Review Article

Network Pharmacology approach for Herbal Drugs Intended for the Therapy of Diseases: A Comprehensive Review

ABSTRACT

The single drug/single target/single disease tactic to medicine detection currently faces many challenges in terms of welfare, efficiency and sustainability. Network biology and multipharmacology approaches have recently gained acceptance as approaches for omics documents incorporation and multi-target drug development, respectively. Combining these two approaches has created a new model termed network pharmacology (NP) that examines the effects of medications on both interaction and disease. Ayurveda, traditional Indian medicine, uses a scientific formula that contains many ingredients and numerous bioactive composites. Though, the scientific basis and methods are still largely unexplored. Network pharmacology is a prediction tool that helps in predicting the bioactives from different databases, respective genes from databases which are expressed during the disease. The genes are also ranked from cytohubba and genes with greater numbers have greater interactions with other genes. The mechanism can be predicted from different pathways like the KEGG pathway. From the obtained data a network can be constructed using cytoscape and represented.

KEYWORDS: Network pharmacology, Gene databases, Cytoscape, KEGG pathway, Protein Protein interactions.

INTRODUCTION:

The one-drug/one-target/one-disease concept of drug development is currently confronting several safety, effectiveness, and sustainability issues. Network biology and polypharmacology concepts have recently acquired popularity as methodologies for integrating omics data and developing multitarget drugs, respectively. The amalgamation of these dual methodologies resulted in a distinct paradigm known as network pharmacology (NP), which examines pharmacological effects together with the interactome and the disease level. Hopkins [1, 2] discovered that network biology and polypharmacology can shed light on drug activity. He coined the term "network pharmacology." This novel strategy to drug discovery has the potential to alter the paradigm away from highly specific magic bullet-based drug discovery and toward multitargeted drug development. NP has the potential to deliver new therapies for multigenic complex illnesses, as well as to lead to the creation of e-therapeutics in which the ligand formulation may be personalized to each complicated indication under each disease type. In the future, this might lead to tailored and personalised therapies. The combination of network biology and polypharmacology can address two primary causes of drug development attrition: effectiveness and toxicity. Furthermore, this connection has the potential to broaden the present opportunity space for drug targets. Hopkins proposed network pharmacology as the next level paradigm in drug development.

An emerging field known as network pharmacology (NP) has evolved to study pharmacological effects and interactions with many targets [1]. It uses computing capacity to catalogue the chemical interactions of a pharmacological molecule in a live cell in a systematic manner. NP emerged as a critical tool for comprehending the underlying intricate interactions between botanical formula and the entire body [3]. It also tries to find novel drug leads and targets, as well as repurpose current drug compounds for alternative therapeutic diseases, by allowing unbiased exploration of prospective target areas [4]. These efforts, however, require some direction in terms of picking the correct sort of targets and novel scaffolds of therapeutic compounds. Traditional knowledge may be quite useful in the process of formulating new medications and repurposing existing models. By integrating developments in the systems biology and NP, it may be possible to rationally design the future of promising drugs [5]. NP analysis not only opens up novel therapeutic options, but it also aims to enhance the safety and efficacy of existing medications.

The efforts of molecular biology and genomics research have provided large data which helped in gaining new in-sights into drug discovery processes. Hopkin, the father of Network Pharmacology, explained that a single drug can target multiple nodes in the disease network [14]. Network pharmacology is based on the integration of multiple disci-plinary concepts including molecular biology, biochemicalbiology and bioinformatics [14-16]. Network pharmacology has gained more interest due to high success rate in clinicalinvestigation, less or affordable side effects, enhanced drug efficacy, regulation of the signaling pathway with multiple channels, interaction of multiple genes and proteins that could easily be targeted causing the disease [17]. In addition, network pharmacology also helps in finding the disease node which is an important disease node. Beside these, it also increases the clinical candidates with potency and re-duces the attrition rate in the disease network [18]. Around 40% of the current drug discoveries are contributed by net-work pharmacology rather than a magic bullet philosophy [17, 18]. Table 1 depicts the key concepts developed in the area of network pharmacology.

