Multiscale Pharmacology of Natural Products: Linking Molecular Features, Cellular Pathways, Organ-Level Effects, and Clinical Relevance

Laura Keller[1]*, Thomas Lehmann[1], Simon Brunner[2], Christoph Meier[3]

[1]Department of Artificial Intelligence for Membrane Transport of Natural Drugs, Faculty of Pharmacy, ETH Zurich, Zurich, Switzerland.
[2]Department of Computational Pharmacokinetics, Faculty of Pharmacy, EPFL Lausanne, Lausanne, Switzerland.
[3]Department of Phytochemical Stability Informatics, Faculty of Pharmacy, University of Bern, Bern, Switzerland.

ABSTRACT

Natural product pharmacology routinely spans multiple biological and interpretive scales, from phytochemical identity and molecular interactions to cellular pathway modulation, tissue responses, organ-level effects, and clinical relevance. This scale diversity creates a recurrent translational problem because evidence generated at one level is often interpreted as if it were sufficient to justify conclusions at another. The purpose of this article is to propose a multiscale pharmacology framework for natural product research that preserves scale-specific evidence while organizing structured links across molecular, cellular, organ-level, exposure, safety, and translational domains. The framework begins with natural product identity, botanical source, phytochemical composition, and molecular feature characterization, then progresses through bioactivity evidence, target annotation, target engagement hypotheses, off-target risk, and cellular pathway mapping supported by omics evidence where available. It next incorporates tissue context, organ-system relevance, pharmacokinetic exposure, ADME considerations, and safety signals so that organ-level interpretation is not detached from exposure-response reasoning. Clinical relevance is addressed through biomarker interpretation, disease-phenotype mapping, clinical endpoint boundaries, and uncertainty-aware translational mapping. Validation is treated as a central boundary condition rather than a downstream formality, with explicit attention to scale-transition gaps, evidence triangulation, expert review, and feedback updating. The main contribution is an original conceptual framework that supports research prioritization and mechanism-oriented interpretation while avoiding unsupported clinical or therapeutic claims.

Key Words: *Multiscale pharmacology, Natural products, Molecular features, Cellular pathways, Organ-level effects, Clinical relevance*

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INTRODUCTION

Natural product pharmacology is inherently multilevel because the same research program may involve botanical materials, phytochemical profiles, purified constituents, molecular targets, cellular phenotypes, organ-relevant biology, and eventual questions of clinical meaning. The continuing importance of natural products in drug discovery reinforces the need for a framework that can organize these diverse evidence forms without collapsing them into a single claim type [1].

A scale-aware approach is necessary because molecular activity, pathway modulation, and organism-level interpretation are not interchangeable. Systems pharmacology has emphasized that biological effects emerge from interacting networks rather than isolated targets, which makes it useful for structuring natural

Corresponding author: Laura Keller
Address: Department of Artificial Intelligence for Membrane Transport of Natural Drugs, Faculty of Pharmacy, ETH Zurich, Zurich, Switzerland.
E-mail: ✉ laura.keller@pharma.ethz.ch
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product evidence while also highlighting the limits of single-mechanism explanations [2].

The translational challenge becomes greater when exposure, delivery, and target-site relevance are considered. Quantitative systems pharmacology perspectives show that pharmacological interpretation depends not only on what a molecule or mixture can do in a controlled assay, but also on whether relevant exposure and residence can plausibly connect that signal to a biological context of interest [3].

These issues are especially important in natural product research, where in silico methods, bioactivity screening, and heterogeneous evidence streams are often combined. Recent analyses of computationally assisted natural product discovery have underscored both the promise of such integration and the risk of overinterpreting preliminary signals [4]. Accordingly, the objective of this article is to propose an original multiscale pharmacology framework that links molecular features, cellular pathways, organ-level effects, exposure, safety, and clinical relevance through explicit validation boundaries and cross-scale claim limits.

Multiscale pharmacology in natural product research

In the present context, multiscale pharmacology refers to the structured interpretation of natural product evidence across connected but distinct levels of biological organization. It is not synonymous with compiling large numbers of targets or pathways. Rather, it requires a disciplined account of how natural product identity, immune or cellular effects, and context-dependent biological responses may be related without assuming that one layer proves another [5].

This definition also distinguishes multiscale pharmacology from network pharmacology alone. Network methods can be valuable for identifying interacting pathways and system-level hypotheses, but causal interpretation still requires attention to evidence quality, scale transitions, and competing explanations. Recent methodological discussion has argued that network pharmacology is most useful when it is oriented toward causal mechanisms rather than symptom-level association patterns [6].

A further distinction is needed from database-driven annotation workflows. Databases and integrative resources can support hypothesis generation by linking compounds, symptoms, targets, and pathways, but they do not by themselves resolve whether a proposed connection is biologically credible in a given experimental or translational setting. Reviews of network pharmacology databases in traditional medicine research illustrate both their utility and their dependence on curation quality, evidence provenance, and careful downstream interpretation [7].

Multiscale pharmacology therefore requires a more explicit evidence architecture than isolated docking, single-pathway reporting, or broad clinical relevance claims. Curated activity resources such as NPASS can provide a useful foundation by connecting species sources, natural products, and reported activities, yet the framework must still preserve uncertainty, integrate exposure and safety, and identify causal gaps before any translational inference is made [8]. In this sense, multiscale pharmacology is best viewed as a scale-preserving interpretive framework rather than a shortcut to therapeutic conclusions.

