endophytic members from phylogenetically distant *Proteobacteria* and *Verrucomicrobia* reported similar expression of flagella-related protein domains in the endophytic lifestyle of both phyla, indicating a habitat-specific adaptation (Bünger et al. 2020). *Enterobacter cloacae* strain Ghats1 genome showed an expression of 22 genes for biosynthesis and assembly of flagella (Shastry et al. 2020). Analysis of plant-associated *Kosakonia radicincitans* revealed the presence of genomic features such as multiple gene clusters for flagellar systems that facilitate plant host invasion as well as provide a competitive advantage for establishment over other microbes (Becker et al. 2018). In addition, endophytes with antimicrobial potential produce compounds with quorum-sensing inhibition and quorum-quenching activities (Joo et al. 2021, Zeng et al. 2022).

Another important cell surface component for endophyte colonization is the presence of exopolysaccharide (EPS), which constitutes the principal matrix component of their biofilm (Meneses et al. 2011). Fungal endophytes from medicinal plants are reported to produce novel EPS with unique homo- and heteropolysaccharide moieties that are actively

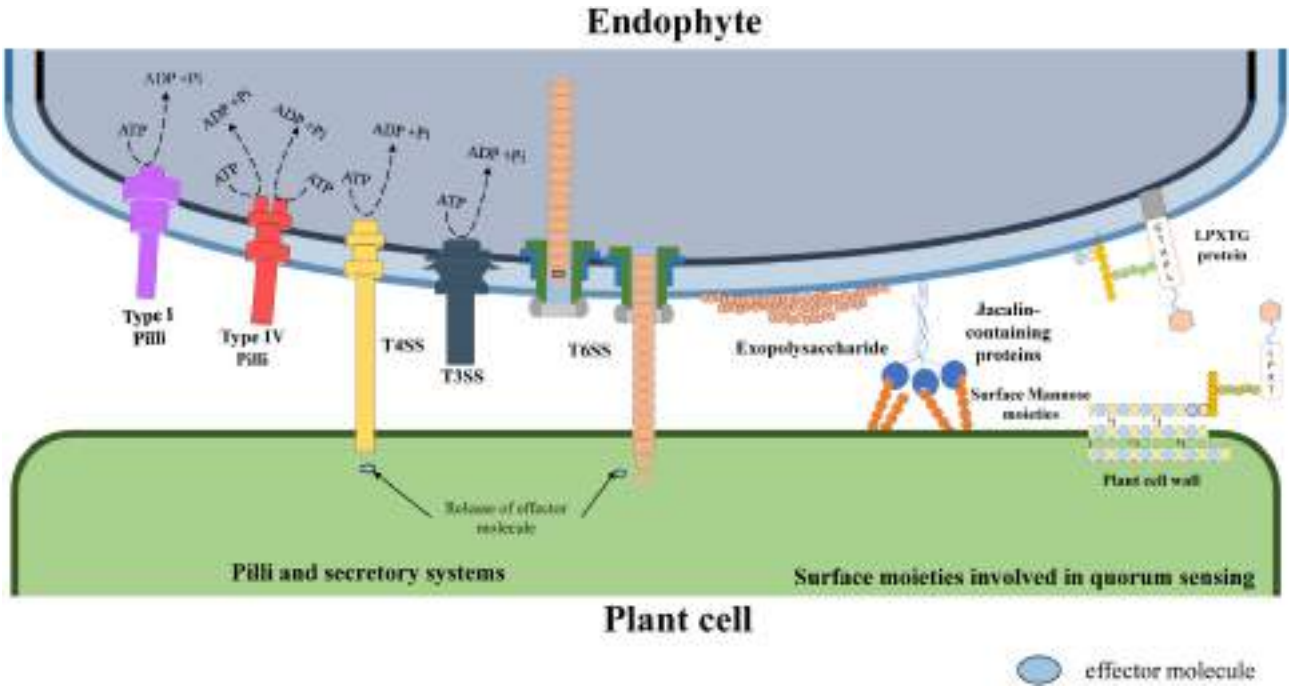

Figure 2. Cell surface motifs involved in host recognition, attachment, and metabolic exchange during endophyte–plant interactions.

involved in cell-to-cell communication and therefore also act as elicitors (Mahapatra and Banerjee 2012, Mahapatra and Banerjee 2016, Zeng et al. 2019b). EPS also have anti-inflammatory, cytotoxic, and antioxidant potential (summarized in Table 1). A recent study demonstrated a qualitative increase in the EPS of *Kosakonia cowanii*, extracted from the folkloric medicinal plant *Lactuca serriola*, during abiotic stress conditions, providing it with a selective advantage for better adaptability (Jeong et al. 2021). EPS thus creates a favourable microenvironment around the endophyte and acts as a barrier against the plant defence system as well as environmental stress, thus preventing impaired colonization and competence (Nian et al. 2010, Rinaudi and Giordano 2010).

