Network Pharmacology: An Emphasis on Traditional Chinese Medicines and Its Adaptability for Ayurveda Medicines in India

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ABSTRACT	ARTICLE DETAILS

Network pharmacology is expanding as a comprehensive paradigm and becoming a breakthrough research topic of pharmaceutical research by providing an extraordinary potential for the comprehensive examination of conventional treatments. The development of network pharmacology has paved the way for the implementation of the complex phytochemical constituents found in diverse natural products. Network pharmacology is a burgeoning field of study that has linked its legs not just to Traditional Chinese Medicine, but also to other natural products, herbs, and ayurvedic medicine. By being a multidisciplinary area that includes network biology, system pharmacology, and even omics, it has demonstrated its unimaginable potential for future research. It is, in particular, a network-based science. Natural products have long served an important role in the advancement of pharmaceutical research, with all the supplementary immense expertise that has yet to be demonstrated, which can be established with the help of this application, which in turn may demonstrate the potential of these natural products to be multitargets, multicomponent characteristics of them rather than the solitary target that is becoming a dilemma in developing drugs. In this review paper, we summarised the notion of network pharmacology and discussed the newer features of how this concept might be used to natural products as well as drug discovery.

KEYWORDS: Network Pharmacology, Natural products, Traditional Chinese Medicine, Ayurveda

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INTRODUCTION

Early drug development was mainly a haphazard hunt for medicinal compounds in plants, animals, and naturally existing minerals. Many tribes and faiths' medicine men and priests tested out such natural elements, or aqueous or alcoholic extracts created from them, and over the centuries, by trial and error, established a materia medica that was passed down from generation to generation with very slight changes[1]. Drug discovery and development in the classic way is time-consuming and high-risk. Repurposing/repositioning of authorised medications is a low-cost and high-efficiency way to developing effective treatments quickly[2]. To develop safe and effective medicines, drug discovery is a dangerous, expensive, and time-consuming process that relies on multidisciplinary methodologies[3]. A crucial step in the validation of a biological impact is the identification of molecular processes

and targets[4]. Despite its widespread success, the one-drug, one-target development paradigm has flaws. A single drug target can be acted on by a variety of medications, and most drugs have several targets. Complex diseases, such as neurological problems, cancer, and cardiovascular ailments, are examples of this. Multiple pathways, genes, and functional proteins interact to cause these disorders. Cancer, for example, is increasingly recognised as a systemic illness caused by the interaction of various biological pathways, genes, and proteins. As a result, in many circumstances, a single pathway, gene, or protein cannot be used to treat cancer. Drugs targeting many targets, on the other hand, have more curative benefits due to their pharmacological properties[5]. Natural products originating from plants play an important role in the discovery of new drug molecules, which are then harnessed to develop novel therapeutic medications for a specific disease target[6]. Natural products are crucial in

medication development. Natural products or natural product derivatives made up around half of all FDA-approved medications. Natural compounds have a unique ability to target specific cellular targets[7]. Natural products for successful treatment of medical conditions provide as inspiration for innovative drug research. Natural products' importance in developing novel medications to treat communicable and noncommunicable diseases cannot be overstated. Technological advancements have enabled researchers to decipher the profiles of these complicated natural chemicals, perhaps leading to the development of novel medications. Natural product lead molecules have been used to isolate or synthesise an astounding number of blockbuster medications. This establishes natural product drug discovery as a highly effective technique for developing innovative therapeutic medicines[8].

As a result, with the growing breakthroughs in network pharmacology, and the key theory of network pharmacology being "network target," Researchers have moved traditional medicine research from a single and isolated method to a multi-faceted and systematic mode as multidisciplinary fields such as computational biology, bioinformatics, artificial intelligence, and big data science have grown in popularity. Understanding drug action mechanisms from the perspective of the biomolecular network is one of the key changes. Using the "network" to reclaim the "whole" has resulted in substantial changes in medical research as well as new obstacles. Network pharmacology is expanding as a systematic paradigm and emerging as a cutting-edge drug discovery and development research topic. It focuses on uncovering the systematic pharmacological mechanisms of pharmaceuticals and guiding drug discovery, development, and clinical therapy from a systematic perspective. Network pharmacology combines computational, experimental, and clinical research, allowing researchers to better understand the properties of traditional medications while also connecting to modern science and technology. Several pioneering works gave rise to network pharmacology[9].

