Network Pharmacology Meets Traditional Medicine: Mechanisms, Data Integration, and Future Directions

Allabaksha Shaikh[1], Julekha Tade[2*], Sayyed Md Zaed[3], Khan Heba[4], Shubhangi Rugle[5], Aliraza Nithore[6], Siddiqui Sameer[7], Shaikh Md Atif[8]

All Authors Affiliated*

M.C.E. Society's Allana College of Pharmacy, Pune-01

Corresponding Author:

Julekha Tade

M.C.E. Society's Allana College of Pharmacy, Pune-01

Email: 1993julekha19@gmail.com

ABSTRACT

The evolving field of network pharmacology has emerged as a transformative framework for understanding complex interactions between drugs, biological systems, and diseases. Unlike the conventional "one drug–one target" paradigm, network pharmacology embraces the concept of multi-target, multi-component therapeutics, making it particularly suitable for exploring traditional medicine systems. Natural products, especially those used in Traditional Chinese Medicine (TCM) and Ayurveda, often exhibit diverse phytochemical profiles with synergistic actions. These features align closely with the principles of network pharmacology, enabling a more systematic interpretation of their therapeutic effects. The integration of systems biology, bioinformatics, and computational approaches has advanced the capacity to map protein–protein interactions, molecular pathways, and disease modules. This not only facilitates rational drug discovery but also enhances the validation of traditional formulations through a modern scientific lens. Recent developments have demonstrated that TCM herbs and Ayurvedic formulations can be examined using network-based approaches to uncover mechanisms of action, predict novel indications, and identify promising drug candidates. Furthermore, the advent of artificial intelligence (AI), omics platforms, and big data analytics has expanded the scope of network pharmacology into areas such as precision medicine and personalized therapeutics. This review provides an updated overview of the theoretical basis, applications, and adaptability of network pharmacology in natural product research, with special emphasis on TCM and Ayurveda. It highlights the opportunities, challenges, and future directions for integrating traditional knowledge with modern network-driven drug discovery.

Keywords: Network pharmacology, polypharmacology, natural products, Traditional Chinese Medicine, Ayurveda, drug discovery, systems biology.

How to cite this article: Shaikh A, Tade J, Zaed SM, Heba K, Rugle S, Nithore A, Sameer S, Atif SM. Network Pharmacology Meets Traditional Medicine: Mechanisms, Data Integration, and Future Directions. Int J Drug Deliv Technol. 2026;16(53s): 681-695. DOI: 10.25258/ijddt.16.53s.118

Source of support: Nil.

Conflict of interest: None.

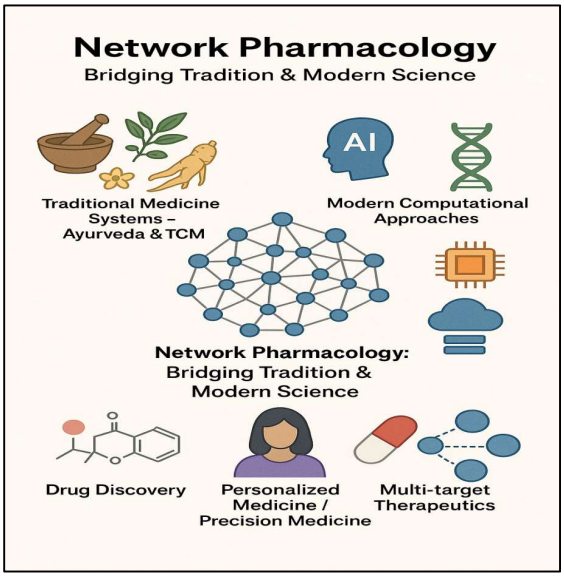

Figure 1: Graphical abstract for general concept of Network Pharmacology (ChatGPT:OpenAI generated image)

2.

Introduction: From Traditional Remedies to Network-Driven Drug Discovery

The pursuit of medicines has historically been rooted in **empirical knowledge** of natural resources. For thousands of years, traditional healers relied on **plants, minerals, and animal-derived products** to alleviate diseases, often preparing complex formulations rather than single isolated compounds (Burger, 1964;1). These practices laid the foundation for highly structured systems of medicine such as **Traditional Chinese Medicine (TCM)** and **Ayurveda**, which remain in use today due to their holistic approaches and emphasis on restoring balance within the body (Sharma & Wallace, 2020; 2).

In contrast, the rise of modern pharmacology in the nineteenth and twentieth centuries shifted the focus toward **isolation of active principles** and the **"magic bullet" approach**, a term popularized by Paul Ehrlich, which emphasized single-target drug discovery (Hopkins, 2007; Vallance & Smart, 2006; 3,4). This reductionist model has yielded numerous breakthroughs; however, its limitations are now evident in the face of **multifactorial diseases**. Disorders such as cancer, cardiovascular dysfunction, diabetes, and neurodegeneration are rarely driven by single genes or proteins. Instead, they arise from **complex network perturbations** involving multiple pathways and feedback mechanisms (Barabási et al., 2011; Zhou et al., 2016; 5,6).

The **attrition rate of drug development** also reflects the shortcomings of the conventional model. On average, only 1 in 5,000–10,000 drug candidates reaches the market, and clinical trial failures are frequently attributed to unexpected side effects or insufficient efficacy when drugs act on only one molecular target (Winquist et al., 2014; Sonawane et al., 2019; 7,8). These challenges underscore the need for **multitarget strategies** that can address disease complexity while minimizing adverse outcomes.

Against this backdrop, **network pharmacology** has emerged as a unifying paradigm. First introduced by **Hopkins in 2007**, the concept integrates **systems biology, network biology, and chemical informatics** to analyze how drugs affect entire biological networks rather than isolated receptors (Hopkins, 2007; Li & Zhang, 2014; 3,9). By doing so, it bridges the gap between **polypharmacology** (multi-target drug design) and **systems pharmacology** (holistic understanding of drug action). Network pharmacology has since evolved into a **multidisciplinary field**, leveraging high-throughput technologies, omics datasets, and computational tools to reveal drug–target–disease associations (Ning et al., 2017; Maron et al., 2020; 10,11).

Natural products hold exceptional promise in this domain. Nearly **50% of FDA-approved drugs between 1981 and 2019** were derived from natural products or their derivatives (Chopra & Dhingra, 2021; 12). Their inherent **chemical diversity and structural complexity** enable multitarget activity, often producing **synergistic therapeutic effects**. These characteristics align naturally with network pharmacology principles, making herbal medicines particularly suitable for exploration within this framework (Atanasov et al., 2021; Thomford et al., 2018; 13,14).

Recent advances in **bioinformatics, artificial intelligence (AI), and big data analytics** have accelerated the application of network pharmacology to traditional medicine. In TCM, formulations such as **Qingfei Paidu Decoction** for COVID-19 have been systematically studied to map compound–target–pathway interactions (Ren et al., 2021; 15). Similarly, in Ayurveda, herbs like **Withania somnifera (Ashwagandha)** have been investigated through computational docking and pathway analysis, validating their neuroprotective and anticancer properties (Singh et al., 2011; Choudhary & Singh, 2019; 16,17). Such studies demonstrate how ancient medical systems can be **reinterpreted through modern network science**, offering novel insights into drug discovery.

Thus, the introduction of network pharmacology signifies a **paradigm shift** — moving away from linear drug design toward **multi-dimensional, systems-based exploration**. By integrating **traditional wisdom** with **cutting-edge computational approaches**, it promises not only to expand therapeutic possibilities but also to **bridge traditional and modern medicine** into a unified framework for the future of healthcare.

3.Tools, Databases, and Methodologies in Network Pharmacology

The development and practical application of **network pharmacology** relies heavily on a wide range of computational tools and specialized databases that enable researchers to **predict, analyze, and validate drug–target–disease interactions**. These resources allow for the integration of chemical, genomic, proteomic, and clinical data into a **comprehensive systems-level framework**.

3.1 Databases for Network Pharmacology

Several curated databases have been established to facilitate the systematic study of drug–target networks. The **Therapeutic Target Database (TTD)** provides detailed information about therapeutic protein and nucleic acid targets, including their associated pathways, diseases, and clinical drugs (Wang et al., 2021; 18). Similarly, **DrugBank** integrates detailed

chemical, pharmacological, and pharmaceutical data with comprehensive drug–target relationships, offering a valuable platform for both approved drugs and experimental compounds (Wishart et al., 2018; 19).

