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Review Article

Network Pharmacology, Multi-Omics Integration, and Future Perspectives for Herbal Medicine Analysis

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Abstract

Herbal medicine has long been characterized by multi-component, multi-target, and multi-pathway therapeutic actions, but its complex mechanisms remain difficult to explain using conventional single-target pharmacology. Network pharmacology provides a systems-level framework for decoding these effects by integrating herbal compound databases, disease-associated gene resources, protein–protein interaction networks, and graph-theoretical algorithms. This review summarizes the most recent advances in herbal network pharmacology, with emphasis on core databases, network topology metrics, hub-target identification, and multiscale interactome analysis. It further discusses how artificial intelligence, especially graph neural networks, knowledge graph embedding, and explainable AI, is improving herb–target prediction and mechanistic interpretation. The integration of single-cell transcriptomics, spatial metabolomics, molecular docking, and transfer-learning frameworks has expanded the field from static pathway mapping toward cell-type-specific and spatially resolved systems pharmacology. Despite these advances, major limitations remain, including overreliance on in silico predictions, insufficient wet-laboratory validation, neglect of dose–response relationships, inadequate consideration of pharmacokinetics and physiological barriers, and poor reproducibility caused by extract heterogeneity. Future development should move toward quantitative, dynamic, and experimentally validated systems pharmacology, supported by standardized reporting guidelines and rigorous biophysical, omics-based, and phenotypic validation. Such advances may help transform herbal medicine into a more precise, reproducible, and internationally acceptable therapeutic resource.

Keywords: Network Pharmacology; Herbal Medicine; Multi-Omics, Artificial Intelligence.

Abbreviations: OB: Oral Bioavailability; DL: Drug-Likeness; AKT1: AKT Serine/Threonine Kinase 1; TNF: Tumor Necrosis Factor; EGFR: Epidermal Growth Factor Receptor; PTGS2: Prostaglandin-Endoperoxide Synthase 2; IL-6: Interleukin 6; TP53: Tumor Protein p53; CDK1: Cyclin Dependent Kinase 1; ESR1: Estrogen Receptor 1; HSP90AA1: Heat Shock Protein 90 Alpha Family Class A Member 1; MAPK1: Mitogen-Activated Protein Kinase 1; PPI: Protein-Protein Interaction.

INTRODUCTION

Over the past half century, the development of innovative drugs worldwide has been largely dominated by the classical reductionist paradigm of "one gene, one target, one disease." This paradigm aims to precisely inhibit or activate a single physiological pathway through the design of highly selective ligands, thereby theoretically minimizing off-target effects and adverse drug reactions [1]. However, with increasing human life expectancy, the major challenges faced by modern medicine have shifted from acute infections caused by single pathogens to chronic and systemic diseases arising from the complex interplay of genetic, environmental, and metabolic factors, such as malignant tumors, cardiovascular diseases, neurodegenerative disorders, and metabolic syndrome [2]. Large-scale functional genomics studies have shown that many single-gene knockouts produce little or no significant phenotypic effect, and only approximately 34% of single-gene knockouts result in overt disease or lethality. This finding reveals the strong homeostatic compensation mechanisms and pathway redundancy inherent in biological systems [1]. Therefore, strategies designed to modulate a single target often show limited clinical efficacy and are prone to drug resistance when applied to complex disease networks, contributing to the persistently high attrition rate in clinical drug development [1].

Against this background, network pharmacology, grounded in the concepts of systems biology and polypharmacology, has emerged as a new research paradigm. Since the British pharmacologist Hopkins first proposed this concept in Nature Biotechnology in 2007, network pharmacology has profoundly reshaped the logic of traditional drug discovery by introducing a new network-based intervention model characterized by "multiple targets, multiple effects, and complex diseases." This frontier concept in modern life sciences resonates strongly with the holistic philosophy and the therapeutic principle of "multiple components, multiple targets, and multiple pathways" emphasized for thousands of years in herbal medicine, including traditional Chinese medicine, Kampo medicine in Japan, and Ayurveda in India [3].