THE CONCEPT OF NETWORK PHARMACOLOGY

The growth of network pharmacology was first highlighted in 2007. The concept of "Network Pharmacology" was first proposed by Andrew L. Hopkins[10]. Because of significant advances in systems biology, network biology, and chemical biology, network pharmacology is quickly becoming a cutting-edge research subject in current drug discovery and development. Network pharmacology has the potential to be the next generation of drug research by combining reductionist and systems approaches, as well as computational and experimental methods[11]. The area of network pharmacology has spawned a new branch of pharmacology research. Network pharmacology can build complex network models to study the biological or pharmacological properties of a target and explore its physiological or pharmacological mechanism using high-throughput data analysis, virtual computing technology, and network public databases, among other things, based on theories of multidirectional pharmacology and systems biology[12]. Network pharmacology is a useful bioinformatics approach for identifying all potential bioactive component targets, functions, and mechanisms in order to cure disease[13].

OBJECTIVES AND SCOPE OF NETWORK PHARMACOLOGY

As a result of improvements in systems biology, network pharmacology has ushered in a radical shift from "one-target, one-drug" treatments to "target-network, multi-component therapeutics."[14]. The scope of network pharmacology research are as follows, and is therefore not confined to:

(1) Highlighting different computational approaches like as network-based and machine learning methods and sources that have been proposed and used to the various processes involved in the research process. There has been a plethora of computational bioinformatics methodologies established and employed in various processes in network pharmacology[15].

(2) To optimise the efficacy and safety of a proposed medicine and their potent combinations, network pharmacology incorporates all of the criteria mentioned [16].

(3) Protein–protein interactions and synergistic activities are mapped via network analysis[17].

(4) Computational and statistical approaches to biological network analysis, network pharmacology research concentrating on chemotherapeutic agents, and network pharmacology studies concentrate on Traditional Chinese Medicine are all instances of network pharmacology studies[18].

(5) Bioinformatics is being used in network pharmacology to advance drug discovery by strengthening our understanding of pharmacological effects[19].

(6) The objective is especially important given that access to increasingly sophisticated omics platforms will define subsequent research periods, shifting the focus away from data collecting and toward integrative data analysis as seen via a network lens [20].

THE APPLICATION OF NETWORK PHARMACOLOGY TO NATURAL PRODUCT DEVELOPMENT

Natural products have been employed in folklore for the treatment of numerous maladies since ancient times. For many years, plant-derived compounds have been recognised as a source of medicinal medicines and structural variety[21]. Natural products and their molecular frameworks have a longstanding experience of serving as important starting points for medicinal chemistry and drug development.

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Consequently, there has also been resurgence of interest in incorporating these chemotypes into compound pools for screening and specific target modulation[22]. According to network properties of natural product-target networks, polypharmacology was significantly enriched to those compounds with a large degree and high betweenness centrality in natural product-target networks[23]. Natural chemicals normally work by regulating a number of targets rather than a single, highly specialised target. Rather than comprehending the logic for their synergistic action and finding methods to separate bioactive from natural resources, technology was leveraged in drug discovery and development to develop highly selective mono-targeted molecules that mimic bioactive from natural chemicals. According to studies, the malfunctioning of numerous proteins causes the majority of disorders. As a result, in order to accomplish comprehensive treatment, it's important to treat numerous targets resulting from a syndrome-related metabolic cascade. As a result, the method will need to develop from a single-target, new chemical entity-focused approach to a multi-target, synergistic formulation-discovery strategy[24]. Natural products remain a valuable source of scaffolds with a wide range of structural diversity and bioactivities that can be developed directly or used as guidelines for future for the development of innovative medications[25].