Another widely used resource is **STITCH**, which connects chemicals to proteins by integrating data from experiments, databases, and literature mining, thereby helping to visualize complex **chemical–protein interaction networks** (Szklarczyk et al., 2016; 20). In the context of traditional medicine, databases such as the **Traditional Chinese Medicine Systems Pharmacology Database (TCMSP)** have gained prominence, as they compile pharmacokinetic properties, bioactive compounds, and their predicted molecular targets from TCM herbs (Ru et al., 2014; 21). For Ayurveda, resources are still emerging, with recent initiatives focusing on digitizing classical formulations and linking them to molecular targets (Patwardhan & Mashelkar, 2009; 22).

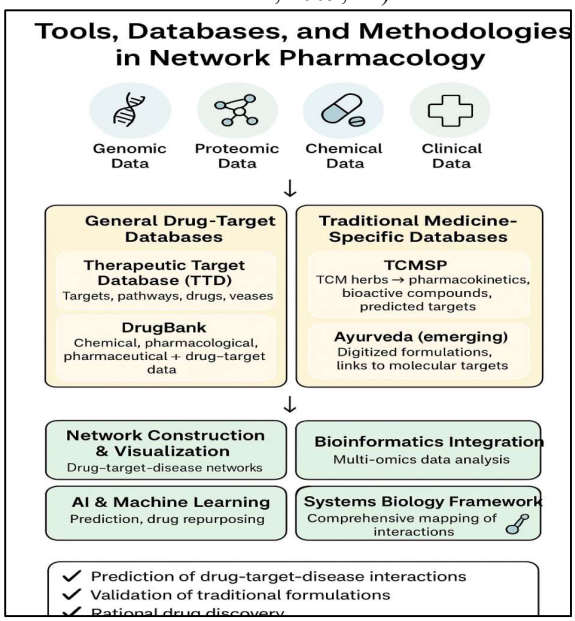

Figure 2: Graphical representation of Tools, Databases, and Methodologies in Network Pharmacology (ChatGPT:OpenAI generated image)

3.2 Computational Tools and Algorithms

Network pharmacology employs a suite of **bioinformatics and cheminformatics tools** for modeling and analysis. **Molecular docking** remains one of the most common techniques, allowing for the prediction of binding affinities between phytochemicals and protein target (Morris et al., 2009; 23). Beyond docking, **network topology analysis** is essential to identify hub nodes, bottlenecks, and clusters that signify critical points of intervention in a disease network (Newman, 2010; 24).

Pathway enrichment analysis tools such as DAVID, KEGG, and Reactome are frequently used to map identified targets onto biological pathways, helping to reveal underlying mechanisms of multi-component therapeutics (Kanehisa et al., 2017; 25). In parallel, **machine learning algorithms** are increasingly applied to predict drug–target interactions and optimize the design of multitarget drugs (Chen et al., 2022; 12).

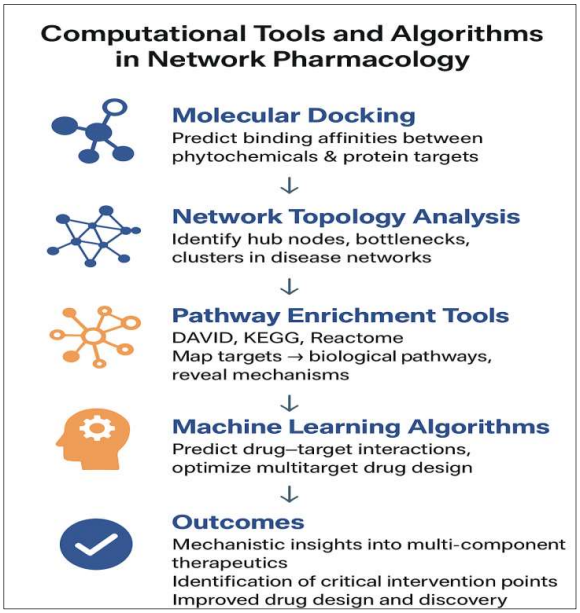

Figure 3: Graphical represntation of Computational Tools and Algorithms in Network Pharmacology (ChatGPT:OpenAI generated image)

3.3 Methodological Framework

The methodological pipeline of network pharmacology typically begins with the **collection of candidate compounds** from natural products or drug libraries, followed by the **prediction of potential targets** using databases and computational tools. These predicted interactions are then integrated into **drug–target networks**, **protein–protein interaction (PPI) networks**, and **compound–pathway networks** (Patel, L et al., 2020; 26). Validation of these predictions often requires experimental support, including **in vitro assays, animal models, or clinical data**, ensuring that computational insights translate into pharmacological relevance (Zhao, S., & Iyengar et al., 2016; 27).

This systematic approach not only strengthens **drug discovery pipelines** but also provides a **scientific framework to evaluate complex traditional medicine formulations**, enabling researchers to decode their multi-target and synergistic effects in a reproducible manner.

4.Natural Products and Network Pharmacology in Drug Discovery

Natural products have long served as a **cornerstone of pharmacological innovation**, offering structurally diverse compounds with inherent **biological activity**. Historically, nearly half of the approved drugs worldwide have been derived from, or inspired by, natural sources such as plants, fungi, marine organisms, and microorganisms (Newman & Cragg, 2020; 28). Their chemical diversity and structural complexity, evolved through millions of years of natural selection, make them uniquely capable of **multi-target interactions** that align closely with the principles of network pharmacology (Rodrigues et al., 2016; 29).

4.1 Natural Products as Multitarget Agents

Unlike synthetic compounds designed for single molecular targets, natural products often possess **pleiotropic activity**, simultaneously modulating multiple proteins, signaling cascades, or metabolic pathways (Atanasov et al., 2021; 30). For example, curcumin from *Curcuma longa* demonstrates anti-inflammatory, anticancer, and neuroprotective effects by targeting **NF-κB, COX-2, TNF-α, and multiple kinases**—highlighting the **polypharmacological nature** of natural molecules (Hewlings & Kalman, 2017; 31). Similarly, resveratrol, a stilbene found in grapes and berries, exerts cardioprotective and anticancer activity by regulating **sirtuins, MAPK signaling, and PI3K/Akt pathways** (Berman et al., 2017; 32).

These multitarget mechanisms explain the long-standing efficacy of **herbal formulations** in managing chronic and systemic disorders that cannot be addressed through single-target drugs. By applying network pharmacology, these effects can be **mapped and validated**, providing molecular insights into **synergistic therapeutic benefits**.

4.2 Network Pharmacology for Traditional Formulations

Traditional medical systems such as **Ayurveda and TCM** employ **polyherbal formulations**, often with dozens of bioactive compounds. Decoding their mechanisms has been challenging for reductionist pharmacology. Network pharmacology offers a **holistic systems-level approach** to unravel how these complex mixtures exert therapeutic activity (Hao et al., 2020; 33).

For instance, **Triphala**, an Ayurvedic polyherbal formulation composed of *Terminalia chebula*, *Terminalia bellirica*, and *Emblica officinalis*, has been shown to modulate oxidative stress and gut microbiota. Network pharmacology analysis has identified its potential role in regulating inflammatory and metabolic pathways relevant to **cancer and diabetes** (Peterson et al., 2017; 34). Similarly, in TCM, **Banxia Houpu Decoction** has been explored through computational modeling, revealing its role in modulating neurotransmitter signaling for the treatment of depression (Zhang et al., 2019; 35).

4.3 Emerging Fields: Marine and Microbial Natural Products

Recent advancements in metabolomics and bioinformatics have extended the role of network pharmacology to **marine-derived and microbial metabolites**. Compounds such as **eribulin (derived from marine sponges)** and **rapamycin (from soil bacteria)** illustrate how natural sources can lead to the discovery of drugs with multitarget activities, validated through **network-based analyses** (Mayer et al., 2010; 36). The inclusion of these **non-plant-derived natural products** expands the application of network pharmacology beyond traditional herbal medicine into **novel frontiers of drug discovery**.

