

Bacterial endophytes of medicinal plants: Diversity, molecular characterisation, antimicrobial potential and prospects for bioactive metabolite discovery

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ABSTRACT: Bacterial endophytes constitute an important but incompletely characterised component of medicinal-plant microbiomes and may contribute to plant–microbe interactions while providing a source of biologically active natural products. However, evidence across the field remains fragmented, with studies frequently emphasising bacterial isolation, taxonomic identification or preliminary antimicrobial screening without establishing clear relationships among microbial identity, biosynthetic capacity, metabolite production and biological function. This review critically synthesises current evidence on bacterial endophytes associated with medicinal plants, with particular emphasis on community diversity, culture-dependent and culture-independent approaches, molecular and phylogenetic identification, antimicrobial evaluation, metabolite characterisation, genome mining and activation of biosynthetic pathways. The available literature indicates that endophytic bacterial communities vary according to host species, tissue type, developmental stage, geography and methodological approach, while culture-dependent and sequencing-based methods each capture different components of the endophytic community. Although antimicrobial activity has been reported for numerous bacterial isolates and crude extracts, inhibition-zone measurements alone provide limited evidence of antimicrobial potency or therapeutic relevance. Stronger evidence is obtained through standardised quantitative susceptibility testing, activity-guided fractionation, chemical characterisation, and mechanistic validation. Similarly, detection of biosynthetic gene clusters indicates metabolic potential but does not establish metabolite expression or production. The review further identifies important gaps in African and Nigerian research, where medicinal plants and their associated bacterial communities remain comparatively underexplored. *Irvingia gabonensis* is discussed as an illustrative candidate for future integrated investigation rather than as a well-characterised bacterial-endophyte system. Future progress will depend on reproducible workflows that connect bacterial diversity and taxonomic identity with genome-based biosynthetic potential, metabolomic outputs, antimicrobial activity and subsequent chemical, safety and functional validation.

Keywords: 16S rRNA sequencing, culture-independent profiling, biosynthetic gene clusters, activity-guided fractionation, metabolomics, genome mining, antimicrobial susceptibility.

INTRODUCTION

Plants harbour complex microbial communities that occupy both external and internal ecological niches. Microorganisms capable of colonising internal plant tissues without producing obvious disease symptoms are generally referred to as endophytes. Although both fungi

and bacteria can occur as endophytes, bacterial endophytes have become increasingly important because of their diverse ecological functions and their potential to produce biologically active metabolites. Endophytic bacteria can establish intimate relationships with their host

plants and participate in processes associated with plant nutrition, growth regulation, stress adaptation and defence (Hardoim *et al.*, 2015; Compant *et al.*, 2021).

The relationship between plants and bacterial endophytes is dynamic rather than uniformly mutualistic. Environmental conditions, plant genotype, tissue type, developmental stage and microbial characteristics can determine whether an association is beneficial, neutral or potentially detrimental. Nevertheless, numerous studies have demonstrated that bacterial endophytes can promote plant growth, improve nutrient availability, stimulate host defence and increase tolerance to environmental stresses (Wu *et al.*, 2021; Tshikhudo *et al.*, 2023). These characteristics have stimulated interest in their application in agriculture, environmental biotechnology and medicine.

One of the most important features of bacterial endophytes is their capacity to produce specialised metabolites. Endophytic bacteria can synthesise antibiotics, siderophores, bacteriocins, enzymes, phytohormones and other compounds with biological activity. Some metabolites may directly inhibit competing microorganisms, while others influence host physiology or contribute to plant defence. Consequently, bacterial endophytes are increasingly regarded as promising sources of natural products with potential pharmaceutical applications (Hnamte *et al.*, 2024; Zotchev, 2024).

The importance of this research has increased with the global expansion of antimicrobial resistance. Resistant bacterial pathogens have reduced the effectiveness of numerous conventional antimicrobial agents, creating an urgent need for new compounds and alternative therapeutic strategies (Murray *et al.*, 2022). Natural-product research remains an important route for discovering chemically diverse antimicrobial agents, and endophytic bacteria provide an attractive microbial resource because of their ecological association with plants and their biosynthetic potential (Atanasov *et al.*, 2021; Zotchev, 2024).

Medicinal plants are particularly interesting in this context. Their tissues contain chemically complex environments that may select for microorganisms with specialised metabolic characteristics. At the same time, endophytic bacteria can influence plant metabolism and may themselves synthesise compounds with biological properties independent of those of their hosts. Recent work has therefore emphasised the importance of studying medicinal plants as integrated plant–microbe systems rather than considering plant phytochemistry and microbial chemistry independently (Semenzato and Fani, 2024; Zotchev, 2024).

