Endophytic Bacteria are Potential Source of Medicinal Plant Therapeutics and Bioactive Compound Synthesis

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Abstract

Background: Endophytic bacteria residing within plant tissues play a crucial role in promoting plant health and enhancing the production of secondary metabolites, thereby increasing the therapeutic value of medicinal plants. These bacteria exhibit significant taxonomic diversity and ecological distribution, forming symbiotic relationships with their host plants, ranging from mutualism to commensalism. Methods: This review discusses the ecological niches, diversity, and interactions of endophytic bacteria within various medicinal plants. Sampling of roots, stems, leaves, and other plant tissues was conducted, followed by isolation and identification of bacterial species using molecular techniques. The relationships between endophytic bacteria and their hosts were analyzed through ecological assessments and bioactivity assays. Results: Endophytic bacteria demonstrated substantial diversity, predominantly belonging to phyla such as Proteobacteria, Actinobacteria, and Firmicutes. Notable genera included Bacillus, Pseudomonas, and Streptomyces, which exhibited plant growth-promoting and antimicrobial properties. The study identified specific endophytes that enhanced the production of key bioactive compounds in medicinal plants, contributing to their therapeutic efficacy. Conclusion: The symbiotic relationships between endophytic bacteria and medicinal plants reveal a largely untapped reservoir of bioactive compounds with promising therapeutic applications. Understanding the ecological dynamics and biochemical pathways involved in these interactions offers opportunities for innovative approaches in drug discovery and sustainable agriculture. Future research should focus on characterizing these microbial communities and their metabolites to unlock their full potential in medicine and beyond.

Keywords: Endophytic bacteria, phytosymbionts, medicinal plants, bioactive compounds, drug discovery, secondary metabolites, antimicrobial agents, plant-microbe interactions, bioprospecting, pharmaceutical potential.

Significance | This review discusses endophytic bacteria, which is a novel, large source of bioactive compounds that enhance plant therapeutics and advance drug discovery potential.

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Introduction

Medicinal plants have been essential to both traditional and modern medicine due to the bioactive compounds they contain—mainly secondary metabolites—which demonstrate antibacterial, anticancer, antioxidant, and anti-inflammatory properties (Rosenblueth & Martínez-Romero, 2006). However, recent insights into the plant microbiome have revealed that many of these therapeutic properties are not solely attributable to the plants themselves. Rather, they are also linked to the symbiotic microorganisms, particularly endophytic bacteria, residing within plant tissues. Known as phytosymbionts, these endophytes are found in plant roots, stems, leaves, and seeds, living within the host without causing harm (Strobel, 2018). Notably, endophytic bacteria have attracted interest as novel sources of bioactive compounds due to their potential to enhance plant secondary metabolite production and even serve as direct contributors to drug discovery (Hardoim et al., 2008).

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Endophytic bacteria represent a broad group of microorganisms that establish symbiotic relationships within plant tissues. These relationships often benefit both the plant and the bacteria, with the bacteria enhancing the plant's stress tolerance, promoting growth, and producing bioactive secondary metabolites with therapeutic potential (Hardoim et al., 2015). Found in a wide array of medicinal plants, endophytes assist in the synthesis of critical bioactive substances, including terpenoids, flavonoids, and alkaloids. These complex, multidimensional interactions often involve nutrient exchange, shared metabolic pathways, and signaling molecules, allowing endophytic bacteria to influence the plant's secondary metabolic processes (Santoyo et al., 2016).

The potential of endophytic bacteria to produce bioactive compounds has garnered significant attention in natural product chemistry and drug development. Studies show that endophytic bacteria can produce a wide range of compounds with antioxidant, antibacterial, and anticancer activities. Some of these compounds are unique metabolites of microbial origin, while others mimic those produced by the plant host. For example, Pestalotiopsis microspora, an endophytic fungus, produces paclitaxel (taxol), a well-known anticancer compound initially thought to be exclusive to the yew tree (Strobel et al., 2004). Additionally, bacterial endophytes can generate substances such as siderophores, antibiotics, and enzymes, which not only protect the host plant from pathogens but also offer potential applications as medicinal agents for human diseases (Castillo et al., 2002).

In response to the growing interest in the therapeutic potential of endophytic bacteria, this review explores how these microbes contribute to the medicinal value of plants. Specifically, it examines the ecological roles, diversity, and types of bioactive compounds produced by endophytic bacteria in medicinal plants. The review will also cover the enhancement of secondary metabolite production, the processes involved in isolating and characterizing these bacteria, and the applications of their metabolites in medicine. By addressing these aspects, this review seeks to highlight the untapped potential of endophytic bacteria as sources of novel bioactive compounds and therapies, as well as the challenges and future directions in this field.