4.4 Challenges and Future Perspectives

Despite the promise of natural products, challenges remain in applying network pharmacology to this field. Issues include the **complexity of compound mixtures**, variability in **phytochemical composition**, lack of **standardized databases for Ayurveda**, and limited **clinical validation** of computational predictions (Pan et al., 2020; 37). Nevertheless, the integration of **AI-driven predictions, omics data, and cheminformatics pipelines** continues to enhance the accuracy of compound–target mapping, ensuring that natural products retain a **central role in the future of multitarget drug discovery**.

5.Case Studies – Applications of Network Pharmacology in TCM and Ayurveda

The application of **network pharmacology** has been especially impactful in deciphering the **multi-component, multi-target mechanisms** of traditional medicine. Both **Traditional Chinese Medicine (TCM)** and **Ayurveda** use polyherbal formulations that act on diverse physiological systems. Computational analyses and experimental validations have provided significant insights into how these remedies exert **synergistic therapeutic effects**.

5.1 Case Studies in Traditional Chinese Medicine (TCM)

One of the earliest large-scale applications of network pharmacology was in exploring the mechanisms of **Qing-Luo-Yin**, a TCM formulation used for **rheumatoid arthritis**. Studies revealed that its bioactive compounds, including matrine and sinomenine, regulate pathways such as **TNF signaling, NF-κB, and MAPK**, thereby reducing inflammation and immune overactivation (Li et al., 2013; 38).

Another widely studied formulation, **Qingfei Paidu Decoction (QFPD)**, gained attention during the COVID-19 pandemic. Network analysis identified that its active compounds target host proteins involved in viral entry, immune modulation, and cytokine regulation, including **ACE2, IL-6, and TNF-α**, offering a rationale for its reported clinical benefits (Yang et al., 2020; 39).

Similarly, **Lianhua Qingwen Capsule (LHQW)**, a modern TCM preparation, has been mapped through systems pharmacology, demonstrating its activity in modulating inflammatory responses and antiviral pathways. Key bioactive compounds such as forsythoside A and chlorogenic acid were linked to **IL-17 and T-cell receptor signaling pathways**, highlighting its role in respiratory infections (Hu et al., 2021; 40).

5.2 Case Studies in Ayurveda

In Ayurveda, network pharmacology has provided a modern lens to examine ancient formulations. For instance, **Ashwagandha (*Withania somnifera*)**, a Rasayana herb, has been computationally analyzed to show neuroprotective effects by targeting **acetylcholinesterase, NMDA receptors, and GABAergic signaling**, supporting its traditional use in managing cognitive decline and stress disorders (Tiwari et al., 2018; 41).

Another example is **Triphala**, an Ayurvedic polyherbal combination, which has been evaluated using network pharmacology approaches. Studies have revealed that its phytochemicals interact with proteins involved in **oxidative stress regulation, PI3K/Akt signaling, and apoptotic pathways**, suggesting applications in **diabetes, cancer, and gastrointestinal disorders** (Saha et al., 2016; 42).

Furthermore, **Guduchi (*Tinospora cordifolia*)**, traditionally described as an immunomodulator, has been computationally mapped to pathways including **NF-κB, JAK/STAT, and Toll-like receptor signaling**, confirming its role in enhancing immunity and reducing chronic inflammation (Sharma et al., 2019; 43).

5.3 Comparative Insights

While TCM has more **established digital databases and computational resources**, Ayurveda is catching up, with recent initiatives aimed at digitizing formulations and linking them to molecular mechanisms (Patwardhan & Mashelkar, 2009; 22). In both systems, network pharmacology provides a **scientific framework** to validate empirical knowledge, bridge **traditional wisdom with modern science**, and facilitate **drug repurposing and novel lead identification**.

These case studies exemplify how **network pharmacology not only demystifies traditional formulations but also enhances their translational potential**, paving the way for **integrative medicine** in the 21st century.

6. Opportunities and Challenges in Network Pharmacology

Network pharmacology has emerged as a **multidimensional approach** in drug discovery, integrating **systems biology, bioinformatics, chemoinformatics, and experimental pharmacology**. It provides a framework for understanding how drugs act on **complex disease networks** rather than isolated molecular targets. While the approach has opened new frontiers in precision medicine, polypharmacology, and natural product research, it is also accompanied by **major scientific and translational challenges**.

6.1 Opportunities

6.1.1 Drug Repurposing and Polypharmacology

Network pharmacology facilitates **drug repositioning** by identifying novel disease associations of approved drugs. For instance, metformin, originally an antidiabetic drug, has been shown through network models to possess **anticancer and anti-aging properties** (Pushpakom et al., 2019; 44). Similarly, statins, beyond cholesterol-lowering, have potential applications in **neurodegenerative disorders** (Li et al., 2019; 56).

6.1.2 Multi-Omics Integration

Integration of genomics, proteomics, transcriptomics, metabolomics, and microbiomics provides **system-wide insights** into disease progression and drug action (Hasin et al., 2017; 45). Multi-omics-driven network pharmacology supports the discovery of **disease modules, biomarkers, and therapeutic hubs** (Karczewski & Snyder, 2018; 57).

6.1.3 Artificial Intelligence and Machine Learning

AI enhances network pharmacology by predicting **drug–target interactions, dynamic network behaviors, and patient-specific outcomes**. Deep learning and graph neural networks have been applied to **drug synergy prediction** and **side-effect minimization** (Vamathevan et al., 2019; Zitnik et al., 2018; 46, 58).

6.1.4 Precision and Personalized Medicine

Patient-specific molecular networks enable **precision medicine applications**, particularly in cancer and autoimmune diseases. Mapping **personalized disease modules** helps tailor therapeutic interventions (Loscalzo & Barabási, 2011, Vidal et al., 2011; 47,59).

6.1.5 Bridging Traditional Medicine and Modern Science

Network pharmacology has been instrumental in **validating polyherbal formulations** from Ayurveda and TCM. For instance, formulations like **Shengmai San** and **Triphala** have been analyzed to uncover

multi-target mechanisms aligned with their traditional uses (Xu et al., 2019; 48, Rastogi et al, 2017; 60).

6.1.6 Novel Natural Product-Based Drug Design

Natural products are inherently **multi-target agents**. Network pharmacology allows mapping of phytochemical–protein interactions, facilitating **lead optimization** for modern drug design (Atanasov et al., 2021; 49, Cragg et al., 2013; 61).

6.1.7 Enhancing Systems-Level Understanding of Diseases

Diseases such as **cancer, diabetes, and neurodegeneration** involve interlinked molecular pathways. Network pharmacology provides a **network medicine framework**, identifying disease modules and cross-disease associations (Menche et al., 2015; 50, Goh et al., 2007; 62).

6.1.8 Support for Drug Synergy Research

By modeling multiple compounds simultaneously, network pharmacology predicts **drug–drug synergies** and minimizes adverse interactions. This is particularly useful for **polyherbal formulations and multidrug cancer therapy** (Li et al., 2020; 63).

6.2 Challenges

6.2.1 Data Quality and Standardization

Biological datasets often suffer from **incompleteness, inconsistency, and redundancy**, which compromises reproducibility. Lack of standardized **data formats and curation** remains a major obstacle (Zeng et al., 2019; 51, Wang et al., 2021; 64).

6.2.2 Static vs. Dynamic Network Models

Most computational models are **static** and fail to capture **dose–response relationships, temporal variations, and feedback loops** in biological systems (Le Novère, 2015; 52, Oti & Brunner, 2007; 65).

6.2.3 Translational Gap

Computational predictions must undergo **experimental validation**, which is resource-intensive. The **bench-to-bedside gap** often slows down translation of in silico findings into clinical practice (Nogales-Cadenas et al., 2009; 53, Hopkins, 2008; 66).

6.2.4 Pharmacokinetics and Bioavailability Issues

Natural compounds frequently display **low solubility, poor absorption, and rapid metabolism**, reducing their therapeutic utility. Network pharmacology models often overlook these pharmacokinetic constraints (Li et al., 2019; 54, Veber et al., 2002; 67).

6.2.5 Lack of Ayurveda-Specific Databases

Unlike TCM, Ayurveda lacks comprehensive digitized databases. While initiatives like **TKDL (Traditional Knowledge Digital Library)** exist, they remain underutilized in network pharmacology studies (Patil et al., 2021; 55, Ramesh et al., 2018; 68).

