ISSN: 2745-455X (Online)
Indonesian Journal of Pharmacology and Therapy

Network pharmacology approach to identifying optimal therapeutic targets in cancer drug discovery and development: Bibliometric analysis and scoping review

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https://doi.org/10.22146/ijpther.13076

Submitted: 2024-04-29
Accepted : 2025-10-13

Keywords:
bioinformatics; drug discovery; network pharmacology; precision medicine; traditional medicine

ABSTRACT

A rise in chronic diseases, including cancer, increasingly strains public health. While conventional drug discovery often focuses on single molecules, this method frequently fails to address complex diseases with multiple causes. Network pharmacology, a systems biology approach, provides a more complete understanding of disease mechanisms by analyzing intricate biological networks. By combining multi-omics data and computational models, network pharmacology helps identify new drug targets and cellular pathways. This approach is especially promising in cancer research, where it can reveal complex interactions between genes, proteins, and metabolites. This review explains the principles of network pharmacology and its use in cancer drug discovery. We cover the process, from network building and analysis to experimental testing. Additionally, we examine how network pharmacology can speed up the development of personalized cancer treatments.

ABSTRAK

Kesehatan masyarakat semakin terbebani oleh meningkatnya penyakit kronis, termasuk kanker. Penemuan obat konvensional sering kali menargetkan molekul tunggal. Pendekatan ini sering gagal dalam menangani penyakit yang kompleks dengan etiologi yang beragam. *Network pharmacology*, sebuah pendekatan biologi sistem, menawarkan pemahaman yang lebih komprehensif tentang mekanisme penyakit dengan menganalisis jaringan biologis kompleks. Dengan mengintegrasikan data multi-omik dan pemodelan komputasi, farmakologi jaringan memungkinkan identifikasi target dan jalur seluler obat baru. Pendekatan ini sangat menjanjikan dalam penelitian kanker, di mana pendekatan ini dapat digunakan untuk mengungkap interaksi kompleks antara gen, protein, dan metabolit. Ulasan ini mendiskusikan prinsip-prinsip *network pharmacology* dan aplikasinya pada penemuan obat kanker. Ulasan ini membahas alur kerja, mulai dari konstruksi dan analisis jaringan hingga validasi eksperimental. Selain itu, kami mengeksplorasi potensi *network pharmacology* untuk mempercepat pengembangan terapi kanker yang dipersonalisasi.

INTRODUCTION

The increasing global prevalence of chronic diseases such as cancer, diabetes, and cardiovascular disease presents a significant public health crisis. These conditions are often characterized by complex, multifaceted biological mechanisms, presenting formidable challenges to healthcare systems worldwide. While natural products have historically served as a valuable source of therapeutic compounds,[1,2] conventional drug discovery methods predominantly

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adopt a single-target, single-drug paradigm.[3,4] This reductionist approach often proves insufficient for addressing the inherent complexity and redundancy of biological networks that control diseases like cancer, thereby reducing the effectiveness and raising the side effects of many current therapies.

Network pharmacology, an advanced systems biology approach, provides a promising solution to this challenge. It moves beyond focusing on a single target by allowing a comprehensive understanding of disease development through examining complex interactions among numerous biological molecules, including genes, proteins, and metabolites.[5,6] This holistic perspective helps researchers identify multiple, synergistic drug targets and understand the overall therapeutic effects of compounds, including those from natural sources.[7-9] In particular, cancer, a leading cause of death worldwide, serves as a quintessential example of a complex disease, marked by diverse molecular subtypes and interconnected, dynamic signaling pathways.[7,10] The potential of network pharmacology to transform cancer treatment lies in its ability to unravel these complex molecular networks involved in tumor initiation, growth, and metastasis. By pinpointing critical hubs and pathways, this approach can speed up the discovery of optimal therapeutic targets for new drugs and repositioning, ultimately supporting the development of more effective and personalized treatments.

Despite the increasing use of network pharmacology in oncology, a systematic, quantitative, and comprehensive overview of its specific role in identifying the best cancer drug targets is still needed. This paper aims to thoroughly examine the field through both a bibliometric analysis and a scoping review. The bibliometric analysis will quantitatively map the intellectual landscape, spot emerging trends, influential authors, major institutions, and key research areas in network pharmacology related to cancer drug discovery. At the same time, the scoping review will qualitatively summarize the current literature, detailing the established and new workflows of network pharmacology—from network creation and analysis to laboratory validation. By combining these two approaches, this review intends to clearly outline the current knowledge, highlight effective strategies for target discovery, and identify areas for future research. Ultimately, it emphasizes how network pharmacology can play a crucial role in speeding up cancer drug development.

