Network Pharmacology of Herbal Medicines: An Integrative Review of Multi-Compound, Multi-Target, and Pathway-Level Therapeutic Discovery

Kenji Tanaka[1]*, Yui Kobayashi[1], Takeshi Nakamura[2]

[1]Department of Artificial Intelligence for Natural Product Biosynthesis, Graduate School of Pharmaceutical Sciences, University of Tokyo, Tokyo, Japan.
[2]Department of Chemoinformatics and Virtual Screening, Graduate School of Pharmacy, Kyoto University, Kyoto, Japan.

ABSTRACT

Network pharmacology has become a prominent systems-oriented approach for studying herbal medicines, medicinal plants, botanical preparations, traditional formulations, phytochemicals, and natural-product-derived compounds as chemically complex therapeutic systems. This integrative review examines how network pharmacology is used to organize herbal multi-component composition into candidate-compound profiles, putative target relationships, disease-associated gene intersections, protein interaction networks, pathway-level hypotheses, and validation-oriented research priorities. The review integrates conceptual, methodological, empirical, and critical literature rather than claiming systematic completeness or pooled effect estimation. It focuses on how compound annotation, target prediction, disease-network mapping, protein–protein interaction analysis, pathway enrichment, and multi-layer interpretation contribute to multi-target discovery and therapeutic mechanism hypothesis generation. The synthesis emphasizes that herbal complexity provides a rationale for network-level analysis, but does not by itself establish pharmacological activity, therapeutic synergy, causal mechanism, or clinical effectiveness. Across the reviewed literature, network pharmacology offers strengths in evidence organization, target prioritization, disease-module exploration, pathway-level interpretation, and experimental planning. However, recurrent weaknesses include database dependency, annotation bias, uncertain target prediction, popular-target and degree bias, limited exposure context, insufficient tissue specificity, pathway redundancy, workflow opacity, and overinterpretation of computational convergence. The review argues that more reliable herbal network pharmacology requires evidence-weighted compound characterization, transparent database provenance, uncertainty-aware target inference, context-specific disease mapping, orthogonal experimental validation, pharmacokinetic plausibility, reproducible computational workflows, and translation-oriented interpretation. Network pharmacology should therefore be understood as a hypothesis-prioritization framework that can guide mechanistic research, not as an independent substitute for experimental or clinical evidence.

Key Words: *Network pharmacology, Herbal medicine, Multi-compound therapeutics, Multi-target pharmacology, Compound–target networks, Pathway analysis*

eIJPPR 2025; 15(1):24-35

HOW TO CITE THIS ARTICLE: Tanaka K, Kobayashi Y, Nakamura T. Network Pharmacology of Herbal Medicines: An Integrative Review of Multi-Compound, Multi-Target, and Pathway-Level Therapeutic Discovery. Int J Pharm Phytopharmacol Res. 2025;15(1):24-35. https://doi.org/10.51847/4DYxCDITMl

INTRODUCTION

Network pharmacology has been increasingly applied to herbal medicines because it offers a systems-oriented way to organize relationships among chemically diverse constituents, putative molecular targets, disease-associated genes, protein interaction networks, and biological pathways. In this context, the value of network pharmacology lies not in replacing experimental pharmacology, but in arranging heterogeneous information

Corresponding author: Kenji Tanaka
Address: Department of Artificial Intelligence for Natural Product Biosynthesis, Graduate School of Pharmaceutical Sciences, University of Tokyo, Tokyo, Japan.
E-mail: ✉ tanaka.kenji@mol.f.u-tokyo.ac.jp
Received: 19 November 2024; **Revised:** 25 Janaury 2025; **Accepted:** 28 January 2025

into testable compound–target–pathway hypotheses. This is especially relevant for herbal medicines and natural products, where multiple constituents may be present simultaneously and where biological interpretation often requires moving beyond a single compound or single target model [1].

Systems pharmacology provides a broader conceptual foundation for this approach by treating herbal medicines as multi-component interventions whose effects may involve distributed molecular and pathway-level relationships. Conventional one-drug–one-target models can be useful for isolated molecules, but they are often insufficient for representing chemically diverse extracts, multi-herb formulations, polypharmacological interactions, and context-dependent biological responses. Systems pharmacology therefore supports a structured way to ask whether specific compounds, targets, and pathways plausibly contribute to a therapeutic hypothesis, while still requiring independent evidence for biological relevance [2].

The central conceptual problem is that herbal complexity may justify network-level analysis, but complexity alone does not validate predicted interactions, mechanisms, or therapeutic claims. Medicinal-plant network pharmacology depends on compound databases, target-prediction tools, disease-gene resources, pathway annotations, and analytical decisions that can shape the resulting network. These dependencies make network pharmacology useful for prioritization, but they also create risks of false-positive targets, incomplete chemical representation, pathway overinterpretation, and weak reproducibility when workflows are not transparently reported [3].

The field has therefore moved toward integrated workflows that combine constituent identification, candidate-compound filtering, target prediction, disease-associated gene retrieval, protein interaction analysis, pathway enrichment, and biological interpretation. Such workflows can help generate mechanistic hypotheses and identify candidate targets or pathways for experimental testing, but their outputs remain inferential until supported by orthogonal evidence. This review aims to integrate conceptual foundations, analytical workflows, disease-mapping strategies, methodological strengths, methodological weaknesses, validation practices, and future priorities in herbal network pharmacology [4]. Recent critical evaluation of herbal network pharmacology reinforces the need to distinguish mechanism identification from mechanism confirmation, particularly when predicted targets and pathway enrichment are used to support therapeutic-effect claims [5].

Herbal medicines as multi-component therapeutics

Herbal medicines are commonly represented as multi-component therapeutic systems because their chemical profiles may include diverse classes of constituents, variable abundance patterns, metabolite mixtures, processing-dependent changes, and formulation-level interactions. Network pharmacology is attractive in this setting because it can represent herbs, compounds, targets, diseases, and pathways as linked analytical layers rather than isolated observations. This representation is especially relevant when a botanical preparation or multi-herb formula cannot be adequately reduced to a single marker compound without losing important chemical and biological context [6].