2. Diversity and Ecology of Endophytic Bacteria in Medicinal Plants

The internal tissues of plants contain endophytic bacteria, which are essential to plant health and secondary metabolite production. This increases the host plant's therapeutic value. These bacteria show a wide variety of taxonomic diversity and are distributed throughout various ecological niches. They create symbiotic associations that vary from mutualism to commensalism (Zhuo et al., 2020). To fully use the bioactive potential of endophytic bacteria, it is essential to comprehend their ecological dispersion, taxonomic variety, and complex interactions with their medicinal plant hosts.

2.1 Ecological Niche and Distribution

Phyllosphere and rhizosphere environments are both home to endophytic bacteria, which are found in a variety of plant tissues such as roots, stems, leaves, flowers, and seeds. Plant species, surrounding microbial populations, soil composition, and environmental factors all affect how these niches become colonized (Dias et al., 2012). Endophytic bacteria, as opposed to free-living bacteria in the rhizosphere, flourish in the comparatively protected conditions of plant tissues, where they are shielded from environmental challenges including UV radiation, desiccation, and predation (Jia et al., 2016).

The colonization of root surfaces is the first step in the formation of endophytic bacterial populations within plant tissues. These bacteria then enter the root tissues through wounds or natural holes, as well as through active mechanisms such the synthesis of enzymes that break down cell walls (Ongena & Jacques, 2008). After entering, these bacteria spread throughout the xylem vessels, apoplastic gaps (between plant cells), and other tissues while preserving a close relationship with the host to prevent inducing a defense mechanism (Pimentel et al., 2011).

There is variability in the distribution of endophytic bacteria among various plant species and tissues. Because medicinal plants depend more on mutualistic connections to survive in stressful settings than other plants, it is thought that they have a greater diversity of endophytic bacteria than other plant species (Selim, 2012). For instance, plants in settings rich in pathogens may benefit from bacterial-mediated disease resistance, but those growing in arid, nutrient-poor soils may depend on endophytic bacteria for improved nutrient absorption (Stierle et al., 1993).

2.2 Diversity of Endophytic Bacteria

Gram-positive and Gram-negative bacteria are both represented by endophytic bacteria, which demonstrate a considerable taxonomic variety. The phyla Proteobacteria, Actinobacteria, Firmicutes, and Bacteroidetes contain the majority of known endophytic bacteria. Many genera, including *Bacillus, Pseudomonas, Streptomyces, Burkholderia, Serratia, Enterobacter*, and *Paenibacillus*, are routinely isolated from medicinal plants within these phyla (Eisenhut et al., 2013).

Environmental factors, tissue type, and plant species all affect the variety of endophytic bacteria. Examples of medicinal plants that have been found to include endophytes from *Pseudomonas* and *Bacillus*, which are well-known for their antibacterial and plant-growth-promoting qualities, are *Withania somnifera* (ashwagandha) and *Ocimum sanctum* (tulsi) (Jia et al., 2016). Likewise, rhizomes and roots of medicinal plants like *Panax ginseng* (ginseng) and *Curcuma longa* (turmeric), which are rich sources of antibiotics and other bioactive substances, are frequently used to extract *Streptomyces* species (Blin et al., 2017).

The variety of endophytic bacteria is impacted by both internal plant variables and external environmental factors. The endophytic community is shaped by the kind of soil, the climate, and the genotype of the plants (Smith et al., 2005). Furthermore, secondary metabolites from plants, which are frequently exclusive to medicinal plants, have the ability to function as selective agents, encouraging the emergence of particular bacterial species that can tolerate or metabolize these substances (Hashem et al., 2023). This complex interaction indicates that the endophytic microbiome is extremely suited to its host plant, which helps the plant produce bioactive chemicals that contribute to its therapeutic qualities.

2.3 Symbiotic Relationships and Plant-Bacteria Interactions

Mutual exchange of nutrients and signaling molecules that is advantageous to both parties characterizes symbiotic partnerships between endophytic bacteria and their medicinal plant hosts. The majority of the time, endophytic bacteria increase the uptake of nutrients via nitrogen fixation or phosphate solubilization, or they stimulate plant growth by generating phytohormones such auxins, cytokinins, and gibberellins **(Djuuna et al., 2022)**. Particularly in nutrient-poor or stress-prone environments, these plant-growth-promoting endophytes (PGPE) are essential for boosting plant biomass **(de Oliveira Costa et al., 2012)**.

Plant-endophyte symbiosis is characterized by the capacity of endophytic bacteria to produce systemic resistance in their host plants. Induced systemic resistance (ISR), a type of plant immunity that primes the plant's defensive mechanisms against pathogens and pests, can be elicited by endophytic bacteria (Maiden et al., 1998). When faced with pathogens, plants can develop a stronger and faster defense thanks to this ISR mechanism, which is controlled by signaling pathways involving salicylic acid, jasmonic acid, and ethylene (Naughton et al., 2017).

Apart from their function of enhancing plant development and defense, endophytic bacteria are also recognized for their ability to generate a diverse range of secondary metabolites that have the potential to either directly benefit the plant or act as possible medicinal agents (Jiang et al., 2022). For example, *Streptomyces* species are well known for their production of antifungal and anticancer chemicals, while endophytic *Pseudomonas* and *Bacillus* species are capable of creating lipopeptides and antibiotics that inhibit plant infections (Rai et al., 2021).