MATERIAL AND METHODS

This study employs a mixed-methods approach, combining a bibliometric analysis to quantitatively map the research landscape and a scoping review to qualitatively synthesize the current evidence regarding the network pharmacology approach in cancer drug discovery. Data for the bibliometric analysis were exclusively retrieved from the Scopus database. Scopus was chosen for its comprehensive coverage of peer-reviewed literature and its robust citation data necessary for network analysis. The search strategy was designed to find documents related to the application of network pharmacology in cancer research: 1) database (Scopus), 2) timeframe (publications from 2015 to 2025), 3) language (English), 4) document type (limited to “Article”), 5) search query (“Network pharmacology” AND “cancer”), and 6) include keyword “Network pharmacology”. All records were exported from Scopus in RIS format, including all metadata such as authors, affiliations, citations, abstracts, and keywords. The extracted data were visualized using VOSviewer software. Additional searches were conducted in other databases (PubMed, Web of Science, and Google Scholar) and through reviewing references from key articles to ensure comprehensive coverage and identify literature that

the specific Scopus query may have overlooked. The collected data were then qualitatively synthesized and organized into thematic categories based on the review objectives.

RESULTS

There is a sharp increase in network pharmacology research for cancer studies from 2020 to 2025, as indicated by a significant rise in Scopus publications (FIGURE 1a). This rapid growth shows a growing recognition of network pharmacology's potential to transform cancer treatment. While the early years experienced modest growth, the recent spike, especially in journals like "Frontiers in Pharmacology," "Journal of Ethnopharmacology," and "Medicine - United States," highlights the field's fast progress (Figure 1b). This trend suggests a future where network pharmacology will play a key role in understanding complex cancer mechanisms, discovering new drug targets, and developing personalized therapies.

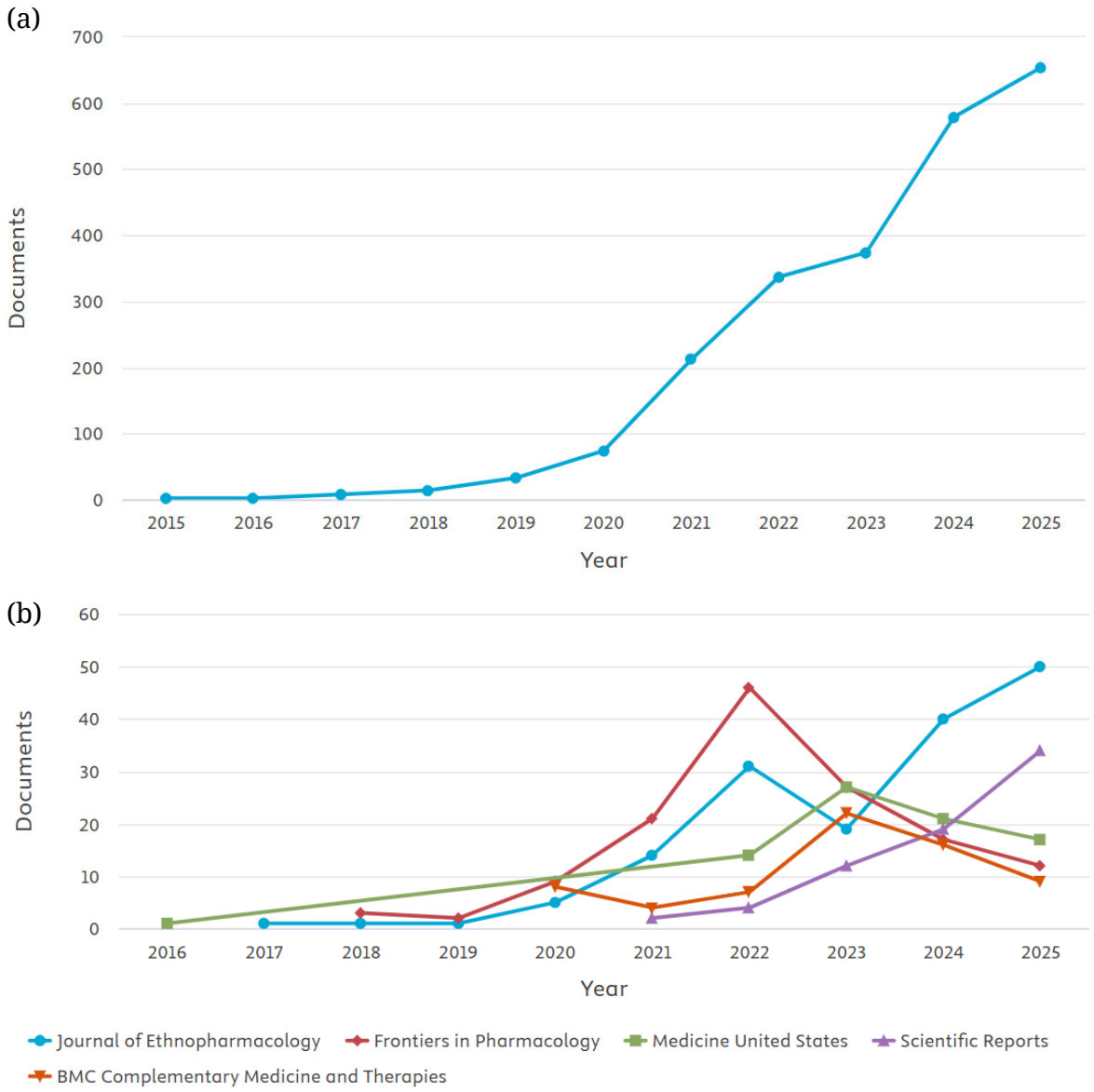


FIGURE 1. The trend in research publications focused on the "network pharmacology approach toward cancer studies" from 2015 to 2025, as extracted from the Scopus database, a) documents by year, b) documents per year by source.