THE FUNDAMENTALS OF NETWORK PHARMACOLOGY

Pharmacology

Pharmacology is an integrated science date back approx. 7000 years. It is the study of how chemicals interact with living organisms to impact normal or pathological biochemical function. In19th century discovered that compound effects were dose dependent. In the twentieth century, pharmacology progressed through successive biochemical, molecular, and genomic periods. Decline of pharmacology coincided with the rise of reductionism as a key focus in biomedical research. Network-based computer models may integrate '-omics' information and optimise drug development combinational regimens. It is encourages the creation of new wave of network-based multi-target pharmaceuticals using medicinal herbs[26-29].

Network Biology

Introduction of random networks in the 1950s by Solomonoff, Rapoport in 1951 and Erdös, Rényi in 1959 sparked the first wave of general interest outside mathematics. Watts, Strogatz and Albert Barabási presented scale-free and small-world networks in 1998 and 1999, respectively. Networks are used to represent biological systems as complex sets of binary interactions or linkages between various bio elements. Network represent the connections between different items like DNA, RNA, proteins, and metabolites, and these networks can be utilised to capture the interactions between these molecules in the biomedical area. Network medicine and network biology provide a platform for methodically investigating, molecular complexity of a disease, leading to the identification of disease modules and pathways and identifying therapeutic targets and biomarkers for complex disorders[30-32].

System Biology

System Biology is an integrative discipline that uses quantitative reasoning, computer models, and high-throughput experimental tools to connect molecular components both within and across biological scales. It looks at interactions and dynamics at different scales, such as within cells, tissues, organs, and organisms. It decodes information flow in signalling, regulatory, and functional pathways from genes, proteins, and other subcellular components. One of the methods it employs is network analysis of pharmacological activity. It refers to the identification of the full therapeutic target as well as the mechanism of action, as well as the characterisation of lead compounds. It characterises protein-ligand interactions on a wide scale, and it also suggests a link between cellular molecular functions and physiological processes through a network of protein-ligand interactions. Thanks to developments in systems biology, complex illnesses can't be effectively addressed by meddling in single proteins. As a result, drug researchers began to embrace the concept of polypharmacology[33-36].

Polypharmacology

The word "polypharmacology" was coined by Bran Roth (2004). It can be a single medicine that acts on several targets in a single illness pathway or a single drug that acts on multiple targets in different disease pathways. A medication with excellent potency and selectivity for a single biological target is competing for attention with a new polypharmacology approach. Polypharmacology claims that by modifying many sites, more effective medications can be produced, and the high number of clinical trial failures, which has risen considerably in recent years, can be reduced. Clinical trial expenditures are rising due to the inadequacy of the "one medicine-one target" approach for predicting pharmacological side effects and toxicities. This problem is being addressed with polypharmacology[37-39].

Network Biology and Network Pharmacology Integration

Network biology and polypharmacology, according to Hopkins[40], can help us better understand drug action. "Network pharmacology" was a phrase he coined. This novel technique to drug discovery may pave the way for a paradigm shift away from highly specific magic bullet drug development and toward multitargeted drug discovery. Network Pharmacology has the potential to deliver new treatments for multigenic complicated diseases and could lead to the creation of e-therapeutics, in which the ligand formulation can be tailored to each complex indication and disease type. This could be broadened in the future, leading

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to personalised and tailored therapies. Efficacy and toxicity are two important causes of attrition in drug development that can be addressed by combining network biology and polypharmacology. Furthermore, this integration has the potential to enlarge the present druggable target opportunity field. The next paradigm in drug discovery, according to Hopkins, is Network Pharmacology[41]. Based on systems biology theory, network pharmacology is a novel science that examines the biological network and screens out nodes of particular interest in order to develop poly-target medicinal molecules. It emphasises the multimodal modulation of the signalling system to maximise therapeutic efficacy while reducing unwanted effects[42]. Network-based drug discovery is seen as a viable technique for cost-effective drug development, given recent advances in bioinformatics,

