Network Pharmacology Without Oversimplification: Designing a Mechanism-Centered Model for Polyherbal Formulations and Multi-Target Therapeutics

Wei Zhang[1]*, Chen Hui[2], Michael Tan[1]

[1]Department of AI-Enabled Traditional Chinese Medicine (TCM) Network Pharmacology, Faculty of Pharmacy, University of Melbourne, Melbourne, Australia.
[2]Department of Intelligent Cheminformatics for Natural Therapeutics, Faculty of Pharmacy, National University of Singapore, Singapore.

ABSTRACT

Network pharmacology has become a prominent strategy for studying multi-component therapeutic systems, yet its application to polyherbal formulations often remains limited by static compound–target–pathway mapping. Polyherbal formulations are chemically heterogeneous, preparation-dependent, exposure-conditioned systems in which botanical identity, plant part, processing, extraction, dose, metabolism, tissue distribution, and temporal exposure may determine whether a constituent is pharmacologically relevant. This article proposes a mechanism-centered network pharmacology model for polyherbal formulations and multi-target therapeutics. The model addresses oversimplified practices that equate compound occurrence with active exposure, predicted targets with validated engagement, protein–protein interaction hubs with causal importance, pathway enrichment with pathway modulation, and multi-target overlap with synergy. Instead, the proposed framework organizes polyherbal modeling through formulation composition, exposure and metabolic state, graded compound–target evidence, directional regulatory interaction, context-specific mechanism modules, cross-module therapeutic logic, and validation and translational evidence. The model distinguishes measured, curated, predicted, inferred, text-derived, and validated evidence states, while preserving activating, inhibitory, modulatory, associative, and unknown-direction relationships as non-equivalent edge types. It also separates additivity, conditional synergy, redundancy, complementarity, compensatory buffering, antagonism, exposure competition, target convergence, and target divergence as alternative therapeutic logics rather than assuming beneficial polypharmacology by default. Validation gates are proposed to prevent unsupported mechanism claims and to require composition integrity, exposure plausibility, target evidence, directionality, context specificity, module coherence, multi-target logic assessment, and experimental challenge before translational interpretation. The central contribution is a revisable, uncertainty-aware model that treats network pharmacology as a disciplined mechanism-hypothesis system rather than a visual demonstration of therapeutic validity.

Key Words: *Network pharmacology, Polyherbal formulations, Multi-target therapeutics, Systems pharmacology, Mechanism-centered modeling, Polypharmacology*

eIJPPR 2025; 15(3):19-28

HOW TO CITE THIS ARTICLE: Zhang W, Hui C, Tan M. Network Pharmacology Without Oversimplification: Designing a Mechanism-Centered Model for Polyherbal Formulations and Multi-Target Therapeutics. Int J Pharm Phytopharmacol Res. 2025;15(3):19-28. https://doi.org/10.51847/vtfEcFfTCT

INTRODUCTION

Network pharmacology was developed to support pharmacological reasoning in complex biological systems, particularly where therapeutic effects may involve distributed molecular interactions rather than single-target modulation. Its conceptual value is strongest when network structure is used to organize causal hypotheses, prioritize

Corresponding author: Wei Zhang
Address: Department of AI-Enabled Traditional Chinese Medicine (TCM) Network Pharmacology, Faculty of Pharmacy, University of Melbourne, Melbourne, Australia.
E-mail: ✉ wei.zhang@unimelb.edu.au
Received: 02 February 2025; **Revised:** 18 May 2025; **Accepted:** 21 May 2025

testable mechanisms, and connect molecular perturbations with disease-relevant biological processes.

However, network construction alone does not establish mechanism, because an observed or inferred relationship among compounds, targets, pathways, and phenotypes may remain associative unless directionality, context, exposure, and validation are made explicit [1].

Polyherbal formulations intensify this challenge because they combine multiple botanical components, chemically diverse constituents, preparation-dependent composition, and potential pharmacokinetic and pharmacodynamic interactions. In traditional medicine and natural-product research, network pharmacology has been widely used to integrate compounds, targets, diseases, and pathways, but the interpretive distance between database-derived networks and pharmacological mechanism is often substantial [2]. A formula may contain numerous detectable molecules, yet only a subset may be sufficiently abundant, bioavailable, metabolically transformed, or contextually relevant to participate in a plausible therapeutic mechanism.

The need for context sensitivity is especially important when network pharmacology is used to support individualized or precision-oriented interpretation. Disease state, tissue environment, cell type, dose, temporal exposure, metabolic capacity, and concurrent biological perturbations can all determine whether a predicted interaction is meaningful. For this reason, a generic compound–target–disease map may be useful for hypothesis generation but insufficient for mechanism construction unless it specifies how biological context modifies candidate relationships [3].