Molecular features and cellular pathways

The molecular layer of natural product pharmacology begins with identity and characterization. Natural product evidence is stronger when botanical source, phytochemical profile, chemical structure, stereochemistry, and compound composition are defined clearly enough to support reproducible interpretation. Computational natural product research further shows that molecular descriptors and related cheminformatic representations can help position compounds within broader pharmacological space, but these representations remain interpretive tools rather than biological proof [9].

Once chemical characterization is established, early-stage pharmacological interpretation benefits from structured appraisal of absorption, distribution, metabolism, excretion, and drug-likeness constraints. Tools such as SwissADME have made this form of evaluation more accessible for small-molecule assessment, helping to frame whether apparent activity aligns with plausible physicochemical behavior [10]. More comprehensive ADMET prediction platforms extend this logic by integrating broader property domains, which can inform hypothesis refinement and identify possible liabilities before overinterpretation of bioactivity data occurs [11].

The next layer concerns bioactivity evidence, assay metadata, and target annotation. Binding knowledge resources provide a way to contextualize reported protein-small molecule interactions and to separate direct evidence from looser target associations, which is essential for judging target confidence and target engagement hypotheses [12]. Integrative resources such as SymMap can connect compounds, targets, and symptom-oriented mappings, while enrichment platforms such as Metascape can support pathway-level interpretation when used transparently and cautiously [13]. However, these tools are most informative when assay conditions, evidence provenance, and off-target possibilities are explicitly considered rather than treated as interchangeable indicators of mechanism [14].

At the cellular scale, pathway modulation should be interpreted as a mechanistic hypothesis that may be strengthened by transcriptomic, proteomic, or metabolomic evidence where such data are available. Multi-omics approaches can improve natural product target discovery and pathway mapping by showing convergent biological signals, yet they also reveal the complexity of moving from molecular interaction to cellular phenotype [15]. The main boundary at this stage is that pathway modulation, even when biologically coherent, does not independently establish validated mechanism, organ-level benefit, or clinical relevance.

Table 1 summarises molecular feature and cellular pathway requirements for multiscale pharmacology of natural products.

Table 1. Molecular Feature and Cellular Pathway Requirements for Multiscale Pharmacology of Natural Products: Phytochemical Identity, Chemical Structure, Stereochemistry, Molecular Descriptors, Bioactivity Evidence, Target Confidence, Target Engagement Hypotheses, Off-Target Risk, Pathway Modulation, Omics Evidence, Cell Phenotypes, and Mechanistic Boundaries

Scale component	Core pharmacology question	Required evidence or input	Multiscale function	Potential output	Risk of overinterpretation	Validation requirement	Framework role
Natural product identity	What material is being studied?	Defined material name, preparation description, provenance, identity confirmation	Anchors all downstream evidence to a traceable entity	Interpretable evidence foundation	Conflating different materials as one intervention	Identity confirmation and reporting transparency	Evidence foundation
Botanical source	Is the source organism specified adequately?	Taxonomic description, source context, collection or sourcing information	Connects pharmacology to biological origin and variability	Source-aware interpretation	Treating heterogeneous sources as equivalent	Source verification and documentation	Context definition
Phytochemical profile	What is known about composition?	Qualitative or semi-quantitative composition information, constituent profile	Links raw material to chemical plausibility	Composition-informed hypothesis generation	Assuming incomplete profiles capture the full active space	Analytical characterization and reproducibility checks	Composition mapping
Chemical structure	Which chemical entities are implicated?	Structural annotation of key constituents	Enables structure-based interpretation and comparison	Structure-informed pharmacology hypotheses	Inferring activity solely from structural resemblance	Structure confirmation	Molecular feature mapping
Stereochemistry	Are stereochemical features relevant?	Stereochemical assignment where supported	Refines target and property interpretation	More precise molecular hypothesis	Ignoring stereochemical differences in activity or disposition	Stereochemical verification where relevant	Precision refinement
Molecular descriptors	Which physicochemical features may shape behavior?	Descriptor set or related cheminformatic representation	Supports ADME and bioactivity plausibility assessment	Prioritized hypotheses	Treating descriptors as efficacy evidence	Independent biological corroboration	Computational support
Compound composition	Is the evidence based on a single	Defined constituent relationships and preparation context	Preserves mixture-versus-single-agent	Scale-aware comparison	Assigning mixture effects to one constituent without support	Fractionation logic or comparative testing	Composition boundary

