

Metagenomic and Functional Profiling of Endophytes from Indonesian Medicinal Plants: Potentials for Sustainable Bioprospecting

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ABSTRACT

Indonesia's extraordinary plant biodiversity remains underutilised in microbial bioprospecting, despite its vast potential to support sustainable biotechnological innovation. This study aims to explore and characterise endophytic microorganisms associated with selected Indonesian medicinal plants, focusing on their genetic and functional traits relevant to bioactive compound production. Addressing a gap in integrative profiling, the study adopts a qualitative literature-based methodology, synthesising findings from over 30 peer-reviewed, Scopus-indexed studies published between 2015 and 2024. These studies involve next-generation sequencing, biosynthetic gene cluster (BGC) analysis, and in vitro functional assays. Notably, endophytes isolated from plants such as *Curcuma longa*, *Andrographis paniculata*, and *Phyllanthus niruri* harbour diverse and unique BGCs, including non-ribosomal peptide synthetases (NRPS) and polyketide synthases (PKS), which are linked to antimicrobial, enzymatic, and plant growth-promoting activities. The originality of this study lies in its interdisciplinary synthesis bridging microbial ecology, genomics, and biotechnology, contributing to the theoretical advancement of microbial symbiosis and offering practical implications for natural product development, sustainable agriculture, and Indonesia's emerging bioeconomy.

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1. INTRODUCTION

Indonesia, as one of the world's most biodiverse countries, harbors an immense variety of medicinal plants with substantial ethnobotanical value. However, the associated endophytic microbial communities—particularly fungi and bacteria that reside asymptotically within plant tissues—remain poorly characterised, despite their potential as reservoirs of novel bioactive

compounds (Compant et al., 2010; Kusari et al., 2012). Endophytes have garnered increasing scientific interest due to their capacity to synthesise secondary metabolites, including alkaloids, flavonoids, terpenoids, and polyketides, which may be analogous or even superior to those produced by their host plants (Barka et al., 2016). These metabolites exhibit promising antimicrobial, anticancer, and plant growth-promoting activities

(Zhang et al., 2019). As global demand intensifies for sustainable, bio-based solutions in agriculture, pharmaceuticals, and environmental management, the bioprospecting of such microbial symbionts presents a strategic avenue for innovation (Trivedi et al., 2020).

Despite these promising developments, there remains a critical lack of integrative, genome-enabled characterisation of endophytic microorganisms from Indonesia's medicinal flora. Most existing studies are fragmented, either focusing on isolated strains or lacking functional genomic depth. This review seeks to address that gap by synthesising current metagenomic and biofunctional research on endophytes derived from Indonesian medicinal plants, evaluating their biosynthetic potential, and identifying their relevance for sustainable biotechnological applications.

2. LITERATURE REVIEW

2.1 *Endophytic Microorganisms and Their Functional Roles*

Endophytes, comprising diverse fungi and bacteria, establish mutualistic interactions with plants, contributing to host health by enhancing nutrient uptake, providing resistance to pathogens, and producing growth-promoting compounds. Many endophytes produce secondary metabolites that mirror or surpass the bioactivities of their plant hosts (Kusari et al., 2012). These metabolites include alkaloids, terpenoids, steroids, and amides that play roles in plant defense, growth promotion, and stress resistance (Hardoim et al., 2015). Functional traits such as nitrogen fixation, phosphate solubilization, production of indole-3-acetic acid (IAA), siderophores, and enzymatic activities (protease, cellulase) are common among endophytic bacteria, enabling them to promote plant growth and suppress pathogens (Tshikhudo et al., 2023).

2.2 *Indonesian Medicinal Plants as Reservoirs of Microbial Diversity*

Indonesia's rich ethnomedicinal flora, including species such as *Curcuma longa*, *Andrographis paniculata*, *Phyllanthus niruri*,

and *Eurycoma longifolia*, harbours unique and diverse endophytic communities with promising bioactivities. For instance, actinobacterial endophytes isolated from *Curcuma* spp. have demonstrated notable antimicrobial properties (Supriatno et al., 2019). However, comprehensive genome-based investigations into these communities remain limited. While *C. longa* and *E. longifolia* have been relatively well-studied, research on endemic species from less-explored regions such as Papua or Kalimantan is notably scarce, indicating both a taxonomic and geographic bias in current literature (Prihartin et al., 2023). This uneven research distribution not only limits our understanding of Indonesia's full microbial potential but also underscores the urgency of including underrepresented bioregions in future bioprospecting initiatives.