In order to achieve a competitive advantage for colonization in an ecological niche, the delivery of effector and/or virulence factors plays a very important role. In both pathogens and symbionts, types III and IV secretion systems are involved in the delivery of effector proteins to plants. However, the type VI secretion system (T6SS) is more widespread in endophytes and facilitates the delivery of antimicrobial compounds (Weiten et al. 2021). T6SS spans the inner and outer membranes of Gram-negative bacteria and is able to translocate multiple effector molecules at once through a phage tail-like contraction mechanism (Costa et al. 2015). This system is thus more contact-dependent and shares structural similarities to bacteriophages (Schwarz et al. 2010). It secretes enzymes that target the cell wall (amidases), cell membrane (phospholipase, lipases), and nucleic acid (nucleases) degradation. Knock-out of T6SS in endophyte *Kosakonia* strains resulted in decreased endosphere colonization ability (Mosquito et al. 2020). Phylogenetic analysis of *Burkholderia thailandensis* suggested loss of T6SS function during non-competitive environments compared to its wild-type relative (Schwarz et al. 2010). However, a relatively recent study on the endophyte *Azoarcus olearius* indicated two functionally diverse variants of T6SS, namely *tss-1* and *tss-2*, where the latter is constitutively expressed and the former is induced only during nitrogen fixation (Jiang et al. 2019).

Host colonization

A common feature of the endophytic lifestyle in microbes is the presence of multiple gene clusters for cell-wall degradation and carbon metabolism, which are necessary adaptations for host tissue penetration and exploitation of host-derived carbon sources, respectively (Becker et al. 2018, Knapp et al. 2018). The endophyte metabolism also constitutes an abundance of aliphatic and aromatic compound degradation genes as well as a wide range of extracellular enzymes (ECE) such as cellulase, amylase, protease, laccase, lipase, and pectinase. Both play a significant role in host nutritional uptake and defence strategies against pathogens (Sunitha et al. 2012, Fouda et al. 2015). During colonization, ECE also played an essential role in the protection of endophytes against secondary metabolites produced by the medicinal plant and has become relevant for potential use in the pharmaceutical industry (Jia et al. 2016, Li et al. 2018). However, the type of ECE secreted by the endophyte(s) may be dependent on the host type, habit, and environmental condition and thus help establish a host-exclusive ecological niche (Sunitha et al. 2012). For example, endophytic *Aspergillus* isolated from two Piperaceae medicinal plants, *Piper longum* and *P. nigrum*, showed varied ECE with high asparaginase combined with cellulose activity in *P. longum* whereas with increased amylase in *P. nigrum* (Uzma et al. 2016). Moreover, ECEs for plant cell wall degradation are also secreted during microbial pathogenesis. The secretome analysis of endophytic (*Harpophora oryzae*) and pathogenic (*Magnaporthe oryzae*, *Gaeumannomyces graminis*, and *M. poae*) microbes, evolved from a common ancestor, revealed a 2-fold comparative upregulation of genes for ECE such as lipase, tyrosinase, cutinase, and cellulase, proteins with carbohydrate-binding module and LysM domains in case of latter (Xu et al. 2016). In addition, genes for oxidation-

Table 1. Bioactivity of endophytic exopolysaccharide (EPS).