Despite increasing global interest, bacterial endophytes associated with many African medicinal plants remain inadequately characterised. This is particularly relevant to Nigeria, where numerous medicinal plants are used traditionally, but their associated microbial communities remain comparatively poorly investigated. Ezeobiola *et al.* (2021) highlighted the potential of Nigerian ethnomedicinal

plants as reservoirs of endophytic microorganisms and bioactive secondary metabolites. Therefore, the objectives of this review are to:

1. synthesise evidence on the diversity, ecological distribution and taxonomic identification of bacterial endophytes associated with medicinal plants;
2. critically evaluate culture-dependent, culture-independent, antimicrobial and chemical-characterisation approaches used to investigate their biological and biosynthetic potential.
3. identify methodological, biological, chemical and translational gaps that currently limit natural-product discovery, with particular attention to African and Nigerian medicinal-plant research.

ENDOPHYTES IN THE MEDICINAL-PLANT ENDOSPHERE

The plant endosphere represents a distinctive ecological environment in which microorganisms interact directly with living plant tissues. Bacterial endophytes may gain entry through natural openings, roots, wounds or other sites and subsequently establish populations within internal tissues. Successful colonisation requires adaptation to host-derived nutrients, plant defence compounds and physicochemical conditions within the plant. (Hardoim *et al.*, 2015; Compant *et al.*, 2021). Recent synthesis also emphasises host and environmental drivers of medicinal-plant endophyte communities and the need to integrate molecular approaches with functional interpretation (Sharma *et al.*, 2025). Broad ecological and genomic perspectives likewise emphasise that endophytic associations span both plant-beneficial and context-dependent interactions (Brader *et al.*, 2017).

Endophytic bacteria can influence plant physiology through several mechanisms. Some fix atmospheric nitrogen, others solubilise otherwise unavailable forms of phosphorus, while siderophore-producing bacteria can improve iron acquisition. Other strains produce or modulate phytohormones, including indole-3-acetic acid and cytokinins, thereby influencing root development and plant growth (Tshikhudo *et al.*, 2023).

Bacterial endophytes may also stimulate plant defence. Colonisation can induce systemic resistance, alter host signalling pathways and increase production of defence-related compounds. In addition, direct antagonism against plant pathogens can occur through antibiotic production, secretion of lytic enzymes, competition for nutrients and iron sequestration through siderophores (Hnamte *et al.*, 2024).

The plant endosphere should therefore be regarded as an active microbial ecosystem. The biological characteristics of individual endophytes are influenced by their host environment, while bacterial activity can in turn affect host physiology. This reciprocal interaction is

particularly important in medicinal plants because changes in microbial communities may influence the production and accumulation of pharmacologically important plant metabolites (Harrison and Griffin, 2020; Webster *et al.*, 2020; Zhang *et al.*, 2023; Hou *et al.*, 2022; Kumari *et al.*, 2023; Tshikhudo *et al.*, 2023).

Bacterial endophytes have been recovered from roots, stems, leaves, fruits, seeds and other plant tissues. The composition of endophytic communities can differ markedly between plant species and between tissues of the same plant. Environmental factors, geographical location, plant developmental stage and host genotype can further influence microbial diversity (Harrison and Griffin, 2020; Webster *et al.*, 2020; Zhang *et al.*, 2023).

Members of Proteobacteria, Firmicutes and Actinobacteria are frequently represented among culturable endophytic bacteria. However, the apparent abundance of particular bacterial groups depends substantially on the methodology used to investigate them (Litao *et al.*, 2023; Webster *et al.*, 2020; Zou *et al.*, 2023).

Culture-dependent studies are inherently selective because only microorganisms capable of growing under the conditions provided by the investigator can be recovered. Riva *et al.* (2022) demonstrated that although some bacterial taxa repeatedly occur among culturable plant endophytes, cultivation does not capture the complete bacterial community. This limitation has major implications for interpretation of endophyte studies. A bacterial species that is not recovered from a plant using a particular culture medium should not automatically be considered absent. Instead, it may require different nutritional, atmospheric or environmental conditions for cultivation. (Riva *et al.*, 2022).

Culture-independent sequencing provides an important complementary perspective because bacterial DNA can be analysed directly from plant tissues. Such approaches have revealed bacterial groups that are rarely or never recovered by conventional cultivation. Nevertheless, sequencing also has limitations because the detection of DNA does not necessarily demonstrate viability or functional activity. (Fadiji and Babalola, 2020; Fadiji *et al.*, 2020).

Consequently, the most informative investigations increasingly combine cultivation with molecular community profiling. Culture-independent approaches provide a broad overview of microbial diversity, whereas cultivation provides viable bacterial isolates that can be experimentally characterised (Harrison and Griffin, 2020; Webster *et al.*, 2020; Zhang *et al.*, 2023; Hou *et al.*, 2022; Kumari *et al.*, 2023; Tshikhudo *et al.*, 2023).

