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Sustainable Resupply Should Begin Before Lead Selection: A Resource-Risk Model for Wild Medicinal Plants, Cultivation, Tissue Culture, Semisynthesis, and Heterologous Production

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ABSTRACT

Natural products can advance discovery while remaining dependent on biological resources and production routes that are fragile, variable, or incompletely developed. Resupply is therefore not only a downstream manufacturing problem; it can influence whether a chemically or pharmacologically attractive candidate remains developable. This article develops an original translational resource-risk model that brings supply considerations forward to lead selection without treating ecological vulnerability, process feasibility, or sustainability as interchangeable. The analysis distinguishes wild collection, cultivation, tissue and cell culture, semisynthetic and chemoenzymatic routes, engineered plant systems, and microbial heterologous production, then examines the distinct fragilities associated with each. The central proposed contribution is a molecule–supply compatibility concept in which source dependence, biosynthetic organization, pathway knowledge, host compatibility, chemical reproducibility, process maturity, and evidential uncertainty are evaluated before a supply route is treated as secure. The model is intentionally nonnumeric because the available literature does not justify universal weights or thresholds. It also treats production feasibility as dynamic: pathway discovery, enzyme characterization, or host engineering can change the resupply outlook of a candidate after initial assessment. Supply risk should alter discovery decisions most strongly when pharmacological promise remains tightly coupled to a vulnerable source and credible alternatives are immature. However, technical independence from wild harvesting does not by itself establish environmental superiority, economic viability, or manufacturing readiness. Prospective portfolio testing, process-scale validation, chemical comparability, technoeconomic analysis, and life-cycle assessment are therefore required before the proposed model can support predictive or implementation claims.

Keywords: Medicinal plants, Natural products, Resupply, Synthetic biology, Sustainability, Lead selection

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Introduction

Natural products remain an important source of chemical matter for drug discovery because evolution has generated structurally diverse metabolites that can engage biological systems in ways not easily reproduced by conventional screening libraries. Contemporary discovery has also benefited from advances in analytical chemistry, genome mining, cultivation, synthetic biology, and heterologous expression, which have expanded access to molecules that were previously difficult to isolate or reproduce [1]. Yet these advances do not remove a practical asymmetry in lead selection: pharmacological attractiveness can be recognized before reliable resupply is understood. A candidate may therefore accumulate analytical, mechanistic, and optimization investment while remaining tied to a biological source or production process that later proves difficult to reproduce at the quantity, quality, or temporal reliability required for development. The resulting problem is not merely procurement. It is a

translational mismatch between what can be discovered and what can be repeatedly supplied. Because resupply requirements become more demanding as characterization and optimization proceed, an unresolved source dependency can progressively narrow experimental options even when the underlying pharmacology remains attractive.

Wild medicinal plants make that mismatch especially visible. Medicinal species exist within ecological systems whose conservation status, distribution, regeneration, and exposure to human pressure vary substantially. Biodiversity loss, overharvesting, land-cover change, and climate pressure can each affect source persistence, and their effects may interact in species- and location-specific ways [2–4]. These pressures do not justify treating all wild-derived natural products as unsustainable. Some species are abundant, readily cultivated, or harvested under effective management. The relevant question is therefore not whether a molecule originated in nature, but how strongly continued access to that molecule depends on a fragile biological resource and whether credible alternatives exist. This framing requires ecological evidence to remain separate from chemical supply evidence: threatened habitat does not establish compound scarcity, just as a high-yielding extract does not establish that long-term harvesting is ecologically secure. It also prevents conservation status from becoming a crude proxy for production risk, because the same molecule may be obtainable through routes with very different dependencies on the original organism.

Existing natural-product scholarship describes many technologies that can reduce dependence on a native source, including cultivation, in vitro production, engineered plant systems, semisynthesis, and microbial biosynthesis [1]. What remains less developed is a cross-route decision logic for deciding when supply uncertainty should influence lead selection itself. The model proposed here treats resupply as a discovery-stage variable rather than a late manufacturing afterthought. It does not rank technologies universally and does not assume that engineered production is intrinsically superior to cultivation or managed harvesting. Instead, it asks whether the molecule and a plausible production route are compatible, how mature the supporting evidence is, and which uncertainties could invalidate an apparently favorable route. This distinction is central because evidence that a compound can be produced once is materially different from evidence that it can be supplied reproducibly, economically, and sustainably over the life of a development program. The intended output is therefore a structured risk interpretation, not a prediction of manufacturing success: it should expose hidden dependencies early enough to inform prioritization while remaining revisable as better biosynthetic, ecological, or process evidence becomes available.

