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Endophyte–Host Chemical Ecology as a Discovery Engine: An Integrative Review of Signaling, Silent Biosynthetic Pathways, Co-Culture, and Natural-Product Expression

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ABSTRACT

Endophytic fungi can harbor extensive biosynthetic capacity, yet natural-product discovery commonly interrogates them after removal from the host and transfer to simplified culture. This creates a central uncertainty: chemistry observed *ex planta* may represent only one state within a larger, interaction-dependent chemical repertoire. This integrative review synthesized ecological, metabolomic, genomic, regulatory, co-culture, and pathway-activation evidence relevant to endophyte chemical expression. A targeted evidence-selection process screened 52 unique DOI-resolved candidate articles, assessed 42 in detail, and retained 36 for synthesis. Evidence types were kept distinct to avoid treating metabolite detection, structural assignment, biosynthetic attribution, and ecological function as equivalent. The literature supports four recurring patterns. First, host-associated and isolated-culture chemical profiles can diverge. Second, host chemistry, microbial competitors, environmental stress, and fungal regulatory state can alter the context in which metabolites or biosynthetic gene clusters are expressed. Third, co-culture and engineered activation can expose chemistry not evident under standard monoculture, but these interventions do not necessarily reproduce native host cues. Fourth, genome mining and metabolomics strengthen discovery when combined, yet assignment confidence increases only through orthogonal validation. We therefore propose an evidence-bounded view of endophyte discovery in which ecological perturbation generates hypotheses, biosynthetic and analytical tools constrain source and structure, and functional interpretation remains a separate validation problem. Endophyte–host chemical ecology is best treated as a conditional discovery space rather than a fixed inventory. Its value lies in experimentally testing context-dependent chemistry while preserving uncertainty about source, mechanism, transferability, and ecological function.

Keywords: Endophytic fungi, Chemical ecology, Natural products, Biosynthetic gene clusters, Silent pathways, Co-culture

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Introduction

Microbial natural-product discovery is increasingly moving beyond repeated activity-first screening of standard monocultures toward combinations of biosynthetic activation, production engineering, and informatics that can expose otherwise inaccessible chemical space [1]. Metabolomics has enlarged the observable fraction of that space, but detection is not equivalent to identification: spectral annotation, dereplication, structural confirmation, and progression from a feature to a validated natural product remain separate analytical tasks [2]. Endophytic fungi sharpen this problem because they are discovered in a biological context but usually screened after that

context has been removed. The central question is therefore not simply what an isolate can produce, but which chemical states become observable under particular host, microbial, and environmental conditions.

Comparative genomics provides a second reason to avoid treating a monoculture extract as a complete representation of an endophyte. Xylarialean endophytes can contain large, evolutionarily dynamic repertoires of biosynthetic gene clusters (BGCs), with cluster diversity associated with ecological generalism [3]. Across microbial natural-product discovery, metabolomics, biosynthetic activation, and ecological/genomic evidence now offer complementary routes into chemical diversity [1-3]. Yet genomic capacity is only the beginning of the inferential chain. Fungal secondary metabolism is governed by pathway-specific regulators, global regulatory networks, chromatin state, development, nutrient conditions, and other environmental inputs [4]. A BGC can therefore be present without being detectably expressed under the conditions chosen for isolation or screening.

This distinction changes the discovery problem. A chemically unproductive monoculture may represent a genuinely low-producing organism, an inappropriate nutritional or physical environment, loss of host-derived regulation, absence of a microbial competitor, or a regulatory state in which genetically encoded pathways remain weakly expressed. Conversely, chemical novelty observed after perturbation does not by itself identify which ecological variable was responsible. Discovery therefore benefits from treating culture condition as part of the phenotype being measured rather than as a neutral container in which an organism reveals a fixed metabolome.