Isolation and molecular characterisation of culturable endophytic bacteria

Isolation of culturable endophytic bacteria begins with careful selection and preparation of plant tissues. Healthy

tissues are generally preferred because they are less likely to contain microorganisms associated with visible disease. Surface sterilisation is then performed to eliminate epiphytic microorganisms while preserving bacteria residing within internal tissues. The effectiveness of surface sterilisation is central to the validity of culture-dependent endophyte studies. Inadequate sterilisation can lead to recovery of surface contaminants and epiphytes, whereas excessive sterilisation can reduce recovery of genuine endophytes. Sterilisation controls are therefore important for demonstrating the effectiveness of the procedure.

Following sterilisation, plant tissues can be macerated or directly placed onto appropriate culture media. Different media and incubation conditions can favour recovery of different bacterial groups. Consequently, use of multiple media and incubation conditions can increase the diversity of isolates obtained. Kandasamy and Kathirvel (2023) emphasised that cultivation strategy strongly influences the bacterial endophytes recovered from plants. Therefore, detailed reporting of tissue preparation, sterilisation, culture media, incubation temperature, incubation period and other conditions is essential for reproducibility.

Initial characterisation commonly involves colony morphology, Gram staining, cell morphology and biochemical tests. These methods remain useful for grouping isolates and providing preliminary identification. However, phenotypic characteristics alone may not provide reliable species-level identification because unrelated bacteria may share similar characteristics. Molecular characterisation is consequently required for stronger taxonomic identification. (Sahu *et al.*, 2022; Kandasamy and Kathirvel, 2023; Riva *et al.*, 2022; Janda and Abbott, 2007; Chun *et al.*, 2018; Felsenstein, 1985; Riesco and Trujillo, 2024). The 16S rRNA gene remains one of the most widely employed molecular markers for bacterial identification. Its combination of conserved and variable regions permits amplification across broad bacterial groups while retaining taxonomically informative sequence variation.

A typical workflow involves genomic-DNA extraction, amplification of the 16S rRNA gene using appropriate primers, sequencing, sequence editing and quality assessment, followed by comparison against curated nucleotide databases. Sequence similarity searches can provide preliminary taxonomic assignments, while phylogenetic analysis can further support relationships between isolates and reference organisms.

The major advantage of 16S rRNA sequencing is its broad applicability. It permits comparison of environmental isolates with previously characterised bacterial taxa and can identify organisms that cannot be reliably assigned using conventional biochemical methods. However, 16S rRNA sequencing also has limitations. Closely related species may possess highly similar sequences, making discrimination difficult. Consequently, a high sequence

similarity should not automatically be interpreted as definitive evidence of strain-level identity. Where precise classification is required, whole-genome sequencing or other high-resolution molecular methods may be necessary (Sahu *et al.*, 2022).

For endophyte research, 16S rRNA sequencing is therefore most appropriately regarded as a robust first-line molecular identification method that can be complemented by phylogenetic and genomic analyses. (Kandasamy and Kathirvel, 2023; Riva *et al.*, 2022; Janda and Abbott, 2007). Phylogenetic analysis provides an evolutionary framework for interpreting molecular identification results. Following alignment of bacterial sequences, isolates can be compared with reference sequences from closely related taxa and represented in phylogenetic trees. Neighbour-joining, maximum-likelihood and other phylogenetic approaches can be used depending on the research objectives and available computational resources. Bootstrap analysis is commonly employed to estimate the reliability of individual branches (Chun *et al.*, 2018; Felsenstein, 1985; Riesco and Trujillo, 2024).

Phylogenetic analysis is particularly useful when several bacterial isolates are recovered from the same plant. It can reveal whether isolates belong to closely related lineages or represent phylogenetically diverse groups. However, phylogenetic proximity does not necessarily imply functional similarity. Closely related bacterial strains may differ substantially in accessory genes, plasmids, resistance determinants and biosynthetic gene clusters. Consequently, phylogenetic results should be interpreted together with phenotypic, antimicrobial and chemical data (Janda and Abbott, 2007; Chun *et al.*, 2018; Riesco and Trujillo, 2024).

Culture-independent and metagenomic approaches

Advances in high-throughput sequencing have expanded the investigation of endophytic bacterial communities beyond organisms that can be cultured. Amplicon sequencing based on bacterial 16S rRNA genes can provide information about community composition, while metagenomic sequencing can reveal broader genomic and functional characteristics. (Fadiji and Babalola, 2020).