Herbal preparations and the phytochemical networks derived from them are not random mixtures of constituents. Rather, they represent complex chemical combinations with specific biological synergistic or antagonistic effects, selected through thousands of years of accumulated clinical experience in humans [4]. In the past, due to the lack of methodological tools capable of effectively deciphering the mechanisms by which such "ultra-complex chemical systems" act on "ultra-complex biological networks," the scientific value and clinical efficacy of herbal medicine were not fully recognized by mainstream modern medicine worldwide [1]. The maturation of network pharmacology has provided a critical tool for decoding herbal medicine. With the aid of high-throughput sequencing, multi-omics technologies, and artificial intelligence algorithms, the international academic community is conducting high-resolution network-topological analyses and target predictions for vast numbers of phytochemical constituents. These efforts not only accelerate the discovery of lead compounds derived from natural products but

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also provide solid molecular mechanistic evidence for the international regulation and standardized evaluation of herbal formulations [3].

This review focuses on the most recent global academic advances and regulatory developments, and provides an in-depth analysis of the evolution of graph-theoretical and artificial intelligence algorithms, the integration of single-cell and spatial multi-omics technologies within the field of herbal network pharmacology. It aims to provide strategic insights and scientific guidance for the future development of precise, sustainable, and internationally acceptable herbal medicines.

Databases and Complex Network Topological Algorithms in Network Pharmacology

The accuracy and predictive power of network pharmacology research are fundamentally constrained by the quality and breadth of its underlying datasets. With the continuous improvement of global data-sharing mechanisms, herbal network pharmacology has established a multidimensional and heterogeneous database ecosystem spanning natural product chemical space to human disease genomics.

At the initial stage of herbal compound identification and target screening, researchers need to integrate multiple layers of databases. These databases can generally be divided into three core categories: natural product and herbal resource databases, drug–protein interaction and target databases, and disease–gene–phenotype association databases (Table 1).

The computational workflow of network analysis usually begins by retrieving the chemical constituents of a target herb from herbal resource databases, such as TCMSP or SymMap. Pharmacokinetic and drug-likeness thresholds, such as oral bioavailability (e.g. OB > 30% DL > 0.18) and drug-likeness (e.g.STRING) are then applied to exclude compounds that are unlikely to be absorbed in humans or lack potential medicinal value [5]. Subsequently, target prediction platforms and protein–protein interaction networks, such as STRING, are used to construct the full set of proteins potentially perturbed by the herbal formula or compound combination. Finally, this target set is integrated with disease-specific pathological networks extracted from DisGeNET or OMIM, followed by overlap and topological analyses to identify the potential therapeutic network through which the herbal intervention may act on the disease [5].

Living systems are not composed of isolated linear pathways. Instead, they exhibit complex topological properties, including scale-free and small-world characteristics. In networks that often contain thousands of nodes, such as proteins, genes, and metabolites, and tens of thousands of edges representing biological interactions, manual interpretation is virtually impossible. Therefore, graph theory and network topology algorithms have become indispensable mathematical tools for extracting the core value of network pharmacology [6].

In current studies, the principal algorithms used to evaluate the importance of network nodes and identify hub targets include the following.

Table 1: Database commonly used in herbal network pharmacology

Database Type	Representative database names	Core Function Description and Application Scenarios	Data resource links and international status
Integrated Platform of Herbal Medicine and Systems Pharmacology	TCMSP (Traditional Chinese Medicine Systems Pharmacology Database)	The world's most widely used systemic pharmacology platform for traditional Chinese medicine, capturing the relationship between traditional Chinese medicine, components, targets, and diseases. Includes oral bioavailability (OB) and drug-likeness (DL) parameter filtering.	Occupies a core position, providing initial high-throughput screening data for a large number of network pharmacology studies [25]
Integrated Platform of Herbal Medicine and Systems Pharmacology	BATMAN-TCM & TCMID	A bioinformatics-based tool for analyzing the molecular mechanisms of traditional Chinese medicine. It supports automatic retrieval of components and construction of multidimensional interaction networks by inputting prescriptions, herbal names, or PubChem IDs.	Bridges the gap between traditional Chinese medicine theory and modern life science databases [16]
Integrated Platform of Herbal Medicine and Systems Pharmacology	HERB & SymMap	A high-throughput experimental and literature-driven database of traditional Chinese medicine. SymMap particularly enhances the mapping between traditional Chinese medicine syndromes and modern disease targets. Mapping).	Improves the computability and interoperability of TCM diagnostic terminology with modern molecular mechanisms [26]
Integrated Platform of Herbal Medicine and Systems Pharmacology	PharmDB-K & African Natural Products Database	PharmDB-K is an international regional database that integrates 262 traditional Korean medicines, 7,815 compounds, and 32,373 protein relationships.	Greatly expands the global perspective of network pharmacology, covering Ayurveda, Korean traditional medicine, and African herbal medicine [27]

