Natural Resources for Human Health
eISSN: 2583-1194

Original Research

Received 16 March 2026
Revised 24 April 2026
Accepted 10 May 2026

Natural Resources for Human Health 2026, Vol. 6 (3): 235–244

KEYWORDS:
Network pharmacology; Molecular docking; Phytochemicals; Computational phytopharmacology; Drug discovery; Protein–protein interaction network; Precision medicine; Natural products; Bioinformatics; Multi-target therapeutics.

Integrating Network Pharmacology and Molecular Docking to Discover Novel Therapeutic Phytochemicals

Amol Somnath Shete[1], Gurtej Singh[2*], Nargiza Mukhamadieva[3], Ibrokhim Sapaev[4], Banashree Barman[5], Mridula Gupta[6], Dr. Prem Nivas R[7]

[1] Krishna Institute of Pharmacy, Krishna Vishwa Vidyapeeth "Deemed to be University", Taluka-Karad, Dist-Satara, Pin-415 539, Maharashtra, India. amol.shete@rediffmail.com
[2] Department of Orthopedics, Noida international University, Greater Noida, Uttar Pradesh 203201, India., gurtejkahlon0729@gmail.com
[3]PhD, Associate Professor, Department of Technological Education, Termez State University, Termez, Uzbekistan nargizamuhammadiyeva84@gmail.com, 0009-0003-0930-6831
[4]1. Head of the Department of Physics and Chemistry, "Tashkent Institute of Irrigation and Agricultural Mechanization Engineers" National Research University, Tashkent, Uzbekistan; 2. Scientific Researcher, University of Tashkent for Applied Science; 3. School of Engineering, Central Asian University, Tashkent, Uzbekistan. sapaevibrokhim@gmail.com, 0000-0003-2365-1554
[5]School of Pharmacy and Research, Dev Bhoomi Uttarakhand University, 2banashree@gmail.com, 0009-0009-0444-4411
[6]Centre for Research Impact & Outcome, Chitkara University Institute of Engineering and Technology, Chitkara University, Rajpura, 140401, Punjab, India. mridula.gupta.orp@chitkara.edu.in https://orcid.org/0009-0002-8961-3059
[7]Associate Professor, Department of ENT, Vinayaka Mission's Kirupananda Variyar Medical College & Hospitals Vinayaka Mission's Research Foundation (DU), Salem, Tamil Nadu, India. premnivas187@gmail.com, 0009-0000-7447-7934

ABSTRACT: The combination of network pharmacology and molecular docking has become a powerful computational approach to boost the phytochemical-based drug discovery and precision medicine. This integrated approach enables systematic exploration of multi-component, multi-target and multi-pathway interactions involved in the therapeutic effects of natural products, which are not possible through conventional single-target approaches. By network pharmacology, disease-related genes, PPI network, hub targets and enriched biological pathways could be identified, and molecular docking could be used to verify the interactions between protein and ligands through binding affinity and structure analysis. All these activities contribute to accelerate the screening and prioritization of bioactive phytochemicals for different disease conditions like cancers, diabetes mellitus, cardiovascular diseases, neurodegenerative diseases, infectious diseases and inflammatory diseases. Prediction accuracy and understanding is further enhanced by the advanced use of bioinformatics databases, molecular dynamics simulations, AI and multi-omics technologies. The computational framework albeit with limitations in data quality and standardization, however, provides a solid framework for evidence-based natural product research, identifying new therapeutic phytochemicals and advancing the science of precision phytomedicine.