Culture-independent approaches are particularly valuable for identifying bacterial taxa that remain inaccessible through conventional culture methods. They can also reveal changes in microbial community structure associated with plant tissue, environment or developmental stage. However, sequencing data must be interpreted carefully. Detection of bacterial DNA does not necessarily demonstrate that the organism is viable or metabolically active, and detection of a functional gene does not automatically establish expression of the corresponding function (Cangelosi and Meschke, 2014). The strongest research strategy is therefore one that combines culture-independent community analysis with culture-dependent isolation. Sequencing can identify

potentially important microbial groups, while cultivation allows researchers to obtain organisms for antimicrobial testing, metabolite extraction, genomic analysis and other functional experiments.

Tlou *et al.* (2024) demonstrated the value of such an integrated strategy in the medicinal plant *Elephantorrhiza elephantina*. Their investigation combined next-generation sequencing with bacterial isolation, 16S rRNA identification, phylogenetic characterisation, antimicrobial testing and LC–MS metabolite profiling (Tlou *et al.*, 2024). Emerging plant-metagenomic workflows also address the substantial host-DNA background that can reduce microbial signal, including host-DNA depletion and adaptive sequencing approaches (Wang *et al.*, 2026; Verhoeven *et al.*, 2025).

Medicinal plants represent particularly promising hosts for bacterial-endophyte research because of their diverse phytochemical environments and biological importance. The chemical composition of medicinal plants can influence microbial colonisation, while bacterial endophytes may affect host metabolism and stress responses. (Chassagne *et al.*, 2021). The medicinal-plant environment may also provide an opportunity for discovery of bacterial metabolites that are chemically distinct from compounds obtained directly from the plant. Zotchev (2024) noted that bacterial endophytes of medicinal plants represent a potentially important source of bioactive secondary metabolites and that genome-based approaches can help uncover biosynthetic potential that may remain silent during conventional cultivation. (Harrison and Griffin, 2020; Webster *et al.*, 2020; Zhang *et al.*, 2023; Hou *et al.*, 2022; Kumari *et al.*, 2023; Tshikhudo *et al.*, 2023)

Endophytic bacteria associated with medicinal plants can contribute to growth promotion, nutrient acquisition and resistance to environmental stress. They may also influence the quantity and quality of plant secondary metabolites. Wu *et al.* (2021) highlighted the beneficial relationships that can occur between endophytic bacteria and medicinal plants, emphasising their potential roles in plant growth, stress tolerance and secondary metabolism. Similarly, Semenzato and Fani (2024) emphasised the importance of bacterial endophytes in sustainable medicinal-plant cultivation and maintenance of microbial diversity.

Antimicrobial potential and quantitative evaluation

The antimicrobial potential of bacterial endophytes is one of the major reasons for their increasing investigation. Endophytic bacteria may produce antibiotics, bacteriocins, siderophores, lytic enzymes and other metabolites capable of inhibiting competing microorganisms.

Antagonistic activity may involve direct killing of pathogens, growth inhibition, disruption of cell membranes, interference with biofilm formation, or competition for essential nutrients. Some endophytes may

also interfere with quorum sensing, thereby affecting communication-dependent processes involved in microbial virulence and colonisation (Hnamte *et al.*, 2024).

The potential to obtain antimicrobial compounds from endophytes is particularly important in the context of antimicrobial resistance. Natural products can provide structurally diverse chemical scaffolds and may reveal mechanisms of antimicrobial action that differ from those of existing antibiotics (Murray *et al.*, 2022; Atanasov *et al.*, 2021). However, preliminary antimicrobial activity should not be equated with drug potential. An isolate that inhibits a pathogen *in vitro* requires further investigation to establish the responsible compound, mechanism, toxicity, stability and pharmacological properties (Hnamte *et al.*, 2024; Zou *et al.*, 2023; Tlou *et al.*, 2024; Eloff, 2019).

Agar diffusion techniques are frequently used as initial screening methods because they are relatively simple and permit simultaneous testing of multiple bacterial isolates or extracts. However, inhibition-zone diameter is influenced by diffusion properties and does not provide a complete measure of antimicrobial potency. A compound with poor diffusion through agar may produce a relatively small inhibition zone despite possessing substantial antimicrobial activity (Eloff, 2019). Quantitative susceptibility testing is therefore important. The minimum inhibitory concentration represents the lowest concentration of a test material that prevents visible growth under defined conditions. MBC and MFC measurements may provide additional information concerning bactericidal or fungicidal effects when appropriately validated methods are used (Clinical and Laboratory Standards Institute, 2024). A strong antimicrobial evaluation therefore follows a logical progression from preliminary screening to quantitative testing and, where appropriate, mechanistic studies (Eloff, 2019; Clinical and Laboratory Standards Institute, 2024).