This review examines endophyte–host chemical ecology as a discovery engine rather than as a claim that the host niche can be faithfully reproduced *in vitro*. It integrates evidence on host-associated versus isolated chemical phenotypes, bidirectional host–microbe chemistry, environmental control, co-culture, regulatory and epigenetic activation, and the analytical problem of linking a detected molecule to a producer and pathway. The proposed synthesis deliberately separates four evidential questions: whether chemistry changes with context, whether a compound can be structurally established, whether its biosynthetic origin can be assigned, and whether it has a demonstrated ecological function. These questions frequently require different experiments and should not be collapsed into a single claim of "activation."

The review uses a targeted integrative evidence-selection process designed for conceptual coverage rather than systematic-effect estimation. The literature spans direct endophyte experiments, broader fungal regulatory studies, plant–microbiome ecology, natural-products chemistry, and genome–metabolome methods. This heterogeneity is necessary to connect ecological conditions with biosynthetic expression, but it also limits universal generalization. The argument developed here is therefore conditional: ecological context can generate and prioritize natural-product hypotheses, whereas strong source, pathway, mechanistic, and functional claims require progressively more direct validation.

Why isolated culture may conceal endophyte chemistry

Isolation is experimentally useful because it separates an organism from the complexity of host tissue, permits controlled perturbation, and makes repeated chemical analysis possible. The same simplification, however, can remove biological variables that shaped the endophyte before culture. In *Astrocaryum sciophilum*, comparative metabolomics of host material and cultivable foliar endophytes revealed limited overlap between host-associated and cultured chemical features and highlighted the difficulty of assigning shared signals to fungal origin [5]. Such discordance does not show that every host-only feature is induced by the plant, because extraction, growth state, cultivability, abundance, or analytical sensitivity can also generate differences. It instead establishes a narrower point: isolated-culture chemistry should not automatically be treated as a complete proxy for the host-associated chemical state.

Microbial interaction adds another source of conditionality. Pairwise coculture of xylarialean fungi generated highly interaction-specific chemical features, including metabolites not observed in corresponding monocultures, with responses varying by competitor identity [6]. This supports using interaction identity as an experimental variable rather than assuming that a single "coculture condition" captures fungal competition. Practical fungal coculture literature likewise shows that partner choice, cultivation format, screening strategy, and producer attribution materially influence the chemistry recovered [7]. Together, host-versus-culture discordance, pair-specific induction, and design sensitivity indicate that observed fungal chemistry is strongly conditioned by the experimental and ecological context in which it is measured [5-7].

This has an important consequence for negative results. Failure to detect a metabolite under standard culture is evidence about that condition, not definitive evidence that the organism lacks the capacity to produce it. At the same time, a compound appearing only after interaction cannot automatically be described as host-regulated,

ecologically necessary, or normally produced *in planta*. Culture comparisons reveal conditional expression; they do not by themselves identify the environmental cue, producer, pathway, or native ecological relevance.

Context dependence also has a regulatory component. In a mechanistic fungal cocultivation model, widespread secondary-metabolite remodeling depended on the VeA1 regulatory background [8]. That result is important not because VeA1 should be extrapolated as a universal endophyte switch, but because it demonstrates that interaction effects can depend on the internal regulatory state of the responding fungus. Consequently, failure to observe a metabolite in monoculture can reflect absence of the relevant cue, an incompatible partner, a different developmental state, or regulatory constraints rather than absence of biosynthetic capacity. This makes isolated culture a controlled experimental state, but not necessarily the chemically representative state against which all other observations should be judged.

Figure 1 reports the verified evidence-selection pathway underlying this integrative synthesis and distinguishes screening and detailed-assessment exclusions without implying systematic-review status.