1. INTRODUCTION

Natural products have always been acknowledged as a significant source for therapeutic agents since they have contributed greatly to the discovery of drugs used in treating cancer, cardiovascular diseases, infectious diseases, metabolic syndromes and neurological diseases. The advent of various biological databases, computational algorithms, and systems biology tools has revolutionized the way the natural product field is studied and transformed it into an interdisciplinary field which brings together bioinformatics, cheminformatics, systems pharmacology and molecular modelling to discover, predict, and optimize plant-based bioactive compounds with therapeutic potential. Contrary to the single-target, single-target pathway approach of the traditional drug discovery process, computational phytopharmacology has the goal of understanding the multi-targeted, multi-component and multi-target nature of phytochemicals to better understand their therapeutic potentials and pharmacological activity. In recent years, network pharmacology has become one of the powerful computational approaches based on systems biology and that involves the interactions between phytochemicals, disease-associated genes, proteins, signaling pathways and biological networks. This multilevel approach is beneficial for overcoming the challenge of the identification of relevant molecular targets, hub genes and pathways related to disease progression and elucidating the synergies between multiple phytochemicals identified in medicinal plants. Functional enrichment analyses, such as Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway and Gene Ontology (GO) analyses, as well as construction of protein-protein interaction (PPI) networks further enriches the interpretation of the biological mechanisms that underlie the phytochemical activity (2).Furthermore, molecular docking can be used in conjunction with network pharmacology to confirm the binding affinity and conformation of predicted target compounds and elucidate the interaction between the two molecules that results in the biological activity. Compared to the conventional drug discovery process, docking based virtual screening can screen a large number of compounds that seem to be good candidates for phytochemical drug action in a short period of time, before experimental testing, and thereby saves time, resources and cost of the conventional drug discovery process and increases the chance of identifying interesting lead compounds (3). Network pharmacology and molecular docking thus have become an essential tool to discover novel therapeutic phytochemicals, obtain mechanism insights from computational prediction and experimental validation. This holistic approach has successfully led to the discovery of candidate drugs for the treatment of cancer, diabetes, cardiovascular, neurodegenerative, inflammatory and infectious diseases, multi-target therapeutic and precision medicine (4). In this context, this chapter intends to give a comprehensive and detailed description of the principles, methods, applications, challenges and future scope of the use of network pharmacology and molecular docking in the process of phytochemical drug discovery and to create a bridge between natural products and clinically relevant drugs (5).

2. FUNDAMENTALS OF NETWORK PHARMACOLOGY

Network pharmacology is an emerging field of study that integrates systems biology, bioinformatics, computational biology, network science, and pharmacology to explore bioactive compound targets, biological pathways, and disease network interactions. This discipline has developed due to the recognition that most complex diseases are polygenetic – involving several genes, several proteins, several signalling pathways, which interact and are dynamic components of the biological systems. Network pharmacology therefore utilizes a holistic "multi-component–multi-target–multi-pathway" strategy, which is especially applicable for the study of medicinal plants and phytochemicals, the therapeutic effects of which are frequently attributed to the synergistic activity of several bioactive components instead of a single active component (6). Biological functions are controlled by a network of interconnected molecular pathways, such as the gene regulatory network, the protein–protein interaction (PPI) network, metabolic pathways, and signaling pathways, from a systems biology point of view. To provide the mechanism of the therapeutic action of natural products, network pharmacology can combine these biological data to find disease-related genes, hub proteins, and important signaling pathways involved in the progression of disease. This systems-level understanding can help support the concept of polypharmacology in which one phytochemical, or a combination of phytochemicals, targets multiple molecular systems simultaneously with an increased therapeutic activity, reduced drug resistance, and enhanced safety for the treatment of complex diseases such as cancer, diabetes, cardiovascular diseases, neurodegenerative diseases, and chronic inflammatory diseases (7). The typical network pharmacology procedure is to find bioactive phytochemicals with desirable pharmacokinetics, forecast the interactions between compounds and targets, gather disease-related genes from public databases, build protein–protein interaction networks, and perform a functional enrichment study through the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway and Gene Ontology (GO) to uncover the underlying biological mechanisms. The visualization of the network also helps to determine hub genes or main regulatory

pathways that can be later confirmed by molecular docking, molecular dynamics simulation, and experimental research (8). It becomes a crucial computational approach with the availability of reliable resources in the field of bioinformatics that support compound screening, target prediction, pathway enrichment, network visualization, and other related fields such as TCMSP, PubChem, ChEMBL, DrugBank, UniProt, GeneCards, OMIM, STRING, DisGeNET, KEGG, DAVID, Metascape, Cytoscape, and SwissTargetPrediction (9). In the era of rapidly developing computer technology, network pharmacology has been gradually used to accelerate the process of discovering phytochemical drugs, making it an irreplaceable platform for precision medicine and scientifically guiding the rational development of evidence-based medicine from herbal constituents based on multi-omics information, artificial intelligence, and systems-level biological analysis. (10)

