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PLANT–MICROBIOME INTERACTIONS AS A NOVEL AXIS FOR SECONDARY METABOLITE DIVERSIFICATION

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ABSTRACT

Plants harbor diverse microbial communities—comprising endophytic and rhizospheric microorganisms—that profoundly influence host secondary metabolism. This review critically examines the emerging evidence for plant-microbiome interactions as a novel axis for secondary metabolite diversification. We synthesize current understanding of the mechanisms by which endophytic and rhizospheric microbes modulate the biosynthesis, structural modification, and biological potency of host plant secondary metabolites. Microbial communities influence plant secondary metabolism through multiple strategies, including activation of plant immune signaling pathways, secretion of phytohormones, nutrient modulation, and direct biotransformation of plant-derived precursors. The resulting metabolic alterations encompass enhanced production of existing bioactive compounds, generation of novel derivatives through microbial enzymatic activity, and discovery of previously unknown metabolites. Furthermore, we assess the implications of these interactions for drug discovery, sustainable agriculture, and the conservation of medicinal plant resources. Despite significant progress, substantial research gaps remain regarding the mechanistic basis of microbial influence on plant metabolism and the translation of these interactions into biotechnological applications. This review provides a comprehensive framework for understanding plant-microbiome interactions in secondary metabolism and identifies promising directions for future research.

Keywords: Plant-Microbiome; Endophytes; Rhizosphere; Secondary Metabolites; Biosynthesis; Metabolic Diversification

1 INTRODUCTION

Plants produce an extraordinary diversity of secondary metabolites, estimated to exceed 100,000 compounds, which serve ecological functions including defense against herbivores and pathogens, attraction of pollinators, and adaptation to environmental stress (Kumari et al., 2023). These compounds also represent a rich source of pharmaceuticals, agrochemicals, and other valuable products (Atanasov et al., 2021). The biosynthesis of plant secondary metabolites is regulated by complex genetic and environmental factors, including interactions with associated microorganisms (Yu et al., 2024).

Plant-associated microbial communities, encompassing both endophytic microorganisms that reside within plant tissues and rhizospheric microbes in the root zone, have emerged as significant modulators of plant secondary metabolism (Yu et al., 2024). These microorganisms establish symbiotic relationships with medicinal plants to promote plant growth, while others can directly synthesize secondary metabolites or promote plant secondary metabolite biosynthesis through multiple strategies, such as activating plant immune signaling pathways and secreting plant hormones into host cells to manipulate hormone-mediated pathways (Yu et al., 2024). The resulting microbial influence on plant secondary metabolism represents a novel axis for metabolic diversification, with significant implications for drug discovery, sustainable agriculture, and ecosystem functioning.

The intricate interplay between plants and endophytic microorganisms has emerged as a captivating subject of scientific investigation, with profound implications for the sustainable biosynthesis of pharmaceutically important secondary metabolites (Kumari et al., 2023). This review delves into the multifaceted interactions between plants and their associated microbiomes that underpin the synthesis of bioactive compounds with medicinal significance. The term "plant microbiome" broadly refers to all distinctive microbial communities that inhabit the endosphere (plant internal tissues), phyllosphere (air-plant interface), and rhizosphere (plant roots-soil interface) (Kumari et al., 2023).

This review provides a comprehensive synthesis of current understanding of plant-microbiome interactions in secondary metabolite diversification. We critically evaluate the mechanisms of microbial influence on plant metabolism, assess the evidence for microbiome-mediated diversification, and identify research gaps and future directions.

2 THE PLANT MICROBIOME: COMPOSITION AND FUNCTION

2.1 Endophytic Microorganisms

Endophytic microorganisms colonize the internal tissues of plants without causing apparent disease symptoms. The endophytes form tight associations with their host and thus play a pivotal role in plant growth, fitness, and development in addition to protecting against biotic and abiotic stresses via secretion of indole-3-acetic acid (IAA), siderophores, phosphate solubilizers, etc. (Kumari et al., 2023). In most cases, the interaction is mutually beneficial as the plant provides carbon in return for other nutrients, metabolites and protection against pests, pathogens and abiotic stresses, thereby altering the plant metabolome in various ways (Kumari et al., 2023).