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	compound or mixture?		interpretation				
Bioactivity evidence	What activity has been observed?	Assay results with context and model description	Connects chemical entities to observed effects	Activity hypothesis	Assuming activity equals mechanism or relevance	Replication and assay-quality review	Activity mapping
Assay metadata	How was activity measured?	Assay type, model system, conditions, controls, endpoint description	Supports evidence quality judgment	Confidence stratification	Comparing incompatible assay outputs directly	Methodological transparency	Evidence-quality filter
Target annotation and target confidence	Which targets are proposed and how strong is the support?	Binding, perturbation, or curated target evidence	Links activity to molecular pharmacology	Ranked target hypotheses	Treating low-confidence annotation as established target engagement	Orthogonal validation and evidence grading	Target mapping
Target engagement hypothesis	Is there a plausible link between exposure and target interaction?	Target evidence plus exposure plausibility and biological context	Bridges molecular and cellular interpretation	Mechanistic hypothesis	Assuming target engagement from nominal activity alone	Context-specific experimental confirmation	Cross-scale bridge
Off-target risk	What unintended interactions may matter?	Selectivity information, liability signals, pathway overlap	Introduces uncertainty and safety perspective	Risk-aware interpretation	Ignoring competing mechanisms or liabilities	Broader profiling and follow-up testing	Safety-aware boundary
Cellular pathway evidence	Which pathways appear modulated?	Pathway analysis, molecular readouts, contextual biology	Connects target hypotheses to cellular processes	Pathway-level explanation	Mistaking association for validated mechanism	Independent confirmation and context review	Cellular mapping
Omics evidence	Do transcriptomic, proteomic, or metabolomic data support the pathway view?	Omics datasets where supported and quality-controlled	Enables convergence assessment across data layers	Stronger mechanistic coherence	Overfitting broad omics signatures to preferred narratives	Cross-platform verification and biological plausibility review	Mechanistic support
Cell phenotype	What cellular response is observed?	Phenotypic assays and biologically interpretable endpoints	Links pathway signals to functional consequences	Cell-response hypothesis	Treating phenotype as organ-level or clinical proof	Replication in relevant models	Functional interpretation
Mechanistic boundary	What cannot yet be claimed?	Integrated review of evidence strength and gaps	Prevents cross-scale inflation	Bounded interpretation	Claiming validated mechanism prematurely	Explicit uncertainty statement and follow-up plan	Claim control

Organ-level effects

Moving from cellular evidence to organ-level interpretation requires an additional layer of biological

context. Tissue architecture, multicellular interactions, and exposure conditions shape whether cellular pathway signals are likely to remain relevant beyond simplified assay systems. Organs-on-chips and related microphysiological platforms have been highlighted as useful intermediates because they can represent tissue context more faithfully than isolated cell systems while still remaining experimental models rather than clinical surrogates [16].

This tissue-context layer is important for interpreting organ-system relevance in domains such as inflammation, oxidative stress, metabolic regulation, and immune modulation. Human organ-on-chip perspectives further show that vascular, neural, hepatic, renal, gastrointestinal, and cardiometabolic questions can be investigated in more physiologically organized settings, but the resulting data still support hypotheses about organ-level effects rather than confirmed therapeutic benefit [17]. In a multiscale framework, these platforms help reduce, but do not eliminate, uncertainty at the transition from cellular pathways to organ biology.

Exposure must also be integrated explicitly. Physiologically based pharmacokinetic modeling has become increasingly prominent in drug development because it helps relate dosing, distribution, and tissue exposure to biological interpretation [18]. In natural product research, ADMET-oriented assessments are especially important because many candidate compounds or mixtures face limitations related to absorption, metabolism, or distribution, and these limitations may constrain whether an observed molecular or cellular effect is relevant at an organ level [19].

A final organ-level boundary concerns safety and interaction liabilities. Natural products can modulate cytochrome P450 enzymes and thereby alter metabolic handling in ways that complicate exposure-response interpretation and herb–drug interaction assessment [20]. They may also affect other metabolic systems such as carboxylesterase pathways, further emphasizing that organ-level interpretation must include biotransformation and interaction risk rather than only intended biological effects [21]. For this reason, the proposed framework treats organ-level effects as context-dependent hypotheses that require exposure evidence, safety assessment, and scale-transition validation before any implication of organ benefit is considered.

Figure 1 illustrates how molecular features and cellular pathway evidence can be connected to tissue context, organ-level effects, exposure, safety, and scale-transition validation in natural product pharmacology.

