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Mycology
An International Journal on Fungal Biology

ISSN: 2150-1203 (Print) 2150-1211 (Online) Journal homepage: www.tandfonline.com/journals/tmyc20

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To cite this article: Asri Peni Wulandari, Erin Nur Lestari, Ayu Wandira, Rezqita Putri Pitaloka, Laita Nurjannah & Azmi Azhari (03 Apr 2026): Biosynthetic potential of endophytic fungi from tropical medicinal plants: genomic and metabolomic perspectives, Mycology, DOI: 10.1080/21501203.2026.2646460

To link to this article: https://doi.org/10.1080/21501203.2026.2646460

Published online: 03 Apr 2026.

MYCOLOGY
https://doi.org/10.1080/21501203.2026.2646460

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REVIEW

Biosynthetic potential of endophytic fungi from tropical medicinal plants: genomic and metabolomic perspectives

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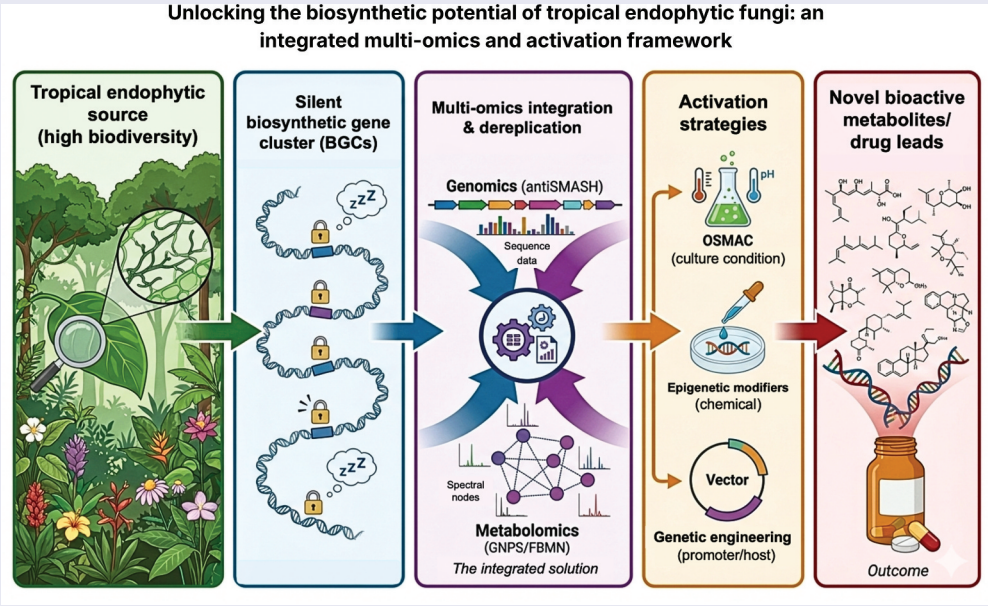
ABSTRACT

The investigation of endophytic fungi from tropical medicinal plants is increasingly conducted due to their ability to produce diverse bioactive secondary metabolites, including polyketides, non-ribosomal peptides, terpenoids, and alkaloids with significant pharmaceutical potential. These compounds are synthesized through biosynthetic gene clusters (BGCs), such as polyketide synthases (PKSs), non-ribosomal peptide synthetases (NRPSs), and hybrid PKS-NRPS systems. However, although systematic prediction of BGCs has advanced, experimental validation of their corresponding metabolites in tropical endophytic fungi remains limited. This mini-review focuses on tropical medicinal plants, highlighting the biosynthetic diversity and pharmaceutical relevance of their endophytic fungi, and recent advances in genomics and metabolomics. Applications of untargeted metabolomics and genome mining (e.g., antiSMASH and BiG-SCAPE) have improved the detection of cryptic and silent gene clusters. In addition, synthetic biology and epigenetic approaches have enabled activation of dormant biosynthetic pathways. Nevertheless, challenges remain in metabolite dereplication, enhancing *in vitro* BGC expression, and sustainable bioprospecting.



ARTICLE HISTORY
Received 14 November 2025
Accepted 13 March 2026

KEYWORDS
Biosynthetic gene clusters; fungal endophytes; genome mining; metabolomics; natural products; secondary metabolites; tropical medicinal plants

1. Introduction

Endophytic fungi colonize internal plant tissues without causing apparent disease and form complex ecological associations that influence host physiology, stress tolerance, and chemical defense (Rokas et al. 2020). Tropical ecosystems harbor exceptionally high

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Published online 03 Apr 2026

levels of plant and fungal diversity, positioning tropical endophytes as promising yet underexplored sources of specialized metabolites with pharmaceutical and agricultural relevance (Gao et al. 2025). Numerous bioactive compounds originally attributed to plants have subsequently been linked to their associated endophytic fungi, underscoring the ecological and biochemical significance of these symbioses.

The structural uniqueness of secondary metabolites in tropical endophytic fungi is profoundly influenced by ecological selection pressures within the host plant tissues. The tropical environment, characterized by high biodiversity and intense resource competition, compels endophytic fungi to undergo metabolic adaptations through the activation of specific biosynthetic pathways, either as defense mechanisms or for symbiotic communication. These adaptations often result in the synthesis of chemically unique modifications, such as the addition of specific functional groups or increased complexity in the carbon framework, which are not typically found in non-endophytic fungi (Wulandari et al. 2022).

Advances in genome sequencing have revealed that fungal genomes contain extensive repertoires of biosynthetic gene clusters (BGCs) encoding polyketide synthases (PKSs), nonribosomal peptide synthetases, hybrid systems, terpene synthases, and shikimate-derived pathways (Rokas et al. 2020). However, only a fraction of these predicted clusters have been experimentally linked to structurally characterized metabolites. This discrepancy between genomic prediction and chemical expression represents a central challenge in contemporary fungal natural product research. Genome mining frequently identifies dozens of candidate clusters per strain, yet many remain transcriptionally silent or poorly expressed under standard laboratory conditions (Blin et al. 2019; Hannigan et al. 2019; Navarro-Muñoz et al. 2020).

The influence of environmental context on fungal secondary metabolism further complicates interpretation. The term "tropical" encompasses ecologically heterogeneous systems, including Southeast Asian rainforests, Amazonian forests, Central African ecosystems, and Pacific island environments. Variations in host phylogeny, climatic gradients, soil chemistry, nutrient availability, and microbial competition may exert selective pressure on fungal genomes, shaping both the retention and expression of BGCs (Nützmann et al. 2018; Rokas et al. 2020). Environmental signals and host-derived metabolites can modulate chromatin accessibility and regulatory networks, thereby influencing the activation of specific biosynthetic pathways (Brakhage 2013). Such ecological modulation provides a plausible explanation for the structural diversity observed among metabolites produced by tropical endophytic fungi.

Global efforts to map the fungal biosynthetic landscape have seen significant contributions from diverse international consortia. While Southeast Asian research has provided extensive data on endophytes, pivotal studies from the Neotropical region have fundamentally shaped our understanding of fungal diversity and its chemical potential (Kim et al. 2025). Similarly, investigations into African tropical forests have introduced unique taxads and alkaloids, further diversifying the known chemical space of tropical endophytes (Song et al. 2014; Ntemafack et al. 2021).

In addition to canonical polyketide and peptide synthetase clusters, fungal genomes often harbor orphan or atypical BGCs whose products remain unknown, representing a substantial reservoir of unexplored chemical scaffolds (Medema and Fischbach 2015; Rokas et al. 2020). Despite improvements in genome mining algorithms and metabolomics platforms (Blin et al. 2021), functional validation of these clusters remains limited, particularly in non-model tropical endophytes. Regulatory bottlenecks, incomplete gene-metabolite linkage, and challenges in heterologous expression continue to constrain translational development.

This review synthesizes recent advances in multi-omics approaches applied to tropical endophytic fungi, with emphasis on ecological drivers of metabolite diversification, structural and regulatory complexity of BGCs, activation strategies for cryptic pathways, and methodological limitations that shape current discovery pipelines. By integrating ecological, genomic, and metabolomic perspectives, we aim to transform this hidden fungal pathway into a reliable drug discovery pathway, enabling ecological support through novel activation strategies.