Endophytic bacteria, part of the plant microbiome, hold significant potential for enhancing the cultivation and sustainability of medicinal plants (Semenzato et al., 2024). These microbes are integral to many plant functions, including growth promotion, nutrient acquisition, and resistance to biotic and abiotic stresses (Semenzato et al., 2024). Endophytic bacteria can directly boost medicinal plant productivity by promoting plant growth and health or indirectly by restoring healthy soil microbiomes (Semenzato et al., 2024). They can also be harnessed as microbial factories to produce valuable natural compounds, either by transforming plant-derived precursors into bioactive substances or by synthesizing unique metabolites that mimic medicinal plant secondary metabolites (Semenzato et al., 2024).

Endophytic fungi form an integral part of plant microbiomes, influencing host physiology, stress resilience, and secondary metabolism. The application of cultivated endophytes from wild plants has demonstrated the potential to restore microbial functions lost during in-vitro propagation and enhance secondary metabolite production in cultivated plants.

2.2 Rhizospheric Microorganisms

The rhizosphere, the narrow zone of soil influenced by plant roots, harbors diverse microbial communities that interact with plants through root exudates and signaling molecules. Rhizosphere microorganisms influence plant metabolic pathways through complex interactions that lead to the increased production of essential oils, amino acids, and other valuable secondary metabolites (Mechanisms and Impact, 2024). These interactions often involve signaling processes that modify the plant's gene expression and enzymatic activity, which in turn alters the synthesis of specific compounds (Mechanisms and Impact, 2024).

Rhizobacteria such as Bacillus subtilis and Streptomyces can enhance amino acid and nitrogen assimilation pathways, contributing to improved plant metabolism. Plant growth-promoting rhizobacteria (PGPR) are a group of beneficial bacteria that can interact with both plants and the soil microbiome and induce the production of secondary metabolites (Beneficial Microbe-Induced Secondary Metabolites, 2024).

Arbuscular mycorrhizal fungi (AMF) significantly improve the production of secondary metabolites in medicinal plants. AMF affects secondary metabolism and the production of active ingredients of medicinal plants and thus influences the quality of herbal medicines (Arbuscular mycorrhizal symbiosis, 2024). Various aspects such as the occurrence of mycorrhizae on growth and yield of medicinal plants, and in the synthesis of secondary metabolites, have been reviewed by various researchers (An appraisal of arbuscular mycorrhiza, 2023).

2.3 The Holobiont Concept

Plants function as complex holobionts, with their therapeutic potential significantly shaped by the associated microbiome, particularly endophytic fungi (OpenLB, 2024). These symbionts engage in a sophisticated "chemical signaling" with their hosts, acting as biotic elicitors that modulate plant secondary metabolism while simultaneously responding to host cues to activate their own cryptic biosynthetic gene clusters (BGCs) (OpenLB, 2024).

A paradigm shift has redefined plants as holobionts, with complex associations between the plant host and its associated microbial communities. Due to "cross-talk" between plant and endophyte metabolic pathways, a diverse metabolic gene cluster repertoire may lead to even further diversification of the metabolite profile in the holobiont (Endophyte genomes, 2023). Increased diversity of both DGCs and BGCs in endophytes may ultimately improve the fitness of the holobiont (a plant and all closely-associated microorganisms) (Endophyte genomes, 2023).

Table 1: Microbial Communities Associated with Plants and Their Roles in Secondary Metabolism

Microbial Group	Habitat	Key Functions	Impact on Secondary Metabolites
Bacterial Endophytes	Internal plant tissues *(stem, leaf, root)*	Plant growth promotion, abiotic/biotic stress resistance, autonomous metabolite synthesis	Direct synthesis of host-like compounds, precursor transformation, and pathway upregulation
Fungal Endophytes	Internal plant tissues	Stress resilience, enhanced nutrient acquisition, inter-species signaling	Biotic elicitation, bio-transformation of metabolic intermediates, and activation of silent/cryptic gene clusters
Rhizobacteria (PGPR)	Root–soil interface *(rhizosphere)*	Solubilization of nutrients, induction of ISR *(Induced Systemic Resistance)*, phytohormone production	Modulation of secondary metabolic pathways and differential gene expression changes in host plants
Arbuscular Mycorrhizal Fungi (AMF)	Root cortex & surrounding soil matrix	Enhanced phosphorus/mineral uptake, improved water relations, stress tolerance	Significant upregulation and accumulation of bioactive secondary metabolites *(e.g., phenolics, terpenoids)*