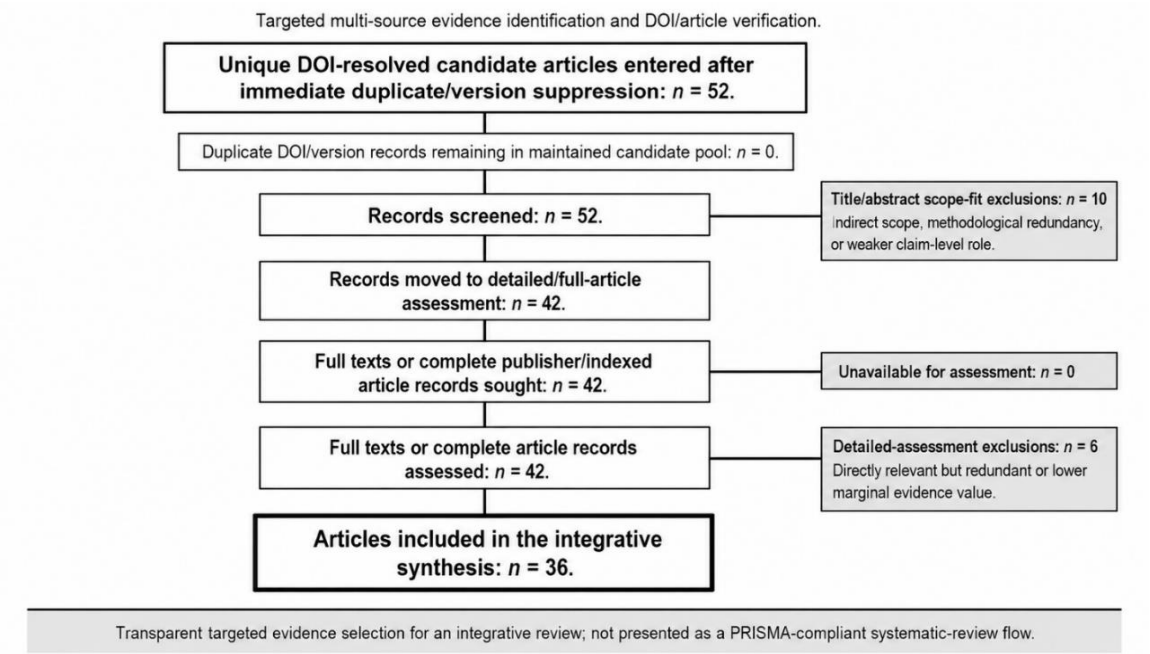

Figure 1. Verified evidence-selection flow for the integrative endophyte chemical-ecology synthesis

Host–microbe chemical signaling

Chemical communication in endophyte systems should not be reduced to a one-way model in which a microorganism simply secretes a natural product into passive host tissue. Experimental evidence supports at least two directional possibilities. In black poplar, colonization by a fungal endophyte altered leaf chemistry, deterred insect feeding, and was associated with changes in insect community assembly [9]. This demonstrates that an endophyte can modify a host chemical phenotype with measurable ecological consequences, but it does not establish that every endophyte is beneficial or that a single metabolite accounts for the ecological response.

The host can also shape the microbial environment chemically. In *Lycoris radiata*, Amaryllidaceae alkaloids were linked experimentally to interactions among plant chemistry, the bacteriome, and phytopathogens [10]. The result supports a host-to-microbiome chemical direction, although it would be overly teleological to classify every specialized metabolite as an evolved “signal” for endophytes. Some molecules may instead operate as selective filters, nutrients, toxins, defense compounds, or multifunctional metabolites whose microbial consequences depend on concentration and context. Bidirectionality therefore describes plausible directions of chemical influence, not proof of a reciprocal molecular conversation.

A further boundary is molecular modality. Two beneficial root endophytes were shown to deploy an antimicrobial GH18-CBM5 chitinase in niche defense and host protection [11]. This mechanism illustrates that chemically mediated endophyte effects include secreted proteins and enzymes as well as specialized small molecules. For a natural-product review, that distinction matters: a change in host phenotype can indicate biologically meaningful interaction without demonstrating secondary-metabolite production, while a metabolite change can occur without

establishing that it mediates the phenotype. Signals, effectors, nutrients, toxins, and specialized metabolites should therefore remain analytically separable until their functions are experimentally resolved.