3. THERAPEUTIC POTENTIAL OF PHYTOCHEMICALS

Plants are the source of many naturally occurring bioactive compounds, called phytochemicals (secondary metabolites), which have numerous health-promoting properties for human beings and are produced by plants for their own growth, defense and adaptation to their environment. Based on the chemical structure and biosynthesis, phytochemicals can be classified into polyphenols (flavonoids, phenolic acids, tannins, and stilbenes), alkaloids, terpenoids, glycosides, saponins, lignans, organosulfur compounds and carotenoids. Their structural diversity and ability to target multiple molecular targets is responsible for the diversity of their biological activities. The extensive pharmacological investigations have highlighted the antioxidant, anti-inflammatory, antimicrobial, antiviral, antifungal, antiparasitic, anticancer, antidiabetic, cardioprotective, hepatoprotective, neuroprotective, immunomodulatory and anti-obesity activities of phytochemicals, which makes them important drugs for the prevention and treatment of various human diseases (11). In contrast to conventional synthetic drugs that typically work on a single molecule, the phytochemicals usually act on multiple targets, such as multiple signaling pathways, transcription factors, enzymes, receptors, cytokines and gene expression networks. They regulate critical cellular pathways such as NF-κB, PI3K/Akt, MAPK, JAK/STAT, AMPK, Wnt/β-catenin, TGF-β, immune responses and cellular metabolism, which are involved in oxidative stress, inflammation, apoptosis, autophagy, angiogenesis and cellular metabolism. This systems-level mode of action will enhance the therapeutic activity and make it more difficult for drug resistance to develop and lead to single-target drug side effects (12).The presence of diverse phytochemicals in a single medicinal plant also encourages the synergic pharmacological activity of these plants as two or more phytochemicals target more than one target that is associated with disease. Hence phytochemicals have gotten a great deal of attention for managing chronic illnesses such as cancer, diabetes mellitus, cardiovascular disorders, obesity, metabolic syndrome, neurodegenerative diseases, autoimmune diseases and chronic inflammatory diseases where complex molecular mechanisms are underlying the progression of the disease (13). Moreover, many phytochemicals along with their broad-spectrum antimicrobial activity can disrupt microbial cell membranes, inhibit key enzymes, interrupt microbial biofilm formation, inhibit nucleic acid synthesis, and modulate host immune response. These properties have been highlighted as potential therapeutic agents that complement other ones in combating new emerging infectious diseases and antimicrobial resistant pathogens (14). In addition, the multi-target natural product therapeutics for precision medicine, the elucidation of novel natural products therapeutic compounds and their molecular mechanisms with the combination of phytochemical research and network pharmacology, molecular docking, artificial intelligence and multi-omics technologies further highlighted the important role of natural products in the future development of novel drug compounds and in the process of translational biomedical research (15).

4. IDENTIFICATION OF DISEASE TARGETS AND NETWORK CONSTRUCTION

The main part of network pharmacology is target identification of the diseases and construction of biological interaction networks, which can be used to elucidate the molecular mechanisms of the therapeutic effects of phytochemicals. Usually starts with disease associated gene mining where genes associated with a specific disease are gathered from publicly available gene databases like GeneCards, OMIM, DisGeNET, CTD and NCBI Gene. These databases combine the genomic, transcriptomic, proteomic and clinical evidence to provide an identification of genes that have an important role in initiation of the disease, disease progression, and prognosis. At the same time, bioactive phytochemicals are filtered based on pharmacokinetic properties like oral bioavailability, drug-likeness and ADMET properties and then compound–target prediction is performed on computational platforms like SwissTargetPrediction, STITCH, SEA, BindingDB, PharmMapper. The targets of both phytochemicals and disease-related genes are then identified and compounds to mimic the pharmacological activity of natural products are identified (16). These predicted targets are added to protein–protein interaction (PPI) networks with the support of online resources such as STRING and then analyzed using a software package called Cytoscape to examine the relationship

between these proteins within the disease pathogenesis pathway (see Figure 1). Using PPI network analysis, highly connected proteins can be identified that can regulate a range of biological processes and provide insights into the functional organization of disease-associated molecular networks (17) (Figure 1).

