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From phytocompounds to poly-pharmacology: A narrative review on network pharmacology

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Abstract

Background: The way drug discovery is conducted has evolved from a singular focus on monotherapy to a more advanced approach which utilizes polypharmacology. The development of such an approach is critical to drug development, especially to drug development which is based on phytocompounds which targets multiple pathways at once.

Objective: The aim of this paper is to conduct a narrative review on the use of network pharmacology poly pharmaceutical approaches to phytocompounds, starting from molecular profiling to therapeutic use.

Methods: We conduct a narrative review on the current approach to the identification of active phytochemicals, bioactive compound screening, and drug discovery by network pharmacology. The review details experimental workflows, computational network pharmacology, database network pharmacology, and validation approaches which network pharmacology to drug development.

Results: The application of network pharmacology to drug discovery has resulted in the refinement of methodologies used to elucidate functional polypharmacy and phytocompounds targeted complex interactions. Notable refinements advanced in bioactivity screening, linkable pharmacochemical repositories, and holistic omics frameworks. Multiple case studies show the delineation of herbal medicine action and the discovery of connected disease network therapeutic fusions. Synthesizing current bioinformatics enables rational, structure-based prediction of the protein in gene-protein interactions

Keywords: Network Pharmacology; Polypharmacology; Phytocompounds; Herbal Medicines; Systems Pharmacology; Multi-Target Drug Discovery; Traditional Chinese Medicine (TCM); Ayurvedic Formulations; Protein–Protein Interaction Networks; Drug–Target Networks; Bioactive Natural Products; Molecular Docking; Systems Biology; Computational Pharmacology; Drug Repurposing; Omics Integration; Artificial Intelligence in Drug Discovery

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1. Introduction

The drug discovery landscape has undergone a significant transformation, moving away from the traditional "one drug–one target" paradigm toward strategies that address the complexity of biological systems through multi-target interventions [1] .This shift has been driven by growing evidence that many diseases arise from dysregulation of interconnected molecular networks rather than isolated targets. In this context, phytocompound research has gained renewed attention, as natural products possess chemically diverse structures capable of interacting with multiple biological pathways simultaneously. Polypharmacology has emerged as a conceptual framework that recognizes and exploits the ability of a single compound to modulate several targets at once. Earlier drug discovery efforts primarily focused on developing highly selective agents aimed at individual molecular targets. However, it is now well established that most drugs exert their therapeutic effects through interactions with multiple proteins and signaling pathways[2] .This multi-target behavior is particularly advantageous in the treatment of complex diseases such as cancer, neurodegenerative disorders, and metabolic syndromes, where modulation of several pathways can enhance therapeutic efficacy and reduce the development of drug resistance.Importantly, polypharmacology differs from polytherapy, which involves the concurrent administration of multiple drugs. Instead, polypharmacology seeks to design or identify single agents capable of acting on multiple key targets in a coordinated manner, thereby achieving synergistic effects while minimizing adverse outcomes associated with non-specific interactions [3] .Network pharmacology provides the methodological foundation to operationalize these concepts by integrating systems biology, bioinformatics, and network analysis. Through the construction and analysis of drug–target–gene–disease networks, network pharmacology offers a holistic view of therapeutic mechanisms that extends beyond the scope of reductionist approaches[4] .The integration of network pharmacology with traditional medical systems, particularly Traditional Chinese Medicine (TCM), further highlights the strength of this approach. TCM inherently adopts a holistic therapeutic philosophy that aligns closely with multi-target drug discovery strategies. By combining traditional knowledge with modern computational and systems-level analyses, network pharmacology bridges ancient medical practices with contemporary drug discovery science [5] .