3. RESEARCH APPROACHES AND AVAILABLE DATABASE RESOURCES

A newly emerged area in the field of drug discovery is network pharmacology which uses mainly two approaches, establishing a network and utilization of public databases. Prediction of drug target disease networks using HTS technology in combination with bioinformatics is among the other approaches in this area [19]. In the area of network pharmacology, the approaches could be divided into compu-tational and experimental approaches. The computational approaches mainly include graph theory, statistical methods, data mining, modeling, and information visualization methods. The experimental approaches include various high-throughput omics technologies and biological and pharmacological experiments. In network pharmacology, some common steps include data sources, big data analytics, network construction, interactions prediction and network analysis.The efforts of molecular biology and genomics research have provided large data which helped in gaining new in-sights into drug discovery processes. Hopkin, the father of Network Pharmacology, explained that a single drug can target multiple nodes in the disease network [14]. Network pharmacology is based on the integration of multiple disci-plinary concepts including molecular biology, biochemical biology and bioinformatics [14-16]. Network pharmacology has gained more interest due to high success rate in clinical investigation, less or affordable side effects, enhanced drug efficacy, regulation of the signaling pathway with multiple channels, interaction of multiple genes and proteins that could be easily be targeted causing the disease [17]. In addi-tion, network pharmacology also helps in finding the disease node which is an important disease node. Beside these, it also increases the clinical candidates with potency and reduces the attrition rate in the disease network [18]. Around 40% of the current drug discoveries are contributed by net-work pharmacology rather than a magic bullet philosophy [17, 18]. Table 1 is depicting the key concepts developed in the area of network pharmacology. (this paragraph is repeatedtwice time)

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The efforts of molecular biology and genomics research have produced a vast amount of data, which has aided in acquiring fresh insights into drug discovery procedures. Hopkin, the pioneer of Network Pharmacology, revealed that a single medicine can target numerous nodes in the disease network [6]. Network pharmacology is based on the integration of different discipline principles such as molecular biology, biochemical biology, and bioinformatics [6]. Network pharmacology has grown in popularity due to its high success rate in clinical trials, low or affordable side effects, improved drug efficacy, regulation of the signalling pathway with multiple channels, and interaction of multiple genes and proteins that can be easily targeted to cause disease. Furthermore, network pharmacology aids in locating the illness node that is an essential disease node. Apart from them, it also enhances the clinical potency and declines the attrition rate in the disease network. Around 40% of the existing drug developments are contributed by network pharmacology instead of a magic bullet philosophy.

Network Pharmacology and Traditional Medicine:

Local people have used therapeutic herbs without scientific investigations over the past decade [7, 8]. Traditional medicines have made use of a variety of therapeutic plant species [9,10]. Although medicinal plants have a positive influence on people's lives by delivering low-cost, natural medicines, unsustainable use and traditional collecting and application methods have resulted in the loss of several plant species of high therapeutic value [11, 12]. Traditional medicines, as defined by holistic philosophy and significant investigation in multicomponent therapies, have the capacity to regulate the complex character of illnesses [13–15]. Using herbal formulations is a distinctive feature of traditional medicine [16]. In this age of big data, ancient medicines may be reengineered simply by understanding the combinatorial nature of herbal formulations as well as their mechanisms [17, 18]. The Network pharmacology not only provides a novel opportunity to examine the complex molecular interactions of herbal formula but also the correlation existing among the herbal formula and complicated diseases in an orderly manner [19, 20]. Herbs that are used in traditional medicines indicate good molecular interactions, which lead to a more consistent network reaction than an individual drug [21-23]. Network based methodologies have gained popularity as research tools in areas of novel drug discoveries. They enable comprehending innovative treatments by using natural products as the active compound responsible for the synergistic and cumulative actions of drugs. These techniques have been found to work in a variety of traditional medications containing herbal composition [24-26].

Network pharmacology is a contemporary strategy for discovering active chemicals and potential molecular targets in a wide range of herbal formulas or basic plants [27-29]. This comprehensive method serves as a foundation for the first screening of bioactive compounds

in medicinal plants, as well as a novel therapeutic idea for future research on mechanisms of active substances for disease therapy [30,31] given in figure 1. As a result, adding network pharmacology into traditional medicine will provide unique and innovative opportunities for discovering active chemicals, biomarkers, and the scientific foundation of traditional medicine based on the complex biological systems of the human body [32, 33].