General compound and target prediction library	PubChem, DrugBank, ChEMBL, ChemSpider	An internationally standardized comprehensive database of chemical structures, physicochemical properties, and drug targets. Used to retrieve the precise three-dimensional structures and known pharmacokinetic characteristics of active monomers.	The cornerstone of drug discovery ensures the global universality and accuracy of chemical information on herbal ingredients [25]
General compound and target prediction library	SwissTargetPrediction, PharmMapper, SEA	An advanced target prediction network server based on molecular similarity and reverse pharmacophore mapping.	Can make high-probability inferences about native targets for rare natural compounds that lack known targets [28]
Disease Target-Gene Phenotype Association Library	DisGeNET & Open Targets	Integrates disease-gene interaction maps from large-scale literature mining, genome association studies (GWAS), and animal model data, and provides association confidence scores.	Provides a decisive basis for defining the core biological network boundaries of complex diseases (such as tumors and age-related diseases) [29].
Disease Target-Gene Phenotype Association Library	OMIM, TTD (Therapeutic Target Database), HPO	OMIM provides a library of human Mendelian genetics and complex phenotypes; TTD focuses on approved or clinically tested therapeutic targets.	Supporting reverse pharmacological screening of herbal network pharmacology to ensure that the targets intervened have real clinical therapeutic significance [25].
Protein Interactions and Biological Pathways Library	STRING, MINT, IntAct	A large-scale protein-protein interaction (PPI) database that integrates experimentally validated and computationally predicted protein interaction data.	Provides the basis for constructing a signal cascade amplification effect, helping to identify key downstream nodes that are not directly bound by drugs but participate in signal transduction [16].

1. Degree Centrality

This is the most basic and widely used topological metric that calculates the number of direct connections that a node has within a network. In herbal medicine–disease protein–protein interaction networks, nodes with very high degree values, such as AKT1, TNF, EGFR, PTGS2, IL-6, and TP53, which have repeatedly been identified in studies of different diseases, are usually regarded as core hubs that maintain the stability of pathological networks [7]. Disrupting or modulating these highly connected nodes may trigger network-level collapse or remodeling with minimal intervention cost. Therefore, they are often considered primary targets through which multi-component herbal medicines exert their pharmacological effects.

2. Betweenness Centrality

Unlike degree centrality, betweenness centrality does not focus on how many direct connections a node possesses. Instead, it measures how frequently a node lies on the shortest paths between all other pairs of nodes in the network. Proteins with high betweenness centrality may not necessarily have extensive direct interactions, but they often occupy key positions that control information flow and signal crosstalk between different biological modules, such as metabolic and inflammatory modules [8]. For herbal interventions, targeting high-betweenness nodes may effectively block the propagation of pathological signals across different biological subsystems [5].

3. Closeness Centrality

Closeness centrality measures the reciprocal of the average shortest path length from a given node to all other nodes in the network. Nodes with high closeness centrality are topologically located near the geometric center of the network. This means that when active herbal constituents act on such nodes, their pharmacological signals can spread rapidly across the entire system through the shortest possible biochemical cascade steps, thereby influencing the global system state [5].

