Sustainable Natural Product Drug Discovery: Biodiversity Protection, Ethical Sourcing, AI Screening, Green Chemistry, and Therapeutic Innovation

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ABSTRACT

Natural products remain important sources of chemical diversity and therapeutic innovation, yet their discovery and development can create ecological, ethical, technical, and translational pressures that are not resolved by natural origin alone. This article proposes an integrated sustainability framework for natural product drug discovery that positions biodiversity protection, ethical sourcing, computational prioritization, green chemistry, therapeutic evaluation, and lifecycle oversight as interdependent decision conditions. The framework begins with conservation-aware definition of the discovery question and assessment of species vulnerability, habitat pressure, harvesting risk, provenance, access and benefit-sharing principles, traditional knowledge considerations, and source-country relationships. It then incorporates natural product databases, dereplication, virtual screening, bioactivity and safety prediction, and uncertainty-aware molecular prioritization to reduce unnecessary collection and experimental burden. Green extraction, safer solvent selection, sustainable synthesis, biocatalysis, biotechnology-enabled production, waste reduction, energy reduction, and process intensification are treated as conditional design options rather than independent proof of sustainability. Therapeutic innovation is linked to target relevance, mechanistic plausibility, safety, developability, validation planning, supply feasibility, equity considerations, and expert and stakeholder oversight. The principal contribution is a stage-gated conceptual framework that connects ecological stewardship and ethical governance with computational, chemical, pharmacological, and translational decision-making. The framework supports responsible discovery planning but does not establish environmental validation, ethical certification, legal sufficiency, therapeutic effectiveness, regulatory acceptance, or commercial readiness.

Key Words: *Sustainable drug discovery, Natural products, Biodiversity protection, Ethical sourcing, AI screening, Green chemistry*

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INTRODUCTION

Natural products have contributed substantially to modern pharmacotherapy as direct medicines, molecular templates, pharmacophores, and sources of structurally distinctive chemical matter. Their continued relevance reflects the capacity of biological systems to generate complex compounds that occupy chemical and functional spaces not always reproduced efficiently by conventional synthetic collections. This historical contribution provides a strong rationale for maintaining natural product research as part of contemporary drug discovery, but it does not

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establish that all natural-product-derived programs are environmentally sustainable, ethically sourced, safe, developable, or therapeutically successful [1].

The biological origins of natural products create responsibilities that extend beyond compound identification and activity testing. Medicinal plants, fungi, microorganisms, and other biological resources occur within taxonomic, evolutionary, ecological, geographic, and cultural contexts that shape their availability and appropriate use. Modern biodiversity science can strengthen discovery by improving species authentication, clarifying biological relationships, connecting specimens with collections and distribution data, and identifying gaps in knowledge about source organisms [2]. These capabilities are particularly important when chemical records are detached from voucher specimens, when closely related species are substituted in trade, or when a promising compound is associated with a biologically vulnerable or poorly characterized source.

Natural-product discovery is also exposed to environmental change. Climatic shifts, habitat modification, altered species distributions, land-use pressure, and changes in ecological interactions may affect the abundance, chemistry, accessibility, and reproducibility of medicinal resources. Sustainable research strategies therefore require attention to conservation status, ecological vulnerability, plant parts used, regeneration capacity, geographical variation, and the possibility that increasing research or commercial demand could intensify pressure on already constrained resources [3]. These concerns are not limited to large-scale harvesting; repeated small collections, poorly documented sampling, destructive acquisition of roots or bark, and duplicated extraction across research groups may collectively create avoidable burdens.

Technological advances offer opportunities to reduce some of these pressures, but their contribution must be interpreted cautiously. Natural product databases, metabolomics, genomics, artificial intelligence, advanced analytical chemistry, green extraction, biocatalysis, and engineered production can improve prioritization and broaden access to complex molecules, yet they do not replace source governance, biological validation, safety assessment, or translational evidence [4]. The objective of this article is therefore to propose an original sustainability framework that integrates biodiversity protection, ethical and traceable sourcing, access and benefit-sharing principles, respectful treatment of traditional knowledge, AI-assisted prioritization, extraction minimization, green chemistry, responsible production, therapeutic evaluation, lifecycle thinking, and explicit claim boundaries within a unified natural product drug discovery pathway.

Sustainability in natural product discovery

Sustainability in natural product discovery is best understood as a framework condition governing how biological resources, knowledge, data, chemical processes, and therapeutic opportunities are selected and managed. It requires the reconciliation of healthcare and discovery objectives with biodiversity conservation, responsible resource use, equitable relationships, and the long-term availability of medicinal species and fungi [5]. This definition differs from descriptions based solely on natural origin, renewable branding, a single lower-hazard solvent, community acknowledgment, or the discovery of a pharmacologically interesting molecule. A natural compound can originate from a threatened species, an extract described as green can depend on ecologically damaging harvesting, and an ethically described collaboration can remain inadequately traceable or governed.

A sustainability assessment must therefore begin before extraction or screening. It should consider the identity and distribution of the source organism, the ecological condition of its habitat, the vulnerability of relevant populations, the plant or organism part required, the geographic concentration of supply, and the potential effect of future demand. Global assessments of medicinal resources demonstrate that exposure to environmental change can be examined systematically and can reveal geographically differentiated vulnerabilities that may be overlooked in compound-centered research [6]. Such assessment does not prove that a particular population is declining, but it can identify uncertainty, direct field verification, and prevent candidate advancement from proceeding without awareness of ecological context.