2.3 *Advances in Metagenomics and Genome Mining*

Metagenomic technologies such as 16S rRNA gene sequencing, shotgun metagenomics, and long-read sequencing have revolutionized the study of microbial diversity by enabling culture-independent analyses (Zhang et al., 2019). Genome mining tools like antiSMASH and PRISM facilitate the identification and annotation of biosynthetic gene clusters (BGCs), including non-ribosomal peptide synthetases (NRPS) and polyketide synthases (PKS), which are responsible for the synthesis of bioactive secondary metabolites (Rahman and Wijaya, 2020). Recent studies have demonstrated the power of metagenomics in uncovering novel metabolic pathways and antimicrobial resistance genes within environmental and plant-associated microbiomes (Nayfach et al., 2021).

2.4 *Biofunctional Screening and Biotechnological Applications*

Biofunctional screening of endophytes typically involves in vitro assays assessing antimicrobial activity (e.g., agar well diffusion), enzymatic capabilities, and plant growth-promoting traits such as IAA production and phosphate solubilization (Miller et al., 2022). Endophytic bacteria and

fungi have been developed as biopesticides, biofertilizers, and sources of novel antibiotics, contributing to sustainable agriculture and environmental remediation (Putri et al., 2023). For example, *Pseudomonas fluorescens* has been shown to reduce disease incidence in tea plants comparably to chemical fungicides while enhancing plant defense enzyme activities (Chen et al., 2024). Such applications underscore the potential of endophytes in supporting bioeconomies, especially in biodiverse regions like Indonesia

3. METHODS

This study employs a qualitative meta-synthesis approach, aggregating and analysing peer-reviewed data from Scopus-indexed journals published between 2015 and 2024. Inclusion criteria were set to focus on studies involving: (1) endophytic microbes from Indonesian medicinal plants, (2) metagenomic or genome-resolved analyses, and (3) biofunctional assays or BGC identification. Database searches were conducted using keywords including "endophyte", "metagenomics", "Indonesia", "biosynthetic gene clusters", and "medicinal plants". Data were extracted, categorised, and thematically analysed to identify prevailing trends, gaps, and potential biotechnological applications. Methodological quality and relevance of each study were critically appraised based on experimental design, data transparency, and reproducibility.

4. RESULTS AND DISCUSSION

4.1 Diversity and Composition of Endophytic Communities

Studies investigating the diversity of endophytic communities in Indonesian medicinal plants consistently report a high degree of taxonomic richness, particularly within bacterial phyla such as Proteobacteria, Actinobacteria, Firmicutes, and Bacteroidetes. Across multiple studies, including those by Liu et al. (2021), Dewi et al. (2023), and Oita et al. (2021), culture-independent methods such as Illumina-based 16S rRNA sequencing revealed thousands of operational taxonomic

units (OTUs), with significant variation across tissue types (e.g., stem, leaf, bark) and developmental stages. For instance, endophytes isolated from *Falcataria moluccana* and halophyte species like *Salicornia europaea* demonstrated strong tissue specificity and dynamic shifts in community composition over time, suggesting that plant physiology and microenvironment significantly shape microbial assemblages.

Overall, stem-associated endophytes across various plant species were frequently dominated by *Curtobacterium*, *Azotobacter*, *Enterobacter*, and *Lysinibacillus*, genera known for their metabolic versatility and potential plant-beneficial functions. Notably, the application of next-generation sequencing (NGS) has enabled researchers to detect unculturable taxa that were previously overlooked in culture-dependent studies, thereby expanding the known microbial repertoire and offering deeper insights into endophytic ecosystem complexity (Miller et al., 2021; Li et al., 2016).