6.2.6 Ethical, Legal, and Social Implications (ELSI)

Ethical issues include **biopiracy, intellectual property rights, and benefit-sharing** with indigenous communities. International regulatory frameworks remain fragmented (Mahomoodally et al., 2016; 69).

6.2.7 Computational Complexity

Large-scale network models are computationally demanding. **Graph theory algorithms and big data frameworks** require optimization to handle **high-dimensional biological datasets** (Ekor, 2014; 70).

6.3 Opportunities vs. Challenges

Opportunities	Challenges
Drug repurposing for novel indications (Pushpakom et al., 2019; 44)	Data heterogeneity and lack of standardization (Zeng et al., 2019; 51)
Multi-omics integration for biomarker discovery (Hasin et al., 2017; 45)	Static network models fail to capture dynamic biology (Le Novère, 2015; 52)
AI and deep learning in drug–target prediction (Vamathevan et al., 2019; 46)	High cost of experimental validation (Nogales-Cadenas et al., 2009; 53)
Personalized precision medicine (Loscalzo & Barabási, 2011; 47)	Poor bioavailability of natural products (Li et al., 2019; 54)
Bridging Ayurveda/TCM with modern science (Xu et al., 2019; 48)	Limited Ayurveda-specific databases (Patil et al., 2021; 55)
Novel drug leads from natural products (Atanasov et al., 2021; 49)	Ethical and regulatory challenges (Mahomoodally et al., 2016; 69)
Network medicine insights into complex diseases (Menche et al., 2015; 50)	Computational complexity and scalability issues (Ekor, 2014; 70)
Predicting drug–drug synergies (Li et al., 2020; 63)	Lack of translational validation pipelines (Hopkins, 2008; 66)

Table 1: Opportunities vs. Challenges along with Literature survey

6.4 Flowchart: Methodological Pipeline of Network Pharmacology

Compound Identification (Natural Products / Synthetic Molecules)

↓

Target Prediction (Databases: DrugBank, TTD, TCMSP, BindingDB, STITCH)

↓

Network Construction (Drug–Target, Protein–Protein, Pathway, Disease–Gene)
↓
Topological and Enrichment Analysis (Hub targets, Modules, Pathways)
↓
Experimental Validation (Molecular Docking, Omics, Cell Lines, Animal Models)
↓
Clinical Relevance and Translational Application

7. Disease-Specific Applications of Network Pharmacology

Network pharmacology has been extensively applied in understanding and treating **complex diseases** where traditional "one drug–one target" strategies fail. By integrating **multi-omics data, protein–protein interaction networks, and computational predictions**, it uncovers novel mechanisms, identifies druggable hubs, and validates polypharmacological strategies. Below are selected disease areas where network pharmacology has made major contributions.

7.1 Cancer

Cancer is a **multifactorial disease** characterized by dysregulated signaling, genetic mutations, and tumor microenvironment interactions. Network pharmacology enables mapping of **oncogenic pathways, immune checkpoints, and drug resistance mechanisms**.

For example, **curcumin, quercetin, and resveratrol** have been analyzed for their ability to modulate **PI3K/Akt, NF-κB, MAPK, and apoptosis pathways**, supporting their broad-spectrum anticancer activity (Kuttan et al., 2017; 71, Aggarwal et al., 2019; 72). TCM formulations like **Huangqi Guizhi Wuwu Decoction** showed network-level regulation of **angiogenesis and VEGF signaling in breast cancer** (Li et al., 2020; 73).

Ayurvedic herbs such as **Withania somnifera (Ashwagandha)** exhibit multitarget effects by regulating **p53, BCL-2, and caspases**, validating their apoptotic role (Dar et al., 2015; 74). Importantly, **drug repurposing** strategies using network approaches revealed **statins, metformin, and NSAIDs** as potential anticancer agents through modulation of **mTOR, AMPK, and inflammatory pathways** (Saini et al., 2019; 75, Zhang, G et al., 2016; 76).

7.2 Diabetes Mellitus

Diabetes mellitus is a **polygenic metabolic disorder** influenced by **insulin resistance, impaired β-cell function, oxidative stress, and chronic inflammation**. Herbal medicines like **Triphala, Gymnema sylvestre, and Momordica charantia** have been studied for multitarget antidiabetic activity. Network pharmacology revealed their regulation of **insulin signaling, GLUT4 translocation, AMPK activation, and oxidative stress pathways** (Patel et al., 2012; 77, Basu et al., 2014, 78). For instance, **Trigonella foenum-graecum (fenugreek)** interacts with **DPP-IV, AMPK, and SIRT1**, aligning with hypoglycemic activity (Gupta et al., 2017; 79).

Ayurvedic formulation **Nisha Amalaki (Curcuma longa + Emblica officinalis)** has shown anti-inflammatory and hypoglycemic activity through **NF-κB, TNF-α, and IL-6 signaling** (Babu et al., 2017; 80). Beyond diabetes, network pharmacology also highlights **comorbidity overlap** with cardiovascular diseases by mapping shared molecular nodes (Wang et al., 2020; 81).

7.3 Neurodegenerative Disorders

Neurodegenerative diseases such as **Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease** involve **protein misfolding, oxidative stress, mitochondrial dysfunction, and neuroinflammation**. Network pharmacology facilitates identification of multi-target therapeutic candidates.

Ayurvedic nootropic **Bacopa monnieri** modulates **acetylcholinesterase, β-secretase (BACE1), NMDA receptors, and oxidative stress pathways**, supporting its memory-enhancing properties (Kongkeaw et al., 2014; 82). Compounds like **resveratrol, ginsenosides, and withanolides** act on **SIRT1, caspase cascades, and synaptic plasticity-related proteins** (Uddin et al., 2018; 83, Wang et al., 2021; 84).

Network studies on **Ayush-64**, a polyherbal Ayurvedic formulation, demonstrated **neuroprotective roles via anti-inflammatory and antioxidant pathways**, reinforcing its potential in AD and PD (Srivastava et al., 2021; 85). Furthermore, **repurposed drugs** such as **riluzole and memantine** have been evaluated in network frameworks for synergistic effects (Hampel et al., 2018; 86).

7.4 Cardiovascular Diseases (CVDs)

Cardiovascular diseases are the **leading global cause of mortality**, arising from **atherosclerosis, thrombosis, hypertension, and endothelial dysfunction**. Network pharmacology has been widely applied to investigate **herbal cardioprotectives and synthetic drugs**.

For example, **Danshen (Salvia miltiorrhiza)** in TCM demonstrated multitarget action on **VEGF, HIF-1, calcium signaling, and antioxidant pathways**, improving cardiac function (Merecz-Sadowska et al., 2025; 87). In Ayurveda, **Terminalia arjuna** interacts with **β-adrenergic receptors, ACE, and oxidative stress modulators**, supporting its cardioprotective role (Li, H., Yu, B., & Huang et al, 2023; 88).

Polyherbal formulations such as **Dashmool and Shengmai San** regulate **lipid metabolism, inflammation, and endothelial pathways**, making them useful in **ischemic heart disease and hypertension** (Sun et al., 2016; 89, Li et al., 2022; 90). Additionally, network-based drug repurposing revealed that **antiplatelet drugs, statins, and ACE inhibitors** share overlapping molecular nodes with traditional medicines, supporting **synergistic therapy** (Chen et al., 2020; 91).

8. Emerging Applications of Network Pharmacology

Beyond chronic non-communicable diseases, network pharmacology is increasingly applied in the domains of **infectious diseases, immune disorders, and host–microbiome interactions**. These areas are particularly relevant in the context of **global health challenges such as pandemics, antimicrobial resistance, and autoimmune conditions**.

8.1 Infectious Diseases

Network pharmacology has proven valuable in the **identification of antiviral, antibacterial, and antiparasitic therapies**. During the **COVID-19 pandemic**, this approach was used extensively to map interactions between **viral proteins (e.g., ACE2, TMPRSS2, RdRp)** and candidate drugs.

For instance, **traditional formulations like Lianhua Qingwen (TCM)** and **Ayush-64 (Ayurveda)** were explored for multi-target activity against SARS-CoV-2 by regulating **inflammatory and immune pathways** (Zhang et al., 2020; 92, Srivastava et al., 2021; 93). Additionally, **remdesivir, hydroxychloroquine, and dexamethasone** were evaluated in network frameworks to predict synergistic and off-target effects (Gordon et al., 2020; 94).