Commercial availability is also an insufficient proxy for sustainable supply. Species used in established herbal markets may lack comprehensive conservation evaluation, may be affected by exploitation, or may enter supply chains through substitutions and poorly documented intermediaries. Evidence from the herbal-medicine sector indicates that conservation status and evaluation coverage can remain incomplete even where species are already in commercial use [7]. Sustainability frameworks should therefore treat missing conservation information as a decision uncertainty rather than as evidence of low risk. Where vulnerability cannot be resolved, the appropriate response may include source substitution, use of archived material, cultivation studies, lower-demand analytical approaches, biotechnology-enabled production, or discontinuation of the candidate.

Social sustainability is inseparable from ecological stewardship because medicinal resources are frequently embedded within local livelihoods, customary practices, and community knowledge systems. Community-level

research has shown that conservation incentives, economic benefits, resource use, and local participation can interact in ways that influence the persistence and governance of medicinal plants [8]. Responsible discovery should consequently include traceability, community engagement, source-country collaboration, supply-chain transparency, equitable participation, and procedures for responding to grievances or changing conditions. These elements must be connected with AI-assisted prioritization, green chemistry, safety evaluation, developability, and lifecycle review so that environmental or social burdens are not shifted from one stage of discovery to another.

Biodiversity protection and ethical sourcing

Biodiversity protection requires discovery teams to assess more than whether sufficient material can be obtained for an initial experiment. Relevant questions include whether collection could affect a threatened or unevaluated species, whether destructive plant parts are required, whether habitat is already under pressure, whether projected development demand could exceed regenerative capacity, and whether the source can be replaced through cultivation, renewable harvesting, microbial production, or synthesis. Ethical sourcing adds a parallel requirement for verifiable origin, documented custody, responsible supplier relationships, and transparent terms governing access and downstream use. Case-based evidence from biodiversity trade demonstrates that traceability, sustainable resource use, value-chain organization, and benefit-sharing arrangements must be considered together rather than treated as interchangeable claims [9]. The use of artificial intelligence or digital biological information does not remove provenance and benefit-sharing concerns, because computational systems may still depend on biological materials, associated knowledge, sequence information, chemical records, or data derived from governed resources [10].

Access and benefit-sharing principles require formal, context-sensitive governance rather than informal assurances that a resource was publicly available or scientifically interesting. Operational experience with genetic resources shows that access conditions, documentation, institutional responsibilities, transfer arrangements, downstream use, and benefit expectations can become complex across custodians, researchers, repositories, and commercial actors [11]. A sustainability framework should therefore include a governance checkpoint capable of identifying when institutional, source-country, provider, or community review is required. Material transfer governance may be incorporated where supported, with records linking the physical material, permitted uses, derivatives, associated data, onward transfers, retention periods, and restrictions. These measures support accountability but should not be represented as universal evidence of legal compliance or ethical certification.

Traditional knowledge can help identify culturally important species, preparations, therapeutic hypotheses, and underexplored biological relationships, but its scientific usefulness does not extinguish the rights or interests of knowledge holders. Responsible use requires attention to knowledge provenance, consent or authorization where applicable, culturally appropriate disclosure, community participation, attribution, protection against decontextualization, and independent evaluation of identity, quality, pharmacology, and safety. Scholarship on indigenous knowledge and medicinal plants emphasizes both its potential contribution to therapeutic research and the challenges of preservation, validation, ownership, and equitable use [12]. Traditional use should therefore be treated as a source of hypotheses and contextual evidence, not as proof of efficacy, safety, consent, ownership transfer, or unrestricted permission to commercialize.

Source-country collaboration can strengthen sustainability when it includes substantive scientific participation, shared capability, locally relevant research priorities, transparent data arrangements, and continuing engagement rather than symbolic affiliation. The development of an Ecuadorian herbal pharmacopoeia illustrates how traditional knowledge, biodiversity information, scientific monographs, linguistic accessibility, institutional participation, and biodiscovery objectives may be organized within a nationally grounded evidence system [13]. Such models are context dependent and do not automatically establish clinical validity, regulatory acceptance, or universal transferability, but they demonstrate the value of connecting biological resources and associated knowledge with source-country institutions and validation processes. **Table 1** summarises biodiversity protection and ethical sourcing requirements for sustainable natural product drug discovery.

Table 1. Biodiversity Protection and Ethical Sourcing Requirements for Sustainable Natural Product Drug Discovery: Species Conservation, Habitat Pressure, Overharvesting Risk, Traceable Sourcing, Access and Benefit-Sharing Principles, Traditional Knowledge Respect, Community Engagement, Supply-Chain Transparency, Renewable Sourcing, and Governance Boundaries