Additionally, endophytic bacteria might be involved in controlling how the plant produces its own secondary metabolites. Research has demonstrated that endophytes can affect the metabolic pathways of medicinal plants, hence improving the synthesis of essential bioactive chemicals in such plants. For instance, it has been observed that endophytic bacteria from *Catharanthus roseus* (Madagascar Periwinkle) increase the synthesis of alkaloids, which are used to cure cancer (Ríos & Recio, 2005). These interactions between endophytic bacteria and medicinal plants highlight the delicate symbiosis that underpins plant health and the synthesis of bioactive chemicals with pharmaceutical value.

3. Bioactive Compounds Produced by Endophytic Bacteria

The endophytic bacteria found in medicinal plants are becoming more and more prominent as a possible source of bioactive chemicals with enormous therapeutic potential. These bacteria produce a wide range of secondary metabolites that improve the medicinal value of their hosts and contribute to the health of plants (Strobel et al., 2004). Endophytic bacteria and medicinal plants have a special relationship that promotes the synthesis of bioactive compounds with antibacterial, anticancer, antioxidant, anti-inflammatory, and other pharmacological properties. With an emphasis on their potential therapeutic uses, this section explores the different kinds of bioactive compounds that endophytic bacteria create (Singh et al., 2017).

3.1 Types of Bioactive Metabolites

Many different secondary metabolites that have important biological actions are produced by endophytic bacteria. Alkaloids, terpenoids, polyketides, lipopeptides, non-ribosomal peptides, and phenolic compounds are some of these metabolites (Gouda et al., 2016). While some of these substances are specific to the metabolism of bacteria, many of them imitate or improve the bioactive chemicals made by their host plants. The endophytic bacteria's interaction with the metabolic pathways of the host plant typically influences the manufacture of these metabolites, resulting in the development of novel bioactive chemicals that can be used therapeutically (Digra & Nonzom, 2023).

The capacity of endophytic bacteria to flourish in certain ecological niches within plant tissues contributes to the increased diversity and originality of these substances. Endophytes are able to create intricate biochemical pathways for the production of chemicals that aid in the adaptation of the bacteria and their host plants to biotic and abiotic challenges due to the protected environment found inside plant tissues (Sessitsch et al., 2002). Genes encoding non-ribosomal peptide synthetases (NRPSs) and polyketide synthases (PKSs), which are in charge of producing structurally varied metabolites with potential therapeutic applications, are frequently involved in these biosynthetic pathways (Ongena & Jacques, 2008).

3.2 Antimicrobial Compounds

The production of antimicrobial substances by endophytic bacteria is one of their most well-documented bioactive characteristics. These comprise antibiotics, antifungals, and antivirals, which are important in preventing pathogenic infections in the plant host and potentially acting as human medicinal agents. Numerous endophytic bacterial species, including *Burkholderia*, *Bacillus*, *Streptomyces*, and *Pseudomonas*, are recognized for their ability to generate powerful antibiotic chemicals that effectively combat many human infections (Verma et al., 2009).

As an example, lipopeptides that are produced by *Bacillus* species, like fengycin, surfactin, and iturin, have potent antibacterial and antifungal characteristics, which makes them attractive candidates for the treatment of infectious disorders (Singh et al., 2017). Pyocyanin and derivatives of phenazine, produced by *Pseudomonas* species, exhibit broad-spectrum antibacterial action and are useful against bacteria resistant to antibiotics. Well-known for producing antibiotics, *Streptomyces* species are also a rich source of glycopeptides and polyketides with potent antibacterial activity (Pimentel et al., 2011).

Given the worldwide problem of antibiotic resistance, endophytic bacteria have a great potential to produce novel antibiotics. The identification of new antibiotics from endophytes provides a fresh approach to creating medications that can defeat resistant bacterial and fungal strains (Rai et al., 2021).

3.3 Anticancer Agents

The capacity of endophytic bacteria to manufacture anticancer drugs has come to light; several of these agents share structural similarities with anticancer chemicals obtained from plants. These bacterial metabolites show promise as cancer therapeutic agents since they are cytotoxic to several cancer cell lines (Gakuubi et al., 2021).

The finding that the endophytic bacterium *Pestalotiopsis microspora*, isolated from the yew tree (*Taxus brevifolia*), produces taxol (paclitaxel) is one of the most well-known examples (El-Shafey et al., 2021). Originating from the yew tree, taxol is a chemotherapeutic drug used to treat lung, ovarian, and breast malignancies. The potential of endophytic bacteria in biosynthesizing valuable anticancer medicines is demonstrated by their capacity to generate taxol (Anand et al., 2023).