Why resupply is a discovery-stage question

The logic for early resupply assessment begins with biosynthetic dependence. Medicinal-plant metabolites can occur at low abundance, arise through long or branched pathways, or require specialized enzymes and cellular contexts that are not yet fully characterized. Modern genomics, transcriptomics, metabolomics, and synthetic-biology approaches can reveal and reconstruct these pathways, but the same literature shows why supply feasibility is molecule-specific rather than a generic property of “natural products” [5]. A structurally complex metabolite with poorly resolved biosynthesis presents a different development problem from a molecule that is abundant in cultivated biomass or accessible through a short chemical sequence. The proposed resource-risk approach therefore asks about supply architecture before candidate optimization creates strong sunk-cost pressure to continue. This does not make supply risk equivalent to pharmacological weakness; rather, it adds a second decision dimension that asks whether experimental and development demand can plausibly be met without creating a new bottleneck.

In vitro production illustrates why route existence and route maturity must be separated. Plant cell, tissue, organ, and related culture technologies can provide controlled production environments and can reduce dependence on field-grown biomass for some metabolites. However, broad commercial translation has remained uneven, with productivity, stability, process control, and economic performance varying strongly among systems [6]. Discovery teams should therefore avoid treating “cell culture is possible” as equivalent to “resupply is solved.” The relevant discovery-stage question is whether the available evidence supports a plausible path from biological production to repeatable material supply at the quality required for subsequent pharmacological and manufacturing work. The same logic applies to other alternative routes: proof of molecule formation establishes feasibility at a particular level, whereas reliable resupply requires additional evidence about reproducibility, throughput, material identity, and process control.

A second reason for early assessment is that plant specialized metabolism is organized across regulatory, subcellular, cellular, and tissue levels rather than being a simple list of freely transferable enzymes [7]. Enzyme localization, precursor access, transport, cofactor availability, and developmental context can influence whether a pathway functions outside its native setting. These features do not predict failure by themselves, but they change the burden of proof for an alternative route. Resupply is therefore proposed here as an early compatibility problem: candidate selection should consider not only whether a molecule is active, but whether its chemistry can plausibly be reproduced through at least one route whose biological and process dependencies are understood well enough to justify continued investment. Early screening is consequently most useful as a warning and comparison system, not as a rigid exclusion rule.

The landscape of natural-product supply routes

Natural-product resupply is better viewed as a portfolio of route families than as a progression from "traditional" to "advanced" production. Cultivation can reduce dependence on unmanaged wild harvesting and can support controlled agricultural supply, yet it remains constrained by species biology, domestication, geography, agronomic inputs, and chemical variability [8]. For some compounds, cultivation may be the most direct and robust route; for others, slow growth, low metabolite content, or ecological sensitivity may make it insufficient. The model therefore treats cultivation as a production option with distinct evidence requirements rather than as an automatic sustainability endpoint.

Plant cell and tissue culture provide a second route family by shifting production into controlled in vitro systems. Such platforms can generate valuable secondary metabolites without repeatedly harvesting whole wild plants, but performance depends on culture type, line stability, differentiation state, and metabolite productivity [9]. Plant cells can also be engineered as heterologous biofactories, preserving aspects of plant biochemistry that may be difficult to reproduce in microorganisms while permitting pathway manipulation [10]. Native in vitro culture and engineered plant-cell production should remain analytically separate because their biological assumptions and engineering burdens are not identical.