There is a significant global interest in network pharmacology research for cancer studies, with China emerging as the leading contributor, followed by India, Saudi Arabia, and the United States (FIGURE 2a). The most productive research team is Efferth, which has published 15 papers (FIGURE 2b). The top eight most cited publications are listed in TABLE 1. This international collaboration, driven by strong research infrastructure, government support, and a focus on innovation, has the potential to accelerate the development of new cancer treatments and improve patient outcomes worldwide. While these three countries dominate the field, other nations such as South Korea, Germany, Hong Kong, Pakistan, Egypt, and Indonesia also make meaningful contributions, highlighting the global recognition of network pharmacology's ability to address cancer challenges.

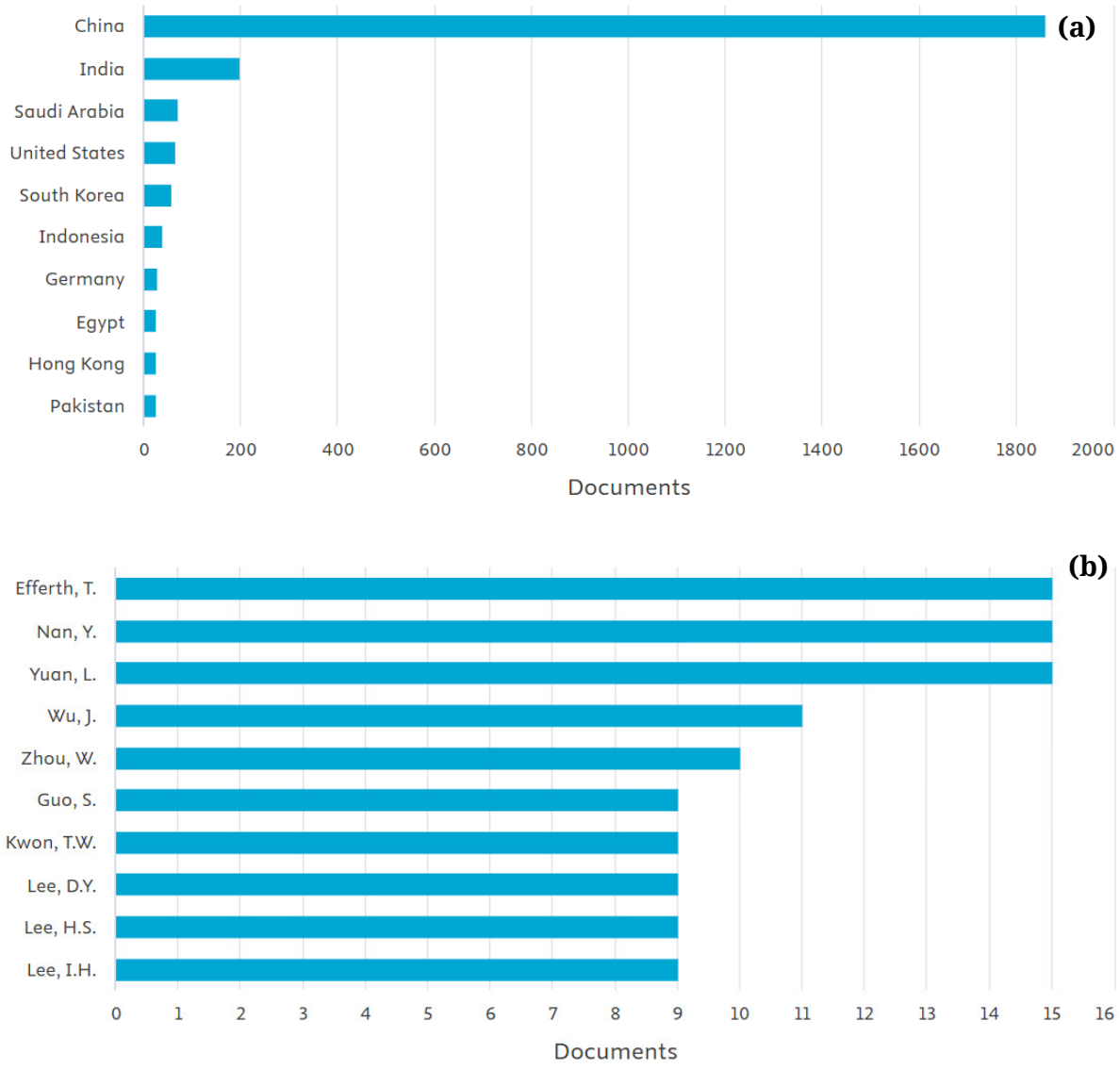


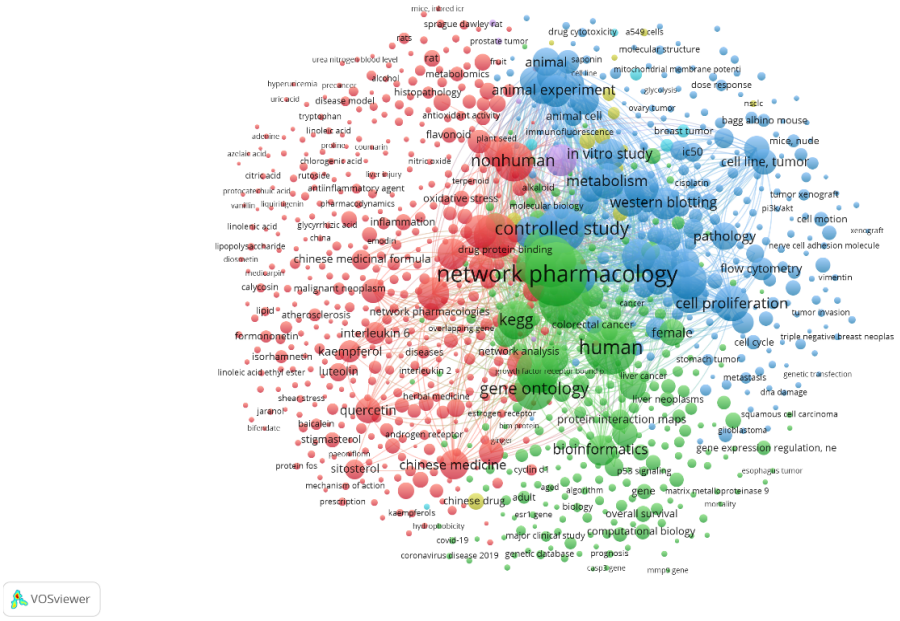
FIGURE 2. The geographic distribution of research publications on "network pharmacology approach toward cancer studies" from 2015 to 2025, as extracted from (a) the Scopus database, and (b) the most productive research team.

TABLE 1. The most cited publication on “Network pharmacology” AND “Cancer”

Title	Author	Source	Citation
Traditional Chinese medicine network pharmacology: Theory, methodology, and application.	7	Chinese Journal of Natural Medicines, 11(2), pp. 110–120	1,497
Mechanism of Sijunzi decoction in the treatment of colorectal cancer based on network pharmacology and experimental validation.	11	Journal of Ethnopharmacology, 302, 115876	206
Models from experiments: Combinatorial drug perturbations of cancer cells.	12	Molecular Systems Biology, 4, 216	163