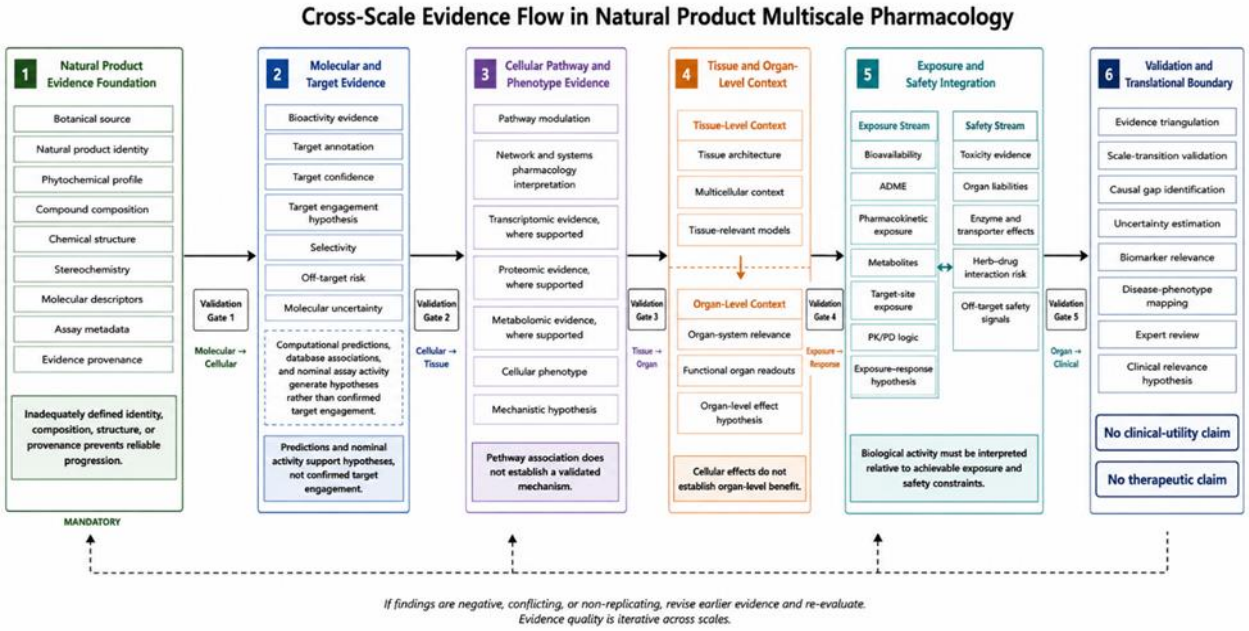

Figure 1. Cross-Scale Evidence Flow in Natural Product Multiscale Pharmacology

Alt-text description

A conceptual multiscale evidence-flow diagram showing natural product identity connected to molecular features, target evidence, cellular pathways, tissue context, organ-level effects, exposure, safety evidence, validation gates, uncertainty, and clinical claim boundaries.

Clinical relevance and translational mapping

Clinical relevance should be treated as a structured hypothesis rather than a direct consequence of molecular or organ-level findings. Natural products continue to provide important opportunities for pharmacological

discovery, but translation requires clear separation between chemical promise, experimental activity, disease relevance, and evidence capable of informing clinical interpretation [22]. Within a multiscale framework, clinical relevance mapping therefore asks whether the biological process represented at earlier scales corresponds plausibly to a defined disease phenotype, biomarker context, exposure condition, or clinically meaningful endpoint. This mapping does not establish efficacy; it identifies where additional translational evidence would be required. The quality of phytopharmacological research also influences whether experimental findings can be interpreted beyond their original setting. Best-practice recommendations emphasize the importance of material characterization, methodological rigor, biologically appropriate models, reproducibility, and restrained interpretation [23]. Transparent reporting is particularly important because variation in source material, extraction procedures, constituent composition, and experimental conditions can undermine comparisons across studies and weaken any proposed transition from mechanistic evidence to clinical relevance [24]. Patient-context relevance, where considered, must therefore be grounded in adequately described populations, disease states, co-exposures, and endpoint definitions rather than inferred from generic biological plausibility.

Safety and interaction evidence form an indispensable part of translational mapping. Systematic evaluation of herbal product–medication interactions indicates that clinically relevant risks may arise through pharmacokinetic or pharmacodynamic mechanisms and that the supporting evidence varies substantially in strength [25]. Warfarin-related evidence further illustrates how foods, herbs, and dietary supplements can alter clinically sensitive treatment contexts, underscoring the need to distinguish a possible interaction signal from a validated prediction for a particular patient or product [26]. The framework therefore requires explicit review of ADMET evidence, toxicity findings, metabolic liabilities, and herb–drug interaction risk before clinical relevance is discussed.

Evidence triangulation should integrate chemical characterization, molecular activity, cellular responses, organ-level findings, exposure plausibility, safety information, and any available clinical observations. Emerging herbal nutraceuticals demonstrate the breadth of contemporary use and pharmacological interest, but also the distance that can remain between patterns of use, experimental evidence, and validated clinical application [27]. Translational mapping should consequently document uncertainty, identify causal gaps, specify scale-transition validation needs, and include expert pharmacology or clinical review where appropriate. Its outputs support research prioritization and validation planning; they do not establish clinical utility, therapeutic value, treatment suitability, or patient-level decision rules. **Table 2** maps organ-level effects, clinical relevance, and translational interpretation requirements for natural product multiscale pharmacology.

Table 2. Organ-Level Effects, Clinical Relevance, and Translational Mapping Requirements in Natural Product Multiscale Pharmacology: Tissue Context, Organ-System Relevance, Exposure, ADME, PK/PD Logic, Biomarker Relevance, Safety Evidence, Evidence Triangulation, Scale-Transition Validation, and Claim Boundaries

Translational component	Core cross-scale question	Evidence needed	Mapping function	Potential output	Failure or uncertainty risk	Validation requirement	Claim boundary
Tissue context	Is the cellular signal relevant within an organized biological environment?	Tissue-relevant models, spatial context, multicellular information, model limitations	Positions cellular findings within a more physiologically structured scale	Tissue-relevance hypothesis	Ignoring architecture, cell interactions, or local exposure	Replication in appropriate tissue models	Does not establish an organ-level benefit
Organ-system relevance	Which organ system could plausibly be affected?	Organ-specific biology, functional readouts, model context	Links tissue findings to a defined physiological domain	Organ-level effect hypothesis	Generalizing findings across organs	Organ-specific functional validation	Does not establish therapeutic organ protection
Inflammation, oxidative stress, metabolic, or immune relevance	Does the observed process have context-specific organ relevance?	Process-specific markers, functional evidence, model appropriateness	Connects pathway activity to organ-associated biology	Contextual biological interpretation	Treating broadly shared stress pathways as disease-specific mechanisms	Orthogonal and functional confirmation	Does not establish disease modification