Sustainability component	Core stewardship question	Required evidence or practice	Responsible function	Failure risk	Governance or validation need	Framework role	Claim boundary
Biodiversity protection	Could discovery or development contribute to species or ecosystem decline?	Verified biological identity, geographic origin, conservation information, collection context, and ecological uncertainty record	Biodiversity lead, sourcing team, and discovery leadership	Candidate advancement despite unresolved ecological vulnerability	Independent ecological review and a documented decision gate	Establishes an ecological entry condition for biological-resource use	Completion of a review does not prove biodiversity protection
Ecosystem stewardship	Could collection or production affect ecological functions beyond the source species?	Habitat context, associated-species considerations, collection method, land-use pressure, and cumulative-impact review	Conservation scientist and environmental assessment function	Compound-level decisions overlook wider ecosystem effects	Place-based assessment proportionate to expected pressure	Extends sustainability analysis beyond isolated organisms	Absence of observed damage does not establish absence of ecosystem risk
Species conservation	Is the source species threatened, data deficient, taxonomically uncertain, or dependent on vulnerable populations?	Taxonomic authentication, voucher documentation, conservation assessment, and uncertainty classification	Taxonomist, conservation specialist, and quality assurance	Misidentification, substitution, or use of threatened material	Species-specific verification before repeated sourcing	Supports exclusion, substitution, escalation, or monitoring decisions	Absence from a threatened-species list does not prove secure status
Habitat pressure reduction	Could collection increase pressure in ecologically sensitive or degraded locations?	Collection-location information, habitat sensitivity, harvesting method, and cumulative-pressure assessment	Ecological stewardship and sourcing functions	Habitat degradation remains invisible to laboratory decision-making	Location-sensitive review and monitoring where appropriate	Links source selection to habitat context	A small research collection does not automatically establish negligible impact
Overharvesting risk	Could current or projected demand exceed regenerative capacity?	Plant-part analysis, regeneration characteristics, harvest intensity, supply projections, and destructive-harvest indicators	Sourcing, conservation, and supply-planning teams	Early success creates future demand that cannot be supplied responsibly	Harvest limits, replenishment strategy, and escalation triggers	Connects discovery-scale use with development-scale demand	Laboratory availability does not establish sustainable scalability

Ethical sourcing	Was the material obtained through a documented and responsible relationship?	Supplier identity, origin records, collection authorization where applicable, terms of use, and grievance mechanism	Ethics, procurement, research governance, and supplier-quality functions	Unverified origin, exploitation, or misleading sourcing claims	Risk-based supplier due diligence and periodic reassessment	Conditions the admissibility of materials within the framework	Purchase, donation, or citation alone does not establish ethical sourcing
Traceable sourcing	Can the material be followed from biological origin through experimental and downstream use?	Chain-of-custody documentation, batch identity, voucher linkage, processing history, and transfer records	Procurement, laboratory operations, data management, and quality assurance	Source substitution, undocumented mixing, or loss of provenance	Auditable records connecting samples, extracts, compounds, and data	Preserves source accountability across discovery stages	Traceability does not independently prove sustainability, legality, or equity
Access and benefit-sharing principles	Are access terms and benefit pathways established with relevant providers and stakeholders?	Documented authorization, negotiated terms, intended-use boundaries, benefit arrangements, and use restrictions where applicable	Institutional governance and authorized source-country partners	Unapproved use, inequitable benefit distribution, or downstream disputes	Formal, context-specific governance review	Governs access, derivatives, data use, and downstream value creation	Acknowledgment, publication, or open access does not by itself satisfy benefit-sharing responsibilities
Traditional knowledge respect	Is associated knowledge used with authorization, cultural respect, and appropriate protection?	Knowledge provenance, engagement records, disclosure controls, attribution practices, and protection of sensitive information	Community liaison, ethics governance, and source-country collaborators	Misappropriation, decontextualization, or disclosure of protected knowledge	Community-defined review and continuing communication	Protects knowledge holders throughout research and translation	Traditional use does not establish efficacy, safety, consent, or ownership transfer
Community engagement	Can affected communities influence relevant decisions and communicate concerns?	Representative engagement, accessible communication, response records, and grievance pathways	Community-engagement function and program leadership	Token consultation or exclusion from decisions affecting resources and knowledge	Continuing engagement proportionate to the project and its implications	Introduces stakeholder feedback and equity considerations	Engagement does not replace formal permissions, rights, or negotiated arrangements
Source-country collaboration	Are discovery and value-creating activities connected to capable and appropriately involved	Defined scientific roles, capacity contribution, data-access terms, authorship principles, and	Program leadership and collaborating institutions	Extractive research with limited local scientific participation	Transparent collaboration plan and role documentation	Supports reciprocal capability and context-sensitive validation	The presence of a collaborator does not alone establish an equitable partnership

	source-country partners?	benefit pathways					
Supply-chain transparency	Are suppliers, intermediaries, transformations, and custody changes visible?	Supplier mapping, material-flow documentation, subcontractor disclosure, and quality controls	Procurement and supply-chain management	Hidden intermediaries, substitution, and unmanaged ecological or social risks	Risk-based audit, issue escalation, and corrective-action process	Extends responsibility beyond primary collection	Transparency does not guarantee that disclosed practices are acceptable
Cultivation and renewable sourcing	Can cultivated, regenerative, or renewable sources replace vulnerable wild collection?	Agronomic feasibility, genetic identity, land and water requirements, input demand, and chemical-quality comparison	Agronomy, cultivation, sourcing, and quality teams	Cultivation shifts pressure to land, water, inputs, or local livelihoods	Comparative ecological, social, and quality assessment	Provides a conditional alternative to wild collection	Cultivation or renewability is not automatically sustainable
Biotechnology-enabled production	Can fermentation, cell culture, pathway engineering, or related systems reduce dependence on vulnerable biomass?	Biosynthetic pathway information, host suitability, process feasibility, containment, and downstream-processing requirements	Biotechnology, process development, and biosafety teams	Technical substitution introduces hidden energy, material, or governance burdens	Product identity, scale, safety, and lifecycle comparison	Provides an alternative supply route where evidence supports it	Engineered production does not automatically establish lower total impact
Material transfer governance where supported	Are transfer, permitted use, retention, derivative, and onward-sharing conditions documented?	Material-transfer terms, use restrictions, retention rules, derivative-data provisions, and transfer history	Institutional research governance and laboratory management	Material or associated data are used outside the agreed scope	Transfer review linked to sample and data systems	Maintains governance continuity across collaborations	A transfer document does not establish every downstream legal or ethical obligation
No ethics-compliance claim boundary	Is the framework described as decision support rather than certification or legal advice?	Claim inventory, uncertainty register, unresolved-governance log, and prohibited-claim review	Framework oversight group and manuscript authors	Conceptual controls are presented as ethical certification or legal sufficiency	Final governance and claim audit	Prevents overstatement of framework status	The framework does not establish legal compliance, ethical certification, community approval, or universal acceptability