Network pharmacology strategies toward multi-target anticancer therapies: From computational models to experimental design principles.	13	Current Pharmaceutical Design, 20(1), pp. 23–36	137
Network pharmacology and molecular docking reveal the mechanism of scopoletin against non-small cell lung cancer.	14	Life Sciences, 270, 119105	133
Exploring the pharmacological mechanism of Yanghe decoction on HER2-positive breast cancer by a network pharmacology approach.	15	Journal of Ethnopharmacology, 199, pp. 68–85	114
Erianin, the main active ingredient of *Dendrobium chrysotoxum* L., inhibits precancerous lesions of gastric cancer (PLGC) by suppressing the HRAS-PI3K-AKT signaling pathway, as revealed by network pharmacology and in vitro experimental verification.	16	Journal of Ethnopharmacology, 279, 114399	107
Network pharmacology to unveil the biological basis of health-strengthening herbal medicine in cancer treatment.	17	Cancers, 10(11), 461	105

The network visualization and distribution emphasize the multidisciplinary focus of network pharmacology research in cancer studies (FIGURE 3). The most common keywords are listed in TABLE 2. Fields such as medicine, pharmacology, toxicology, biochemistry, genetics, and molecular biology are prominent, reflecting the clinical importance and molecular insights of cancer. However, other disciplines like chemistry, computer science, and immunology also contribute, highlighting the interdisciplinary nature of this field. This collaborative effort, involving researchers from diverse backgrounds, has the potential to accelerate the development of innovative cancer treatments and improve patient outcomes worldwide.