The study by Tlou *et al.* (2024) provides a useful African example. Extracts from bacterial endophytes isolated from *E. elephantina* exhibited antimicrobial activity against several pathogens, and MIC values were subsequently determined. Such studies demonstrate why antimicrobial screening should not end with reporting inhibition zones. Quantitative assays provide stronger evidence for selecting bacterial isolates or extracts for subsequent chemical investigation (Eloff, 2019; Clinical and Laboratory Standards Institute, 2024; Tlou *et al.*, 2024).

Bioactive metabolites, chemical characterisation, genome mining and mechanisms

Bacterial endophytes are capable of producing chemically diverse secondary metabolites. These compounds may serve ecological functions such as competition, signalling or host interaction, but they can also possess pharmaceutical or industrial value (Zotchev, 2024; Biju and Osborne, 2026). Reported endophyte-derived metabolites include antibiotics, siderophores, lipopeptides, polyketides,

non-ribosomal peptides and other specialised compounds. Their activities may include antibacterial, antifungal, antioxidant, anticancer and anti-inflammatory effects (Damavandi *et al.*, 2023; Schalk, 2025; Zhang *et al.*, 2025) (Passari *et al.*, 2023).

Primary studies illustrate the value of linking antimicrobial activity with chemical profiling. In *Elephantorrhiza elephantina*, Tlou *et al.* (2024) combined next-generation sequencing, bacterial isolation, 16S rRNA identification and antimicrobial testing with LC–MS profiling of endophyte extracts. In another southern African medicinal plant, *Harpagophytum procumbens*, Lang *et al.* (2023) recovered 140 actinobacterial isolates, of which 23 showed antimicrobial activity; 16S rRNA analysis placed the active isolates within seven genera, while PCR-based screening detected PKS-I and NRPS-associated genes and GC–MS identified volatile compounds in selected extracts. These studies illustrate that taxonomic diversity, antimicrobial activity and chemical features can be connected experimentally, but they do not by themselves establish the identity or therapeutic value of individual metabolites. The biosynthetic capacity of bacterial endophytes is increasingly being investigated through genomic approaches. Biosynthetic gene clusters can provide evidence of the potential for production of specialised metabolites even when those compounds are not detected under conventional laboratory conditions (Sekurova *et al.*, 2019; Zotchev, 2024).

Zotchev (2024) emphasised that conventional cultivation may underestimate the biosynthetic capacity of bacterial endophytes from medicinal plants. Genome mining, metabolic engineering and other approaches therefore offer opportunities to identify and activate previously inaccessible pathways. This distinction between biosynthetic potential and experimentally detected metabolites is important. The presence of a biosynthetic gene cluster indicates genetic capacity, but expression and production of the corresponding metabolite require experimental confirmation (Sekurova *et al.*, 2019; Zotchev, 2024).

Chemical characterisation provides a bridge between biological activity and metabolite identity. Gas chromatography–mass spectrometry is particularly useful for profiling volatile and thermally stable compounds, whereas liquid chromatography–mass spectrometry is more appropriate for many non-volatile and thermolabile metabolites. Selection of analytical platforms and reporting of quality-control and identification information are important for reproducible metabolomics (Sumner *et al.*, 2007). Fourier-transform infrared spectroscopy can provide information about functional groups present in an extract or purified fraction. Additional analytical techniques may subsequently be required to establish the structures of individual compounds (Enders *et al.*, 2021). An important consideration is that library-based mass-spectral identification should generally be described as tentative identification unless supported by authentic standards or additional structural evidence. Metabolomics reporting

standards emphasise explicit communication of identification confidence and analytical evidence (Sumner *et al.*, 2007).

Activity-guided fractionation provides a stronger means of linking chemistry with biological activity. Extracts can be separated into fractions; each fraction can be tested for antimicrobial activity, and the most active fractions can subsequently be purified and structurally characterised. (Bode *et al.*, 2002). This approach reduces the likelihood of attributing biological activity incorrectly to abundant but inactive compounds (Atanasov *et al.*, 2021; Zotchev, 2024; Biju and Osborne, 2026).

Antimicrobial resistance represents one of the major challenges confronting modern infectious-disease management. The emergence and dissemination of resistant bacterial pathogens have increased the need for antimicrobial agents with novel structures and mechanisms (Murray *et al.*, 2022). Bacterial endophytes provide one possible source of such compounds. Their specialised metabolic pathways may produce molecules capable of inhibiting pathogens through mechanisms distinct from conventional antibiotics (Hnamte *et al.*, 2024; Zotchev, 2024). Hnamte *et al.* (2024) emphasised that endophytic bacteria can act against both plant and human pathogens and possess multiple mechanisms of antimicrobial action. Semenzato *et al.* (2024) likewise demonstrated antagonistic activity of medicinal-plant endophytes against multidrug-resistant pathogens and linked selected strains with volatile organic compound production.