However, multi-component composition should not be treated as automatic evidence of multi-target efficacy, therapeutic synergy, or systems-level benefit. A herb may contain many annotated constituents, but only a subset may be chemically reliable, bioavailable, metabolically relevant, or present at concentrations capable of biological activity. Personalized or precision-oriented interpretations of herbal medicine are therefore conceptually appealing, yet they remain inferential unless compound identity, exposure, target relevance, disease context, and biological response are evaluated together [7].

The conceptual relationship among multi-component composition, multi-target action, polypharmacology, synergy, additivity, antagonism, and network effects requires careful separation. Multiple predicted targets do not necessarily demonstrate polypharmacology, and shared targets among several compounds do not prove synergy. Artificial-intelligence-supported approaches may expand compound annotation, target prediction, and pattern recognition in herbal medicine research, but these tools also require transparent training data, uncertainty reporting, and validation against independent biological evidence [8].

For herbal network pharmacology to be therapeutically meaningful, chemical complexity must be translated into analytically defensible evidence. This includes botanical authentication, compound identification, quality control, concentration context, extraction dependence, batch reproducibility, bioavailability, metabolism, and pharmacokinetic plausibility. Network models can then help prioritize candidate compounds, target classes, disease modules, and pathways, but they cannot independently establish whether a constituent reaches a relevant site of action or modulates a pathway in vivo. Precision-oriented network pharmacology is therefore strongest when it treats network outputs as testable hypotheses rather than confirmed mechanisms [9]. **Table 1** summarises the major conceptual features that distinguish herbal medicines as multi-component therapeutic systems and links these features to

corresponding network pharmacology questions, analytical requirements, and interpretation risks.

Table 1. Herbal Medicines as Multi-Component Therapeutic Systems: Sources of Chemical Complexity, Multi-Target Features, Network Pharmacology Questions, Analytical Requirements, Therapeutic Interpretation, Validation Needs, and Risks of Overclaiming

Herbal-system feature	Underlying source of complexity	Network pharmacology question	Relevant analytical representation	Potential therapeutic interpretation	Validation requirement	Major uncertainty	Risk of overclaiming
Chemically diverse botanical extract	Multiple constituent classes, variable abundance, extraction-dependent recovery	Which annotated compounds are plausible contributors to activity?	Herb–compound network; compound-prioritization layer	Candidate compounds may provide a starting point for mechanistic exploration	Chemical profiling, quality control, exposure assessment	Detected constituents may not be bioavailable or active	Treating all detected compounds as pharmacologically relevant
Multi-herb formulation	Multiple botanical inputs, preparation rules, processing effects	How do compounds from different herbs converge or diverge across targets?	Herb–compound–target network	Distributed targeting may be hypothesized across formula components	Batch reproducibility, constituent quantification, formulation standardization	Formula composition may vary across sources and preparations	Inferring formula-level synergy from network overlap alone
Phytochemical mixture	Shared scaffolds, related metabolites, unknown minor constituents	Which compound classes map to putative targets or pathways?	Compound-class–target map; chemical similarity layer	Related compounds may support target prioritization	Target assays and metabolite-aware testing	Similarity does not guarantee shared activity	Assuming structurally related compounds have equivalent effects
Multi-target prediction	Known and predicted compound–protein relationships	Which predicted targets are most plausible for follow-up?	Bipartite compound–target network	Multiple targets may indicate polypharmacological potential	Orthogonal target validation and negative controls	Prediction confidence varies by algorithm and data coverage	Treating predicted targets as validated pharmacological targets
Disease-network intersection	Overlap between predicted targets and disease-associated genes	Which disease-relevant nodes or modules intersect with herbal target sets?	Target–disease network; PPI module	Disease mapping may guide mechanism hypotheses	Disease-context validation, tissue relevance, perturbation studies	Disease-gene annotations may be broad or context-insensitive	Treating database overlap as proof of therapeutic mechanism
Pathway enrichment	Functional annotation of target or disease-intersection lists	Which biological processes are overrepresented in the mapped target set?	Target–pathway network; enrichment map	Pathways may identify plausible biological themes	Experimental measurement of pathway modulation	Enrichment may reflect annotation bias or redundant pathways	Treating enrichment as demonstrated pathway regulation
Putative polypharmacology	Several compounds linked to multiple targets or pathways	Are distributed target relationships biologically coherent?	Multi-layer compound–target–pathway network	Network convergence may prioritize testable hypotheses	Combined compound testing and perturbation analysis	Connectivity may arise from shared database bias	Claiming synergy or systems-level efficacy without functional evidence
Translational plausibility	Exposure, dose,	Can network-prioritized	Evidence-weighted	Mechanistic hypotheses may be	Pharmacokinetic, safety, and	Network models often	Assuming computational

	metabolism, safety, and formulation consistency	compounds and targets be linked to realistic biological exposure?	translational assessment layer	ranked by plausibility	clinical-context evaluation	omit dose and exposure	plausibility equals clinical relevance

Integrative review approach

This article uses an integrative review approach to bring together heterogeneous conceptual, methodological, empirical, and validation-oriented literature relevant to herbal network pharmacology. The purpose is not to estimate pooled effects or to claim exhaustive systematic retrieval, but to synthesize how different bodies of evidence define the field, structure analytical workflows, support disease-mechanism hypotheses, reveal methodological weaknesses, and guide future research. Integrative review methodology is appropriate when a field contains diverse study designs and when the aim is to compare concepts, methods, assumptions, and evidence patterns rather than calculate a summary effect [10].