AI screening and green chemistry

AI-assisted natural product discovery depends on the quality, coverage, standardization, accessibility, and provenance of its underlying evidence. Natural product databases can provide structures, names, source organisms, spectra, bioactivity records, and links among related compounds, but these resources differ substantially in curation, duplication, annotation quality, chemical representation, and interoperability [14]. Database search should consequently be paired with identity checks, source verification, uncertainty labeling, and recognition that absence from a database is not evidence of novelty. Dereplication provides a particularly direct opportunity to reduce unnecessary resource use because mass-spectral searching and related analytical approaches can identify known microbial metabolites before repeated isolation and characterization are undertaken [15]. A tentative spectral match, however, remains an identification hypothesis until supported by appropriate analytical confirmation.

Virtual screening, similarity analysis, machine learning, and other predictive methods can help rank compounds for defined targets, biological endpoints, pharmacokinetic

properties, and toxicity concerns. Their sustainability contribution arises primarily from reducing low-value testing, narrowing experimental portfolios, identifying uncertainty, and directing scarce biological material toward higher-priority questions. Reviews of artificial intelligence in natural product drug discovery show that these approaches can support compound prioritization, bioactivity prediction, ADMET assessment, toxicity prediction, and data integration, while also remaining limited by heterogeneous datasets, sparse labels, model bias, inadequate benchmarking, and uncertain applicability domains [16]. AI rankings should therefore be interpreted as decision-support outputs requiring expert review and prospective experimental validation, not as proof of molecular activity, mechanism, safety, therapeutic value, ethical acceptability, or sustainability.

Computational prioritization should be linked to extraction and process design rather than treated as an isolated screening layer. Once a candidate or extract has sufficient evidentiary justification, green chemistry planning can compare extraction methods, solvent hazards, energy requirements, material efficiency, selectivity, purification burden, waste generation, and possibilities for recovery or reuse. Green extraction scholarship emphasizes reduced solvent use, safer inputs, lower energy demand, process intensification, and improved selectivity, but also shows that performance depends on the biological matrix, target compounds, equipment, scale, and complete process configuration [17]. A solvent described as natural, renewable, or alternative may still create toxicity, recovery, land-use, or energy burdens, while a low-energy extraction may be undermined by unsustainable harvesting or inefficient downstream purification.

Where direct extraction is ecologically constrained or chemically inefficient, sustainable synthesis, biocatalysis, microbial production, cell-based production, and synthetic biology may provide alternative routes to selected compounds or precursors. Synthetic-biology approaches can assist pathway discovery, access cryptic chemistry, reconstruct biosynthetic systems, and produce natural products in engineered hosts, but feasibility, productivity, containment, downstream processing, scale, and lifecycle performance remain compound specific [18]. These approaches should therefore enter the framework as conditional production options rather than preferred solutions by default. Waste reduction, energy reduction, process intensification, safety evaluation, and feedback from experimental results should be integrated into route selection. **Figure 1** illustrates how AI screening and green chemistry can reduce redundant extraction, prioritize candidates, support safer design, and guide sustainable natural product discovery workflows.