2. Materials and methods

A comprehensive literature search was conducted using Scopus, PubMed, Web of Science, and Google

Scholar to identify prior publications on endophytic tropical plants from 2020 to 2025. Keywords included "endophytic fungi", "biosynthetic gene clusters", "PKS", "NRPS", "genome mining", "antiSMASH", "GNPS", "tropical medicinal plants", and "metabolomics". The search yielded 235 articles, of which 162 were retained after abstract screening and 27 were included for full-text review, including those predicted to contain a core enzyme domain, some processed from bioinformatic data on BGC prediction or integrated omics strategies. Additional information on the types of BGCs was confirmed using public genome databases (NCBI GenBank, JGI MycoCosm, and Ensembl Fungi) and analyzed using mining tools such as antiSMASH and DeepBGC. Although the literature search was prioritized for the 2020–2025 period to ensure currency, seminal theoretical works (e.g., Brakhage 2013; Keller 2019) were retained as they provide the indispensable mechanistic foundations for fungal BGC regulation.

3. Endophytic fungi in tropical medicinal plants

Tropical medicinal plants offer a unique ecosystem that is an ideal habitat for the growth of endophytic fungi with the ability to produce a variety of bioactive metabolites. The diversity of endophytic microbiota that inhabit these plant tissues is strongly influenced by environmental factors, ranging from host specificity and geographic origin to other specific ecological conditions. As a symbiont, this fungus builds a mutualistic relationship with its host without causing negative impacts (Adeleke and Babalola 2021). These interactions are shaped by long co-evolutionary processes that not only determine the composition of fungal communities but also direct the resulting metabolic profiles (Tanvir et al. 2017; Subasinghe and Hettiarachchige 2022). Globally, this community is dominated by core taxa such as *Alternaria, Aspergillus*, *Colletotrichum*, *Fusarium*, *Penicillium*, and *Phoma* (Chowdhary and Kaushik 2015; Jia et al. 2016; Rashmi 2019; Wen et al. 2022; Priyadarshini and Sarojini 2025; Tandon et al. 2025).

Explorations across tropical biodiversity regions reveal distinct and dense endophytic communities. In Neotropical regions, particularly in Brazil, host plants such as *Vochysia divergens*, *Stryphnodendron adstringens*, and *Carapa guianensis* harbor diverse fungal taxa, including many newly identified or previously undescribed genera and species (Noriler et al. 2018; Ferreira et al. 2021; Mayrhofer et al. 2024).

Similar research is accelerating across Africa, notably in South Africa, Nigeria, Egypt, and Kenya, to document microbiota that, despite their immense pharmacological potential, remain largely underexplored (Abdalla and McGaw 2018; Ibrahim et al. 2021; Ali et al. 2023; Kubayi et al. 2025; Osman et al. 2025). These tropical endophytes exhibit promising antidiabetic, antibacterial, and antioxidant properties, reinforcing the global significance of tropical flora in drug discovery (Hamed et al. 2023).

The chemical profiles documented in Table 1 underscore the structural diversity of metabolites derived from tropical endophytes. In Southeast Asia, particularly Indonesia, recent studies have identified intricate compounds such as cytotoxic steroids from *Lasiodiplodia theobromae* (associated with *Aglaia argentea*) and *Periconia pseudobyssoides* (from *Toona sureni*), the latter showing potential antimalarial properties (Azhari et al. 2023a; Supratman et al. 2023). Similar cytotoxic efficacy is observed in mangrove-associated fungi, such as *Penicillium steckii,* which produces arohynapene A (Mulyani et al. 2024a).

For instance, Southeast Asian isolates such as *Cladosporium velox* and *C. tennissimum* exhibit activity against respiratory and enteric pathogens (Wulandari et al. 2021, 2022) and show antidiabetics potential (Nurjannah et al. 2023). In addition, endophytes from India, Neotropical, and African regions contribute significantly to the discovery of novel antimicrobial scaffolds (Iantas et al. 2021; Goyal et al. 2022; Magagula et al. 2025). This global convergence of the metabolic potential, spanning from marine algae like *Sargassum* sp. to terrestrial medicinal plants such as *Etlingera elatior* and *Kaempferia galanga*, reinforces the necessity of cross-regional bioprospecting to identify novel candidates for drug development.

4. Recent isolated secondary metabolites of endophytic fungi (2019–2024)

Metabolic profiles of tropical endophytes are not merely random collections of small molecules but rather a finely tuned chemical arsenal shaped by millions of years of co-evolution. The dominance of specific chemical classes, including polyketides,

Table 1. Endophytic fungi's biodiversity in tropical medicinal plants.

Plant host	Reported endophytes	Region	Biological activity	Reference
Vochysia divergens, *Stryphnodendron adstringens*	*Diaporthe* sp., *Aspergillus* sp., *Coniochaeta* sp., *Nemaniaprimolutea* sp., and *Pseudofusicoccum stromaticum*	Brazil	Antifungal	Iantas et al. (2021)
Palicourea rigida	*Colletotrichum* sp., *Pestalotiopsis* sp., *Botryosphaeriales*, and *Diaporthe* sp.	Brazil	Antioxidant, antimicrobial	Dos Santos et al. (2021)
Aegle marmelos, Glochidion calocarpum, and *Cassia sophera*	*Fusarium falciforme*, *Fusarium incarnatum*, and *Sarocladium strictum*	India	Antimicrobial	Goyal et al. (2022)
Memecylon umbellatum	*Endomelanconiopsis endophytica, Lasiodiplodia iranensis, L. theobromae*, *Phyllosticta capitalensis, Aspergillus niger, Cochlibolus lunatus*, and *Pestalotiopsis guepinii*	India	Antibacterial	Suryavamshi and Shivanna (2020)
Kirkia acuminata Oliv.	*Alternaria, Aspergillus, Colletotrichum, Fusarium, Penicillium, Talaromyces, Diaporthe, Macrophomina*, and *Neofusicoccum*	South Africa	Antimicrobial, antioxidant, anticancer	Abdalla et al. (2020); Kubayi et al. (2025); Magagula et al. (2025)
Centella asiatica, *Curcuma xanthorrhiza*, *Guazuma ulmifolia*, *Hydrocotyle verticillata*	*Colletotrichum* spp.	Indonesia	Antifungal	Sukarno et al. (2021)
Syzygium aqueum	*Trichordema reesei*	Indonesia	Antioxidant	Habisukan et al. (2021)
Medinilla speciosa	*Colletotrichum* sp., *Penicillium* sp., *Trichophyton* sp., *Botrytis* sp., and *Trichophyton* sp.	Indonesia	Antibacteria	Amelia et al. (2021)
Kaempferia galanga L.	*Torulla* sp., *Fusarium* sp., and *Drechcera* sp.	Indonesia	Antibacteria	Efendi et al. (2020)
Zingiber officinale	*Fusarium* sp. and *Aspergillus* sp.	Indonesia	MRSA	Sari et al. (2020); Ariantari et al. (2024)
Boehmeria nivea	*Cladosporium tennissimum, Fusarium falciforme*, and *Penicillium citrinum*	Indonesia	Antifungal	Wulandari et al. (2018, 2022)
Etlingera elatior	*Daldinia eschscholtzii*, *Hypoxylon trugodes* voucher YMJ 57	Indonesia	Antidiabetic	Nurjannah et al. (2023)
Avicennia marina	*Cladosporium anthropophilum*, *Penicillium steckii* JB-NW-2-1	Indonesia	Antibacterial steroids; HeLa cervical, MCF-7 breast cancer, B16-F10 melanoma, and A549 lung adenocarcinoma	Mulyani et al. (2023, 2024a)
Sargassum sp.	*Cladosporium velox*	Indonesia	Bactericidal activity against pneumonia and diarrhea pathogens	Wulandari et al. (2021)
Aglaia argentea	*Lasiodiplodia theobromae* BPPCA144	Indonesia	Steroids; cytotoxic activity against HeLa cells	Supratman et al. (2023); Purbaya et al. (2024)
Toona sureni	*Periconia pseudobyssoides* K5	Indonesia	New steroid; heme polymerazation inhibition activity	Azhari et al. (2023b); Nurjannah et al. (2023b)

terpenoids, and alkaloids, reflects a functional requirement to mediate complex interspecies interactions within high-density tropical canopies (Kim et al. 2025).

Various studies demonstrate that endophytic fungi associated with tropical medicinal plants can produce diverse secondary metabolites with significant biological activity. Chemical profiles of isolates such as *Aspergillus niveus*, *Cladosporium anthropophilum*, *Lasiodiplodia theobromae*, *Penicillium steckii*, and *Periconia* species have revealed the presence of bioactive compounds ranging from polyketides and hybrid metabolites to phenolic derivatives and various steroids (Fan et al. 2019; Azhari et al. 2023a; Hamed et al. 2023; Supratman et al. 2023; Mulyani et al. 2024b; Purbaya et al. 2024).

