Multi-Omics Phytopharmacology: Integrating Metabolomics, Transcriptomics, Proteomics, Microbiome Data, and Pathway Biology for Natural Product Therapeutics

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ABSTRACT

Multi-omics phytopharmacology is emerging as a mechanism-centered strategy for interpreting the biological actions of plant-derived compounds, herbal extracts, natural product mixtures, and phytotherapeutic candidates. Rather than treating metabolite, transcript, protein, microbiome, or pathway signals as isolated evidence, this article develops an original integrative framework that connects compound-level characterization with biological-response evidence and validation-oriented interpretation. The framework positions metabolomics as a bridge between phytochemical exposure, endogenous metabolic response, and pathway perturbation, while transcriptomics is used to evaluate host gene-expression responses, regulatory programs, and pathway involvement. Proteomics adds protein-level evidence that may clarify functional pathway responses beyond transcript abundance, whereas microbiome data support interpretation of microbial metabolism, host–microbiome interactions, and natural product biotransformation. Pathway biology is treated as an interpretive layer rather than as proof of mechanism. The proposed logic emphasizes cross-omics convergence, exposure plausibility, quality control, feature annotation confidence, batch-effect awareness, safety consideration, and causal validation. The framework contributes a structured approach for transforming multi-omics observations into mechanistic hypotheses, validation priorities, and translational research decisions without overstating efficacy or causality. It supports more reproducible, exposure-aware, and biologically disciplined natural product therapeutics research.

Key Words: *Multi-omics, Phytopharmacology, Natural products, Metabolomics, Transcriptomics, Proteomics*

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INTRODUCTION

Natural products continue to provide a major source of pharmacologically relevant chemical diversity, but their therapeutic interpretation increasingly requires methods that can connect chemical identity, biological response, and plausible mechanism rather than relying only on traditional use or single-assay activity. Omics and multi-omics strategies have therefore become important tools for natural product target discovery and mechanism-oriented phytopharmacology because they can help link plant-derived compounds or complex preparations with molecular response patterns [1, 2].

Phytopharmacology is especially suited to systems-level reasoning because plant-derived interventions may contain multiple constituents, partially characterized metabolites, preparation-dependent chemical profiles, and biological

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effects distributed across host pathways. Systems pharmacology approaches in herbal medicine research provide a conceptual basis for interpreting such complexity through networks, pathways, and multi-target response structures rather than through a single-target reductionist model [3].

However, multi-omics evidence does not automatically establish therapeutic mechanism. Mass spectrometry-based metabolomics in herbal medicine has been used to investigate effects, toxicities, and action mechanisms, but the interpretation of metabolic signals still depends on analytical reproducibility, sample context, annotation confidence, and linkage to pharmacological evidence [4].

This article develops an original integrative framework for multi-omics phytopharmacology and natural product therapeutics. The aim is to clarify how metabolomics, transcriptomics, proteomics, microbiome data, and pathway biology can be combined to support mechanism-centered hypothesis generation, exposure-aware interpretation, validation planning, safety consideration, and translational prioritization without presenting pathway enrichment or cross-omics convergence as experimental proof.

Multi-omics logic in phytopharmacology

Multi-omics phytopharmacology can be defined as the structured integration of compound characterization, metabolite profiling, host transcriptomic response, protein-level evidence, microbiome information, and pathway biology to interpret how natural products may influence biological systems. The logic begins with analytical discipline: plant natural product metabolomics requires careful sample preparation, data acquisition, metabolite analysis, and annotation because weak upstream workflows can distort downstream biological interpretation [5].

A second principle is that natural product identity and quality must be treated as part of the mechanism problem. Medicinal plant materials can vary by species, plant part, processing, preparation, extraction, storage, and batch context, and metabolomics-based quality evaluation helps establish whether the tested material is sufficiently characterized for pharmacological interpretation [6].