2. Polypharmacology and network pharmacology: concepts and evolution

Polypharmacology is now attracting great interest because it is a paradigm change from the targeted drug discovery, in which drugs generally interact with plenty of targets or activate multiple disease pathways at the same time in a given dosage range. This is of special interest for complex diseases, especially cancer, neurodegenerative diseases, and metabolic syndromes, in which simultaneous targeting of multiple biological pathways might result in better treatment response and lower drug resistance. Unlike polytherapy, which is the use of several drugs, Polypharmacology focuses on a single agent designed or understood to exert effects on multiple key proteins or pathways, enabling synergistic outcomes and minimizing adverse effects caused by off-target interaction[6].The foundational work by[7] 2013 introduces the concept of compound promiscuity, emphasizing that many drugs are designed to interact with multiple targets and signaling pathways. Their findings suggest that while the traditional view of drug design focused on target selectivity, the emerging paradigm of polypharmacology acknowledges the significance of compounds binding to several targets. This shift is particularly noteworthy in oncology, where the multifaceted nature of diseases necessitates a broader approach to treatment. The authors highlight the challenges in fully understanding compound promiscuity due to data incompleteness, which complicates the comprehensive testing of all compounds against all targets.Building on this foundation[8] Systems-Mapping of Herbal Effects on Complex Diseases Using the Network-Perturbation Signatures delve into the complexities of herbal medicine, particularly within the framework of Traditional Chinese Medicine (TCM). Their research integrates gene expression profiles from a wide array of diseases with chemical data from various herbs, creating perturbation signatures that elucidate the multi-target effects of herbal ingredients. This systems-mapping approach underscores the potential of herbal medicine to address complex diseases through multi-component interactions. However, the authors note that while TCM demonstrates significant therapeutic efficacy, the underlying mechanisms of synergy among herbal formulas remain inadequately understood, posing challenges for their application in modern medicine. Further advancing the discussion, Panossian and Efferth [9]explore the network pharmacology of adaptogens, showcasing how natural products can embody the principles of polypharmacology. Their analysis illustrates that many herbal compounds possess structural diversity and the ability to modulate multiple biological targets, thereby enhancing therapeutic efficacy. The authors argue that this multi-specific activity not only aligns with the polypharmacological approach but also provides a strategic advantage in drug discovery. By leveraging the inherent complexities of herbal mixtures, researchers can develop more effective treatments that align with the principles of modern pharmacology. Together, these articles present a nuanced understanding of polypharmacology in herbal medicine, revealing both the potential and the challenges of integrating traditional practices with contemporary scientific frameworks. The literature suggests a need for continued exploration into the mechanisms of action and interactions within herbal formulations, paving the way for innovative therapeutic strategies that harness the power of

Polypharmacology. Network pharmacology, as a methodological framework and practical implementation of Polypharmacology, uses in a drug discovery context the systems biology, bioinformatics and network science tools applied in nearly all fields of public health research. It models drug, target, pathway, disease and their complex associations as network structures and computationally predicts such interactions that are then experimentally validated in high-throughput. In this proposal we embrace the "network target" model to address biological networks beneath the disease as the advocated therapeutic object, as opposed to single molecular targets. Network pharmacology, first proposed by Hopkins (2007) [10]provides a new approach for studying multi-constituent, multi-target complex traditional Chinese medicine.

3. Phytochemical profiling and bioactivity screening

The exploration of phytocompound profiling and bioactivity screening has garnered significant attention in recent years, as researchers seek to unravel the potential therapeutic benefits of plant-derived substances. The literature on this topic reveals a progressive understanding of phytochemical identification, bioactivity assessment methodologies, and the increasing reliance on advanced technologies and databases to facilitate research. In 2012, Pandith's study highlighted the variability in phytochemical composition across different plant species, emphasizing the importance of extraction methods in isolating bioactive compounds. The research demonstrated that ethanol extraction yielded a higher concentration of phytocompounds compared to other solvents, suggesting that the choice of extraction method is crucial for maximizing the therapeutic potential of plants. Pandith's findings laid the groundwork for subsequent studies by establishing a connection between specific genera and their pharmacological applications, particularly focusing on the genus Achyranthes aspera[11]. Building on this foundation (Zhuo et al)introduced the concept of ligand fishing as a novel approach to identify bioactive compounds from complex mixtures. Their work underscored the limitations of traditional methods in discerning the relationships between phytochemical constituents and their biological targets. By advocating for the development of multi-target ligand fishing systems, the authors highlighted the need for innovative screening techniques that could enhance our understanding of the mechanisms of action of natural products. This perspective is crucial as it aligns with the growing complexity of natural product chemistry and the necessity for more sophisticated analytical methods[12]. The application of metabolomics in bioactivity screening was further advanced in the study by Choi et al., which explored the bioactive metabolites present in indigenous Korean plants. Their multi-parallel metabolomic approach not only identified key compounds, such as biflavonoids and phenolic acids, but also established a direct link between specific metabolites and their biological activities. This research exemplified the potential of tailored metabolite profiling to inform therapeutic applications, suggesting that systematic screening can lead to the discovery of significant bioactive compounds relevant for health and medicine [13].

