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Review Article

Network Pharmacology of Medicinal Plants in Cardiometabolic Disorders: A Narrative Review of Molecular Networks, Validation Evidence, and Translational Challenges

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ABSTRACT

Background: Cardiometabolic disorders arise from interconnected disturbances involving inflammation, oxidative stress, insulin resistance, endothelial dysfunction, mitochondrial impairment, lipid dysregulation, apoptosis, and tissue remodeling. Medicinal plants contain multiple bioactive constituents that may influence several of these mechanisms simultaneously, making network pharmacology a potentially useful framework for systems-level natural-product research. Objective: To critically synthesize the principles, computational resources, analytical workflows, reported molecular networks, validation levels, and translational limitations of medicinal-plant network pharmacology in type 2 diabetes mellitus, hypertension, coronary artery disease, heart failure, and atherosclerosis. Methods: A narrative-review approach was used to integrate foundational methodological publications, database and software reports, computational target-prediction studies, molecular-docking and molecular-dynamics investigations, ADMET analyses, experimental studies, clinical investigations, and authoritative reviews. Evidence was organized by analytical stage, phytochemical class, disease area, recurrent molecular target, signaling pathway, and depth of validation. Computational predictions were interpreted as hypothesis-generating, whereas in vitro, in vivo, and human studies were considered progressively stronger levels of validation. No meta-analysis or formal risk-of-bias assessment was undertaken because of substantial methodological and clinical heterogeneity. Results: Recurrently reported targets included AKT1, TNF, IL6, VEGFA, PPARG, NOS3, MAPK proteins, RELA, TP53, and CASP3. Common pathways included PI3K/Akt, AMPK, MAPK, NF-κB, AGE–RAGE, HIF-1, Nrf2, apoptosis, calcium signaling, and renin–angiotensin–aldosterone signaling. Berberine, Salvia miltiorrhiza, Astragalus-derived compounds, ginsenosides, Compound Danshen Dripping Pills, Qishen Yiqi Dropping Pills, and Yiqi Fumai Injection had evidence extending beyond computational prediction. Nevertheless, most studies remained limited to database analysis, enrichment, docking, or preclinical validation, and repeated pathway identification was vulnerable to database and topology-related bias. Conclusion: Network pharmacology is valuable for prioritizing medicinal-plant compounds, targets, and pathways, but it does not independently establish therapeutic efficacy. Translation requires standardized phytochemical characterization, reproducible analysis, direct target validation, pharmacokinetic and safety assessment, herb–drug interaction evaluation, and rigorous human studies.

Keywords: Network Pharmacology; Medicinal Plants; Cardiometabolic Diseases; Phytochemicals; Systems Biology; Molecular Docking; Multi-Omics; Drug Discovery

INTRODUCTION

Conventional drug discovery has historically been dominated by the "one drug–one target–one disease" model, which has produced effective therapies for conditions driven by discrete molecular abnormalities. However, most chronic noncommunicable diseases arise from disturbances across interconnected molecular, cellular, metabolic, and environmental networks rather than from dysfunction of a single protein or signaling pathway. This recognition has encouraged a transition toward systems-oriented pharmacology, in which therapeutic effects are evaluated through coordinated interactions among compounds, molecular targets, signaling pathways, and disease-associated biological networks (1).

Network pharmacology represents a central component of this systems-based transition. It integrates pharmacology, systems biology, bioinformatics, cheminformatics, molecular biology, and network science to investigate how therapeutic compounds influence multiple biological targets simultaneously. By combining chemical information with disease-associated genes, protein–protein interaction networks, functional pathways, and pharmacological datasets, network pharmacology facilitates the construction of compound–target–pathway–disease relationships and the prioritization of molecular mechanisms for subsequent experimental investigation. Advances in high-throughput sequencing, molecular docking, molecular dynamics simulation, artificial intelligence, machine learning, and multi-omics technologies have further expanded the capacity of this approach to identify candidate compounds, predict therapeutic targets, and generate mechanistic hypotheses during early drug discovery (1, 2).

Medicinal plants are particularly suitable for network-pharmacology investigation because they contain chemically diverse mixtures of secondary metabolites that may interact with numerous molecular targets. Flavonoids, alkaloids, terpenoids, phenolic acids, glycosides, saponins, lignans, coumarins, and other phytochemical classes can collectively modulate inflammatory mediators, metabolic enzymes, transcription factors, receptors, ion channels, and intracellular signaling pathways. The multi-component nature of medicinal plants therefore aligns conceptually with network pharmacology, although multi-target activity should not automatically be interpreted as therapeutically beneficial because it may also produce antagonistic interactions, off-target effects, unpredictable pharmacokinetics, or toxicity. Nevertheless, the contribution of natural products to pharmaceutical development is well established, as illustrated by clinically important agents derived directly or indirectly from natural sources, including paclitaxel, artemisinin, digoxin, morphine, and salicylate-based therapeutics (3).

The integration of computational approaches with natural-product research has changed how plant-derived therapeutic candidates are investigated. Conventional screening of large numbers of phytochemicals through isolated laboratory experiments is resource intensive and may fail to capture interactions among multiple constituents. Network pharmacology provides a hypothesis-generating framework through which phytochemicals can be characterized, potential targets can be predicted, protein–protein interaction networks can be constructed, functional enrichment can be performed, and promising compounds can be prioritized for molecular docking, molecular dynamics simulation, and biological validation. These methods may reduce the number of compounds requiring initial experimental testing; however, their outputs remain dependent on database completeness, algorithmic assumptions, chemical annotation quality, and the availability of experimentally validated interaction data (2).

Cardiometabolic disorders constitute an appropriate clinical context for systems-level investigation because their development and progression involve multiple overlapping pathological processes. Cardiovascular diseases remain a major cause of global morbidity and mortality, while the prevalence of obesity, metabolic syndrome, and type 2 diabetes mellitus continues to increase worldwide (4–6). Although obesity, diabetes mellitus, hypertension, coronary artery disease, heart failure, and atherosclerosis differ in their clinical presentation, they share several interrelated biological mechanisms, including insulin resistance, chronic low-grade inflammation, oxidative stress, endothelial dysfunction, mitochondrial impairment, adipokine imbalance, neurohormonal activation, and dysregulated glucose and lipid metabolism (7–9).

Excess adipose tissue, for example, contributes to systemic metabolic dysfunction through the release of pro-inflammatory cytokines and adipokines, including tumor necrosis factor-alpha, interleukin-6, and monocyte chemoattractant protein-1. These mediators can impair insulin signaling, promote endothelial injury, enhance oxidative stress, and accelerate atherosclerotic vascular remodeling. Similarly, activation of the renin–angiotensin–aldosterone system, nuclear factor-kappa B signaling, mitogen-activated protein kinase pathways, advanced glycation end product–receptor signaling, and dysregulated phosphoinositide 3-kinase/protein kinase B signaling may contribute simultaneously to

metabolic and cardiovascular disease progression. This biological overlap helps explain why patients frequently require multiple pharmacological agents and why isolated target inhibition may provide incomplete control of the broader disease process.

Network pharmacology offers a structured approach for examining these shared mechanisms by mapping interactions among plant-derived compounds, disease-associated genes, hub proteins, and signaling pathways. Nevertheless, frequently reported targets such as AKT1, TNF, IL6, VEGFA, TP53, and MAPK proteins are highly connected and extensively annotated within biomedical databases. Their repeated identification across diseases and medicinal plants may therefore reflect both genuine biological importance and database-degree bias. Similarly, recurrent enrichment of PI3K/Akt, MAPK, NF-κB, AMPK, HIF-1, and apoptosis pathways does not independently establish plant-specific therapeutic mechanisms. Computational findings must consequently be interpreted as prioritized hypotheses rather than confirmation of target engagement, pharmacological efficacy, or clinical benefit.

Several previous publications have reviewed network pharmacology in medicinal-plant research, natural-product drug discovery, traditional Chinese medicine, diabetes mellitus, and cardiovascular disease (2, 10–14). However, the evidence remains fragmented across methodological reviews, disease-specific analyses, individual medicinal plants, phytochemicals, and traditional multi-herb formulations. In addition, many published reviews emphasize the potential benefits of network pharmacology without sufficiently distinguishing database-derived predictions from molecular docking, experimental validation, and human clinical evidence. Critical synthesis is therefore needed to examine not only the reported compounds, targets, and pathways but also the methodological quality, validation depth, reproducibility, and translational limitations of the available evidence.

Accordingly, this narrative review aimed to critically synthesize the principles, databases, and analytical workflows used in network pharmacology; examine their application to medicinal plants and plant-derived compounds in type 2 diabetes mellitus, hypertension, coronary artery disease, heart failure, and atherosclerosis; and evaluate the extent to which reported computational mechanisms have been supported by molecular, cellular, animal, or clinical evidence. The review further sought to identify recurrent methodological weaknesses, including database heterogeneity, pathway overrepresentation, target-prediction uncertainty, insufficient phytochemical standardization, limited experimental validation, and barriers to clinical translation, while outlining priorities for reproducible and evidence-based natural-product drug discovery.

MATERIALS AND METHODS

This article was designed as a narrative review because its objective was to provide a broad conceptual and critical synthesis of network-pharmacology principles, computational resources, medicinal-plant applications, and translational challenges across several cardiometabolic disorders rather than to answer a narrowly defined intervention question or generate pooled quantitative estimates. The narrative approach was selected to permit the integration of methodologically heterogeneous evidence, including foundational network-pharmacology literature, database and software publications, computational target-prediction studies, molecular-docking investigations, molecular dynamics simulations, experimental validation studies, clinical investigations, and authoritative reviews of natural products and cardiometabolic disease mechanisms.