Anticancer substances such angucyclines and anthracyclines, which stop cancer cells from proliferating by causing apoptosis and preventing cell division, are also produced by endophytic *Streptomyces* species (Kousar et al., 2022). Further producing alkaloids, terpenoids, and derivatives of indole that exhibit selective cytotoxicity against cancer cells while sparing normal cells, some bacterial endophytes are appealing targets for targeted cancer therapy (Loeven et al., 2020).

3.4 Antioxidants and Anti-inflammatory Agents

Significant antioxidant and anti-inflammatory bioactive substances produced by endophytic bacteria are also essential for preventing and treating inflammatory disorders and diseases linked to oxidative stress (Tshikhudo et al., 2023).

It has been found that phenolic compounds, flavonoids, and terpenoids produced by a number of endophytic bacteria isolated from medicinal plants have considerable antioxidant activity because they scavenge free radicals and prevent cellular damage (Goggin, 2007). For instance, phenolic substances produced by endophytic bacteria from plants such as *Withania somnifera* and *Ocimum sanctum* shield cells from oxidative stress and lessen the effects of persistent inflammation (Tsipinana et al., 2023).

Lipopeptides and alkaloids, which control inflammatory signaling pathways and reduce the production of pro-inflammatory cytokines and suppress the activation of inflammatory mediators like NF-κB and COX-2, are examples of anti-inflammatory compounds produced by endophytic bacteria (Alvin et al., 2014). These substances are especially important for the development of therapies for degenerative diseases, cardiovascular illnesses, and chronic inflammatory conditions like arthritis (Singh et al., 2021).

3.5 Other Therapeutic Applications

Apart from their antibacterial, anticancer, antioxidant, and anti-inflammatory characteristics, endophytic bacteria generate an extensive variety of chemicals that have additional medicinal uses. Among them are agents that are neuroprotective, antiviral, antiparasitic, and antidiabetic (Muthu Narayanan et al., 2022).

For example, it has been demonstrated that endophytic bacteria from medicinal plants like *Tinospora cordifolia* and *Aloe vera* create substances with antidiabetic action by improving insulin sensitivity and modifying glucose metabolism (Medison et al., 2022). Antiviral chemicals produced by other bacterial endophytes can hinder the replication of viruses such herpes simplex virus, HIV, and influenza. This presents an opportunity for the development of novel antiviral medicines (Uzma et al., 2018).

Furthermore, new avenues for the treatment of neurodegenerative illnesses including Parkinson's and Alzheimer's have been opened up by the identification of neuroprotective chemicals from endophytic bacteria (El-Shafey et al., 2021). Certain bacterial endophytes have the ability to create metabolites that shield neurons from amyloid-beta toxicity and oxidative stress, which makes them promising candidates for treatments for neurodegenerative diseases (Xia et al., 2022).

4. Mechanisms of Endophytic Bacteria in Enhancing Medicinal Plant Properties

Through a variety of processes that support defensive systems, encourage plant growth, and make it easier for beneficial secondary metabolites to be biosynthesized (Table-1), endophytic bacteria significantly contribute to the improvement of medicinal plants' qualities (Figure-1). Comprehending these pathways is imperative in order to fully utilize endophytes for sustainable agriculture and medicinal purposes (Eid et al., 2021).

4.1 Plant Growth Promotion

By a number of processes, including as the synthesis of phytohormones, nutrient solubilization, and the promotion of root development, endophytic bacteria aid in the promotion of plant growth. Important phytohormones including auxins, cytokinins, and gibberellins, which stimulate several physiological processes in plants and improve root elongation, shoot growth, and total biomass, can be produced by these advantageous bacteria (Watts et al., 2023). Auxins, for example, are produced by *Bacillus* and *Pseudomonas* species and have been shown to stimulate cell division and elongation, hence considerably increasing plant growth (Salvi et al., 2022).

Apart from generating phytohormones, endophytic bacteria also improve nutrient accessibility by dissolving vital minerals like potassium and phosphorus. The breakdown of complicated nutritional forms into more accessible ones is accomplished by the release of organic acids and enzymes (Eberl et al., 2019). For instance, *Bacillus subtilis* is known to solubilize phosphate, which enhances the host plant's nutritional condition, especially in soils lacking in nutrients (Shaffique et al., 2022).

Additionally, by encouraging the growth of lateral roots and root hairs, endophytic bacteria can enhance root architecture. The plant's capacity to absorb water and nutrients is increased by this strengthened root system, which improves the plant's general health and productivity. According to studies, plants with beneficial endophytes colonized them are more resilient to stressors like drought, which is important for medicinal plants because they frequently thrive in difficult conditions (Singh & Jain, 2022).

4.2 Induced Systemic Resistance (ISR)

By a mechanism called induced systemic resistance, endophytic bacteria also strengthen the defenses of therapeutic plants (ISR). Through this process, a plant's innate immune response is triggered, strengthening its defenses against pests and diseases. By releasing signaling chemicals like salicylic acid and jasmonic acid, which set off the host plant's systemic defense mechanisms, endophytes can cause induced stress reactions (ISR) in plants (Gakuubi et al., 2021).