4. Multiscale Interactome Algorithms and Degree-Weighted Path Count

With the increasing depth of research, simple undirected graph analysis has become insufficient. Recent methodological studies have introduced weighted algorithms that incorporate drug dosage and interaction strength, such as dose-weighted network pharmacology [9], as well as the Degree-Weighted Path Count algorithm. These approaches analyze the differential effects of drug treatment and disease perturbation on multiscale interactome networks that integrate proteins and biological functions. As a result, they substantially improve the accuracy of distinguishing known therapeutic effects and predicting new indications [10].

5. Community Detection Algorithms

Community detection algorithms, such as the recursive Louvain method and greedy modularity-based algorithms, are widely used to identify subgraphs or communities within complex networks that are densely connected internally but sparsely connected with other modules [6]. In herbal medicine network pharmacology, these algorithms help reveal how different groups of constituents in complex herbal formulas target distinct pathophysiological modules. For example, one group of compounds may primarily act on an immune-evasion community, whereas another group may target an angiogenesis-related community [6].

Artificial Intelligence and Multi-Omics-Driven Precision Systems Pharmacology

Although traditional network pharmacology has achieved considerable success in elucidating the multi-target mechanisms of herbal medicines, it remains heavily dependent on static associations derived from existing databases. As a result, it faces major limitations, including high-dimensional data noise, an inability to capture dynamic time-series processes, and insufficient spatial resolution for specific

cellular microenvironments [11]. From 2024 to 2026, this field has been undergoing a transformative upgrade driven by artificial intelligence and multi-omics technologies, greatly enhancing the precision and target specificity of mechanistic studies on herbal medicines.

In large-scale herb–disease networks, data are organized as highly non-Euclidean graph data. The development of deep learning, particularly graph neural networks, has provided revolutionary algorithmic support for processing heterogeneous networks with rich topological structures and node features [12].

In cutting-edge studies on herbal target prediction and interaction analysis, graph neural networks have demonstrated outstanding performance in capturing hidden cross-dimensional relationships. For example, a study proposed a graph neural network model named MAMGN-HTI, which constructs traditional herbal formulas, therapeutic phenotypes, active ingredients, and gene targets into a large-scale heterogeneous graph. This model innovatively integrates residual graph convolution, dense graph convolution, and cross-layer skip connections. More importantly, it introduces an attention mechanism that dynamically assigns weights to metapaths capturing potential relationships between nodes. As a result, the model shows strong robustness and generalizability in predicting herb–target interactions and screening candidate therapeutic agents [13].

In another research, the HTINet2 framework constructs a large-scale knowledge graph incorporating herbal attributes, such as the four properties, five flavors, and meridian tropism, together with accumulated clinical treatment experience. By using deep knowledge embedding and a Bayesian personalized ranking loss function, this framework has achieved important progress in overcoming the incompleteness of clinical experience data and the limitations of unsupervised models [14].

To meet the stringent mechanistic interpretability requirements of modern pharmacology, path-based explainable graph neural network models, such as SDCInterpreter, have been developed. This model uses relational graph convolutional networks for node representation learning and applies mask learning together with Dijkstra's shortest-path algorithm. It can not only predict the synergistic effects of combined herbal constituents but also automatically generate simulated signal transduction paths, thereby identifying the specific edge-level interactions that dominate the observed synergy. In addition, layer-wise relevance propagation has been applied to reverse-infer artificial intelligence-based predictions of multi-target actions in traditional herbal medicine. This provides a clear biological traceability path for the holistic efficacy of herbal formulas and greatly enhances the clinical persuasiveness of computational predictions [15].

Static network pharmacology usually relies on tissue-level bulk omics data. The averaged signals from mixed cell populations can completely mask critical intra-tissue heterogeneity, especially rare cell subpopulations that play decisive roles in drug resistance or tumor immune escape [16]. The introduction of single-cell multi-omics and spatial metabolomics has enabled herbal network pharmacology to achieve, for the first time, a cross-scale spatial transition from "macroscopic organ-level networks" to "microscopic cell–cell communication networks"[11].