Finally, the relevant ecological unit may contain more than one host and one fungal metabolite producer. Chemical-ecology work on cycad symbioses illustrates how multiple symbiotic partners can contribute chemically distinct interaction layers and complicate source attribution [12]. At larger scales, host availability strongly structures fungal-endophyte distributions, demonstrating that the opportunity for interaction itself is ecologically filtered [13]. Plant–microbiome research further shows that host, microbial, and environmental factors interact during community assembly and plant-health outcomes, making causal separation essential [14]. The synthesis proposed here therefore treats host–microbe chemical signaling as directional, context-dependent chemical influence embedded within prior ecological filtering. It does not assume a universal signaling vocabulary, fixed mutualistic outcome, or one-to-one correspondence between a detected molecule and a host phenotype.

Environmental control of biosynthetic expression

Environmental conditions can influence endophyte chemistry at several levels simultaneously: they can alter the host, change microbial abundance or community composition, and shift the regulatory state of the endophyte itself. Holo-omic analysis of a sorghum–endophyte–pathogen system under drought showed that drought state was associated with changes in endophyte BGC expression and with reorganization of relationships among the plant, endophyte, and pathogen [15]. This is stronger than an argument based solely on BGC presence because expression was measured in ecological context. It nevertheless does not establish that a particular expressed cluster produced the metabolite or phenotype under consideration; product-level linkage remains necessary.

Climate perturbation can also destabilize the host–endophyte relationship itself. Experimental warming across grassland systems disrupted plant–fungal endophyte symbiosis more strongly in leaves than roots and altered coupling between endophyte composition and host metabolomic variation [16]. The dependence on tissue and experimental context is important: “environmental control” should not be interpreted as a uniform directional response. Temperature, duration, host compartment, microbial composition, and acclimation can change whether a chemical association strengthens, weakens, or disappears. Consequently, sampling one tissue at one environmental state can miss both temporal transitions and compartment-specific chemical relationships.

Community composition introduces another level of uncertainty. Synthetic phyllosphere fungal communities produced pervasive nonadditive effects on plant performance, showing that the outcome of multiple fungal partners cannot always be reconstructed by summing isolate effects [17]. That finding concerns plant performance rather than metabolite-by-metabolite nonadditivity, but it provides a strong warning against assuming that isolated strain phenotypes scale linearly into communities. For discovery experiments, community composition is therefore not merely background variation: it can alter the biological context in which a focal endophyte experiences competition, resource limitation, or host-mediated selection.

Within the fungus, conditionality is also regulatory. In the endophytic fungus *Pestalotiopsis fici*, the CsdA/RsdA RNA-binding regulatory complex materially shaped secondary metabolism, demonstrating post-transcriptional control beyond simple BGC presence [18]. More broadly, fungal secondary metabolism integrates developmental and environmental regulation, and many pathways remain conditionally expressed [19]. Environmental perturbations therefore need not act directly on a BGC to change metabolite output; they may alter growth, development, regulatory networks, host physiology, or community composition first.

The proposed interpretation is consequently multilevel. Environmental effects on natural-product expression can arise through ecological restructuring, host-state change, altered encounter structure, and intracellular regulation, with these processes potentially operating on different time scales. Repeated sampling across environmental states and host compartments may therefore be more informative than treating a single culture or collection condition as representative. These routes should nevertheless remain analytically separate unless experiments directly connect them, because environmental association, regulatory response, BGC expression, metabolite production, structural identity, and ecological function are distinct evidential endpoints.