In 2022, Mahmud et al. contributed to the field by developing phytochemdb, a platform designed for virtual screening and computer-aided drug design. This publicly accessible database enables researchers to retrieve detailed phytochemical information and supports in silico drug development efforts. The emphasis on structured datasets and the integration of computational methods underscore the evolving landscape of phytocompound research, where digital tools play a pivotal role in accelerating drug discovery processes[14]. Most recently, Simsek and Whitney examined the health impacts of primary and secondary metabolites derived from plant-based diets. Their findings reinforced the significance of these compounds in preventing chronic diseases and promoting overall health. However, they also pointed out the necessity for more comprehensive clinical trials to substantiate the health benefits attributed to these phytochemicals [15]. This call for further research highlights the ongoing challenges in validating the therapeutic efficacy of plant-derived compounds and emphasizes the importance of translating laboratory findings into clinical practice [15]. Together, these articles reflect a dynamic and evolving field of study that integrates phytocompound profiling, advanced screening techniques, and the utilization of databases and omics technologies to enhance our understanding of the bioactivity of natural products. The collective insights from these works provide a robust framework for future research aimed at harnessing the therapeutic potential of phytochemicals.

4. Methodology of network pharmacology

4.1. Data Collection and Active Compound Screening

Active compounds of the medicinal plant were retrieved from the Traditional Chinese Medicine Systems Pharmacology (TCMSP) analysis platform(http://tcmspw.com/tcmsp.php)

The ADME (absorption, distribution, metabolism, and excretion) model was employed to screen compounds with favorable pharmacokinetic properties.Bioactive compounds were filtered using established criteria of oral bioavailability (OB) ≥ 30% and drug-likeness (DL) ≥ 0.18 to identify candidates with enhanced potency and therapeutic

potential. The canonical SMILES (Simplified Molecular Input Line Entry System) of selected active compounds were obtained from PubChemdatabase(https://pubchem.ncbi.nlm.nih.gov/) for subsequent target prediction.

4.2. Target Prediction and Disease-Related Gene Identification

Potential targets for bioactive compounds were predicted using multiple databases including SwissTargetPrediction(http://www.swisstargetprediction.ch/), DrugBank (https://www.drugbank.ca/), and (http://www.lilabecust.cn/pharmmapper/) . All target proteins were converted to gene symbols using the UniProt database (https://www.uniprot.org/) with species limited to "Homo sapiens" . Disease-related targets DisGeNET(https://www.disgenet.org/), GeneCards (https://www.genecards.org/), NCBI Gene database, and Online Mendelian Inheritance in Man (OMIM) databases . Targets with relevance scores greater than 10 were selected from GeneCards database to ensure high confidence . Common targets between compounds and disease were identified using Venn diagram analysis to obtain potential therapeutic targets.

4.3. Protein-Protein Interaction Network Construction

The protein-protein interaction (PPI) network of common targets was constructed using the STRING database (https://string-db.org/) with interaction confidence score ≥ 0.4 and species restricted to "Homo sapiens".The resulting network was imported into Cytoscape 3.8.0 software for visualization and topological analysis . Hub genes were identified using the CytoHubba plugin with multiple algorithms including Degree, Maximal Clique Centrality (MCC), Maximum Neighborhood Component (MNC), and Closeness centrality . The top-ranking genes from each algorithm were intersected to determine core targets with high network importance.