In a representative case of hepatocellular carcinoma, researchers integrated network pharmacology, single-cell transcriptomic analysis, and molecular dynamics simulation to deeply investigate the anticancer mechanism of the traditional medicinal herb Polygonum cuspidatum. Single-cell multi-omics enabled researchers to precisely identify specific immune-cell and fibroblast subpopulations within the tumor microenvironment. The study revealed that physcion diglucoside, a core active constituent of Polygonum cuspidatum, could specifically target aberrantly expressed CDK1 and ESR1 and improve tumor prognosis by modulating the HSP90AA1 and MAPK1 pathways. Such precise characterization of drug response at single-cell resolution is beyond the reach of conventional network pharmacology [16,17].

In studies of non-small cell lung cancer, international researchers have deeply integrated network pharmacology with spatial metabolomics, combined with matrix-assisted laser desorption/ionization mass spectrometry imaging. This approach revealed the underlying mechanisms by which Achyrocline satureioides may exert anti-lung-cancer effects. The study not only identified six core pharmacodynamic constituents represented by quercetin but also, for the first time, visually traced the spatial aggregation of 32 related metabolites within the three-dimensional tumor tissue context. It precisely reconstructed how herbal constituents reprogram metabolic networks within specific tumor microenvironmental niches and regulate seven key anticancer pathways [16].

Constructing single-cell-level drug response networks presents enormous challenges in data dimensionality. Current state-of-the-art computational frameworks, such as scDEAL and SCAD, use deep transfer learning and domain adaptation strategies. These algorithms can extract high-dimensional features learned from large-scale transcriptome-wide in vitro drug screening datasets and map them onto single-cell sequencing data from clinical patients. Through this unsupervised knowledge transfer, researchers can predict, in a virtual environment, changes in the sensitivity of different cell types within residual tumor lesions to specific herbal constituents. This further reveals the complex network dynamics by which chemotherapy-induced transcriptional stress states and inflammatory stromal cells co-evolve [18]. These advances indicate that herbal drug development is formally entering a new era of dynamic network pharmacology based on spatiotemporal dynamics [19].

Current Challenges in Herbal Network Pharmacology

Although herbal network pharmacology based on big data and computational biology has grown explosively worldwide, scientists have raised serious methodological concerns regarding the apparent prosperity of this discipline. For example, in an in-depth review, a highly critical assessment of the "academic bubble" underlying this rapid expansion was proposed [20]. Unless the following limitations are recognized and overcome, many discoveries generated by network pharmacology will remain unable to translate into genuine clinical therapies.

The most critical challenge currently facing network pharmacology is the translational gap. A systematic review and meta-analysis of recent high-impact studies meeting predefined inclusion criteria showed that as many as 61.1% of herbal network pharmacology studies were entirely based on in silico analysis. Only 22.2% included additional in vitro validation at the cellular level, while studies that further verified target interactions in in vivo animal models accounted for only 16.7% [21]. These findings indicate a clear tendency in the academic community to rely on an easy "pipeline-running" approach based on open-access databases.

Because many studies are excessively dependent on platforms such as TCMSP and STRING, which inevitably contain missing data and historical biases, a large number of papers have produced conclusions that appear comprehensive but lack a solid evidential basis. This not only distorts the true historical trajectory of many discoveries in plant science but also generates hypotheses that lack reliability for clinical translation because they have not been confirmed by rigorous wet-laboratory experiments [22]. The absence of high-quality validation based on real biophysical affinity measurements, such as surface plasmon resonance and biolayer interferometry, has therefore cast serious doubt on the scientific rigor of the entire field [23].

In addition, when constructing "compound–protein" networks, traditional network pharmacology usually evaluates target binding

using Boolean logic, namely the presence or absence of an interaction. From a pharmacological perspective, this is an extremely hazardous oversimplification. Panossian explicitly pointed out that the pharmacological effects of phytochemicals are highly dependent on their absolute concentrations at the target site, yet this dosage dependency is almost entirely ignored in existing network topological analyses [20].

A key issue in drug discovery is whether a molecule can effectively reach its site of action. However, current computational predictions for herbal medicines are often seriously detached from real pharmacokinetic profiles and physiological barrier contexts. Even if molecular docking suggests that an active constituent has high binding affinity for an intracellular kinase, such a conclusion may be invalid if actual resistance mechanisms in the physiological environment are ignored. For example, before large natural product molecules enter target cells, they may be rapidly pumped out by efflux transporters such as P-glycoprotein in the intestine and liver. This systemic physiological resistance can physically prevent compounds from reaching the intracellular environment, thereby overriding and nullifying any downstream complex signaling cascades predicted by network pharmacology [20].