The literature was selected through a purposive, topic-driven process centered on the principal domains addressed by the review. These domains included the conceptual development of network pharmacology; medicinal-plant and phytochemical databases; chemical, protein, gene, disease, pathway, and interaction resources; compound screening and target-prediction methods; protein–protein interaction analysis; network construction and topological analysis; functional enrichment; molecular docking; molecular dynamics simulation; pharmacokinetic and toxicity prediction; ethnopharmacology; and the application of these approaches to type 2 diabetes mellitus, hypertension,

coronary artery disease, heart failure, and atherosclerosis. Seminal methodological publications were considered alongside more recent studies to reflect both the historical development and contemporary applications of the field.

Publications were considered relevant when they addressed at least one of the following areas: development or validation of a network-pharmacology database or computational platform; application of network pharmacology to a medicinal plant, plant-derived compound, or herbal formulation; identification of disease-associated targets, hub genes, or signaling pathways relevant to cardiometabolic disorders; integration of network pharmacology with molecular docking, molecular dynamics simulation, ADMET prediction, transcriptomics, proteomics, metabolomics, lipidomics, or other multi-omics methods; experimental validation of computationally predicted mechanisms; or assessment of the clinical or translational implications of plant-derived therapeutic candidates. General pharmacology, epidemiology, and disease-mechanism publications were retained when they provided essential biological or clinical context for interpreting network-pharmacology findings.

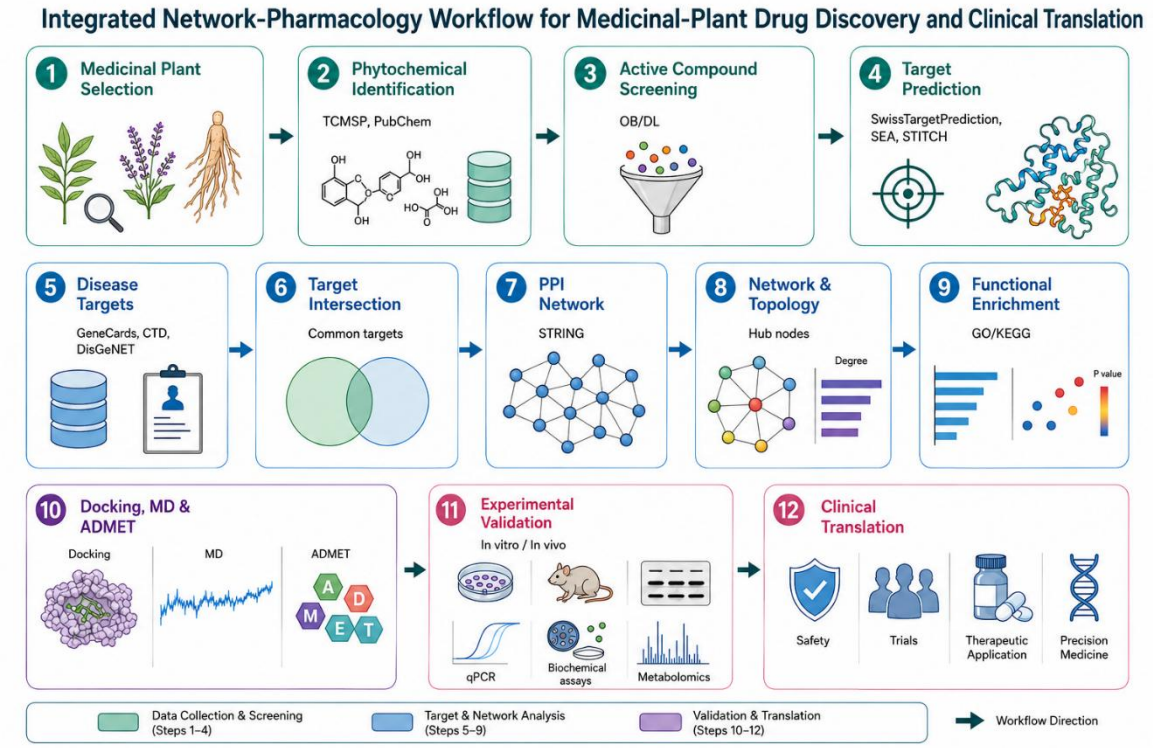

Figure 1. The integrated workflow illustrates the sequential application of medicinal-plant selection, phytochemical identification, active-compound screening, target prediction, disease-target mapping, protein–protein interaction analysis, network topology, functional enrichment, molecular docking, molecular dynamics, ADMET assessment, experimental validation, and eventual clinical translation.

Sources were excluded from the main mechanistic synthesis when their subject matter was unrelated to cardiometabolic disease, when the cited disease context did not correspond to the claim being discussed, or when the publication did not provide sufficient information to determine the medicinal plant, bioactive compound, predicted target, signaling pathway, or validation approach. During revision, citations were evaluated for alignment between the statement made in the manuscript and the disease, intervention, and outcome addressed by the referenced publication. Evidence from unrelated disease models was not treated as direct support for cardiometabolic efficacy, although it could be considered as indirect mechanistic evidence when this distinction was explicitly stated.

The evidence was organized conceptually and thematically. The methodological component of the review was structured according to the principal stages of a network-pharmacology workflow: identification and screening of phytochemicals, prediction and standardization of molecular targets,

collection of disease-associated genes, identification of overlapping targets, construction and analysis of protein–protein interaction networks, functional and pathway enrichment, molecular docking, molecular dynamics simulation, ADMET assessment, and experimental or clinical validation. Disease-specific evidence was subsequently synthesized for diabetes mellitus, hypertension, coronary artery disease, heart failure, and atherosclerosis using a consistent framework that considered representative medicinal plants or formulations, principal bioactive compounds, reported molecular targets, enriched signaling pathways, level of validation, therapeutic interpretation, and major methodological limitations.

To avoid conflating prediction with biological confirmation, the evidentiary strength of the cited literature was interpreted according to the depth of validation reported. Database-based target prediction and pathway-enrichment findings were considered hypothesis-generating. Molecular docking was considered supportive structural evidence of a potential interaction but not proof of binding under physiological conditions. Molecular dynamics simulation was considered an additional assessment of predicted complex stability. In vitro biochemical, cellular, or gene-expression studies were regarded as experimental mechanistic validation, whereas animal studies were considered preclinical evidence. Evidence from observational human studies, controlled clinical investigations, or randomized trials was considered the highest level of translational support within the scope of this narrative synthesis. Findings were described cautiously when evidence was limited to computational prediction or docking.

No formal meta-analysis was undertaken because the included literature was heterogeneous in its disease models, medicinal plants, phytochemical composition, computational platforms, target-prediction algorithms, screening thresholds, validation procedures, and reported outcomes. Formal pooled effect estimates, statistical heterogeneity measures, publication-bias analyses, and certainty-of-evidence grading were therefore not applicable. Similarly, no formal risk-of-bias tool was applied across the full evidence base because the review incorporated diverse publication types that could not be assessed using a single appraisal instrument.

The methodological and interpretive limitations inherent in a narrative review were considered throughout the synthesis. The purposive selection of literature may have introduced selection and citation bias, and the review was not designed to establish that all eligible publications had been identified. In addition, the prominence of extensively studied pathways and highly connected hub genes may reflect database annotation density and algorithmic preference rather than disease- or plant-specific biological importance. Differences in plant species, geographical origin, cultivation, extraction, processing, compound identification, oral-bioavailability thresholds, target-prediction tools, disease databases, and interaction-confidence cutoffs further limited direct comparison among studies. Consequently, the review emphasized reproducibility, evidence attribution, validation depth, and cautious interpretation rather than numerical aggregation or claims of exhaustive coverage.

Results and Evidence Synthesis

Scope and Organization of the Evidence

The reviewed literature demonstrated that network pharmacology has been applied across multiple stages of medicinal-plant drug discovery, including phytochemical identification, compound screening, target prediction, disease-gene mapping, protein–protein interaction analysis, pathway enrichment, molecular docking, molecular dynamics simulation, pharmacokinetic and toxicity prediction, and experimental validation. The evidence base was methodologically heterogeneous and included database and software publications, computational studies of individual phytochemicals, investigations of single medicinal plants, analyses of multi-herb formulations, mechanistic laboratory studies, animal experiments, clinical investigations, and broader methodological reviews.

Because this was a narrative rather than systematic review, no formal search yield, study-selection flow, or total number of included publications was available. The synthesis was therefore organized according to the principal computational resources, phytochemical classes, cardiometabolic disease areas, recurrent molecular targets, signaling pathways, and depth of biological validation. Computational target prediction and enrichment findings were interpreted as hypothesis-generating, molecular docking and molecular dynamics as supportive structural evidence, in vitro and animal studies as experimental or preclinical validation, and human studies as translational evidence.

Across the cardiometabolic literature, the most frequently reported molecular targets included AKT1, TNF, IL6, VEGFA, MAPK1, MAPK3, PPARG, NOS3, CASP3, TP53, JUN, RELA, and STAT3. The signaling pathways most identified were PI3K/Akt, AMPK, MAPK, NF-κB, AGE–RAGE, HIF-1, Nrf2, TNF, apoptosis, calcium signaling, and Toll-like receptor pathways. These recurrent findings were biologically plausible because they corresponded to shared mechanisms of insulin resistance, chronic inflammation, oxidative stress, endothelial dysfunction, mitochondrial impairment, apoptosis, vascular remodeling, and dysregulated lipid metabolism. However, the recurrence of highly connected proteins and broad signaling pathways across unrelated medicinal plants also suggested potential database-degree bias, pathway overrepresentation, and limited biological specificity.