The conceptual boundaries of the review include network pharmacology, systems pharmacology, network medicine, herbal medicines, medicinal plants, traditional formulas, phytochemicals, compound–target relationships, disease-gene mapping, protein interaction networks, pathway enrichment, polypharmacology, validation, and translational assessment. Relevant literature was identified through scholarly database searching using combinations of terms related to network pharmacology, herbal medicine, medicinal plants, phytochemicals, systems pharmacology, compound–target networks, disease mechanisms, pathway enrichment, molecular docking, omics, validation, reproducibility, limitations, database bias, and translational challenges. Eligibility focused on peer-reviewed journal articles with DOI information that could support a specific conceptual, methodological, empirical, validation-related, or critical claim. Integrative review conduct requires transparent eligibility logic, evidence extraction, categorization, and synthesis so that the reader can see how heterogeneous evidence is compared [11].

Evidence extraction emphasized study type, herbal or phytochemical context, disease context, network pharmacology strategy, compound identification, target identification, network representation, pathway or functional analysis, complementary computational methods, experimental validation, main claimed contribution, evidence actually demonstrated, methodological strength, methodological weakness, risk of overclaiming, translational relevance, and research gaps. The critical comparison focused on whether studies distinguished compound occurrence from compound activity, predicted target from validated target, disease-gene association from mechanism, PPI centrality from causal importance, pathway enrichment from demonstrated pathway modulation, and computational convergence from biological confirmation. This approach also supports explicit limitation statements because an integrative review should avoid implying systematic-review completeness when the design is intended for interpretive synthesis across diverse evidence types [12].

The synthesis was organized around recurring analytical architectures rather than a disease-by-disease catalogue. It compared how studies move from herbal composition to candidate compounds, from candidate compounds to target inference, from target sets to disease networks, from disease networks to pathway interpretation, and from pathway interpretation to experimental or translational evaluation. Areas of convergence were treated as stronger only when they were supported by complementary evidence layers rather than repeated database overlap. Conversely, apparent convergence was interpreted cautiously when it could have arisen from shared databases, popular targets, broad pathway annotations, or circular reuse of evidence sources.

Compound–target–pathway networks

The core workflow of herbal network pharmacology usually begins with compound identification or annotation, followed by candidate-compound filtering, target prediction or known-target retrieval, network construction, disease-gene intersection, protein interaction analysis, pathway enrichment, and therapeutic mechanism hypothesis generation. Specialized TCM and herbal medicine resources have supported this workflow by organizing relationships among preparations, herbs, compounds, targets, diseases, and pathways into searchable analytical systems [13]. At the same time, database choice can influence which constituents and targets enter the analysis, meaning that compound–target–pathway networks partly reflect the structure, completeness, and assumptions of the underlying resources [14].

Curated herbal medicine databases can improve standardization by linking herbs, ingredients, targets, functions, and disease information in formats that support network construction. Such resources are useful because they reduce fragmentation across chemical, biological, and

traditional-medicine knowledge sources, but they do not remove the need to evaluate evidence provenance, update frequency, and biological relevance [15]. Experiment- and reference-guided resources can further improve traceability by connecting herb–target relationships to supporting evidence, although literature-derived resources may still reflect publication bias, uneven research attention, and incomplete negative evidence [16].

Target inference is one of the most consequential and uncertain steps in compound–target–pathway network construction. Enhanced TCM interaction databases can provide known and predicted ingredient–target associations, allowing researchers to construct larger and more connected networks, but predicted interactions should be weighted differently from experimentally supported interactions [17]. Ligand-based target-prediction tools can also generate candidate protein targets for small molecules, including phytochemical-like structures, yet such predictions are best interpreted as target-generation hypotheses rather than evidence of binding or biological modulation [18].

Target fishing and reverse pharmacophore mapping provide another route for identifying putative targets of herbal compounds or natural-product-derived molecules. These methods can be useful when direct target evidence is sparse, but their outputs depend on molecular representation, reference pharmacophore coverage, similarity assumptions, and scoring rules. A pharmacophore-derived target match may justify experimental follow-up, but it does not establish target engagement, functional effect, pathway modulation, or disease relevance without additional evidence [19].

Network representations in this field include herb–compound networks, compound–target networks, target–disease networks, compound–target–disease networks, protein interaction networks, compound–target–pathway networks, and multi-layer networks. Their analytical value lies in organizing complex relationships and prioritizing candidate compounds, targets, modules, and pathways for follow-up. Interpretation becomes weaker when degree, betweenness, closeness, hub status, module membership, or network proximity are treated as causal evidence rather than prioritization metrics. A high-degree node may be well annotated, broadly studied, or technically central in a database-derived network, but centrality does not by itself prove pharmacological relevance. **Table 2** compares the principal analytical layers used to construct and interpret compound–target–pathway networks in herbal medicine research.

Table 2. Analytical Architecture of Compound–Target–Pathway Networks in Herbal Medicine Research: Inputs, Network Representations, Computational Objectives, Biological Outputs, Validation Requirements, Methodological Limitations, and Interpretive Safeguards

Analytical layer	Typical input	Network representation	Primary computational objective	Typical output	Biological interpretation	Validation requirement	Main methodological weakness	Interpretive safeguard
Herbal constituent annotation	Chemical profiles, literature reports, curated herb databases	Herb–compound network	Define candidate chemical space	List of annotated constituents and herb–compound links	Establishes possible chemical inputs for analysis	Chemical profiling, identity confirmation, batch quality control	Missing, misannotated, or preparation-specific compounds	Separate detected, reported, and quantified compounds
Candidate compound prioritization	Annotated compounds, bioavailability filters, activity evidence, quality markers	Compound-prioritization layer	Select compounds for target mapping	Prioritized candidate compounds	Identifies compounds for hypothesis generation	Exposure, metabolism, concentration, and activity assessment	Arbitrary filtering thresholds and incomplete pharmacokinetic data	Report filtering rationale and retain uncertainty categories
Known target retrieval	Curated compound–protein interaction databases	Compound–known target network	Map experimentally supported relationships	Known compound–target links	Provides higher-confidence target evidence	Evidence-source verification and assay-context review	Evidence may be indirect, non-human, or context-specific	Weight target evidence by support type and biological context
Target prediction	Compound structures, similarity models, pharmacophore	Compound–predicted target network	Generate candidate targets where direct evidence is limited	Putative target set	Supports prioritization for testing	Orthogonal target assays and negative controls	False positives, algorithmic bias, incomplete chemical space	Label predicted targets separately from validated targets