3 MECHANISMS OF MICROBIAL INFLUENCE ON SECONDARY METABOLISM

3.1 Activation of Plant Immune Signaling Pathways

Microorganisms can activate plant immune signaling pathways that trigger secondary metabolite biosynthesis. While some microorganisms establish symbiotic relationships with medicinal plants to promote plant growth, other microorganisms can directly synthesize secondary metabolites or promote plant secondary metabolite biosynthesis through multiple strategies, such as activating plant immune signaling pathways and secreting plant hormones into host cells to manipulate hormone-mediated pathways (Yu et al., 2024).

Induced systemic resistance (ISR) is a mechanism by which certain plant beneficial rhizobacteria and fungi produce immunity, which activates the gene expression of ISR, the synthesis of secondary metabolites, various enzymes, and volatile compounds that ultimately induce defense mechanisms in plants (Rabari et al., 2023). ISR involves the jasmonic acid (JA) and ethylene (ET) pathways, which activate the gene expression of ISR, the synthesis of secondary metabolites, various enzymes, and volatile compounds that ultimately induce defense mechanisms in plant (Rabari et al., 2023).

Endophytic fungi have been shown to modulate tanshinone biosynthesis in Salvia miltiorrhiza roots via salicylic acid signaling pathways. While endophytic fungi are known to influence plant secondary metabolism, the underlying hormonal mechanisms remain an active area of investigation.

3.2 Secretion of Plant Hormones

Microorganisms can secrete plant hormones into host cells to manipulate hormone-mediated pathways, thereby influencing secondary metabolite accumulation (Yu et al., 2024). Endophytic bacteria can secrete indole-3-acetic acid (IAA), siderophores, and phosphate solubilizers that promote plant growth and development while also influencing metabolic pathways (Kumari et al., 2023).

The auxin signaling pathway activated by endophytic cross-kingdom synthetic microbiota improves the quality of medicinal plants by regulating secondary metabolic pathways (Auxin signaling activated, 2025). Endophytes assist medicinal plants in the synthesis of important pharmacologically bioactive molecules by regulating secondary metabolic pathways (Auxin signaling activated, 2025).

3.3 Nutrient Modulation and Resource Allocation

Microorganisms can alter nutrient availability, which in turn influences the allocation of resources between primary and secondary metabolism. Seed bacterization with siderophore-producing bacteria has been shown to play a vital role in optimizing iron uptake, which is crucial for secondary metabolite biosynthesis (Seed bacterization, 2025). This research highlights the potential of using microbial biotechnology to improve the yield of valuable pharmaceutical compounds in medicinal plants (Seed bacterization, 2025).

Arbuscular mycorrhizal fungi enhance nutrient uptake, particularly phosphorus, which can stimulate the production of secondary metabolites in medicinal plants (Arbuscular mycorrhizal symbiosis, 2024). The improved nutrient status of AMF-colonized plants may allow for increased investment in defensive secondary metabolites.

3.4 Direct Synthesis of Secondary Metabolites

Some microorganisms can directly synthesize secondary metabolites or transform plant-derived precursors into bioactive substances (Semenzato et al., 2024). Endophytic bacteria can be harnessed as microbial factories to produce valuable natural compounds, either by transforming plant-derived precursors into bioactive substances or by synthesizing unique metabolites that mimic medicinal plant secondary metabolites (Semenzato et al., 2024).

Endophytic fungi have been shown to biotransform chemical structures of biologically active compounds, acting as powerful catalytic cells for the modification of plant metabolites (Plant Endophytic Fungi, 2025). In this process, endophytes act as an enzyme source to catalyze chemical reactions and modify the structures of bioactive compounds (Plant Endophytic Fungi, 2025).