A third principle is that multi-omics should support hypothesis generation rather than replace validation. Mass spectrometry-driven herbal drug discovery illustrates how metabolite-level evidence may help identify active ingredients, response signatures, and development leads when it is connected to pharmacological context and not interpreted as a stand-alone proof of efficacy [7].

A fourth principle is that target-level interpretation requires orthogonal molecular evidence. Chemical proteomics can contribute to natural medicine research by supporting probe synthesis, target fishing, and protein identification, but target assignment still requires validation-aware interpretation because binding or enrichment alone may not establish functional mechanism [8].

Table 1 summarises the major omics layers and their interpretive roles in multi-omics phytopharmacology.

Table 1. Major Omics Layers in Multi-Omics Phytopharmacology: Metabolomics, Transcriptomics, Proteomics, Microbiome Data, Pathway Biology, Data Outputs, Interpretive Strengths, Limitations, and Validation Needs

Omics layer	Primary data output	Phytopharmacology relevance	Mechanistic interpretation role	Key strength	Main limitation	Validation need	Framework contribution
Compound characterization	Phytochemical profile, chemical fingerprints, quality markers, preparation context	Establishes what natural product material or phytotherapeutic candidate is being interpreted	Links biological response to a defined chemical or preparation context	Improves exposure plausibility and reproducibility	Incomplete annotation or batch variability may weaken interpretation	Orthogonal chemical profiling, quality-marker confirmation, preparation documentation	Provides the starting identity layer for the framework
Metabolomics	Endogenous metabolites, absorbed constituents, metabolic pathway signatures	Connects phytochemical exposure with host metabolic response	Suggests metabolic pathway involvement and response phenotypes	Sensitive to biochemical state and treatment response	Metabolite annotation uncertainty and confounding from diet, tissue, or model context	Targeted metabolite assays, isotope or exposure studies where appropriate	Supports exposure-aware and pathway-oriented interpretation
Transcriptomics	Gene-expression patterns,	Evaluates host biological response to	Suggests transcriptional programs and	Broad coverage of host	Transcript abundance does not	qPCR, perturbation	Provides host-response and

	regulatory signatures, pathway-associated transcripts	natural products or extracts	pathway activation or suppression	response networks	necessarily equal protein function	studies, time-course analysis	regulatory-network evidence
Proteomics	Protein abundance, modified proteins, target-enriched proteins, pathway proteins	Adds protein-level evidence closer to functional biology	Clarifies whether transcript-level signals correspond to protein-level changes	Improves interpretation of functional pathway response	Protein detection coverage and target-capture bias may limit conclusions	Targeted proteomics, immunoblotting, enzyme or binding assays	Strengthens mechanism plausibility and target-validation logic
Microbiome data	Microbial composition, inferred function, microbial metabolites, community shifts	Interprets microbial metabolism, biotransformation, and host–microbiome effects	Helps identify microbiome-mediated mechanisms or confounders	Adds ecological and metabolic context for orally administered natural products	Association does not prove microbial causality	Germ-free, antibiotic, fecal transfer, or microbial perturbation studies	Provides a host–microbiome mediation layer
Pathway biology	Enriched pathways, mapped networks, biological-process modules	Bridges molecular features and pharmacological interpretation	Organizes multi-layer signals into biological hypotheses	Helps compare evidence across omics platforms	Pathway enrichment can reflect database bias or non-causal association	Functional assays and pathway perturbation	Serves as the interpretive map for cross-omics convergence
Cross-omics integration	Shared modules, convergent pathways, network-ranked hypotheses	Combines compound, host, microbial, and pathway evidence	Prioritizes mechanism hypotheses and validation targets	Reduces dependence on a single evidence layer	Integration can amplify bias if inputs are low quality	Independent replication and orthogonal validation	Provides the core synthesis engine of the framework
Translational interpretation	Candidate mechanisms, validation gaps, safety signals, readiness decisions	Connects omics findings to research decision-making	Distinguishes hypothesis support from therapeutic readiness	Supports disciplined prioritization	May overstate clinical relevance if validation is weak	Preclinical, safety, exposure, and clinical-context validation	Converts omics interpretation into research decisions

Metabolomics and transcriptomics integration

Metabolomics and transcriptomics occupy complementary positions in phytopharmacology. Efficacy evaluation, active-ingredient exploration, and multitarget interpretation in herbal medicine require evidence that links chemical constituents, biological responses, and plausible therapeutic mechanisms, while chinmedomics illustrates how metabolomics and serum pharmacochemistry can be used to connect absorbed constituents with efficacy-oriented interpretation [9, 10].