	models, machine-learning tools							
Disease-gene mapping	Disease databases, omics studies, genetic associations, literature-derived gene sets	Target–disease network	Identify overlap between herbal targets and disease-associated genes	Compound–disease intersection targets	Suggests disease-relevant nodes for follow-up	Tissue-, cell-, and disease-stage-specific validation	Broad disease annotations and popular-gene bias	Distinguish disease association from causal disease mechanism
Protein interaction analysis	Intersected targets, PPI databases	PPI network; disease module	Identify connected targets, modules, and candidate hubs	PPI modules, central nodes, subnetworks	Provides functional context for target sets	Perturbation experiments and context-specific protein evidence	PPI associations may not occur in the relevant tissue or state	Treat topology as prioritization, not causal dominance
Network topology analysis	Compound–target and PPI networks	Ranked nodes and modules	Prioritize nodes by degree, betweenness, closeness, or module membership	Candidate hubs or bridge nodes	Highlights structurally influential network positions	Functional testing of prioritized nodes	Degree bias and annotation density	Avoid equating centrality with pharmacological importance
Pathway enrichment	Target lists, disease-intersection genes, module genes	Target–pathway or pathway-enrichment map	Identify overrepresented biological processes	Enriched pathways and functions	Suggests biological themes and mechanism hypotheses	Direct measurement of pathway activity or perturbation	Pathway redundancy, broad annotations, multiple-testing instability	Interpret enrichment as hypothesis generation
Integrated therapeutic hypothesis	Prioritized compounds, targets, modules, pathways, validation evidence	Multi-layer compound–target–disease–pathway framework	Combine evidence into testable mechanism propositions	Priority compounds, targets, modules, pathways	Supports experimental planning and translational ranking	Target-level, cellular, in vivo, exposure, and safety validation	Shared database bias may create false convergence	Require independent evidence layers before stronger inference

Disease mechanisms and therapeutic mapping

Network pharmacology is used in herbal medicine research to connect candidate compounds and putative targets with disease-associated genes, biological modules, and pathway-level hypotheses. In disease-oriented applications, the analytical question is not simply whether a herb contains multiple compounds, but whether the predicted target set intersects with disease-relevant molecular networks in a way that can guide testable mechanistic research. Network medicine frameworks can help relate herbal knowledge to symptom or disease contexts, but such associations should be interpreted as evidence for prioritization rather than proof of therapeutic causality [20].

Cancer-focused applications illustrate both the promise and limits of disease-mechanism mapping. Formula-based studies can construct herb–compound–target–disease networks, identify overlapping disease-associated targets, and use pathway enrichment to generate hypotheses about tumor-related signaling, immune regulation, apoptosis, proliferation, or inflammatory microenvironments. A network pharmacology study of Yanghe Decoction in a HER2-positive breast cancer context demonstrates how formula constituents can be mapped to cancer-associated targets and pathways, but the resulting network should be treated as a mechanistic hypothesis that requires biological validation rather than as confirmation of anticancer efficacy [21].

Natural-product-derived compound studies often use similar logic at a smaller chemical scale. For example, scopoletin has been examined through network pharmacology and molecular docking in a non-small cell lung cancer context, where predicted targets and docking outputs were used to prioritize possible molecular relationships. Such work can be useful for narrowing experimental questions, but docking does not confirm binding, predicted target overlap does not establish target

engagement, and pathway association does not demonstrate pathway modulation in a living system [22].

Disease mapping is also used in chronic and multifactorial disorders, where herbal medicines are often proposed to act through distributed biological processes rather than a single target. Evidence construction around Huangkui capsule in chronic glomerulonephritis shows how disease-focused network pharmacology can combine prior evidence with compound–target and pathway mapping to structure mechanistic hypotheses [23]. In cardiovascular research, analysis of total salvianolic acid injection in myocardial ischemia-reperfusion injury similarly illustrates how natural-product-related interventions may be linked to disease-associated targets and pathways for mechanistic prioritization rather than definitive causal inference [24].

Inflammatory and immune-mediated disease contexts further show why validation is central to therapeutic mapping. A study of Huashibaidu formula in sepsis-induced acute lung injury used network-oriented reasoning alongside experimental evaluation of inflammatory mechanisms, providing a stronger model for testing selected network-derived hypotheses than computation alone [25]. Across disease contexts, the same target or pathway may have different meanings depending on tissue, cell type, disease stage, comorbidity, exposure, and biological timing. Disease-network mapping is therefore most useful when it helps identify testable subnetworks, candidate mechanisms, or experimental priorities, and least reliable when computational overlap is treated as therapeutic validation.

Methodological strengths and weaknesses

A major strength of network pharmacology is that it provides a structured way to organize complex evidence across herbs, compounds, targets, diseases, protein interactions, and pathways. It can make assumptions explicit, visualize multi-target hypotheses, and support prioritization of compounds, targets, subnetworks, or pathways for experimental follow-up. Nevertheless, critical assessment of herbal network pharmacology shows that the same workflows can encourage overinterpretation when database-derived associations, predicted targets, hub rankings, or enriched pathways are presented as confirmed pharmacological mechanisms [26].