Hybrid chemical–biological production adds another layer. Chemoenzymatic and semisynthetic strategies can combine selective biocatalytic steps with conventional synthesis to reach natural-product-inspired structures or convert accessible precursors into more complex products [11]. Engineered plant systems similarly allow elucidated pathways to be reconstructed or redirected in a plant context [12]. Microbial platforms instead require coordinated host, pathway, and enzyme engineering to make plant natural products outside their native organism [13]. These routes are not ordered by sophistication or presumed sustainability; they differ in precursor dependence, enzyme compatibility, purification demands, scalability, and evidential maturity. They may also be combined: cultivation can supply a precursor for semisynthesis, or heterologous production can supply an intermediate completed chemically. Route comparison should therefore follow the actual material chain rather than assigning a candidate to a single technology label.

Complex medicinal alkaloids show both the power and the limits of heterologous production. Reconstruction of medicinal tropane alkaloid biosynthesis in yeast demonstrates that long plant pathways can be transferred into a microbial host through extensive engineering [14]. Such feasibility is translationally important, but laboratory reconstruction does not by itself establish manufacturing robustness, favorable economics, or long-term supply security. The route landscape should therefore be compared at the level of molecule-specific dependencies rather than reduced to a single preferred technology.

Sources of supply fragility

Supply fragility can arise even when raw biomass is available. Plant metabolomes are chemically diverse and responsive to genotype, organ, developmental stage, environment, sampling, and analytical method, making compositional reproducibility a distinct concern from gross biomass yield [15]. For development, this matters because a reliable source must repeatedly deliver the relevant molecule or precursor within an analytically controlled material system. Apparent variation may reflect true biology, technical measurement, or both; the proposed model therefore treats chemical reproducibility as a measured attribute rather than inferring it from species identity or cultivation status. A cultivated source can consequently remain fragile if the desired metabolite is unstable across harvests, while a lower-volume route may be more useful if it produces chemically consistent material. Availability and reproducibility are related but non-equivalent dimensions.

Fragility can also be embedded in pathway organization. Single-cell multi-omics in *Catharanthus roseus* has shown that monoterpenoid indole alkaloid biosynthesis is distributed across specialized cellular contexts rather than occurring as an undifferentiated pathway in one generic cell state [16]. This is not evidence that all medicinal pathways have the same architecture. It is evidence that spatial organization can be a genuine production constraint. When a pathway depends on transport between cell types, organellar localization, or tissue-specific regulation, moving the chemistry into culture or a heterologous host may require more than transferring a list of enzymes. The resource question is therefore partly mechanistic: how much of the native production context must be recreated, bypassed, or replaced before material can be supplied reliably?

A third fragility is epistemic: incomplete pathway knowledge can make a route appear more mature than it is. Integrative omics can nominate biosynthetic genes and connect metabolites with candidate enzymes, but association and coexpression do not replace functional validation [17]. Unassigned steps, uncertain enzyme specificity, unstable intermediates, or missing transport functions can all remain hidden until reconstruction is attempted. Process fragility then emerges downstream when a technically functioning route remains sensitive to host physiology, intermediate toxicity, productivity loss, purification burden, or scale-dependent behavior. The proposed model therefore separates source fragility, chemical reproducibility, pathway completeness, host compatibility, and process maturity rather than collapsing them into one supply label. Their interaction is important, but interaction does not justify treating them as interchangeable.

Figure 1 integrates these distinct fragilities with the available route choices and shows where the article's proposed resource-risk reasoning begins, while keeping manufacturing robustness and sustainability as separate validation boundaries.