Computational Resources and Analytical Functions

The reviewed resources covered six principal analytical domains: identification of herbal ingredients and phytochemicals, chemical characterization, target prediction, disease-gene identification, network and pathway analysis, and structural or pharmacokinetic validation. No single database provided complete coverage of medicinal-plant chemistry, molecular targets, disease associations, and experimental validation. Reliable network-pharmacology investigations therefore generally required cross-referencing several databases and standardizing compound and protein identifiers before network construction.

Table 1. Principal Resources Used in Medicinal-Plant Network Pharmacology

Analytical Domain	Representative Databases or Tools	Principal Function	Major Strength	Principal Limitation
Herbal medicine and phytochemical identification	TCMSP, TCMID, HERB, ETCM, SymMap, IMPPAT, BATMAN-TCM	Identification of herbal ingredients, traditional indications, predicted targets, oral bioavailability, and drug-likeness	Enables rapid screening of multi-component herbal medicines	Coverage is uneven across medical traditions; chemical records may be incomplete, duplicated, or based on predicted rather than experimentally confirmed constituents
Chemical and compound characterization	PubChem, ChEMBL, DrugBank, ChemSpider, BindingDB, ZINC, MassBank, HMDB	Chemical structures, physicochemical properties, bioactivity, binding data, metabolites, and virtual-screening compounds	Provides standardized structures and experimentally curated pharmacological information	Database records may represent isolated compounds rather than the composition or concentration present in a specific plant extract
Molecular target prediction	SwissTargetPrediction, SEA, STITCH, BindingDB, DrugBank	Prediction or retrieval of compound–protein interactions	Prioritizes potential protein targets for large numbers of phytochemicals	Predictions depend on chemical similarity, known ligands, and training datasets; novel scaffolds and non-small-molecule constituents may be poorly represented
Protein information and interaction analysis	UniProtKB, STRING, BioGRID, AlphaFold Protein Structure Database	Protein annotation, protein–protein interaction mapping, and structural information	Supports target standardization, PPI construction, and structure-based analyses	PPI data may combine species, tissues, cell types, and experimental conditions that do not reflect the disease context under study
Disease and gene identification	GeneCards, DisGeNET, OMIM, CTD, Open Targets Platform, MalaCards, HPO	Identification and prioritization of disease-	Integrates multiple genomic, clinical, and experimental sources	Broad search terms may retrieve large, nonspecific

Analytical Domain	Representative Databases or Tools	Principal Function	Major Strength	Principal Limitation
		associated genes and phenotypes		gene sets; ranking criteria differ among databases
Functional enrichment and pathways	KEGG, Gene Ontology, Reactome, WikiPathways, Metascape, DAVID, Enrichr, g:Profiler	Biological-process, molecular-function, cellular-component, and pathway enrichment	Converts target lists into interpretable biological themes	Frequently studied pathways may be preferentially enriched; statistical significance does not establish causal involvement
Network construction and topology	Cytoscape, CytoHubba, MCODE, ClueGO, NetworkAnalyst, Gephi	Visualization, centrality analysis, hub identification, cluster detection, and functional annotation	Facilitates systems-level interpretation of complex interaction networks	Hub selection is highly sensitive to network source, confidence threshold, topology metric, and input-list size
Molecular docking and structural visualization	AutoDock Vina, CB-Dock2, DockThor, AutoDock Tools, PyMOL, BIOVIA Discovery Studio Visualizer	Prediction and visualization of ligand–protein binding poses and affinity scores	Provides structural plausibility for predicted compound–target interactions	Docking scores are model-dependent and do not establish target engagement, biological activity, selectivity, or clinical efficacy
ADMET and toxicity prediction	SwissADME, ADMETlab, pkCSM, ProTox, admetSAR, ToxCast/Tox21	Prediction of absorption, distribution, metabolism, excretion, toxicity, and drug-likeness	Supports early exclusion of compounds with unfavorable predicted properties	Computational predictions cannot replace experimental pharmacokinetic or toxicological testing
Molecular dynamics and advanced validation	Molecular dynamics platforms, transcriptomics, proteomics, metabolomics, lipidomics, and single-cell methods	Assessment of complex stability and biological responses after treatment	Improves confidence in predicted interactions and enables tissue- or cell-specific interpretation	Requires substantial computational resources, standardized experimental designs, and independent validation

The reviewed workflow publications indicated that reliable analyses should incorporate standardized compound structures, species-specific protein identifiers, clearly defined disease terms, transparent confidence thresholds, and sensitivity analyses using alternative databases or centrality measures. Nevertheless, many medicinal-plant studies used different oral-bioavailability thresholds, drug-likeness filters, disease-gene cutoffs, PPI confidence scores, and enrichment criteria, limiting reproducibility and direct comparison among investigations.

Phytochemical Classes and Shared Pharmacological Networks

The evidence consistently identified flavonoids, alkaloids, terpenoids, phenolic acids, glycosides, and saponins as major phytochemical classes relevant to cardiometabolic network pharmacology. These classes were linked to overlapping inflammatory, metabolic, antioxidant, vascular, and apoptotic pathways. The relationships were not uniform across all members of a chemical class, and the reported targets should therefore be interpreted as representative rather than universal.

Table 2. Major Phytochemical Classes and Their Reported Cardiometabolic Networks

Phytochemical Class	Representative Compounds	Representative Reported Targets or Pathways	Principal Cardiometabolic Functions	Typical Evidence Level
Flavonoids	Quercetin, kaempferol, luteolin, epigallocatechin gallate	PI3K/Akt, AMPK, MAPK, NF-κB, Nrf2, VEGF	Antioxidant activity, inflammatory modulation, endothelial protection, glucose and lipid regulation	Network prediction and docking, with variable in vitro, animal, and limited human support
Alkaloids	Berberine, piperine, matrine	AMPK, PPARG, IRS-1/PI3K/Akt, TNF, NF-κB	Improved insulin signaling, suppression of hepatic gluconeogenesis, lipid regulation, inflammatory modulation	Computational, experimental, animal, and selected clinical evidence, strongest for berberine
Terpenoids	Ginsenosides, ursolic acid, artemisinin-related terpenoids	PI3K/Akt, MAPK, Nrf2, TGF-β, apoptosis-related proteins	Cardiomyocyte protection, oxidative-stress reduction, inflammatory regulation, vascular effects	Network and preclinical evidence; clinical support varies by compound and formulation

Phytochemical Class	Representative Compounds	Representative Reported Targets or Pathways	Principal Cardiometabolic Functions	Typical Evidence Level
Phenolic acids	Gallic acid, caffeic acid, ferulic acid, chlorogenic acid, salvianolic acids	Nrf2/HO-1, NF-κB, MAPK, COX-2, lipid-related targets	Antioxidant activity, endothelial protection, inflammatory regulation, lipid and glucose modulation	Computational and experimental evidence; selected cardiovascular formulations have clinical data
Glycosides	Salidroside, oleuropein, cardiac glycosides	PI3K/Akt, AMPK, eNOS, Na^+/K^+-ATPase	Cardiovascular protection, vascular modulation, antioxidant activity, and, for cardiac glycosides, direct inotropic effects	Highly compound-specific; safety and therapeutic-index considerations are essential
Saponins	Ginsenosides, dioscin, astragaloside IV	PI3K/Akt, AMPK, NF-κB, PPAR-related signaling	Lipid regulation, anti-inflammatory effects, mitochondrial protection, and cardiomyocyte survival	Network, docking, and preclinical validation; human evidence remains formulation-dependent

Flavonoids were the most broadly represented compounds and were repeatedly associated with antioxidant and anti-inflammatory pathways. Berberine was among the most extensively investigated individual phytochemicals and had support extending beyond target prediction to metabolic, inflammatory, and clinical studies. Ginsenosides, astragaloside IV, and salvianolic acids also demonstrated relatively mature preclinical evidence. However, the phytochemical concentration achieved in experimental systems, oral bioavailability, metabolism, interactions among plant constituents, and correspondence between isolated compounds and whole-plant preparations were inconsistently addressed.

Evidence in Type 2 Diabetes Mellitus

Network-pharmacology studies of type 2 diabetes mellitus predominantly focused on impaired insulin signaling, hepatic glucose production, pancreatic β-cell dysfunction, chronic inflammation, oxidative stress, endothelial injury, and mitochondrial impairment. Commonly prioritized targets included AKT1, INS, PIK3CA, PPARG, TNF, IL6, MAPK1, and VEGFA. The principal enriched pathways were PI3K/Akt, AMPK, MAPK, AGE–RAGE, NF-κB, HIF-1, FoxO, and Nrf2 signaling.

Berberine, derived from plants including Berberis vulgaris and Coptis chinensis, was consistently linked to AMPK activation, improved insulin sensitivity, reduced hepatic gluconeogenesis, inflammatory modulation, and improved glucose utilization. Unlike many phytochemicals represented only by computational analyses, berberine was also supported by experimental and human metabolic studies, although variations in dose, formulation, bioavailability, and adverse-event monitoring limited direct clinical generalization.

Gegen–Qinlian Decoction was characterized as a multi-component formulation containing compounds such as berberine, baicalin, and wogonin. Network analyses associated these constituents with TNF, IL6, AKT1, and signaling pathways involving PI3K/Akt, AMPK, AGE–RAGE, NF-κB, and HIF-1. These findings suggested coordinated effects on glucose uptake, inflammatory signaling, oxidative stress, and β-cell protection, but the contribution of each constituent and the reproducibility of the proposed synergistic interactions remained incompletely resolved.

Green-tea catechins, particularly epigallocatechin gallate, were associated with AKT1, MAPK1, PI3K/Akt, MAPK, FoxO, and Nrf2 signaling. Experimental literature supported antioxidant, endothelial, and metabolic effects, although evidence derived from green-tea consumption, purified catechins, concentrated extracts, and computational studies was not directly interchangeable.