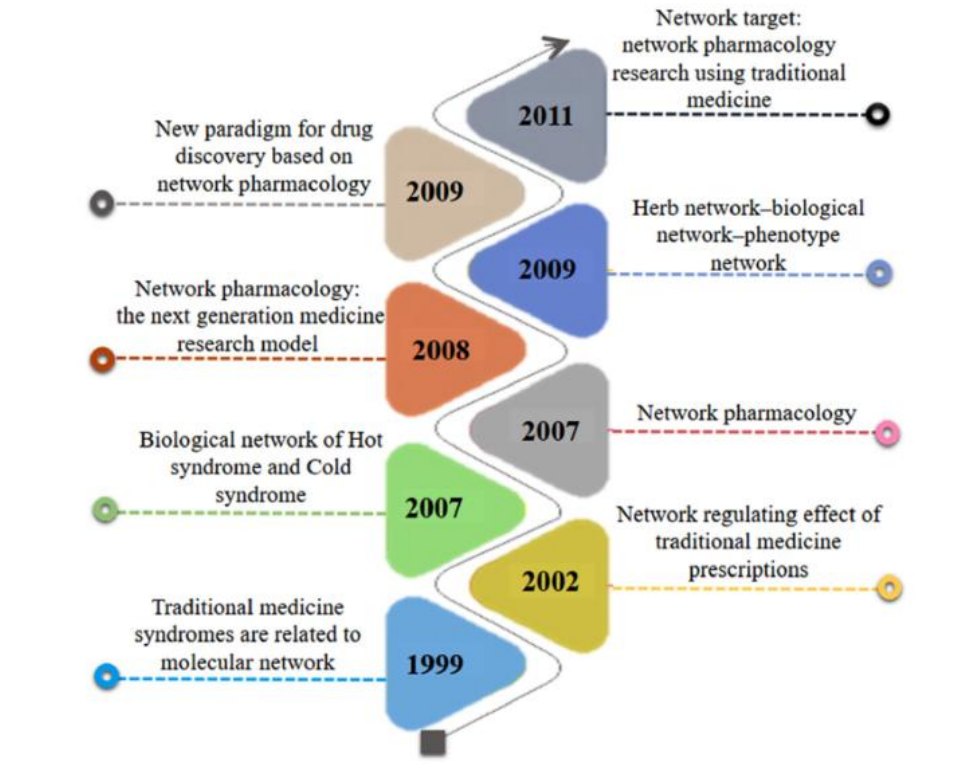

Figure 1. Timeline diagram representing the origin of network pharmacology.

Ayurveda, India's ancient medical system employs clever formulations including various components and bioactive chemicals; nevertheless, the scientific rationale and processes remain mostly unknown. NP methods can be a significant tool for evidence-based Ayurveda in understanding the possible effects, indications, and mechanisms of medications.

Traditional Chinese medicine (TCM) has evolved over thousands of years and collected a wealth of clinical expertise, resulting in a complete and one-of-a-kind medical system. TCM herbal formulas administration is a notable component of therapy based on Syndrome (ZHENG in Chinese) distinction, as well as holistic thinking in TCM theory. TCM has recently attracted the curiosity of people all over the world. Understanding the scientific foundation of TCM herbal formulations at the molecular and systems levels, however, remains one of the greatest obstacles for evidence-based TCM. The recent use of cutting-edge

technology in analytical chemistry and chemical biology to describe frequently used herbs or herbal formulations has enabled the identification of TCM active components and their biological targets. It is very likely that the investigations of the molecular structures of herbal formula will improve the rate of acceptance of TCM worldwide. Such efforts have aided in the discovery of the key active compounds and synergistic ingredient combinations, and in some cases, have resulted in TCM-based medication discoveries. However, because TCM herbs or herbal formulas contain a large number of constituents and various molecular transformations are involved in diseases and TCM Syndromes, the combinatorial rules and functions of most herbal formulae in complicated diseases remain unknown.

Thus, integrating emerging network science and ancient TCM will provide innovative techniques and opportunities for discovering bioactive components and biomarkers, potentially revealing mechanisms of action, and investigating the scientific evidence of herbal formulae based on complex biological systems. In 1999 [34], Li postulated a probable link between TCM Syndrome and molecular networks as the beginning of "TCM network pharmacology," and in 2007, he created a network-based TCM research approach [35] and executed a network study for Cold/Hot Syndromes and Hot/Cold herbal formulas [36]. Following that, Li revised the TCM research framework to be an "Herb network-Biological network-Phenotype network" [37] and presented a new notion of "Network target" [38]. In 2007, 2008, the topic of "Network Pharmacology" was introduced, and it is quickly becoming a cutting-edge research field in current drug studies and the next-generation form of drug research.