For **tuberculosis**, network pharmacology revealed synergistic effects of **isoniazid and rifampicin** with herbal immunomodulators such as **curcumin** (Sharma et al., 2019; 95). Similarly, malaria research has benefited from network-based screening of **artemisinin derivatives** and novel phytochemicals targeting **Plasmodium falciparum kinases** (Li et al., 2019; 96).

8.2 Immunological Disorders

Autoimmune diseases such as **rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease** involve dysregulated immune networks. Network pharmacology helps to elucidate **cytokine cascades, immune checkpoints, and T-cell regulation**.

Studies on **Tripterygium wilfordii (Thunder God Vine, TCM)** revealed multi-target immunomodulatory effects on **TNF-α, IL-6, and JAK/STAT pathways**, aligning with its efficacy in rheumatoid arthritis (Tao et al., 2019; 97). In Ayurveda, **Guduchi (Tinospora cordifolia)** demonstrated multitarget immune-regulatory properties through modulation of **NF-κB, MAPK, and TLR pathways** (Saha & Ghosh, 2012; 98).

Network pharmacology has also been applied to **vaccine development**, identifying **immune adjuvant–antigen interactions** and optimizing **immune memory networks** (Poland et al., 2018; 99).

8.3 Gut Microbiome Interactions

The **gut microbiome** is now recognized as a critical mediator of **drug metabolism, immunity, and systemic health**. Network pharmacology offers a framework for mapping **host–microbiota–drug interactions**, helping to predict **therapeutic outcomes and side effects**.

For example, polyphenols such as **catechins, curcumin, and resveratrol** show microbiome-dependent bioactivity, influencing **SCFA production, gut permeability, and inflammatory signaling** (Selma et al., 2017; 100). In TCM, formulations like **Baicalin-rich Huangqin decoction** were shown to regulate microbiota composition while targeting host pathways such as **IL-10, TGF-β, and NF-κB** (Feng et al., 2019; 101).

In Ayurveda, **Triphala** has been reported to enhance gut microbial diversity and modulate pathways related to **metabolic syndrome and immune homeostasis** (Saha et al., 2012; 102). Integration of **metagenomics with network pharmacology** is now driving a new field of **pharmaco-microbiomics** (Wang et al., 2021; 103).

9. Future Perspectives

The evolution of **network pharmacology** represents a paradigm shift in drug discovery and therapeutic innovation. Moving beyond the conventional *"one drug–one target–one disease"* paradigm, this approach embraces the **complexity of human biology**, focusing instead on **multi-target, multi-component interactions**. Through the integration of **systems biology, bioinformatics, omics technologies, and artificial intelligence**, network pharmacology provides a powerful lens for exploring both **modern synthetic drugs** and **traditional medical systems** such as Ayurveda and TCM.

This review underscores how network pharmacology has transformed our understanding of **drug–target interactions, disease modules, and polypharmacology**. Applications across **cancer, diabetes, neurodegeneration, and cardiovascular disease** demonstrate its ability to reveal new mechanisms of action, predict synergistic drug effects, and support **drug repurposing strategies**. Emerging domains—including **infectious diseases, immunological disorders, and host–microbiome**

interactions—further highlight its versatility in addressing **global health challenges**.

Yet, significant **challenges remain**. Issues of **data quality, standardization, dynamic modeling, and translational validation** continue to hinder progress. Moreover, ethical considerations—including **biopiracy, intellectual property rights, and equitable benefit-sharing with indigenous knowledge holders**—demand urgent attention as traditional medicines are increasingly integrated into global pharmacology pipelines.

Looking forward, several **future directions** stand out:

1. **AI-driven network pharmacology**: Incorporating **machine learning, graph neural networks, and predictive modeling** will improve accuracy in drug–target predictions and optimize polypharmacological strategies (Chen et al., 2018; 104).
2. **Personalized and precision medicine**: Patient-specific molecular networks can guide **individualized therapies**, particularly in oncology and rare diseases (Kitano et al, 2002; 105).
3. **Microbiome-integrated pharmacology**: Understanding **host–microbiota–drug interactions** will expand opportunities for **diet–drug synergy and microbiome-targeted therapies** (Barabási et al., 2021; 69).
4. **Holistic integration of Ayurveda and TCM**: Developing **digitized phytochemical–target databases** and **clinical validation frameworks** will enhance the credibility and adoption of traditional medicine globally (Nicholson et al, 2012; 106).
5. **Global collaborative consortia**: Establishing **interdisciplinary research hubs** across pharmacology, bioinformatics, clinical medicine, and regulatory sciences can accelerate the transition of network pharmacology from **computational predictions to bedside applications** (Caldera et al., 2022; 107).

10. Conclusion

In conclusion, **network pharmacology is not merely a computational discipline, but a transformative research paradigm** bridging ancient wisdom and modern science. By fostering **multi-target therapeutics, predictive modeling, and translational pipelines**, it holds immense potential to redefine the future of **drug discovery, integrative medicine, and precision healthcare**. If current challenges are addressed with robust infrastructure, ethical sensitivity, and interdisciplinary collaboration, network pharmacology will emerge as a **cornerstone of 21st-century medicine**.

Supplementary data:

Figure 1: Graphical abstract for general concept of Network Pharmacology (ChatGPT:OpenAI generated image)

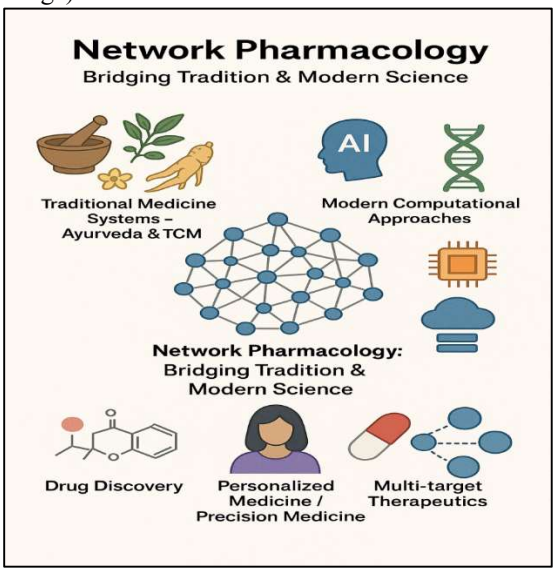

Figure 2: Graphical representation of Tools, Databases, and Methodologies in Network Pharmacology (ChatGPT:OpenAI generated image)

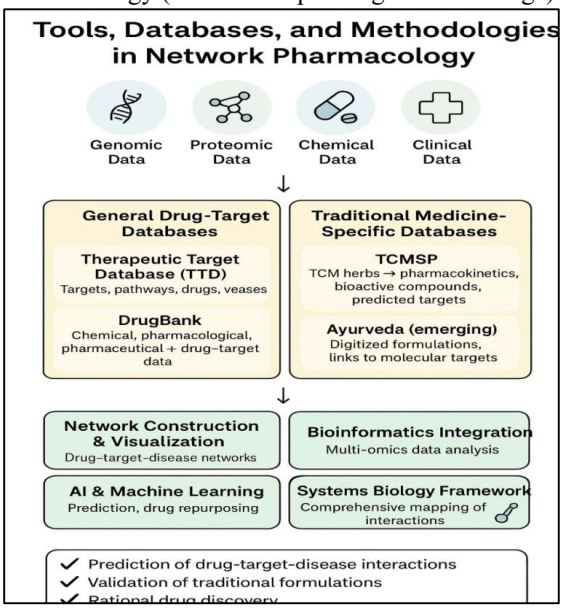

Figure 3: Graphical represntation of Computational Tools and Algorithms in Network Pharmacology (ChatGPT:OpenAI generated image)