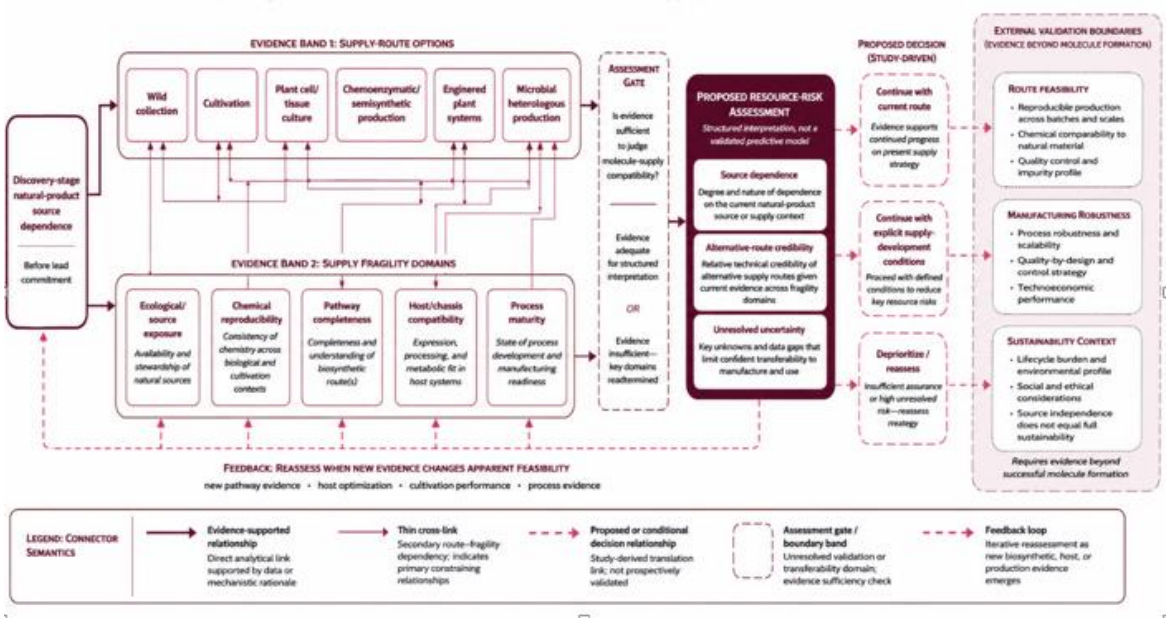

Figure 1. Discovery-Stage Resource Risk across Natural-Product Supply Routes

Evaluating molecule–supply compatibility

Molecule–supply compatibility is proposed here as the fit between a candidate's chemistry and at least one credible route capable of reproducing it without dependence on assumptions that are already known to be fragile. This is not a molecular property alone. Host choice, pathway architecture, precursor availability, enzyme activity, compartmentation, and engineering context influence whether an alternative route can function [18]. Compatibility should therefore be assessed route by route. A molecule may be poorly compatible with direct cultivation because of low or unstable accumulation yet comparatively compatible with semisynthesis from an abundant precursor; another may be difficult to transfer into microbes but suitable for a plant chassis. The model does not presume that the most technologically advanced route is preferable. It asks whether the chosen route matches what is known about the molecule's biosynthesis and material requirements.

Material identity also constrains route substitution. An alternative process is useful only if it supplies the chemical entity, stereochemical form, precursor, or defined mixture needed by the development program rather than a

superficially related product. This makes analytical comparability part of compatibility even when the production biology appears favorable. Route switching should therefore be judged by what material must be reproduced and how tightly downstream pharmacology depends on that material definition, not by production-platform novelty alone.

Plant chassis illustrate this dependence. *Nicotiana benthamiana* has become a useful platform for reconstructing and engineering natural-product pathways, but expression success, yield, purity, and pathway behavior remain optimization problems rather than guaranteed platform characteristics [19]. Consequently, detection of the intended molecule should be interpreted as evidence of technical feasibility, not sufficient evidence of supply security. Pathway completeness creates a second compatibility test. The identification of previously missing vinblastine-biosynthetic enzymes demonstrates that unresolved enzymology can materially limit attempts to reproduce a pathway outside its native plant [20]. An apparently attractive heterologous route may therefore be premature when key transformations remain assigned only by association or when transport and compartmentation requirements are unknown.

Compatibility should also be comparative rather than absolute. Vinblastine-related work demonstrates that engineered yeast and an engineered plant chassis can each support different architectures for accessing relevant pathway products, while retaining distinct engineering constraints [21, 22]. Neither result establishes that one host is universally superior or economically preferable. Instead, such studies support a route-selection principle: the same molecule family may have several technically credible resupply strategies, and the strongest option depends on the evidence supporting pathway completeness, host performance, precursor access, reproducibility, and downstream processing. **Table 1** converts this reasoning into a concise proposed classification for discovery-stage assessment.