The development of pathogenesis-related (PR) proteins and the production of antimicrobial compounds are caused by the activation of ISR, which increases the plant's resistance to a variety of biotic stressors. For example, endophytic *Pseudomonas fluorescens* has been demonstrated to increase a variety of plants' resistance to fungal infections by inducing systemic resistance (Fazeli, 2024). Furthermore, volatile organic compounds (VOCs) produced by endophytes have the potential to intensify a plant's defense systems (Guo et al., 2008).

By modifying the expression of genes linked to stress, endophytes not only directly shield plants from infections but also increase their resistance to abiotic conditions such drought and salinity (Strobel & Daisy, 2003). Because endophytic bacteria have the ability to both promote growth and increase resistance, they are extremely beneficial partners for medicinal plants, which frequently encounter many stresses in their natural habitats (Ryan et al., 2008).

4.3 Biosynthesis of Secondary Metabolites

The capacity of endophytic bacteria to affect the manufacture of secondary metabolites in medicinal plants is one of their most intriguing features. Alkaloids, terpenoids, flavonoids, and phenolic chemicals are examples of secondary metabolites that are vital to a plant's therapeutic qualities and defense mechanisms (Anand et al., 2023).

Through a variety of processes, endophytic bacteria can increase the synthesis of these important chemicals. By supplying the precursors or enzymes needed for the synthesis of secondary metabolites, they might directly support the biosynthetic pathways (Glick & Gamalero, 2021). Research has demonstrated, for example, that co-cultivating Catharanthus roseus with endophytic bacteria increases the production of the powerful anticancer alkaloids vinblastine and vincristine (Afzal et al., 2019).

Furthermore, endophytic bacteria have the ability to activate the plant's own metabolic pathways, increasing the production of secondary metabolites. The secretion of signaling molecules that promote gene expression linked to the metabolic pathways of secondary metabolite formation is frequently used to accomplish this (Wu et al., 2021). For instance, it has been demonstrated that endophytes extracted from *Withania somnifera* increase the amounts of withanolides, a class of steroidal lactones with important medical advantages (Guha & Mandal Biswas, 2024). Endophytic bacteria and medicinal plants work in harmony to produce more valuable secondary metabolites. This relationship also increases the diversity of these compounds, which may lead to the discovery of new bioactive agents with potential for use in pharmacological applications (Marchut-Mikołajczyk et al., 2023).

5. Applications of Endophytic Bacteria in Drug Discovery

Endophytic bacteria are found in plant tissues, and because of their distinct metabolic processes and capacity to generate a wide variety of bioactive chemicals (Table-2), they have become attractive candidates for use in drug discovery (Figure-2). This section delves into the potential of endophytic bacteria in the search for new drugs, their pharmaceutical uses, and the opportunities and obstacles that come with commercializing them (Singh et al., 2017).

5.1 Potential for Novel Drug Discovery

The capacity of endophytic bacteria to generate unique substances with noteworthy pharmacological characteristics is becoming more well acknowledged. Their capacity for biosynthesis is distinct; they frequently produce secondary metabolites that are absent from the host plant or other microbes (Manganyi & Ateba, 2020). For instance, it has been demonstrated that endophytic bacteria with a variety of biological activities, such as antibacterial, anti-inflammatory, and anticancer properties, create alkaloids, polyketides, and non-ribosomal peptides (Kamat et al., 2022).

An instance of note is the finding of the anticancer chemical pyrrolo [1,2-a] quinoline-1,4-dione, which originates from the endophytic

Table 1. The possible activity and mechanism of action of bioactive substances derived from medicinal plant endophytes

Bioactive compounds	**Activity**	**Mechanisms of Action**	**References**
Quinones	Antimicrobial	-Binds to adhesins, complex with cell wall, inactivates enzymes	(Krabel et al., 2013)
Flavonoids	Antimicrobial	- Complex with cell wall, binds to adhesins -Inhibits release of autocoids and prostaglandins	(Hu et al., 2024)
	Antidiarrheal	-Inhibits contractions caused by spasmogens -Stimulates normalization of the deranged water transport across the mucosal cells -Inhibits Gl release of acetylcholine	(Renugadevi et al., 2021)
Polyphenols and Tannins	Antimicrobial	- Binds to adhesins, enzyme inhibition, substrate deprivation, complex with cell wall, membrane disruption, metal ion complexation	(Brader et al., 2017)
	Antidiarrheal	- Makes intestinal mucosa more resistant and reduces secretion, stimulates normalization of deranged water transport across the mucosal cells and reduction of the intestinal transit, blocks the binding of B subunit of heat-labile enterotoxin to GM, resulting in the suppression of heat-labile enterotoxin-induced diarrhea, astringent action	(Brader et al., 2017) (Shaffique et al., 2022)
	Anthelminthic	- Increases supply of digestible proteins by animals by forming protein complexes in rumen, interferes with energy generation by uncoupling oxidative phosphorylation, causes a decrease in G.I. metabolism	(Anand et al., 2023)
Coumarins	Antiviral	Interaction with eukaryotic DNA	(Tiwari & Bae, 2020)
Terpenoids and essential oils	Antimicrobial	Membrane disruption	(Covington et al., 2017)
	Antidiarrheal	Inhibits release of autocoids and prostaglandins	(Gazis et al., 2014)
Alkaloids	Antimicrobial	It interacts into the cell wall and the DNA of parasites, Inhibiting the release of autocoids and prostaglandins	(Blin et al., 2017)
	Antidiarrheal	It has anti-oxidating effects, thus reducing nitrate generation, which is useful for protein synthesis. It suppresses the transfer of sucrose from the stomach to the small intestine	(Madasi et al., 2021)
	Anthelmintic	Diminishing the support of glucose to the helminths. It also acts on the CNS, causing paralysis.	(Medison et al., 2022)
Lectins and Polypeptides	Antiviral	Blocks viral fusion or adsorption, forms disulfide bridges	(Eisenhut et al., 2013)
Glycosides	Antidiarrheal	Inhibits release of autocoids and prostaglandins	(Naughton et al., 2017)
Steroids	Antidiarrheal	Enhance intestinal absorption of Na^+ and water	(Santoyo et al., 2016)