Metabolomics can clarify whether a natural product intervention is associated with endogenous metabolic changes, absorbed constituents, or disease-relevant biochemical responses, whereas transcriptomics can indicate whether host gene-expression programs are consistent with those biochemical changes. Integrated omics analysis of Danggui Buxue Tang and calycosin in osteoblastic differentiation and proliferation illustrates how formula-level and compound-level evidence can be connected to biological response interpretation when omics signals are evaluated within a defined experimental context [11].

Biofluid metabolomics can be especially useful for capturing systemic response patterns, although it should be interpreted as pathway-suggestive rather than mechanism-confirming. Urinary metabolomics applied to Si-Miao-Yong-An-Tang in a thromboangiitis obliterans model supports the idea that metabolic signatures can help identify candidate pathways associated with phytotherapeutic response, provided that biological interpretation remains anchored to the model and validation context [12].

Transcriptomics contributes a host-response layer by identifying gene-expression changes, immune or inflammatory pathway involvement, and regulatory networks that may be affected by herbal interventions. Integration of transcriptomics and system pharmacology in Qingfei Xiaoyan Wan research supports transcriptome-informed interpretation of allergic asthma-related pathways, while comparative transcriptomics and network pharmacology analysis of celastrol illustrates how phytochemical mechanisms can be prioritized through gene-expression and network evidence [13]. Such prioritization remains hypothesis-generating and requires causal testing before target or pathway claims are treated as validated mechanisms [14].

Table 2 maps how metabolomics and transcriptomics can be integrated to interpret phytochemical exposure, host response, and pathway-level mechanisms.

Table 2. Integrating Metabolomics and Transcriptomics in Phytopharmacology: Compound Exposure, Metabolic Signatures, Gene-Expression Responses, Pathway Mapping, Mechanistic Hypothesis Generation, and Interpretation Risks

Integration dimension	Metabolomics contribution	Transcriptomics contribution	Combined mechanistic value	Typical interpretation risk	Quality-control requirement	Validation requirement	Research implication
Compound exposure	Detects absorbed constituents, metabolites, or chemical-response signatures	Identifies host response potentially associated with exposure	Links chemical plausibility with biological response	Assuming all profiled constituents reach relevant tissues	Chemical annotation confidence and exposure-context documentation	Serum or tissue exposure confirmation where feasible	Encourages exposure-aware study design
Metabolic response	Captures endogenous metabolic shifts after intervention	Identifies genes related to metabolic regulation	Connects biochemical phenotype to regulatory response	Treating metabolic association as causal mechanism	Sample timing, matrix control, normalization, and annotation rigor	Targeted metabolite confirmation and pathway assays	Supports metabolic mechanism hypotheses
Host pathway response	Indicates pathway-associated metabolite changes	Indicates pathway-associated transcript changes	Provides cross-layer pathway convergence	Overinterpreting pathway enrichment	Consistent pathway mapping across platforms	Functional perturbation of candidate pathway	Improves pathway prioritization
Active constituent interpretation	Helps distinguish compound markers from response metabolites	Shows whether host programs respond in biologically relevant directions	Helps connect constituent evidence with host biology	Confusing marker presence with bioactivity	Chemical profiling and batch documentation	Compound-level testing and dose-relevance assessment	Supports candidate ranking
Disease-context interpretation	Captures disease- or model-associated biochemical correction patterns	Captures disease- or model-associated transcriptional response	Suggests disease-relevant biological modules	Assuming model reversal equals clinical benefit	Matched controls, model relevance, and replication	Disease-relevant functional assays	Encourages translational caution
Time-course reasoning	Reveals dynamic metabolic changes	Reveals early or late gene-expression patterns	Helps separate upstream response from downstream adaptation	Misaligning sampling times across omics layers	Harmonized sampling design	Time-course validation	Supports temporal mechanism mapping
Network interpretation	Provides metabolite nodes and biochemical edges	Provides gene nodes and regulatory modules	Enables metabolite–gene–pathway networks	Network density and database bias	Transparent network construction and edge confidence	Node perturbation or targeted validation	Improves interpretable network hypotheses
Safety-sensitive interpretation	Captures metabolic disturbance or toxicity-	Captures stress, inflammatory, or detoxification gene programs	Helps flag potential safety concerns	Treating adaptive stress as therapeutic effect	Inclusion of toxicity-relevant controls	Safety assays and dose-response evaluation	Integrates benefit-risk awareness