This biosynthetic diversity is a global phenomenon. For instance, Brazilian *Colletotrichum* species yield cytotoxic cytochalasans that are structurally distinct from Asian isolates, while African endophytes produce rare xanthone derivatives with potent antimalarial properties. Such variations underscore how distinct evolutionary pressures and micro-climates across different tropical continents drive the evolution of specialized metabolites (Santos et al. 2020; Kim et al. 2025; Amaeze et al. 2026).

4.1. Polyketides

Polyketides represent the most abundant class of metabolites in tropical endophytes, not merely due to genetic frequency but as a functional adaptation to hyper-

diverse ecosystems. In the competitive environment of tropical biomes, these compounds serve as essential chemical weapons for niche occupation and interspecies signaling (Brakhage 2013; Santos et al. 2020). Their structural plasticity allows tropical fungi to rapidly evolve defenses against a broad spectrum of sympatric pathogens found in high-humidity habitats.

As illustrated in Figure 1, the structural diversity of polyketides is derived from tropical endophytic fungi, with compounds isolated from *Penicillium steckii* and *Lasiodiplodia theobromae* exhibiting distinct polyketide scaffolds. These compounds, such as arohynapene A and mellein, demonstrate the capacity of the PKS pathway to produce both aromatic and aliphatic compounds (Supratman et al. 2023; Mulyani et al. 2024b; Purbaya et al. 2024). The structural diversity indicates the involvement of various PKS pathways and highlights the adaptability of endophytic fungi to produce bioactive compounds under different cultural and environmental conditions. These polyketide compounds exhibit a diverse range of biological activities from cytotoxicity (arohynapene A) to antibacterial properties (mellein). While some compounds, such as citrinin (5), are also produced by non-endophytic (saprophytic) fungi from the genus *Aspergillus*, compounds like arohynapene A (1) from *Penicillium steckii* are more commonly found in endophytic isolates. This specificity is likely due to their association with host interactions in mangrove environments.

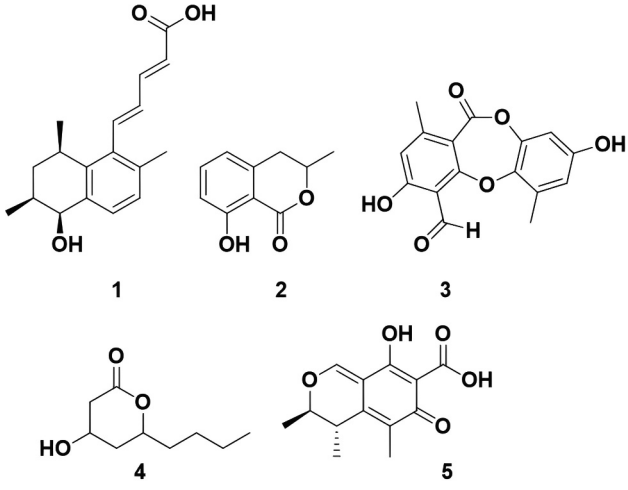

Figure 1. Polyketide derivates from tropical endophytic fungi: (1) arohynapene A; (2) (–)-mellein; (3) botryorhodine A; (4) 4-hydroxy-6-n-propyl-oxasylhexane-2-one; and (5) citrinin.

Lasiodiplodia theobromae generates three polyketides that may originate from distinct biosynthetic processes and differ structurally from one another. (–)-Mellein (2) is an aromatic isocoumarin that is often linked to fungal PKS activity. While type III enzymes have been suggested in similar pathways, this link does not yet apply to all mellein producers. Botryorhodine A (3) is a polyoxygenated aromatic polyketide with a fused benzofuranone core and a substituted phenyl structure. It represents a highly oxygenated aromatic scaffold made by *L. theobromae*. Meanwhile, 4-hydroxy-6-*n*-propyl-oxasylhexane-2-one (4) is an oxygenated aliphatic scaffold that may have been made through a non-aromatic polyketide pathway, although this assignment remains inferential based on structural interpretation (Supratman et al. 2023; Purbaya et al. 2024).

Beyond these isolates, the endophyte *Aspergillus niveus* Fv-er401 has been reported to produce the aromatic polyketide citrinin (5), a mycotoxin with a highly oxygenated benzopyran framework whose biosynthesis is directed by well-characterized PKS genes in several *Aspergillus* species. In the context of this study, the presence of citrinin signifies the involvement of a benzopyran-type PKS cluster previously identified in this genus, while also enhancing the recognized chemical diversity of endophytic polyketides (Storm et al. 2017; Hamed et al. 2023).

The presence of compounds 1–5 indicates that the endophytic fungi studied utilize various PKS pathways to synthesize both aromatic and non-aromatic polyketide frameworks. Under the examined culture conditions, *P. steckii* appears to preferentially generate reduced oxygenated aliphatic structures, *L. theobromae* produces both aromatic and aliphatic polyketides, and *A. niveus* represents a well-established source of aromatic benzopyranoid metabolites. This variation demonstrates the biosynthetic adaptability of endophytic fungi in producing structurally distinct polyketides; nevertheless, overarching generalizations concerning species-level biosynthetic tendencies must be limited by isolate-specific characteristics and experimental parameters (Hamed et al. 2023; Supratman et al. 2023; Mulyani et al. 2024a; Purbaya et al. 2024).

4.2. Hybrid metabolites

Hybrid metabolites reported from tropical endophytic fungi comprise structurally diverse scaffolds originating from PKS-terpenoid, PKS-NRPS, and amino acid–based biosynthetic systems. As illustrated in Figure 2, these compounds reflect the capacity of endophytes to adapt to the dynamic and competitive conditions of tropical ecosystems through diverse biosynthetic origins and pathway integrations.

The pericoannosins C (6), D (7), E (8), and F (9), which were obtained from the endophytic fungus *Periconia* sp. F-31, isolated from the medicinal plant *Annona muricata*. These compounds share a tetramate core linked to a substituted sesquiterpenoid backbone, indicative of a meroterpenoid biosynthetic origin. This structural arrangement aligns with previously suggested biosynthetic models, where terpenoid units are integrated with β-ketoacyl intermediates from PKS, followed by cyclization and enzyme modifications (Fan et al. 2019). The stereochemical and redox changes observed in compounds 6–9 underscore how enzymes can mediate late-stage alterations such as oxidation, reduction, and chiral center shifting, contributing to the structural diversity of these metabolites.

Another hybrid metabolite of interest is terrequinone A (10), synthesized by *Aspergillus niveus* isolated from the roots of *Foeniculum vulgare* (Apiaceae). This bis-indolyl benzoquinone scaffold with prenyl groups is derived from tryptophan and undergoes extensive oxidative processing. The biosynthesis of this compound follows indole meroterpenoid metabolic routes, as previously documented in the *Aspergillus* genus (Hamed et al. 2023), highlighting the versatility of endophytes in adapting their biosynthetic pathways to produce complex, biologically active metabolites.