systems biology, and polypharmacology. Systems biology investigates biological systems by methodically perturbing them, monitoring gene, protein, and informational pathway responses, integrating the data, and finally building mathematical models to characterise the system's structure and reaction to specific alterations[43]. Continuous advancements in information technology, as well as networks involving network biology, system pharmacology, and polypharmacology, as well as computational techniques, are all important components of research. Understanding the pathway and mechanisms, as well as guaranteeing efficacy and optimization, can help a drug go from being a single targeted for a specific disease to being a multi-targeted therapy. There has also been progress in the development of this network pharmacology.
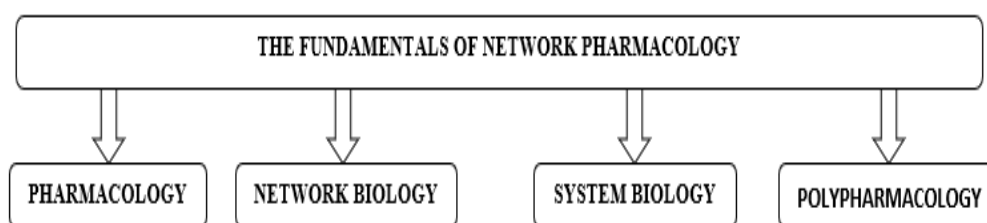

Fig1. The Fundamentals of Network Pharmacology

THE NETWORK PHARMACOLOGY FRAMEWORK

To prioritise disease-associated genes, predict the target profiles and pharmacological actions of herbal compounds, uncover drug-gene-disease co-module associations, screen synergistic multi-compounds from herbal formulae in a high-throughput manner, and interpret the combinatorial rules and network regulation effects of herbal formulae, network pharmacology methods were developed[44].

Analysis of Data

The research data is derived from the trials as well as formerly acquired and collected literature on the topic. The data collected from both of these sources poses two problems. First, the data must be organised consistently in a way that allows for both individual queries and global searches. The second, and arguably more challenging, task is maintaining the databases up to speed with the growing volume of biological information. All of these are tracked in databases if analytical approaches are available to assist biologists in accessing, displaying, and interpreting data, which is useful for network analysis, network constructions, and additional drug target-based network investigations [45]. The discovery and validation of therapeutic targets that are responsible for drug efficacy and the targeted medications is aided by data analysis. It was created to provide thorough information regarding effectiveness targets and the authorised, clinical trial, and investigational treatments that correspond to them.

These upgrades aid target identification and validation, drug lead identification and optimization, and the development of multi-target medicines and medication combinations [46].

Network Construction

Network pharmacology emphasizes the integration of biological networks with drug action networks, to analyses the relationship of the active ingredients of the drug and disease-associated genes by nodes or network modules in the network, from finding a single ingredient to a comprehensive network analysis. The assessed pharmaceutically active compounds are incorporated into the "drug-disease" common target gene, and Cytoscape software constructs a visual composition network of active ingredient-targets. The active ingredients of natural products and gene proteins are represented by nodes in the network diagram, while edges encode the interaction between the active ingredient and the target of action. Furthermore, the number of lines linking the target genes in the network determines the relevance of the interaction between nodes[47]. In genomes, proteomics, transcriptomics, metabolomics, and interactomics, recent discoveries in high-throughput approaches have resulted in data deluges. These data can be represented as networks, with nodes acting as surrogates for proteins, metabolites, or transcripts and edges connecting them to depict interactions, responses, or regulations. The function of a single node and the collaboration with other nodes can be better understood

via network analysis. For example, network centralities assign value to nodes in a biological network [48]. The most used software for network creation is Cytoscape. Cytoscape is an open-source, general-purpose software platform for large-scale molecular interaction network data integration. Cytoscape is most useful when combined with extensive datasets of protein-protein, protein-DNA, and genetic interactions for humans and model organisms, which are becoming more widely available. The Core software from Cytoscape allows you to set up and query your network, as well as graphically integrate it with expression profiles, phenotypes, and other molecular states, and link it to databases of functional annotations[49]. Further explorations of pharmacological trials including multi-targeted medicines rely heavily on network development. It essentially includes all of the parameters needed for scientific research, such as protein-protein interaction networks, metabolic networks, signalling networks, gene networks, gene regulatory networks, neural networks, and so on.