Database dependency is one of the most important validity threats. Herbal network pharmacology often depends on compound databases, TCM resources, drug–target interaction repositories, disease-gene databases, pathway resources, and PPI databases. A critical assessment of TCM databases indicates that differences in database coverage, annotation quality, update frequency, evidence provenance, and identifier mapping can shape downstream drug-discovery claims [27]. This means that the apparent importance of a target or pathway may partly reflect database architecture rather than biological dominance.

Network topology offers analytical value, but it also introduces interpretive risk. Degree, betweenness, closeness, hub status, module membership, and random-walk ranking can help prioritize nodes for follow-up, especially in multi-layer network settings. However, topology is not equivalent to causality, and a highly connected node may be prominent because it is well studied, broadly annotated, or technically central in a generic network. Methodological work on essential-node identification in network pharmacology supports topology-aware prioritization, but it also reinforces the need to avoid equating network importance with pharmacological importance [28].

Protein interaction and disease-gene resources add biological context, yet they can also amplify uncertainty. STRING provides protein–protein association networks and enrichment functions that are valuable for exploring functional relationships, but PPI edges may represent associations that are not active in the relevant tissue, cell state, disease stage, or exposure condition [29]. Disease-gene platforms such as DisGeNET support disease mapping, but disease annotations may combine heterogeneous evidence types and can be influenced by popular-gene bias, publication density, and broad disease definitions [30].

Functional enrichment analysis is useful for interpreting target lists, but it is especially vulnerable to overclaiming. DAVID and related enrichment tools can annotate gene lists with biological processes and pathway terms, yet enrichment does not prove that an herbal medicine modulates a pathway. Pathway redundancy, multiple testing, broad annotation terms, arbitrary target filtering, and unstable input lists can create an appearance of mechanistic depth without improving evidentiary validity [31]. **Table 3** synthesizes the principal methodological strengths, recurrent weaknesses, validity threats, and improvement priorities across network pharmacology workflows for herbal medicines.

Table 3. Methodological Strengths and Weaknesses of Network Pharmacology for Herbal Medicines: Analytical Opportunities, Sources of Bias, Validity Threats, Reproducibility Challenges, Validation Requirements, and Improvement Priorities

Methodological dimension	Potential strength	Recurrent weakness	Source of bias or uncertainty	Impact on interpretation	Validation requirement	Reproducibility concern	Recommended improvement	Future research priority
Compound annotation	Represents herbal chemical complexity	Incomplete or inconsistent compound lists	Database coverage, extraction method, batch variation	Candidate compound space may be distorted	Chemical profiling and identity confirmation	Poor reporting of compound source and filtering	Report provenance, preparation context, and confidence level	Evidence-weighted compound libraries
Candidate prioritization	Reduces analytical noise	Arbitrary bioavailability or drug-likeness thresholds	Missing pharmacokinetic data and unvalidated filters	Relevant compounds may be excluded or weak compounds retained	Exposure, metabolism, and activity assessment	Unclear threshold selection	Justify filters and conduct sensitivity analyses	Quantitative exposure-aware prioritization
Target prediction	Expands target hypotheses where direct evidence is sparse	High false-positive risk	Algorithmic bias, similarity assumptions, uneven training data	Predicted targets may be mistaken for validated targets	Orthogonal target assays and negative controls	Tool/version dependence	Separate known, predicted, and experimentally supported targets	Benchmarking and uncertainty scoring
Disease-gene mapping	Links herbal targets to disease context	Broad or heterogeneous disease annotations	Popular-gene bias, publication density, disease-definition variability	Disease overlap may be overinterpreted	Disease-context and tissue-specific validation	Inconsistent disease-gene sources	Weight disease evidence and report source categories	Context-specific disease modules
PPI network analysis	Provides functional context and subnetwork structure	PPI edges may be context-insensitive	Generic interaction databases and annotation density	Network modules may not exist in relevant biological setting	Tissue-, cell-, and condition-specific confirmation	Database version and confidence-score variation	Use context-aware PPI filtering where possible	Tissue- and cell-type-specific networks
Topology and hub analysis	Prioritizes candidate nodes and modules	Hub overinterpretation and degree bias	Well-studied proteins and network density	Central nodes may be mistaken for causal drivers	Perturbation experiments	Incomplete reporting of algorithms and thresholds	Compare multiple centrality methods and report assumptions	Causal network modeling
Pathway enrichment	Identifies biological themes	Redundant and unstable pathway outputs	Input-list instability, annotation bias, multiple testing	Enrichment may be mistaken for pathway modulation	Direct pathway activity measurement	Incomplete reporting of enrichment parameters	Report background sets, correction methods, and pathway filtering	Robust enrichment and pathway-crosstalk analysis
Docking-adjacent validation	Prioritizes possible ligand–target pairs	Overreliance on binding-score interpretation	Protein structure choice, ligand preparation, scoring limitations	Docking may be mistaken for confirmed binding	Biophysical and cellular target engagement assays	Poor parameter reporting	Treat docking as complementary, not confirmatory	Integrated target-engagement validation

Experimental validation	Tests selected network-derived hypotheses	Often limited to downstream markers	Narrow assay selection and weak perturbation design	Validation may not test the predicted target directly	Target-level, cellular, and in vivo confirmation	Selective reporting of positive results	Include negative controls and perturbation experiments	Prospective validation pipelines
Translational interpretation	Connects mechanisms to exposure, safety, and clinical relevance	Dose, metabolism, and formulation often omitted	Lack of pharmacokinetic and quality-control data	Mechanistic plausibility may not translate biologically	Exposure, safety, reproducibility, and clinical-context evaluation	Poor formulation reporting	Integrate pharmacokinetics and formulation standardization	Translation-oriented network pharmacology

Integrative synthesis

The integrated evidence suggests that network pharmacology is most valuable in herbal medicine research when it is used as a disciplined framework for moving from chemical complexity to testable biological hypotheses. Herbal multi-component inputs create a need for compound characterization and prioritization; compound prioritization creates a need for target inference; target inference becomes meaningful only when connected to disease context; disease-network mapping gains interpretive value when supported by protein interaction, pathway, and validation evidence. Multi-omics approaches can strengthen this chain by adding transcriptomic, proteomic, metabolomic, or other orthogonal evidence layers that help evaluate whether network-prioritized pathways are biologically plausible [32].