	associated signatures

Proteomics, microbiome data, and pathway biology

Proteomics adds an evidence layer that is closer to functional biology than transcript abundance alone, especially when protein-level changes are aligned with metabolite shifts. Multi-omics analysis of brain tissue metabolome and proteome in a rat ischemic stroke model treated with gross saponins of Tribulus terrestris fruit supports the value of metabolome–proteome integration for identifying convergent response pathways in natural product research [15]. Proteomic analysis of sodium tanshinone IIA sulfonate in cerebral ischemic stroke further illustrates how protein-level response signals may contribute to pathway-level interpretation in phytochemical pharmacology [16].

Microbiome data are particularly important for orally administered natural products, herbal formulas, dietary phytochemicals, and compounds subject to microbial transformation. Multi-omics assessment of Zhen-Wu-Bu-Qi Decoction in chronic colitis supports the relevance of connecting host responses with microbial signals when interpreting gut inflammation and phytotherapeutic mechanisms [17].

Microbiome interpretation must remain cautious because microbial community shifts, inferred function, and host response can be associated without establishing directionality or causality. The literature on microbiota–natural product interactions and phytochemical–colonic microbiota interplay supports the concept that natural products and microbial communities can influence each other through biotransformation, ecological response, and host-mediated effects [18, 19].

Microbiome–metabolomics integration can strengthen interpretation when microbial shifts are connected to metabolite-level evidence, but it still requires validation to distinguish correlation from mediation. Comparative microbiome–metabolomics analysis of metabolites from Wolfiporia cocos in mice supports the framework idea that microbial and metabolic layers can be integrated to interpret gut ecological responses to natural product-derived metabolites [20].

Table 3 summarises the contribution of proteomics, microbiome data, and pathway biology to cross-layer interpretation of natural product mechanisms.

Table 3. Proteomics, Microbiome Data, and Pathway Biology in Multi-Omics Phytopharmacology: Protein-Level Responses, Microbial Mediation, Pathway Enrichment, Host–Microbiome Interactions, Mechanistic Convergence, and Validation Priorities

Evidence layer	Primary biological signal	Natural product relevance	Pathway interpretation role	Host or microbiome contribution	Main uncertainty source	Validation priority	Framework relevance
Global proteomics	Protein abundance or protein-response patterns	Evaluates whether natural products affect functional molecular layers	Maps protein changes to biological processes and pathways	Host protein response	Coverage limitations and tissue specificity	Targeted proteomics or immunoblotting	Adds protein-level support to mechanism hypotheses
Chemical proteomics	Target-enriched proteins or binding-associated candidates	Helps identify candidate protein targets of natural products	Connects compound interaction evidence to target pathways	Host target identification	Probe bias, non-specific binding, and functional uncertainty	Binding validation and functional target assays	Supports validation-aware target discovery
Metabolome–proteome integration	Concordant metabolite and protein pathway signals	Links biochemical state with protein regulation	Strengthens pathway-level convergence	Host metabolic and protein response	Platform normalization and pathway mapping complexity	Enzyme, pathway, and perturbation assays	Provides biochemical mechanism convergence
Microbiome composition	Microbial community structure	Interprets ecological response to orally administered natural products	Suggests microbial involvement in response patterns	Microbiome contribution	Compositional bias and confounding	Microbial perturbation or longitudinal sampling	Adds ecological context