This article proposes a mechanism-centered model for network pharmacology of polyherbal formulations and multi-target therapeutics. The model responds to the current need for stronger validation logic, clearer evidence grading, and more cautious interpretation in herbal network pharmacology [4]. Its purpose is not to reject network pharmacology, but to redesign its conceptual workflow so that formulation composition, exposure relevance, target evidence, directional regulation, context-specific modules, multi-target therapeutic logic, uncertainty, and validation gates are represented as necessary components of mechanistic inference.

Polyherbal formulations as complex therapeutics

Polyherbal formulations should be represented as complex therapeutic systems rather than as simple aggregations of plant names or compound lists. At minimum, a formulation model must account for botanical identity, plant part, preparation method, processing, extraction procedure, relative abundance, and batch context. Formula-level network pharmacology, polyherbal pharmacokinetic profiling, and absorption-informed network approaches collectively show why composition and exposure should be considered before candidate compounds are carried into target-level modeling [5-7].

The chemical identity of a formulation is not fixed by its label alone. Plant-to-extract ratio, extraction conditions, processing, and preparation context can alter which constituents are present, enriched, depleted, transformed, or analytically detectable. Integrated approaches that combine network pharmacology with metabolomics and pharmacokinetic/pharmacodynamic evidence illustrate how candidate quality markers or mechanism-relevant constituents can be refined when chemical profiling is linked to exposure and biological response information [8]. This kind of integration supports the principle that formulation composition should be treated as a structured input layer, not as a decorative preface to target prediction.

Composition, however, is only the first level of pharmacological relevance. A detected constituent may be abundant in the preparation yet poorly absorbed, rapidly metabolized, protein-bound, excluded from the relevant tissue, or present at a time that does not match the proposed biological effect. Conversely, a metabolite may be more relevant than the parent compound if it is the entity that reaches the biological context of interest. Therefore, polyherbal modeling should distinguish compound occurrence, compound abundance, bioavailable compound, active metabolite, and exposure-relevant compound state as different epistemic categories rather than as interchangeable nodes.

Formulation complexity is also not equivalent to therapeutic sophistication. A polyherbal preparation may contain compounds that act additively, redundantly, competitively, antagonistically, or conditionally synergistically depending on dose, timing, tissue distribution, and target direction. Multiple components acting near the same biological pathway may support a candidate mechanism, but they do not by themselves demonstrate synergy, therapeutic breadth, or clinical benefit. Claims of synergy require direct evidence that the combined effect exceeds an appropriate expectation under defined experimental conditions.

A mechanism-centered view therefore separates composition, exposure, biological activity, mechanistic interpretation, and therapeutic effect. Composition defines what may enter the model; exposure defines what plausibly reaches relevant contexts; target evidence defines which molecular interactions deserve mechanistic consideration; directionality defines how those interactions may alter regulatory systems; and validation determines whether the proposed mechanism can progress beyond hypothesis. Without these distinctions, a visually complex polyherbal

network can appear mechanistically rich while remaining pharmacologically underdetermined.

Limits of simplified network pharmacology

A recurrent weakness in simplified network pharmacology is the conversion of uncertain inputs into visually authoritative networks. Database-derived compound lists, predicted target accumulation, disease-gene overlap, generic protein–protein interaction maps, hub ranking, and pathway enrichment may all be useful exploratory tools, but they do not prove compound action or causal mechanism. Critical assessments of natural-product and medicinal-plant network pharmacology, together with target-prediction methodology, support a cautious distinction between predicted associations and validated pharmacological engagement [9-11].

One major limitation is the frequent absence of exposure relevance. When all listed compounds are treated as equally available, the model ignores abundance, dose, absorption, distribution, metabolism, clearance, and tissue access. ADME-oriented evaluation can help prioritize compounds with plausible pharmacokinetic properties, but such computational filtering should be interpreted as a constraint on hypothesis generation rather than as proof of in vivo exposure or target engagement [12]. Exposure uncertainty should therefore remain visible in the network rather than being hidden behind binary compound–target edges.

A second limitation is the interpretation of pathway enrichment as pathway modulation. Enrichment analysis can identify overrepresented annotations among candidate targets, but it is sensitive to gene-list construction, annotation density, pathway redundancy, background selection, and database bias. Methodological guidance on enrichment analysis supports careful interpretation because enriched pathways may indicate functional themes for follow-up, not demonstrated pathway activation, inhibition, or therapeutic correction [13]. In polyherbal research, this distinction is crucial because pathway labels can easily create the appearance of mechanism without establishing direction or function.

A third limitation is the overuse of generic PPI topology. Protein–protein interaction networks often represent physical or functional associations that are not necessarily drug-modulated, tissue-specific, disease-relevant, directional, or causal. High node degree may reflect research intensity, annotation density, or database coverage rather than therapeutic dominance. Similarly, a hub target may be biologically important but pharmacologically unreachable, nonselectively toxic, contextually irrelevant, or downstream of the actual perturbation. Degree centrality should therefore support prioritization only when combined with exposure, target evidence, directionality, context, and validation.