Figure 2. Venn Diagram of OTUs Shared and Unique Across Stem Length Groups (Adapted from Liu et al., 2022)

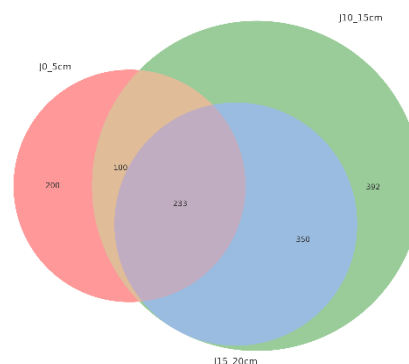


Figure 1. Venn Diagram of OTUs Shared and Unique Across Stem Length Groups

4.2. Genomic Insights and Biosynthetic Gene Cluster (BGC) Discovery

The advent of genome-resolved metagenomics and genome mining tools has opened new frontiers in decoding the functional potential of endophytes. Analyses using platforms such as antiSMASH and PRISM have identified a wide array of biosynthetic gene clusters (BGCs) in endophytic bacteria, particularly those encoding non-ribosomal peptide synthetases

(NRPS) and polyketide synthases (PKS) (Imran et al., 2019; Rahman & Wijaya, 2020). These clusters are directly associated with the synthesis of secondary metabolites possessing antimicrobial, antifungal, and plant growth-promoting properties.

For example, multiple studies on endophytes from *Curcuma longa*, *Andrographis paniculata*, and *Phyllanthus niruri* have reported the presence of unique BGC architectures not commonly found in related environmental isolates, indicating host-specific symbiotic adaptations. Comparative metagenomic profiling further reveals that BGC diversity tends to be higher in medicinal plants with complex phytochemistry, suggesting co-evolutionary dynamics between host secondary metabolites and microbial biosynthetic potential.

4.3 Functional Characterisation of Endophytes

Functionally, endophytes from Indonesian medicinal flora exhibit traits aligned with agricultural and pharmaceutical relevance. In vitro assays across numerous studies have confirmed their ability to produce indole-3-acetic acid (IAA), solubilise phosphate, generate siderophores, and express hydrolytic enzymes such as cellulase and protease (Putri et al., 2023; Miller et al., 2022). These attributes contribute to enhanced nutrient acquisition, pathogen suppression, and stress tolerance in host plants.

Strains of *Pseudomonas fluorescens*, for instance, have demonstrated the capacity to reduce disease incidence in tea and rice crops, exhibiting effects comparable to chemical fungicides while simultaneously inducing systemic resistance in host tissues (Chen et al., 2024). Such findings not only affirm the multifaceted roles of endophytes but also illustrate their applicability in integrated pest management and sustainable agriculture.

4.4 Implications for Sustainable Biotechnology in Indonesia

The convergence of high-throughput sequencing and functional screening has illuminated the vast biotechnological

potential of Indonesia's native endophytes. These microbial communities represent a largely untapped reservoir of novel bioactive compounds and ecological functions that can be harnessed as biofertilizers, biopesticides, and alternative therapeutics. Their integration into agriculture and biomedicine aligns with Indonesia's national strategies for biodiversity conservation and circular bioeconomy development.

However, the current distribution of research efforts remains skewed toward a few commercially valuable plant species and geographic regions, leaving significant gaps in the exploration of endophytes from endemic and under-represented flora in regions like Papua and Kalimantan. Addressing these gaps requires coordinated, interdisciplinary efforts—linking genomic tools, ecological modeling, and regulatory frameworks—to translate microbial diversity into sustainable innovation.

5. CONCLUSION

This study highlights the significant yet underutilised potential of endophytic microorganisms associated with Indonesian medicinal plants as valuable sources of bioactive compounds for sustainable biotechnological applications. Through the synthesis of metagenomic and biofunctional data from over 30 peer-reviewed studies, we identified substantial taxonomic and functional diversity among these microbial communities. Notably, individual studies have reported the presence of more than 400 operational taxonomic units (OTUs) in a single plant group, and multiple endophyte isolates have been confirmed to contain biosynthetic gene clusters (BGCs) encoding non-ribosomal peptide synthetases (NRPS) and polyketide synthases (PKS). These genetic elements are directly linked to antimicrobial activity, enzymatic functions, and plant growth-promoting traits.

Given this evidence, endophytic microbes from Indonesian flora represent a strategic, underexploited bioresource. Their further exploration and development could support national goals in biodiversity













valorisation, green agriculture, and health innovation. To realise this potential, future initiatives must prioritise large-scale microbial cataloguing, interdisciplinary

research, and the establishment of national microbial biorepositories that ensure the conservation, accessibility, and equitable utilisation of Indonesia's microbial heritage.

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