Endophytic bacteria associated with medicinal plants are an underexplored source of bioactive compounds (Endophytic bacteria webinar, 2024). These microorganisms significantly contribute to plant growth, stress resilience, and secondary metabolite production, making them valuable candidates for drug discovery (Endophytic bacteria webinar, 2024).

3.5 Elicitation and Cryptic Pathway Activation

Table 2: Mechanisms of Microbial Influence on Plant Secondary Metabolism

Mechanism	Description	Key Microbial Types	Evidence Level
Immune Signaling Activation	Triggering of jasmonic acid (JA) and ethylene (ET) defense pathways, driving secondary metabolite (SM) biosynthesis	Rhizobacteria, Endophytes	High
Phytohormone Secretion	Synthesis of indole-3-acetic acid (IAA) and other growth regulators that modulate plant metabolic pathways	Endophytic bacteria	Moderate
Nutrient Modulation	Facilitation of enhanced macro/micronutrient uptake, providing precursors and energy for SM production	Arbuscular Mycorrhizal Fungi (AMF), Rhizobacteria	High
Direct SM Synthesis	Autonomous microbial production of specialized bioactive natural products within host tissues	Endophytic bacteria, Endophytic fungi	Moderate
Biotransformation	Enzymatic alteration and structural modification of existing plant secondary metabolites	Endophytic fungi	Moderate
Cryptic Pathway Activation	Host-microbe interaction signaling that induces expression of silent biosynthetic gene clusters (BGCs)	Endophytic fungi	Emerging

Recent insights into the essential role of the plant microbiota provide new opportunities for elicitation strategies by microbial coculture in a controlled environment (Laffon et al., 2024). The successful co-culture of in vitro medicinal plants with synthetic microbial communities could enable sustainable production of pharmaceutically important specialized metabolites (Laffon et al., 2024).

Endophytic fungi act as biotic elicitors that modulate plant secondary metabolism while simultaneously responding to host cues to activate their own cryptic biosynthetic gene clusters (BGCs) (OpenLB, 2024). Epigenetic manipulation has emerged as a strategy for secondary metabolite activation in endophytic fungi, with epigenetic elicitors showing capacity to boost the production of secondary metabolites from endophytes (Epigenetic manipulation, 2023). This approach has the potential to rejuvenate the drug discovery pipeline by introducing new chemical compounds (Epigenetic manipulation, 2023).

4 EVIDENCE FOR MICROBIOME-MEDIATED DIVERSIFICATION

4.1 Enhancement of Bioactive Compound Production

Microbial interactions can significantly enhance the production of bioactive compounds in medicinal plants. Endophytic bacteria inoculation is an effective strategy for enhancing the essential oil content and metabolic profile of medicinal plants (Isolated endophytic bacteria, 2025). Exploring novel endophytic isolates and assessing their influence on medicinal plants can boost plant health and improve metabolite synthesis (Isolated endophytic bacteria, 2025).

Endophytic bacteria's phenylalanine and trans-cinnamic acid serve as exogenous precursors involved in modulating the colchicine biosynthesis pathway in Gloriosa superba (Endophytic bacterial's phenylalanine, 2025). Metabolite analysis identifies essential precursors for colchicine biosynthesis, and Bacilli inoculation shows higher colchicine in G. superba by enhancing nutrient uptake and activating biosynthetic enzymes (Endophytic bacterial's phenylalanine, 2025).

Arbuscular mycorrhizal fungi significantly improve the production of secondary metabolites in medicinal plants (An appraisal of arbuscular mycorrhiza, 2023). The influences of AMF on the production of important secondary metabolites have been highlighted, with future prospects identified for AMF in the cultivation of medicinal plants (An appraisal of arbuscular mycorrhiza, 2023).

4.2 Structural Modification and Biotransformation

Endophytic fungi can biotransform plant secondary metabolites, generating novel derivatives with altered biological activities. The transformation and catalysis of metabolic intermediates by endophytic fungi have become a new factor and resource attracting attention in recent years (Progress on metabolites of Astragalus, 2024). Endophytic fungi from Astragalus medicinal plants have shown the ability to biotransform four saponin compounds, resulting in the production of 66 new compounds (Progress on metabolites of Astragalus, 2024). This provides a scientific basis for improving the cultivation quality of Astragalus (Progress on metabolites of Astragalus, 2024).