Table 3. Representative Network-Pharmacology Evidence in Type 2 Diabetes Mellitus

Plant, Formulation, or Compound	Principal Reported Targets	Main Pathways	Reported Biological Interpretation	Validation Depth	Key Limitation
Berberine from Berberis vulgaris or Coptis chinensis	AKT1, PPARG, INS and	AMPK, PI3K/Akt, NF-κB	Improved insulin sensitivity, reduced gluconeogenesis, and	Computational, experimental, animal,	Low and variable oral bioavailability;

Plant, Formulation, or Compound	Principal Reported Targets	Main Pathways	Reported Biological Interpretation	Validation Depth	Key Limitation
	inflammatory targets		inflammatory modulation	and selected clinical evidence	formulations and doses differ
Gegen–Qinlian Decoction	TNF, IL6, AKT1 and related metabolic targets	PI3K/Akt, AMPK, AGE–RAGE, NF-κB, HIF-1	Increased glucose uptake, β-cell protection, and reduction of oxidative and inflammatory injury	Network, docking, and variable experimental evidence	Multi-component attribution and batch standardization remain difficult
Camellia sinensis and epigallocatechin gallate	AKT1, MAPK1 and oxidative-stress targets	PI3K/Akt, MAPK, FoxO, Nrf2	Glucose-metabolism regulation and endothelial protection	Computational and experimental evidence, with broader human dietary literature	Findings from beverages, extracts, and isolated compounds are heterogeneous
Polyherbal antidiabetic extracts	Multiple metabolic and inflammatory targets	PI3K/Akt, AMPK, NF-κB and antioxidant pathways	Multi-pathway metabolic regulation	Network pharmacology with selected experimental validation	Extract composition and individual constituent contributions may be uncertain

Overall, diabetes represented one of the more developed areas of medicinal-plant network pharmacology because several compounds had complementary experimental evidence. Nevertheless, most published analyses did not independently confirm all predicted targets, and recurrent enrichment of broad metabolic pathways limited the specificity of mechanistic conclusions.

Evidence in Hypertension

The hypertension literature focused on the renin–angiotensin–aldosterone system, endothelial nitric oxide bioavailability, vascular smooth-muscle contraction, oxidative stress, inflammation, neurohumoral activation, and vascular remodeling. Frequently reported targets included ACE, AGTR1, NOS3, AKT1, TNF, IL6, RELA, ICAM1, PTGS enzymes, adrenergic receptors, and calcium-signaling proteins. Enriched pathways commonly included RAAS-related signaling, PI3K/Akt, MAPK, NF-κB, Nrf2, AGE–RAGE, nitric oxide–cGMP, calcium signaling, cAMP signaling, and neuroactive ligand–receptor interactions. Studies of Allium species suggested possible interactions between sulfur-containing compounds, flavonoids, ACE, NOS3, AGTR1, and inflammatory mediators. However, botanical attribution required careful verification because allicin, ajoene, and diallyl disulfide are most strongly associated with garlic, Allium sativum, and should not be uncritically generalized to other Allium species without phytochemical confirmation.

Uncaria rhynchophylla was associated with targets involved in vascular smooth-muscle contraction, autonomic regulation, prostaglandin signaling, calcium signaling, cAMP signaling, serotonergic synapses, and neuroactive ligand–receptor interactions. These findings supported a possible neurovascular rather than exclusively RAAS-mediated mechanism, although the evidence was largely computational. Green-tea catechins were associated with PI3K/Akt, Nrf2, NF-κB, VEGF, and nitric oxide–cGMP signaling. The broader experimental literature suggested endothelial and modest blood-pressure effects, but network-pharmacology findings did not by themselves establish an antihypertensive treatment effect. Apocynum venetum was linked to TNF, IL6, RELA, BCL2, ICAM1, and AKT1, with enrichment of TNF, NF-κB, AGE–RAGE, and vascular shear-stress pathways. These findings suggested anti-inflammatory and endothelial-protective mechanisms but required stronger experimental and clinical validation.

Table 4. Representative Network-Pharmacology Evidence in Hypertension

Plant or Compound	Principal Reported Targets	Main Pathways	Proposed Effects	Validation Depth	Interpretive Caution
Sulfur-containing compounds from verified Allium preparations	ACE, AGTR1, NOS3, AKT1	RAAS, PI3K/Akt, nitric oxide signaling	Reduced vascular resistance and improved endothelial function	Network and docking, with broader experimental literature for garlic	Species and phytochemical identity must be confirmed

Plant or Compound	Principal Reported Targets	Main Pathways	Proposed Effects	Validation Depth	Interpretive Caution
Uncaria rhynchophylla	PTGS1, PTGS2, CHRM1, ADRA1B and calcium-related proteins	Calcium, cAMP, serotonergic, neuroactive ligand–receptor signaling	Modulation of vascular tone and autonomic regulation	Predominantly computational	Direct target engagement and clinical blood-pressure effects remain uncertain
Camellia sinensis catechins	AKT1, NOS-related and oxidative-stress targets	PI3K/Akt, Nrf2, NF-κB, VEGF, NO–cGMP	Endothelial protection, antioxidant effects, and vascular relaxation	Computational, experimental, and dietary human evidence	Heterogeneous preparations and doses
Apocynum venetum	TNF, IL6, RELA, BCL2, ICAM1, AKT1	TNF, NF-κB, AGE–RAGE, shear-stress pathways	Reduction of vascular inflammation and endothelial injury	Network and limited preclinical evidence	Clinical relevance has not been firmly established

The hypertension evidence was less mature than the diabetes literature. Many reports remained at the level of target prediction and docking, and some plant–disease associations were supported by general reviews rather than directly matched primary investigations. Consequently, antihypertensive claims should be framed as mechanistic hypotheses unless validated by standardized experimental or human studies.

Evidence in Coronary Artery Disease

Network-pharmacology studies of coronary artery disease and myocardial ischemia commonly prioritized AKT1, VEGFA, TNF, IL6, MAPK1, MAPK3, STAT3, TP53, CASP3, JUN, NOS3, PTGS2, and matrix-remodeling proteins. The principal pathways included PI3K/Akt, MAPK, NF-κB, HIF-1, VEGF, FoxO, Toll-like receptor signaling, apoptosis, platelet activation, lipid metabolism, and mitochondrial function.

Salvia miltiorrhiza was among the most extensively investigated cardiovascular medicinal plants. Its salvianolic acids and tanshinones were linked to endothelial protection, inflammatory modulation, oxidative-stress reduction, apoptosis regulation, angiogenesis, and platelet-related pathways. Salvianolic acid combinations were also associated with sphingolipid metabolism and vascular function. The evidence included network pharmacology, docking, lipidomic analyses, experimental validation, and selected clinical investigations of standardized formulations.

Compound Danshen Dripping Pills, comprising Salvia miltiorrhiza, Panax notoginseng, and borneol, were associated with inflammatory cytokines, nitric oxide production, lipid metabolism, platelet activation, angiogenesis, and apoptosis. The existence of randomized or clinical studies provided greater translational relevance than was available for many computationally studied plants. However, clinical findings for the standardized formulation could not be automatically attributed to an individual constituent or predicted target.

Qishen Yiqi Dropping Pills were linked to AKT1, IL6, VEGFA, MAPK8, TNF, and STAT3 and to PI3K/Akt, FoxO, NF-κB, Toll-like receptor, apoptosis, and HIF-1 signaling. The unrelated ovarian-cancer statements previously included in this section were removed because they did not support coronary artery disease mechanisms. Evidence for Qishen Yiqi was most relevant to coronary disease complicated by ischemic heart failure rather than uncomplicated coronary atherosclerosis.

Xuefu Zhuyu Decoction was associated with IL6, VEGFA, ALB, MAPK3, and AKT1 and with pathways related to inflammation, coagulation, angiogenesis, endothelial repair, and vascular remodeling. Cardiovascular claims were retained only when supported by cardiovascular or atherosclerosis-focused sources; evidence derived from malignant pleural effusion was not treated as direct support for coronary artery disease.

Table 5. Representative Network-Pharmacology Evidence in Coronary Artery Disease

Plant or Formulation	Principal Reported Targets	Main Pathways	Proposed Cardiovascular Effects	Validation Depth	Key Limitation
Salvia miltiorrhiza and salvianolic acids or tanshinones	AKT1, VEGFA, TNF, IL6, MAPK proteins, CASP3, NOS3	PI3K/Akt, MAPK, NF-κB, HIF-1, VEGF, apoptosis	Endothelial protection, reduced oxidative and inflammatory injury, angiogenesis, and cardiomyocyte survival	Network, docking, lipidomic, experimental, and selected clinical evidence	Chemical composition varies among extracts and formulations
Compound Danshen Dripping Pills	Multiple vascular, inflammatory, platelet, and apoptotic targets	PI3K/Akt, nitric oxide, inflammatory, platelet, lipid, and apoptosis pathways	Improved myocardial perfusion and angina-related outcomes in selected studies	Computational, experimental, and clinical evidence	Multi-component formulation prevents attribution to a single compound
Qishen Yiqi Dropping Pills	AKT1, IL6, VEGFA, MAPK8, TNF, STAT3	PI3K/Akt, FoxO, NF-κB, Toll-like receptor, apoptosis, HIF-1	Modulation of inflammation, angiogenesis, mitochondrial function, and myocardial remodeling	Network, docking, systematic-review, and clinical evidence in ischemic heart failure contexts	Disease phenotype and concomitant therapy vary
Xuefu Zhuyu Decoction	IL6, VEGFA, ALB, MAPK3, AKT1	Inflammation, coagulation, endothelial repair, angiogenesis, and remodeling pathways	Potential anti-atherosclerotic and ventricular-remodeling effects	Network, docking, molecular dynamics, and selected experimental evidence	Cardiovascular conclusions must rely on disease-matched studies

Among the reviewed disease areas, coronary artery disease contained some of the strongest translational examples because several standardized traditional formulations had been examined clinically. Nevertheless, network-derived mechanisms remained supportive explanations rather than independent evidence of efficacy.