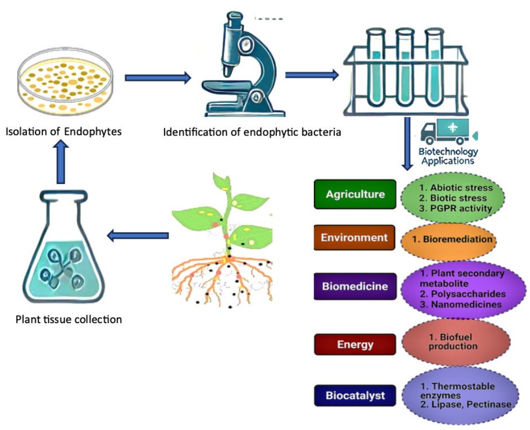

Figure 2. Endophyte isolation from plants and potential endophytes from medicinal plants used in a variety of biotechnological applications.

Table 2. Medicinal plants that harbor endophytes with potentially bioactive chemicals and their functions

Endophytes	Plant host	Activity	Compounds	References
Endophytic bacteria:				
B. subtilis	-	Antifungal	Bacilysocin Terpene	(Guha & Mandal Biswas, 2024)
B. substilis	*Allanmands cathartica*	Antibacterial	Subtilin	(Guo et al., 2008)
B.atrophaeus, B.mojavensis, Lysinbacillus	*Glycyrrhiza uralensis* (Licorice)	Antifungal	1,2-bezenedicarboxyl acid, Methyl ester	(Strobel & Daisy, 2003)
B.licheniformis, B. subtilis subsp. Inaquosorum, B. pumilus	*Combretum molle*	Antibacterial	Decanodioic acid, bis(2-ehtylhexyl) ester	(Fazeli, 2024)
Endophytic fungi:				
Streptomyces nourses	mollissimum	Antibacterial and antifungal	-	(Alvin et al., 2014)
Streptomyces sp.	*Phyllanthus reticulatus*	Antifungal	-	(Matsumoto & Takahashi, 2017)
Streptomyces sp. TP-A0595 *Aeromicrobium ponti*	*Aconitum carmichaeli*	Antifungal	5-hydroxyramulsin	(Strobel et al., 2004)
	Abies holophylla, Ginkgo biloba	Antifungal	-	(Guo et al., 2008)
	Mangifera indica Linn *Bauhinia guianensis*	Antibacterial	-	(Manganyi & Ateba, 2020)
	Garcinia sp. Indigofera suffruticosa Miller	Antibacterial	Gavodermside and Clavasterols Griseofulvin	(Johnston-Monje et al., 2019)
	Catharanthus roseus and *Euphorbia hirta*	Antibacterial and antifungal Antibacterial	Chaetomugilin A and D4-(2,4,7-trioxa-bicyclo[4,10]- heptan-3-yl)	(Hu et al., 2024)
Streptomyces sp. neau-D50	-	-	Fumigaclavine C	(Tshikhudo et al., 2023)

