



Network Pharmacology: A New Paradigm in Drug Discovery & Development

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ABSTRACT

Network pharmacology is a rapidly growing field that has the potential to revolutionize the way drugs are discovered, developed, and used. It provides a more comprehensive and integrated understanding of the complex relationships between drugs, targets, and biological pathways, and offers new insights into the mechanisms of drug action. This understanding can be used to identify new targets for existing drugs and to design more effective and safer drugs. One of the key features of network pharmacology is its ability to integrate multiple types of data, including genomic, transcriptomic, proteomic, and metabolic data, to construct comprehensive and dynamic drug-target networks. These networks can be used to predict the effects of drugs on biological pathways and to identify potential off-target effects. They can also be used to understand how genetic and environmental factors affect drug response and to predict drug-drug interactions. In addition, network pharmacology has the potential to improve the efficiency of drug discovery and development by enabling the identification of new drug targets and the optimization of drug candidates. For example, it can be used to identify new targets for existing drugs, to design combination therapies that target multiple pathways, and to optimize drug dosing and administration schedules. Finally, network pharmacology can contribute to the development of personalized medicine by enabling the identification of individualized drug-response profiles based on a patient's genetic and environmental factors. This could lead to the development of personalized treatment plans that are tailored to the individual needs of each patient.

Keywords: Network Pharmacology, Drug-target network, Biological pathways, Off-target effects, Personalized medicine.

Introduction

Network pharmacology is an interdisciplinary field that combines system biology, network theory, and pharmacology to study the complex interaction between multiple drug molecules, targets and pathways in the body. Understanding how different physiological systems and pathways interact with medications for the purpose of anticipating and enhancing their therapeutic effects is the aim of network pharmacology [1]. This method can be applied to find novel drug targets, create more targeted, efficient medications, and comprehend how pharmaceuticals become resistant to them.

In network pharmacology, massive data sets of drug-target interactions and gene expression patterns are analysed using systems biology

techniques, including computational models and bioinformatics tools. As a result, important signalling pathways and pharmacological targets involved in a drug's therapeutic benefits can be identified, as well as any possible negative effects.

The study of polypharmacology, which refers to the fact that many medications interact with many targets in the body, is a crucial component of network pharmacology. This can result in a more complicated mechanism of action and possibly more effective treatment, but it also raises the possibility of adverse effects [2,3].

Potential uses for network pharmacology in the development and repurposing of medications can be found in another area. It may be feasible to uncover novel therapeutic targets and repurpose current medications for new indications by analysing large-scale data sets of drug-target interactions.

History

The term "network pharmacology" first used in a 2003 publication by Chinese researchers, indicating the relative youth of the topic. On the other hand, earlier work in systems biology and pharmacology can be used to trace the concept of examining the interactions between various parts of a drug and the body.

Network biology and polypharmacology, according to Hopkins (Hopkins, 2007, Hopkins, 2008), can shed light on how drugs function. "Network pharmacology" was a phrase he coined [4]. With the use of this innovative new approach to drug discovery, multitargeted drug discovery may replace highly specialised, magic bullet-based drug development. NP has the potential to generate e-therapeutics with ligand formulations that can be tailored for each complicated indication under each disease type, perhaps bringing new treatments for multigenic complex disorders. Future development of this could result in medicines that are individualised and specially tailored. The two main causes of attrition in the drug development process, efficacy and toxicity, can be addressed by integrating network biology with polypharmacology. Additionally, this connection has the potential to grow [5].

As technology and computational biology advances made it possible to incorporate massive amounts of "omics" data into drug discovery and development, the field started to pick up steam in the 2000s. Although network pharmacology is still relatively new and the field is still actively researching it, it has been used in a number of studies in the areas of cancer, immune-inflammatory diseases, and traditional Chinese medicine. As a result, it is now recognised as a promising new area for research in the area of drug discovery and development.