The transition from multi-compound input to translational interpretation should therefore be understood as a sequence of evidence levels rather than a single computational pipeline. Compound occurrence is not compound activity, compound annotation is not bioavailability, predicted target interaction is not target engagement, disease-gene overlap is not disease mechanism, PPI centrality is not causal dominance, and pathway enrichment is not demonstrated pathway modulation. Metabolomics-coupled network pharmacology illustrates how additional biological data can refine biomarker and pathway prioritization, but even these integrated approaches require careful interpretation because omics associations can also reflect downstream consequences, compensatory responses, or non-specific disease biology [33]. **Figure 1** presents an integrated evidence-to-mechanism framework linking herbal multi-component composition, compound–target inference, disease-network mapping, pathway-level interpretation, validation, and translational assessment.

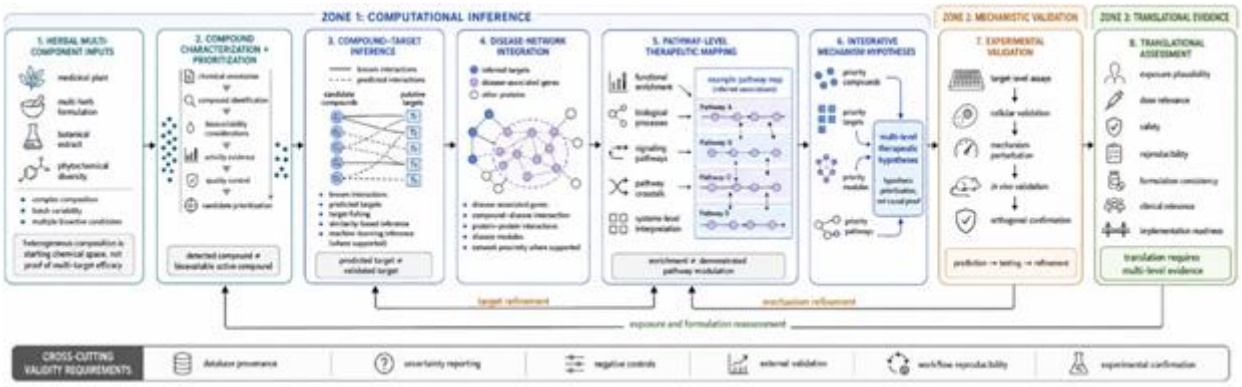

Figure 1. Integrated Network Pharmacology Framework for Multi-Compound, Multi-Target, and Pathway-Level Discovery in Herbal Medicines

Alt-text description

A wide left-to-right conceptual framework beginning with medicinal plants, herbal formulations, and phytochemical profiles. Candidate compounds progress through compound annotation and prioritization, predicted target mapping, disease-gene intersection, protein interaction and disease-module analysis, pathway-level interpretation, and integrated therapeutic hypothesis generation. The pathway then proceeds through experimental validation and translational assessment, with feedback arrows returning validated evidence to compound, target, and pathway refinement. Caution labels distinguish computational prediction from confirmed pharmacological mechanism.

The most defensible integrative argument is that network pharmacology can increase confidence when independent evidence layers converge for transparent reasons. For

example, confidence may increase when chemically verified compounds are plausible at relevant exposure levels, predicted or known targets are supported by independent target evidence, disease-network intersections are biologically context-specific, pathway findings are consistent with omics data, and experimental validation tests the prioritized target or pathway directly. A multi-omics and network pharmacology synthesis in vascular cognitive impairment shows why such integration is valuable: it can connect disease context, biological pathways, and herbal mechanisms more coherently than a single database-derived network, while still requiring caution about causal interpretation [34].

At the same time, false convergence is a recurring threat. If several analytical layers draw from overlapping databases, literature-derived annotations, popular disease genes, or broadly annotated pathways, then agreement across compound–target networks, PPI hubs, and enrichment outputs may reflect shared bias rather than biological truth. This is especially important for claims of polypharmacology and synergy. A compound–target network may suggest that several constituents interact with several proteins, but polypharmacological relevance depends on exposure, target engagement, functional directionality, and disease context. Synergy requires functional evidence that combined constituents produce an interaction beyond additivity, not simply that they share targets or pathways.

Therefore, the contribution of network pharmacology should be framed as hypothesis prioritization, evidence organization, and experimental planning. It can help identify which compounds should be chemically verified, which targets should be tested, which pathways should be measured, which disease modules may be relevant, and which validation experiments should be prioritized. It cannot independently determine that an herbal medicine is clinically effective, that a predicted target is confirmed, that a hub is a master regulator, or that a pathway is modulated in vivo. The integrative value of the field depends on moving from database-driven association toward evidence-weighted, uncertainty-aware, context-specific, experimentally anchored, and translationally realistic workflows.

Future research directions

Future herbal network pharmacology should move toward standardized reporting, transparent database provenance, chemical traceability, and uncertainty-aware interpretation. Responsible integration of artificial intelligence may improve compound annotation, target prediction, multimodal pattern recognition, and prioritization, but AI-supported network pharmacology should not intensify opaque inference. Future studies should report compound sources, database versions, prediction tools, confidence thresholds, negative controls, evidence categories, and sensitivity analyses so that readers can distinguish known interactions from predicted relationships and high-confidence evidence from speculative associations [35].

Greater attention is needed to botanical authentication, chemical standardization, quantitative constituent data, extraction conditions, processing effects, batch reproducibility, bioavailability, metabolism, dose context, and exposure relevance. Without these layers, compound–target networks risk representing chemically possible relationships rather than pharmacologically plausible ones. Future workflows should incorporate pharmacokinetic plausibility, formulation consistency, safety considerations, and exposure-informed prioritization before making translational claims. This would help shift the field from broad compound enumeration toward biologically meaningful compound selection.