Vascular, neural, hepatic, renal, gastrointestinal, or cardiometabolic relevance	Is the evidence specific to the proposed physiological domain?	Domain-relevant models, exposure information, functional measurements	Refines organ-system interpretation	Prioritized organ-validation question	Selecting a preferred organ narrative from nonspecific data	Independent organ-specific testing	No organ-benefit claim
Pharmacokinetic exposure	Can the relevant constituent or mixture reach the proposed site?	Concentration-time information, disposition evidence, formulation context	Links administered material to plausible biological exposure	Exposure plausibility assessment	Comparing nominal assay concentrations with unverified in vivo exposure	Empirical or well-supported model-based exposure evaluation	Exposure plausibility does not prove response
Bioavailability and ADME	Are absorption and disposition compatible with the proposed effect?	Absorption, distribution, metabolism, elimination, stability information	Identifies barriers between administration and tissue action	ADME-informed prioritization	Ignoring metabolites, poor absorption, or rapid clearance	Experimental ADME characterization	Does not establish effective tissue delivery
PK/PD logic	Is there a defensible relationship between exposure and response?	Aligned exposure and pharmacodynamic observations where supported	Connects time-dependent exposure to biological effect	Exposure-response hypothesis	Assuming temporal association is causal	Prospective exposure-response testing	No efficacy inference without validation
Biomarker relevance	Does a measured marker correspond to a meaningful biological or clinical process?	Analytical validity, biological context, disease relevance	Bridges mechanistic findings and translational assessment	Biomarker hypothesis	Treating nonspecific markers as surrogate endpoints	Biomarker qualification appropriate to intended use	Does not establish a clinical endpoint
Disease phenotype mapping	Does the proposed mechanism align with a defined disease phenotype?	Phenotype definition, mechanistic correspondence, contextual evidence	Evaluates disease-level plausibility	Translational research hypothesis	Mapping broad pathways to heterogeneous diseases	Disease-specific experimental or clinical corroboration	Does not establish treatment benefit
Patient-context relevance	Could population factors alter interpretation?	Population characteristics where supported, co-medications, comorbidities, exposure context	Identifies contextual modifiers	Context-sensitive validation plan	Extrapolating across populations without evidence	Appropriate population-level study	No patient stratification or treatment recommendation
Safety evidence	What adverse or unintended effects may limit interpretation?	Toxicology, tolerability, organ liability, exposure margin information	Integrates benefit-independent risk assessment	Safety evidence profile	Assuming natural origin implies safety	Proportionate safety testing	No safety assurance
ADMET and toxicity evidence	Are disposition-related or toxicological liabilities present?	ADMET assays, mechanistic toxicology, relevant exposure data	Identifies translational constraints	Liability hypothesis	Treating predictions as confirmed safety outcomes	Experimental confirmation and context review	Does not establish acceptable risk
Herb–drug interaction risk	Could the natural product alter concomitant treatment effects?	Enzyme, transporter, pharmacodynamic, and clinical	Adds co-exposure risk to translational mapping	Interaction-risk prioritization	Generalizing from one constituent or formulation to another	Product-specific and clinically appropriate evaluation	No medication-management recommendation

		interaction evidence					
Clinical relevance hypothesis	Is there a justified reason to investigate a clinical connection?	Convergent molecular, cellular, organ, exposure, safety, and disease evidence	Defines the next translational question	Bounded clinical-relevance hypothesis	Presenting plausibility as demonstrated relevance	Prospective translational validation	Does not establish clinical utility
Clinical endpoint boundary	Is the proposed outcome directly measured and clinically meaningful?	Prespecified and validated endpoints in appropriate studies	Separates mechanistic markers from clinical outcomes	Endpoint-validation requirement	Substituting laboratory signals for patient outcomes	Appropriate clinical study design	No clinical-effect claim
Evidence triangulation	Do independent evidence types converge?	Multiple methods, models, scales, and sources	Tests coherence across scales	Confidence-weighted interpretation	Counting correlated evidence as independent confirmation	Independent replication and discrepancy analysis	Convergence does not prove causality
Uncertainty estimation	What is known, uncertain, missing, or conflicting?	Evidence grading, sensitivity analysis, alternative explanations	Makes confidence and limitations explicit	Uncertainty profile	Hiding uncertainty behind integrated diagrams or scores	Transparent uncertainty documentation	No definitive claim when uncertainty remains material
Causal gap identification	Which transitions lack causal support?	Cross-scale comparison and alternative mechanism assessment	Locates weak links in the evidence chain	Targeted validation question	Filling gaps with narrative assumptions	Mechanistic perturbation or other suitable testing	No mechanism claim across an unresolved gap
Scale-transition validation	Has each proposed transition been tested appropriately?	Transition-specific experiments or validated models	Evaluates molecular-to-cellular, cellular-to-organ, and organ-to-clinical links	Scale-specific confidence judgment	Validating one scale and assuming all others follow	Independent validation at each material transition	No cross-scale proof by association
Expert review	Has interpretation been assessed by relevant expertise?	Pharmacology, analytical, toxicology, modeling, and clinical input as appropriate	Challenges assumptions and identifies missing evidence	Revised and bounded interpretation	Authority substitution for empirical validation	Documented multidisciplinary review	Expert opinion does not establish efficacy
No therapeutic-claim boundary	What claims remain impermissible?	Explicit synthesis of evidence gaps and study limitations	Prevents conversion of research hypotheses into treatment statements	Responsible research conclusion	Implicit recommendation through overstated wording	Claim audit before dissemination	No treatment recommendation
No clinical-utility boundary	Has usefulness for clinical decisions been demonstrated?	Prospective clinical performance and utility evidence	Separates relevance from decision value	Clinical-utility research requirement	Treating biological relevance as actionable utility	Appropriate clinical utility evaluation	No patient-level decision support