Plant endophytic fungi serve as powerful catalytic cells for the biotransformation of chemical structures of biologically active compounds (Plant Endophytic Fungi, 2025). This review focuses on the utilization of endophytic fungi in the biotransformation process of bioactive compounds to improve their pharmacological, pharmacokinetic, or toxicological parameters (Plant Endophytic Fungi, 2025). The microbial biotransformation of plant metabolites through a mechanism-focused framework that integrates enzymology and reaction chemistry represents an emerging frontier (Plant Endophytic Fungi, 2025).

4.3 Discovery of Novel Compounds

Endophytes associated with medicinal plants can produce unique metabolites that mimic or complement host secondary metabolites (Semenzato et al., 2024). The research highlights the importance of exploring endophytic microbiomes of medicinal plants to uncover their potential for secondary metabolite production and their role in the biosynthesis of host-derived compounds (Antibacterial and antioxidant potentials, 2025).

The core microbiome of medicinal plants serves as a rich reservoir of beneficial microbes for secondary metabolism (Core microbiome, 2024). Unlocking the potential of bacterial endophytes from medicinal plants for drug discovery represents a promising direction (Unlocking the potential, 2024).

4.4 Case Studies

Salvia miltiorrhiza: Endophytic fungi have been shown to modulate tanshinone biosynthesis via hormonal signaling pathways. Co-culture experiments showed that endophytic strains had different effects on the biomass and the accumulation of secondary metabolites in the hairy roots of S. miltiorrhiza (Isolation of Endophytic Fungi, 2024). The core microbiome of Salvia miltiorrhiza seed has been identified as a rich reservoir of beneficial microbes for secondary metabolism (Core microbiome, 2024).

Catharanthus roseus: Seed bacterization with siderophore-producing bacteria has been shown to enhance growth and alkaloid content in Catharanthus roseus (Seed bacterization, 2025). Bacterial siderophores play a vital role in optimizing iron uptake, which is crucial for secondary metabolite biosynthesis (Seed bacterization, 2025).

Atractylodes chinensis: Endophytic cross-kingdom synthetic microbiota activated by auxin signaling improves the quality of Atractylodes chinensis (Auxin signaling activated, 2025). Endophytes assist medicinal plants in the synthesis of important pharmacologically bioactive molecules by regulating secondary metabolic pathways (Auxin signaling activated, 2025).