4.4. Network Topological Analysis

Network topological properties were analyzed using CytoNCA plugin in Cytoscape to calculate betweenness centrality (BC), closeness centrality (CC), and degree centrality (DC) for each node. Nodes with degree values above twice the median and centrality values above the median thresholds were identified as hub targets. The component-target network was constructed to visualize relationships between active compounds and their corresponding targets.

4.5. Functional Enrichment Analysis

Gene Ontology (GO) enrichment analysis encompassing biological processes (BP), cellular components (CC), and molecular functions (MF) was performed using the DAVID database (https://david.ncifcrf.gov/) . Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis was conducted to identify relevant signaling pathways . Enrichment analyses were performed using R software (version 4.3.1) with packages including clusterProfiler, org.Hs.eg.db, enrichplot, and ggplot2. Statistical significance was set at $p < 0.05$, and the top 10 GO terms and top 20 KEGG pathways were selected for visualization.

4.6. Network Construction and Visualization

A comprehensive drug-disease-target-pathway network was constructed using Cytoscape 3.8.0 to illustrate the multi-component, multi-target, and multi-pathway characteristics of the therapeutic mechanism. Network nodes represented.

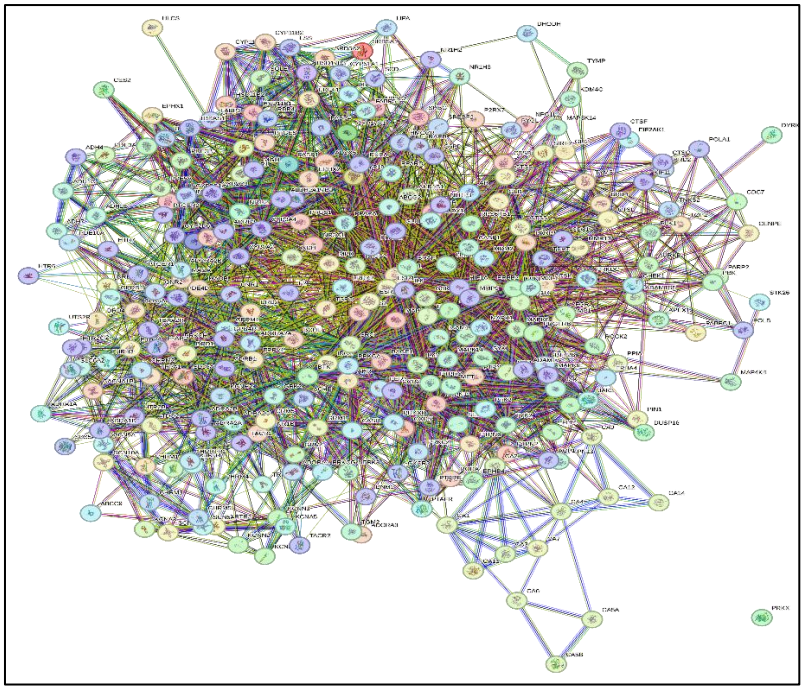

Figure 1 Network Construction of disease and Proteins

Compounds, targets, and pathways, while edges denoted their interactions. The network layout was optimized to clearly display the relationships between different network components.