Furthermore, the integration of PKS-NRPS systems is illustrated by colletopeptide B (11) from *Lasiodiplodia theobromae* and the diketopiperazine cyclo-(S-Pro-R-Leu) (12) produced by *Periconia pseudobyssoides* K5 from *Toona sureni* (Azhari et al. 2023b; Purbaya et al. 2024). Colletopeptide B is a complex peptide-polyketide hybrid featuring a macrocyclic depsipeptide framework,

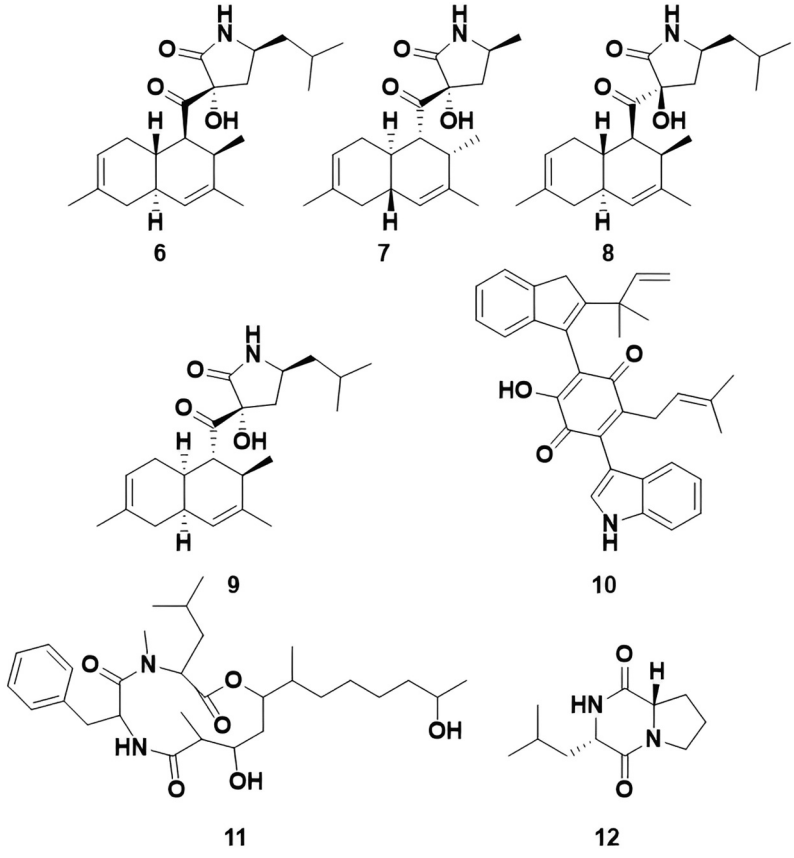

Figure 2. Hybrid metabolites from tropical endophytic fungi: (6) pericoannosin C; (7) pericoannosin D; (8) pericoannosin E; (9) pericoannosin F; (10) terrequinone A; (11) colletopeptide B; and (12) diketopiperazine cyclo-(S-Pro-R-Leu).

where amino acid-based cores are linked with PKS-derived lipid chains. Extensive post-assembly tailoring including hydroxylation, esterification, and methylation that emphasizes the modular nature of this biosynthesis. In contrast, the diketopiperazine cyclo-(S-Pro-R-Leu) represents a simpler biosynthetic product formed by combining proline and leucine through NRPS. Despite its simpler structure, diketopiperazines are significant as biosynthetic intermediates or precursors in more complex metabolic pathways.

The prevalence of these hybrid metabolites (6–12) confirms the flexible biosynthetic capacity of fungal endophytes, driven by modular enzyme assembly and pathway crosstalk. This chemical creativity provides endophytes with a competitive advantage in chemical defense and symbiotic interactions within high-pressure tropical environments. Similarly, the presence of terpenoids is often linked to their role as volatile organic compounds, which serve as long-distance signals facilitating communication with the host or acting as deterrents against herbivorous insects (Amaeze et al. 2026).

4.3. Phenolic and aromatic derivatives

The production of phenolic and aromatic compounds in tropical endophytes often mirrors the chemical defense strategy of their host plants. These metabolites are frequently synthesized to mitigate oxidative stress caused by high UV radiation and temperature fluctuations characteristic of tropical latitudes (Amaeze et al. 2026). Globally, phenolic compounds produced highly by endophytes in tropical regions, such as Southeast Asia, the Amazon, and Central Africa, serve a critical role in environmental adaptation, as these ecosystems are often exposed to intense biotic and abiotic pressures (Sharma et al. 2020; Ramatsitsi and Manyevere 2025; Dos Santos et al. 2026). This global context demonstrates that the synthesis of phenolic compounds is not just a local adaptation but also part of a broader ecological strategy that varies depending on regional environmental challenges.

A prominent example, as illustrated in Figure 3, is found in the endophytic fungus *Lasiodiplodia theobromae,* which produces three aromatic compounds (13–15) through the shikimate-derived phenylalanine-tyrosine pathway. This pathway works in tandem with the PKS machinery, adding a unique class of small aromatic molecules to the isolate's chemical fingerprint. The first two metabolites, 2-phenylethanol (13) and tyrosol (14), are aromatic alcohols formed by stepwise decarboxylation of aromatic amino acids (Purbaya et al. 2024). These structures suggest that the shikimate pathway is used conservatively, keeping the core phenyl ring intact. The biosynthesis of these compounds is strongly influenced by environmental factors, such as temperature and light (Alum et al. 2025), and their production can be triggered by precursors supplied by the host or in response to the plant's immune system in humid tropical environments. In a study, it was shown that the biosynthesis of such aromatic compounds is not just a response to abiotic stress but also an essential part of endophyte-host interactions in ecosystems worldwide (Koza et al. 2022). Tyrosol and 2-phenylethanol are influenced by environmental factors such as temperature and light (Shende et al. 2024).

The third compound, 2-(4-hydroxyphenyl) acetic acid (15), represents a further oxidized product of this same metabolic route, indicating a shift toward the formation of simple aromatic acids (Supratman et al. 2023). By maintaining the para-hydroxyl group, this metabolite remains within the phenolic family while adding structural variation to the chemical output of *L. theobromae*. The biosynthesis of these simple aromatics is closely tied

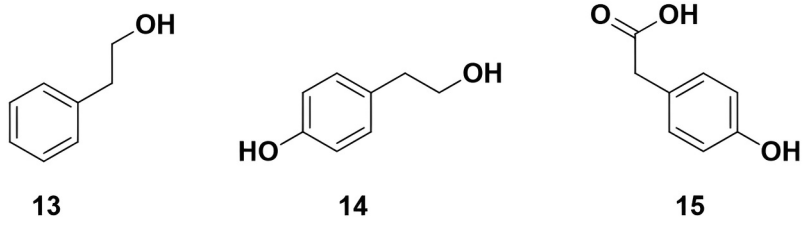

Figure 3. Phenolic and aromatic derivatives: (13) 2-phenylethanol; (14) tyrosol; and (15) 2-(4-hydroxyphenyl) acetic acid.

to plant stress responses and is influenced by environmental factors such as temperature and light. These findings are consistent with studies on African endophytes where phenolic derivatives are implicated in mediating plant defense signaling (Ramatsitsi and Manyevere 2025). Their production can be triggered by precursors supplied by the host or in response to the plant's immune system in the humid tropical environment. This dual-pathway biosynthesis is evident not only in tropical environments but also in temperate climates, where phenolic compounds provide defense mechanisms against fungal pathogens and herbivores (Alum et al. 2025).

4.4. Steroid

Steroidal metabolites represent one of the most recurrent and structurally conserved metabolite classes identified in tropical endophytic fungi between 2019 and 2024. Fourteen compounds belonging to the ergostane, stigmastane, campestane, and cholestane families were reported in Figure 4, indicating that sterol-derived metabolites remain a dominant chemical framework across multiple tropical endophytic taxa. Unlike highly diversified polyketides or hybrid metabolites, steroids reflect a conserved biosynthetic backbone with diversification occurring primarily through downstream oxidation and peroxide formation.

The predominance of ergostane-type steroids, particularly ergosterol (16) and ergosterol-5,8-peroxide (17), across *Cladosporium anthropophilum*, *Lasiodiplodia theobromae*, and *Periconia pseudobyssoides* suggests that sterol biosynthesis remains metabolically central in tropical endophytes (Azhari et al. 2023a; Supratman et al. 2023; Mulyani et al. 2024b). Importantly, sterols are not typically encoded within canonical secondary metabolite BGCs but originate from the conserved mevalonate pathway. Their structural diversification therefore reflects enzymatic