Disease-network modeling also needs greater context specificity. Tissue-specific networks, cell-type-specific networks, temporal networks, disease-stage-aware models, comorbidity-sensitive interpretation, causal network modeling, multi-layer networks, dynamic networks, and network proximity methods may help refine disease mapping. However, such methods should be accompanied by uncertainty quantification, external validation, benchmark datasets, transparent parameter reporting, open code, versioned databases, and FAIR data practices where appropriate. Multi-omics, single-cell data, and spatial data may strengthen mechanism mapping when they are used to test rather than merely decorate network hypotheses.

The most important future priority is to anchor computational predictions in prospective and orthogonal validation. Validation-oriented research in medicinal herbs and natural compounds for psoriasis illustrates a stronger direction for the field because network-derived multi-target hypotheses are connected with experimental evaluation rather than left as computational claims [36]. Future studies should prioritize target-level assays, cellular perturbation, in vivo confirmation, pathway activity measurement, exposure plausibility, safety assessment, and reproducible computational pipelines. This movement from database-driven association toward evidence-weighted network pharmacology will be necessary for translationally meaningful herbal mechanism research.

CONCLUSION

This integrative review examined network pharmacology in herbal medicine research with emphasis on multi-compound, multi-target, and pathway-level therapeutic discovery. The synthesis shows that network

pharmacology can support systems-level organization, target prioritization, disease-network mapping, pathway interpretation, hypothesis generation, and experimental planning. Its strongest contribution is not mechanism confirmation, but the structured prioritization of compounds, targets, disease modules, and pathways for further testing. Reliable mechanistic and translational inference depends on high-quality chemical data, transparent database provenance, context-specific target evidence, appropriate network analysis, uncertainty reporting, reproducibility, experimental validation, pharmacokinetic plausibility, safety assessment, and clinical relevance. Herbal complexity justifies network-level analysis, but it does not independently prove multi-target efficacy, therapeutic synergy, causal mechanism, or clinical effectiveness.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

REFERENCES

1. Zhou Z, Chen B, Chen S, Lin M, Chen Y, Jin S, et al. Applications of network pharmacology in traditional Chinese medicine research. Evid Based Complement Alternat Med. 2020;2020:1646905. doi:10.1155/2020/1646905
2. Lee M, Shin H, Park M, Kim A, Cha S, Lee H. Systems pharmacology approaches in herbal medicine research: A brief review. BMB Rep. 2022;55(9):417-28. doi:10.5483/BMBRep.2022.55.9.102
3. Noor F, Qamar MTU, Ashfaq UA, Albutti A, Alwashmi ASS, Aljasir MA. Network pharmacology approach for medicinal plants: Review and assessment. Pharmaceuticals (Basel). 2022;15(5):572. doi:10.3390/ph15050572
4. Wu J, Zhang F, Li Z, Jin W, Shi Y. Integration strategy of network pharmacology in traditional Chinese medicine: A narrative review. J Tradit Chin Med. 2022;42(3):479-86. doi:10.19852/j.cnki.jtcm.20220408.003
5. Lee WY, Park KI, Bak SB, Lee S, Bae SJ, Kim MJ, et al. Evaluating current status of network pharmacology for herbal medicine focusing on identifying mechanisms and therapeutic effects. J Adv Res. 2025;76:799-815. doi:10.1016/j.jare.2024.12.040
6. Zhai Y, Liu L, Zhang F, Chen X, Wang H, Zhou J, et al. Network pharmacology: A crucial approach in traditional Chinese medicine research. Chin Med. 2025;20(1):8. doi:10.1186/s13020-024-01056-z
7. Li L, Yang L, Yang L, He C, He Y, Chen L, et al. Network pharmacology: A bright guiding light on the way to explore the personalized precise medication of traditional Chinese medicine. Chin Med. 2023;18(1):146. doi:10.1186/s13020-023-00853-2
8. Zhao W, Wang B, Li S. Network pharmacology for traditional Chinese medicine in era of artificial intelligence. Chin Herb Med. 2024;16(4):558-60. doi:10.1016/j.chmed.2024.08.004
9. Zhang P, Zhang D, Zhou W, Wang L, Wang B, Zhang T, et al. Network pharmacology: Towards the artificial intelligence-based precision traditional Chinese medicine. Brief Bioinform. 2024;25(1):bbad518. doi:10.1093/bib/bbad518
10. Snyder H. Literature review as a research methodology: An overview and guidelines. J Bus Res. 2019;104:333-9. doi:10.1016/j.jbusres.2019.07.039
11. Dhollande S, Taylor A, Meyer S, Scott M. Conducting integrative reviews: A guide for novice nursing researchers. J Res Nurs. 2021;26(5):427-38. doi:10.1177/1744987121997907
12. Kutcher AM, LeBaron VT. A simple guide for completing an integrative review using an example article. J Prof Nurs. 2022;40:13-9. doi:10.1016/j.profnurs.2022.02.004
13. Zhang RZ, Yu SJ, Bai H, Ning K. TCM-Mesh: The database and analytical system for network pharmacology analysis for TCM preparations. Sci Rep. 2017;7(1):2821. doi:10.1038/s41598-017-03039-7
14. Zhang R, Zhu X, Bai H, Ning K. Network pharmacology databases for traditional Chinese medicine: Review and assessment. Front Pharmacol. 2019;10:123. doi:10.3389/fphar.2019.00123
15. Xu HY, Zhang YQ, Liu ZM, Chen T, Lv CY, Tang SH, et al. ETCM: An encyclopaedia of traditional Chinese medicine. Nucleic Acids Res. 2019;47(D1):D976-82. doi:10.1093/nar/gky987
16. Fang S, Dong L, Liu L, Guo J, Zhao L, Zhang J, et al. HERB: A high-throughput experiment- and reference-guided database of traditional Chinese medicine. Nucleic Acids Res. 2021;49(D1):D1197-206. doi:10.1093/nar/gkaa1063
17. Kong X, Liu C, Zhang Z, Cheng M, Mei Z, Li X, et al. BATMAN-TCM 2.0: An enhanced integrative database for known and predicted interactions between traditional Chinese medicine ingredients