(a)



(b)

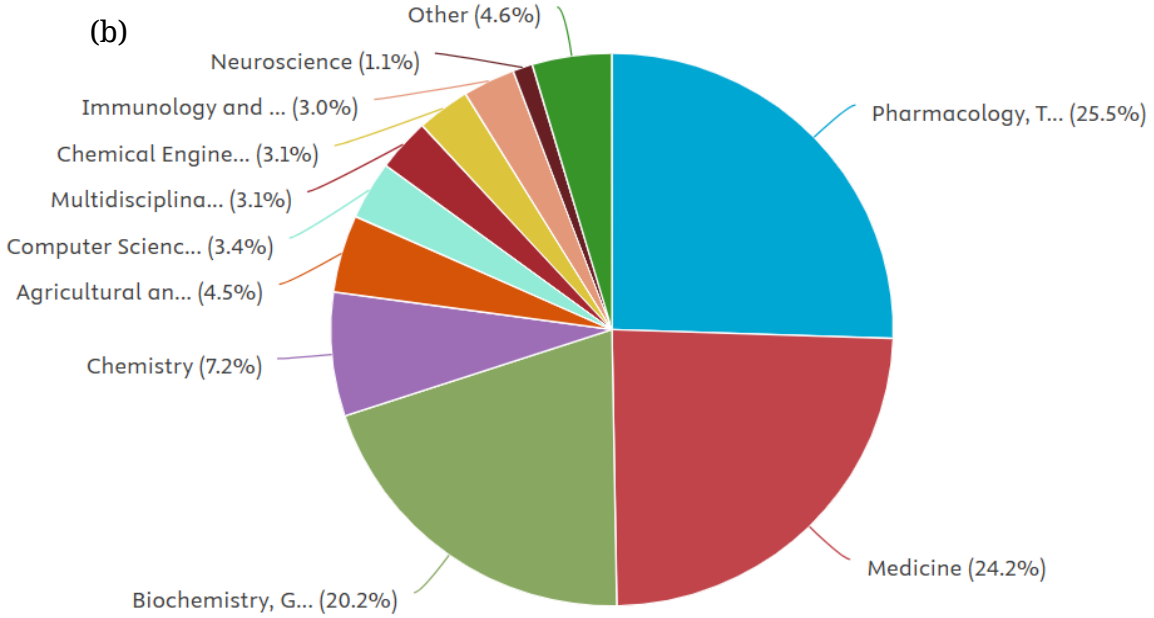


FIGURE 3. (a) The network visualization of frequent keywords related to “network pharmacology research in cancer studies” and (b) the distribution of research publications across different subject areas, based on data from the Scopus database.

TABLE 2. The frequent keywords related to "network pharmacology research in cancer studies".

Keyword	Occurences	Total link strength
Network pharmacology	2296	82792
Human	1646	69108
Systems pharmacology	1518	65299
Molecular docking	1503	57874
Unclassified drug	1132	52431
Protein-protein interaction	1098	48820
Gene ontology	957	43290
Nonhuman	882	42009
Signal transduction	920	41964
KEGG	850	39175

DISCUSSION

From network biology to network pharmacology

The human body is a complex network of interconnected systems. After about 13 years, the project to sequence the entire human genome was finally finished in early April 2003. While sequencing the human genome has given us invaluable insights into our genetic makeup, it is only the first step in understanding the detailed mechanisms behind health and disease.

Traditional biology often studies individual genes or proteins.[18] However, this reductionist approach fails to capture the complex interactions within biological systems. Network biology, on the other hand, takes a holistic approach, analyzing the intricate network of interactions between genes, proteins, and other molecules.[19,20] This systems-level perspective is essential for understanding the development of complex diseases such as cancer, which is often caused by dysregulation of multiple biological pathways.

Network pharmacology, a field closely tied to network biology, uses network-based methods for drug discovery and development. By identifying a drug's multiple molecular targets and understanding their interactions, network pharmacology helps create more effective and safer treatments.[7,20] This method is beneficial for tackling complex diseases with multiple roots, where traditional single-target drug approaches often fail.

Network pharmacology uses advanced computational tools and bioinformatics techniques to build and analyze biological networks.[5,7] By combining different data sources, such as genomics, proteomics, and metabolomics, researchers can find key nodes and pathways vital for disease progression.[17,21] This systems approach helps in identifying new drug targets, predicting drug interactions, and developing personalized medicine (FIGURE 4).