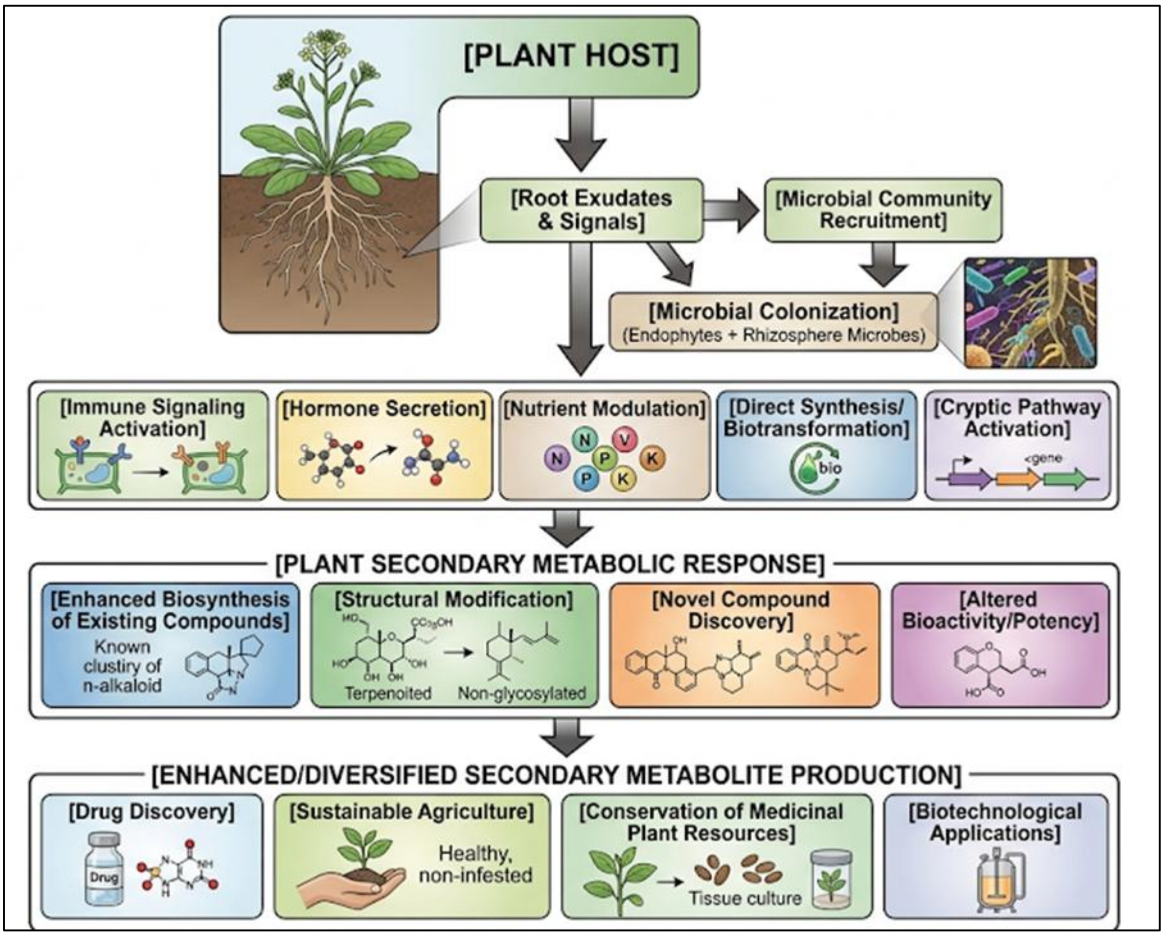

Figure 1: Conceptual Framework for Plant-Microbiome Interactions in Secondary Metabolite Diversification

5 IMPLICATIONS FOR DRUG DISCOVERY AND BIOTECHNOLOGY

5.1 Microbiome-Guided Drug Discovery

The influence of plant-associated microorganisms on secondary metabolite production has significant implications for drug discovery. Microbiome-guided screening strategies can identify plants with enhanced production of bioactive compounds. The endophytic microbiome of medicinal plants represents an underexplored source of bioactive compounds with therapeutic potential (Endophytic bacteria webinar, 2024).

The successful co-culture of in vitro medicinal plants with synthetic microbial communities could enable sustainable production of pharmaceutically important specialized metabolites (Laffon et al., 2024). Biotization with pure microbial strains improves specialized metabolite productivity, and co-culture with living microbes offers new opportunities for elicitation strategies (Laffon et al., 2024).

5.2 Biotechnological Applications

The manipulation of plant-associated microbial communities offers opportunities for enhancing secondary metabolite production. Endophytic bacteria can be harnessed as microbial factories to produce valuable natural compounds, either by transforming plant-derived precursors into bioactive substances or by synthesizing unique metabolites that mimic medicinal plant secondary metabolites (Semenzato et al., 2024). This offers a sustainable and low-cost alternative to traditional medicinal plant cultivation, reducing the carbon footprint and preserving endangered species (Semenzato et al., 2024).

Microbial inoculation is a sustainable strategy to stimulate the production of secondary metabolites. Inoculation with Bacillus velezensis FZB42 has been shown to promote growth and secondary metabolism in medicinal plants, offering insights into the regulations of growth–metabolism trade-off.

5.3 Sustainable Agriculture and Conservation

Understanding plant-microbiome interactions in secondary metabolism has implications for sustainable agriculture and conservation. Traditional cultivation practices often overlook the importance of beneficial microbes, leading to reduced crop yields, lower phytochemical quality, and increased susceptibility to diseases (Semenzato et al., 2024). The domestication of medicinal plants and the use of chemical fertilizers disrupt the natural microbial diversity in soils, essential for the health and productivity of plants (Semenzato et al., 2024). Integrating microbiome research with traditional agricultural practices could revolutionize medicinal plant cultivation (Semenzato et al., 2024).

