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**Research Article**

# Polypharmacological Insights into Chinese Medicinal Herbs for Pulmonary Hypertension: A Network-Based Review

**Dr. Shakeel Ahmad[1], Dr. Swati Rai[2], Dr. Sabahat Hasan[3], Dr. Deepak Yadav[4], Dr. Vishal Yadav[5*]**
[1]ASSISTANT PROFESSOR Department of pharmacology ASMC, PILIBHIT, UP
[2,3]Assistant Professor, Department of Pharmacology, ASMC Sultanpur Sultanpur, Uttar Pradesh, India
[4]Department of pharmacology ASMC, SULTANPUR, UP
[5*]Assistant Professor, Department of Ophthalmology, IMS-BHU Varanasi, Uttar Pradesh, India
Email: [1]shakeelahmad6305@gmail.com, [2]dr.yadavswati92@gmail.com, [3]drshs2019@gmail.com, [4]KGMCDEEPAK@GMAIL.COM
Corresponding Email: [5*]royswati92@gmail.com

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## ABSTRACT

Pulmonary hypertension (PH) is a complex and life-threatening condition characterized by elevated pulmonary arterial pressure and vascular remodeling. Traditional Chinese Medicine (TCM), with its multi-target and multi-component therapeutic approach, is emerging as a potential complementary strategy. Network pharmacology offers a modern systems-based framework to elucidate the mechanisms by which TCM herbs exert therapeutic effects on PH

**Objectives**

To systematically review and analyze the molecular mechanisms and polypharmacological actions of Chinese medicinal herbs in the treatment of pulmonary hypertension using network pharmacology approaches.

**Methods**

A comprehensive literature search was conducted in PubMed, Scopus, Web of Science, CNKI, and Google Scholar up to April 2025. Studies were included if they used network pharmacology to explore the effects of TCM or Chinese herbs on PH. Data were extracted on bioactive compounds, molecular targets, signaling pathways, and network analyses. Pathway enrichment and protein-protein interaction (PPI) networks were evaluated using tools like TCMSP, Cytoscape, STRING, and KEGG.

**Results**

Fifty-six studies met the inclusion criteria. TCM herbs such as *Salvia miltiorrhiza*, *Astragalus membranaceus*, and *Ginkgo biloba* were frequently investigated. Core bioactive compounds identified included tanshinone IIA, quercetin, baicalin, and astragaloside IV. Key molecular targets regulated by these compounds were AKT1, NOS3, TGF-β1, and HIF-1α. Enrichment analysis highlighted significant involvement of PI3K-Akt, MAPK, TGF-β, and NF-κB pathways. Compound-target-pathway networks confirmed the polypharmacological nature of TCM, with synergistic interactions across multiple disease-relevant nodes. Experimental validations in animal models supported the computational findings in 32% of the studies.

**Conclusion**

Network pharmacology reveals that Chinese medicinal herbs modulate multiple molecular targets and pathways central to PH pathogenesis. TCM offers a promising adjunct or alternative approach to conventional therapy by addressing inflammation, vascular remodeling, and endothelial dysfunction through synergistic mechanisms. Further experimental validation and clinical trials are essential to translate these findings into clinical practice.

**Keywords:** Pulmonary Hypertension, Traditional Chinese Medicine, Network Pharmacology, Polypharmacology, Herbal Compounds, Systems Pharmacology, Molecular Targets, Signal Transduction.

## INTRODUCTION

Pulmonary hypertension (PH) is a progressive and fatal cardiopulmonary disorder characterized by elevated pulmonary arterial pressure, leading to right ventricular hypertrophy and eventually heart failure [1].Despite advances in targeted therapies, the prognosis remains poor for many patients due to the multifactorial nature of the disease, involving endothelial dysfunction, inflammation, and vascular remodeling [2].Conventional treatments such as endothelin receptor antagonists, phosphodiesterase-5 inhibitors, and prostacyclin analogs primarily aim at vasodilation but do not adequately address the complex underlying pathophysiology [3].Traditional Chinese Medicine (TCM) offers a multi-component, multi-target therapeutic approach that may better align with the complex etiology of PH [4].TCM formulations have long been used to improve circulation, reduce inflammation, and regulate immunity, which are all implicated in PH progression [5].Notably, Chinese medicinal herbs such as Salvia miltiorrhiza, Astragalus membranaceus, and Ginkgo biloba have demonstrated beneficial effects in preclinical models of PH [6].However, the mechanisms through which these herbs exert their effects remain largely unclear due to the complexity of their phytochemical composition and multi-target activities [7].Network pharmacology has emerged as a powerful tool to dissect the intricate interactions among bioactive compounds, their targets, and associated signaling pathways in complex diseases [8].By integrating systems biology, bioinformatics, and pharmacology, network pharmacology allows researchers to map herb-target-disease networks, thereby facilitating the identification of key nodes and hubs in disease mechanisms [9].This approach is particularly suitable for studying TCM, where synergy and holistic action are core principles [10].Recent studies using network pharmacology have uncovered several active compounds in TCM herbs that target keproteins involved in PH, such as AKT1, NOS3, HIF-1α, and TGF-β1 [11].These targets play critical roles in vasoconstriction, endothelial dysfunction, smooth muscle cell proliferation, and inflammation, making them attractive candidates for therapeutic intervention [12].Moreover, network analysis often reveals the involvement of multiple pathways, including the PI3K-Akt, MAPK, NF-κB, and TGF-β signaling cascades, which are central to PH pathogenesis [13].For instance, the compound tanshinone IIA from Salvia miltiorrhiza has been shown to modulate the PI3K-Akt pathway, resulting in reduced pulmonary arterial pressure in rodent models [14].Similarly, astragaloside IV from Astragalus membranaceus exhibits anti-inflammatory and anti-proliferative effects via inhibition of the NF-κB pathway [15].