METHODOLOGY:

Concepts:

- Hypothesis on the relationship between TCM Syndrome and molecular networks 1999 [34]
- A network-based TCM research framework relevant to TCM network pharmacology is proposed. 2007 [35]
- A network-based case study of Cold/Hot herbal formulas and Hot/Cold Syndromes [36, 37] 2009 proposed the "Herb network-Biological network-Phenotype network."
- TCM network pharmacology concepts 2011 proposed a new idea of "Network target"[38, 39].

Methods:

- CIPHER- Network-based screening of Disease Genes 2008
- Drug CIPHER -Network-based prediction of medication (herbal ingredient) targets and functions 2010 [40]
- Com CIPHER Drug-gene-disease co-module analysis 2012 [41]
- CIPHER-HIT Modularity-based Disease Gene Prediction 2011 [42]
- DMIM Herb network building and co-module analysis for herbal formulas 2010 [46]
- NADA Network-based assessment of drug (herbal ingredient) effect 2010 [47]
- NIMS Network-based detection of multi-component synergy and medication (herbal ingredient) combinations 2011 [39, 50, 51]
- Model for drug combination A formal approach for assessing the effects of medication combinations 2010 [52]
- LMMA Disease-Specific Biomolecular Network Construction 2006 [43]
- Disease-specific route network creation 2010 [44]
- Methods ClustEx Disease-Specific Responsive Gene Module Identification 2010 [45]
- LWDH idea of "co-module" across herb-biomolecule-disease multilayer networks to investigate the potential combination mechanism of herbal formulas [48,49].

Databases:

- HerbBioMap is a repository of molecular data for herbs and TCM phenotypes. 2010 [53]
- dbNEI is a database for neuro-endocrine-immune interactions and the drug-NEI-disease network 2006, 2008 [54, 55].

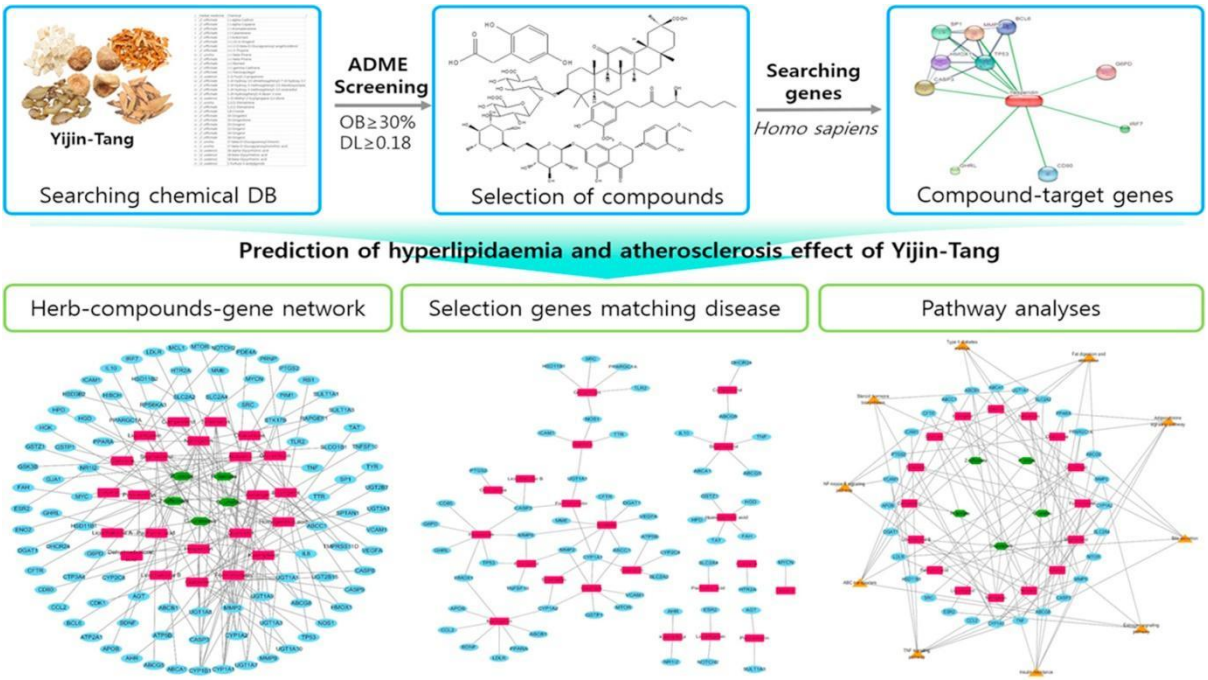

Figure 2: An example of a network pharmacology approach methodology

Data Mining:

The first stage in network pharmacology research is to identify active components of medicinal plants and disease-related targets. Generally, a literature search is conducted to find active compounds; however, many public databases give a user-friendly interface to determine the active compounds of the medicinal plant. After collecting active compounds, the canonical SMILES of active compounds are obtained from databases that are publicly available. There are some online and standalone programs available that may be used to detect canonical SMILES [56]. After getting canonical SMILES, network pharmacology research revolves around gene prediction or from canonical SMILES. A number of user-friendly tools and databases are available to assist with the process. Another key point is that we may get statistically significant genes by using a precise threshold on the probability of genes and resulting in highly significant genes. The estimation of disease-related genes is a first step in investigating the molecular mechanism of plants and herbs for treating a wide range of diseases and disorders [57, 58]. Furthermore, rather than relying on literature data, researchers have now analysed the transcriptome-wide gene expression microarray profiles of isolated tissues in response to exposure to plant extracts, their combinations, or purified compounds, accompanied by innovative pathway assessments *in silico* to illustrate their mechanisms of action and activated molecular networks behind estimated therapeutic effects in various health conditions [59-61].

Network Construction:

A network is a visual illustration of the interaction of multiple elements known as nodes. Bioactives, targets, tissue, tissue kinds, disease, disease categories, and pathways are all nodes in pharmacological networks. These nodes are linked by lines called edges, which show their connection [62]. Building a network requires two opposing approaches: a bottom-up approach based on existing biological knowledge and a top-down approach based on statistical analysis of available data. A biological network can be constructed and illustrated in a variety of ways. The de novo building of a network through direct experimental or computational interactions, such as chemical/gene/protein screens, is perhaps the most adaptable and broad method. Networks that include physiologically significant nodes (genes, proteins, and metabolites), their interactions (regulatory and biochemical), and modules (functional units and pathways) give an authentic idea about the original biological phenomenon [63].

Cytoscape [64], a Java-based open source software platform, is a powerful tool for visualising molecular interaction networks and combining them with any sort of attribute data. In addition to the core set of functions for data integration, analysis, and visualisation, applications with network and molecular profiling analysis and connections to other databases are available. There are more visualisation tools available in addition to Cytoscape. Visual network pharmacology (VNP) [65], which was developed to depict the complicated interactions between diseases, targets, and medications, consists primarily of three functional modules: drug-centric, target-centric, and disease-centric VNP. This disease-target-drug database catalogues known interactions between diseases, targets, and USFDA-approved medications. Users can search the database using disease, target, or medicine name strings; chemical structures and substructures; or protein sequence similarities, and then examine the obtained records in an online interactive network view. Each node in the produced network view represents a disease, target, or treatment, and each edge represents a known link between two of them. The Connectivity Map, often known as the CMap tool, enables users to compare gene-expression patterns. The similarities and contrasts between the signature transcriptional expression profile and the small molecule transcriptional response profile may lead to the identification of the small molecule's mechanism of action. The response profile is also compared to drug response profiles in the CMap database in terms of transcriptional response similarity. To have a better understanding of the mechanism of action, a network is built and the medications that seem similar to the small molecule are chosen. Other

applications, such as Gephi, a network exploration platform, and Cell Illustrator, a Java-based program specialising in biological processes and systems, can also be used to design networks [65].

Venn diagrams are preferred for discovering disease and chemical targets that overlap. This step's primary goal is to forecast disease-related genes and then discover common genes across illnesses and chemicals. The shared genes serve as first screening touchstones [66, 67]. To better understand the mechanism of medicinal plants in illness therapy, network analysis is used. Protein-protein interactions (PPI) are extremely important due to their diversity, adaptability, and specificity [68]. Databases that offer functional interactions among important targets are used to generate the PPI network of key targets (common genes) [69]. The network analysis is then used to determine the hub genes with the highest degree of interaction. Biological networks provide a wealth of data [70]. The crucial aspect is how to obtain essential data from networks. By identifying targets, network analysis attempts to reveal significant targets, active substances, and their linked pathways. A variety of approaches are used in network analysis, the most prevalent of which being network functional analysis. Many effective drugs have therapeutic effects by modifying multiple proteins rather than a single protein, and biological networks have been revealed to have a modular element. Topological study has revealed several subnet works with specific roles and topologies in big and intricate networks. GO enrichment analysis and KEGG are two functional analyses which provide key target features by exploring their integrated pathways.