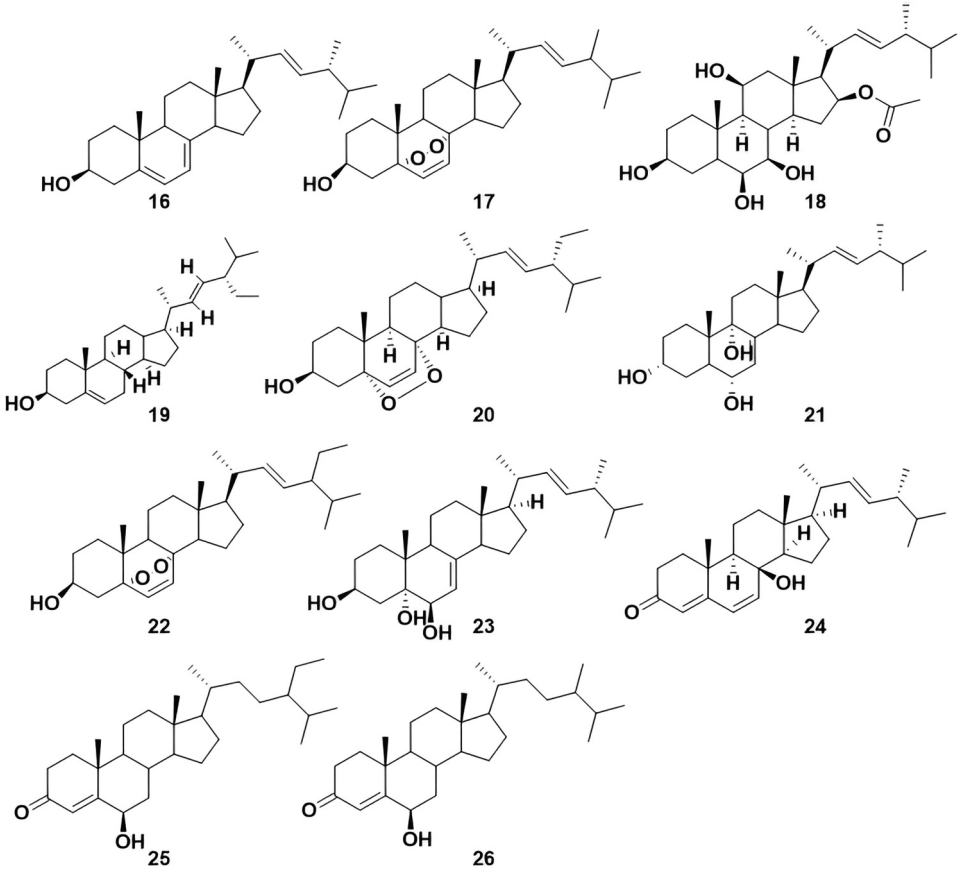

Figure 4. Steroid from tropical endophytic fungi: (16) ergosterol; (17) ergosterol-5,8-peroxide; (18) penicisteroid A; (19) stigmasterol; (20) stigmasterol-5,8-peroxide; (21) (22E)-3α,6α,9α-ergosta-7,22-diene-3,6,9-triol; (22) 5α-8α-epidioxy-24-ethyl-cholest-6,22-diene-3β-ol; (23) cerevisterol; (24) isocyathisterol; (25) 6β-hydroxystigmast-4-en-3-one; and (26) 6β-hydroxy-4-campesten-3-one.

tailoring rather than a novel gene cluster architecture. This observation provides a critical contrast to PKS- and NRPS-derived metabolites discussed in Sections 4.1–4.3.

Species variations between species occur at the level of oxidative modification. *C. anthropophilum* predominantly produces ergostane derivatives with frequent peroxide formation, including penicisteroid A (18), stigmasterol (19), and stigmasterol-5,8-peroxide (20), indicating a sterol-modifying enzyme system biased toward oxidative stress-related transformations. In contrast, *P. pseudobyssoides* K5 exhibits broader structural plasticity, generating ergostane, stigmastane, campestane, and cholestane derivatives (21–26), including highly oxygenated sterols such as (22E)-3α,6α,9α-ergosta-7,22-diene-3,6,9-triol and 5α,8α-epidioxy-24-ethyl-cholest-6-en-3β-ol (Azhari et al. 2023b). This expanded oxidation pattern suggests enhanced downstream enzymatic flexibility rather than divergence in core sterol biosynthesis.

The frequent occurrence of peroxide-type steroids across diverse taxa is noteworthy. Peroxide formation is often associated with oxidative stress responses and membrane adaptation mechanisms. In highly competitive tropical environments, such modifications may provide advantages in membrane stabilization, signaling functions, or chemical defense. Thus, this recurrent oxidative tailoring represents an adaptive metabolic strategy rather than simply biosynthetic redundancy. In addition to their pharmaceutical potential, these metabolites play important ecological roles as chemical mediators that facilitate niche occupation and protect hosts from sympatric pathogens resulting from environmental stress and host-symbiont co-evolution (Dos Santos et al. 2021; Usman et al. 2024; Kim et al. 2025).

5. Genomic mining of biosynthetic gene clusters (BGCs)

The latest technological developments are highly significant in the field of genome mining techniques, particularly in the analysis of biosynthetic systems in endophytic fungi. BGCs for secondary metabolite synthesis in fungi, in the form of a collection of genes coding for complex enzymes, can be predicted accurately (Medema and Fischbach 2015; Keller 2019). Biosynthetic domains consist of the catalytic structures of PKSs, non-ribosomal peptide synthetases (NRPSs), or PKS-NRPS hybrid systems. These synthases augment structural diversity via domain recombination and comprise critical functional units, including ketosynthase (KS), acyltransferase (AT), acyl carrier protein (ACP), adenylation (A), and thiolation (T, or peptidyl carrier protein/PCP) (Hwang et al. 2020; Tittes et al. 2022).

Bioinformatics platforms are indispensable for the annotation and prediction of BGCs. While antiSMASH remains the gold standard for identifying canonical BGCs based on rule-based pHMM algorithms, it often faces limitations in detecting non-canonical or novel architectures (Blin et al. 2023). These gaps are increasingly filled by machine-learning-based tools like DeepBGC, GECCO, and GATOR-GC, which offer higher sensitivity toward ”orphan” clusters (Hannigan et al. 2019; Kautsar et al. 2021). Furthermore, large-scale clustering tools such as BiG-SCAPE and BiG-FAM allow for a global diversity analysis by grouping BGCs into Gene Cluster Families (Navarro-Muñoz et al. 2020). Currently, a consensus-based approach integrating both rule-based and machine learning strategies is the primary framework for accurate biosynthetic mapping in tropical endophytes.

As summarized in Table 2, substantial diversity in biosynthetic mechanisms is observed across fungal species, characterized by distinct BGC architectures. In PKS systems, such as those found in *Aspergillus nidulans* and *A. terreus*, clusters mediate the stepwise incorporation of malonyl-CoA units. This process is further refined by auxiliary domains such as ketoreductase (KR), dehydratase (DH), and enoyl reductase (ER) to produce bioactive metabolites like orsellinic acid, emodin, and lovastatin (Cox 2007; Klejnstrup et al. 2012).

In contrast, NRPS systems in species such as *Penicillium thymicola* and *A. fumigatus* facilitate the assembly of structurally complex peptides through the modular A–T(PCP)–C–TE architecture, exemplified by the biosynthesis of penicillin (Ali et al. 2014; Vassaux et al. 2019). Moreover, heterologous expression studies in *A. nidulans* have validated findings from *Cordyceps gunnii*, revealing a rare non-enzymatic N–C cyclization step involved in the formation of the alkaloid 4-hydroxy-2-pyrrolidinone via a hybrid biosynthetic pathway (Cox 2007; Brakhage 2013; Zhang et al. 2016; Fan et al. 2019; Rao et al. 2022).

Table 2. Core structure and functional domains of major biosynthetic gene clusters (BGCs) in endophytic fungi.

BGC type	Fungal species	Core enzymatic domains	Biosynthetic mechanism summary	Representative products	Key references
PKS	*Aspergillus nidulans*	KS, AT, ACP	Sequential condensation of malonyl-CoA units via modular enzymes. Structure determined by presence/absence of KR, DH, ER domains.	Naphthopyrone, sterigmatocystin, orsellinic acid, emodin, austinol	Klejnstrup et al. (2012)
PKS	*Aspergillus terreus*	KS, AT, ACP	Malonyl-CoA-based elongation using modular enzymes. Modifications affect macrocycle formation.	Lovastatin	Cox (2007)
NRPS	*Penicillium thymicola, Aspergillus fumigatus, Talaromyces islandicus, Beauveria bassiana*	A, T (PCP), C, TE, ±E, ±MT	Incorporates amino acids into peptides via adenylation and condensation modules. Stereochemistry modified by E and MT domains.	Penicillin, chrysogine, cyclic tetrapeptides	Vassaux et al. (2019)
NRPS	*Penicillium chrysogenum*	$(C–A–PCP)_n$, MT, E	Tetra-modular NRPS synthesizes d-(L-α-aminoadipyl)-L-cysteinyl-D-valine (ACV); additional tailoring via HcpA.	Penicillin	Ali et al. (2014)
Hybrid PKS-NRPS, terpene, unknown	*Periconia* sp. F-31	Predicted: KS–AT–DH–ER–KR–ACP and A–T–TE	Combines acetate/malonate-derived polyketide with amino acids via hybrid megasynthase. Cyclization yields isochroman-pyrrolidone scaffold. Predicted terpenoids, uncharacterized scaffolds.	Pericoannosin A–F	Brakhage (2013); Zhang et al. (2016); Fan et al. (2019); Liu et al. (2022)
Hybrid PKS-NRPS	*Fusarium moniliforme, Fusarium venenatum*	A, PCP, C, KS, AT, ACP	Merges polyketide and peptide biosynthesis modules. Produces dual-origin complex molecules.	Fusarin C	Cox (2007)
Hybrid PKS-NRPS	*Cordyceps gunnii*	A–MT–T–KS–AT–KR–ACP–R–TE	Involves spontaneous N–1/C–2 cyclization. Mechanism confirmed by heterologous expression in *Aspergillus nidulans*.	4-hydroxy-2-pyrrolidinone alkaloid	Rao et al. (2022)
T1PKS, NRPS, terpene, unknown	*Lasiodiplodia theobromae*	KS, AT, DH, ER, KR, ACP; C, A, PCP, TE; terpene cyclase	Assembles acetate units via hrPKS; terpenoid synthesis via mevalonate pathway & cyclases.	Lasiodiplodin, mellein, taxadiene (terpene)	Salvatore et al. (2020); Li et al. (2023a)