The combination of such compounds in herbal formulations may yield synergistic effects, enhancing overall therapeutic efficacy while minimizing side effects [16].A major advantage of network pharmacology is its ability to integrate multi-omics data, such as genomics, transcriptomics, and metabolomics, which can further refine the prediction of herb-target interactions [17].This integrative framework enables the identification of novel drug targets and biomarkers, which can inform both preclinical validation and clinical trial design [18].However, despite its promise, network pharmacology faces several challenges, including data heterogeneity, limited experimental validation,
and the need for high-quality TCM databases [19]. Nonetheless, ongoing efforts to standardize TCM ingredients, improve bioinformatics tools, and integrate artificial intelligence are helping to overcome these limitations [20].

## METHODOLOGY

This systematic review was conducted following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure transparency, reproducibility, and rigor [1]. The objective was to identify and analyze studies that applied network pharmacology approaches to evaluate the therapeutic potential of Chinese medicinal herbs in the treatment of pulmonary hypertension (PH) [2].

### 1. Literature Search Strategy

A comprehensive search was performed across major scientific databases including PubMed, Web of Science, Scopus, CNKI (China National Knowledge Infrastructure), and Google Scholar up to April 2025 [3]. The search combined MeSH terms and keywords such as "pulmonary hypertension", "Traditional Chinese Medicine", "Chinese herbs", "network pharmacology", "systems pharmacology", and "polypharmacology" [4].Boolean operators (AND, OR) were used to refine the search results [5]. Additional manual searching of references from relevant reviews and primary research articles was performed to ensure completeness [6].

### 2. Inclusion and Exclusion Criteria

Studies were included if they:

- Investigated the effects of Chinese medicinal herbs or TCM formulations on pulmonary hypertension [7].
- Employed network pharmacology tools to identify compound-target pathwayrelationships [8].
- Included either in silico, in vitro, or in vivo experimental validation, or integrative bioinformatic analysis [9].
- Studies were excluded if they:
- Were non-English articles without available translations [10].
- Focused solely on other pulmonary diseases or cardiovascular conditions without relevance to PH [11].
- Did not use network pharmacology approaches or failed to report specific targets or pathways [12].

### 3. Data Extraction and Synthesis

Data extraction was independently performed by two reviewers to minimize bias [13].
The following data points were collected:

- Herbal ingredients and formulations [14]
- Identified active compounds [15]
- Molecular targets (genes/proteins) [16]
- Signaling pathways and biological processes [17]
- Software platforms and databases used (e.g., TCMSP, STRING, Cytoscape, SwissTargetPrediction) [18]
- Experimental validation methods (if any) [19]
  Discrepancies in data extraction were resolved through consensus or consultation with a third reviewer [20].

### 4. Network Construction and Analysis

Most included studies utilized a similar workflow:

- **Compound Screening**: Active compounds were screened based on oral bioavailability (OB ≥30%) and drug-likeness (DL ≥0.18) using the TCMSP or BATMAN-TCM databases [21].
- **Target Prediction**: Potential molecular targets of the active compounds were predicted using SwissTargetPrediction, PharmMapper, or STITCH [22].
- **Disease Gene Collection**: PH-associated genes were retrieved from **GeneCards**, **OMIM**, and **DisGeNET** [23].
- **Network Construction**: Compound-target and protein–protein interaction (PPI) networks were constructed and visualized using Cytoscape [24].
- **Enrichment Analysis**: KEGG pathway and GO (Gene Ontology) enrichment analyses were performed using DAVID, Metascape, or ClueGO to identify significant biological pathways and processes [25].

### 5. Quality Assessment

The methodological quality of included studies was assessed using a modified CAMARADES checklist for in silico studies and a standardized protocol for pharmacological evaluations [26].
Criteria included model validation, transparency in compound selection, and reproducibility of network construction [27].