A fourth limitation is the creation of predicted-to-predicted evidence chains. For example, a predicted compound target may be linked to a database disease gene, then placed in a generic PPI network, then used for pathway enrichment, then supported by molecular docking. Such a chain may appear internally consistent while still lacking direct evidence that the compound is bioavailable, engages the target, modulates the pathway, affects the phenotype, or improves therapeutic outcome. Larger networks can increase visual complexity without increasing mechanistic credibility when uncertainty is not explicitly represented.

Table 1 summarizes recurrent oversimplifications in network pharmacology of polyherbal formulations and links them to mechanistic consequences, validity threats, and corrective modeling requirements.

Table 1. Recurrent Oversimplifications in Network Pharmacology of Polyherbal Formulations: Analytical Assumptions, Mechanistic Consequences, Validity Threats, and Corrective Modeling Requirements

Oversimplification	Typical analytical assumption	Mechanistic information lost	Potential validity threat	Likely interpretation error	Required contextual variable	Corrective modeling strategy	Validation safeguard
Treating formula name as composition	The named formulation sufficiently defines the chemical system	Plant part, preparation, processing, extraction, batch, constituent abundance	Mis-specified starting entities	Formulation identity mistaken for pharmacological composition	Botanical identity, preparation method, extract ratio, batch context	Build a formulation composition layer before compound selection	Analytical profiling and quality-marker confirmation
Treating detected compounds as active entities	Any detected constituent may be modeled as pharmacologically active	Absorption, metabolism, tissue access, temporal exposure	Inclusion of irrelevant compounds	Detected compound mistaken for exposure-relevant compound	Dose, route, bioavailability, metabolism, time	Convert compounds into exposure-relevant parent or metabolite states	PK, absorption, metabolism, or ADME plausibility assessment

Treating predicted targets as engaged targets	Target-prediction output is sufficient for mechanism construction	Binding evidence, functional modulation, negative evidence	False target map	Predicted target mistaken for validated engagement	Assay context, species, concentration, exposure	Grade target edges as predicted, curated, measured, functional, or contradicted	Target engagement, activity, or perturbation assay
Treating PPI connectivity as compound action	Network neighbors represent pharmacological mechanism	Direction, causality, tissue relevance, druggability	Topological inflation	Protein association mistaken for compound-induced regulation	Tissue, disease state, cell type, regulatory sign	Separate association edges from directional regulatory edges	Signed signaling evidence and perturbation testing
Treating hub rank as causal importance	High-degree nodes are dominant therapeutic targets	Annotation bias, degree bias, exposure feasibility	Popular-target bias	Hub status mistaken for therapeutic dominance	Disease context, expression, target accessibility	Use hub ranking only as one prioritization input	Orthogonal target validation and context checking
Treating pathway enrichment as pathway modulation	Enriched pathways are affected by the formulation	Direction, magnitude, cell context, causal role	Pathway-label overclaiming	Enrichment mistaken for functional modulation	Background gene set, tissue, phenotype, pathway state	Use enrichment to propose modules, not to prove them	Pathway activity and phenotype-linked assays
Treating multi-target overlap as synergy	Multiple compounds or targets imply cooperative action	Dose interaction, response surface, antagonism, redundancy	False synergy claim	Shared targets mistaken for synergistic pharmacology	Dose, timing, exposure, response metric	Classify additivity, redundancy, antagonism, convergence, divergence, or conditional synergy separately	Combination-response testing
Treating docking as target confirmation	Favorable docking supports validated binding	Experimental binding, kinetics, cellular engagement	Unsupported target validation	Docking pose mistaken for engagement	Protein state, compound state, concentration, cellular context	Treat docking only as prioritization unless experimentally supported	Binding/activity assay and cellular target engagement
Ignoring contradictory or negative evidence	Only supportive edges are retained	Model falsification, uncertainty, safety conflict	Confirmation bias	Coherent-looking model mistaken for robust mechanism	Negative evidence, adverse signals, failed assays	Encode contradiction and uncertainty as model states	Revision, pause, or rejection gates
Using generic disease networks	Disease genes apply equally across biological contexts	Disease subtype, stage, tissue, cell type, temporal dynamics	Context mismatch	Generic disease association mistaken for relevant mechanism	Disease stage, tissue, cell type, time	Construct context-specific mechanism modules	Context-matched omics or phenotypic validation

Mechanism-centered network modeling

Mechanism-centered network modeling shifts the analytical question from "How many compounds and targets can be connected?" to "Which exposure-relevant entities plausibly perturb which context-specific biological mechanisms, with what evidence and uncertainty?" Network prediction becomes more credible when it is linked to external validation logic rather than interpreted from topology alone [14]. In this model, network pharmacology is therefore treated as a mechanism-hypothesis system whose outputs must remain revisable as new exposure, target, functional, safety, or contradictory evidence appears.