Proposed multiscale framework

The proposed framework begins with research question definition. The intended pharmacological question, natural product form, biological scale, and permissible claim level should be specified before evidence is assembled. Quantitative systems pharmacology experience indicates that model-informed integration is most useful when it is linked to explicit questions, defined assumptions, and decision-relevant evidence rather than used as an unrestricted aggregation exercise [28]. The first framework

stage therefore records the botanical and chemical evidence foundation, including natural product identity, provenance, phytochemical profile, composition, structure, stereochemistry, molecular descriptors, assay metadata, and the limits of material characterization.

The second and third stages map molecular features, target evidence, bioactivity, and cellular pathways. Target annotations are graded according to evidence type and confidence, while target engagement and off-target effects remain hypotheses unless supported experimentally in an exposure-relevant context. Quantitative systems pharmacology has developed as a discipline for connecting mechanistic knowledge across biological organization, but its history also demonstrates that model scope, assumptions, and intended use must be defined carefully [29]. Accordingly, pathway and omics evidence is integrated only when provenance, analytical quality, and biological context are sufficient, and all proposed mechanisms are accompanied by explicit alternatives and uncertainty statements.

The fourth and fifth stages address tissue and organ-level mapping, exposure, PK/PD reasoning, and safety. Cellular observations are evaluated against tissue architecture, organ-system context, functional evidence, bioavailability, metabolism, and plausible target-site exposure. Credible modeling practice requires transparent assumptions, appropriate verification, validation, uncertainty analysis, and communication of limitations [30]. These principles are used here as framework requirements rather than as evidence that any particular natural product model is already credible. Safety integration runs in parallel with organ mapping and includes toxicity, ADMET liabilities, off-target effects, and herb–drug interaction risk.

The sixth stage maps clinical relevance and identifies cross-scale gaps. A clinical relevance hypothesis is permitted only when molecular, cellular, organ-level, exposure, and safety evidence can be traced transparently, while a clinical utility or therapeutic claim remains prohibited without appropriate clinical evidence. Evaluation of mechanistic in silico models has emphasized that credibility is context dependent and must be judged against the model's intended use, available verification, validation evidence, and uncertainty [31]. The framework therefore introduces transition-specific gates for molecular-to-cellular, cellular-to-tissue, tissue-to-organ, exposure-to-response, and organ-to-clinical mappings. Reproducibility principles further support complete reporting, accessible reasoning, robustness checks, and independent scrutiny of the evidence chain [32].

The final stage combines evidence triangulation, expert review, validation planning, and iterative feedback. Translational failure frequently reflects unresolved differences between preclinical models, human biology, exposure conditions, and clinical study contexts [33]. The framework therefore treats negative, conflicting, or non-replicating findings as informative feedback rather than evidence to be excluded. A structured credibility rubric may be used to audit whether the proposed evidence integration follows accepted practices for question definition, verification, validation, uncertainty management, and reporting, but successful rubric completion does not itself validate a pharmacological mechanism or clinical application [34]. The output is a prioritized and revisable research plan with explicit no-clinical-claim and no-therapeutic-claim boundaries.

Table 3 presents the proposed multiscale pharmacology framework for natural product research.

Table 3. Proposed Multiscale Pharmacology Framework for Natural Product Research: Evidence Foundation, Molecular Feature Mapping, Target and Bioactivity Mapping, Cellular Pathway Mapping, Tissue and Organ-Level Mapping, Exposure and PK/PD Mapping, Safety Integration, Clinical Relevance Mapping, Evidence Triangulation, Expert Review, Validation Planning, Feedback, and Claim Boundaries