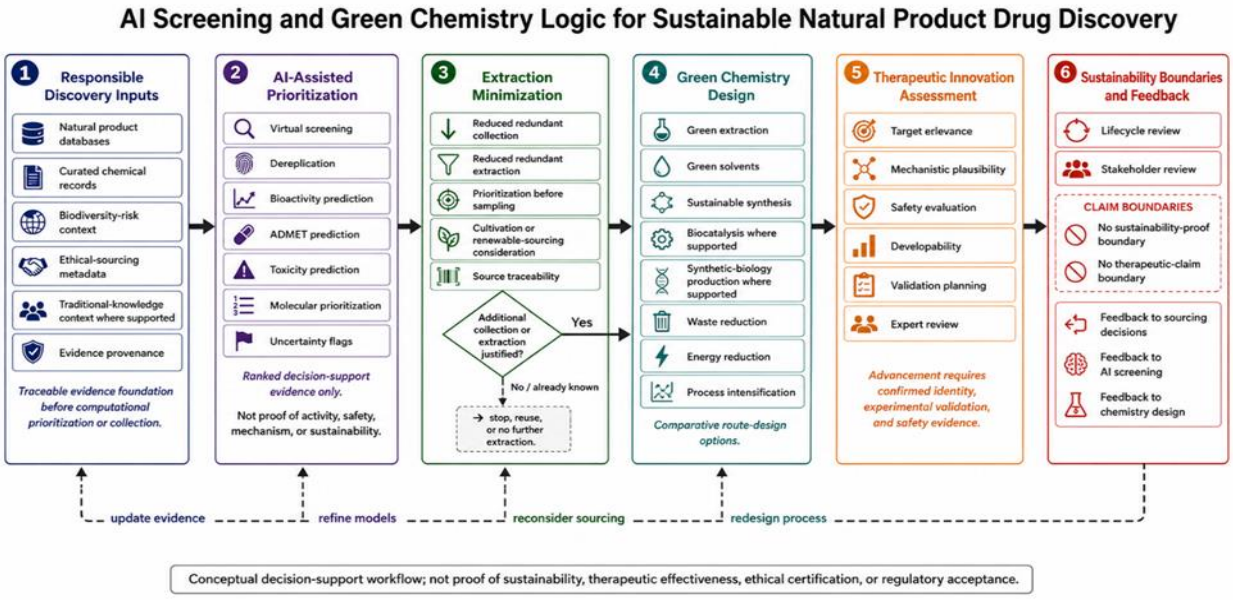

Figure 1. AI Screening and Green Chemistry Logic for Sustainable Natural Product Drug Discovery

Alt-text description

A conceptual workflow showing natural product evidence flowing through AI screening, dereplication, bioactivity and safety prediction, extraction minimization, green chemistry, sustainable synthesis, validation planning, and sustainability boundaries.

Therapeutic innovation pathways

Therapeutic innovation begins only after chemical identity and bioactivity have been separated from broader claims of medical usefulness. A natural product may produce an assay response yet remain unsuitable because of uncertain

target relevance, nonspecific activity, instability, poor exposure, toxicity, limited supply, or an impractical manufacturing route. Reviews of natural bioactive products emphasize that discovery must progress through mechanistic investigation, safety assessment, pharmacokinetic characterization, formulation, and development planning before a compound can be treated as a credible therapeutic candidate [19]. Within a sustainability framework, these requirements also prevent ecological and social burdens from being justified by preliminary activity that may never translate into a viable intervention.

Modern development pathways may involve the original natural compound, a standardized mixture, a semisynthetic derivative, a simplified analogue, a biosynthetically produced molecule, or a pharmacophore-inspired scaffold. Contemporary approaches to plant-derived natural products combine chemical identification, computational screening, analogue generation, formulation, and experimental evaluation to address potency, selectivity, stability, supply, and safety limitations [20]. Responsible candidate prioritization should therefore compare therapeutic relevance with sourcing feasibility, ecological pressure, production alternatives, anticipated process burden, and equity considerations. A more potent analogue is not necessarily a more sustainable option if its synthesis requires hazardous reagents or if its development depends on continued extraction from a vulnerable source.

Integrated metabolomic and genomic approaches can improve novelty assessment, associate compounds with biosynthetic pathways, and focus isolation on chemical entities that are better supported by multiple evidence streams [21]. These methods may reduce untargeted extraction, but predicted biosynthetic relationships and molecular annotations still require structural and functional confirmation. Renewable production may also be considered where selected natural products can be produced through microorganisms, pathway engineering, or related biotechnological systems. Reviews of microbial production show that these platforms can support the manufacture of bioactive natural products and biologics, although productivity, genetic stability, scale-up, fermentation inputs, downstream purification, and process reproducibility remain compound dependent [22].

Therapeutic innovation should consequently be evaluated through a stage-gated process that combines target relevance, mechanistic plausibility, safety, developability, supply resilience, ecological safeguards, ethical governance, and expert review. Retrospective analyses suggest that natural-product-associated development programs can show favorable aggregate patterns across clinical development, but such findings cannot predict the success, safety, or approval of any individual candidate [23]. The proposed framework therefore treats clinical-development trends as contextual evidence rather than candidate-level validation. No discovery score, traditional-use history, mechanistic hypothesis, production route, or sustainability assessment permits a therapeutic claim without the appropriate experimental and clinical evidence.

Proposed sustainability framework

The proposed framework begins with definition of a bounded discovery question, followed by biodiversity and sourcing assessment and an ethical governance review. The discovery question should identify the therapeutic problem, intended biological hypothesis, relevant alternatives, and the minimum biological material and evidence needed to investigate it. Biodiversity assessment then examines species identity, conservation uncertainty, habitat pressure, harvesting method, projected demand, and the feasibility of cultivation, renewable sourcing, or alternative production. Ethical governance examines provenance, access conditions, benefit-sharing principles, traditional knowledge, community relationships, source-country collaboration, transfer conditions, and supply-chain accountability. Engineered production may be evaluated as an alternative to continued plant extraction when a biosynthetic route is technically plausible, as illustrated by synthetic-biology strategies proposed for ginsenoside production [24]. Such substitution remains conditional on comparative ecological, process, safety, and lifecycle evidence.

The next stages establish a natural product evidence foundation and apply AI-assisted prioritization, dereplication, and extraction minimization. Existing chemical records, spectra, biological assays, voucher information, source metadata, and knowledge provenance should be consolidated before new collection is considered. Computational approaches may then rank candidates, identify uncertainty, predict selected bioactivity or safety endpoints, and direct experimental resources toward defined hypotheses. Dereplication determines whether known chemistry can be recognized through archived materials or analytical comparison before additional biomass is processed. Green chemistry planning follows only after a candidate passes these evidentiary and governance gates. Biocatalysis may provide selective and potentially lower-burden routes to complex natural-product-related structures, although the complete route, enzyme production, solvents, cofactors, purification, and scale must be assessed rather than assuming superiority from the use of an enzyme [25].