KS = Ketosynthase; AT = Acyltransferase; ACP = Acyl carrier protein; KR = Ketoreductase; DH = Dehydratase; ER = Enoyl reductase; A = Adenylation domain; T = Thiolation domain (also known as PCP); C = Condensation domain; TE = Thioesterase; MT = Methyltransferase; E = Epimerase; R = Reductase.

Remarkable enzymatic flexibility is also found in PKS-NRPS hybrid systems. For example, *Periconia* sp. F-31 exhibits a megasynthetic architecture combining a polyketide module with an NRPS element, resulting in the synthesis of pericoannosin A–F on an isochromane–pyrrolidone scaffold (Zhang et al. 2016; Fan et al. 2019). In addition to the well-documented PKS and NRPS pathways, genomic analyses have revealed that a significant portion of the fungal genome is dedicated to terpene BGCs and unidentified clusters known as orphan BGCs (Brakhage 2013; Liu et al. 2022).

These orphan clusters represent the "dark matter" of fungal metabolism because they lack significant homology with biosynthetic pathways characterized in public databases (Amos et al. 2017; Gregory et al. 2019; Meesil et al. 2023; Mahmud et al. 2025). The potential of these clusters to encode novel chemical scaffolds with unique biological activities is vast yet largely uncharted. The identification of orphan BGCs through advanced tools like DeepBGC and BiG-SCAPE further emphasizes the limitations of our current knowledge and highlights the urgency of systematic activation strategies such as heterologous expression or epigenetic modification to uncover their hidden chemical outputs.

The full potential of genome mining can only be realized if it is directly integrated with metabolomic profiling through frameworks like Feature-Based Molecular Networking. By leveraging the GNPS platform, researchers can now map predicted biosynthetic pathways into tangible spectral signatures. This "Genome-to-Metabolite" mapping enables rapid dereplication of known compounds while prioritizing novel cryptic metabolites that typically remain silent under standard laboratory conditions. This integrative approach between genomics (BGC) and metabolomics (LC-MS/MS) ensures that every single mass feature can be directly correlated with a specific biosynthetic cluster (Soldatou et al. 2019; Merwin et al. 2020; Caesar et al. 2021; Leão et al. 2021; McCaughey et al. 2021).

6. Metabolomic approaches in natural product discovery

Genome mining reveals that endophytic fungi possess the ability to synthesize secondary metabolites.

Moreover, metabolomics techniques provide empirical evidence linking genes to chemical compounds via mass spectrometry (MS). LC-HRMS is currently considered the most sophisticated instrument for both targeted and non-targeted metabolomics studies, providing exceptional sensitivity in spectral database analysis (Sands et al. 2021). Furthermore, nuclear magnetic resonance (NMR) spectroscopy and associated instrumentation enhance our ability to identify, dereplicate, and characterize fungal natural products, such as novel polyketides, peptides, and alkaloids (Mohimani et al. 2018; Emwas et al. 2019; Wishart 2019). These methodologies have shown significant effectiveness in clarifying secondary metabolites associated with non-modular or cryptic BGCs, utilizing tools like the PRISM algorithm for predictive structural analysis (Skinnider et al. 2017).

The application of MS-based molecular networking is now a global standard, with major contributions originating from international platforms that integrate data from various tropical biomes (Jamilatun 2023; Amaeze et al. 2026). These global datasets allow for the comparison of metabolic profiles across different continents, reducing the reliance on localized case studies. Table 3 summarizes the metabolomic validation in tropical endophytic fungi, where methodologies used vary depending on the level of characterization specificity and the chemical nature of the metabolites studied.

While traditional techniques, such as column chromatography, thin-layer chromatography (TLC), and one- or two-dimensional NMR spectroscopy, continue to be employed for specific studies requiring thorough compound isolation and structural confirmation. Comprehensive investigations to promote the development of untargeted or semi-targeted metabolomic profiling of *Trichoderma reesei* and *Lasiodiplodia theobromae* utilize high-resolution MS techniques, including UHPLC-MS/MS and LC-HRMS (Habisukan et al. 2021; Elfita Oktiansyah et al. 2023). These techniques are particularly useful when the primary goal is to discover new compounds or conclusively confirm their structures.

Metabolomics research has evolved by combining chemical analysis techniques with bioactivity assays, therefore increasing the functional relevance of metabolite profiling results from tropical endophyte studies. Modern multi-omics methodologies are largely focused on integrating genomic prediction with metabolomics validation. UHPLC-MS/MS was used to identify cholinesterase-inhibiting alkaloids derived from *Aspergillus niveus* Fv-er401, an isolate of *Foeniculum vulgare* (Apiaceae), a subtropical plant that thrives in tropical climates (Hamed et al. 2023). Meanwhile, LC-HRMS was used in the study of *Diaporthe fraxini* ED2, extracted from *Orthosiphon stamineus*, to characterize its metabolite diversity (Tan et al. 2022). Evaluation of antioxidant and antimicrobial activities indicated that compounds are derived from *Cercospora* sp. PM018, isolated from *Aerva javanica* (Mookherjee et al. 2020). A separate study examined *Penicillium chrysogenum* and *Fusarium verticillioides*, isolated from *Avicennia marina*, using MS and NMR techniques, as well as comprehensive bioactivity evaluation (Mulyani et al. 2024a).

7. Integrative strategies, limitations, and future outlook

7.1. Data integration challenges

The synergistic integration of genome mining and non-targeted metabolomic profiling has improved the ability to predict and validate BGCs and their

Table 3. Summarizes representative LC-MS and NMR validations linking fungal metabolites to their predicted BGCs.

Endophytic fungus	Host plant	Metabolomic/ structure validation	Reference
Trichoderma reesei	*Syzygium aqueum*	Column chromatography, TLC, structure validation by NMR 1D and 2D	Habisukan et al. (2021)
Penicillium chrysogenum, *Fusarium verticillioides*	*Avicennia marina*	MS, 1D-, and 2D-NMR	Mulyani et al. (2024a)
Cercospora sp. PM018	*Aerva javanica*	GC-MS; antioxidant and antimicrobial activity	Mookherjee et al. (2020)
Aspergillus niveus Fv-er401	*Foeniculum vulgare* (Apiaceae)	UHPLC-MS/MS; cholinesterase inhibition; isolation of alkaloids	Hamed et al. (2023)
Lasiodiplodia theobromae	*Peronema canescens*	Column chromatography, TLC	Elfita Oktiansyah et al. (2023)
Diaporthe fraxini ED2	*Orthosiphon stamineus*	LC-HRMS	Tan et al. (2022)

associated metabolites. The use of advanced tools such as antiSMASH, DeepBGC, and Global Natural Products Social Molecular Networking (GNPS) enables the systematic identification of hidden biosynthetic pathways and facilitates the annotation of complex metabolite networks (Jamilatun 2023; Amaeze et al. 2026). However, specific technical barriers to heterologous expression of tropical endophytes exist, including the high GC content and numerous introns in their BGCs, which often lead to transcriptional silencing or truncated proteins in model hosts (Beijen et al. 2024). Unlike fungi from temperate regions, tropical isolates have evolved to respond to a wide range of ecological triggers, which are difficult to replicate using constitutive promoters in the laboratory (Gacek-Matthews et al. 2016).