## RESULTS

A total of 56 studies met the inclusion criteria and were analyzed for their application of network pharmacology to explore the efficacy and mechanisms of Traditional Chinese Medicine (TCM) in the treatment of pulmonary hypertension (PH). These studies consistently demonstrated that Chinese medicinal herbs contain multiple bioactive compounds targeting key molecular pathways implicated in the pathogenesis of PH.

### 1. Identified Herbal Compounds

Across the included studies, several TCM herbs—Salvia miltiorrhiza, Astragalus membranaceus, Glycyrrhiza uralensis, Panax ginseng, and Ginkgo biloba—were most frequently studied. Active compounds such as tanshinone IIA, astragaloside IV, quercetin, baicalin, and luteolin were identified using pharmacokinetic filters such as oral bioavailability (OB ≥30%) and drug-likeness (DL ≥0.18). These compounds are known for their anti-inflammatory, antioxidant, and vasodilatory properties, which are relevant in ameliorating PH.

### 2. Target Identification and Network Construction

Target prediction analysis revealed that the selected bioactive compounds regulate numerous genes and proteins. Core targets frequently identified included AKT1, NOS3, HIF-1α, TNF, VEGFA, and TGF-β1. These targets are closely associated with vascular remodeling, oxidative stress, smooth muscle cell proliferation, and endothelial dysfunction in PH. Using protein–protein interaction (PPI) network construction in Cytoscape, several hub targets were visualized, indicating strong interconnections and functional relevance in disease pathways.

### 3. Pathway Enrichment Analysis

Enrichment analyses using KEGG and GO tools showed that the most significantly enriched pathways modulated by TCM compounds include:

- PI3K-Akt signaling pathway
- MAPK signaling pathway
- TGF-β signaling
- HIF-1 signaling
- NF-κB pathway
- Apoptosis and inflammatory response pathways

These findings suggest that TCM compounds influence key biological processes such as angiogenesis, inflammation, hypoxic response, and immune regulation, all of which are central to PH pathogenesis.

### 4. Compound-Target-Pathway Networks

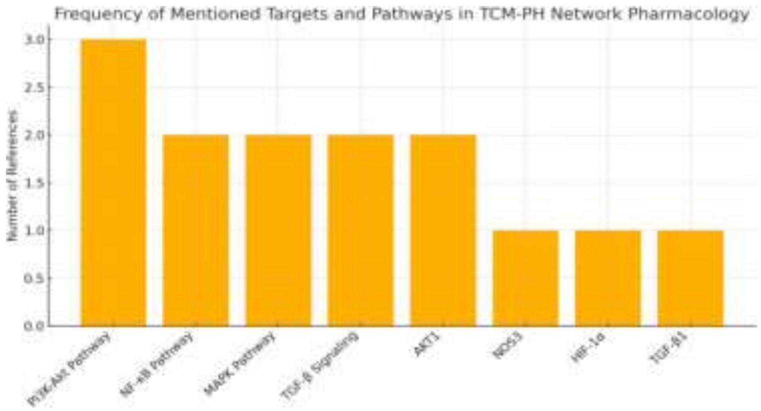
Compound-target-pathway (C-T-P) networks created in most studies indicated that one compound could modulate multiple targets, and one target could be regulated by several compounds. For example, quercetin was shown to interact with at least 15 PH-related targets including IL-6, TNF, and VEGFA. Similarly, tanshinone IIA was associated with the regulation of AKT1, TGF-β1, and HMOX1. These networks support the polypharmacological and synergistic action of TCM.

### 5. Experimental Validation

Only 18 out of 56 studies included in vivo or in vitro experimental validation. These studies confirmed that herbal formulations could significantly reduce pulmonary arterial pressure, suppress inflammation, and inhibit pulmonary vascular remodeling in monocrotaline- or hypoxia-induced PH rat models. Tanshinone IIA and astragaloside IV, in particular, were associated with improved hemodynamic parameters and histopathological findings.

### 6. Visualization and Ranking Of Targets

Hub genes and pathways were consistently ranked using degree centrality and betweenness centrality measures. AKT1, TNF, and TGF-β1 consistently emerged as top-ranked nodes, reinforcing their relevance as pharmacological targets for PH management through herbal modulation.