ISSN (Online) 2249-6084 (Print) 2250-1029

The first two layers establish pharmacological eligibility. The Formulation Composition Layer defines botanical components, plant parts, processing, extraction, preparation, batch context, measured constituents, and predicted constituents. The Exposure and Metabolic State Layer then asks which parent compounds, metabolites, or exposure-relevant states can plausibly reach the biological context of interest. These layers prevent a formulation label or constituent list from being collapsed into a pharmacological mechanism and create explicit failure conditions when composition is unresolved or exposure is implausible.

The third layer is the Compound–Target Evidence Layer, where every candidate edge is graded rather than treated as binary. Measured, curated, predicted, inferred, text-derived, and validated evidence states must be distinguished because they carry different levels of mechanistic confidence. A predicted compound–target relationship can support prioritization, but it should not be written as target engagement unless supported by direct or orthogonal evidence. Similarly, a curated association should retain its source context, and a measured interaction should preserve the experimental system in which it was observed.

The fourth layer is the Directional Regulatory Interaction Layer. Mechanistic interpretation requires the model to distinguish activation, inhibition, modulation, association, and unknown direction. Directionality cannot be inferred merely from the presence of a target in a pathway or from a PPI edge. Tissue-specific regulatory architecture reinforces this point because the same gene or regulatory relationship may differ across biological contexts [15]. A mechanism-centered network must therefore preserve disease state, tissue, cell type, dose, exposure, and time as modifiers of regulatory meaning rather than as optional annotations.

The fifth layer is the Context-Specific Mechanism Module Layer. A module is not simply an enriched pathway or a cluster of connected proteins; it is a bounded hypothesis linking exposure-relevant compounds or metabolites to graded targets, directional regulatory edges, context labels, and phenotype-relevant biological processes. Single-cell chemical transcriptomics illustrates why chemical perturbations may vary across cell states and why context-aware measurement can be necessary before a compound effect is generalized [16]. In this model, potential modules may include inflammatory regulation, oxidative stress regulation, metabolic adaptation, cell-survival control, immune modulation, vascular regulation, neuroregulatory signaling, or tissue-homeostasis regulation, but no formulation is assumed to contain all modules.

The sixth and seventh layers connect modules to therapeutic interpretation and validation. The Cross-Module Therapeutic Logic Layer distinguishes additivity, conditional synergy, functional redundancy, pathway complementarity, compensatory buffering, antagonism, exposure competition, target convergence, and target divergence. The Validation and Translational Evidence Layer then tests whether the proposed mechanism should be supported, partially supported, revised, paused, rejected, or considered inconclusive. Signed signaling resources and integrated intra- and intercellular signaling frameworks support the need to encode direction and context explicitly when moving from target lists to mechanism modules [17]. Integrated signaling knowledge further reinforces that regulatory relationships can operate across cellular contexts and should not be reduced to undirected associations [18].

Multi-target therapeutic logic

Multi-target therapeutic logic should be treated as a set of competing interpretive possibilities rather than as a default claim of beneficial synergy. Polypharmacology may be relevant to complex diseases because distributed perturbations can influence more than one biological process, but the value of multi-target action depends on target relevance, exposure, directionality, dose, safety, and context [19-21]. In a polyherbal formulation, a large number of predicted compound–target links may therefore indicate only a broad hypothesis space unless the model specifies which targets are plausible, which interactions are supported, and which biological contexts make the combined pattern meaningful.

Additivity occurs when two or more components contribute independently to a combined functional response. Conditional synergy requires stronger evidence: the combined response must exceed an appropriate expectation under defined exposure, dose, assay, and biological context. Natural-product mixtures can also display antagonism, and the same formulation may contain components that enhance, weaken, mask, or redirect each other's effects [22]. For this reason, shared targets, overlapping pathways, or multiple compounds connected to one module should never be written as synergy without direct combination-response evidence.

Functional redundancy and pathway complementarity require separate interpretation. Redundancy may be beneficial if it stabilizes a desired response under biological variability, but it may also be neutral or increase exposure burden without improving mechanism coherence. Pathway complementarity may suggest that different modules address distinct aspects of disease biology, but it may also broaden off-target risk if module direction, tissue context, or safety state is unresolved. Structured combination-response resources illustrate why empirical combination evidence is needed before

classifying multi-component effects as synergistic, antagonistic, or otherwise interactive [23].