Mechanistic and therapeutic evaluation, safety evaluation, and developability assessment form the scientific validation core of the framework. Confirmed chemical

identity should precede target-engagement studies, and mechanistic claims should be supported by orthogonal, reproducible, and concentration-aware evidence. Safety assessment should address purity, metabolites, exposure, structural alerts, relevant toxicity endpoints, and formulation effects. Developability assessment should consider solubility, stability, pharmacokinetics, manufacturability, supply continuity, and quality control. At the process level, biocatalysis and other catalytic options should be compared through selectivity, reaction conditions, solvent requirements, material inputs, energy demand, waste generation, and downstream processing [26]. These comparisons enable route selection but do not independently establish environmental sustainability or therapeutic suitability.

A therapeutic innovation pathway is selected only after the evidence supports a defensible route for further investigation. The pathway may retain the original compound, modify it, reproduce it through biotechnology, redesign its synthesis, or discontinue it where ecological, ethical, safety, or developability risks outweigh the scientific opportunity. Green extraction and synthesis claims should be evaluated using multidimensional criteria because high yield, fewer steps, solvent substitution, or renewable feedstock can each conceal burdens elsewhere in the process [27]. The framework therefore requires transparent assumptions, relevant material and hazard indicators, uncertainty reporting, and comparison of realistic alternatives. These requirements are proposed decision controls rather than validated sustainability metrics or certification criteria.

The final stages comprise lifecycle sustainability review, expert and stakeholder review, feedback updating, and explicit claim boundaries. Lifecycle review considers sourcing, cultivation or fermentation, extraction, synthesis, utilities, purification, packaging, transport, use, and end-of-life processes where they are relevant to the proposed product system. Pharmaceutical life-cycle scholarship shows that conclusions depend strongly on the functional unit, system boundaries, inventory quality, toxicity treatment, manufacturing data, and the availability of comparable alternatives [28]. Expert and stakeholder review should integrate ecological, community, chemical, pharmacological, manufacturing, and equity perspectives, while feedback from validation, sourcing, process development, and engagement should be permitted to revise or reverse earlier decisions. The framework supports responsible planning but does not establish legal compliance, ethical certification, environmental validation, clinical effectiveness, regulatory acceptance, or commercialization readiness. **Table 2** presents the proposed sustainability framework for natural product drug discovery.

Table 2. Proposed Sustainability Framework for Natural Product Drug Discovery: Biodiversity Protection, Ethical Sourcing, AI-Assisted Prioritization, Dereplication, Extraction Minimization, Green Chemistry, Safety Evaluation, Developability, Therapeutic Innovation, Lifecycle Review, Stakeholder Oversight, Feedback, and Claim Boundaries

Framework stage	Core purpose	Required input	Sustainability function	Potential output	Validation need	Failure risk	Feedback mechanism	Decision boundary
Discovery question definition	Establish a justified therapeutic or scientific problem before biological resources are used	Unmet-need rationale, target or phenotype hypothesis, intended product concept, alternatives, and evidence gaps	Prevents indiscriminate collection and unfocused screening	Bounded discovery question and evidence plan	Scientific, pharmacological, and clinical expert review	Broad bioprospecting without a defensible question	Revise the scope when target evidence or alternative solutions change	A discovery question does not authorize collection or establish therapeutic relevance
Biodiversity and sourcing assessment	Determine whether the source and anticipated demand are ecologically acceptable for further investigation	Taxonomy, geographic origin, conservation information, habitat context, harvesting method, and projected material demand	Identifies species, habitat, and overharvesting risks before candidate advancement	Ecological risk classification, sourcing conditions, substitution plan, or stop decision	Species- and location-specific verification proportional to risk	Candidate proceeds despite unresolved vulnerability or uncertain identity	Update when conservation status, supply, location, or demand changes	Unresolved high ecological risk requires hold, substitution, or rejection
Ethical governance review	Establish responsible access, knowledge use,	Material provenance, provider information,	Protects rights, relationships, equitable	Governance plan, use restrictions, engagement	Authorized institutional, provider, source-country,	Token engagement, undocumented use, or	Continuing provider, community, collaborator,	Scientific promise cannot override