The network pharmacology approach, which focuses on the complex interactions between numerous targets and various compounds, is anticipated to open up new possibilities for the development of novel drugs. Additionally, it may lower the chance of side effects, increase the general safety and efficacy of medications, and make drug efficacy more predictable [6].

Network Pharmacology's founder:

Network pharmacology is a relatively new field, and there is no single "father" of the field. It combines systems biology and conventional pharmacology to study the intricate interactions between drugs and the body. However, a number of scientists have significantly aided the growth and development of network pharmacology.

Dr. Yves A. Lussier, a professor of pharmacy and the director of the Division of Experimental Therapeutics at the University of Alberta in Canada, is a well-known researcher in this area. For his ground-breaking work in using network pharmacology to study complex diseases like cancer, Dr. Lussier has received recognition. He has also played a key role in the development of computational techniques for the identification of potential new drug targets and the prediction of drug-target interactions [7].

Dr. Jun Yan, a professor in the Department of Pharmaceutical Sciences and the Centre for Systems Biology at the University of Michigan in the United States, is a different researcher. Dr. Yan is renowned for his work in developing computational techniques for foretelling drug-target interactions and drug repurposing. He also conducts research on the systems pharmacology of natural products [8].

Network pharmacology is, in general, a multidisciplinary field that includes numerous researchers and scientists from various backgrounds who are making significant contributions to the field.

From Network Pharmacology to Network Biology

In order to analyse and explore the biological data that is currently available, computational biology techniques have developed quickly in the postgenomic era. The main objective of postgenomic biomedical research was to

comprehensively list every molecule and every interaction it has with other molecules inside a living cell. Understanding how these molecules and their interactions affect how this incredibly complex machinery operates, both on its own and in the presence of other cells, is crucial. This resulted in network biology's development and emergence, which suggests that cellular networks are governed by universal laws and provides a fresh conceptual framework that may completely alter how we think about biology and disease pathologies in the twenty-first century. Several strategies for building biological networks were developed in the first decade of the twenty-first century [9]. In order to understand the relationship between disease phenotypes and genotypes, several approaches for building biological networks were proposed during the first decade of the twenty-first century. These approaches used computational methods, and literature mining in particular.

LMMA (literature mining and microarray analysis), a novel method of reconstructing gene networks by fusing microarray analysis and literature mining, was consequently proposed. As a result, a global network was first created using the cooccurrence method based on literature, which was then improved using microarray data. The LMMA biological network approach enables researchers to make sense of the pertinent large-scale microarray dataset and stay up to date with pertinent literature on specialised biological topics. LMMA is also a helpful tool for creating specialised biological networks and experimental layouts. When studying the regulation of various complex biological, physiological, and pathological systems, LMMA-like representations are useful because they allow a systemic recognition of the specific diseases in the context of complex gene interactions [10,11].

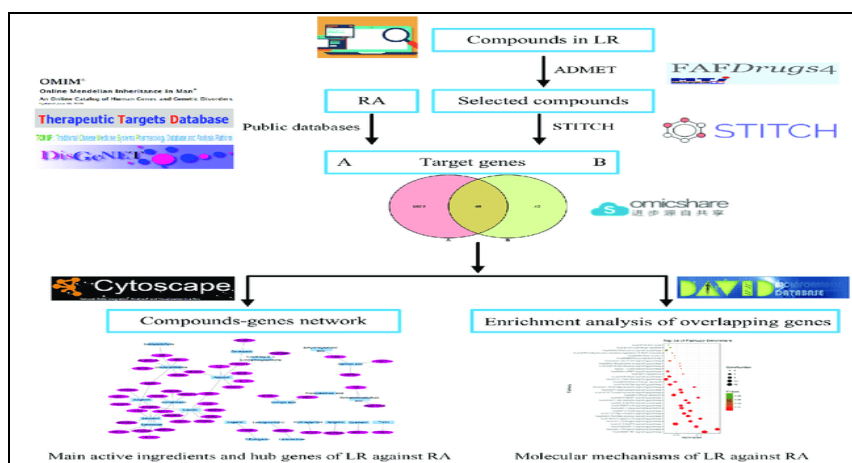


Figure 1: Workflow of Network Pharmacology

Network Pharmacology's (Scope) Purpose

The study of drug-target interactions and the application of medications to the treatment of complex diseases are among the many topics covered by network pharmacology, which has a very broad scope. The following are some of the important topics covered by network pharmacology:

1. Identification of new drug targets: By examining the interactions of medications with the body on a systems level, network pharmacology approaches can be used to locate potential new drug targets.