Nevertheless, the discovery of an antimicrobial endophyte is only the beginning of a drug-development pathway. The active compound must be identified and purified, its mechanism of action established, and its toxicity and pharmacological characteristics investigated. Therefore, endophyte research should distinguish clearly between antimicrobial screening and drug development (Atanasov *et al.*, 2021; Biju and Osborne, 2026; Zotchev, 2024).

AFRICAN AND NIGERIAN PERSPECTIVES: MEDICINAL-PLANT ENDOPHYTES AND *IRVINGIA GABONENSIS* AS A RESEARCH MODEL

African medicinal plants represent an important but incompletely characterised resource for bacterial-endophyte discovery. Evidence from Nigeria demonstrates that medicinal plants can harbour taxonomically diverse bacterial endophytes with measurable antimicrobial activity and biosynthetic potential. Ezeobiora *et al.* (2024) recovered 13 endophytic Actinobacteria from Nigerian medicinal plants, comprising *Streptomyces*, *Saccharomonospora* and *Saccharopolyspora*, and combined morphological characterisation, 16S rRNA sequencing, phylogenetic analysis and antimicrobial screening. The study also demonstrated that antibiotic production by a selected *Saccharomonospora* isolate

could be optimised under defined culture conditions, illustrating the importance of moving beyond isolate recovery towards functional evaluation.

More recent genomic evidence strengthens this observation. Ezeobiora *et al.* (2026) investigated two rare endophytic Actinobacteria isolated from Nigerian medicinal plants using whole-genome sequencing, average nucleotide identity, digital DNA–DNA hybridisation, and genome mining. AntiSMASH analysis identified 24 biosynthetic gene clusters in *Saccharomonospora xinjiangensis* PNSac2 and 28 in *Saccharopolyspora cebuensis* PGLac3, including predicted clusters associated with polyketides, nonribosomal peptides, siderophores, terpenes and ribosomally synthesised and post-translationally modified peptides. Importantly, these findings demonstrate biosynthetic potential rather than automatically establishing production of the predicted metabolites; chemical detection, purification and structural characterisation remain necessary to establish actual metabolite production.

These Nigerian studies illustrate a broader principle for African medicinal-plant research: meaningful discovery requires progression from bacterial isolation and taxonomic identification to quantitative biological testing, genome-based biosynthetic prediction, metabolomic analysis and chemical validation. Comparisons among African studies should nevertheless be made cautiously because plant species, tissues, sterilisation procedures, culture media, identification methods and antimicrobial assays differ substantially between investigations.

Within this context, *Irvingia gabonensis* represents a suitable candidate for future integrated investigation because of its ethnomedicinal importance and biological relevance. However, its medicinal status should not be used as evidence that it possesses a defined or unusually productive bacterial-endophyte community. Rather, *I. gabonensis* should be presented as an illustrative research model in which authenticated plant material, validated surface sterilisation, culture-dependent isolation, culture-independent community profiling, molecular or genomic identification, antimicrobial testing, genome mining and metabolomic characterisation can be integrated. Such an approach would allow the bacterial endophytic community and its functional potential to be established empirically rather than inferred from the properties of the host plant. Table 1 places this proposed model alongside representative African medicinal-plant endophyte studies.

RESEARCH GAPS, TRANSLATIONAL BARRIERS AND FUTURE DISCOVERY PIPELINE

Taxonomic and methodological gaps

A major limitation is the lack of methodological standardisation across endophyte studies. Differences in plant

Table 1. Representative bacterial endophytes associated with medicinal plants.

Medicinal plant	Country/region	Tissue	Representative taxa	Identification approach	Main evidence
<i>Elephantorrhiza elephantina</i>	South Africa	Leaves and rhizomes	<i>Pseudomonas</i> spp.; <i>Microbacterium oxydans</i> ; <i>Stenotrophomonas maltophilia</i>	NGS, culture, 16S rRNA and phylogeny	Antimicrobial activity and LC–MS metabolite profiling (Tlou <i>et al.</i> , 2024)
<i>Harpagophytum procumbens</i>	Southern Africa	Plant tissues	Endophytic Actinobacteria	Culture and 16S rRNA	Antimicrobial activity; PKS-I/NRPS-associated potential; GC–MS profiling (Lang <i>et al.</i> , 2023).
Nigerian medicinal plants	Nigeria	Multiple tissues	<i>Streptomyces</i> ; <i>Saccharomonospora</i> ; <i>Saccharopolyspora</i>	Culture, 16S rRNA and phylogeny	Antimicrobial activity and antibiotic-biosynthetic potential (Ezeobiora <i>et al.</i> , 2024).
<i>Irvingia gabonensis</i>	Nigeria/ West Africa	Not yet comprehensively established	Not yet sufficiently characterised	Requires integrated culture and culture-independent investigation	Research opportunity; not an established bacterial-endophyte community (Hassan <i>et al.</i> , 2024).

sampling, tissue selection, surface-sterilisation procedures, culture media, incubation conditions and identification methods can substantially influence which bacteria are recovered and how community diversity is interpreted (Harrison and Griffin, 2020; Riva *et al.*, 2022; Sahu *et al.*, 2022). Consequently, differences in reported diversity between studies may reflect methodological variation as well as genuine ecological differences.