Microbiome function	Predicted or measured microbial functional potential	Supports interpretation of biotransformation and microbial metabolism	Links microbial functions to host-relevant pathways	Microbiome metabolic contribution	Inferred function may not equal activity	Metagenomic, metatranscriptomic, or metabolite confirmation	Supports microbiome-mediated mechanism hypotheses
Microbiome–metabolomics	Microbe–metabolite associations	Connects natural product-derived metabolites with gut ecological response	Maps microbial metabolism to host or luminal metabolites	Host–microbiome interface	Correlation mistaken for mediation	Germ-free, antibiotic, fecal transfer, or isotope studies	Strengthens mediation-focused hypotheses
Pathway enrichment	Enriched biological processes or pathway modules	Organizes multi-layer natural product response evidence	Provides interpretable biological maps	Host and microbiome signals can both contribute	Database bias and non-causal enrichment	Functional pathway perturbation	Provides interpretive structure
Cross-layer pathway biology	Convergent pathway signals across proteins, metabolites, microbes, and transcripts	Prioritizes mechanisms for natural product research	Identifies coherent biological modules	Integrated host–microbiome response	False convergence from biased annotations	Orthogonal validation and replication	Serves as the bridge to mechanistic interpretation

Cross-omics mechanistic interpretation

Cross-omics mechanistic interpretation should be understood as evidence triangulation rather than confirmation. In natural product therapeutics research, joint analysis of multiple molecular layers can identify convergent biological themes, but the strength of interpretation depends on whether metabolite, transcript, protein, microbial, and pathway signals point toward a coherent and biologically plausible mechanism. Multi-omics joint analysis of *Marsdenia tenacissima* in hepatocellular carcinoma research supports this convergence logic by showing how multiple omics layers can be used to generate mechanism-centered hypotheses in a defined disease context [21].

Network-supported integration can further help organize cross-layer evidence, especially when phytotherapeutic effects are expected to involve immune, inflammatory, metabolic, or stress-response modules rather than a single linear target. A combined multi-omics and network pharmacology approach applied to *Tripterygium wilfordii* Hook F in HIV immunological non-responders supports the idea that integrated omics and network logic may prioritize immune-related mechanisms, although such prioritization remains dependent on validation and disease-context interpretation [22].

Cross-omics convergence can also be useful when the biological outcome is complex, such as neurobehavioral response, inflammatory remodeling, or metabolic adaptation. Multi-omics investigation of the low-polarity fraction of *Bupleuri Radix* in antidepressant-like research illustrates how convergent molecular signals can suggest pathway involvement and mechanism hypotheses, but these signals should not be interpreted as direct proof of clinical benefit or causal efficacy [23].

The most defensible interpretation arises when cross-layer evidence is connected to model relevance, exposure plausibility, and validation planning. Integration of transcriptomics, proteomics, metabolomics, and systems pharmacology in Bufei Yishen formula research supports the principle that host multi-omics can strengthen mechanistic interpretation when several molecular layers converge [24]. Long-term profiling of Bufei Jianpi formula further indicates that temporal and systems-level context can help distinguish sustained therapeutic-response hypotheses from isolated molecular observations [25]. Multiomics analysis of geniposide hepatoprotection supports the additional caution that candidate causal nodes identified through cross-layer analysis still require experimental validation before they are treated as confirmed mechanisms [26].

Figure 1 illustrates how metabolomics, transcriptomics, proteomics, microbiome data, and pathway biology can be integrated to support cross-omics mechanistic interpretation in phytopharmacology.