Conservation strategies for medicinal plants should consider the preservation of associated microbial communities, as these microbes are integral to the production of bioactive compounds with therapeutic properties. By focusing on the microbial component, particularly endophytes, we can develop more sustainable and productive methods for cultivating medicinal plants, ultimately contributing to biodiversity conservation and the production of high-value natural products (Semenzato et al., 2024).

6 CHALLENGES AND RESEARCH GAPS

6.1 Mechanistic Understanding

Despite significant progress, the mechanistic basis of microbial influence on plant secondary metabolism remains incompletely understood. While endophytic fungi are known to influence plant secondary metabolism, the underlying hormonal mechanisms remain poorly understood. The specific signaling pathways, regulatory networks, and causal relationships between particular microbial taxa and specific metabolic outcomes require further elucidation.

6.2 Complexity and Variability

Plant-microbiome interactions are inherently complex and influenced by multiple environmental factors, making experimental reproducibility challenging. Temporal and spatial variation in microbial communities adds additional complexity. The translation of findings from controlled laboratory conditions to field settings remains challenging. SM accumulation is affected by multiple factors, including genetic background, climate, soil physical and chemical properties, and environmental changes (Yu et al., 2024).

6.3 Application Challenges

The development of microbial inoculants for enhancing secondary metabolite production faces challenges including strain selection, formulation stability, and field performance consistency. Further studies should focus on the application of utilizing microorganisms to enhance the accumulation of bioactive secondary metabolites in medicinal plants (Yu et al., 2024). Regulatory approval for microbial inoculants can be time-consuming and resource-intensive. Intellectual property issues related to microbial strains and their metabolites require careful consideration.

6.4 Knowledge Gaps in Biotransformation

While endophytic fungi have demonstrated significant potential for biotransformation of plant metabolites, the full scope of their catalytic capabilities and the enzymes involved remain to be fully characterized. The mechanisms by which endophytes select, recognize, and modify specific plant metabolites require further investigation.

7 FUTURE PERSPECTIVES

The future of research on plant-microbiome interactions in secondary metabolism lies in the integration of multi-omics approaches and systems biology. Metagenomic and metatranscriptomic analyses will enable comprehensive characterization of microbial communities and their functional activities. The application of synthetic biology approaches for engineering plant-microbiome interactions promises to enhance secondary metabolite production.

The development of predictive models for plant-microbiome interactions in secondary metabolism will facilitate the design of microbial inoculants for specific applications. The exploration of plant-microbiome interactions in diverse ecosystems, including extreme environments, may reveal novel mechanisms and compounds. The successful implementation of in situ microbiome manipulation through high-end techniques can pave the way towards a more sustainable and pharmaceutically enriched future.

The development of synthetic microbial communities (SynComs) for controlled co-culture with medicinal plants represents a promising direction for sustainable production of specialized metabolites. Continued investment in fundamental research is essential for translating basic knowledge into practical applications for drug discovery, agriculture, and conservation.

8 CONCLUSION

Plant-associated microbial communities play a significant role in modulating the biosynthesis, structural modification, and biological potency of host plant secondary metabolites. Rhizospheric and endophytic microorganisms regulate the accumulation of secondary metabolites in medicinal plants through multiple strategies, including activating plant immune signaling pathways, secreting plant hormones, modulating nutrient availability, directly synthesizing metabolites, and biotransforming plant-derived precursors. The resulting metabolic alterations encompass enhanced production of existing bioactive compounds, generation of novel derivatives through microbial enzymatic activity, and discovery of previously unknown metabolites.

The holobiont concept, recognizing plants and their associated microbiomes as integrated functional units, provides a framework for understanding the full scope of metabolic interactions. Endophytic fungi and bacteria, as well as rhizospheric microorganisms including AMF and PGPR, contribute to the chemical diversity of medicinal plants through diverse mechanisms. These interactions have significant implications for drug discovery, sustainable agriculture, and the conservation of medicinal plant resources. The integration of microbiome research with traditional cultivation practices and biotechnological approaches promises to revolutionize medicinal plant production and natural product discovery. Continued research, employing integrated multi-omics approaches and mechanistic investigation, will advance understanding of plant-microbiome interactions in secondary metabolism and facilitate the development of practical applications for biotechnology and medicine.

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