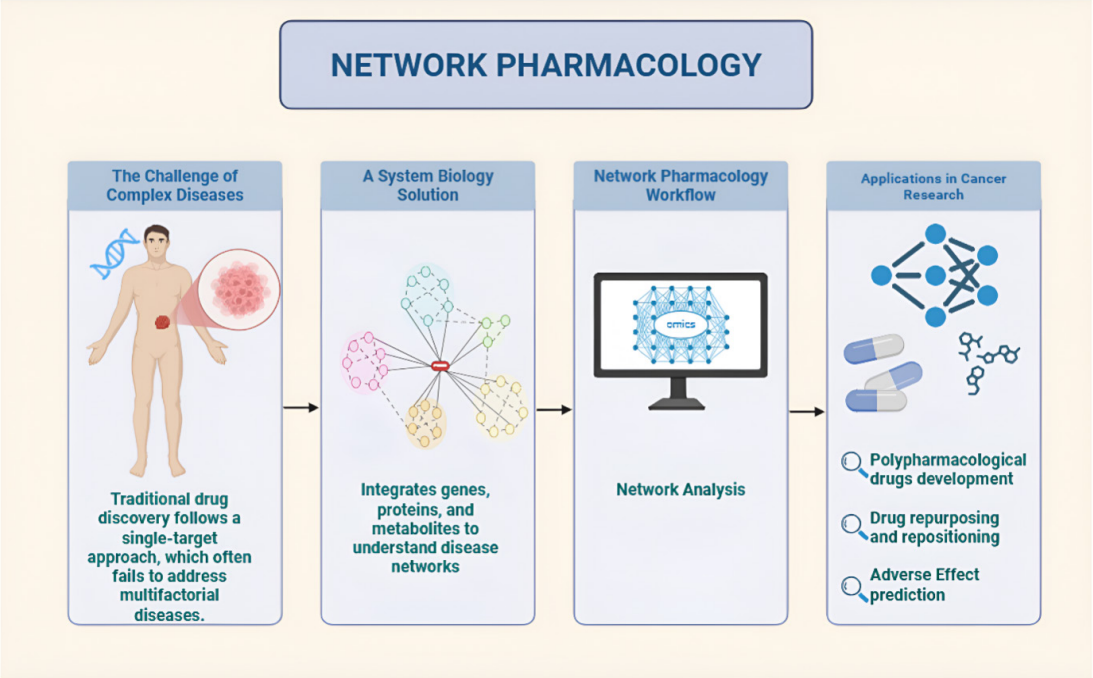


FIGURE 4. The use of network pharmacology in discovering new drug targets, predicting drug interactions, and developing personalized medicine (designed with Biorender.com).

Network ethnopharmacology

Traditional medicine has been practiced for centuries in China and Indonesia.[1,2,21,22] It offers a wealth of knowledge and potential therapeutic benefits. While TM has shown effectiveness in treating various diseases, its complex mechanisms of action often remain unknown.[23] Network pharmacology provides a promising way to modernize and connect traditional and modern medicine. By analyzing the complex network of interactions between bioactive compounds, target proteins, and biological pathways, network pharmacology offers a comprehensive understanding of the synergistic effects of herbal medicines.[22,23]

Traditional Chinese medicine, with its multi-component, multi-target, and multi-mechanism nature[7,24], is especially suitable for network pharmacology analysis. Researchers can identify potential drug targets by combining computational methods with experimental validation, predict drug interactions, and refine therapeutic strategies. Chemoinformatic tools, such as PharmMapper, Cytoscape, and KEGG, have become essential for network pharmacology research.[4,8,9,21] These tools allow for the analysis of large-scale biological networks, prediction of drug-target interactions, and identification of potential drug candidates.[23] Integrating in silico, in vitro, and in vivo studies can speed up drug discovery and help develop more effective and safer therapies.

Knowledge base for network pharmacology

The rise of network pharmacology has transformed drug discovery by moving from single-target treatments to multi-target strategies.[6,7] Traditional drug development often focuses on a single molecular target, which can lead to limited effectiveness and side effects.

In contrast, network pharmacology acknowledges the complex interactions among biological molecules and pathways, allowing for the identification of multiple targets to be modulated for therapeutic benefits.[7,25]

Bioinformatics is essential in network pharmacology because it offers computational tools to analyze large biological datasets. It can identify key molecular interactions and pathways involved in disease development by combining data from sources like genomics, proteomics, and metabolomics.[16,25] This systemic understanding helps researchers find new drug targets and anticipate potential drug interactions.

The workflow of network pharmacology begins with constructing the network. This process involves data mining to gather relevant datasets from diverse databases.[26,27]. Selecting and removing datasets are crucial steps that must be done carefully to ensure proper network integration. The datasets are mapped and visualized to observe interactions. These interactions include gene-to-gene, protein-to-protein, and protein-chemical compound networks.[7,26,27]

Network construction involves data sets obtained from various databases. There are two types of databases: direct and indirect. Direct databases contain data that can be displayed and visualized directly as a network. Meanwhile, indirect databases contain annotated data that allows network-based analysis even though it is not directly visualized.[21] The databases can be collaborated on to elaborate biological mechanisms in more detail, comprehensively, and as closely as possible to predict the actual conditions (TABLE 3).

The data obtained from the database must be processed using bioinformatics tools, either software or website-based (TABLE 4), to interpret the interactions formed between molecules. Additionally, it can be further evaluated for its affinity for a particular ligand and the type of bond formed, which can then be used to explain which molecular pathway is involved.[27,28]

TABLE 3. Database of biomolecules and chemical compounds.