Co-culture and interaction-based discovery

Co-culture is valuable because it converts microbial interaction from an uncontrolled ecological possibility into an experimentally manipulable variable. Its outputs, however, are not all equivalent. Cocultivation can increase the abundance of metabolites already produced in monoculture as well as reveal chemistry that was previously undetected [20]. An increase in peak intensity or isolated yield therefore supports altered production, not

necessarily activation of a previously silent pathway. For discovery, novelty, abundance, pathway activation, and ecological relevance should be treated as separate observations.

Direct endophyte evidence shows why this distinction matters. Coculture of *Chaetomium virescens* and *Xylaria grammica* yielded new chromones that were isolated and structurally characterized [21]. This establishes that interaction-based cultivation can expose new chemical structures, but not that those structures are produced in the host or mediate the native interaction. Reciprocal responses add another complication: a *Penicillium–Aspergillus* pairing induced distinct products from both partners, with a putative biosynthetic assignment for one response [22]. Mixed-culture extracts therefore require producer-resolved analysis whenever possible.

The interpretive problem is especially acute when only the combined extract is analyzed. A coculture-only feature may reflect *de novo* biosynthesis, conversion of a precursor supplied by the other organism, relief of repression, altered nutrient competition, or simply a concentration change that crosses the analytical detection threshold. The reviewed co-culture literature does not resolve these possibilities uniformly [20]. Accordingly, a discovery claim should be matched to the observation actually made: "interaction-associated feature," "newly isolated structure," "producer-resolved product," and "BGC-linked product" represent progressively different evidential statements rather than stylistic alternatives. This vocabulary reduces the risk that chemical novelty, pathway novelty, and ecological function are treated as synonymous.

Mechanistic confidence increases when chemistry is paired with expression data. In an *Aspergillus oryzae–Epicoccum dendrobii* coculture, transcriptomic and metabolomic changes jointly supported interaction-associated remodeling of biosynthetic expression [23]. Even so, a differentially expressed BGC is not automatically linked to every newly observed feature. More broadly, cross-species coculture remains dependent on partner choice, cultivation format, reproducibility, and scale [24]. It is best interpreted as an ecology-inspired perturbation rather than a reconstruction of the host niche.

Table 1 distinguishes the principal evidence states produced by interaction-based experiments and the additional validation each state still requires.

Table 1. Evidence states in interaction-based endophyte natural-product discovery

Observed state	What it establishes	Main unresolved question	Stronger next test
Higher abundance of known metabolite	Production changed under interaction	New pathway or altered flux?	Quantitative replication plus expression analysis
New structurally assigned compound	Chemical novelty under tested coculture	Which partner/pathway produced it?	Producer-resolved culture and biosynthetic linkage
Partner-specific reciprocal products	Both organisms respond chemically	Which response is direct or indirect?	Separated controls and pathway-level testing
BGC expression plus altered metabolome	Interaction affects biosynthetic state	Which BGC maps to which product?	Orthogonal metabolite–BGC linkage
Ecology-inspired pairing	Manipulable interaction model	Does it reflect host-associated biology?	*In-planta* or host-mimetic validation

Abbreviation: BGC, biosynthetic gene cluster.

Silent chemistry and pathway activation

"Silent" is most useful as a condition-dependent operational description, not as a claim that a pathway is intrinsically inactive. Endophytic fungal chemistry can be altered by epigenetic manipulation, and recent synthesis shows that chromatin-targeting or related interventions can reveal metabolites weakly expressed under standard cultivation [25]. Such interventions are discovery tools, but their breadth creates interpretive ambiguity: an induced product does not identify the native ecological signal that would regulate the same pathway.

Targeted activation offers a different evidential advantage. CRISPR-mediated transcriptional activation can directly test whether increasing expression of a nominated fungal BGC changes metabolite production [26]. This strengthens inference about biosynthetic capacity because the perturbation is pathway-directed. It still does not establish that the pathway is naturally activated by a host, competitor, or environmental cue. Capacity validation and ecological regulation therefore occupy different levels of evidence.