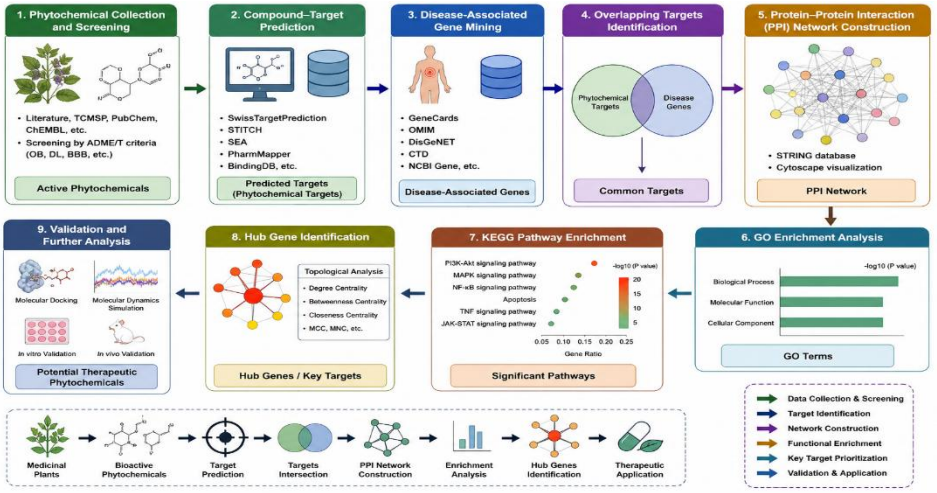

Figure 1. Integrated Workflow of Network Pharmacology for Therapeutic Phytochemical Discovery

To gain deeper insight into the biological significance of these targets, Gene Ontology (GO) enrichment analysis is carried out to classify genes based on biological processes, molecular functions and cellular components and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment finds the major signaling pathways affected by phytochemicals such as PI3K/Akt, MAPK, NF-κB, JAK/STAT, apoptosis, oxidative stress, and immune-related pathways. The analyses provide insightful, mechanistically relevant clues about understanding how phytochemicals affect a wide array of interconnected pathways to achieve therapeutic effects against a complex disease (18). Finally, network topology analyses are performed to select the most central genes (hub genes) from the network based on the degree centrality, betweenness centrality, closeness centrality, and maximal clique centrality for the network that will be used to identify the most promising therapeutic targets for molecular docking, molecular dynamics simulation, and experimental validation. Modulation of key regulatory molecules is often represented by hub genes and can have a significant impact on the progression and treatment outcomes of diseases (19). Disease-associated gene mining, compound–target prediction, PPI network construction, GO and KEGG enrichment analyses and hub gene identification offer a solid computational approach to novel therapeutic phytochemical discovery, and will also provide scientific support for precision medicine and evidence-based natural product drug discovery, as summarized in Figure 1 (20).

5. MOLECULAR DOCKING FOR TARGET VALIDATION

Molecular docking is one of the most widely used structure based computational techniques used in the modern days of drug discovery and is an accurate approach to predict binding between a small bioactive compound and target protein in an atomic level. Molecular docking is also an important model validation method in the field of phytochemicals that can be used to validate the binding efficiency of the bioactive compound predicted by the network pharmacology analysis with the target protein related to the disease. The very basic idea behind molecular docking is to determine the orientation of attachment of a ligand to the active site or allosteric site of the receptor, at which the ligand will have the least amount of energy, and calculate the strength and stability of the protein–ligand complex. Molecular recognition, shape complementarity, electrostatic interactions, hydrogen bonding, hydrophobic contacts, van der Waals forces and conformational flexibility are used in docking simulations to predict biologically relevant binding modes that could be responsible for therapeutic activity (20). The docking accuracy is highly dependent on the correct structure of the protein and the ligand to be prepared for computational analysis. The Protein preparation involves downloading the high resolution 3D structure of the protein from the Protein Data Bank (PDB), removing water molecules, co-crystallized ligands, and non-essential ions, adding water molecules to the surface of the protein, correcting missing residues, correcting protonation states, and energy-minimizing. Similarly, the procedure for preparation of the ligands includes data retrieval from databases like PubChem or ChEMBL, 3D conformation, optimization, assignment of atomic