	collaboration, and benefit pathways	access terms, traditional knowledge context, intended uses, and stakeholder relationships	participation, and governance continuity	pathway, and unresolved-issue register	and stakeholder review where applicable	activity beyond the agreed scope	and governance feedback	unresolved ethical governance
Natural product evidence foundation	Consolidate existing chemical, biological, ecological, and provenance evidence	Literature, databases, voucher records, spectra, analytical data, assays, source records, and knowledge provenance	Reduces unnecessary collection, duplication, and poorly informed screening	Curated evidence dossier with confidence and uncertainty labels	Data-quality, identity, provenance, and reproducibility audit	Incomplete, duplicated, or erroneous records are treated as established evidence	Continuous updating as structures, assays, provenance, or sourcing information changes	Database presence does not confirm identity, activity, novelty, sustainability, or rights of use
AI-assisted prioritization	Focus experimental resources on candidates with transparent and testable hypotheses	Curated structures, labeled data, target information, endpoint definitions, provenance metadata, and applicability-domain information	Reduces low-value screening and exposes evidence uncertainty	Ranked candidates, predicted risks, and experimental priorities	External or prospective validation, applicability assessment, and expert review	Data leakage, bias, poor transferability, or scores interpreted as biological proof	Recalibrate models and rankings after experimental results	AI output is decision support, not proof of activity, mechanism, safety, or sustainability
Dereplication and extraction minimization	Recognize known chemistry before additional collection, extraction, or isolation	Analytical profiles, spectral libraries, archived samples, known structures, and confidence criteria	Reduces repeated collection, extraction, fractionation, and characterization	Stop, reuse, targeted-isolation, or provisional novelty decision	Orthogonal analytical confirmation and expert review	False novelty increases resource use or false dereplication eliminates a useful candidate	Add confirmed structures and spectra to the evidence foundation	Tentative annotation cannot support definitive identity or novelty claims
Green chemistry planning	Compare extraction, synthesis, and production routes using material, hazard, energy, and process considerations	Candidate routes, solvents, reagents, catalysts, energy needs, waste streams, equipment, and scale assumptions	Reduces selected chemical and operational burdens without shifting them unexamined	Comparative route plan and improvement priorities	Measured process performance, hazard review, and realistic alternative comparison	A single favorable attribute is presented as proof of a green process	Reassess after laboratory, pilot, recovery, and scale data become available	A greener individual step does not prove a sustainable lifecycle
Mechanistic and therapeutic evaluation	Test whether the confirmed compound or preparation supports a biologically relevant and reproducible mechanism	Verified identity, purity, target or phenotype hypothesis, assay controls, and concentration range	Prevents ecological and process investment in unsupported candidates	Mechanistic evidence, uncertainty statement, and go/no-go recommendation	Orthogonal assays, reproducibility, interference controls, and relevant biological models	Assay artefacts, correlation, or computational prediction are treated as mechanism	Feed results back into candidate ranking, evidence quality, and pathway selection	Mechanistic plausibility does not establish therapeutic efficacy
Safety evaluation	Identify hazards, exposure	Purity profile, dose assumptions,	Prevents natural origin or sustainable	Safety-risk profile and fit-	Appropriate in vitro, in vivo, alternative-	Absence of predicted toxicity or	Update when metabolites, impurities,	No safety claim may be based

	concerns, metabolites, interactions, and toxicity risks early	metabolites, structural alerts, formulation, and experimental safety information	sourcing from obscuring patient-safety requirements	for-purpose testing plan	method, and exposure-based evaluation	history of use is treated as proof of safety	exposure, combinations, or formulations change	solely on natural origin, traditional use, or prediction
Developability assessment	Determine whether the candidate can become a reproducible, stable, and manufacturable product	Solubility, stability, permeability, pharmacokinetics, formulation, supply, analytical controls, and process options	Avoids scaling ecologically or chemically burdensome candidates with poor development prospects	Developability profile, mitigation strategy, redesign option, or termination decision	Experimental pharmaceutical characterization and supply feasibility review	Bioactivity is mistaken for product feasibility	Reformulate, redesign an analogue, change production route, or discontinue	Bioactivity and mechanism do not establish developability
Therapeutic innovation pathway	Select the most responsible route for continued development	Mechanism, safety, developability, sourcing, production, equity, and lifecycle evidence	Aligns innovation strategy with ecological and ethical constraints	Defined pathway for the original compound, analogue, mixture, bioproduct, alternative modality, or discontinuation	Comparative scientific, supply, manufacturing, and sustainability review	Innovation language is used to justify biodiversity loss or inequitable sourcing	Revisit when source availability, production performance, safety, or therapeutic evidence changes	Therapeutic novelty cannot override ecological or ethical safeguards
Lifecycle sustainability review	Examine burdens and trade-offs across the proposed product system	Sourcing, cultivation, fermentation, extraction, synthesis, utilities, purification, packaging, transport, use, and end-of-life information	Detects burden shifting and identifies material, energy, hazard, and supply hotspots	Lifecycle risk profile, uncertainty statement, and improvement plan	Transparent functional unit, system boundary, inventory quality, and sensitivity analysis	Narrow boundaries or incomplete data create misleading superiority claims	Update with pilot, manufacturing, supplier, transport, and disposal data	Incomplete lifecycle evidence cannot establish sustainability proof
Expert and stakeholder review	Integrate ecological, ethical, chemical, pharmacological, manufacturing, community, and equity perspectives	Full evidence dossier, unresolved-risk register, alternatives, and proposed decision	Prevents a single discipline, model, or performance indicator from dominating	Conditional advance, revision, hold, substitution, or rejection	Conflict-of-interest management, documented reasoning, and appropriate representation	Review becomes ceremonial endorsement without influence on decisions	Structured response, issue resolution, and reassessment	Review does not constitute regulatory approval, legal certification, or community consent
Feedback updating	Maintain an adaptive framework that learns from emerging evidence	New validation, conservation, sourcing, community, AI, chemistry, safety, and manufacturing information	Ensures decisions remain responsive to changing ecological, technical, and social conditions	Updated evidence dossier, rankings, controls, and decision status	Version control, decision traceability, and reproducibility	Outdated assumptions persist after material conditions change	Scheduled and event-triggered reassessment	Earlier advancement within the framework is reversible
No therapeutic-	Prevent research-stage outputs from	Evidence hierarchy, claim inventory,	Preserves translational accuracy and	Qualified research recommendati	Final scientific-claims review	Candidate is described as effective,	Correct claims when	The framework does not

claim boundary	being described as clinical evidence	intended audience, and validation status	patient-safety boundaries	on or hypothesis		safe, or clinically useful prematurely	the evidence level changes	establish efficacy, safety, clinical utility, or approval
No sustainability-proof boundary	Prevent partial ecological, ethical, AI, or green-chemistry evidence from becoming a total sustainability claim	Cross-domain evidence, lifecycle information, unresolved uncertainty, and stakeholder input	Preserves ecological, social, and technical accuracy	Bounded sustainability-support statement, conditional hold, or rejection	Independent multidisciplinary review and transparent uncertainty reporting	A favorable model score, solvent choice, sourcing record, or production route is marketed as proof of sustainability	Reassess across sourcing, lifecycle, validation, and stakeholder domains	The framework supports responsible planning and comparison; it does not certify sustainability