4.7. Molecular docking Validation

Molecular docking was performed to validate the binding affinity between key active compounds and core protein targets . Three-dimensional structures of target proteins were retrieved from the Protein Data Bank (PDB) database (https://www.rcsb.org/). Compound structures were obtained from PubChem and prepared using ChemBio3D software . Protein preparation included removal of water molecules, co-crystallized ligands, and energy minimization using PyMOL software .Molecular docking was conducted using AutoDock Vina with default parameters . Binding energies below -5.0 kcal/mol indicated medium affinity, while values below -7.0 kcal/mol suggested high binding affinity . Docking poses were visualized and analyzed using PyMOL 2.5.0 software. Network analysis revealed significant clustering of targets in cancer-related pathways, including p53 signaling, apoptosis, cell cycle regulation, and immune system processes.therapeutic outcomes through systems-level interventions[20].Network pharmacology offers fresh perspectives on complex diseases by mapping how different biological systems interact. It looks at protein connections, metabolic pathways, and gene networks together rather than focusing on single targets. This approach works well for tough cases like cancer or heart disease where traditional methods often fall short due to overlapping mechanism[21].The process uses advanced computing tools to build detailed disease maps. Researchers pull data from sources like DrugBank and KEGG then apply graph theory to spot key proteins and pathways worth targeting. These models help uncover critical disease drivers while showing how they connect at a molecular level.For lung conditions like interstitial lung disease, network methods blend traditional medicine insights with modern tech. They reveal how inflammation, scarring, and oxidative stress pathways intertwine in these respiratory issues[22]Cardiovascular studies show similar promise—a mix of Salvia and Pueraria herbs demonstrated protective effects by hitting multiple targets like STAT3 and TNF signaling paths simultaneously.Cancer research benefits greatly from this approach too. Tumors thrive through complex genetic webs that single drugs can't easily disrupt. Network models help identify drug combinations that attack several cancer mechanisms at once through pathways linked to growth signals and metabolism.The real strength lies in finding synergy between treatments. Take stroke research—scientists combined Nox4 inhibitors with Nos-targeting drugs at lower doses than usual and saw better results than either treatment alone gave. Less brain cell death, smaller damaged areas, and better motor function emerged from hitting complementary targets in the network. [23]Well-established traditional medicines gets a stronger scientific evidence behind them also within this perspective [24].For herbal formulas are frequently through several ingredients hitting multiple points of a disease network—say, modulating inflammation at more than one node, not a single one [25].AI tools can turbo-charge these efforts by processing huge amounts of biological data in ways that humans could never do, never mind do it faster than they would ever be able to do [26].Machine learning detects-hidden patterns that predict what combinations of drugs can maximally benefit some patients without posing too much risk of side effects[27].

5. Application

The application of network pharmacology has gained significant traction in recent years, as evidenced by a series of pivotal studies that explore its potential in drug discovery and disease treatment[28]. laid the groundwork by emphasizing the necessity of using molecular networks as interfaces between drug interactions and phenotypic outcomes. Their research highlights that most pharmacological agents interact with multiple network nodes, thereby disrupting the activity of biomolecules rather than targeting specific interactions. This paradigm shift supports drug repurposing and enhances the understanding of complex disease mechanisms, advocating for a more integrated approach to pharmacology.Building on this foundation[29] introduced an innovative web-based tool for interactive visual network pharmacology, which facilitates the exploration of intricate relationships among diseases, targets, and drugs. Their findings underscore the utility of dynamic network graphs in clinical pharmacology, providing a platform for target selection, drug repositioning, and investigation of side effects. This interactive approach not only accelerates research but also enhances the comprehension of multifaceted drug-disease interactions (Hu et al., 2014).Further expanding the discourse[30]contextualized network pharmacology within Traditional Chinese Medicine (TCM), advocating for a shift from the conventional one-gene, one-drug model to a more holistic, network-targeted strategy for addressing complex diseases such as AIDS and cancer. They highlighted the development of computational methods that systematically interpret TCM through various biological and herb networks. Their work emphasizes the importance of tools like drugCIPHER and comCIPHER for drug-target identification and the analysis of drug-gene-disease relationships, showcasing the efficacy of network analysis in herbal pharmacology[31]further explored the integration of network pharmacology with TCM, illustrating how the holistic philosophy of TCM aligns with modern drug discovery methods that prioritize multi-target interactions. Their review articulates the significance of systems biology and bioinformatics in understanding the complex interactions among compounds, proteins, genes, and diseases. This approach not only elucidates the pharmacological mechanisms underpinning TCM but also facilitates a transition toward evidence-based medicine, addressing the limitations inherent in traditional

single-target drug design. The insights provided by these studies collectively underscore the transformative potential of network pharmacology in advancing therapeutic strategies and enhancing patient outcomes[31].