Pharmacology via visual networks

VNP stands for visual network pharmacology and is used to display the complicated interactions between diseases, targets, and drugs. It consists of three functional modules: drug-centric, target-centric, and disease-centric VNP. Users can use disease, target, or medicine name strings, chemical structures and substructures, or protein sequence similarity to search the database, and then get an online interactive network representation of the results. Each node in the resulting network view represents a disease, target, or treatment, and each edge represents a known link between two of them[50]. The top four candidates for viewing, modification, exploration, and analysis of very large networks are Cytoscape (v3.5.1), Tulip (v4.10.0), Gephi (v0.9.1), and Pajek (v5.01)[51]. CellChat is a new technology that uses single-cell RNA-sequencing (scRNA-seq) data to statistically predict and analyse intercellular communication networks [52].
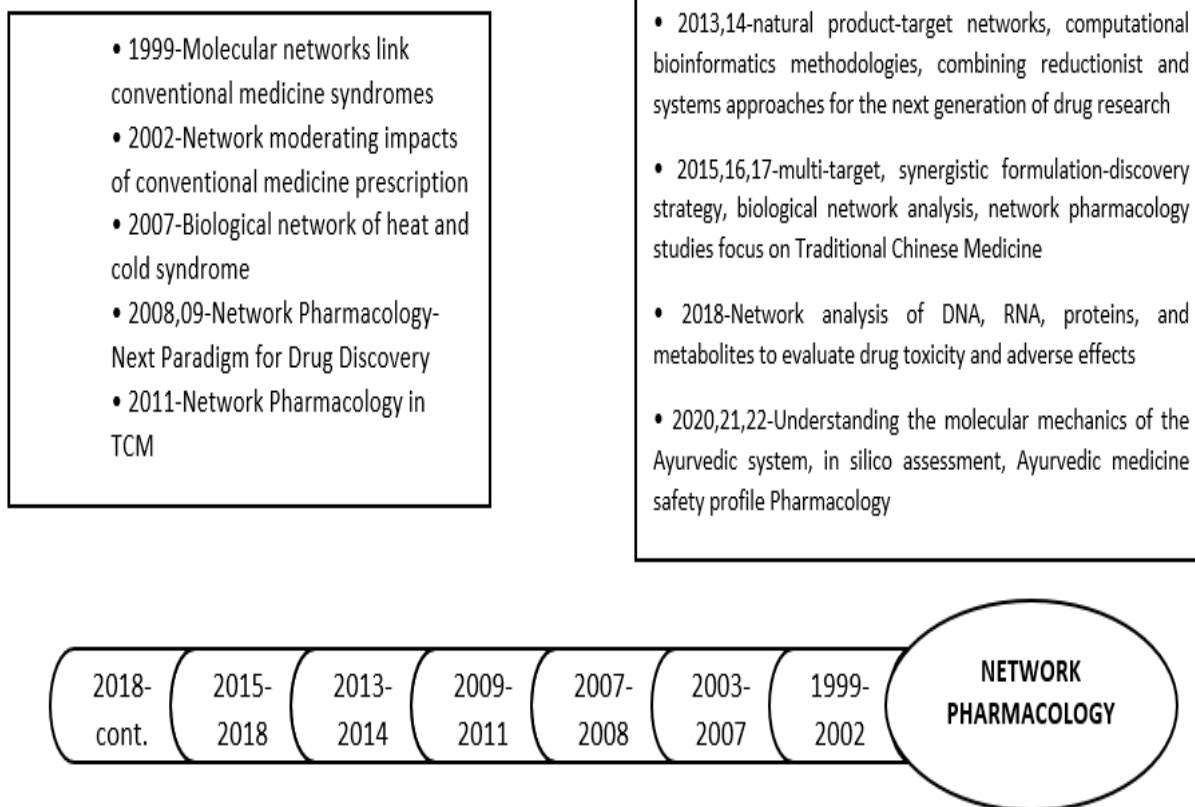
- 1999-Molecular networks link conventional medicine syndromes
- 2002-Network moderating impacts of conventional medicine prescription
- 2007-Biological network of heat and cold syndrome
- 2008,09-Network Pharmacology-Next Paradigm for Drug Discovery
- 2011-Network Pharmacology in TCM