Chromatin itself should not be treated as a universal master switch. Fungal BGC regulation involves multiple chromatin states, and perturbing familiar histone modifications activates only subsets of pathways [27].

Manipulation of global or pathway-specific transcriptional regulators can likewise expose cryptic chemistry, but broad regulators may alter development and many metabolic programs simultaneously [28]. The resulting metabolome can therefore contain both pathway-proximal effects and indirect consequences.

These activation modes also differ in what a negative experiment means. Failure of a chromatin modifier to reveal a product may reflect poor access to the relevant regulatory node rather than absence of the cluster, whereas failure of targeted activation after verified transcription places a different constraint on the hypothesized pathway. For endophyte discovery, this argues against scoring activation strategies solely by the number of new LC–MS features. The more informative comparison is whether a perturbation narrows a specific biosynthetic hypothesis and whether the induced product can subsequently be linked to native or host-associated conditions.

Mechanistic studies of multicomponent chromatin regulation reinforce this caution. The KdmB–EcoA–RpdA–SntB complex in *Aspergillus* links developmental control with secondary-metabolite synthesis [29]. This cannot be assumed to operate identically in endophytes, but it demonstrates why pathway activation may be pleiotropic. The proposed distinction in this review is therefore between ecological elicitation, broad regulatory perturbation, and targeted biosynthetic activation. Each can reveal hidden chemistry, but they answer different questions about why a metabolite appeared.

Integrating ecological and biosynthetic evidence

The discovery problem becomes most tractable when evidence is layered rather than collapsed. Genome mining with tools such as antiSMASH can nominate BGCs and biosynthetic features, but a predicted cluster remains evidence of capacity rather than expression or product identity [30]. Curated resources such as MIBiG improve comparison with experimentally characterized BGCs while remaining biased toward the chemistry and taxa that have already been studied [31]. Feature-based molecular networking can then organize related LC–MS/MS signals and highlight interaction-responsive chemical families, but network proximity is not structural proof [32]. Genome mining, characterized BGC references, and molecular networking therefore provide complementary but non-equivalent evidence [30-32].

Paired genomic and metabolomic resources strengthen candidate linkage because the two evidence types derive from matched biological material [33]. Stronger assignment is possible when experiments introduce additional constraints. Stable-isotope labeling can connect precursor incorporation patterns to BGC-predicted biosynthetic logic and thereby strengthen metabolite–cluster linkage beyond simple co-occurrence [34]. Computational integration can also prioritize hypotheses within defined chemical classes; Seq2PKS, for example, links tandem mass-spectrometric information with type I cis-AT polyketide biosynthetic predictions [35]. Such models remain chemotype-bounded and require experimental confirmation.

Orthogonal evidence is particularly valuable when modalities disagree. A BGC predicted from a genome but lacking a detectable product may indicate conditional expression, analytical insensitivity, incorrect cluster boundaries, or an untested substrate state; a metabolite family without a plausible genomic counterpart may reflect incomplete assembly, annotation limits, or production by another organism. Such discordance should therefore be treated as information that directs the next experiment, not simply as failed integration. The proposed architecture prioritizes tests that discriminate among these alternatives rather than accumulating additional correlated observations.

The synthesis proposed here therefore separates four questions that are often compressed into “discovery”: Was a chemical feature context-responsive? What is its structure? Which organism and BGC produced it? Does it perform a demonstrated ecological function? Evidence can become strong at one level while remaining weak at another. A structurally validated coculture product may have uncertain *in-planta* relevance; an expressed BGC may lack a linked metabolite; and a metabolite–BGC assignment may still say nothing about ecological function. **Figure 2** summarizes this proposed evidence architecture, preserving ecological context, activation strategy, biosynthetic assignment, and functional interpretation as connected but non-interchangeable layers.