Evidence in Heart Failure

Heart-failure investigations focused on myocardial inflammation, apoptosis, fibrosis, mitochondrial dysfunction, impaired energy metabolism, calcium dysregulation, angiogenesis, and ventricular remodeling. Common hub targets included AKT1, MAPK14, TNF, IL6, RELA, JUN, STAT3, TP53, CASP3, VEGFA, EGFR, HSP90AA1, SRC, and FOS. Enriched pathways included PI3K/Akt, MAPK, NF-κB, TNF, IL-17, AGE–RAGE, HIF-1, FoxO, cGMP–PKG, calcium signaling, apoptosis, and oxidative phosphorylation.

Berberine was associated with AKT1, MAPK14, RELA, TNF, IL6, JUN, and FOS and with inflammatory, oxidative, apoptotic, and remodeling pathways. Experimental evidence supported effects on inflammatory cytokines, fibrosis, and mitochondrial metabolism, but studies using arsenic-induced cardiotoxicity were considered indirect mechanistic evidence rather than direct confirmation of efficacy in clinical heart failure.

Astragalus membranaceus and astragaloside-containing preparations were linked to TP53, AKT1, JUN, HSP90AA1, VEGFA, and ERBB2. Proposed pathways included PI3K/Akt, MAPK, TNF, Toll-like receptor, HIF-1, and apoptosis. Several investigations incorporated molecular docking or experimental verification, providing stronger mechanistic support than database prediction alone.

Codonopsis pilosula, alone or in herbal combinations, was associated with SRC, MAPK1, MAPK3, AKT1, and EGFR and with cGMP–PKG, PI3K/Akt, calcium, and MAPK signaling. Evidence from a laryngeal-cancer model was excluded as direct support for heart failure. Cardiovascular interpretation was based on heart-failure-specific or herbal-pairing studies.

Yiqi Fumai Injection was linked to AKT1, MAPK8, CASP3, VEGFA, IL6, and STAT3 and to pathways governing apoptosis, oxidative phosphorylation, mitochondrial energy metabolism, and inflammatory injury. Proteomic and experimental studies supported effects on myocardial energy metabolism and MAPK signaling.

Qishen Yiqi Dropping Pills had evidence spanning network pharmacology, clinical trials, and systematic synthesis in coronary disease with chronic heart failure. However, heterogeneity in heart-failure phenotype, background medical therapy, formulation, and outcome assessment limited direct comparison among studies.

Table 6. Representative Network-Pharmacology Evidence in Heart Failure

Plant, Compound, or Formulation	Principal Reported Targets	Main Pathways	Proposed Effects	Validation Depth	Key Limitation
Berberine	AKT1, MAPK14, RELA, TNF, IL6, JUN, FOS	PI3K/Akt, TNF, NF-κB, IL-17, AGE–RAGE	Reduced inflammation, oxidative stress, fibrosis, and adverse remodeling	Network and experimental evidence, with indirect cardiotoxicity models	Direct clinical heart-failure evidence remains limited
Astragalus membranaceus	TP53, AKT1, JUN, HSP90AA1, VEGFA, ERBB2	PI3K/Akt, MAPK, TNF, Toll-like receptor, HIF-1, apoptosis	Cardiomyocyte survival, mitochondrial protection, angiogenesis, and repair	Network, docking, and experimental validation	Extract composition and heart-failure models vary
Codonopsis pilosula and Astragalus–Codonopsis combinations	SRC, MAPK1, MAPK3, AKT1, EGFR	cGMP–PKG, PI3K/Akt, calcium, MAPK	Energy-metabolism regulation, contractile support, and anti-apoptotic effects	Heart-failure-specific network and selected experimental evidence	Limited direct human validation
Yiqi Fumai Injection	AKT1, MAPK8, CASP3, VEGFA, IL6, STAT3	PI3K/Akt, MAPK, apoptosis, oxidative phosphorylation	Improved myocardial energy metabolism and reduced remodeling	Proteomic, network, experimental, and clinical-use evidence	Injectable multi-herb formulation; constituent attribution is difficult
Qishen Yiqi Dropping Pills	AKT1, IL6, VEGFA, MAPK8, TNF, STAT3	PI3K/Akt, FoxO, NF-κB, HIF-1, apoptosis	Improved cardiac-function-related outcomes and attenuation of remodeling	Network, trial, and systematic-review evidence	Variable patient phenotype and concomitant therapy

Heart failure had substantial preclinical and formulation-level evidence, but most studies treated heart failure as a single entity. The distinct molecular phenotypes of heart failure with reduced versus preserved ejection fraction were rarely considered, limiting precision and clinical applicability.

Evidence in Atherosclerosis

Atherosclerosis studies focused on lipid accumulation, endothelial dysfunction, vascular inflammation, macrophage activation, foam-cell formation, smooth-muscle proliferation, oxidative stress, apoptosis, extracellular-matrix remodeling, and plaque stability. Frequently reported targets included AKT1, MAPK3, VEGFA, IL6, TNF, NOS3, CASP3, SRC, and PPAR-related proteins. The principal pathways included PI3K/Akt, MAPK, NF-κB, HIF-1, VEGF, AMPK, Toll-like receptor, PPAR, Nrf2, and apoptosis signaling.

Salvia miltiorrhiza was associated with AKT1, MAPK3, VEGFA, IL6, TNF, CASP3, and NOS3. Network and experimental studies suggested effects on endothelial function, vascular inflammation, oxidative stress, smooth-muscle proliferation, and plaque stability. However, evidence from myocardial infarction or ischemia–reperfusion studies was considered supportive but not identical to direct anti-atherosclerotic evidence.

Ligusticum chuanxiong was associated with targets involved in endothelial repair, calcium regulation, vascular remodeling, thrombosis, and inflammation. Network, docking, and experimental investigations supported cardiovascular protective effects, although species nomenclature and extract standardization required consistency.

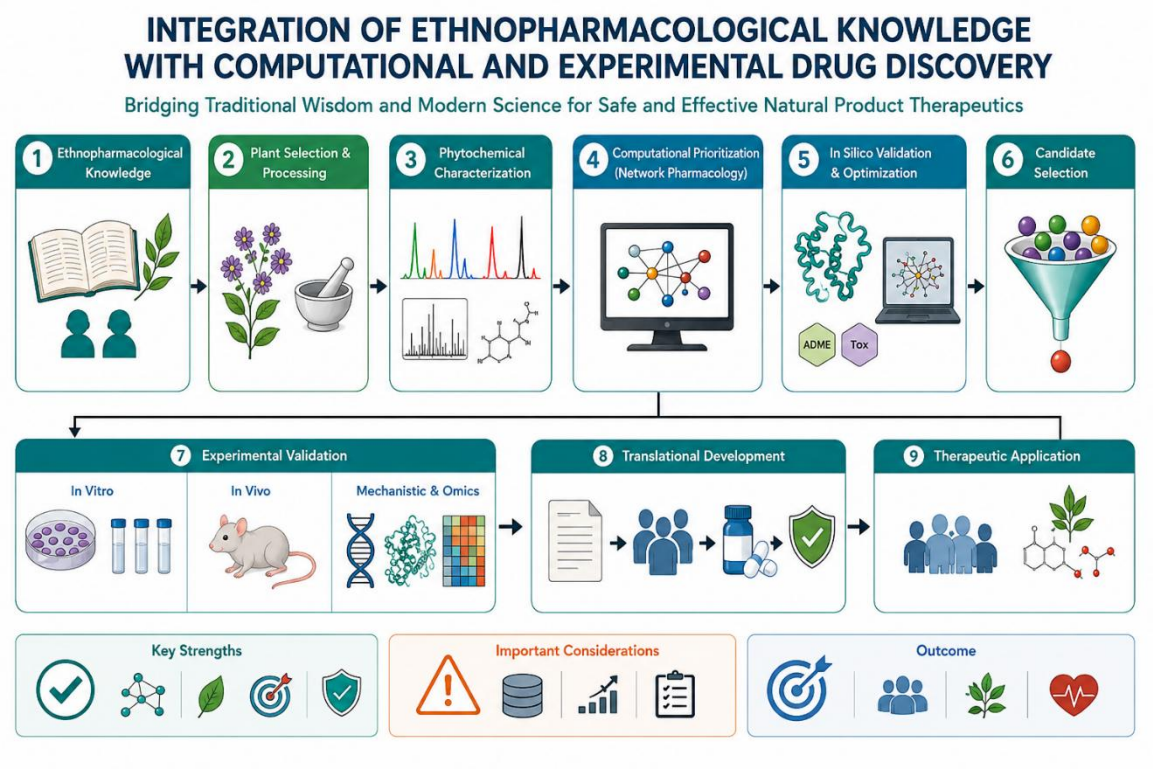

Figure 2. The ethnopharmacology framework shows how traditional knowledge, authenticated plant selection, phytochemical characterization, computational prioritization, in silico optimization, experimental validation, translational development, and therapeutic application are combined within a unified natural-product drug-discovery pathway.

Angelica sinensis was linked to PPARα, AKT1, IL6, TNF, and VEGFA and to pathways involved in lipid metabolism, macrophage activity, inflammatory regulation, and endothelial integrity. Evidence was predominantly network-based and preclinical.

Panax notoginseng saponins were associated with NF-κB, PI3K/Akt, MAPK, and Toll-like receptor signaling. Experimental studies supported reduced macrophage infiltration, inflammatory activity, foam-cell formation, and endothelial injury. However, some publications addressed coronary disease or gastrointestinal protection rather than atherosclerosis directly and were not treated as equivalent disease-specific evidence.