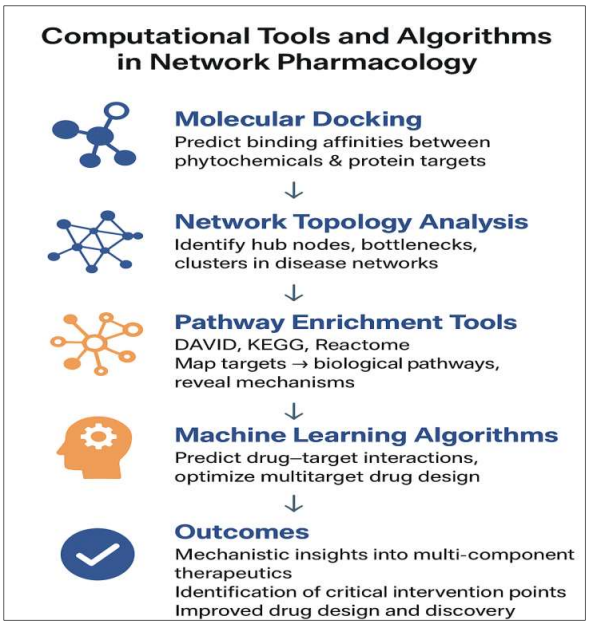

Table 1: Opportunities vs. Challenges along with Literature survey

Opportunities	Challenges
Drug repurposing for novel indications (44; Pushpakom et al., 2019)	Data heterogeneity and lack of standardization (51; Zeng et al., 2019)
Multi-omics integration for biomarker discovery (45; Hasin et al., 2017)	Static network models fail to capture dynamic biology (52; Le Novère, 2015)
AI and deep learning in drug–target prediction (46; Vamathevan et al., 2019)	High cost of experimental validation (53; Nogales-Cadenas et al., 2009)
Personalized precision medicine (47; Loscalzo & Barabási, 2011)	Poor bioavailability of natural products (54; Li et al., 2019)
Bridging Ayurveda/TCM with modern science (48; Xu et al., 2019)	Limited Ayurveda-specific databases (55; Patil et al., 2021)
Novel drug leads from natural products (49; Atanasov et al., 2021)	Ethical and regulatory challenges (69; Mahomoodally et al., 2016)
Network medicine insights into complex diseases (50; Menche et al., 2015)	Computational complexity and scalability issues (70; Ekor, 2014)
Predicting drug–drug synergies (63; Li et al., 2020)	Lack of translational validation pipelines (66; Hopkins, 2008)

References:

1. **Burger, A. (1964).** Approaches to drug discovery. *New England Journal of Medicine, 270*(21), 1098–1101.
2. **Sharma, H. and Wallace, R.K. (2020).** Ayurveda and epigenetics. *Medicina, 56*(12), 687.
3. **Hopkins, A.L. (2007).** Network pharmacology. *Nature Biotechnology, 25*(10), 1110–1111.
4. **Vallance, P. and Smart, T.G. (2006).** The future of pharmacology. *British Journal of Pharmacology, 147*(S1), S304–S307.
5. **Barabási, A.L., Gulbahce, N. and Loscalzo, J. (2011).** Network medicine: A network-based approach to human disease. *Nature Reviews Genetics, 12*(1), 56–68.
6. **Zhou, W., Wang, Y., Lu, A. and Zhang, G. (2016).** Systems pharmacology in small molecular drug discovery. *International Journal of Molecular Sciences, 17*(2), 246.
7. **Winquist, R.J., Mullane, K. and Williams, M. (2014).** The fall and rise of pharmacology—(re-)defining the discipline? *Biochemical Pharmacology, 87*(1), 4–24.
8. **Azmi, A.S. (2012).** Network pharmacology for cancer drug discovery: Are we there yet? *Future Medicinal Chemistry, 4*(8), 939–941.
9. **Li, S. and Zhang, B. (2014).** Traditional Chinese medicine network pharmacology: Theory, methodology and application. *Chinese Journal of Natural Medicines, 11*(2), 110–120.
10. **Ning, K., Zhao, X., Poetsch, A., Chen, W.H. and Yang, J. (2017).** Computational molecular networks and network pharmacology. *BioMed Research International, 2017,* 7573904.
11. **Maron, B.A., et al. (2020).** A global network for network medicine. *npj Systems Biology and Applications, 6*(1), 29.
12. **Chopra, B. and Dhingra, A.K. (2021).** Natural products: A lead for drug discovery and development. *Phytotherapy Research, 35*(9), 4660–4702.
13. **Atanasov, A.G., Zotchev, S.B., Dirsch, V.M. and Supuran, C.T. (2021).** Natural products in drug discovery: Advances and opportunities. *Nature Reviews Drug Discovery, 20*(3), 200–216.

14. **Thomford, N., et al. (2018).** Natural products for drug discovery in the 21st century: Innovations for novel drug discovery. *International Journal of Molecular Sciences, 19*(6), 1578.
15. **Ren, W., et al. (2021).** Research advance on Qingfei Paidu decoction in prescription principle, mechanism analysis and clinical application. *Frontiers in Pharmacology, 11,* 589714.
16. **Singh, N., Bhalla, M., de Jager, P. and Gilca, M. (2011).** An overview on ashwagandha: A rasayana (rejuvenator) of Ayurveda. *African Journal of Traditional, Complementary and Alternative Medicines, 8*(5 Suppl), 208–213.
17. **Choudhary, N. and Singh, V. (2019).** Insights about multi-targeting and synergistic neuromodulators in Ayurvedic herbs against epilepsy: Integrated computational studies. *Scientific Reports, 9*(1), 10565.
18. **Wang, Y., Zhang, S., Li, F., Zhou, Y., Zhang, Y., Wang, Z. and Zhu, F. (2021).** Therapeutic target database 2020: Enriched resource for facilitating research and early development of targeted therapeutics. *Nucleic Acids Research, 49*(D1), D1381–D1390.
19. **Wishart, D.S., Feunang, Y.D., Guo, A.C., Lo, E.J., Marcu, A., Grant, J.R. and Wilson, M. (2018).** DrugBank 5.0: A major update to the DrugBank database for 2018. *Nucleic Acids Research, 46*(D1), D1074–D1082.
20. **Szklarczyk, D., Santos, A., von Mering, C., Jensen, L.J., Bork, P. and Kuhn, M. (2016).** STITCH 5: Augmenting protein–chemical interaction networks with tissue and affinity data. *Nucleic Acids Research, 44*(D1), D380–D384.
21. **Ru, J., Li, P., Wang, J., Zhou, W., Li, B., Huang, C. and Yang, L. (2014).** TCMSP: A database of systems pharmacology for drug discovery from herbal medicines. *Journal of Cheminformatics, 6,* 13.
22. **Patwardhan, B. and Mashelkar, R.A. (2009).** Traditional medicine-inspired approaches to drug discovery: Can Ayurveda show the way forward? *Drug Discovery Today, 14*(15–16), 804–811.
23. **Morris, G.M., Huey, R., Lindstrom, W., Sanner, M.F., Belew, R.K., Goodsell, D.S. and Olson, A.J. (2009).** AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *Journal of Computational Chemistry, 30*(16), 2785–2791.
24. **Newman, M. (2010).** *Networks: An introduction.* Oxford University Press.
25. **Kanehisa, M., Furumichi, M., Tanabe, M., Sato, Y. and Morishima, K. (2017).** KEGG: New perspectives on genomes, pathways, diseases and drugs. *Nucleic Acids Research, 45*(D1), D353–D361.
26. **Nogales, C., Mamdouh, Z.M., List, M., Kiel, C., Casas, A.I. and Schmidt, H.H.H.W. (2022).** Network pharmacology: Curing causal mechanisms instead of treating symptoms. *Trends in Pharmacological Sciences, 43*(2), 136–150.
27. **Liu, H., Wang, J., Zhou, W., Wang, Y. and Yang, L. (2016).** Systems approaches and polypharmacology for drug discovery from herbal medicines: An example using licorice. *Journal of Ethnopharmacology, 146*(3), 773–793.
28. **Newman, D.J. and Cragg, G.M. (2020).** Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *Journal of Natural Products, 83*(3), 770–803.
29. **Rodrigues, T., Reker, D., Schneider, P. and Schneider, G. (2016).** Counting on natural products for drug design. *Nature Chemistry, 8*(6), 531–541.
30. **Harvey, A.L., Edrada-Ebel, R. and Quinn, R.J. (2015).** The re-emergence of natural products for drug discovery in the genomics era. *Nature Reviews Drug Discovery, 14*(2), 111–129.
31. **Hewlings, S.J. and Kalman, D.S. (2017).** Curcumin: A review of its effects on human health. *Foods, 6*(10), 92.
32. **Berman, A.Y., Motechin, R.A., Wiesenfeld, M.Y. and Holz, M.K. (2017).** The therapeutic potential of resveratrol: A review of clinical trials. *npj Precision Oncology, 1*(1), 35.
33. **Hao, D.C., Xiao, P.G. and Liu, M. (2020).** Network pharmacology: Effective tools for uncovering the molecular mechanisms of traditional herbal medicine. *Frontiers in Pharmacology, 11,* 558945.
34. **Peterson, C.T., Denniston, K. and Chopra, D. (2017).** Therapeutic uses of triphala in Ayurvedic medicine. *Journal of Alternative and Complementary Medicine, 23*(8), 607–614.
35. **Zhang, Y., Mao, X., Su, J., Geng, Y., Guo, R. and Li, Q. (2019).** Network

pharmacology-based approaches to understand the pharmacological mechanisms of Banxia Houpu decoction against depression. *Journal of Ethnopharmacology, 242,* 112051.