charges and minimization of the molecular energy for correct docking calculation (21).Many softwares like AutoDock, AutoDock Vina, Glide, GOLD, FlexX, MOE and Discovery Studio use sophisticated search algorithms and scoring functions to explore possible binding orientations and to calculate the binding strength of the ligand. Such algorithms calculate multiple different poses and rank them according to the free energy of binding predicted for the pose – lower docking scores indicate more favorable, stable protein–ligand interactions (22). The detailed analyses of the hydrogen bonds, hydrophobic interactions, π–π stacking, salt bridges and amino acid residues present within the active binding pocket is crucial in the identification of the molecular determinants of the biological activity, thus facilitating the binding affinity evaluation. While the docking prediction quality and its reliability may be further improved with the aid of molecular dynamics simulations and binding free energy calculations such as MM/PBSA and MM/GBSA (23), it is quite clear that the quality of the proposed docking poses is only good.It is quite clear that the quality of the proposed docking poses is good, but it can be further improved with the help of molecular dynamics simulations and binding free energy calculations like MM/PBSA and MM/GBSA (23). Lastly, protein-ligand complexes can be visualized in 2D and 3D using visualization packages like PyMOL, UCSF Chimera, BIOVIA Discovery Studio Visualizer and LigPlot+ where it can help interpret all aspects of the protein-ligand interaction and aid in the selection of possible phytochemicals for experimental validation. Due to this, molecular docking has become a crucial computational tool that can be used to validate the therapeutic targets acquired from the network pharmacology and discover new drug candidates from plants for precision medicine (24).

6. INTEGRATION OF NETWORK PHARMACOLOGY AND MOLECULAR DOCKING

The combination of systems-level biological analysis and structure-based molecular validation is an effective computational approach that can be used to accelerate the process of phytochemical based drug discovery, and is now being made easier by the development of Network Pharmacology and Molecular Docking. It serves as a single solution for identifying bioactive phytochemicals, foresee protein molecular targets, deciphering disease related signaling pathways and validation of protein–ligands interactions in an all-encompassing and economical manner. The process usually begins by finding medicinal plants containing bioactive phytochemicals using the rules of pharmacokinetic parameters including the permeability of the cells Caco-2, the permeability of the blood–brain barrier, drug-likeness, blood–placenta barrier permeability and ADMET properties. The information on phytochemicals from public databases like TCMSP, PubChem, ChEMBL and IMPPAT etc. helps identifying compounds with desirable pharmacological properties prior to computational target analysis (24). The selection of phytochemicals is followed by a network pharmacology approach to prioritize therapeutic targets, including compound–target prediction, mining disease-associated genes, construction of protein–protein interaction (PPI) network and topological network analysis. To identify the hub genes, different centrality parameters, including degree centrality, betweenness centrality, closeness centrality and maximal clique centrality, are computed during disease progression. To prioritize the biologically-relevant molecular targets, functional enrichment analyses based on Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways and Gene Ontology (GO) were performed, which revealed the main biological processes and signaling pathways associated with the selected phytochemicals (25).

Validation of the predicted hub targets is then carried out using molecular docking to assess the binding affinity, binding orientation and intermolecular interactions between phytochemicals and their target proteins. The biological relevance of the predicted compound–target relationships are supported by the docking scores, hydrogen bonding, hydrophobic interactions, electrostatic contacts and the favorable binding conformation. Many studies include molecular dynamics simulation and binding free-energy calculations to complement the analyses and assessment of the stability and reliability of protein–ligand complexes in physiological conditions (26). Interpretation of integrated computational results includes correlating network topology, pathway enrichment, docking affinity and molecular interaction analyses to identify the best therapeutic phytochemicals and their mechanisms of action. This comprehensive approach leads to significant improvement in the accuracy of the target identification, decreases the false positive predictions and provides mechanistic evidence for future in vitro and in vivo validation studies. The combination of network pharmacology and molecular docking is an integral part of the modern computational phytopharmacology, and the main databases, software platforms and computational tools used in the whole process are summarized in Table 1 (27).

Table 1. Major Databases, Software, and Computational Tools Used in Network Pharmacology and Molecular Docking Studies

Category	Database/Software	Primary Application
Phytochemical Database	TCMSP	Herbal compounds, ADME properties, target prediction
Phytochemical Database	IMPPAT	Indian medicinal plant phytochemicals
Chemical Database	PubChem	Chemical structures and physicochemical properties
Chemical Database	ChEMBL	Bioactive compounds and bioactivity data
Drug Database	DrugBank	Drug-target interactions and pharmacological information
Protein Database	UniProt	Protein sequence and functional annotation
Disease Gene Database	GeneCards	Disease-associated genes
Disease Gene Database	OMIM	Human genetic disorders and disease genes
Disease Gene Database	DisGeNET	Gene–disease association analysis
Target Prediction	SwissTargetPrediction	Compound–target prediction
Target Prediction	PharmMapper	Reverse pharmacophore target prediction
Interaction Database	STRING	Protein–protein interaction (PPI) network construction
Functional Analysis	DAVID	GO and KEGG enrichment analysis
Functional Analysis	Metascape	Multi-omics enrichment and pathway analysis
Pathway Database	KEGG	Biological pathway mapping
Network Visualization	Cytoscape	Construction and visualization of biological networks
Protein Structure	Protein Data Bank (PDB)	Three-dimensional protein structures
Docking Software	AutoDock Vina	Molecular docking and binding affinity prediction
Docking Software	Glide (Schrödinger)	High-precision molecular docking
Docking Software	GOLD	Genetic algorithm-based docking
Molecular Dynamics	GROMACS	Molecular dynamics simulation
Molecular Dynamics	AMBER	Protein–ligand stability analysis
Visualization	PyMOL	Three-dimensional molecular visualization
Visualization	BIOVIA Discovery Studio Visualizer	Protein–ligand interaction analysis
Visualization	UCSF Chimera	Structural visualization and molecular analysis