Database	Data provided	Web access
PDB	Protein structure	https://www.rcsb.org/
UniProt	Protein sequence and functions	https://www.uniprot.org/
STRING	Protein-protein interaction networks	https://string-db.org/
GeneCards	Human genes and functions	https://www.genecards.org/
CheMBL	Bioactive molecules with drug-like properties	https://www.ebi.ac.uk/chembl/
PubChem	Chemical information	https://pubchem.ncbi.nlm.nih.gov/
KEGG	Molecular pathways	https://www.genome.jp/kegg/
GEO	Functional genomics data	https://www.ncbi.nlm.nih.gov/geo/
GO	Functions of genes	https://geneontology.org/
DEG	Essential genomic elements among prokaryotes and eukaryotes	http://origin.tubic.org/deg/public/index.php
TTD	Therapeutic targets by disease	https://db.idrblab.net/ttd/
BioCyc	Genome sequences and metabolic pathways	https://biocyc.org/

TABLE 4. Bioinformatics tools for analyzing data sets from databases to find therapeutic targets.

Tools	Type	Function	Web access
Cytoscape	Software	Network data integration, analysis, and visualization	https://cytoscape.org/
Network Analyst	Website	Profiling gene expression via network visual analytics	https://www.networkanalyst.ca/NetworkAnalyst/
MOE	Software	Molecular design and visualization	https://www.chemcomp.com/Products.htm
AutoDock Vina	Software	Molecular design and visualization	https://vina.scripps.edu/
NetworkX	Software	Creating and manipulating the structure and functions of complex networks	https://networkx.org/
pyDockWEB	Software	Predicting the structures of protein-protein interactions	https://life.bsc.es/pid/pydockweb/
GOLD	Software	3D visualisation pre- and post-docking	https://www.ch.cam.ac.uk/computing/software/gold-suite
HIPPIE	Website	Generating human protein-protein interaction networks	https://cbdm-01.zdv.uni-mainz.de/~mschaefer/hippie/
LigandFit	Software (Python-based)	Determining macromolecular structure and ligand fitting	https://phenix-online.org/
PatchDock	Web server and software	Protein-ligand docking, protein structure comparison, and protein binding site prediction	https://bio.tools/patchdock

Network pharmacology in cancer research

Cancer remains a leading cause of death due to its poor prognosis. Current treatments, including surgery, chemotherapy, and hormone therapy, often prove less effective once cancer has metastasized. Additionally, chemotherapy comes with various side effects.[8,9] As a result, traditional medicine has gained significant attention in drug development. Network pharmacology provides a holistic view of disease development and drug action by integrating diverse biological data sources.

The workflow of network pharmacology usually includes three main steps: network construction, analysis, and validation (FIGURE 5). During network construction, biological entities such as genes, proteins, and metabolites are represented as nodes, and their interactions are shown as edges. These networks can be built using various bioinformatics tools and databases, including STRING, Cytoscape, and GeneMANIA. After the network is created, methods like topological analysis, clustering, and pathway enrichment analysis are used to identify essential nodes and modules related to the disease of interest.[28] By understanding how different biological components interact, researchers can gain insights into the underlying mechanisms of disease and find potential therapeutic targets.

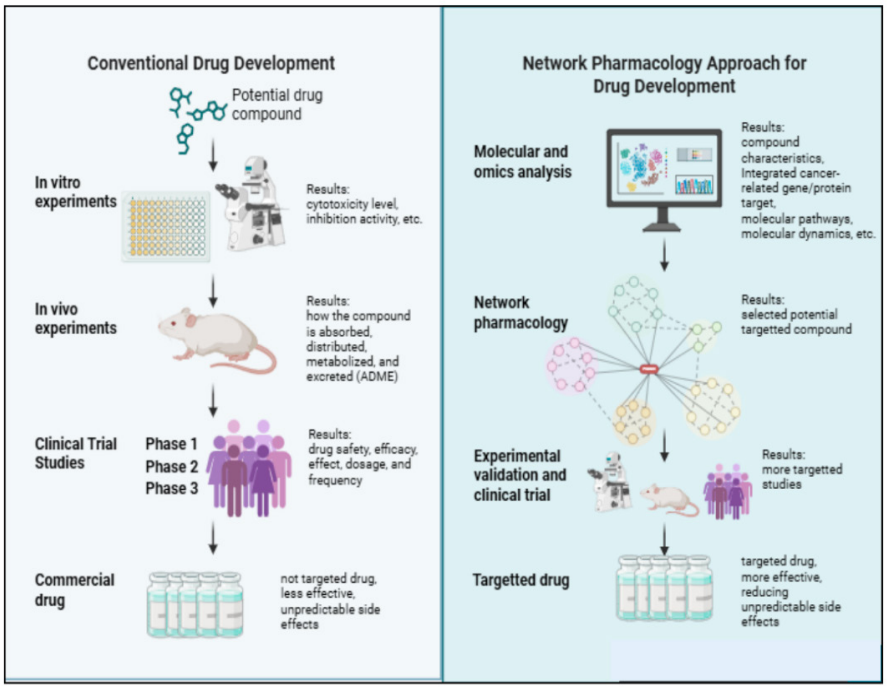


FIGURE 5. The process of network pharmacology in cancer drug discovery and development (designed with Biorender.com).