- 2013,14-natural product-target networks, computational bioinformatics methodologies, combining reductionist and systems approaches for the next generation of drug research
- 2015,16,17-multi-target, synergistic formulation-discovery strategy, biological network analysis, network pharmacology studies focus on Traditional Chinese Medicine
- 2018-Network analysis of DNA, RNA, proteins, and metabolites to evaluate drug toxicity and adverse effects
- 2020,21,22-Understanding the molecular mechanics of the Ayurvedic system, in silico assessment, Ayurvedic medicine safety profile Pharmacology

2018-cont. | 2015-2018 | 2013-2014 | 2009-2011 | 2007-2008 | 2003-2007 | 1999-2002 | NETWORK PHARMACOLOGY

Fig2. Trends in Network Pharmacology research

CONCEPTUAL APPLICATION OF NETWORK PHARMACOLOGY IN NATURAL PRODUCTS

In ethnomedicine, natural products are often used. Natural compounds have rich and diverse chemical structures that can be used to modulate a variety of biological targets. Natural substances have a multitargeted effect that can be additive, synergistic, or antagonistic. The assessment of possible multiple activities of natural chemicals is required for rational

design of more safe and potent medicines[53]. It's conceivable that the ability to connect to many target molecules is due to the way natural products are made. Many natural chemicals used in medicine have a complicated structure, and their synthesis necessitates the involvement of several enzymes. Within context of quercetin biosynthesis, for example, the concluding steps require no less than three synthetases, each of which has its own layout and molecule-binding cavity, and

all of which the quercetin molecule under synthesis must be able to connect with. To be able to attach to various enzymes, the basic structure of quercetin has inherited a variety of binding groups as well as some flexibility. As a result of its diversity and flexibility, it can interact with unwanted proteins with comparable binding sites[54]. Combinations of interacting molecules formed by natural products of plants could give crucial combination therapies that influence numerous pharmacological targets at the same time and provide therapeutic efficacy beyond the scope of single compound-based medications[55]. By employing network pharmacology in natural products to combat complicated diseases like cancer, cardiovascular disease, AIDS, and neurodegenerative disorders, single focused combinations are discouraged in favour of numerous target medications or combinations. There is so much potential that has yet to be uncovered and explored[56].

THE EFFECTIVE USE OF NETWORK PHARMACOLOGY IN TCM

In medical research, a reductionist approach can only provide a limited understanding of complexity aetiology and multi-target pathologies of systemic diseases, and it might be challenging to identify relevant remedies to target such complexities. Because complex biological networks govern and depend on numerous phases of genetic and environmental obstacles to advance, mono-target medication intervention cannot successfully battle the complex pathologies of systemic diseases like malignancies, cardiovascular diseases, and neurodegenerative disorders. Because of the illness nature of natural evolution of feedback loop and route redundancy, several monotherapies have been demonstrated in clinic to have limited effects or too many detrimental effects in long-term treatment for systemic disorders. For example, mono-target cancer therapy may allow cancer cells to evolve acquired resistance to the drug, whereas multi-target therapeutics may be more effective or less vulnerable to allowing adaptive drug resistance because the biological system is less able to compensate for multiple actions produced by two or more drugs at the same time[57].