Compensatory buffering, exposure competition, target convergence, and target divergence are especially important for polyherbal systems. Compensatory buffering occurs when one module limits an undesirable adaptive response generated by another module, but this logic requires temporal and functional evidence. Exposure competition occurs when constituents influence absorption, metabolism, transport, protein binding, or clearance, thereby changing the active compound state before target engagement. Target convergence may reinforce modulation of one mechanism, whereas target divergence may distribute effects across several modules; neither pattern alone proves therapeutic advantage.

In the proposed model, multi-target therapeutic logic functions as an experimental design guide. If the model predicts additivity, validation should test whether individual and combined effects are consistent with independent contribution. If it predicts conditional synergy, the experiment must define the relevant context and exposure condition. If it predicts antagonism or exposure competition, pharmacokinetic or combination-response testing becomes essential. Thus, cross-module logic should not be used to decorate a network with therapeutic claims; it should specify what kind of evidence would be required to support, revise, or reject the proposed interaction logic.

Table 2 compares major multi-target therapeutic logic patterns and specifies the evidence needed to distinguish additivity, conditional synergy, redundancy, complementarity, compensation, and antagonism.

Table 2. Multi-Target Therapeutic Logic in Polyherbal Formulations: Network Patterns, Evidence Requirements, Context Dependence, Potential Benefits, Failure Risks, and Validation Strategies

Therapeutic logic type	Core definition	Typical network pattern	Required evidence	Context dependence	Potential therapeutic benefit	Potential failure risk	Interpretive safeguard	Validation strategy
Additivity	Independent effects contribute to a combined response without requiring interaction	Parallel compound or module effects linked to related phenotype	Individual and combined response evidence	Dose, exposure, timing, assay system	Broader or stronger effect without true interaction	Mistakenly labeled as synergy	Do not call additive effects synergistic	Individual-versus-combined dose-response testing
Conditional synergy	Combined effect exceeds expected additivity only under defined conditions	Complementary or convergent modules active in a specific context	Combination-response evidence under specified exposure and biological context	Strongly dependent on dose, timing, tissue, disease state	Enhanced effect in a defined context	False generalization across contexts	Specify the condition under which synergy is supported	Formal combination-response analysis and replication
Functional redundancy	Multiple entities influence similar functions or targets	Several compounds or targets converge on the same module	Evidence that contributors are exposed and functionally overlapping	Depends on biological variability and module vulnerability	Robustness if one contributor is weak or absent	Neutral duplication or increased toxicity	Redundancy may be beneficial, neutral, or harmful	Perturb individual contributors and combined system
Pathway complementarity	Different modules influence distinct but disease-relevant processes	Separate mechanism modules linked to a phenotype	Module coherence plus phenotype relevance	Tissue, disease stage, target direction	Multidimensional disease coverage	Excessively broad or incoherent mechanism	Pathway diversity is not therapeutic breadth	Multi-endpoint phenotypic and pathway activity assays
Compensatory buffering	One module reduces a counterproducti	Module-to-module	Time-resolved evidence of	Highly dependent on	Stabilized therapeutic response	Cancellation mistaken for	Distinguish buffering from	Temporal perturbation

	ve adaptive response caused by another	counter-regulation	adaptive response and buffering	feedback and timing		beneficial buffering	antagonistic loss of effect	and rescue experiments
Antagonism	One component or module reduces another's effect	Opposing directional edges or reduced combined response	Combination evidence showing reduced response	Dose, exposure, sequence, tissue	May reduce undesired toxicity in some contexts	Loss of desired efficacy	Antagonism may occur within the same formulation	Combination-response testing with mechanistic follow-up
Exposure competition	Components compete before reaching targets	Compound–compound interaction at absorption, metabolism, transport, or clearance level	PK, ADME, transporter, metabolism, or exposure evidence	Route, dose, formulation matrix, host metabolism	May modulate exposure favorably	Reduced active exposure or increased toxicity	Target networks cannot be interpreted without exposure state	PK interaction, metabolite, and tissue-exposure studies
Target convergence	Multiple constituents affect the same target or module	Several exposure-relevant entities point to one target or module	Exposure-supported target evidence	Depends on target accessibility and direction	Reinforced modulation of a relevant mechanism	False hub or false synergy interpretation	Shared targets do not prove synergy	Target engagement and dose-response validation
Target divergence	Constituents affect different targets or modules	Distributed target or module effects	Evidence for distinct, context-relevant targets	Disease complexity, tissue, safety state	Distributed disease modulation	Uncoordinated activity or toxicity	Multi-target does not equal beneficial polypharmacology	Multi-endpoint efficacy and safety evaluation

Proposed model

The proposed model represents polyherbal formulations as exposure-conditioned, evidence-graded, directional, context-specific, multi-module therapeutic systems. Its starting point is not the largest possible compound list but the most defensible formulation representation: botanical identity, plant part, processing, preparation method, extract ratio, batch context, quantified constituents where available, and uncertainty around unresolved composition. Botanical-extract methodology supports the need to define plant-to-extract relationships and formulation identity before downstream pharmacological interpretation [24].