2. Drug repurposing: Using network pharmacology, it is possible to find existing medications that can be used to treat previously undiagnosed conditions.

3. Drug-target interactions: Interactions between drugs and their targets can be studied using network pharmacology at a systems level, giving researchers a more thorough understanding of how drugs affect the body.

4. Systems pharmacology: Network pharmacology can be used to examine how drugs interact with the body on a systems level, giving researchers a more thorough

understanding of how they can be used to treat complex diseases.

5. **Personalized medicine:** By taking into account a patient's genetic make-up, environment, and lifestyle, network pharmacology can be used to develop personalised treatment plans for them.

6. **Drug-drug interactions:** Network pharmacology makes it easier to comprehend how various medications interact with one another. This is particularly crucial for patients who are taking multiple medications.

7. **Adverse Drug Reactions:** Network pharmacology can also be used to investigate the underlying causes of unfavourable drug reactions, which may help to find new therapeutic targets or create safer medications [12,13].

Overall, network pharmacology covers a wide range of topics related to the investigation of drug-target interactions and the application of pharmaceuticals in the management of complex diseases.

Procedure of Network Pharmacology

Utilizing network pharmacology for drug development involves a number of procedures. These consist of:

Data gathering: The initial phase is to gather information on metabolic pathways, protein-protein interactions, and drug-target interactions. Several sources, including open databases, literature searches, and experimental investigations, can be used to gather this information.

Integrating the gathered data into a single network—which can be visualised as a graph containing nodes (such as proteins, medications, and pathways) and edges—is the next stage (e.g., interactions, regulations).

To reflect the connections between pharmaceuticals and biological systems, such as protein-protein interactions, metabolic processes, and signalling pathways, a biological network is built based on the integrated data [14].

Network analysis: After the network has been built, it can be analysed using a variety of

computer techniques, including clustering algorithms, pathway analysis, and graph centrality metrics. These techniques can be used to locate important nodes, such as druggable targets, and to forecast possible adverse effects of medications.

Validation: Experimentation, including cell-based assays, animal models, and clinical investigations, is used to confirm the predictions produced by network pharmacology.

Application: Drug discovery, personalised medicine, drug repositioning, understanding drug mechanism of action, and DDI prediction can all benefit from the findings of network pharmacology [15].

The fact that these processes are not exactly linear should be noted, and iteration between the steps is frequently required to develop the network and comprehend the drug's activity.

TCM for treating colitis uses dragon's blood (DB) pills, which are formed of resins from *Dracaena* species, *Daemonorops* species, *Croton* species, and *Pterocarpus* species. An NP-based methodology was used in a study to offer fresh perceptions on the molecular mechanisms and active components underlying the effects of DB (Xu et al., 2014a). Using an ultra-performance liquid chromatography-electrospray ionization-tandem mass spectrometry technique, the formulation's chemical components were identified. The literature was mined for the known targets of those 48 compounds, and computational approaches were used to forecast putative targets [16]. The compounds were then subjected to additional bioavailability testing before being subjected to a thorough examination of the known and potential targets for colitis. The network analysis demonstrated that the NOD-like receptor signalling pathway's proteins are modulated by DB bioactives to cause colitis (Fig:1).