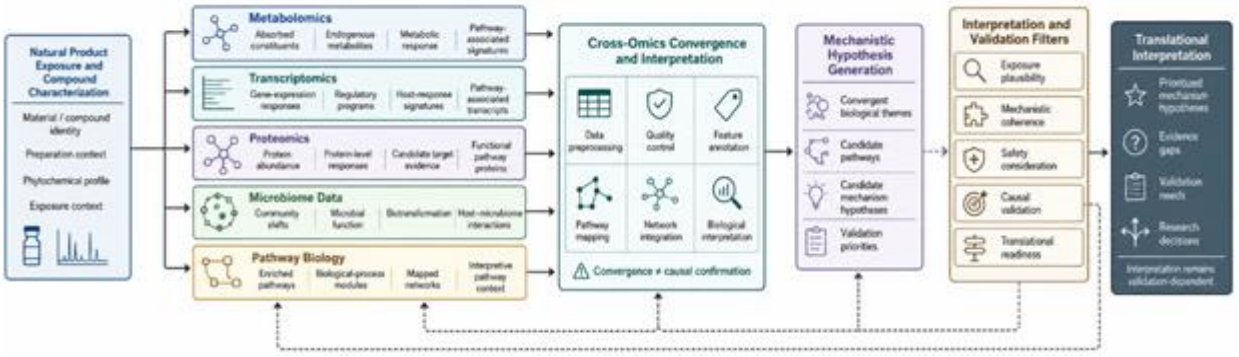

Figure 1. Cross-Omics Mechanistic Interpretation in Multi-Omics Phytopharmacology

Alt-text description

A conceptual diagram showing natural product exposure connected to five evidence layers: metabolomics, transcriptomics, proteomics, microbiome data, and pathway biology. These layers converge through data integration, pathway mapping, biological interpretation, exposure plausibility, validation, and translational readiness filters.

Proposed integrative framework

The proposed framework begins with natural product identity and compound characterization. This stage requires attention to botanical or natural source, preparation context, processing, extraction, chemical profile, and the distinction between crude material, processed material, formula, fraction, and isolated component. Multi-omics analysis of components from crude and salt-processed *Achyranthes bidentata* Blume supports the importance of distinguishing component-level and processing-aware evidence before interpreting anti-osteoporosis mechanisms [27].

The second stage is omics evidence generation, in which metabolomics, transcriptomics, proteomics, microbiome profiling, and pathway biology are selected according to the biological question rather than used as decorative data layers. Systems biology analysis of total flavonoids from *Astragali Radix* in cyclophosphamide-induced leucopenia supports the framework principle that pathway-centered evidence can help connect phytochemical intervention with hematopoietic or immune-response hypotheses [28].

The third stage is quality-controlled integration. Before cross-omics interpretation, the framework requires feature annotation confidence, batch-effect awareness, data normalization, model-context documentation, and transparent mapping of features to pathways or networks. A thrombin-based discovery strategy using metabolomics and chemometrics for pollen of *Typha orientalis* supports the need to connect chemical quality markers with bioactivity-oriented interpretation before advancing mechanistic claims [29].

The fourth stage is interpretation through pathway biology, exposure plausibility, safety consideration, and validation need. Multi-omics analysis of processed *Radix Clematidis* in rheumatoid arthritis research supports the framework concept that processing may modify both composition and biological response, making preparation context central to mechanistic interpretation [30]. Mass spectrometry-based multi-omics analysis of herbal medicine in a yeast-induced fever model further supports the idea that pathway-level interpretation can connect herbal response with inflammatory or thermoregulatory biology when model limitations are acknowledged [31].

The fifth stage is translational readiness, where cross-omics convergence is converted into research decisions rather than therapeutic claims. Mass spectrometry-based metabolomics in herbal medicine research supports the use of active-ingredient and pharmacodynamic assessment as part of a translational evidence chain [32]. Chemical proteomics for natural product target discovery supports the complementary need for target-identification strategies that remain validation-aware and functionally testable [33].