Flavonoids including quercetin, kaempferol, luteolin, and epigallocatechin gallate were repeatedly associated with PI3K/Akt, AMPK, NF-κB, Nrf2, and apoptosis pathways. Their broad pleiotropic profiles supported potential vascular protection but also illustrated the limited specificity of network-derived pathway enrichment.

Table 7. Representative Network-Pharmacology Evidence in Atherosclerosis

Plant or Compound	Principal Reported Targets	Main Pathways	Proposed Anti-Atherosclerotic Effects	Validation Depth	Key Limitation
Salvia miltiorrhiza	AKT1, MAPK3, VEGFA, IL6, TNF, CASP3, NOS3	PI3K/Akt, MAPK, NF-κB, HIF-1, VEGF, apoptosis	Endothelial protection, reduced inflammation, smooth-muscle regulation, and plaque stabilization	Network, lipidomic, docking, and experimental evidence	Some supporting studies address related ischemic conditions rather than atherosclerosis itself
Ligusticum chuanxiong	SRC, MAPK3, NOS3 and calcium-related targets	HIF-1, calcium, inflammatory, and thrombosis pathways	Reduced endothelial injury, oxidative stress, thrombosis, and vascular remodeling	Network, docking, and experimental validation	Botanical nomenclature and preparation standardization vary
Angelica sinensis	PPARα, AKT1, IL6, TNF, VEGFA	PPAR-related, PI3K/Akt, inflammatory, and angiogenic signaling	Lipid regulation, endothelial support, and reduced vascular inflammation	Network and preclinical evidence	Limited direct clinical validation

Plant or Compound	Principal Reported Targets	Main Pathways	Proposed Anti-Atherosclerotic Effects	Validation Depth	Key Limitation
Panax notoginseng saponins	AKT1 and inflammatory or immune targets	NF-κB, PI3K/Akt, MAPK, Toll-like receptor	Reduced macrophage infiltration, foam-cell formation, and endothelial injury	Network and experimental evidence	Disease-specific relevance differs among studies
Quercetin and related flavonoids	Multiple oxidative, inflammatory, and metabolic targets	PI3K/Akt, AMPK, NF-κB, Nrf2, apoptosis	Antioxidant, anti-inflammatory, endothelial, and lipid-regulatory effects	Broad computational and preclinical evidence	High pathway promiscuity and limited target specificity

The anti-atherosclerotic literature supported coordinated effects on lipid metabolism, inflammation, endothelial function, oxidative stress, and plaque biology. Nevertheless, the cellular heterogeneity of atherosclerotic plaques was rarely captured in conventional network models, which generally combined gene associations across tissues and disease stages.

Cross-Disease Comparison of Targets and Pathways

The comparative synthesis showed extensive overlap in reported molecular targets and pathways across diabetes mellitus, hypertension, coronary artery disease, heart failure, and atherosclerosis. AKT1, TNF, IL6, VEGFA, MAPK proteins, NOS3, and apoptosis-related targets appeared across several disease areas. Similarly, PI3K/Akt, MAPK, NF-κB, AMPK, HIF-1, AGE–RAGE, Nrf2, and apoptosis pathways were repeatedly enriched.

Table 8. Cross-Disease Distribution of Recurrently Reported Molecular Networks

Molecular Target or Pathway	Diabetes Mellitus	Hypertension	Coronary Artery Disease	Heart Failure	Atherosclerosis	Principal Biological Interpretation
AKT1 / PI3K–Akt	✓	✓	✓	✓	✓	Insulin signaling, cell survival, endothelial function, angiogenesis, and metabolism
AMPK	✓	Occasional	Occasional	Occasional	✓	Energy sensing, glucose and lipid metabolism, and mitochondrial regulation
TNF / IL6 / NF-κB	✓	✓	✓	✓	✓	Chronic inflammation, endothelial injury, fibrosis, and immune activation
MAPK signaling	✓	✓	✓	✓	✓	Stress responses, proliferation, apoptosis, inflammation, and remodeling
AGE–RAGE	✓	✓	Occasional	✓	Occasional	Oxidative stress, inflammation, diabetic vascular injury, and remodeling
HIF-1 / VEGFA	✓	✓	✓	✓	✓	Hypoxic response, angiogenesis, vascular adaptation, and tissue repair
Nrf2	✓	✓	Occasional	Occasional	✓	Antioxidant defense and cellular protection
NOS3 / NO–cGMP	Occasional	✓	✓	Occasional	✓	Endothelial nitric oxide production and vascular homeostasis
Apoptosis / CASP3 / TP53	✓	Occasional	✓	✓	✓	β-cell loss, cardiomyocyte injury, endothelial damage, and plaque instability
Calcium / cGMP–PKG signaling	Limited	✓	Occasional	✓	Occasional	Vascular tone, myocardial contraction, and cellular calcium homeostasis

The overlap supported the concept that cardiometabolic disorders share central biological mechanisms. However, it also demonstrated that pathway enrichment alone was insufficient to establish disease-specific or plant-specific mechanisms. Highly connected targets such as AKT1, TNF, IL6, and TP53 may be preferentially selected because of extensive database annotation and centrality within PPI networks. Stronger mechanistic inference required confirmation that the predicted compound reached the relevant tissue, interacted with the proposed target at physiologically plausible concentrations, altered downstream signaling, and produced reproducible functional outcomes.

Comparative Depth of Validation

The depth of validation differed substantially across plants and disease areas. Berberine, Salvia miltiorrhiza, selected ginsenosides, Astragalus-derived compounds, Compound Danshen Dripping Pills, Qishen Yiqi Dropping Pills, and Yiqi Fumai Injection had evidence extending beyond computational prediction. In contrast, many other medicinal plants were represented primarily by target prediction, pathway enrichment, and docking studies.

Table 9. Evidence-Validation Framework Applied to the Reviewed Literature

Evidence Tier	Defining Characteristics	Interpretation
Tier 1: Database prediction	Compound identification, disease-gene retrieval, intersecting targets, PPI network, and enrichment analysis	Generates candidate targets and pathways; high risk of database and algorithmic bias
Tier 2: Structural prediction	Molecular docking with or without binding-site visualization	Supports structural plausibility but does not prove biological binding or efficacy
Tier 3: Dynamic or pharmacokinetic prediction	Molecular dynamics simulation and computational ADMET or toxicity analysis	Adds information regarding predicted complex stability and drug-like properties
Tier 4: In vitro validation	Binding assays, enzyme assays, cell viability, gene expression, western blotting, or pathway modulation	Provides direct experimental support under controlled laboratory conditions
Tier 5: In vivo validation	Animal disease models, pharmacokinetics, histology, biochemical outcomes, or physiological measures	Establishes preclinical biological activity but may not predict human effectiveness
Tier 6: Human evidence	Observational studies, controlled clinical trials, randomized trials, or high-quality evidence synthesis	Provides translational support, with confidence dependent on design, sample size, standardization, and bias control

Most network-pharmacology publications occupied Tiers 1–3. Fewer progressed to in vitro or animal validation, and only a limited subset of standardized formulations or well-characterized compounds had human evidence. Consequently, the overall literature was stronger for identifying plausible mechanistic networks than for establishing clinical effectiveness.

Evidence Gaps and Internal Inconsistencies

Several recurring evidence gaps were identified. First, phytochemical profiles were frequently derived from public databases rather than direct chemical analysis of the plant material used experimentally. Second, many investigations applied oral-bioavailability or drug-likeness thresholds that may exclude active metabolites or poorly absorbed compounds with local, microbiome-mediated, or metabolite-dependent effects. Third, target predictions were rarely tested across alternative algorithms or validated using direct binding assays. Fourth, PPI networks often lacked tissue, cell-type, disease-stage, and treatment-context specificity.

Fifth, the same broad pathways were repeatedly identified across unrelated plants, raising concerns regarding enrichment bias and limited mechanistic discrimination. Sixth, molecular docking was sometimes described as confirmation of therapeutic action even though it provided only a predicted static interaction. Seventh, experimental studies frequently validated a small subset of predicted targets without assessing whether those targets were necessary for the observed effect. Eighth, few studies evaluated pharmacokinetics, dose–response relationships, toxicity, herb–drug interactions, batch variability, or clinically achievable compound concentrations.

The source manuscript also contained several internal inconsistencies that were corrected during synthesis. Duplicated limitation paragraphs in the diabetes section were consolidated. Repeated paragraphs concerning residual cardiovascular risk in atherosclerosis were removed. The reference to a nonexistent Table 4 was resolved by providing a complete sequence of evidence tables. Unrelated ovarian-cancer statements were removed from the coronary artery disease section. Evidence from laryngeal cancer, malignant pleural effusion, arsenic-induced cardiotoxicity, gastrointestinal injury, or other non-cardiometabolic models was not treated as direct confirmation of cardiometabolic efficacy. Botanical and phytochemical attribution within the Allium discussion was qualified to avoid assigning garlic-specific compounds to a different species without verification.

Integrated Interpretation of the Synthesis

Taken together, the reviewed evidence indicated that network pharmacology was most useful as a structured method for prioritizing phytochemicals, molecular targets, and biological pathways for subsequent testing. The approach was particularly informative for medicinal plants and herbal formulations containing multiple constituents because it enabled simultaneous visualization of compound–target–pathway relationships that could not be represented adequately by a single-target model.

The strongest recurring biological themes involved regulation of inflammation, oxidative stress, glucose and lipid metabolism, endothelial function, mitochondrial activity, apoptosis, angiogenesis, neurohormonal signaling, and tissue remodeling. Diabetes mellitus, coronary artery disease, and heart failure contained the greatest number of examples with experimental or clinical support, whereas several hypertension and atherosclerosis investigations remained predominantly computational. Even in the more developed disease areas, the clinical evidence applied mainly to selected compounds or standardized formulations rather than medicinal plants as a general therapeutic category.