Framework stage	Core purpose	Required input	Multiscale function	Potential output	Validation need	Failure risk	Feedback mechanism	Decision boundary
Research question definition	Define the intended problem, scale, context, and permissible inference	Specific research question, intended use, biological scope, material form	Aligns evidence collection with a bounded objective	Predefined analysis and validation plan	Expert review of scope and intended use	Unfocused evidence aggregation and retrospective claim inflation	Revise scope when evidence cannot address the original question	No claim beyond the predefined intended use
Natural product evidence foundation	Establish traceable material identity and composition	Botanical source, identity, provenance, preparation, phytochemical	Anchors downstream findings to a reproducible evidence object	Characterized evidence foundation	Analytical and documentation checks	Results cannot be attributed reliably to the studied material	Update characterization when batches or sources differ	No pharmacological inference from inadequately

		profile, composition, assay metadata						defined material
Molecular feature mapping	Describe chemical properties relevant to pharmacology	Structure, stereochemistry, descriptors, fingerprints where used, constituent relationships	Organizes chemical plausibility and comparison	Molecular feature profile	Structural and analytical confirmation	Treating computational representations as biological evidence	Refine features after new analytical data	No efficacy or mechanism claim
Target and bioactivity mapping	Grade molecular interactions and activity evidence	Assay results, target annotations, binding or perturbation evidence, assay conditions	Connects chemical evidence to molecular hypotheses	Confidence-ranked target and activity map	Orthogonal testing, replication, selectivity assessment	Database propagation, assay artifacts, unsupported target assignment	Re-rank targets after confirmatory or contradictory evidence	No target-engagement claim without suitable evidence
Cellular pathway mapping	Evaluate pathway and phenotype consequences	Cellular assays, pathway evidence, transcriptomics, proteomics, metabolomics where supported	Links molecular hypotheses to cellular processes	Cellular mechanism hypothesis	Perturbation studies, replication, model-context assessment	Correlation presented as causation	Update mechanism map after functional tests	No validated-mechanism claim from pathway association alone
Tissue and organ-level mapping	Test relevance within organized biological contexts	Tissue-relevant models, multicellular information, functional organ readouts	Bridges cellular evidence to organ-associated biology	Organ-level effect hypothesis	Organ-specific functional validation	Extrapolating isolated cell effects to whole-organ benefit	Revise mapping after tissue or organ-model findings	No organ-benefit claim
Exposure and PK/PD mapping	Relate administration and disposition to biological response	Bioavailability, ADME, concentration-time data, metabolites, response timing	Tests whether proposed interactions are exposure plausible	Exposure-response hypothesis	Empirical exposure studies or fit-for-purpose modeling	Nominal assay activity disconnected from achievable exposure	Update target and pathway priorities using exposure evidence	No response claim without exposure relevance
Safety evidence integration	Identify toxicological and interaction constraints	ADMET, toxicity, off-target, enzyme, transporter, and co-exposure evidence	Runs risk assessment alongside intended pharmacology	Safety and interaction evidence profile	Context-appropriate experimental and clinical evaluation	Natural-origin safety assumption or selective reporting	Feed safety findings back into composition and exposure stages	No safety assurance or medication recommendation
Clinical relevance mapping	Define whether further clinical investigation is justified	Disease phenotype, biomarker context, endpoint boundaries, exposure and safety synthesis	Connects preclinical evidence to bounded translational questions	Clinical-relevance hypothesis	Prospective translational or clinical validation	Mechanistic plausibility presented as clinical evidence	Revise hypothesis when phenotype or endpoint correspondence fails	No clinical-utility or therapeutic claim
Cross-scale gap	Locate unsupported transitions	Evidence map, uncertainty profile,	Makes causal and evidentiary	Gap register and	Transition-specific testing	Narrative bridging of	Update gap register after each	No progression across

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identification		alternative explanations	discontinuities explicit	prioritized questions		missing evidence	validation cycle	unresolved critical gaps
Evidence triangulation	Assess convergence across independent methods and scales	Chemical, molecular, cellular, organ, exposure, safety, and translational evidence	Evaluates consistency without collapsing scale distinctions	Confidence-weighted synthesis	Independence assessment, replication, discrepancy analysis	Double-counting correlated evidence or majority-vote reasoning	Conflicting evidence triggers targeted reassessment	Convergence alone does not establish causality
Uncertainty estimation	Represent confidence, limitations, and alternatives	Evidence grading, model assumptions, sensitivity analyses, missing-data assessment	Controls interpretive strength	Explicit uncertainty profile	Transparent methods and robustness checks	False precision or hidden assumptions	Update uncertainty with new data	No definitive claim under material unresolved uncertainty
Expert review	Subject assumptions and mappings to multidisciplinary scrutiny	Complete evidence package and audit trail	Detects omissions, implausible links, and domain-specific risks	Revised interpretation and validation priorities	Documented review by relevant expertise	Deference to authority or incomplete disciplinary coverage	Review findings return to all prior stages	Expert agreement does not replace validation
Validation planning	Define tests required to strengthen or reject each transition	Gap register, intended use, uncertainty profile	Converts framework synthesis into executable research priorities	Stage-specific validation plan	Appropriate experimental, modeling, or clinical design	Generic validation language without falsifiable tests	Results revise evidence confidence and framework structure	No claim before required validation is completed
Feedback updating	Maintain a living evidence structure	New positive, negative, null, or conflicting results	Prevents static conclusions and supports iterative refinement	Updated evidence and decision map	Version control and transparent change documentation	Selective updating or confirmation bias	Bidirectional feedback to source, molecular, cellular, organ, safety, and clinical layers	Earlier conclusions may be downgraded or withdrawn
No clinical-claim boundary	Prevent unsupported statements of clinical relevance, utility, efficacy, or safety	Full evidence and gap assessment	Applies a final claim-control gate	Bounded scientific conclusion	Claim audit and appropriate review	Implicit clinical promise despite insufficient evidence	Claims revised when boundaries are exceeded	No clinical prediction, utility, or efficacy claim
No therapeutic-claim boundary	Prevent conversion of research prioritization into treatment advice	Intended use statement and evidence-limit summary	Separates research outputs from therapeutic decisions	Non-prescriptive framework output	Editorial and expert claim review	Treatment recommendation inferred from mechanistic evidence	Remove or qualify impermissible language	No treatment recommendation or patient-level decision support

Figure 2 presents the proposed multiscale pharmacology framework for natural product research, integrating molecular features, cellular pathways, organ-level effects, clinical relevance, safety evidence, validation planning, expert review, and feedback updating.