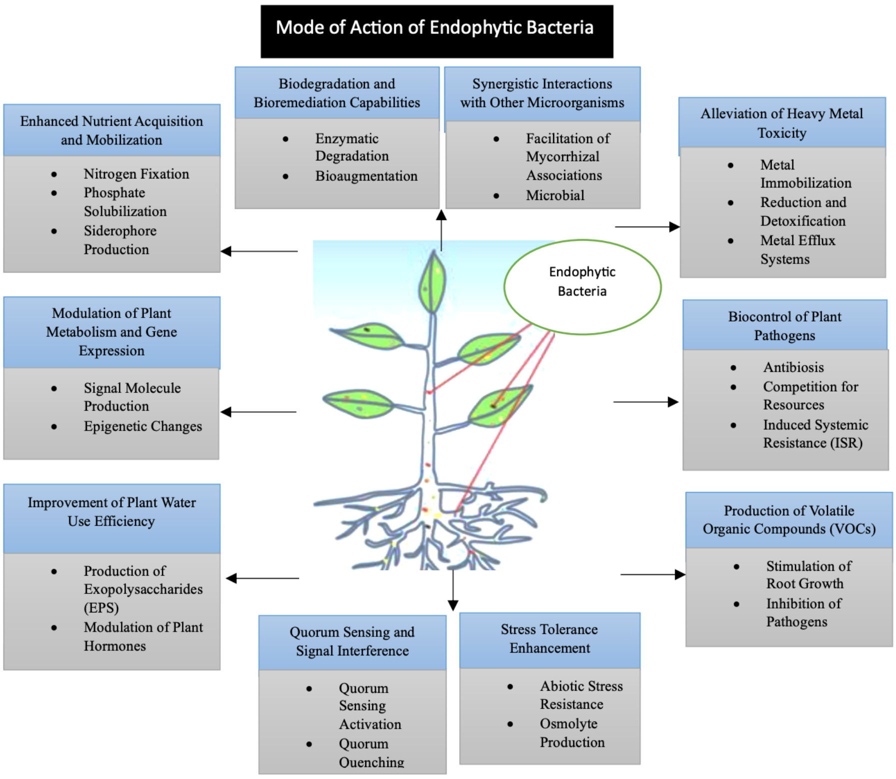

Figure 1. The role and mode of action of plant endophytes in relation to their host plants and surroundings.

bacterium *Micromonospora sp.* connected to the medicinal plant *Euphorbia antiquorum*. Furthermore, endophytes connected to conventionally used medicinal plants have been found to be sources of bioactive substances, adding to the pharmacological benefit of these plants. For example, strains of *Streptomyces* isolated from *Vinca rosea* have demonstrated the ability to yield chemicals like vinblastine and vincristine, which are well-known anticancer drugs (Matsumoto & Takahashi, 2017).

Endophytic bacteria are extremely useful in the quest for novel medications because of their capacity to create unique chemicals, especially in light of the need for new therapeutic agents due to the rise in antibiotic resistance.

5.2 Pharmaceutical Applications

Beyond the conventional discovery of antibiotics, endophytic bacteria have a wide range of therapeutic applications. Their metabolites have been linked to treatment in a number of fields, such as immunomodulation, antimicrobial therapy, and oncology. Numerous substances generated from endophytes show cytotoxic effects on cancer cell lines, which makes them promising candidates for the development of anticancer drugs (Moussa, 2024).

Furthermore, endophytic bacteria's antibacterial qualities have been established. Products of the *Bacillus* species, such as lipopeptides, show considerable efficacy against a variety of pathogens, including fungus and bacteria, and are being investigated for application in both clinical and agricultural contexts (Madasi et al., 2021). For example, *Bacillus subtilis* has been used because of its bio-fungicidal qualities, which minimize environmental effect while shielding crops from fungal infestations (Gakuubi et al., 2021).

Furthermore, endophytes can aid in the synthesis of immunomodulatory substances that strengthen the host's defenses against infection. As an illustration, polysaccharides extracted from endophytic bacteria have demonstrated promise as immunostimulants, suggesting possible uses in the creation of vaccines (Renugadevi et al., 2021).

5.3 Challenges and Opportunities in Commercialization

Endophytic bacteria have a bright future in drug development; however, commercialization is hampered by several issues. The heterogeneity in the generation of bioactive chemicals between strains, and even within the same strain under varied environmental circumstances, is a noteworthy concern. The development process may become more difficult as a result of this unpredictability, which might result in inconsistent product efficacy and quality (Johnston-Monje et al., 2019). Furthermore, it might take a lot of time and effort to isolate and cultivate endophytic bacteria because many strains are challenging to grow in typical laboratory settings. By enabling the identification of novel strains and enhancing growing conditions, the application of sophisticated cultivation techniques, such as high-throughput screening and metagenomic approaches, may help address these issues (Gupta et al., 2020).

Opportunities for commercialization exist in developing bioproducts that leverage the unique properties of endophytic bacteria. Collaborations between academic institutions and pharmaceutical companies can foster innovation in drug development, focusing on bioprospecting for new compounds (Brader et al., 2017). Furthermore, the increasing interest in natural products and sustainable bioprospecting aligns well with the potential of endophytic bacteria to contribute to the development of new therapeutics.

In summary, there are a lot of chances to identify new bioactive chemicals with a variety of pharmaceutical uses by using endophytic bacteria in drug development. Technology breakthroughs and teamwork can open the door to successful commercialization, even though obstacles still exist (Christinaki et al., 2024).

6. Challenges and Future Prospects in the Study of Endophytic Bacteria

Owing to their potential to increase the therapeutic value of plants, endophytic bacteria have attracted a lot of research interest. Progress in this subject is still hampered by a number of issues, though. In addition to outlining future objectives for the study of endophytic bacteria, this section covers various research problems.