The synthesis therefore supported the biological plausibility of multi-target phytochemical activity but did not establish that multi-target action was inherently superior to selective pharmacology. Therapeutic benefit depended on chemical standardization, target engagement, dose, tissue exposure, pharmacokinetics, safety, interaction with conventional treatment, and reproducible clinical outcomes. Network pharmacology should accordingly be interpreted as a hypothesis-prioritization framework within an integrated discovery pipeline rather than as independent proof of therapeutic effectiveness.

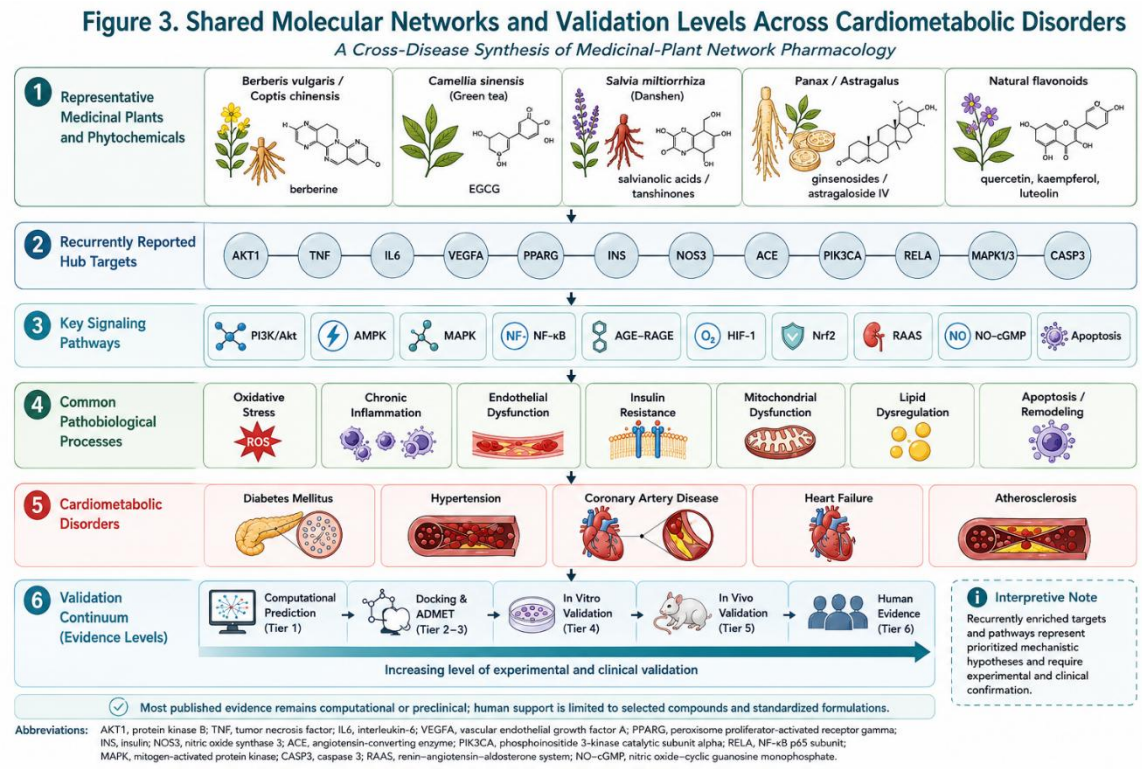

Figure 3. The cross-disease synthesis summarizes representative medicinal plants and phytochemicals, recurrent hub targets, major signaling pathways, shared pathological processes, and their relevance to diabetes mellitus, hypertension, coronary artery disease, heart failure, and atherosclerosis, while also indicating the progression from computational prediction to human evidence.

DISCUSSION

This narrative review critically examined how network pharmacology has been applied to medicinal plants and plant-derived compounds in type 2 diabetes mellitus, hypertension, coronary artery disease, heart failure, and atherosclerosis. Three principal findings emerged from the synthesis. First, medicinal-

plant network-pharmacology studies repeatedly prioritized a relatively limited group of highly connected molecular targets, particularly AKT1, TNF, IL6, VEGFA, MAPK proteins, PPARG, NOS3, RELA, TP53, and CASP3. Second, the principal enriched pathways—PI3K/Akt, AMPK, MAPK, NF-κB, AGE–RAGE, HIF-1, Nrf2, apoptosis, calcium signaling, and renin–angiotensin–aldosterone signaling—corresponded to shared mechanisms of inflammation, oxidative stress, insulin resistance, endothelial dysfunction, mitochondrial impairment, lipid dysregulation, and tissue remodeling. Third, although these recurring networks supported the biological plausibility of multi-component and multi-target activity, most of the available evidence remained computational or preclinical, with human evidence concentrated in a limited number of compounds and standardized herbal formulations.

The findings were consistent with the original systems-level concept of network pharmacology, which proposed that therapeutic responses in complex diseases frequently arise through modulation of interconnected biological networks rather than isolated molecular targets (1). Medicinal plants are particularly compatible with this conceptual framework because they contain multiple constituents capable of interacting with several proteins and pathways simultaneously (2, 3). However, the results of the present synthesis also indicated that multi-target activity should not be regarded automatically as therapeutically advantageous. A compound or herbal formulation may influence several beneficial pathways, but the same pharmacological promiscuity may also produce antagonistic interactions, off-target effects, dose-dependent toxicity, or unpredictable interactions with conventional medicines. Consequently, the number of predicted targets or enriched pathways should not be interpreted as a direct measure of therapeutic effectiveness.

The repeated identification of AKT1, TNF, IL6, VEGFA, MAPK1, MAPK3, TP53, and related proteins across multiple medicinal plants and cardiometabolic disorders requires cautious interpretation. These proteins are central regulators of cell survival, inflammation, metabolism, angiogenesis, and stress responses, but they are also among the most extensively studied and highly connected nodes in biomedical interaction databases. Their recurrence may therefore reflect a combination of genuine biological importance, extensive annotation, and preferential selection by topological algorithms. Degree centrality, betweenness centrality, and other network measures identify nodes that are structurally prominent within a selected network, but they do not independently demonstrate that those proteins are directly bound or functionally altered by a phytochemical. Hub-gene findings should therefore be interpreted as target-prioritization outputs requiring experimental verification rather than as confirmed mechanisms or biomarkers.

A similar limitation applied to pathway-enrichment findings. PI3K/Akt, MAPK, NF-κB, HIF-1, AGE–RAGE, apoptosis, and inflammatory signaling were repeatedly enriched across diabetes mellitus, hypertension, coronary artery disease, heart failure, and atherosclerosis. This overlap was partly expected because these disorders share metabolic, vascular, inflammatory, and oxidative mechanisms. Nevertheless, the recurrence of broad pathways across unrelated plants may also indicate pathway overrepresentation, database circularity, or the use of large nonspecific disease-gene sets. Statistical enrichment establishes that a target list contains more pathway-associated genes than expected under a selected background model; it does not establish pathway activation, inhibition, direction of effect, tissue specificity, or clinical relevance. Mechanistic claims are therefore strengthened substantially when enrichment findings are supported by transcriptomic, proteomic, metabolomic, gene-expression, or functional intervention data.

Among the disease areas examined, type 2 diabetes mellitus contained some of the most developed evidence for individual phytochemicals, particularly berberine. Network analyses repeatedly associated berberine with AMPK, PI3K/Akt, PPARG, insulin signaling, inflammatory mediators, and hepatic glucose metabolism. These predictions were supported by experimental and selected human studies reporting effects on glucose regulation and insulin sensitivity (11, 78, 83). Nevertheless, clinical interpretation remained constrained by heterogeneous formulations, dosing schedules, bioavailability,

treatment durations, and concomitant therapies. Berberine also illustrates a broader translational issue: a phytochemical may demonstrate biologically plausible activity and clinical signals while still having limited oral absorption, extensive metabolism, and variable exposure among individuals.

Green-tea catechins and multi-component formulations such as Gegen–Qinlian Decoction were also associated with glucose-regulatory, antioxidant, inflammatory, and endothelial pathways (11, 84, 85). However, findings derived from dietary tea consumption, concentrated extracts, isolated epigallocatechin gallate, and multi-herb formulations should not be considered interchangeable. The chemical dose, matrix, absorption profile, metabolism, and interaction among constituents differ considerably among these preparations. Future investigations should clearly define the intervention, characterize its chemical composition, and avoid extrapolating results from isolated compounds to whole-plant preparations without direct supporting evidence.

The hypertension literature was comparatively less mature and frequently remained limited to compound screening, target prediction, pathway enrichment, and molecular docking. Reported mechanisms commonly involved ACE, AGTR1, NOS3, oxidative stress, inflammation, calcium signaling, and nitric oxide pathways. Although these pathways were relevant to blood-pressure regulation, direct evidence of target engagement and clinically meaningful antihypertensive effects was limited for several plants. Botanical and phytochemical authentication also required greater attention. For example, sulfur-containing compounds such as allicin, ajoene, and diallyl disulfide are strongly associated with garlic and should not be attributed to other Allium species without direct chemical confirmation. This issue demonstrates why plant identity, voucher specimens, geographical origin, extraction procedures, and analytical profiling are essential for reproducible medicinal-plant research.