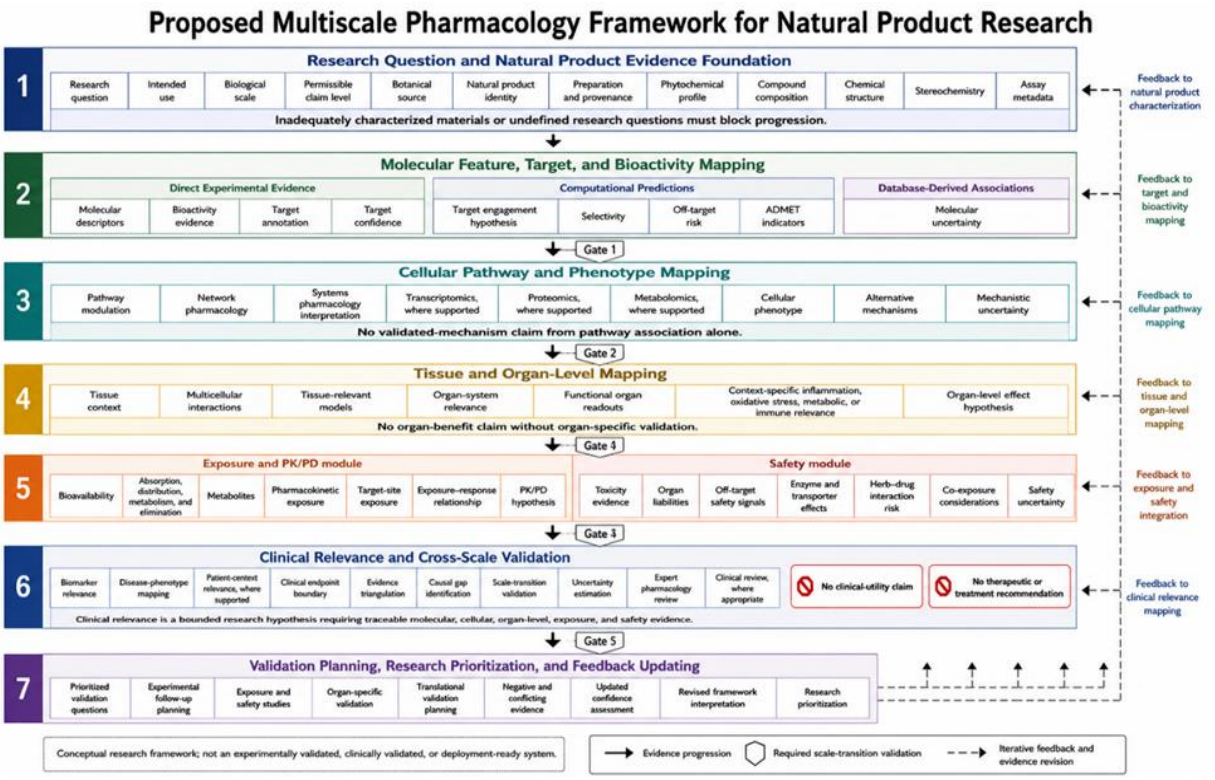

Figure 2. Proposed Multiscale Pharmacology Framework for Natural Product Research

Alt-text description
A conceptual framework showing natural product evidence moving through molecular feature mapping, target and bioactivity evidence, cellular pathways, organ-level effects, exposure and PK/PD logic, safety evidence, clinical relevance mapping, validation planning, expert review, and feedback loops.

CONCLUSION

The proposed multiscale pharmacology framework provides a structured approach for connecting natural product identity and molecular features with target evidence, cellular pathways, tissue context, organ-level effects, exposure, safety, and clinical relevance. Its principal contribution is not the production of a unified efficacy claim, but the preservation of distinctions among evidence scales and the explicit identification of transitions that require validation. Evidence triangulation, uncertainty estimation, expert review, and iterative feedback can strengthen research prioritization when they are applied transparently and when contradictory findings are retained within the evidence structure. Exposure limitations, ADME behavior, toxicity, and herb–drug interaction risks must be considered alongside intended pharmacological effects. Clinical relevance remains a bounded hypothesis until disease-context correspondence, appropriate endpoints, safety, and relevant clinical evidence are established. By embedding no-clinical-claim and no-therapeutic-claim boundaries throughout the workflow, the framework supports responsible mechanistic inquiry and validation planning without presenting cross-scale integration as proof of clinical efficacy, safety, utility, or treatment suitability.

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