Endophyte source	EPS	Polysaccharide moieties	Bioactivity	Reference
Fusarium solani DO7	Galactoglucan DG2	Gal*p*, Man*p*, Glc*p*, and Ara*p*	Immunomodulatory activity on RAW 264.7 cells (monocyte/macrophage cell line) with increased expression of TNF-α, IL-6, and iNOs mRNA	Zeng et al. (2019a)
	DY1	Glc*p*, Rha*f*, Xyl*p*, and Gal*p*	Antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*	Zeng et al. (2019b)
	DY2	Glc*p*, Rha*f*, Ara*f*, and Gal*p*		
Fusarium oxysporum Dzf17	WPS SPS	Crude EPS	*In-vitro* antioxidant activity	Li et al. (2021)
Fusarium equiseti ANP2	MF-1	Man and Glc (with minor fraction of Fuc, Rha, Xyl, and Ara	*In-vitro* antioxidant activity	Prathyusha et al. (2018)
Fusarium sp. A14	A14EPS-1	Rha, Ara, Glc, and Gal	Both showed in-vitro antioxidant activity; A14EPS-2 showed antiproliferation activity against human hepatocellular carcinoma HepG2 cells.	Pan et al. (2019)
	A14EPS-2	Rha, Xyl, Ara and Glc		
Glutamicibacter halophytocola KLBMP 5180	5180EPS-1	GlcA, Rha, Glu, and GalA	*In-vitro* antioxidant activity	Xiong et al. (2020)
	5180EPS-2	Rha, Glc, GalA, Xyl, Ara		
Penicillium citreonigrum CSL-27	EPS-2	α-D-Manp, α-D-Xylp, β-D-Araf, α-D-Glcp, and α-D-Galp	Attenuated cytotoxicity on gentamicin-induced HEI-OC1 cells	Li et al. (2019)
Alternaria tenuissima F1	*Alternaria tenuissima* F1 EPS	D- GalA, Rha, D-Man, Glc, and D-Gal	In-vitro antioxidant activity	Wang et al. (2019)
Rhodotorula sp. CAH2	*Rhodotorula* sp. CAH2 EPS	Glc, Man, and Gal	Protects plant growth promoting endophytic yeast by forming biofilm under abiotic stress	Silambarasan et al. (2019)
Rhodotorula minuta (IBRC-M 30135)	*Rhodotorula minuta* (IBRC-M 30135) EPSs	Glc, Man, and Rha	Emulsifying and antioxidant properties, non-toxic biopolymers so can be used in food and pharmaceuticals	Seveiri Mirzaei et al. (2019)
Chaetomium sp. JY25	*Chaetomium* sp. JY25 EPS	Glc, Man, Ara, and Gal	Antioxidant and anti-proliferative activities	Zhang et al. (2017)
14- DS-1	14- DS-1 EPS (DSPS)	Gal, Glc, Rha, Fuc, Ara, and Man	S-phase arrest and apoptosis in cancer cells	Chen et al. (2018b)
Lysinibacillus sphaericus Ya6	*Lysinibacillus sphaericus* Ya6 EPS	Man and Glc	*In-vitro* antioxidant activity	Yang et al. (2022)
Bacillus sp. B3	EPS-B3	Gal, Glc, and Man (with minor fractions of Rha, Fuc and Fru)	*In-vitro* antioxidant and anti-tumour activity against S180 tumour cells	Zhang et al. (2021)
Bacillus thuringiensis strain SMJR	*Bacillus thuringiensis* strain SMJR EPS	Crude EPS	Antibacterial activity against foodborne pathogens such as *E. coli* and *K. pneumoniae*	Natarajan et al. (2022)
Bacillus licheniformis MS3	*Bacillus licheniformis* MS3 EPS	Man, Glc, and Fru	Emulsifying properties	Asgher et al. (2020)

Table 1. Continued

Endophyte source	EPS	Polysaccharide moieties	Bioactivity	Reference
Bacillus subtilis NCIB 3610	FM1	Rha, Fuc, Gal, and Man (1.67: 1.14: 1.02: 1)	Cytotoxic activity against HCT116, HepG2, and MCF7 human cell lines	Matloub et al. (2020)
	FM2	Gal, Man, and Glc (2.43: 1.19: 1)		
	FM3	Gal, Man, and Glc (1.66:1.30: 1)		
Phomopsis liquidambari NJUSTb1	PLN-1	α-Glcp	*In-vitro* proliferation of RAW 264.7 cells (macrophage-like cells)	Liu et al. (2021)

reduction processes (such as FAD binding, GMC oxred, and Cu-oxidase domains) were also upregulated in *M. oryzae*. Contrary to these studies, the secretome of *Frankia* sp., a facultative endosymbiont of actinorhizal plants, did not contain well-conserved polysaccharide-degrading enzymes but instead was rich in lipases and esterases enzymes to degrade plant cell walls and/or modify lipid-based signalling molecules (Mastronunzio et al. 2008). Since pectin is mainly located on the primary cell wall and middle lamella of the plant cell, the presence of genomic islands for the pectin-degrading enzyme in the endophyte indicates their ability to colonize the interspatial regions of the tissues (Taghavi et al. 2010). Endophytic ECE has been commercially employed in the pharmaceutical industry due to these properties.