Figure 2 presents the proposed sustainability framework for natural product drug discovery, integrating biodiversity protection, ethical sourcing, AI screening, green chemistry, therapeutic innovation, stakeholder oversight, and lifecycle feedback.

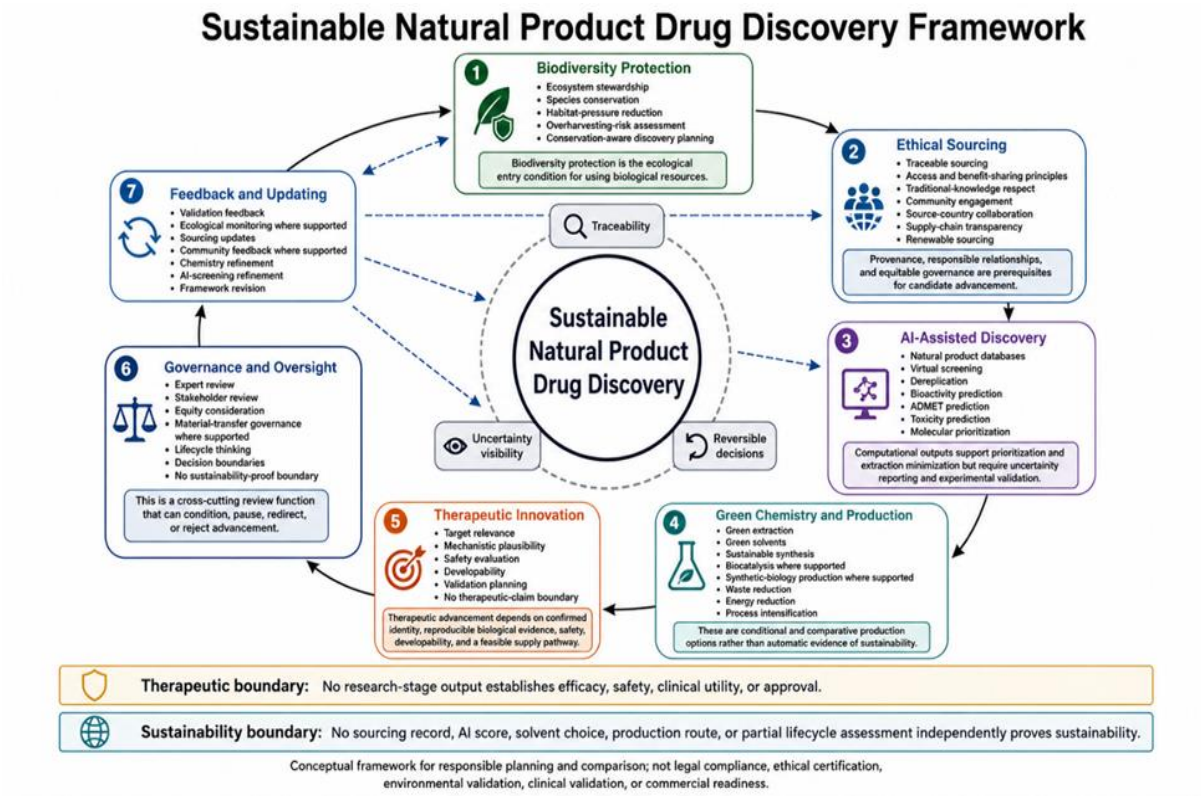

Figure 2. Sustainable Natural Product Drug Discovery Framework

Alt-text description

A conceptual sustainability framework showing biodiversity protection, ethical sourcing, traceability, AI screening, green chemistry, therapeutic innovation, safety evaluation, lifecycle review, stakeholder oversight, feedback loops, and sustainability and therapeutic-claim boundaries.

CONCLUSION

This article proposes a sustainability framework for natural product drug discovery that integrates biodiversity protection, ecosystem stewardship, ethical and traceable sourcing, access and benefit-sharing principles, respectful treatment of traditional knowledge, AI-assisted

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prioritization, dereplication, extraction minimization, green chemistry, responsible production, therapeutic evaluation, lifecycle review, and expert and stakeholder oversight. Its central contribution is to position sustainability as a sequence of linked ecological, ethical, computational, chemical, pharmacological, and translational decisions rather than as an inherent property of natural origin, an AI-enabled workflow, or a process described as green. The framework requires uncertainty to remain visible, permits earlier decisions to be revised, and establishes explicit boundaries against unsupported therapeutic, compliance, certification, and sustainability claims. Its value lies in supporting more responsible discovery planning and transparent comparison of alternatives, while recognizing that sustainability must ultimately be demonstrated through traceable practices, ecological safeguards, ethical governance, validated technical performance, lifecycle evidence, and accountable engagement.

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