Table 1. Proposed Molecule–Supply Compatibility Classification for Discovery-Stage Resupply Assessment

Dimension	Question for lead selection	More favorable evidence state	Residual boundary
Source dependence	Can supply move beyond a vulnerable native source?	Multiple credible source or production options	Source independence does not prove sustainability
Chemical reproducibility	Is the required molecule obtained consistently?	Repeated identity and composition control	Biomass abundance alone is insufficient
Pathway completeness	Are necessary transformations functionally resolved?	Key steps experimentally supported	Omics nomination is not functional proof
Host compatibility	Can the route reproduce required biological context?	Demonstrated pathway function in a suitable chassis	Product detection is not process robustness
Process maturity	Can material be supplied repeatedly at useful quality?	Reproducible production and downstream handling	Feasibility is not manufacturing readiness

A Resource-risk model for lead selection

The proposed resource-risk model uses these compatibility dimensions to interpret supply vulnerability before a candidate is treated as development-ready. It deliberately avoids a universal numerical score. The evidence base contains route-specific demonstrations, mechanistic studies, and reviews, but it does not provide a validated dataset from which fixed weights, probability estimates, or exclusion thresholds could be derived. Instead, the model separates three questions: how dependent the candidate remains on a potentially fragile source; how credible the available alternative routes are; and how mature the evidence is for reproducing the required material. These questions should be considered alongside pharmacological merit, not substituted for it. A highly active candidate with unresolved supply may remain worth pursuing, but its development case should explicitly include the cost and uncertainty of converting feasibility into reliable resupply.

The model is also dynamic. Recent taxane studies demonstrate that production feasibility can change when previously uncertain biosynthetic steps are resolved. Identification of a minimal gene set for paclitaxel-related biosynthesis in a plant chassis and subsequent characterization and heterologous reconstruction of enzymes leading to baccatin III show how improved pathway knowledge can alter what is technically accessible [23, 24]. These examples do not establish industrial paclitaxel manufacture through the reported systems. They establish a more limited but important principle: a candidate's supply outlook is partly conditional on the current state of biosynthetic knowledge. Resource risk should therefore be revisited when new enzymes, pathway organizations, precursor routes, or host solutions become available rather than frozen at the moment of lead nomination.

Heterologous expression similarly broadens the range of possible medicine-production routes, while remaining dependent on pathway and platform context [25]. The model therefore distinguishes a credible alternative from a mature alternative. A credible route has mechanistic and experimental support sufficient to justify further development; a mature route additionally requires evidence that material can be produced reproducibly with appropriate identity, quality, throughput, and downstream control. The persistent commercialization limitations of many in vitro systems illustrate why those states cannot be merged [6]. Likewise, pathway candidates inferred from integrative omics require functional confirmation before they are treated as solved production steps [17].

For interpretation, three evidence states are more defensible than an invented score. A route can be sufficiently characterized for routine planning, credible but conditional on defined resupply work, or presently too uncertain to support the intended development demand. These are proposed decision states, not validated categories. Their value is that the reason for concern remains visible: a candidate can be conditional because of source exposure, pathway uncertainty, host performance, chemical reproducibility, or process immaturity, and those problems require different experiments rather than one generic "supply-risk" intervention.

Operationally, the proposed assessment yields a structured profile rather than a single rank. Source dependence, chemical reproducibility, pathway completeness, host compatibility, and process maturity remain visible as separate dimensions. Uncertainty is recorded where evidence is absent or indirect instead of being converted into an arbitrary penalty. This architecture prevents a candidate from appearing secure merely because one favorable production experiment compensates numerically for a severe unresolved dependency elsewhere. It also makes the assessment revisable: new evidence can change one dimension without rewriting the entire lead rationale.

When supply should alter discovery decisions

Supply should influence discovery decisions most strongly when three conditions coincide: the candidate remains materially dependent on a fragile source, alternative routes require substantial unresolved engineering, and later development would demand substantially more material than current access can support. The vinblastine microbial supply-chain work illustrates how extensive pathway and process engineering may be required to create an alternative route for a complex plant-derived medicine [21]. The proposed model does not convert that burden into an automatic rejection rule. Instead, it distinguishes candidates that can proceed with routine supply planning from those that should proceed conditionally, with explicit resupply work treated as part of lead development rather than deferred until scale becomes urgent.