7.2. Synthetic biology pathways and activation strategies

Rapid advances in synthetic biology and the development of co-culture systems have been key factors accelerating the discovery of novel secondary metabolites from tropical endophytic fungi. Through an integrative approach that synergizes molecular networking with genomic analysis, researchers are now able to identify "silent" BGCs. These clusters are genetically conserved in the fungal genome but are not expressed or produce metabolites when grown under standard laboratory conditions (Santos et al. 2020). This phenomenon often not only poses a major obstacle to bioprospecting, but also opens up significant opportunities for discovering entirely new chemical structures through targeted manipulation.

Activation strategies through synthetic biology are now at the forefront, particularly with the use of CRISPR-Cas9 technology. This technique enables precise genome editing, either through promoter activation to enforce target gene expression or through the deletion of negative regulatory genes that currently inhibit metabolite biosynthesis (Beijen et al. 2024). Furthermore, heterologous expression transferring BGCs from native fungi to more manageable model hosts, such as *Saccharomyces cerevisiae,* has become a crucial pathway for producing large quantities of compounds (Gacek-Matthews et al. 2016). In addition to genetic approaches, co-culture strategies (growing endophytes with other microbes) have proven highly effective. By simulating interspecific competition occurring in competitive tropical biomes, endophytes are triggered to release bioactive metabolites that typically remain silent in pure culture (Santos et al. 2020). The use of chemical signaling molecules or external ecological stressors also serves as a trigger to unlock uncharted metabolic pathways.

To unlock the "dark matter" of the fungal genome, an integrated activation strategy is essential, as the vast majority of BGCs remains silent under standard laboratory conditions. As illustrated in Figures 5 and 6, this process is typically sequential. It begins with ecological manipulation using the OSMAC (One Strain, Many Compounds) approach, which is often enhanced by introducing host-derived elicitors or external stressors to trigger dormant metabolic pathways (Newman et al. 2017; Romano et al. 2018; Li et al. 2023b; Zhang et al. 2024).

Furthermore, co-culture strategies mimic the interspecific competition found in tropical biomes, inducing the production of cryptic metabolites through interorganismal crosstalk (Pillay et al. 2022; Pinedo-Rivilla et al. 2022). When ecological triggers are insufficient, genetic and epigenetic interventions are employed. Small-molecule inhibitors, such as 5-azacytidine or SAHA, are used to bypass repressive chromatin states, while CRISPR-Cas9 technology allows for precise promoter activation or the deletion of negative regulators (Verma et al. 2023; Beijen et al. 2024). For high-level production, BGCs are often transferred to model hosts via heterologous expression, where native promoters are replaced with strong constitutive or inducible ones, such as gpdA or alcA (Wei et al. 2021; Yang et al. 2022; Hur et al. 2023; Wang and Mao 2025).

The final structural diversification of these metabolites is driven by a sophisticated "assembly line" of tailoring enzymes (Figure 7). Beyond the initial backbone assembly by core PKS or NRPS modules, enzymes such as P450 hydroxylases and methyltransferases introduce critical functional groups. These modifications adjust the molecule's lipophilicity and target affinity, determined by the evolutionary pressures of highly competitive tropical niches (Skellam 2021; Zhang et al. 2021; Prajapati et al. 2025).

7.3. Metadata and repository needs

Currently, research data on tropical endophytic fungi, including metabolite profiles, bioactivity test results,

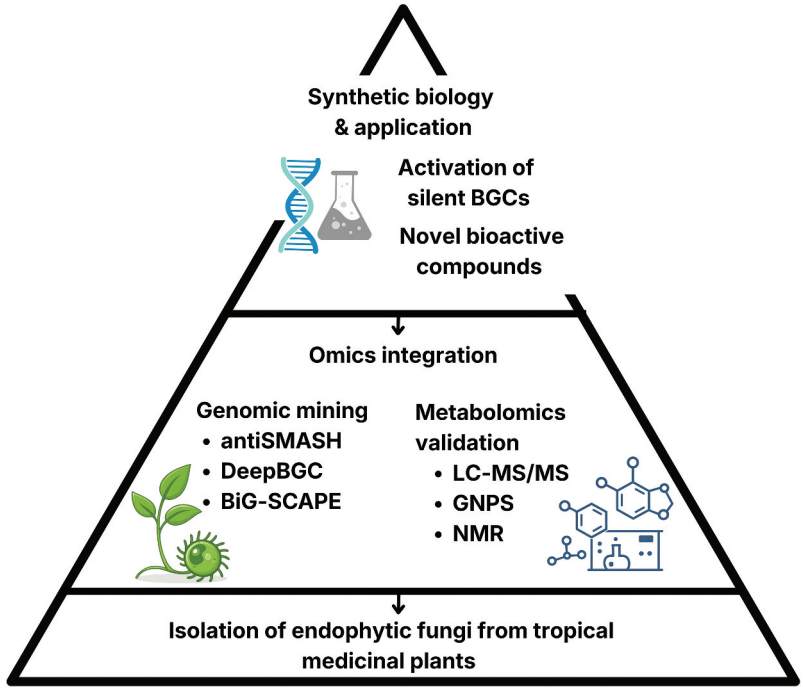

Figure 5. A schematic framework illustrating a multi-layered integrative strategy linking genome mining, metabolomics validation, and synthetic biology approaches in tropical endophytic fungi.

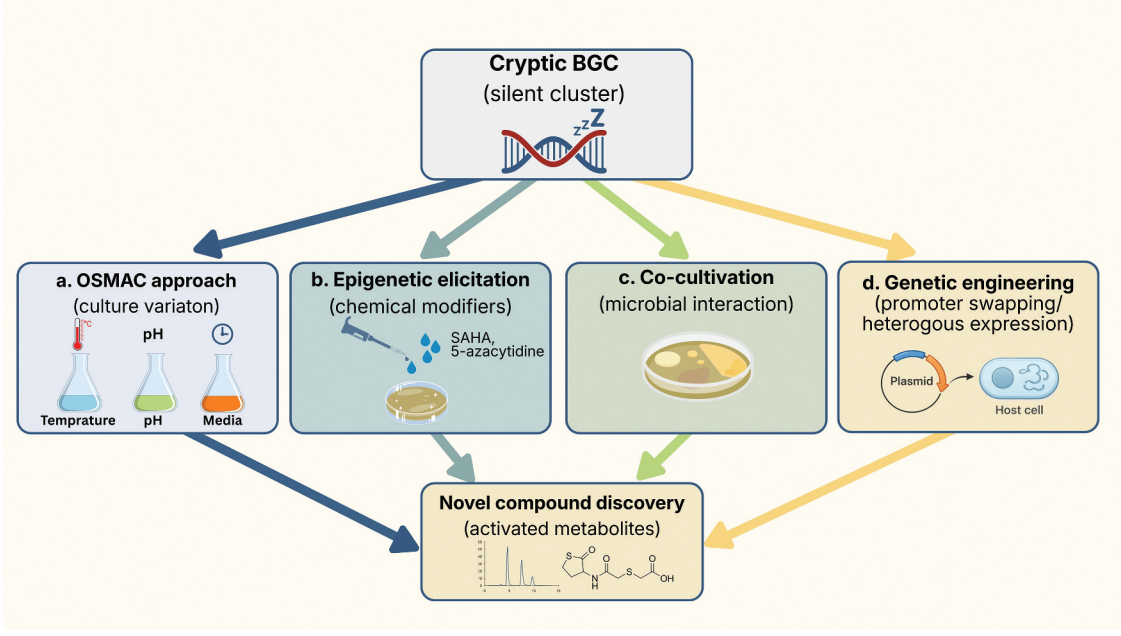

Figure 6. Strategic workflow for awakening cryptic biosynthetic gene clusters (BGCs) in endophytic fungi. The diagram highlights four major approaches: (a) OSMAC approach (modifying culture conditions); (b) epigenetic elicitation (using HDAC/DNMT inhibitors); (c) co-cultivation (mimicking interspecies interactions); and (d) genetic engineering (promoter swapping and heterologous expression in model hosts). This integrated pipeline facilitates the discovery of novel metabolites that are not produced under standard laboratory conditions.