Furthermore, the fundamental distinction between herbal medicines and purified single compounds lies in the inherently high chemical variability of herbal preparations. Because of differences in soil conditions, climate, harvesting season, and extraction procedures, even plant extracts derived from the same species may show markedly different chemical fingerprints [20]. The current practice of relying excessively on idealized and generalized compound lists from public databases directly causes analytical results to diverge from the actual pharmaceutical-grade standardized herbal preparations used in the market, which usually contain defined ranges of specific active markers. This will greatly undermine the reproducibility of research findings.

Last but not least, most models focus on verifying how different constituents synergistically enhance the regulation of specific pathways, but very few computationally model or quantify the traditional compatibility principles of counteraction or incompatibility, such as “mutual suppression,” in which antagonistic interactions reduce therapeutic efficacy, or “mutual incompatibility,” in which combined use produces toxicity. This methodological defect may seriously violates the scientific objectivity required by systems biology.

To address these problems, international collaborative networks, such as the EQUATOR Network and the GP-TCM Research Association in Europe, are urgently developing extended reporting guidelines for systematic reviews and meta-analyses, including the proposed PRISMA-NP framework. These initiatives aim to impose stricter standards on data transparency, validation hierarchy, and analytical procedures in network pharmacology literature [24-29].

CONCLUSION AND FUTURE PERSPECTIVES

Over the more than a decade since Hopkins proposed the concept of network pharmacology, research on herbal medicine has undergone a profound cognitive transformation. With the support of high-density database engines such as TCMSP and Open Targets, together with the powerful computational capacity of graph neural networks, the previously abstract and ambiguous multi-target synergistic effects of herbal medicines can now be quantified and visualized within highly refined protein interaction topology maps. The full-scale integration of single-cell multi-omics and spatial metabolomics has further endowed this technology with a high-resolution perspective capable of penetrating complex tumor microenvironments and capturing spatiotemporal dynamic changes.

However, the other side of this rapid development cannot be ignored. The fact that approximately 60% of current studies remain purely computational indicates that the field has become overly dependent on data mining and, in some cases, detached from the biological essence of living systems. For herbal preparations, current static topological networks remain overly idealized when dealing with extreme extract heterogeneity, stringent concentration-dependent toxicological effects such as hormesis, and systematically underestimated physiological and metabolic barriers, including P-glycoprotein-mediated efflux.

Looking ahead to the next decade, the internationalization and modernization of herbal network pharmacology must achieve decisive breakthroughs in two major dimensions. Firstly, the field must move from static fitting toward spatiotemporally dynamic quantitative systems pharmacology. Rigid networks based solely on Boolean logic, namely the presence or absence of interactions, should be replaced by dynamic modeling technologies based on large-model transfer learning, such as the scDEAL framework. Future artificial intelligence models should be able to accurately integrate time-series changes in drug concentration, gradients of cell–cell communication within specific tissue spaces, and realistic pharmacokinetic dynamics. Such integration will enable the construction of multidimensional digital twin models that not only describe whether an interaction exists, but also clarify the magnitude and direction of synergistic actions, including activation and antagonism [11]. Secondly, rigorous wet-laboratory validation must be enforced. Data-transparency and implementation guidelines must be promoted. Any isolated in silico hypothesis should be accompanied by high-standard biophysical interaction assays, such as surface plasmon resonance or biolayer interferometry, multi-omics expression analysis, and, where appropriate, phenotypic confirmation using organoids or transgenic animal models. Only through such validation can the field cross the “valley of death” in translational research.

Herbal network pharmacology is not merely using cutting-edge modern technologies to explain ancient natural medicine. It is also nurturing and defining a new paradigm for how humanity may address complex systemic diseases in the next generation. In this new era where computation and life sciences converge, scientific validation and ancient empirical knowledge will move forward together, illuminating the future path toward precise botanical medicine.

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