6.1 Research Challenges

6.1.1 Diversity and Characterization

The great diversity that exists among endophytic bacteria is one of the main obstacles to research in this field. Isolating and characterizing endophytes' metabolites is hampered by the fact that many of them are unculturable in typical laboratory settings (Covington et al., 2017). Although molecular methods, like next-generation sequencing (NGS), can shed light on the make-up of endophytic communities, deciphering complicated datasets is still a difficulty (Hu et al., 2024).

6.1.2 Variability in Bioactive Compound Production

Depending on the host plant species, cultivation circumstances, and environmental factors, endophytic bacteria frequently show heterogeneity in their synthesis of bioactive substances. This variability creates difficulties for commercialization by making it more difficult to standardize the extraction of bioactive compounds and to produce consistent therapeutic profiles (Zimmerman & Vitousek, 2012).

6.1.3 Understanding Plant-Endophyte Interactions

Endophytic bacteria and their host plants interact in ways that are yet not entirely understood by the mechanisms underpinning these interactions. Utilizing endophytes to their maximum potential in augmenting plant therapeutic qualities requires identifying the signaling pathways and molecular interactions that mediate these associations (Hardoim et al., 2015).

6.1.4 Regulatory and Safety Concerns

Regulation and public safety are at risk with the commercialization of bioactive substances produced by endophytic bacteria. Comprehensive safety investigations are necessary before these chemicals may be approved for use in agriculture and medicines due to the possibility of creating hazardous metabolites, such as mycotoxins (Tiwari & Bae, 2020).

6.2 Future Directions

6.2.1 Integration of Multi-Omics Approaches

In order to provide a comprehensive understanding of endophytic bacteria, future research should concentrate on integrating multi-omics approaches (genomics, transcriptomics, proteomics, and metabolomics). These methods can clarify the intricate relationships between metabolite synthesis and gene expression, making it possible to identify new bioactive substances and maximize their yields (Renugadevi et al., 2021).

6.2.2 Biotechnological Applications

A possible path is using endophytic bacteria for biotechnological purposes such bioremediation, improving agriculture, and developing sustainable pharmaceuticals. Engineering endophytes to produce desired metabolites more efficiently could result in the creation of novel bioproducts with important industrial and medical uses (Gazis et al., 2014).

6.2.3 Exploration of Underutilized Plant Species

Investigating the endophytic ecosystems connected to underutilized and poorly researched medicinal plants is necessary. Numerous conventionally used therapeutic plants might have special endophytes that can generate brand-new bioactive substances. By focusing on these plants, one may find new sources of medicinal substances (Zanne et al., 2020).

6.2.4 In Situ Studies and Natural Habitat Preservation

Investigating endophytic bacteria in their natural environments through in situ research can yield important information on the roles and interactions these organisms play in the ecosystem. By guaranteeing long-term access to these biological resources, this strategy can also support the conservation of plant species that include important endophytes (Uzma et al., 2018).

6.2.5 Collaboration and Interdisciplinary Research

Fostering cooperation amongst botanists, biotechnologists, pharmacologists, and microbiologists is essential to the advancement of this field of study. Multidisciplinary studies can help researchers exchange ideas and methods, which can result in more creative ways to use endophytic bacteria in medicine (Krabel et al., 2013). In summary, even though studying endophytic bacteria presents certain difficulties, there are still a lot of untapped possibilities for further investigation and use. It is possible to fully grasp the promise of endophytic bacteria as bioactive treasure troves by tackling these obstacles and venturing into uncharted territory.

7. Conclusion

Endophytic bacteria represent an extraordinary, largely untapped source of bioactive compounds with immense potential for drug discovery and the development of new therapeutic agents. Their unique symbiotic relationship with medicinal plants enables them to produce a wide array of metabolites with significant pharmacological properties, enhancing both the therapeutic value of these plants and the resilience of their host. This review underscores the multifaceted roles of endophytic bacteria, including bioactive compound production, plant growth promotion, and systemic resistance induction, which collectively contribute to plant health and therapeutic potential.

Despite promising findings, challenges remain in harnessing the full potential of endophytic bacteria. Issues such as the vast microbial diversity, variability in metabolite production, and the need for advanced isolation and characterization techniques limit progress in this field. Additionally, regulatory challenges surrounding natural products further complicate the commercialization of endophyte-derived compounds.

Future research should focus on applying advanced omics techniques to deepen our understanding of the intricate interactions between endophytic bacteria and their host plants. Investigating underutilized medicinal plants and leveraging biotechnological strategies to enhance bioactive compound production will also be essential. Cross-disciplinary collaboration will be key to overcoming these challenges, facilitating innovation, and paving the way for novel therapeutic developments.

Author contributions

T.C. contributed to the conceptualization, data analysis, and drafting of the manuscript.M.A. supervised the study, reviewed the methodology, and provided critical revisions to the manuscript.

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Competing financial interests

The authors have no conflict of interest.

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