The coronary artery disease literature contained several comparatively advanced translational examples, including Salvia miltiorrhiza, Compound Danshen Dripping Pills, Qishen Yiqi Dropping Pills, and Xuefu Zhuyu Decoction. These interventions were associated with inflammatory signaling, endothelial function, platelet activation, apoptosis, angiogenesis, lipid metabolism, mitochondrial function, and myocardial remodeling (95–104). Selected standardized formulations had also been examined in clinical investigations or evidence syntheses, providing greater translational support than was available for many database-only studies (98, 99, 101). However, the existence of clinical data for a multi-component formulation did not validate every compound–target interaction predicted by network pharmacology. Clinical effectiveness, where demonstrated, represented the integrated effect of the formulation, dose, production standard, patient population, background therapy, and study design rather than confirmation of each proposed molecular mechanism.

Heart failure studies similarly identified inflammation, apoptosis, fibrosis, mitochondrial dysfunction, calcium handling, angiogenesis, and energy metabolism as central therapeutic networks. Astragalus membranaceus, Codonopsis pilosula, Yiqi Fumai Injection, Qishen Yiqi Dropping Pills, and berberine were among the most frequently discussed interventions (100, 108–121). Proteomic and experimental investigations of Yiqi Fumai Injection provided stronger support for effects on myocardial energy metabolism and MAPK-related signaling than computational prediction alone (117–119). Nevertheless, many studies treated heart failure as a homogeneous syndrome. Heart failure with reduced ejection fraction and heart failure with preserved ejection fraction differ substantially in ventricular structure, inflammatory state, metabolic phenotype, comorbidities, and treatment response. Future network models should therefore be phenotype-specific rather than relying on broad heart-failure gene sets.

The atherosclerosis literature supported the involvement of lipid metabolism, endothelial injury, macrophage activation, foam-cell formation, oxidative stress, vascular smooth-muscle proliferation, extracellular-matrix remodeling, and plaque stability. Salvia miltiorrhiza, Ligusticum chuanxiong, Angelica sinensis, Panax notoginseng, quercetin, and other flavonoids were associated with these processes through PI3K/Akt, MAPK, NF-κB, Nrf2, PPAR, HIF-1, and Toll-like receptor pathways (77, 124–136). However, atherosclerotic plaques contain heterogeneous populations of endothelial cells, smooth-

muscle cells, macrophages, fibroblasts, and lymphocytes that vary across disease stages. Conventional network-pharmacology models generally aggregate gene associations across tissues and stages and may therefore fail to capture cell-specific mechanisms. Single-cell transcriptomics, spatial proteomics, and plaque-stage-specific datasets offer opportunities to improve biological resolution (105, 123).

The evidence-validation continuum developed in this review highlighted an important imbalance in the literature. Most studies progressed from compound identification to target prediction, PPI analysis, enrichment, and molecular docking, but fewer advanced to direct binding assays, pathway-intervention experiments, animal pharmacokinetics, toxicological assessment, or controlled human studies. Molecular docking was particularly prone to overinterpretation. A favorable docking score does not demonstrate that a compound reaches the relevant tissue, binds selectively at physiologically achievable concentrations, modulates the predicted pathway, or improves a clinical outcome. Docking should therefore be used to prioritize interactions for testing, ideally followed by molecular dynamics simulation, biophysical binding assays, target-engagement studies, genetic or pharmacological pathway interruption, and dose–response experiments.

Molecular dynamics simulation can provide additional information on the stability and behavior of a predicted protein–ligand complex, but its conclusions remain sensitive to force fields, simulation duration, starting structures, protonation states, solvent models, and analytical choices. Similarly, computational ADMET tools are useful for prioritizing compounds but cannot substitute for experimental pharmacokinetics or toxicology. Predicted oral bioavailability, blood–brain barrier penetration, metabolism, or toxicity may differ considerably from in vivo behavior, particularly for herbal preparations containing multiple constituents and metabolites.

Phytochemical standardization represented another major translational limitation. The chemical composition of medicinal plants may vary according to species, subspecies, geographical origin, soil, climate, cultivation conditions, harvest stage, storage, processing, extraction solvent, and manufacturing procedures. Database-derived compound lists may therefore not represent the preparation used in a laboratory or clinical study. Future investigations should incorporate botanical authentication, voucher-specimen documentation, chromatographic or spectrometric profiling, marker-compound quantification, batch-to-batch testing, and stability assessment. Computational analyses should be based preferentially on experimentally detected constituents rather than unverified database inventories.

The frequent use of oral-bioavailability and drug-likeness thresholds also warrants reconsideration. Uniform screening cutoffs may exclude compounds that are poorly absorbed but biologically active through intestinal mechanisms, microbial transformation, active metabolites, or synergistic interactions. Conversely, database-predicted drug-likeness does not ensure adequate exposure, efficacy, or safety. Compound-screening rules should therefore be biologically justified and reported transparently, with sensitivity analyses assessing how alternative thresholds influence the resulting target network.

Safety was underrepresented in much of the reviewed literature. Medicinal plants can produce toxicity, contamination-related harm, and clinically important interactions with conventional treatments. This is particularly relevant in cardiometabolic disease, where patients frequently receive antiplatelet agents, anticoagulants, antihypertensive medicines, glucose-lowering drugs, lipid-lowering treatments, diuretics, renin–angiotensin system inhibitors, and heart-failure therapies. Plant constituents may alter cytochrome P450 enzymes, drug transporters, platelet activity, coagulation, glucose levels, blood pressure, electrolyte balance, or cardiac conduction. Multi-target activity may therefore increase interaction risk as well as potential efficacy. Future network-pharmacology investigations should integrate herb–drug interaction databases, transporter and enzyme predictions, toxicogenomic resources, and experimental safety assessment from the beginning of the discovery pipeline.

Artificial intelligence and machine learning offer important opportunities to improve compound–target prediction, chemical representation, protein-structure analysis, multi-omics integration, drug

repurposing, and patient stratification (13, 73). Nevertheless, AI models inherit limitations from their training data. Overrepresentation of well-studied proteins, compounds, diseases, and chemical scaffolds may reinforce existing biases and create apparently precise but poorly generalizable predictions. Transparent model reporting, external validation, uncertainty estimation, explainability, and prospective experimental testing will be essential if AI-enhanced network pharmacology is to improve rather than amplify current methodological weaknesses.

The integration of multi-omics data can increase the biological specificity of network-pharmacology models. Transcriptomics can identify disease- or treatment-associated gene-expression changes, proteomics can assess protein abundance and post-translational modifications, metabolomics and lipidomics can characterize functional metabolic consequences, and single-cell or spatial methods can identify cell- and tissue-specific responses (14, 105, 137). Combining these datasets with experimentally characterized phytochemicals would allow construction of context-specific rather than generic interaction networks. However, multi-omics integration introduces additional challenges involving batch effects, dimensionality, platform heterogeneity, missing data, multiple testing, and independent validation.

This review had several limitations. The narrative design permitted integration of heterogeneous methodological, preclinical, and clinical literature but did not ensure exhaustive study identification. No formal risk-of-bias assessment, certainty grading, or quantitative synthesis was undertaken. The purposive selection of representative studies may have introduced selection and citation bias, and positive mechanistic studies may have been more visible than null or negative findings. The evidence base also contained substantial heterogeneity in plant materials, target-prediction algorithms, disease databases, PPI thresholds, enrichment methods, docking procedures, experimental models, and clinical interventions. These limitations prevented direct comparison of the relative effectiveness of different plants or formulations.

A further limitation was the reliance of many primary studies on overlapping public databases. Independent publications may therefore not represent fully independent biological evidence. Repeated retrieval of the same compound records, disease genes, PPI interactions, and pathways can create an appearance of reproducibility even when studies share the same underlying information sources. Future reviews should quantify database overlap, distinguish independent validation from repeated computational retrieval, and assess whether reported mechanisms remain stable across alternative data sources and analytical thresholds.

Future research should move beyond the routine sequence of target intersection, PPI construction, enrichment, and docking. Priority should be given to preregistered analytical protocols, experimentally verified phytochemical profiles, transparent thresholds, cross-database sensitivity analyses, tissue- and cell-specific disease networks, direct target-engagement experiments, pathway-interruption studies, pharmacokinetics, dose–response assessment, toxicology, and adequately controlled clinical trials. Studies of multi-herb formulations should examine constituent interactions and determine whether predicted synergy is additive, synergistic, antagonistic, or clinically negligible. Reporting standards specifically designed for network-pharmacology investigations would improve transparency, reproducibility, and comparison across studies.

Overall, the synthesis indicated that network pharmacology provided substantial value for organizing complex medicinal-plant data and prioritizing compounds, targets, and pathways for experimental investigation. Its principal strength lay in hypothesis generation and systems-level integration rather than independent confirmation of therapeutic efficacy. Translation into evidence-based phytotherapy will require a sequential pipeline connecting authenticated plant materials, analytical chemistry, computational prioritization, direct experimental validation, pharmacokinetics, safety evaluation, standardized manufacturing, and rigorous human investigation.

CONCLUSION

Network pharmacology provides a useful systems-level framework for investigating medicinal plants as multi-component interventions in complex cardiometabolic disorders. Across diabetes mellitus, hypertension, coronary artery disease, heart failure, and atherosclerosis, the literature repeatedly implicated inflammatory, oxidative, metabolic, endothelial, mitochondrial, apoptotic, and remodeling networks, with recurrent prioritization of AKT1, TNF, IL6, VEGFA, MAPK-related proteins, PI3K/Akt, AMPK, NF-κB, HIF-1, AGE–RAGE, and Nrf2 signaling. However, most of these findings remain computational or preclinical and may partly reflect database annotation density, pathway overrepresentation, and heterogeneous analytical methods. Network pharmacology should therefore be used to generate and prioritize testable mechanistic hypotheses rather than as independent evidence of efficacy. Future progress will depend on authenticated and chemically standardized plant materials, reproducible computational pipelines, tissue- and cell-specific multi-omics integration, direct target and pathway validation, pharmacokinetic and toxicological assessment, evaluation of herb–drug interactions, and well-designed clinical trials of standardized preparations.

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