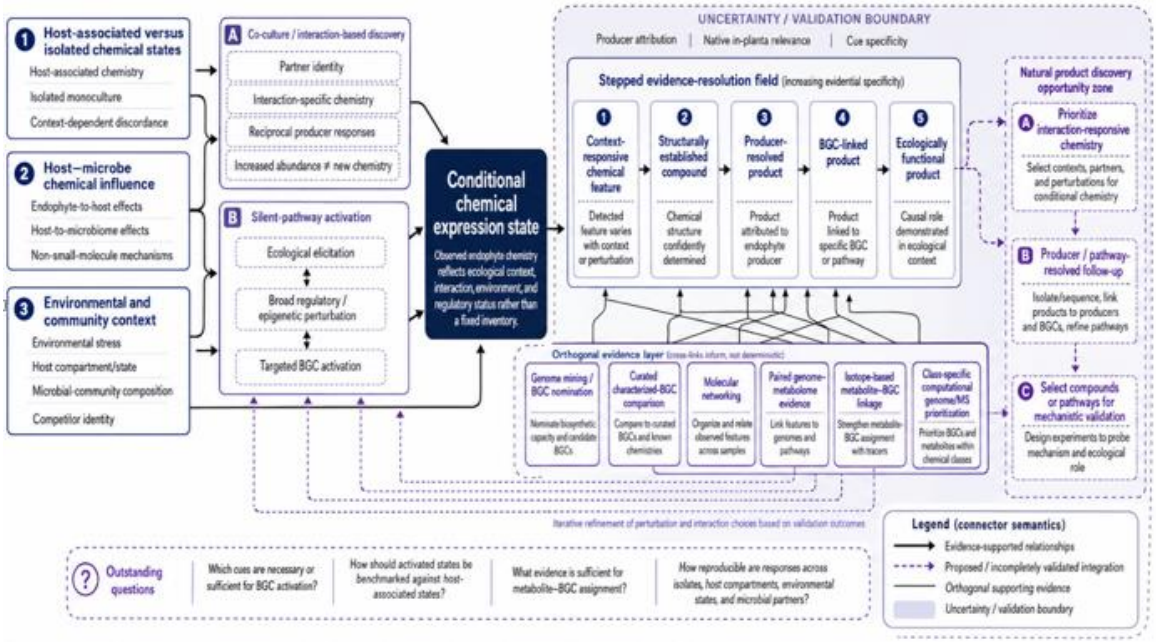

Figure 2. From context-responsive endophyte chemistry to evidence-bounded natural-product assignment

Opportunities for natural-product discovery

The strongest opportunity is not simply to increase the number of peaks in an extract, but to design experiments in which ecological perturbation and assignment evidence are collected together. Modern fungal metabolomics is most informative when interpreted with genomic, transcriptomic, and ecological information rather than as a stand-alone catalogue of features [36]. For endophytes, this favors comparative designs that retain a reference monoculture while adding host-derived conditions, defined competitors, environmental perturbations, or targeted regulatory interventions.

Defined, reversible perturbations are especially useful because they can increase interpretability: the objective is not maximal disturbance, but maximal information about why a chemical state changed.

The resulting chemical gains should be classified by what actually changed. Increased production of a known metabolite is useful for process development but is not equivalent to new chemistry [20]. A newly isolated and structurally characterized coculture product provides stronger evidence of chemical novelty [21]. Epigenetic activation can broaden accessible expression states but may be pleiotropic [25]. By contrast, experimental isotope-based linkage can materially strengthen a candidate BGC–metabolite relationship [34]. These are complementary discovery outcomes, not interchangeable rankings of success.

A practical research program should therefore combine ecological perturbation with producer resolution, genomic context, metabolite annotation, and replication across relevant host or environmental states. Drought-dependent changes in endophyte BGC expression illustrate why ecological state can be informative [15], whereas coculture transcriptome–metabolome studies show the value of measuring biosynthetic response and chemistry together [23]. Domain-specific genome/MS approaches can then help prioritize particular biosynthetic hypotheses for validation [35]. The proposed workflow is not a validated decision algorithm; its purpose is to reduce avoidable ambiguity before labor-intensive isolation or mechanistic experiments.