The model contains exactly seven layers: L1. Formulation Composition Layer; L2. Exposure and Metabolic State Layer; L3. Compound–Target Evidence Layer; L4. Directional Regulatory Interaction Layer; L5. Context-Specific Mechanism Module Layer; L6. Cross-Module Therapeutic Logic Layer; and L7. Validation and Translational Evidence Layer. Within these layers, pathway and signaling knowledge are used to organize mechanism modules only when evidence states, directionality, and biological context are made explicit, because mechanism modeling requires more than pathway membership or target overlap [25].

Figure 1 presents the proposed mechanism-centered network pharmacology model linking formulation composition, exposure and metabolism, graded compound–target evidence, directional regulation, context-specific mechanism modules, multi-target therapeutic logic, and staged validation.

ISSN (Online) 2249-6084 (Print) 2250-1029

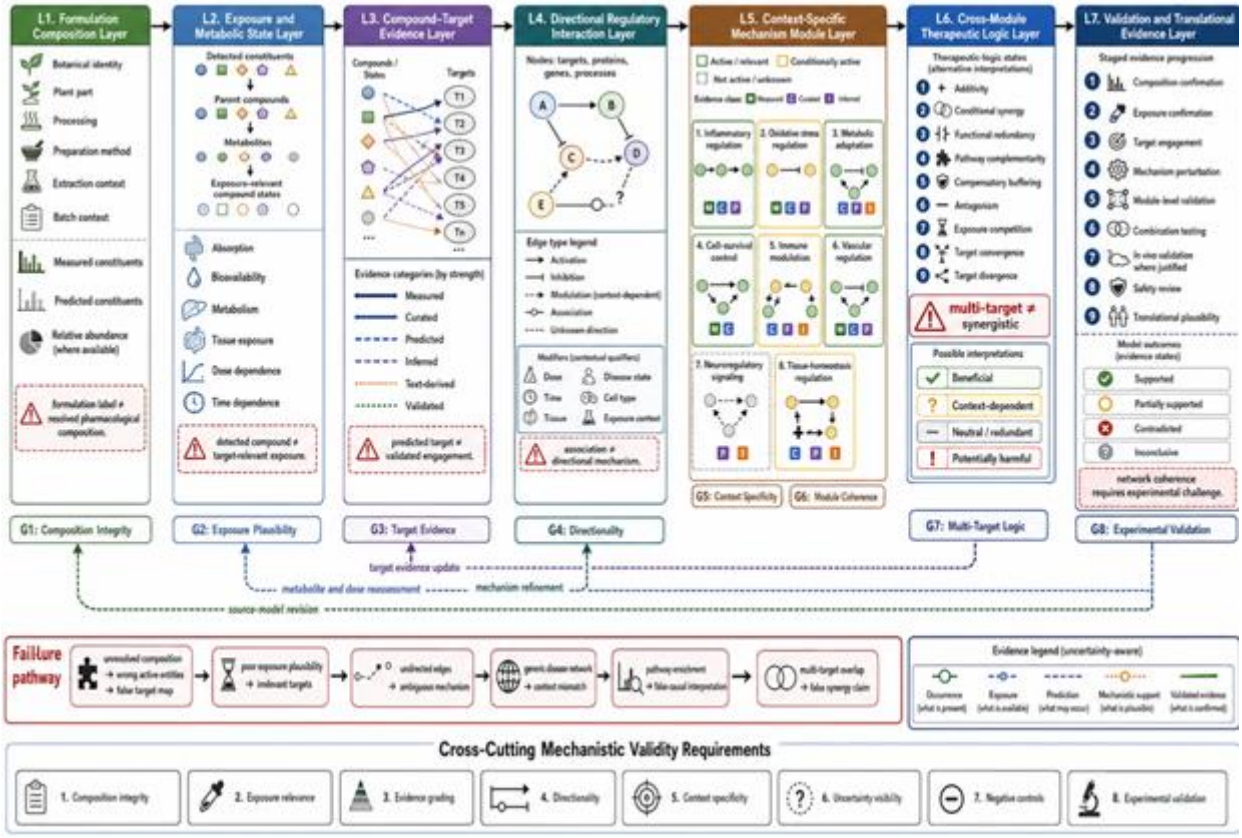

Figure 1. Mechanism-Centered Network Pharmacology Model for Polyherbal Formulations and Multi-Target Therapeutics

The model replaces static compound–target–pathway mapping with a layered architecture that begins with formulation composition and exposure-relevant compound states, progresses through graded compound–target evidence and directional regulatory relationships, constructs context-specific mechanism modules, and evaluates cross-module therapeutic logic including additivity, conditional synergy, redundancy, complementarity, compensatory buffering, antagonism, exposure competition, target convergence, and target divergence. Explicit validation gates prevent predicted interactions, hub centrality, pathway enrichment, and network density from being interpreted as confirmed mechanisms. Feedback from experimental and translational evidence updates earlier layers and may strengthen, revise, pause, or reject proposed mechanisms.