Table 4 presents the proposed integrative framework for multi-omics phytopharmacology and natural product therapeutics.

Table 4. Proposed Integrative Framework for Multi-Omics Phytopharmacology: Compound Characterization, Omics Layer Integration, Pathway Biology, Cross-Omics Convergence, Exposure Plausibility, Validation Requirements, Translational Readiness, and Research Decision Points

Framework stage	Core question	Required evidence	Omics layers involved	Integration method	High-confidence signal	Caution or failure risk	Recommended validation step

Natural product identity	What material or compound is being interpreted?	Source identity, preparation context, processing, batch information, chemical profile	Compound characterization, metabolomics	Chemical fingerprinting, quality-marker mapping, annotation review	Defined preparation linked to reproducible chemical profile	Vague extract identity or uncharacterized mixture	Orthogonal chemical profiling and preparation documentation
Compound characterization	Which constituents or markers are plausible contributors?	Annotated constituents, absorbed compounds where available, marker compounds	Metabolomics, serum or tissue chemistry	Feature annotation, chemometric comparison, exposure mapping	Plausible constituent-response link	Treating marker presence as proof of bioactivity	Targeted compound confirmation and exposure assessment
Omics evidence generation	Which biological layers respond to the intervention?	Metabolite, transcript, protein, microbial, and pathway signals	Metabolomics, transcriptomics, proteomics, microbiome data	Platform-specific preprocessing and quality control	Reproducible response pattern within model context	Inconsistent sampling, weak QC, or underpowered design	Replication and transparent reporting
Cross-omics integration	Do different layers converge on coherent biological modules?	Matched features across pathways, networks, or biological processes	All relevant omics layers	Pathway mapping, network integration, module analysis	Concordant signals across independent evidence layers	False convergence from database bias or annotation uncertainty	Orthogonal pathway and target validation
Pathway biology interpretation	Which pathways are plausible mechanistic candidates?	Enriched pathways, biological-process modules, known disease relevance	Transcriptomics, proteomics, metabolomics, microbiome function	Pathway enrichment and biological curation	Pathway signal aligned with disease model and exposure	Treating enrichment as mechanism proof	Functional perturbation or pathway-specific assay
Exposure plausibility	Can the proposed mechanism occur at plausible exposure?	Absorbed constituents, metabolite evidence, dose relevance, tissue context	Metabolomics, pharmacochemical profiling	Exposure-response linkage	Mechanism linked to detected or plausible bioactive exposure	Assuming all formula constituents reach targets	Serum, tissue, or cellular exposure confirmation
Microbiome mediation	Could microbial metabolism or host–microbiome interaction contribute?	Microbial composition, function, metabolites, host response	Microbiome data, metabolomics, transcriptomics	Microbe–metabolite–host mapping	Microbial and metabolic evidence aligned with host biology	Inferring causality from association	Microbial perturbation, longitudinal sampling, or transfer studies
Safety and toxicity filtering	Are omics signals consistent with benefit, stress, or possible harm?	Toxicity-relevant metabolic, transcript, protein, or microbial signals	Metabolomics, transcriptomics, proteomics, microbiome data	Safety-oriented pathway review	Benefit hypothesis not contradicted by strong stress/toxicity signals	Mistaking stress adaptation for therapeutic mechanism	Safety profiling and dose-response assessment
Validation planning	Which hypotheses should be tested first?	Ranked mechanisms, target candidates, pathway modules, uncertainty map	Cross-omics synthesis	Evidence weighting and validation prioritization	Testable mechanism with exposure and pathway support	Overprioritizing visually dense networks	Targeted assays, perturbation, rescue, or model-relevant testing

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Translational readiness	Is the evidence suitable for further therapeutic development research?	Mechanistic coherence, reproducibility, exposure plausibility, safety profile, validation evidence	Integrated framework output	Readiness assessment and research decision mapping	Mechanism-supported hypothesis with clear evidence gaps	Presenting conceptual convergence as clinical readiness	Preclinical confirmation, safety testing, and clinically relevant model evaluation

Figure 2 presents the proposed integrative framework for using multi-omics evidence to support natural product therapeutics research.