This perspective also changes how negative results are interpreted. Failure of one coculture, elicitor, or host-mimetic condition to induce chemistry should narrow the tested condition space rather than establish pathway absence. Conversely, a positive result should trigger stronger source and pathway tests before ecological interpretation. Discovery efficiency may therefore improve not by maximizing perturbations, but by choosing experiments that generate discriminating evidence about context, producer, pathway, and chemical identity.

Outstanding questions

The most important unresolved question is what connects ecological encounter to specific biosynthetic response. Host-associated and cultured metabolomes can differ [5], fungal competitors can induce pair-specific chemistry [6], and endophytes can alter host chemical phenotypes [9], yet these observations do not provide a general map

from host or competitor cues to individual BGCs. Defined-cue perturbation, time-resolved expression, and source-resolved metabolomics are needed to distinguish sufficient signals from correlated environmental changes.

A second problem is benchmarking. Epigenetic activation can reveal hidden chemistry [25], genome mining can nominate latent biosynthetic capacity [30], and molecular networking can organize the resulting features [32], but these methods interrogate different levels of evidence. Future comparisons should ask whether an activated state resembles any host-associated state rather than judging success only against an unperturbed monoculture. Even then, the host metabolome is not a perfect gold standard because producer attribution and low-abundance signals remain difficult.

A third question is how much validation is enough. Environmental state can alter biosynthetic expression [15] and destabilize host–endophyte chemical coupling [16], while isotope-based linkage [34] and integrated genome/MS approaches [35] can strengthen biosynthetic assignment. No single experiment in the reviewed evidence spans context, structure, producer, BGC, mechanism, and ecological function simultaneously. A proposed staged validation strategy should therefore be tested prospectively across taxonomically and chemically diverse endophyte systems rather than treated as an established standard.

Finally, transferability remains uncertain. Endophytes differ in host range, regulatory architecture, cultivability, and biosynthetic repertoire. Methods that work in tractable fungal models may fail in genetically inaccessible isolates, and interaction phenotypes may change across host tissues, seasons, or microbial communities. The discovery challenge is thus not merely to awaken silent chemistry, but to determine which experimentally accessible chemical states correspond to biologically meaningful states.

Conclusion

Endophyte natural-product discovery is frequently performed after removing fungi from precisely the ecological setting in which their biosynthetic programs evolved and operate. The evidence synthesized here shows why that simplification matters: host-associated and cultured chemical states can diverge; microbial competitors and environmental perturbations can alter expression; regulatory interventions can reveal otherwise weakly expressed chemistry; and genome–metabolome tools can progressively strengthen, but not collapse, assignments of chemical identity and biosynthetic origin.

The principal contribution of this review is a proposed evidence-bounded interpretation of endophyte chemical ecology as a discovery engine. Ecological perturbations are most useful when they generate testable chemical hypotheses. Structural characterization answers what a compound is. Producer- and BGC-resolved experiments address where it came from. Functional assays are still required to establish what it does in the host-associated system. None of these evidential steps should substitute automatically for another.

This framework also preserves difficult negative and alternative interpretations. Failure to observe a compound may reflect the tested condition rather than absent biosynthetic capacity, while induction in coculture or after regulatory manipulation may reflect an artificial state rather than native ecological expression. Community composition, host compartment, environmental history, regulatory genotype, analytical coverage, and model tractability all constrain transferability.

In this sense, ecological realism and analytical rigor are complementary rather than competing goals.

Endophyte–host chemical ecology therefore offers a productive way to design discovery experiments, not a guarantee of novel compounds or ecological relevance. Its strongest use is to connect conditional expression with progressively stronger chemical and biosynthetic evidence while making uncertainty explicit.

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