Culture-dependent isolation remains important because it provides viable strains that can subsequently be tested experimentally, but cultivation alone does not represent the complete endophytic community. Conversely, culture-independent sequencing provides broader community coverage but may detect DNA from organisms that are inactive or no longer viable and cannot by itself demonstrate metabolite production (Fadiji and Babalola, 2020; Cangelosi and Meschke, 2014). Future studies should therefore combine standardised cultivation with sequencing-based community profiling rather than treating either approach as a complete representation of endophytic diversity.

Taxonomic resolution also remains an important consideration. Although 16S rRNA sequencing is widely used for bacterial identification, closely related species may not always be reliably distinguished using this marker alone. Sequence quality, database curation, alignment coverage and the taxonomic context of the isolate should therefore be considered when assigning species-level identities (Janda and Abbott, 2007; Chun *et al.*, 2018; Riesco and Trujillo, 2024). Genome-based approaches can provide greater resolution for isolates for which 16S rRNA sequencing is insufficient.

Biological and functional gaps

The presence of a bacterial endophyte does not

necessarily establish a beneficial function for the host plant. Many studies infer plant-growth-promoting, biocontrol or host-protective functions from *in vitro* assays, although these activities may not occur at comparable levels within plant tissues. Functional claims should therefore be supported by appropriate experimental evidence, including plant-association studies where relevant (Compant *et al.*, 2021; Kumari *et al.*, 2023).

A related gap concerns the distinction between biosynthetic potential and actual biological activity. Genome sequencing may reveal genes or biosynthetic gene clusters associated with secondary metabolism, but gene presence does not demonstrate transcription, translation or production of the predicted metabolite. Recent genomic studies of Nigerian endophytic Actinobacteria illustrate both the value and limitation of this approach: whole-genome analysis revealed numerous biosynthetic gene clusters, but these predictions require complementary chemical and functional validation before specific metabolites can be attributed to the isolates (Ezeobiora *et al.*, 2026).

Chemical-characterisation gaps

Many reports of endophyte-derived metabolites remain based on crude extracts or chromatographic library matching. Such approaches are valuable for preliminary chemical profiling but should not automatically be interpreted as definitive structural identification. Reliable assignment of a novel bioactive compound generally requires complementary evidence, including accurate mass measurements, fragmentation analysis, purification and, where appropriate, nuclear magnetic resonance spectroscopy and comparison with authentic standards (Sumner *et al.*, 2007; Enders *et al.*, 2021).

Another important challenge is the large proportion of

predicted biosynthetic pathways that remain poorly expressed under conventional laboratory conditions. Genome mining can reveal potentially valuable biosynthetic gene clusters, but many pathways may remain silent or cryptic under standard culture conditions. Changes in culture medium, nutrient availability, pH, temperature, aeration, co-culture or other elicitation strategies can therefore be used to explore otherwise inaccessible chemical diversity (Rutledge and Challis, 2015; Sekurova *et al.*, 2019; Thissera *et al.*, 2025; Zotchev, 2024).

Translational gaps

The transition from antimicrobial screening to drug discovery remains a major barrier. Agar diffusion assays are useful for identifying active isolates or extracts, but inhibition-zone measurements are influenced by compound diffusion, solubility, molecular properties, concentration and assay conditions and therefore do not provide a direct measure of antimicrobial potency (Eloff, 2019). Quantitative assays such as MIC, MBC and MFC provide stronger evidence of concentration-dependent activity when performed under appropriately standardised conditions (CLSI, 2024).

Even when potent activity is demonstrated, additional stages are necessary before therapeutic relevance can be considered. These include purification of the active constituent, structural characterisation, mechanism-of-action studies, selectivity and cytotoxicity assessment, pharmacological evaluation and, where justified, preclinical efficacy studies. Consequently, antimicrobial activity of a crude bacterial extract should be described as preliminary bioactivity rather than as evidence of a therapeutic agent.

Data integration and reproducibility

Another important gap is the limited integration of taxonomic, genomic, chemical and biological datasets within individual studies. Bacterial identification, antimicrobial screening, genome mining and metabolomics are often reported as separate outputs, making it difficult to establish whether a particular biosynthetic pathway is responsible for a detected metabolite or observed biological activity. Integrated workflows that connect strain identity, genome content, metabolite profiles and experimentally measured activity are more informative for natural-product discovery (Sekurova *et al.*, 2019; Zotchev, 2024).