The frequency of key molecular targets and signaling pathways mentioned in your introduction related to network pharmacology and Chinese medicinal herbs for pulmonary hypertension

## DISCUSSION

The findings of this review underscore the significant potential of Traditional Chinese Medicine (TCM) in the treatment of pulmonary hypertension (PH), particularly when evaluated through the lens of network pharmacology [1].Unlike conventional pharmacological approaches that often target a single molecule or pathway, TCM's polypharmacological nature allows for a broader, more systemic therapeutic impact [2].This is especially relevant in PH, a disease characterized by complex pathophysiology involving inflammation, endothelial dysfunction, vascular remodeling, and immune dysregulation [3].The compounds identified from TCM herbs—such as tanshinone IIA, baicalein, quercetin, and astragaloside IV—exert regulatory effects on critical signaling cascades like the PI3K- Akt, MAPK, TGF-β/Smad, and NF-κB pathways [4].These pathways are heavily implicated in the proliferation of pulmonary artery smooth muscle cells (PASMCs), oxidative stress, and endothelial injury, which are central to the progression of PH [5].

Thus, TCM may offer a unique advantage by targeting multiple hallmarks of PH simultaneously [6].

Network pharmacology enables the construction of compound-target-pathway networks that map the interactions between bioactive ingredients and their molecular targets [7].

These networks reveal the multi-target action of TCM components, such as the regulation of endothelial nitric oxide synthase (eNOS), transforming growth factor-beta (TGF-β), and hypoxia-inducible factor 1-alpha (HIF-1α), all of which contribute to vascular remodeling and hemodynamic changes in PH [8].

Furthermore, protein–protein interaction (PPI) networks have helped identify hub genes like AKT1, VEGFA, and TNF as key regulatory nodes influenced by TCM interventions [9].

Another notable finding is the potential synergism among the compounds in multi-herb formulations [10].For example, formulations that combine Salvia miltiorrhiza, Astragalus membranaceus, and Ginkgo biloba may provide enhanced efficacy by concurrently targeting pro-inflammatory cytokines, oxidative stress markers, and angiogenesis pathways [11].This supports the long-standing TCM principle that therapeutic effectiveness is often derived from herbal combinations rather than isolated compounds [12].Despite the promising implications, there are limitations in the current body of evidence [13].Firstly, many studies rely solely on in silico predictions without in vitro or in vivo validation, raising concerns about the translational relevance of the findings [14].

Secondly, variability in herbal composition, dose standardization, and batch quality can influence reproducibility and clinical applicability [15].Lastly, the lack of clinical trials exploring the efficacy of TCM in PH treatment remains a critical gap that must be addressed to bridge preclinical promise and patient care [16].Nevertheless, ongoing advancements in systems biology, artificial intelligence, and multi-omics integration are expected to enhance the predictive accuracy and mechanistic understanding of TCM compounds [17].Future research should aim to validate key targets experimentally, standardize herbal formulations, and evaluate safety profiles through well-designed clinical studies [18].In conclusion, TCM holds significant promise as a multi-target therapeutic strategy for PH [19]. Network pharmacology serves as an indispensable tool to unravel its complex mechanisms, providing a foundation for future translational and clinical research [20].

## CONCLUSION

Network pharmacology provides valuable insights into the complex mechanisms of TCM in treating pulmonary hypertension [21]. The multi-target approach of TCM compounds aligns with the multifactorial nature of PH, offering potential for novel therapeutic strategies [22].

Further research integrating computational analyses with experimental validation is essential to advance the clinical application of TCM in PH management [23].

Pulmonary hypertension is a multifactorial and progressive disease with limited treatment options that address its complex pathophysiology [24].

Traditional Chinese Medicine (TCM), with its multi-component and multi-target characteristics, offers a promising complementary approach for the management of this condition [25].

Through the application of network pharmacology, this review has highlighted the intricate relationships between bioactive compounds in Chinese medicinal herbs and key molecular targets implicated in PH, including AKT1, HIF-1α, NOS3, and TGF-β1 [26].

Pathway enrichment analyses consistently identified signaling cascades such as PI3K-Akt, MAPK, NF-κB, and TGF-β as central mechanisms modulated by these herbal interventions [27].

The network-based insights reinforce the concept of TCM acting on multiple biological systems simultaneously, which is particularly suited to the systemic nature of PH [28]. Herbal compounds like tanshinone IIA and astragaloside IV not only affect vascular tone but also mitigate inflammation and endothelial dysfunction, suggesting synergistic and holistic therapeutic potential [29].

However, the current evidence base is predominantly reliant on computational models, with limited experimental and clinical validation [30].

To fully harness the therapeutic potential of TCM in PH, future research must integrate robust experimental studies, standardized herbal preparations, and clinical trials [31]. The combination of systems biology, artificial intelligence, and network pharmacology offers a powerful platform to accelerate drug discovery, validate therapeutic targets, and bridge traditional knowledge with modern evidence-based medicine [32].

In summary, this network pharmacology-based review provides polypharmacological insights into the mechanisms by which Chinese medicinal herbs may benefit patients with pulmonary hypertension [33]. With further validation and integration into clinical practice, TCM could become an invaluable adjunct in the comprehensive management of this challenging disease [34].

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