7. APPLICATIONS IN DRUG DISCOVERY

With the advent of network pharmacology and molecular docking, the current process of drug discovery has been changed to a systematic way of discovering bioactive phytochemicals and their molecular mechanisms through a large number of human diseases. This computational-integrated approach has been widely applied in the search for phytochemicals to target multiple oncogenic signaling pathways including PI3K/Akt, MAPK, Wnt/β-catenin, NF-ϰB, JAK/STAT, p53 and apoptotic pathways, which can be applied in cancer therapeutics. All of these would speed up the development of potentially more effective and less toxic anticancer agents, such as identification of the hub genes associated with tumor progression and identification of

interaction between phytochemicals and proteins associated with cancer by network analysis and molecular docking, respectively (27). Computational phytopharmacology has been indispensable in the identification of natural compounds with potential to combat insulin resistance, glucose metabolism, pancreatic β-cell dysfunction, oxidative stress and inflammatory signaling in the field of diabetes mellitus. A number of phytochemicals, like flavonoids, alkaloids, terpenoids and phenolic acids, exhibited high binding affinity for important therapeutic targets, such as α-glucosidase, α-amylase, DPP-4, PPARγ, AMPK, AKT1, and insulin receptors, paving the way for multi-target antidiabetic drugs that can act on multiple metabolic pathways (28). These methods have been similarly applied to cardiovascular diseases, to identify genes involved in atherosclerosis, hypertension, myocardial ischemia, thrombosis, heart failure, etc., and to validate interactions with proteins involved in endothelial function, oxidative stress, lipid metabolism, inflammation and vascular remodeling, respectively, through molecular docking. Thus, this polyvalent approach has allowed the identification of several phytochemicals whose actions on various pathways are considered cardioprotective, all of which include the maintenance of cardiovascular homeostasis (29).Furthermore, phytochemicals have exhibited remarkable potential in the context of neurodegenerative diseases including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, etc. and have shown to have an effect on the aggregation of amyloid-β, hyper-phosphorylation of tau, cholinesterases, oxidative stress, neuroinflammation, mitochondrial dysfunction, and synaptic degeneration. This strategy is also well used to discover antiviral, antibacterial, antifungal and antiparasitic phytochemicals, which are directed towards essential microbial proteins, host receptors and immune regulatory pathways of infectious diseases. Moreover, network pharmacology and molecular docking provided the discovery of natural compounds that could control inflammatory cytokines, chemokines and the signaling and transcription factors of immune cells in autoimmune and immune-mediated diseases including rheumatoid arthritis, inflammatory bowel disease, psoriasis, asthma and systemic lupus erythematosus. The combination of these computational approaches has thus emerged as an essential platform to engage in multi-target drug discovery, precision medicine and evidence-based rational development of phytotherapeutics for chronic and infectious diseases (30).

8. REPRESENTATIVE CASE STUDIES

Combined with the network pharmacology and molecular docking, a number of phytochemicals have been uncovered to possess strong therapeutic potential. The pharmacological properties of Curcuma longa have been thoroughly investigated for its different anti-cancer properties, anti-inflammatory and anti-oxidant properties due to its regulation of NF-ϰB, PI3K/Akt, STAT3, MAPK signaling pathways etc. (30). Quercetin is widely distributed and binds to the proteins AKT1, TP53, IL-6, TNF and VEGFA, thus possessing cardioprotective, antiviral, antidiabetic and neuroprotective effects. Resveratrol has been shown to have an exceptional effect on oxidative stress, mitochondrial dysfunction, apoptosis and inflammatory signaling in cardiovascular and neurodegenerative diseases (31). Berberine helps to control glucose metabolism, lipid homeostasis, and inflammatory pathways, all via activation of AMPK and insulin signaling. Epigallocatechin gallate (EGCG), the major catechin of green tea, is known to have strong antioxidant, anticancer and antiviral properties and has been demonstrated to have effects on several pathways in the cell (32). Likewise, the withanolides exhibit a variety of pharmacologic effects against cancer, inflammation, and neurodegeneration, which were revealed by network pharmacology and molecular docking studies, and thus have potential as targets in precision phytomedicine (33).