Implications of Network Pharmacology for Therapy:

The common failure of independent candidate drugs to proceed from pre-clinical to clinical trials brings up the question of whether a specific drug development approach is the best. Even employing drugs working on established targets connected to solid biological networks is problematic due to patients' poor knowledge and validation of these targets [71]. As a result, network pharmacology is becoming increasingly important and gaining a lot of attention in modern drug development [72]. Pleiotropically active substances, for example, that target several proteins and biological processes in cancer-related networks, might be beneficial. Herbal medicine treatments are utilized to keep people healthy all over the world. Herbal medications are acknowledged as a key source of novel drugs due to their variety in structure, bioactivity, and nontoxicity that provide effective drug discovery and drawing global attention [73]. The "one disease, one medication, one target" paradigm is giving way

to "one disease, one drug, numerous targets." Network pharmacology investigates when and where one target can inhibit disease features such as tumour growth, resulting in the creation of treatments with no adverse effects. The advantages of network pharmacology have been extremely significant in drug development, notably in the repurposing of existing medications [74]. Computational drug design, facilitated by network-based approaches, aids in drug toxicity prediction and aids the drug molecule in locating its target binding site [75]. Network pharmacology provides novel drug development opportunities that may be more productive than employing traditional medicine with no scientific backing. This notion attracted people's curiosity since it suggested the prospect of better focused medicines with fewer side effects in normal physiological cells. Network pharmacology might provide potential approaches for rigorous target selection and the creation of multi-target, unique active molecules to treat those [76]. Highly connected areas are preferred in the PPI network since these nodes are regarded as the primary focus in the illness state. As a result, by focusing on such nodes, we may achieve our objective. Drugs, on the other hand, cannot inhibit all targets in a regulatory network. Only around 15% of nodes in a given network are druggable [77, 78]. Variety of approaches to generate appropriate Phyto-therapies based on network data can be considered:

- If the potentially active constituents in herbs or herbal mixtures are discovered, they can be considered. This approach is primarily inspired by their usage in herbal medicine. Herbal formulations are analogous to multiple-drug targeted treatment [79].
- Using selective poly-pharmacological approaches, active molecules may simply be employed to create multi-target specific treatments [80, 81].
- Proteins that aren't needed in normal cells may become therapeutically significant if connected together in a cancer network. Their combined elimination or inhibition may result in more efficient, if not synergistic, tumour cell eradication. Creating considerable therapy possibilities makes great sense in the human physiological process. A potential solution to this problem might be to employ polypharmacology to disrupt whole disease-causing networks with botanicals or sophisticated herbal extract that act on numerous targets, rather than knocking out individual proteins [82, 83].

APPLICATIONS:

Table 1 : Various applications of Network Pharmacology in several aspects include

Traditional medicine	Scientific evidence supporting the use of Ayurvedic medicine Understanding the reasoning behind conventional formulations Understanding Ayurvedic medicine's mechanism of action

	Ayurvedic medications' safety and efficacy Possible replacements for endangered botanicals Plant formulation design and prescription through a network The study of synergistic effect of several bioactives Quality control with botanical biomarkers
Pharmacology	Creating new leads from natural products Understanding drug mechanisms of action Identifying adverse effects of potential medication New indicators prediction Toxicology prediction Prediction of potential drug-drug interactions Drug rational design based on a set of interacting proteins Repurposing of drugs
Drug research	Developing new medicinal targets *In silico* assessment saves money and time. Understanding disease-specific signalling pathways Experiment design based on medications and targets Multigene-dependent disease therapies Identification of disease-causing genes Biomarkers for diagnosis Drug resistance or antibiotic resistance research [84]

CONCLUSION:

Network pharmacology analysis provides the finest possibility to seek conventional knowledge in order to find solutions to modern drug discovery issues. NEPs can also be useful in drug discovery, repurposing, and drug discovery. Several bioactive-target combinations have been tested in the lab. Based on their bioactive qualities, data synthesis utilising NP gives insights into the mode of action of traditional medications. It is a reverse approach that uses sophisticated integration methods to determine the molecular mechanism of action of a formulation. The present network analysis is based on existing research and data. As a result, the information is not up to date because much research is still on-going and new data is continually being generated. Despite its flaws, it is nonetheless an important resource since it gives insight into contemporary medicine's hidden discoveries. NP aids in

the analysis of knowledge, which may then be utilised to perceive information and provide innovative answers to existing medical problems.

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