TCM integrated with Network Pharmacology for drug discovery

By examining how single targeted medications are ineffective in treatment using past clinical trials and other large data analyses, such as tolerance studies, and building algorithms for assessing potential drug combinations they narrowed their focus to emerging areas of network utilisation in drug discovery for treating epilepsy. Antiepileptogenesis (the prevention of symptomatic epilepsy) is a major unmet clinical need in those at risk. Clinical trials for epilepsy prevention were conducted on a number of medications; however, none of them were successful. Most previous preclinical attempts to create antiepileptogenic therapies also failed. Drugs were used as monotherapy in the majority of studies. Epilepsy, on the other hand, is a complicated network phenomenon; therefore, a single medicine is unlikely to stop epileptogenesis[79]. The cardiovascular disease herbal database aims to integrate herbal remedies, natural products, cardiovascular disease-related target proteins, docking results, illnesses, and clinical biomarkers into a comprehensive database for natural product drug development from medicinal herbs. It is possible to find a drug or a lead for a single target or a set of proteins connected to a disease or biological process. The cardiovascular disease herbal database is valuable for studying network pharmacology of natural products associated to cardiovascular disease. The herbs contain a wide range of components, and the chemicals would interact with a wide range of cellular targets[80]. By developing a website for virtual screening and comprehending the therapeutic characteristics of the drugs utilised through it, a newer platform for cardiovascular illness and the utilisation of natural products, i.e., TCM, was understood.

Table 1. Network Pharmacology Applications in TCM

TCM Herb/Formula	Diseases	Conclusion of the research	References
Astragaloside IV	Diabetic nephropathy	transition properties, and ability to suppress the Wnt/-catenin signalling pathway	58
Bushen Zhuanggu formula	Breast Cancer	pharmacokinetic analysis with network pharmacology to investigate the effect	59
Cynarin	Hyperlipidemia	usage to treat hyperlipidemia in the future	60
Danhong injection with t-PA	Thrombolytic therapy	improve BBB disruption, and minimise infarction, brain edoema, and haemorrhage following ischemic stroke	61
Erigeron breviscapus	Cerebrovascular disease	activity against CBVDs by regulating various pathways and interacting with multiple targets	62
Fufang Danshen formula	Cardiovascular	association of 9 metabolites alter 42 cardiovascular genes linked to 30 disorders	63

Ge-Gen-Qin-Lian Decoction	Type 2 Diabetes	4-Hydroxymephenytoin as a new antidiabetic component enhancing insulin secretion in RIN-5F cells and decreased insulin resistance in 3T3-L1 adipocytes	64
Hedyotis diffusa Willd	Colorectal Cancer	aid CRC patients by altering cancer, infectious disease, endocrine, immunological, and neurological system pathways	65
Jian-Gan-Bao	Liver disease	study of hepatoprotective properties	66
Kushen Injection	Lung Cancer	validation and prediction of mechanism	67
Liu-wei-di-huang-wan	Diabetic ketoacidosis	minimise the risk of diabetic ketoacidosis	68
Ma Huang Tang	Bronchial asthma	reduce the pathological alterations of acute asthma-like syndrome	69
Naoxintong	cardiovascular and CBVDs	benefits on angiogenesis and blood flow recovery	70
Panax notoginseng	Cardiovascular disease	multidrug combination therapy for cardiovascular disease is a possibility.	71
Qingfei Paidu Decoction	COVID-19	treatment of COVID-19 in various stages	72
Realgar-Indigo naturalis	Promyelocytic leukemia	examine the possible therapeutic impacts of formulae	73
Shen-qi-Yi-zhu Decoction	Antigastric Cancer	systematic technique for elucidating SQYZD's anti-GC mechanism	74
Taohong Siwu decoction	Osteoarthritis	potential to prevent diseases like OA in a holistic and integrated way	75
Xuesaitong injection	Antimyocardial infarction	identified 70 prospective XST targets	76
Yanghe Decoction	Breast cancer	acts on HER2-positive breast cancer,	77
Zhi-zi-da-huang decoction	Alcoholic liver disease	effective therapeutic method to treat alcoholic liver disease	78