In some endophytes, intracellular levels of the second messenger such as cyclic di-GMP also modulate endophytism as they influence increased motility in the microbes through c-di-GMP-dependent post-transcriptional regulation (Fernández-Llamosas et al. 2021). Thus, the adaptation of an endophytic lifestyle is mainly based on their metabolic reprogramming to circumvent plant immune responses as well as utilize plant metabolic reserves.

Endophyte consortium: inter-community interactions

Endophytes thrive in a complex environment involving both plant–endophyte as well as endophyte–endophyte interactions. Thus, the metabolic profile of one microorganism could inexplicably affect another species sharing the same habitat. The microbes often use signalling molecules such as autoinducers, quormones, and pheromones for quorum sensing, which act as cell density-dependent control systems (Joo et al. 2021). Christian et al. (2007) predicted that, compared to the system in isolation, the functional capability of the biosynthesis network increases during interaction in a microbial consortium. A recent study indicated that plant growth and development are controlled by the independent interactions of these species rather than the richness of their constituent microbes (Tripathi et al. 2020). It has also been reported that molecular signals from one species are able to induce density-dependent responses in the interacting species.

A study on a bacterial consortium of sugar beet seedlings reported ∼730 biosynthetic gene clusters, some of which were NRPS and PKS-derived products such as thanamycin and brabantamide involved in host defence (Carrión et al. 2019). A constituent microbe may complement the deficiency of one microbe by upregulating multiple genes of the biosynthesis process, as observed in the production of therapeutic compounds by the benzylisoquinoline alkaloids biosynthetic pathway of *Papaver somniferum* (Ray et al. 2019). Contrary to this, combinations of different endophytes can affect the quantitative production of compounds of a single pathway (Pandey et al. 2016b, Singh et al. 2021). This interaction may be tissue-specific (such as leaves or roots), where most endophytes are able to modulate key genes for secondary metabolite(s) biosynthesis. A prominent example is the selective production of morphine, papaverine, and noscapine in *P. somniferum* through the benzylisoquinoline pathway (Pandey et al. 2016a). Interestingly, the interaction and presence of similar bioactivity in the endophyte community may also be the result of horizontal gene transfer. For example, in the rhizobacterium *Bacillus velezensis,* genomic islands, formed via HGT

from root colonizers, constitute a hybrid of the type I fatty acid synthase (FAS)-PKS system and an ABC transporter, which produce the antibacterial compounds Bacillunoic acid to eliminate competition (Wang et al. 2019). However, the overall relevance of such an enormous consortium of microbes is yet to be determined, when only a limited number of the microbes contribute to the production of bioactive compounds in the plant. This also raises the question as to why the majority of the microbes contribute towards plant growth and development.

Biofilm formed by bacterial attachment on mycelium, produces more plant growth promoters (such as indoleacetic acid-like substances); however, such interaction may not take place in the case of endophytes due to a lack of cell-density-dependent quorum sensing inside restricted plant tissue space (Bandara et al. 2006). Moreover, many studies have reported endophytes producing quorum sensing inhibitors, which impair cell communication between microbes and disrupt the formation of biofilms (Rodrigues et al. 2022). Natural antibiofilm agents such as Flavipesin A, asterrelenin, and glycolipids reported from medicinal plant endophytes show inhibition of bacterial pathogens such as *Staphylococcus aureus* and *Pseudomonas aeruginosa*, indicating their potential application in therapeutics (Bai et al. 2014, Radhakrishnan and Mathew 2020, Elkhouly et al. 2021).

Synthesis of bioactive compounds: how is fungal interaction different from bacteria?

Production of bioactive compounds by the bacterial endophyte is either direct, where the microbial counter-part produces compounds for their own survival and competition, or indirect, by influencing plant defence and fitness via secretion of phytohormones and growth promoters (Castronovo et al. 2021). Comparative microbial and plant genomics has revealed a convergent evolutionary relationship between plants and bacterial microbiota, due to the horizontal transfer of effector proteins from the host to the microbes that facilitate the fitness of the latter (Levy et al. 2018). Alternatively, a study on *Arabidopsis* described the latent capacity for biosynthesis of 50 unusual triterpenes that were under the selective modulation of bacterial operons (Huang et al. 2019). Furthermore, bacterial endophytes, especially those residing in roots, are more resilient to antibiotics or secondary metabolites due to horizontal gene transfer or selection pressure during co-evolution (Mengoni et al. 2014). Thus, bacterial-plant interactions exhibit a molecular co-dependency for secondary metabolism.