The validation phase is essential to confirm the predictions made by network pharmacology. Experimental validation methods, such as molecular docking, molecular dynamics simulations, and biological assays, are used to evaluate the binding affinity of drug candidates to their target proteins and to test their effectiveness in cellular and animal models. By combining experimental data with computational predictions, network pharmacology can significantly accelerate the drug discovery process and lower the cost of clinical trials.

Network pharmacology has the potential to speed up drug discovery and development in several ways. First, by identifying multiple targets for a single disease, network pharmacology can help develop polypharmacological drugs that target several pathways at once. This can improve treatment effectiveness and lower the risk of drug resistance. Second, network pharmacology can help find opportunities for drug repurposing by uncovering unexpected links between drugs and diseases.[29,30] Researchers can save significant time and money by reusing existing drugs. Third, network pharmacology can predict adverse drug reactions by detecting off-target effects. By understanding possible side effects, researchers can create safer and more effective treatments.

Traditional medicine has gained significant attention in drug development. Zheng *et al.* investigated Fu-Zheng, a Chinese health-boosting herbal medicine, for its potential to treat cancer.[17] Constructing a network pharmacology model based on 22 health-boosting herbs, they analyzed the target profiles of 1,446 TCM compounds and 166 compounds on 420 immune-related antitumor genes. The findings revealed that compounds within the same herb can exhibit diverse mechanisms of action in cancer treatment, influencing gene expression pathways in either the same or opposite directions. For instance, ursolic acid and spectnuezhenide upregulate gene expression in the T cell receptor signaling pathway.

A study on *Hedyotis diffusa*, a

herb commonly used in prostate cancer treatment, demonstrated the effectiveness of network pharmacology in identifying potential target compounds and proteins. By using various chemoinformatics, protein, and genome databases, researchers identified 14 active components and 295 potential targets related to prostate cancer, with quercetin and ursolic acid emerging as key components. Several proteins, including MAPK8, IL6, VEGFA, and STAT3, were identified as important targets. Enrichment analysis revealed that the molecular mechanisms behind *H. diffusa*'s anti-prostate cancer effects involve angiogenesis, apoptosis, cell differentiation, migration, proliferation, and invasion.[31] Another study focused on Zuojin capsules, a traditional formula used to improve health conditions in patients with gastrointestinal diseases and colorectal cancer. Through experiments on CRC cells and HCT-116 xenografted mice, researchers demonstrated Zuojin's ability to inhibit CRC and tumor growth. Twenty-two compounds, 51 targets, and 20 pathways were identified as participating in Zuojin's cancer-inhibiting effects.[32]

Future direction

The integration of network pharmacology into cancer drug discovery is quickly developing into a dynamic, systems-oriented discipline. The future relies on the thorough combination of network pharmacology with multi-omics data (genomics, proteomics, etc.) to create high-resolution biological networks that reflect the dynamic, time-based complexity of disease (FIGURE 5). This collaboration will help researchers move beyond static analysis, accurately pinpointing key molecular drivers, mapping complex causal relationships, and detecting subtle disease subtypes. Ultimately, this will unlock the full potential of systems pharmacology, leading to the discovery of reliable biomarkers and the understanding of complex drug mechanisms that support the synergistic and polypharmacological effects essential for treating multifactorial diseases like cancer.

To bridge the gap between computational predictions and clinical relevance, the field must strongly focus on thorough experimental validation. Theoretical frameworks need confirmation through advanced, high-throughput in vitro and in vivo validation steps, including RT-qPCR, Western Blotting, and animal models, paired with effective target prioritization algorithms to direct costly follow-up efforts toward the most promising network nodes. However, NP faces major methodological hurdles, especially the difficulty of managing and standardizing large-scale data heterogeneity across public repositories. Additionally, translating highly complex network findings—featuring numerous interacting nodes—into simple, druggable therapeutic targets without causing systemic toxicity remains a major challenge.

The successful translation of network pharmacology depends on dedicated cross-disciplinary collaboration among computational scientists, molecular biologists, data experts, and clinicians. Beyond academia, network pharmacology must evolve into a scalable, high-throughput industrial platform to make an impact in the pharmaceutical industry. This requires obtaining regulatory approval (such as from the FDA and BPOM) for network-based evidence in investigational new drug (IND) applications, incorporating network pharmacology early in the pipeline to improve efficiency by predicting off-target effects, and establishing effective strategies for monetizing polypharmacology.

CONCLUSION

Understanding network pharmacology provides a comprehensive approach to drug development, broadening the target space, enhancing therapeutic outcomes, and refining treatment strategies. It offers a new framework for innovating drug discovery from natural products, especially as the pharmaceutical industry faces challenges in translation.

ACKNOWLEDGEMENT

The author thanks all researchers who contributed to the development of network pharmacology tools and databases.

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