9. CHALLENGES, LIMITATIONS, AND FUTURE PERSPECTIVES

The integrated network pharmacology and molecular docking has developed steadily, but there are still some issues to be addressed to prevent the widespread use of phytochemical drugs from having a disruptive impact on the discovery of new drugs. Some factors may influence the accuracy of the prediction, such as data quality, incomplete biological databases, and the absence of standardised phytochemical data. The complexity of the biological networks makes the interpretation more difficult, as do the dynamics of molecular interactions, which is not yet known. The molecular docking process is used only for static predictions of binding, and should be supplemented with molecular dynamics simulations and testing in order to make valid conclusions. The integration of AI, machine learning, multi-omics, and precision phytomedicine, as detailed in Figure 2, will further boost the predictive value, target identification and speed of discovering therapeutics based on natural products for clinical use.

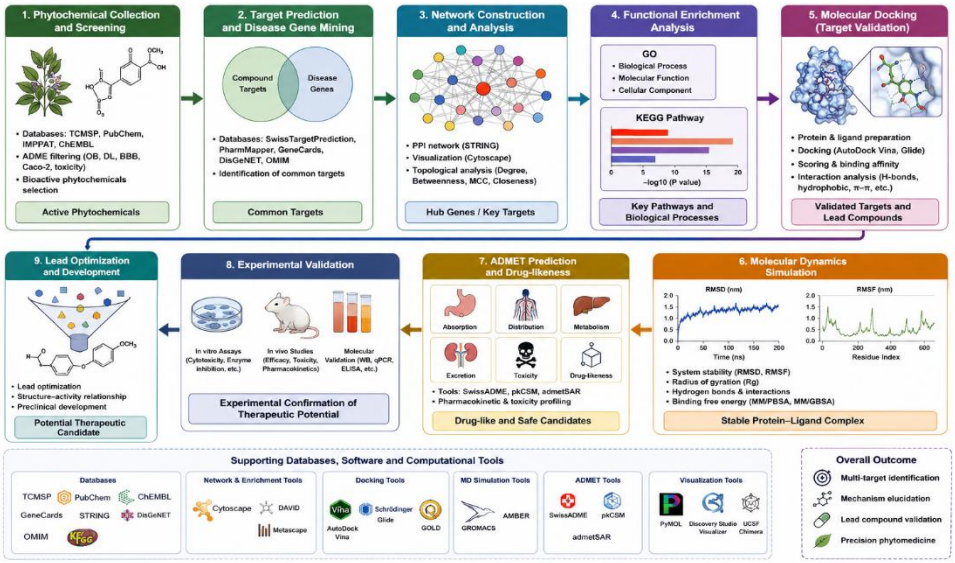

Figure 2. Integrated Computational Drug Discovery Pipeline Combining Network Pharmacology, Molecular Docking, Molecular Dynamics Simulation, ADMET Prediction, and Experimental Validation

10. CONCLUSION

The combination of network pharmacology and molecular docking has greatly changed the landscape of phytochemical drug discovery, allowing for efficient identification of multi-target therapeutic agents and their mechanisms of action. The computational approach helps understand complex biological interactions, speeds up lead compound discovery, and aids in cost-effective drug development. The future of computational phytopharmacology continues to look bright, with recent developments in artificial intelligence, machine learning, and the integration of multiple omics approaches, along with molecular dynamics simulation and high-throughput virtual screening, enhancing the precision and productivity of the field. Standardized datasets, experimental validation, explainable computational models, and precision medicine are the areas that need to be emphasized in future studies for the clinical translation of natural product-derived therapeutics for complex human diseases.

DECLARATIONS

Funding: The authors received no specific funding for this work.

Conflict of Interest: The authors declare that they have no competing interests.

Author Contributions: All authors contributed to the conceptualization, literature review, writing, revision, and final approval of the manuscript.

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