6. Tools and databases for network pharmacology analysis

Table 1 List of Tools and Database for Network Pharmacology Analysis

Tool / Database	Description / Focus	Scopus Ref. / Pub Year
TCMSP	TCM systems pharmacology & drug discovery data	https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2019.00123/full
STRING	Protein-protein interaction networks	https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2019.00123/full
Cytoscape	Network construction& visualization	https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2019.00123/full
NPASS	Natural product activity & source	https://pmc.ncbi.nlm.nih.gov/articles/PMC11095338/
CMAUP	Useful plant activities & molecular data	https://www.plantsjournal.com/archives/2025/vol13issue3/PartC/13-2-34-369.pdf
DrugBank	Drug and compound data	https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2019.00123/full
AutoDock/MOE	Molecular docking platforms	https://www.wjgnet.com/2307-8960/full/v11/i19/4579.htm
HERB	TCM compound database	https://pmc.ncbi.nlm.nih.gov/articles/PMC11095338/

Limitations and future directions

The field of network pharmacology has emerged as a promising approach to drug discovery and disease treatment, yet it is not without its limitations and challenges. [28]highlight several critical constraints faced by network pharmacology, particularly the reliance on large-scale genome-wide expression data. This dependence poses scalability issues when addressing the complexity of regulatory networks in higher eukaryotes. The authors argue for the necessity of improving interaction data and constructing condition-specific networks that can better reflect the dynamic nature of molecular processes. Their insights underscore the pressing need for enhanced data quality and specificity in network analyses, which are vital for understanding drug mechanisms and their effects on biomolecular activities.

Abbreviations

- TCM- Traditional Chinese Medicine,
- PPI-Protein Protein Interaction,
- TNF- Tumour Necrosis Factor

7. Conclusion

Network pharmacology really changed things in drug discovery. You know, it flipped how we see phytocompounds messing with all those tricky biological systems. This whole review shows how we moved from just hitting one target to these smarter ways that tackle multiple spots at once. It fits way better with how diseases actually work in tangled networks. Bringing network pharmacology into phytocompound stuff has been super helpful. Like, tons of case studies back it up, from old Chinese medicine mixes to Ayurvedic ones. Turns out natural products are built for this polypharmacology thing. A single compound or some herbs can tweak a bunch of targets through linked paths all at the same time. That lines up great with tough chronic illnesses, cancer or brain disorders or metabolic issues. Single shots just don't cut it there. Methods have gotten way better too. Compound screening, guessing targets, checking protein links, pathway stuff. All that gives researchers solid ways to figure out why herbal meds work. Databases like TCMSP, STRING, DrugBank make it easier. Tools such as Cytoscape and AutoDock let more people dive in, no matter the setup. Oh and, tossing in AI and machine learning speeds up finding new drug links and tweaking combos. Still, problems stick around. Data quality's iffy sometimes, not complete. We need networks tuned to specific conditions. Turning computer guesses into real clinic use is hard. Big genomic data and those wild regulatory nets in bigger critters make scaling tough. Plus, network pharmacology's ace at sparking ideas and explaining how stuff works, but you gotta test it in labs to prove it and show real healing power. Looking ahead, a few big things point the way. Building fancier models that grab the changing, situation-based side of networks. That's key. Mixing in multi-omics, genomics, proteomics, metabolomics, for deeper looks at drug-target-disease ties. Personalized meds using networks to fit treatments to a patient's own profile sounds promising. And keep validating with solid experiments and clinic trials to turn ideas into actual help. Blending old medicine smarts with today's computer bio via network pharmacology. It's a strong mix, respecting the past while pushing science forward. As we tweak these tools and spread them out, it'll take a bigger spot in tackling 21st-century health messes. Going from phytocompounds to this polypharmacology, steered by networks, lays out a good road to better, whole-person, custom treatments for folks everywhere.So network pharmacology backs up a lot of traditional ways and cracks open fresh paths for smart drug making and combo therapies. Field keeps growing, grabbing new tech and fixing weak spots. It could totally shake up how we find, build, and roll out treatments in this wild healthcare world.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no competing interests.

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