and BGCs, remain widely scattered and poorly curated. To address this challenge, a comprehensive metadata system is needed that includes specific details such as host information, isolate origin, cultivation conditions, and relevant environmental parameters. The existence of an open-access repository dedicated to tropical fungal resources, including curated BGC data, metabolite spectra, and bioactivity

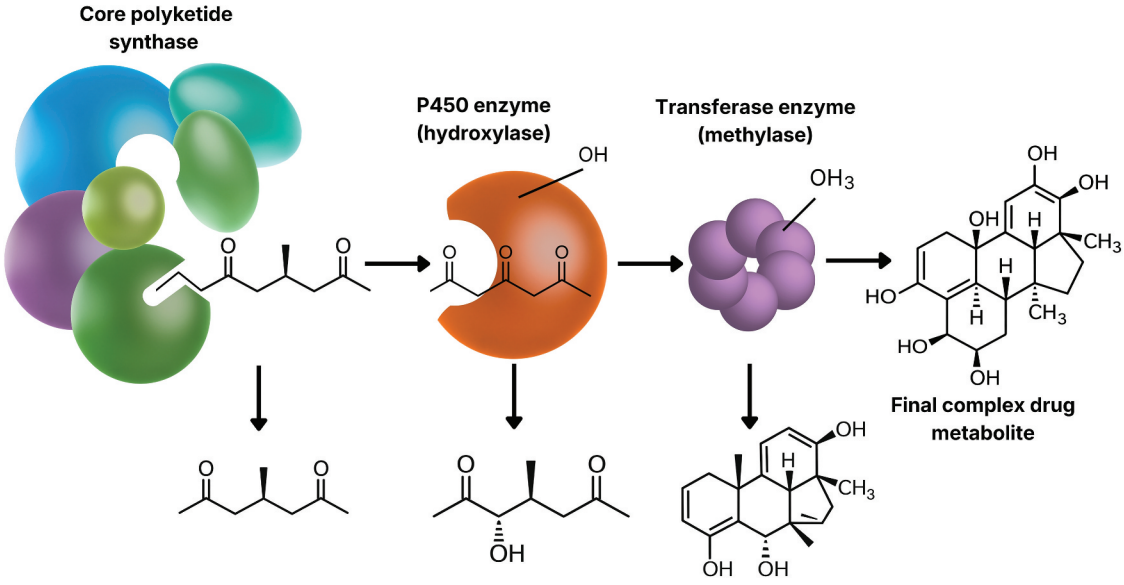

Figure 7. Schematic representation of the enzymatic assembly line in fungal secondary metabolism. The biosynthetic process initiates with a core polyketide synthase (PKS), which assembles the foundational carbon backbone from simple acyl-CoA precursors. This intermediate scaffold subsequently undergoes regiospecific modifications by tailoring enzymes, including cytochrome P450 monooxygenases (performing hydroxylation, –OH) and transferases (mediating methylation, $–CH_3$). These sequential enzymatic transformations culminate in the synthesis of a structurally complex final drug metabolite, demonstrating the biochemical granularity required to produce bioactive scaffolds in tropical endophytes.

profiles, is essential. Beyond technical aspects, future research on tropical endophytes must adhere to the principles of Access and Benefit-Sharing to ensure the ethical and equitable use of biodiversity resources for provider countries.

Although the tropics possess extraordinary biodiversity, existing research remains geographically fragmented. The establishment of a global network that integrates data from various tropical biomes, from the Neotropics to the Paleotropics, is crucial to address the current fragmentation in endophytic natural product research (Jamilatun 2023). Such a collaborative framework enables cross-continental comparative genomics, potentially revealing how distinct tropical environments uniquely shape the evolution of BGCs.

Achieving this vision requires a multidisciplinary consortium involving experts in natural product chemistry, microbiology, pharmacology, and biotechnology. This synergy is crucial for transforming fungal discoveries in the laboratory into products that are meaningful to society. By addressing current challenges and limitations, the bioprospecting principles for specific fungal endophyte bioresources in tropical regions demonstrate the importance of collaborative and ethical frameworks for ensuring the sustainability of natural product research in the future.

7.4. Towards a dynamic biosynthetic atlas

The transition toward an integrative "multi-omics" framework is a strategic evolution to ensure sustainable bioprospecting and minimize redundant discovery. By synergizing genomics, metabolomics, and synthetic biology, we can minimize redundant discovery and accelerate the translation of tropical endophytic metabolites into sustainable biotechnological applications (Santos et al. 2020; Jamilatun 2023). This atlas will facilitate the prioritization of compounds for development by identifying biosynthetic "hotspots" within fungal tissues and enhancing the efficacy of engineered heterologous expression systems.

A critical interrogation of the field reveals that BGCs often remain "silent" because their activation is governed by complex epigenetic layers, such as histone acetylation and methylation, which are typically suppressed under standard laboratory fermentation. These "cryptic" states serve as evolutionary safeguards, ensuring that energy-intensive secondary metabolism is only triggered by specific host-derived cues or interspecies competition (Brakhage 2013; Gacek-Matthews et al. 2016). Consequently, omics tools alone are insufficient without incorporating OSMAC strategies or chemical epigenetics to bypass these regulatory bottlenecks.

Successful integration has already been demonstrated in tropical isolates. For instance, the use of molecular networking via GNPS has effectively dereplicated known metabolites in *Lasiodiplodia* and *Penicillium* species, allowing researchers to prioritize unique chemical scaffolds. Similarly, the strategic use of epigenetic modifiers, such as HDAC inhibitors, has awakened silent clusters in *Aspergillus*, yielding novel polyketides absent under standard conditions (Pillay et al. 2022).

However, the high attrition rate of endophytic metabolites in clinical pipelines remains a significant hurdle. Many compounds with potent *in vitro* cytotoxicity fail *in vivo* due to poor ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiles. To bridge this gap, we must shift from bioactivity-guided isolation to a holistic, pharmacology-first approach, utilizing synthetic biology to optimize scaffolds for human compatibility (Jamilatun 2023).

To advance beyond current models, we propose the "Sentinel Fungal Hypothesis", which posits that endophytic BGCs function as evolutionary sensors tailored to host-environmental stressors. The next frontier lies in "Ecological-driven Genome Mining", a framework that integrates in situ transcriptomic data from stressed tropical hosts directly into BGC prediction algorithms (Kim et al. 2025). By treating the fungal BGC as a dynamic responder to host signaling rather than a static factory, we can develop "precision activation" strategies that synchronize natural product discovery with the complex ecological reality of tropical biomes.

8. Conclusions

The potential of tropical endophytic fungi has been interesting and increasingly explored, although their utilization as a significant biogenetic resource is not yet fully recognized. Integrative omics methodologies are currently being used to bridge this knowledge gap. Recent advances in genome mining and metabolomics have led to the association of bioactive compounds and the identification of BGCs. This approach not only builds the foundation for more targeted bioprospecting but also paves the way for more precise synthetic biology applications in the future. However, substantial challenges remain, including transcriptional ambiguity within uncharacterized BGCs, the lack of standardized metabolomics protocols, and limited access to spectral and genomic databases for tropical fungi.

To transform endophytic fungi into potential bioresources, providing metadata facilities to facilitate curated data exchange and fostering interdisciplinary collaboration are crucial. Understanding the ecological drivers that trigger BGC expression in situ will be key to successful lab-scale activation. With open multi-omics data, bioprospecting principles prioritizing ethical access and equitable benefit sharing can ensure responsible and sustainable research.

In conclusion, the integration of CRISPR-based activation systems, machine learning for rapid dereplication, and the development of a curated tropical omics database are transformative steps that will unlock the previously hidden secrets of endophyte biosynthesis. Endophytic fungi in tropical flora are not simply inhabitants of plant tissues but rather dynamic chemical factories that offer limitless opportunities for future biotechnology innovation and drug discovery.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This research was funded by Riset dan Inovasi untuk Indonesia Maju (RIIM) Gelombang 1, Year 3, from the National Research and Innovation Agency (BRIN) and the Educational Fund Management Institution (LPDP) [44/IV/KS/06/2022]. The publication charge is funded by Universitas Padjadjaran through the Indonesian Endowment Fund for Education (LPDP), under the Ministry of Higher Education, Science and Technology, and managed under the EQUITY Program [Contract No. 4303/B3/DT.03.08/2025 and 3927/UN6.RKT/HK.07.00/2025].

Author contributions

APW: conceptualization, writing-original draft, and supervision; ENL, LN, and AA: literature analysis and writing-review & editing; AW and RPP: writing-review & editing.

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