Applications

A systems biology approach called network pharmacology uses computational techniques to examine how drugs interact with biological networks like protein-protein interactions and

metabolic pathway. Applications of network pharmacology include:

- 1. Drug discovery:** Network pharmacology can be used to locate fresh drug targets and forecast possible adverse effects.
- 2. Personalized medicine:** Network pharmacology can be used to forecast a drug's effectiveness in various patient populations based on the patients' genetic profiles and the particular biological networks that the disease has an impact on [17].
- 3. Network construction:** Using the combined data, a biological network is built to depict how drugs interact with various biological systems, such as metabolic pathways, signalling pathways, and protein-protein interactions.
- 4. Network analysis:** After the network has been created, it can be analysed using a variety of computational techniques, including graph centrality metrics, clustering algorithms, and pathway analysis. These techniques can be used to locate important nodes, such as druggable targets, and to forecast possible adverse effects of medications.
- 5. Validation:** Experimental data from cell-based assays, animal models, and clinical studies is used to confirm the predictions made by network pharmacology [18].
- 6. Application:** The outcomes of network pharmacology can be applied to drug development, personalised medicine, drug repositioning, comprehension of drug mechanism of action, and DDI prediction [19].

It is significant to note that these steps are not strictly linear and that iteration between the steps is frequently required to improve the network and our understanding of the action of the drug.

By combining knowledge about drug-target interactions, gene expression, and signalling pathways, network pharmacology aims to provide a comprehensive understanding of how drugs interact with the body. This method can aid in the design and development of more

targeted, effective drugs with fewer side effects [20].

Drawbacks

Given that network pharmacology is a young field, there are a number of problems with its current use. Some of these include:

- 1. Lack of experimental validation:** Many network pharmacology model predictions have not yet undergone experimental validation, making it difficult to determine how accurate they are.
- 2. Complexity:** Due to their complexity, network pharmacology models can be challenging to interpret and comprehend [21].
- 3. Limited data accessibility:** Network pharmacology relies on a substantial amount of data, including details on how drugs interact with their target proteins and clinical information on drug effectiveness and side effects. Network pharmacology's applicability may be constrained by the fact that such data are not always readily available [22].
- 4. Network pharmacology models need a lot of computing power,** which can be expensive to acquire and maintain. This results in a high computational cost.
- 5. Lack of standardisation:** The field of network pharmacology currently lacks standardisation, which can make it challenging to compare outcomes across various studies.

Network pharmacology is a promising field overall, but it is still young and needs a lot of development before it can be fully realised [23].

Resolving Network Pharmacology Issues

Utilizing computational techniques such as systems biology and bioinformatics to model and analyse these interactions is one way to overcome the difficulties of network pharmacology [24]. Additionally, research using cell cultures or animal models can shed light on the mechanisms by which medicines and other treatments work. A holistic understanding of the complexity of the human body can also be attained through the

combination of modern pharmacology and conventional medical systems like Chinese medicine and Ayurveda. Collaboration between researchers in various fields, such as clinical medicine, medicinal chemistry, and computational biology, can also aid in overcoming the difficulties associated with network pharmacology [25].

Conclusion

Network pharmacology is an approach to drug design that encompasses systems biology, network analysis, connectivity, redundancy and pleiotropy. Traditional knowledge can be explored using network pharmacological analysis to discover solutions to the current challenges facing the drug discovery industry. In addition, rational formulation discovery, new drug discovery, and drug repurposing all require NP. Experiments on a variety of bioactive–target combinations have been conducted. Based on the bioactives that make up the traditional medicine, the NP data synthesis reveals the mode of action of the formulations. Utilizing cutting-edge, integrated technologies, this is a sort of backwards approach to determining the formulations' molecular mechanism of action. The research that has been done and the available literature serve as the foundation for the current network analysis. As a result, the data are inconclusive due to the ongoing nature of numerous studies and the continuous generation of new data. This is still a good strategy, despite its drawbacks, because it reveals the buried wisdom of our ancient traditional medicine. NP facilitates the logical analysis of this knowledge, which can be used to comprehend the knowledge and develop novel pharmacological problem-solving strategies.

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