The practical consequence should be proportional to the dependency being exposed. A supply concern that can be resolved by confirming a second cultivated source is different from one requiring discovery of missing enzymes, construction of a new chassis, or replacement of a threatened wild source. Accordingly, the model proposes escalation of resupply work before it proposes abandonment of pharmacologically valuable chemistry. Deprioritization becomes reasonable only when the expected material demand and unresolved dependency are sufficiently serious that continued discovery would rely on a supply assumption with no credible development path.

A second decision state is reassessment rather than rejection. Paclitaxel-pathway reconstruction shows that route feasibility can improve as functional gene assignments and pathway organization become clearer [23]. A candidate classified as high resource risk today may therefore become more tractable when new biosynthetic evidence or host technology emerges. Conversely, apparent security can deteriorate if cultivation proves chemically inconsistent, a host loses productivity, or an assumed pathway step fails validation. The decision architecture should consequently support revision in both directions. Supply risk is a time-dependent evidential judgment, not an intrinsic and permanent label attached to a molecule.

Ecological vulnerability creates a distinct trigger when continued discovery materially depends on wild harvesting. Modelling of a heavily used South African medicinal plant demonstrates that harvesting pressure can interact with climate and land-cover change in ways that threaten future populations [3]. Such evidence cannot be generalized quantitatively to other species, but it shows why ecological dependence should not remain invisible in lead selection. **Figure 2** summarizes the proposed decision states and the conditions under which supply evidence should modify, condition, or reopen a discovery decision.