Alt-text description

A wide left-to-right seven-layer systems model begins with polyherbal formulation composition and preparation context, then moves to exposure and metabolic states, graded compound–target evidence, directional regulatory interactions, context-specific mechanism modules, cross-module therapeutic logic, and validation and translational evidence. Decision gates between layers assess composition integrity, exposure plausibility, target evidence, directionality, context specificity, mechanism coherence, multi-target logic, and experimental validation. Feedback arrows return new evidence to earlier layers.

The validation gates define progression without invented numerical thresholds. G1, the Composition Integrity Gate, asks whether the formulation identity and preparation context are sufficiently resolved. G2, the Exposure Plausibility Gate, asks whether candidate active entities can plausibly reach the relevant biological context. G3, the Target Evidence Gate, asks whether target relationships are evidence-labeled and credible. G4, the Directionality Gate, asks whether the effect is activating, inhibitory, modulatory, associative, or unknown. G5, the Context Specificity Gate, asks whether the interaction applies to the relevant tissue, cell type, disease state, and time. G6, the Mechanism Module Coherence Gate, asks whether the evidence supports a coherent mechanism module rather than a pathway list. G7, the Multi-Target Logic Gate, asks what interaction logic is actually supported. G8, the Experimental Validation Gate, asks whether the proposed mechanism can withstand experimental challenge. Causal-inference principles reinforce that mechanistic claims require explicit assumptions, uncertainty visibility, and validation beyond concordant associations [26].

Feedback is essential because the model is not a static graph. Negative target evidence can remove or downgrade

an edge; contradictory directionality can split or reject a module; exposure reassessment can replace a parent-compound hypothesis with a metabolite-state hypothesis; safety evidence can pause a therapeutic interpretation even when a mechanism appears coherent. Herbal-product adverse-event evidence supports the principle that safety signals should be treated as translational constraints rather than as post hoc annotations after mechanism claims have already been advanced [27]. In this framework, safety, contradiction, and failed validation are not external criticisms of the model; they are internal revision signals.

The proposed model should therefore be viewed as a revisable mechanism-hypothesis system. It does not claim that a polyherbal formulation is effective because its network is dense, because it contains many compounds, because it connects to many targets, or because several pathways are enriched. Instead, it asks whether each proposed mechanism can pass through composition integrity, exposure plausibility, graded target evidence, directional regulation, context specificity, module coherence, multi-target logic assessment, and experimental validation. A claim may remain useful as a prioritized hypothesis even when it does not yet qualify as a supported mechanism, provided that its uncertainty and required validation are explicitly stated.

CONCLUSION

This article proposes an original mechanism-centered network pharmacology model for polyherbal formulations and multi-target therapeutics. The model emphasizes that robust network pharmacology requires more than compound lists, target lists, hub genes, PPI networks, pathway enrichment, or docking add-ons. Credible mechanistic inference depends on formulation composition integrity, exposure relevance, metabolism, graded target evidence, regulatory directionality, tissue and cell-type specificity, temporal and disease-state context, coherent mechanism modules, explicit multi-target interaction logic, uncertainty visibility, negative evidence, and experimental validation. Network complexity should not be confused with mechanism. A polyherbal network becomes mechanistically meaningful only when its entities, edges, contexts, assumptions, uncertainties, and validation requirements are represented clearly enough to support experimental challenge and model revision.

Acknowledgments: None

Conflict of interest: None

Financial support: None

Ethics statement: None

REFERENCES

[1] Nogales C, Mamdouh ZM, List M, Kiel C, Casas AI, Schmidt HHHW. Network pharmacology: Curing causal mechanisms instead of treating symptoms. Trends Pharmacol Sci. 2022;43(2):136-50. doi:10.1016/j.tips.2021.11.004

[2] 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

[3] 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

[4] 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

[5] Zuo H, Zhang Q, Su S, Chen Q, Yang F, Hu Y. A network pharmacology-based approach to analyse potential targets of traditional herbal formulas: An example of Yu Ping Feng decoction. Sci Rep. 2018;8(1):11418. doi:10.1038/s41598-018-29764-1

[6] Salunkhe R, Gadgoli C, Naik A, Patil N. Pharmacokinetic profile and oral bioavailability of diosgenin, charantin, and hydroxychalcone from a polyherbal formulation. Front Pharmacol. 2021;12:629272. doi:10.3389/fphar.2021.629272