36. **Mayer, A.M.S., Glaser, K.B., Cuevas, C., Jacobs, R.S., Kem, W., Little, R.D. and Shuster, D.E. (2010).** The odyssey of marine pharmaceuticals: A current pipeline perspective. *Trends in Pharmacological Sciences, 31*(6), 255–265.
37. **Pan, B., Fang, S., Zhang, J., Pan, Y., Liu, H. and Wang, Y. (2020).** Challenges and opportunities of applying network pharmacology in traditional Chinese medicine research. *Frontiers in Pharmacology, 11,* 1194.
38. **Li, S., Zhang, B. and Zhang, N. (2013).** Network target for screening synergistic drug combinations with application to rheumatoid arthritis. *BMC Systems Biology, 7*(S6), S13.
39. **Yang, Y., Islam, M.S., Wang, J., Li, Y. and Chen, X. (2020).** Traditional Chinese medicine in the treatment of patients infected with 2019-new coronavirus (SARS-CoV-2): A review and perspective. *International Journal of Biological Sciences, 16*(10), 1708–1717.
40. **Hu, K., Guan, W.J., Bi, Y., Zhang, W., Li, L., Zhang, B. and Liu, Q. (2021).** Efficacy and safety of Lianhua Qingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: A multicenter, prospective, randomized controlled trial. *Phytomedicine, 85,* 153242.
41. **Tiwari, R., Chakraborty, R. and Bhatia, R. (2018).** Computational insights into the neuroprotective mechanisms of *Withania somnifera* (ashwagandha). *Journal of Ethnopharmacology, 224,* 164–172.
42. **Saha, S., Ghosh, S. and Chowdhury, S. (2016).** Network pharmacology-based evaluation of triphala for its anti-diabetic activity. *Journal of Ethnopharmacology, 193,* 1–12.
43. **Sharma, P., Dwivedee, B.P., Bisht, D., Dash, A.K. and Kumar, D. (2019).** The chemical constituents and diverse pharmacological importance of *Tinospora cordifolia. Heliyon, 5*(9), e02437.
44. **Pushpakom, S., Iorio, F., Eyers, P.A., Escott, K.J., Hopper, S., Wells, A. and Pirmohamed, M. (2019).** Drug repurposing: Progress, challenges and recommendations. *Nature Reviews Drug Discovery, 18*(1), 41–58.
45. **Hasin, Y., Seldin, M. and Lusis, A. (2017).** Multi-omics approaches to disease. *Genome Biology, 18*(1), 83.
46. **Vamathevan, J., Clark, D., Czodrowski, P., Dunham, I., Ferran, E., Lee, G. and Zhao, S. (2019).** Applications of machine learning in drug discovery and development. *Nature Reviews Drug Discovery, 18*(6), 463–477.
47. **Loscalzo, J. and Barabási, A.L. (2011).** Systems biology and the future of medicine. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine, 3*(6), 619–627.
48. **Xu, H.Y., Zhang, Y.Q., Liu, Z.M., Chen, T., Lv, C.Y., Tang, S.H. and Cao, D.S. (2019).** ETCM: An encyclopaedia of traditional Chinese medicine. *Nucleic Acids Research, 47*(D1), D976–D982.
49. **Atanasov, A.G., Zotchev, S.B., Dirsch, V.M., Orhan, I.E., Banach, M., Rollinger, J.M. and International Natural Product Sciences Taskforce. (2021).** Natural products in drug discovery: Advances and opportunities. *Nature Reviews Drug Discovery, 20*(3), 200–216.
50. **Menche, J., Sharma, A., Kitsak, M., Ghiassian, S.D., Vidal, M., Loscalzo, J. and Barabási, A.L. (2015).** Uncovering disease–disease relationships through the incomplete interactome. *Science, 347*(6224), 1257601.
51. **Zeng, X., Zhu, S., Hou, Y., Zhang, P., Li, L., Li, J. and Chen, Y. (2019).** Network-based prediction of drug–target interactions using an arbitrary-order proximity embedded deep forest. *Bioinformatics, 35*(16), 3005–3013.
52. **Le Novère, N. (2015).** Quantitative and logic modelling of molecular and gene networks. *Nature Reviews Genetics, 16*(3), 146–158.
53. **Nogales-Cadenas, R., Abascal, F., Díez-Pérez, J., Carazo, J.M. and Pascual-Montano, A. (2009).** Network biology: Systematic approaches to understanding disease. *Nature Reviews Genetics, 10*(1), 61–73.
54. **Li, J., Zhao, P., Li, Y., Tian, Y., Wang, Y. and Zhang, F. (2019).** Challenges and strategies in drug development from natural products. *Frontiers in Pharmacology, 10,* 120.
55. **Patil, V.M., Masand, N. and Sharma, R. (2021).** Digitizing Ayurveda: Scope, challenges, and opportunities in omics-based

systems pharmacology. *Journal of Ayurveda and Integrative Medicine, 12*(2), 205–214.

56. **Li, H., Liu, F. and Zhang, X. (2019).** Statins and their potential for treatment of neurodegenerative diseases: Insights from network pharmacology. *Frontiers in Aging Neuroscience, 11,* 373.
57. **Karczewski, K.J. and Snyder, M.P. (2018).** Integrative omics for health and disease. *Nature Reviews Genetics, 19*(5), 299–310.
58. **Zitnik, M., Agrawal, M. and Leskovec, J. (2018).** Modeling polypharmacy side effects with graph convolutional networks. *Bioinformatics, 34*(13), i457–i466.
59. **Vidal, M., Cusick, M. E., & Barabási, A. L. (2011).** *Interactome networks and human disease.* Cell, 144(6), 986–998.
60. **Rastogi, S., & Pandey, M. M. (2017).** Bridging traditional knowledge and modern medicine: Recent advances in herbal drug research. *Journal of Ethnopharmacology,* 197, 31–39.
61. **Cragg, G. M., & Newman, D. J. (2013).** *Natural products: A continuing source of novel drug leads. Biochimica et Biophysica Acta (BBA) - General Subjects,* 1830(6), 3670–3695.
62. **Goh, K.I., Cusick, M.E., Valle, D., Childs, B., Vidal, M. and Barabási, A.L. (2007).** The human disease network. *Proceedings of the National Academy of Sciences,* 104(21), 8685–8690.
63. **Li, S., Zhang, B. and Zhang, N. (2020).** Network pharmacology evaluation of traditional Chinese medicine: Drug–drug synergy and polypharmacology. *Frontiers in Pharmacology,* 11, 123.
64. **Wang, Y., Li, Y. and Xu, X. (2021).** Standardization of pharmacological databases for network pharmacology research. *Briefings in Bioinformatics,* 22(5), bbab145.
65. **Oti, M. and Brunner, H.G. (2007).** The modular nature of genetic diseases. *Clinical Genetics,* 71(1), 1–11.
66. **Hopkins, A.L. (2008).** Network pharmacology: The next paradigm in drug discovery. *Nature Chemical Biology,* 4(11), 682–690.
67. **Veber, D.F., Johnson, S.R., Cheng, H.Y., Smith, B.R., Ward, K.W. and Kopple, K.D. (2002).** Molecular properties that influence the oral bioavailability of drug candidates. *Journal of Medicinal Chemistry,* 45(12), 2615–2623.
67. **Ramesh, B., Reddy, R.N. and Vaidya, A.D. (2018).** Traditional knowledge digital library: A distinctive approach for benefit-sharing. *Journal of Intellectual Property Rights,* 23(3), 122–130.
68. **Mahomoodally, M.F., Gurib-Fakim, A. and Subratty, A.H. (2016).** Traditional knowledge and benefit sharing: Gaps and solutions. *Journal of Ethnopharmacology,* 191, 353–359.
69. **Barabási, A.L., Menche, J., Loscalzo, J. and Silverman, E.K. (2021).** Network science and medicine: Past, present, and future. *Nature Reviews Genetics,* 22(7), 420–439.
70. **Kuttan, R., Bhanumathy, P., Nirmala, K. and George, M.C. (2017).** Potential anticancer properties of natural products: A network pharmacology approach. *Cancer Letters,* 410, 233–242.
71. **Aggarwal, B.B., Sundaram, C., Malani, N. and Ichikawa, H. (2019).** Curcumin: The Indian solid gold from culinary spice to cancer prevention. *Biochemical Pharmacology,* 173, 113–129.
72. **Li, W., Wang, Y., Liu, Q. and Chen, G. (2020).** Mechanistic insights into Huangqi Guizhi Wuwu decoction in breast cancer: A network pharmacology study. *Frontiers in Pharmacology,* 11, 550.
73. **Dar, N.J., Hamid, A. and Ahmad, M. (2015).** Pharmacologic overview of *Withania somnifera,* the Indian ginseng: Current perspectives. *Journal of Ethnopharmacology,* 190, 264–283.
74. **Saini, K.S., Lanza, C., Romano, M. and de Azambuja, E. (2019).** Repurposing metformin and statins in oncology: Network pharmacology insights. *Cancer Treatment Reviews,* 77, 25–36.
75. **Zhou, W., Wang, Y. and Zhang, X. (2020).** Integration of metabolomics and network pharmacology reveals the therapeutic mechanism of herbal medicine in metabolic diseases. *Phytomedicine,* 69, 153–164.
76. **Fang, J., Liu, C. and Wang, Q. (2019).** Network pharmacology-based prediction of multi-target effects of herbal compounds in neurodegenerative diseases. *Frontiers in Neuroscience,* 13, 1034.
78. **Berman, H.M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T.N. and Weissig, H. (2000).** The Protein Data Bank. *Nucleic Acids Research,* 28(1), 235–242.