Reproducibility is also affected by incomplete reporting of experimental parameters. Future studies should provide sufficient information on plant authentication, tissue type, sterilisation validation, isolation media, incubation conditions, strain identification, sequence-processing

procedures, antimicrobial assay conditions and chemical-analysis parameters. Such reporting would improve comparison between studies and facilitate independent validation.

A sequential discovery pipeline

Based on these limitations, a more rigorous bacterial-endophyte discovery strategy should proceed through a sequential evidence-building pipeline:

1. Standardised plant sampling and authentication — document plant identity, tissue type, developmental stage, geographical origin and environmental context.
2. Validated surface sterilisation — combine appropriate sterilisation with sterility controls such as final-rinse plating and/or tissue-imprint testing.
3. Parallel culture-dependent and culture-independent analysis — recover viable bacteria while simultaneously characterising broader community diversity.
4. Molecular or genomic identification — use 16S rRNA sequencing as appropriate and apply genome-based approaches when species-level resolution is uncertain.
5. Preliminary biological screening — identify isolates or extracts with reproducible antimicrobial or other relevant activities.
6. Quantitative susceptibility testing — determine MIC and, where appropriate, MBC or MFC under standardised conditions.
7. Genome mining and biosynthetic gene cluster prioritisation — identify strains with promising and potentially novel biosynthetic capacity.
8. Metabolomic profiling and pathway induction — compare chemical profiles under appropriate culture conditions and explore strategies for activating cryptic pathways.
9. Activity-guided fractionation — separate crude extracts and track biological activity through successive purification steps.
10. Definitive chemical characterisation — combine high-resolution mass spectrometry, NMR and authentic standards where available to establish compound identity.
11. Mechanistic and safety validation — determine biological targets or mechanisms and evaluate cytotoxicity and selectivity.
12. Preclinical evaluation — where the evidence warrants progression, assess pharmacological efficacy and safety in appropriate experimental models.

This sequence establishes an evidence chain from microbial association → taxonomic identity → biological activity → quantitative potency → biosynthetic potential → metabolite detection → purified compound → structural

confirmation → mechanism → safety and efficacy. Each stage addresses a different scientific question and should not be interpreted as a substitute for the subsequent stages.

Priority agenda for African and Nigerian research

For African research programmes, the immediate priority should not simply be to increase the number of bacterial isolates reported. Greater value would come from studies that combine rigorous sampling with deeper taxonomic, genomic, chemical and functional characterisation. Nigerian medicinal plants provide particularly relevant opportunities because recent studies have already demonstrated both antimicrobial activity and substantial biosynthetic potential in endophytic *Actinobacteria* (Ezeobiora *et al.*, 2024, 2026).

Future investigations should therefore prioritise authenticated medicinal plants, standardised endophyte-recovery procedures, representative community profiling, genome-informed strain selection, quantitative antimicrobial testing and integrated metabolomic analysis. This approach would help move African endophyte research from descriptive cataloguing towards reproducible natural-product discovery and functional validation.

CONCLUSION

Bacterial endophytes represent a diverse and incompletely characterised component of medicinal-plant microbiomes and constitute a promising resource for natural-product discovery. However, the evidence reviewed here shows that their diversity, biosynthetic potential and biological activities are strongly influenced by host plant, tissue, environmental conditions and methodological choices. Culture-dependent isolation provides experimentally accessible strains, whereas culture-independent approaches broaden community coverage; neither approach alone provides a complete understanding of the endophytic bacterial system.

A central limitation across the field is the frequent separation of taxonomic identification, biosynthetic prediction, metabolite detection and biological validation. High 16S rRNA sequence similarity does not necessarily provide definitive species-level identification, detection of biosynthetic gene clusters demonstrates genetic potential rather than metabolite production, and antimicrobial activity of crude extracts does not by itself establish therapeutic efficacy. Progress therefore requires stronger links between microbial identity, genome content, chemical output and experimentally validated biological function.

African and Nigerian medicinal plants remain particularly valuable for such investigations because recent studies

demonstrate both bacterial diversity and substantial biosynthetic potential, while important taxonomic and chemical resources remain underexplored. *Irvingia gabonensis* is best regarded within this review as an illustrative research model rather than as an established source of a defined bacterial-endophyte community.

Future research should prioritise standardised sampling and sterilisation, complementary culture-dependent and culture-independent approaches, genome-informed strain characterisation, quantitative antimicrobial testing, metabolomic analysis, activity-guided purification and definitive structural elucidation. These approaches, followed by mechanistic, safety and preclinical evaluation when justified, can provide the evidence required to move bacterial endophyte research from descriptive biodiversity studies toward reproducible and scientifically validated natural-product discovery.

CONFLICT OF INTEREST

The author declares that they have no conflict of interest.

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