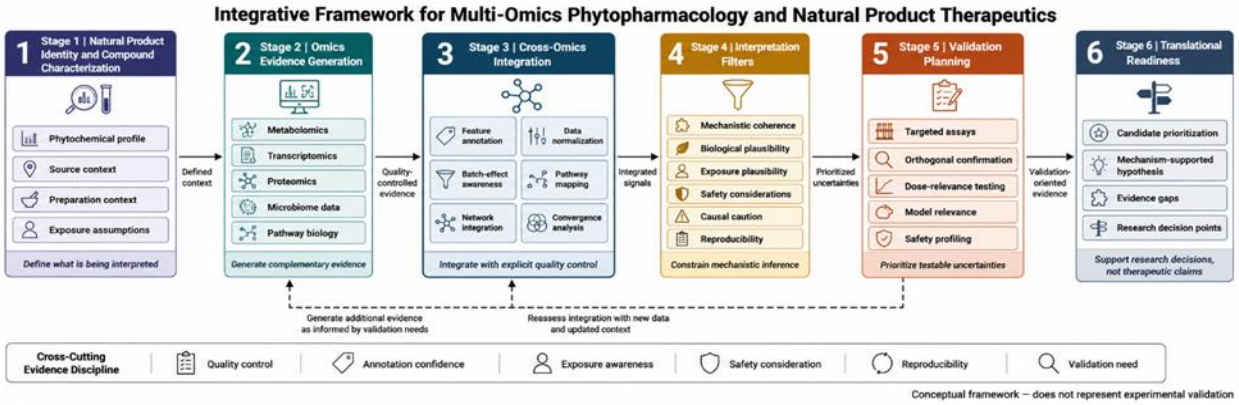

Figure 2. Integrative Framework for Multi-Omics Phytopharmacology and Natural Product Therapeutics

Alt-text description

A framework diagram showing natural product identity and compound characterization feeding into omics evidence generation. Metabolomics, transcriptomics, proteomics, microbiome data, and pathway biology are integrated through cross-omics analysis, mechanistic convergence, exposure plausibility, safety filtering, validation planning, and translational readiness assessment.

Research implications

The framework implies that phytopharmacology studies should be designed around coherent evidence chains rather than around isolated omics outputs. Recent discussion of multi-omics applications in traditional medicine supports the need for standardized workflows that connect composition, quality control, mechanism interpretation, and biological validation in a transparent research structure [34].

For natural product discovery, the framework encourages researchers to move from descriptive molecular signatures toward exposure-aware, pathway-informed, and validation-ready hypotheses. Multi-omics and network pharmacology research in vascular cognitive impairment highlights the importance of disease-context mapping, but it also reinforces the need to avoid treating network proximity or pathway overlap as validated pharmacological mechanism [35].

Future research should prioritize standardized reporting, cross-platform validation, causal microbiome studies, exposure-aware omics, safety profiling, and model systems that reflect translational decision needs. Omic-based approaches to traditional medicine support the broader direction of using integrated molecular evidence to decipher complex interventions, but reproducibility, interpretability, and validation discipline remain essential for responsible therapeutic research [36].

CONCLUSION

Multi-omics phytopharmacology can strengthen natural product therapeutics research when metabolomics, transcriptomics, proteomics, microbiome data, and pathway biology are integrated through a disciplined interpretive framework. The framework proposed here links natural product identity, compound characterization, omics evidence generation, pathway mapping, cross-omics convergence, exposure plausibility, safety consideration, validation planning, and translational readiness. Its central contribution is not to claim that multi-omics evidence proves efficacy or mechanism, but to provide a structured way to transform molecular observations into testable, biologically plausible, and research-ready mechanistic

hypotheses. Used carefully, this approach can help reduce overclaiming, improve reproducibility, and support more rigorous development of natural product therapeutics.

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