[7] Duan S, Niu L, Yin T, Li L, Gao S, Yuan D, et al. A novel strategy for screening bioavailable quality markers of traditional Chinese medicine by integrating intestinal absorption and network pharmacology: Application to Wu Ji Bai Feng Pill. Phytomedicine. 2020;76:153226. doi:10.1016/j.phymed.2020.153226

[8] Wang T, Lin S, Li H, Liu R, Liu Z, Xu H, et al. A stepwise integrated multi-system to screen quality markers of Chinese classic prescription Qingzao Jiufei decoction on the treatment of acute lung injury by combining network pharmacology-metabolomics-PK/PD modeling. Phytomedicine. 2020;78:153313. doi:10.1016/j.phymed.2020.153313

[9] 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

[10] Noor F, Tahir Ul Qamar M, 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

[11] 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

[12] Daina A, Michielin O, Zoete V. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness. Sci Rep. 2017;7(1):42717. doi:10.1038/srep42717

[13] Chicco D, Agapito G. Nine quick tips for pathway enrichment analysis. PLoS Comput Biol. 2022;18(8):e1010348. doi:10.1371/journal.pcbi.1010348

[14] Cheng F, Desai RJ, Handy DE, Wang R, Schneeweiss S, Barabási AL, et al. Network-based approach to prediction and population-based validation of in silico drug repurposing. Nat Commun. 2018;9(1):2691. doi:10.1038/s41467-018-05116-5

[15] Sonawane AR, Platig J, Fagny M, Chen CY, Paulson JN, Lopes-Ramos CM, et al. Understanding tissue-specific gene regulation. Cell Rep. 2017;21(4):1077-88. doi:10.1016/j.celrep.2017.10.001

[16] Srivatsan SR, McFaline-Figueroa JL, Ramani V, Saunders L, Cao J, Packer J, et al. Massively multiplex chemical transcriptomics at single-cell resolution. Science. 2020;367(6473):45-51. doi:10.1126/science.aax6234

[17] Licata L, Lo Surdo P, Iannuccelli M, Palma A, Micarelli E, Perfetto L, et al. SIGNOR 2.0, the SIGnaling Network Open Resource 2.0: 2019 update. Nucleic Acids Res. 2020;48(D1):D504-10. doi:10.1093/nar/gkz949

[18] Türei D, Valdeolivas A, Gul L, Palacio-Escat N, Klein M, Ivanova O, et al. Integrated intra- and intercellular signaling knowledge for multicellular omics analysis. Mol Syst Biol. 2021;17(3):e9923. doi:10.15252/msb.20209923

[19] Kabir A, Muth A. Polypharmacology: The science of multi-targeting molecules. Pharmacol Res. 2022;176:106055. doi:10.1016/j.phrs.2021.106055

[20] Ryszkiewicz P, Malinowska B, Schlicker E. Polypharmacology: promises and new drugs in 2022. Pharmacol Rep. 2023;75(4):755-70. doi:10.1007/s43440-023-00501-4

[21] Makhoba XH, Viegas C Jr, Mosa RA, Viegas FPD, Pooe OJ. Potential impact of the multi-target drug approach in the treatment of some complex diseases. Drug Des Devel Ther. 2020;14:3235-49. doi:10.2147/DDDT.S257494

[22] Caesar LK, Cech NB. Synergy and antagonism in natural product extracts: When 1 + 1 does not equal 2. Nat Prod Rep. 2019;36(6):869-88. doi:10.1039/C9NP00011A

[23] Zagidullin B, Aldahdooh J, Zheng S, Wang W, Wang Y, Saad J, et al. DrugComb: An integrative cancer drug combination data portal. Nucleic Acids Res. 2019;47(W1):W43-51. doi:10.1093/nar/gkz337

[24] Monagas M, Brendler T, Brinckmann J, Dentali S, Gafner S, Giancaspro G, et al. Understanding plant to extract ratios in botanical extracts. Front Pharmacol. 2022;13:981978. doi:10.3389/fphar.2022.981978

[25] Rian K, Hidalgo MR, Çubuk C, Falco MM, Loucera C, Esteban-Medina M, et al. Genome-scale mechanistic modeling of signaling pathways made easy: A Bioconductor/Cytoscape/web server framework for the analysis of omic data. Comput Struct Biotechnol J. 2021;19:2968-78. doi:10.1016/j.csbj.2021.05.022

[26] Michoel T, Zhang JD. Causal inference in drug discovery and development. Drug Discov Today. 2023;28(10):103737. doi:10.1016/j.drudis.2023.103737

[27] Choi Y, Shin HK. Adverse events associated with herbal medicine products reported in the Korea Adverse Event Reporting System from 2012 to 2021. Front Pharmacol. 2024;15:1378208. doi:10.3389/fphar.2024.1378208