Network Pharmacology in Ayurveda

Ayurveda is a holistic, natural health care method that dates back to India's ancient Vedic period. Ayurveda means "Science of Life" in Sanskrit[81]. Ayurveda uses natural products derived from plants or herbs to treat a variety of ailments. These plant extracts include numerous components, and their mechanisms involved are not very well established. The data is diverse, and if gathered and evaluated effectively, it can help identify targets from the interactome by combining network pharmacology with. A fundamental finding in this paradigm is that Phyto molecules with established structures and bioactive components are more likely to interact with the most promising targets, and so can help lead target selection without straying from the mainstream path of translating large data into interactome. This strategy could save time, money, and effort in medication development while also identifying new targets for future research[82]. Due to its various pharmacological activities such as anti-stress, neuroprotective, anticancer, anti-arthritic, analgesic, and anti-inflammatory, Ashwagandha is a real potent regenerative tonic (Rasayana of Ayurveda). Parkinson's disease, dementia, memory loss, stress-related disorders, malignoma, and other diseases benefit from it[83]. Ayurvedic anti-epileptic herbs were studied, and their effectiveness was determined utilising a network pharmacology technique. The anti-epileptic herbs of Ayurveda were painstakingly reviewed and identified using various literature resources. A large database of phytochemicals found in recognised herbs was examined for drug-likeness features and chemical classification. In addition, data on protein molecules targeted by phytochemicals was gathered, and the polypharmacological activity of each was evaluated based on the number of protein targets that a phytochemical may target. The route and module relationships were used to determine the functional importance of protein targets. In-silico docking experiments were used to examine the molecular interactions of high confidence phytochemical-protein target pairs involved in this illness. In the future, combining these computational discoveries with experimental investigations will be extremely beneficial in creating a better and deeper understanding of the underlying mechanisms of epilepsy. This was discovered through investigation[84].

Table 2. Some Examples of the Herbs in Network Pharmacology

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Herb/Formulation	Disease	References
Phyllanthus emblica	SARS-CoV-2	85
Bioflavonoids	COVID-19	86
Saikosaponin compounds	COVID-19	87
The Genus Terminalia (Combretaceae)	anticancer, anti-HIV-1, antifungal, antibacterial, antimalarial, antioxidant, diarrhoea, and analgesic bioactivities in vitro or in vivo	88
Piper longum	neurological disorders	89
Triphala	gynaecological cancers	90

APPLICATIONS OF NETWORK PHARMACOLOGY

Conventional treatments-Network-based development and administration of plant compositions, assessment of numerous active ingredients, analysing synergistic interaction, natural product diagnostic markers for quality management, clarifying the explanation of similar system of traditional formulations, understanding the molecular mechanisms of Ayurvedic system of medicine, safety profile of Ayurvedic medicines, possible replacements for facing extinction botanicals.

Pharmacological studies-To create fresh leads with natural products specifying prospective pharmacological adverse reactions, estimating additional applications, estimating toxicology, estimating possible drug–drug interactions, precision medicine design based on group of protein complexes, drug retrofitting.

Drug discovery-Studying the signalling network of diseases varieties, developing investigations based on medications and targets, biomedical research, determining new therapeutic sites, improved time and expenses along in silico assessment, drugs for multigene illnesses, finding disease-causing genes, developing diagnostic biomarkers, Researching medication or antibiotic resistance[91].

Toxicological studies- Network toxicology is a subset of toxicology that focuses on the toxicity of a single component in a complex system and aids in drug safety research and review. For network toxicology investigations, databases like the comparative toxicogenomic database, the National Toxicology Program, and the Toxicology Data Network are frequently employed[92].

CONCLUSION

The undeniable emergence of network biology, system pharmacology, and polypharmacology has resulted in a massive expansion of network pharmacology. The prospects of using network pharmacological investigations in their individual findings have been summarised using all of the material from the sources and the conclusions acquired thus far. It has shown how far this technology can advance in the future. By using this strategy deliberately to the development of medications or research utilising natural goods, plants, herbs, or even ayurveda, which man has been using for ages

without fully comprehending the statistically significant consequences. Instead of the single-targeted approach that has been adopted so far, network pharmacology will provide a scientific basis for future study into multi-targeted consequences. It is the most recent study setup for using huge data sources, their network constructions, network analysis, and network visualisation for productive development, as well as a stepping stone for continual upgrades in drug discovery. This article paves the way for future network pharmacology research in the context of natural products, along with network pharmacology applications in drug discovery.

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