Being eukaryotic symbionts, fungi show a greater degree of metabolic synchrony with the plant host due to the presence of eukaryotic machinery for transcription, post-transcriptional modifications, and translation. Many fungal endophytes produce diverse and unique metabolites, mainly due to the presence of cluster-specific transcription factors (Gakuubi et al. 2021). A study indicated the role of small-molecule modifiers of histone deacetylase and DNA methyltransferase in the induction of silent metabolic pathways in fungal endophytes (González-Menéndez et al. 2016). These mediators reduce DNA methylation-mediated silencing and mediate the activation of differential pathways. These endophytes are dependent on the plant for their basic carbon and nitrogen requirements. Therefore, decreased plant nutrition can impair their secondary metabolism.

The interaction of fungal and bacterial endophytes also differs in their respective modes of action to various response elements in the host. For example, vindoline biosynthesis in *Catharanthus roseus* is regulated differently by bacterial and fungal endophytes. Bacterial endophytes (*Staphylococcus sciuri* and *Micrococcus* sp.) modulate vindoline biosynthesis through allene oxide cyclase, which is under Jasmonic Acid (JA) regulation (Mall et al. 2022). Contrary to this, fungal endophytes (*Curvularia* sp. and *Choanephora infundibulifera*) enhance *in-planta* production of vindolines via upregulation of a transcription factor (the octadecanoid-responsive Catharanthus AP2-domain protein) (Pandey et al. 2016b). A similar pattern of phytohormonal regulation is also observed in *Panax ginseng* during the biosynthesis of ginsenoside, where fungal endophytes regulate salicylic acid (SA)-based genes (such as *PR1* and *PAL* genes) and bacterial endophytes modulate JA pathway genes (Song et al. 2017, Xu et al. 2021). This variation between fungal and bacterial interactions with the host plant may be due to the respective elicitors produced by them.

Conclusion

Medicinal plants are highly competitive environments, as the endophyte needs specific adaptive features not only to outcompete microbial niches but also the host's bioactive metabolites. This lifestyle ensures the dispersion of these microbes via passive transfer. Moreover, interactions with endophytes also facilitate the plants at the molecular level in functions such as chemotaxis, adhesion, biofilm production, transcription, and stress protection. Distribution patterns as well as the molecular influence of endophytes within different parts of medicinal plants also affect the yield of the bioactive compounds. Another important factor is understanding the mode of action of the bacterial and fungal endophyte interactions with the medicinal plant, which mainly differ in their feedback to the host-response elements. Bacterial endophytes mainly show convergent evolutionary patterns with the host involving horizontal transfer for effector proteins, whereas fungal endophytes show both metabolic synchrony as well as the host-independent mechanism for the production of bioactive metabolites. Nevertheless, a crucial inquiry arises as to whether the compounds synthesized during the symbiotic relationship are primarily for the benefit of the plant, and if the endophytes have evolved to exploit them. There are three possibilities to explain the establishment of such an interaction. First, the symbiosis was essentially established to benefit the host but during the co-evolution, the endophytes have adapted to utilize these metabolites. Second, the production of such compounds is done by one of the symbiotic partners but is utilized by both. Third, since it mutually benefited both the host and the endophyte, it is produced when both partners act together.

Host-independent mechanisms of endophytes have been utilized under the concept of OSMAC (One Strain, Many Compounds), wherein variations of culture media or conditions direct the biosynthesis of distinct metabolites. In a recent study, OSMAC combined with metabolic shunting of major PKS systems led to the activation of cryptic gene clusters, producing trace novel compounds (Wei et al. 2021). Biochemical transformations using endophytes are another approach for promoting the accumulation of limited bioactive compounds in medicinal plants. A major limitation in medicinal plant endophyte research is the need to unlock the

functional potential of unculturable microbial subsets. Conventional approaches to culture this microbial subset are limited due to the inability to mimic plant micro-environmental conditions for their growth. With upcoming plant-based culture media, the cultivability of some previously unculturable bacterial strains has become possible, although the applications of the same are still limited. However, possibilities of high-throughput screening techniques combined with genome mining and function-based metagenomics library construction can help in the prediction of bioactive compounds-producing strains. These methodologies can broaden our prospects for not only novel drug discovery but also for genes or pathways elucidating specific bioactive compounds. Moreover, these approaches could aid in establishing functional libraries of endangered medicinal plant species.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

GS contributed in the conceptualization of the study, data curation (lead), writing original draft of the manuscript, its review and editing. SA and KV contributed in data curation (supporting), writing drafts (supporting). RB contributed in supervision (Supporting) of the manuscript. VM contributed in conceptualization of the study, supervision (lead), writing, review and editing of the manuscript.

Data availability

There are no new data associated with this article.

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