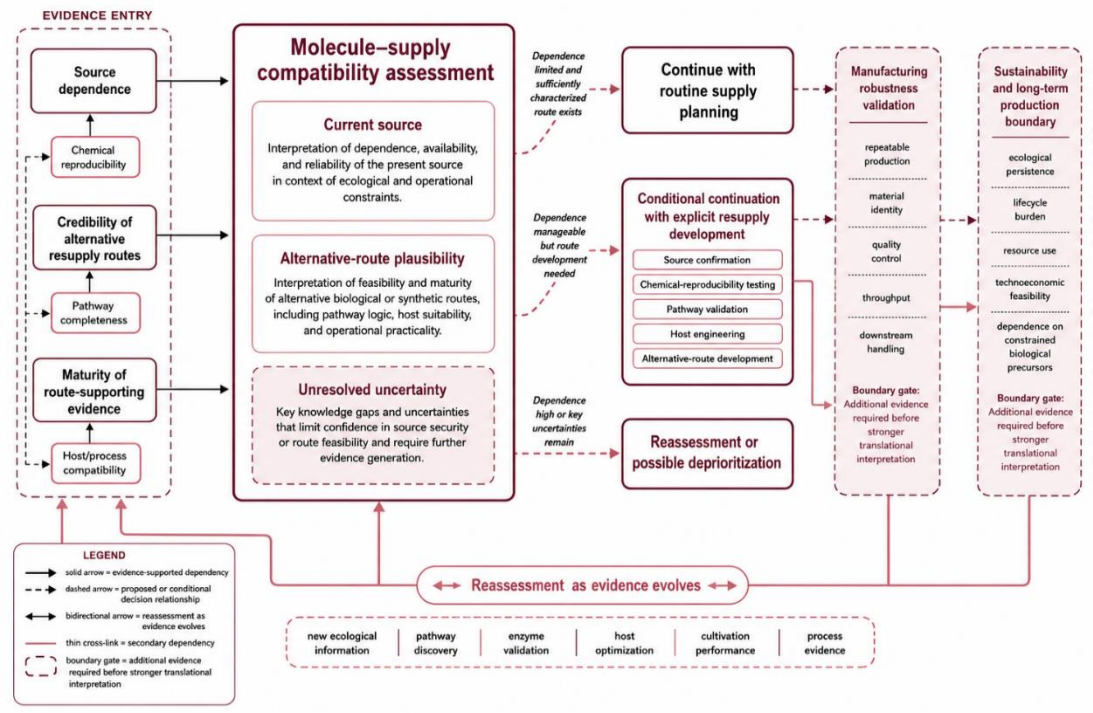

Figure 2. Conditional Discovery Decisions under Dynamic Resource Risk

Sustainability and long-term production implications

A resource-risk model becomes misleading if it treats elimination of wild harvesting as equivalent to sustainability. Cultivation can reduce pressure on some wild populations and create more controllable supply, but it also requires land, propagules, agronomic inputs, appropriate growing conditions, and management of biological variability [8]. These burdens differ by species and production system. A cultivated route can therefore be preferable from a conservation perspective without necessarily being superior in every environmental or economic dimension. The appropriate comparison is not "natural" versus "engineered," but the complete resource requirements and consequences of the routes that are realistically available for a particular molecule.

The same caution applies to heterologous production. Synthetic biology can create access to medicinal products outside their native organisms and can reduce direct dependence on scarce biological material [25]. Yet source independence does not, by itself, demonstrate lower energy use, reduced solvent burden, favorable feedstock demand, simple purification, lower waste, or lower cost. Those questions require process-specific evidence. Life-cycle assessment and technoeconomic analysis should therefore be treated as downstream validation tools for the proposed model rather than assumptions embedded in an early resource-risk classification. Their role is especially important when two technically feasible routes shift burdens between land use, fermentation infrastructure, chemical conversion, purification, and waste management.

Long-term production also retains a biodiversity dimension whenever wild biological resources remain part of the material chain. Medicinal plants are components of ecosystems and evolutionary diversity rather than interchangeable containers of target compounds [2]. Responsible resupply planning should therefore consider whether collection affects population persistence, whether cultivation genuinely substitutes for wild material, and whether a semisynthetic or heterologous route continues to depend on a biologically constrained precursor. This broader view also prevents sustainability language from becoming a marketing label for any engineered process.

The proposed model consequently ends at a boundary rather than a declaration of sustainability. Discovery-stage screening can identify dependence, fragility, plausible alternatives, and evidence gaps; it cannot establish long-term environmental performance or manufacturing viability without additional data. Prospective portfolio studies should test whether resource-risk profiles actually improve lead decisions, while process-scale studies should examine reproducibility, chemical comparability, yield stability, downstream handling, and failure modes. External validation across taxa and compound classes is needed because pathways and ecological contexts differ substantially. Technoeconomic and life-cycle analyses can then determine whether moving away from a wild source reduces total resource burden or merely relocates it.

Conclusion

Sustainable resupply should be considered before lead selection when a natural-product candidate remains dependent on a biological source or production architecture whose reliability is uncertain. The central contribution of this article is a proposed translational resource-risk model that keeps source dependence, chemical reproducibility, pathway completeness, host compatibility, process maturity, and sustainability analytically distinct while allowing them to inform one discovery decision. This separation matters because a threatened source does not prove compound scarcity, cultivation does not guarantee chemical consistency, successful pathway reconstruction does not establish manufacturing robustness, and independence from wild harvest does not demonstrate full environmental superiority.

The model is intended to expose development dependencies rather than eliminate chemically difficult molecules. A high-risk classification should trigger explicit supply work, comparison of alternative routes, or reassessment of investment; it should not function as an unvalidated exclusion threshold. Equally, the assessment must remain dynamic because advances in pathway discovery, enzyme characterization, host engineering, cultivation, or hybrid synthesis can alter the supply outlook of a candidate. Difficult chemistry can therefore remain worth pursuing when the unresolved resupply problem is identifiable, testable, and proportionate to the expected scientific value.

Its principal limitation is evidential. The component risks are supported by ecological, biochemical, analytical, and synthetic-biology literature, but the combined decision architecture has not been prospectively validated. It therefore cannot yet predict manufacturing success, sustainability, cost, or portfolio outcomes. Testing requires prospective and retrospective lead comparisons, reproducibility and chemical-comparability studies, process-scale validation, assessor-agreement analysis, technoeconomic evaluation, life-cycle assessment, and external examination across multiple compound classes and source organisms. Used within those boundaries, resource-risk reasoning can make the hidden material dependencies of natural-product discovery visible at the point when they are still actionable.

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