and target proteins. Nucleic Acids Res. 2024;52(D1):D1110-20. doi:10.1093/nar/gkad926
18. Daina A, Michielin O, Zoete V. SwissTargetPrediction: Updated data and new features for efficient prediction of protein targets of small molecules. Nucleic Acids Res. 2019;47(W1):W357-64. doi:10.1093/nar/gkz382
19. Wang X, Shen Y, Wang S, Li S, Zhang W, Liu X, et al. PharmMapper 2017 update: A web server for potential drug target identification with a comprehensive target pharmacophore database. Nucleic Acids Res. 2017;45(W1):W356-60. doi:10.1093/nar/gkx374
20. Gan X, Shu Z, Wang X, Yan D, Li J, Ofaim S, et al. Network medicine framework reveals generic herb-symptom effectiveness of traditional Chinese medicine. Sci Adv. 2023;9(43):eadh0215. doi:10.1126/sciadv.adh0215
21. Zeng L, Yang K. Exploring the pharmacological mechanism of Yanghe Decoction on HER2-positive breast cancer by a network pharmacology approach. J Ethnopharmacol. 2017;199:68-85. doi:10.1016/j.jep.2017.01.045
22. Yuan C, Wang MH, Wang F, Chen PY, Ke XG, Yu B, et al. Network pharmacology and molecular docking reveal the mechanism of scopoletin against non-small cell lung cancer. Life Sci. 2021;270:119105. doi:10.1016/j.lfs.2021.119105
23. Dai Y, Chen X, Yang H, Yang J, Hu Q, Xiao X, et al. Evidence construction of Huangkui capsule against chronic glomerulonephritis: A systematic review and network pharmacology. Phytomedicine. 2022;102:154189. doi:10.1016/j.phymed.2022.154189
24. Li N, Gu X, Liu F, Zhang Y, Sun Y, Gao S, et al. Network pharmacology-based analysis of potential mechanisms of myocardial ischemia-reperfusion injury by total salvianolic acid injection. Front Pharmacol. 2023;14:1202718. doi:10.3389/fphar.2023.1202718
25. Zhang F, Guo F, Zhang Y, Xu H, Liu Y, Lin L, et al. Huashibaidu formula attenuates sepsis-induced acute lung injury via suppressing cytokine storm: Implications for treatment of COVID-19. Phytomedicine. 2023;109:154549. doi:10.1016/j.phymed.2022.154549
26. Panossian A. Trends and pitfalls in the progress of network pharmacology research on natural products. Pharmaceuticals (Basel). 2025;18(4):538. doi:10.3390/ph18040538
27. Wang Y, Liu M, Jafari M, Tang J. A critical assessment of traditional Chinese medicine databases as a source for drug discovery. Front Pharmacol. 2024;15:1303693. doi:10.3389/fphar.2024.1303693
28. Chen X, Xu M, An Y. Identifying the essential nodes in network pharmacology based on multilayer network combined with random walk algorithm. J Biomed Inform. 2021;114:103666. doi:10.1016/j.jbi.2020.103666
29. Szklarczyk D, Kirsch R, Koutrouli M, Nastou K, Mehryary F, Hachilif R, et al. The STRING database in 2023: Protein-protein association networks and functional enrichment analyses for any sequenced genome of interest. Nucleic Acids Res. 2023;51(D1):D638-46. doi:10.1093/nar/gkac1000
30. Piñero J, Ramírez-Anguita JM, Saüch-Pitarch J, Ronzano F, Centeno E, Sanz F, et al. The DisGeNET knowledge platform for disease genomics: 2019 update. Nucleic Acids Res. 2020;48(D1):D845-55. doi:10.1093/nar/gkz1021
31. Sherman BT, Hao M, Qiu J, Jiao X, Baseler MW, Lane HC, et al. DAVID: A web server for functional enrichment analysis and functional annotation of gene lists (2021 update). Nucleic Acids Res. 2022;50(W1):W216-21. doi:10.1093/nar/gkac194
32. Zhu X, Yao Q, Yang P, Zhao D, Yang R, Bai H, et al. Multi-omics approaches for in-depth understanding of therapeutic mechanism for traditional Chinese medicine. Front Pharmacol. 2022;13:1031051. doi:10.3389/fphar.2022.1031051
33. Zhang W, Chen Y, Jiang H, Yang J, Wang Q, Du Y, et al. Integrated strategy for accurately screening biomarkers based on metabolomics coupled with network pharmacology. Talanta. 2020;211:120710. doi:10.1016/j.talanta.2020.120710
34. Lv S, Wang Q, Zhang X, Ning F, Liu W, Cui M, et al. Mechanisms of multi-omics and network pharmacology to explain traditional Chinese medicine for vascular cognitive impairment: A narrative review. Phytomedicine. 2024;123:155231. doi:10.1016/j.phymed.2023.155231
35. Song Z, Chen G, Chen CYC. AI empowering traditional Chinese medicine? Chem Sci. 2024;15(41):16844-86. doi:10.1039/d4sc04107k
36. Jo HG, Seo J, Jang B, Kim Y, Kim H, Baek E, et al. Integrating network pharmacology and experimental validation to advance psoriasis treatment: Multi-target mechanistic elucidation of medicinal herbs and natural compounds. Autoimmun Rev. 2025;24(8):103836. doi:10.1016/j.autrev.2025.103836