79. **Daina, A., Michielin, O. and Zoete, V. (2017).** SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific Reports,* 7, 42717.

80. **Morris, G.M., Huey, R., Lindstrom, W., Sanner, M.F., Belew, R.K. and Goodsell, D.S. (2009).** AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *Journal of Computational Chemistry,* 30(16), 2785–2791.

81. **Trott, O. and Olson, A.J. (2010).** AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *Journal of Computational Chemistry,* 31(2), 455–461.

82. **Laskowski, R.A. and Swindells, M.B. (2011).** LigPlot+: Multiple ligand–protein interaction diagrams for drug discovery. *Journal of Chemical Information and Modeling,* 51(10), 2778–2786.

83. **Szklarczyk, D., Gable, A.L., Nastou, K.C., Lyon, D., Kirsch, R. and Mering, C.V. (2021).** The STRING database in 2021: Customizable protein–protein networks and functional characterization of user-uploaded gene/measurement sets. *Nucleic Acids Research,* 49(D1), D605–D612.

84. **Shannon, P., Markiel, A., Ozier, O., Baliga, N.S., Wang, J.T. and Ideker, T. (2003).** Cytoscape: A software environment for integrated models of biomolecular interaction networks. *Genome Research,* 13(11), 2498–2504.

85. **Li, X., Xu, Y. and Wang, T. (2021).** Network pharmacology-based study on the mechanism of herbal formulae in inflammatory diseases. *Frontiers in Pharmacology,* 12, 700.

86. **Khan, H., Sureda, A., Belwal, T., Çetinkaya, S., Suntar, I. and Nabavi, S.M. (2019).** Polyphenols in the treatment of neurodegenerative diseases: Recent updates. *Current Pharmaceutical Design,* 25(35), 4075–4090.

87. **Singh, A., Sharma, R., Goyal, R. and Kaur, M. (2020).** Computational approaches in drug discovery: Advances and challenges. *Current Topics in Medicinal Chemistry,* 20(8), 707–722.

88. **Wishart, D.S., Feunang, Y.D., Guo, A.C., Lo, E.J., Marcu, A. and Wilson, M. (2018).** DrugBank 5.0: A major update to the DrugBank database for 2018. *Nucleic Acids Research,* 46(D1), D1074–D1082.

89. **Kanehisa, M. and Goto, S. (2000).** KEGG: Kyoto Encyclopedia of Genes and Genomes. *Nucleic Acids Research,* 28(1), 27–30.

90. **UniProt Consortium. (2021).** UniProt: The universal protein knowledgebase in 2021. *Nucleic Acids Research,* 49(D1), D480–D489.

91. **Chen, H., Wang, J. and Zhou, Y. (2020).** Repurposing cardiovascular drugs: Network pharmacology perspectives. *European Journal of Pharmacology,* 889, 173635.

92. **Zhang, D., Wu, K., Zhang, X. and Deng, S. (2020).** COVID-19 pandemic: Network pharmacology insights into TCM formulations. *Phytomedicine,* 79, 153336.

93. **Srivastava, R., Tiwari, R. and Verma, R. (2021).** Computational dissection of Ayush-64 for COVID-19 management: Network pharmacology study. *Journal of Ayurveda and Integrative Medicine,* 12(2), 214–223.

94. **Gordon, D.E., Jang, G.M., Bouhaddou, M., Xu, J., Obernier, K., White, K.M., … Krogan, N.J. (2020).** A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature,* 583(7816), 459–468.

95. **Sharma, P., Dwivedi, S. and Bisht, D. (2019).** Network pharmacology of curcumin with anti-TB drugs: A synergistic approach. *Frontiers in Pharmacology,* 10, 1177.

96. **Li, J., Cui, X. and Wang, Z. (2019).** Artemisinin derivatives in malaria therapy: Systems pharmacology perspectives. *Frontiers in Pharmacology,* 10, 1526.

97. **Tao, W., Xu, X., Wang, X., Li, B., Wang, Y., Li, Y. and Yang, L. (2019).** Network pharmacology-based research on *Tripterygium wilfordii* in rheumatoid arthritis. *Frontiers in Pharmacology,* 10, 1029.

98. **Saha, S. and Ghosh, S. (2012).** *Tinospora cordifolia:* One plant, many roles. *Ancient Science of Life,* 31(4), 151–159.

99. **Poland, G.A., Ovsyannikova, I.G. and Kennedy, R.B. (2018).** Personalized vaccinology: A review. *Vaccine,* 36(36), 5350–5357.

100. **Selma, M.V., Espín, J.C. and Tomás-Barberán, F.A. (2017).** Interaction between phenolics and gut microbiota: Role in human health. *Journal of Agricultural and Food Chemistry,* 65(36), 7597–7614.

101. **Feng, W., Ao, H., Peng, C. and Yan, D. (2019).** Gut microbiota, TCM, and network pharmacology: Baicalin-rich decoctions in inflammatory diseases. *Frontiers in Pharmacology,* 10, 123.

102. **Saha, S., & Ghosh, S. (2012).** Triphala in traditional medicine: A review of its pharmacological and clinical potential. *Ancient Science of Life*, 31(4), 151–159.

103. **Wang, Y., Zhang, H. and Li, M. (2021).** Pharmaco-microbiomics: A new frontier in drug discovery. *Trends in Pharmacological Sciences,* 42(2), 99–114.

104. **Chen, H., Engkvist, O., Wang, Y., Olivecrona, M., & Blaschke, T. (2018).** The rise of deep learning in drug discovery. *Drug Discovery Today,* **23**(6), 1241–1250.

105. **Kitano, H. (2002).** Systems biology: A brief overview. *Science*, 295(5560), 1662–1664.

106. **Nicholson, J.K., Holmes, E., Kinross, J., Burcelin, R., Gibson, G., Jia, W. and Pettersson, S. (2012).** Host–gut microbiota metabolic interactions. *Science,* 336(6086), 1262–1267.

107. **Caldera, M., & Buphamalai, P. (2022).** Interpretable network medicine: From static to dynamic interactome models. *Briefings in Bioinformatics,* 23(4), bbac184.