J. Pharm. Res. 2025;24(4):239-244

Print ISSN: 0973-7200
Online ISSN: 2454-8405

Journal of Pharmaceutical Research

REVIEW ARTICLE

Network Pharmacology in the Treatment of Hepatitis B: Insights from Traditional Chinese Medicine-Based Studies

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ARTICLE INFO

Article history:
Received 15-09-2025
Accepted 23-12-2025
Published 30-12-2025

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https://doi.org/10.18579/jopcr/v24.i4.115

ABSTRACT

Chronic hepatitis B (CHB) has been identified to be a major health problem in the world with an estimated number of 250 million individuals being affected by the disease. Though traditional antiviral treatments were proved to be effective, complications like poor cure rates, resistance, and adverse effects are still the burning issues. Network pharmacology has gained great strength in recent years as a possible strategy of recognizing how natural products systematically affect numerous disease targets. Four studies relating to four major formulations of traditional Chinese medicine identified as Jiawei Yinchenhao decoction, Fructus Schisandrae, Ganweikang tablets, Bupleuri Radix, and Scutellariae Radix were based on network pharmacological analysis and synthesized in the review to determine their hepatoprotective effects on CHB. We investigate their bioactive compounds, in silico targets, enriched pathways, noteworthy molecular processes, including management of TNF, IL-6, MAPK, NF-KB and JAK-STAT signalling. This integrative analysis is meant to enhance our knowledge on the use of multi-target therapeutic in management of HBV and provides insights on future investigations regarding adopting network pharmacology as the cornerstone of bridging the traditional and precision medicine.

Keywords: Network pharmacology, Hepatitis B, Traditional Chinese medicine, Molecular docking, Multi-target therapy, Hepatoprotection

INTRODUCTION

The Hepatitis B virus (HBV) infection still presents a major threat to the global human health. Considering the facts that there are over 1.5 million new HBV infections every year, and over a million of the annual deaths are attributed to various complications of HBV, including cirrhosis and hepatocellular cancers (HCC), it becomes evident that more efficient and comprehensive treatment approaches are highly necessary [1]. Even though the antiviral drugs such as nucleos(t)ide analogues and interferons have enhanced the management of the disease, in most cases they do not lead to an achievable functional cure which refers to lifelong loss of HBsAg. Resistance, relapse, and severe side effects due to drug use may limit patient adherence and outcomes, which is a problem that may arise because of long-term drug use. It is in this therapeutic vacuum that there has been a recent awakening in traditional Chinese medicine (TCM), and when traditional Chinese medicine is studied using modern systems biology tools like network pharmacology [2]. Network pharmacology can provide a very particular perspective with regard to interpreting the intricate relationship between numerous bioactive agents and disease-relevant targets that would be quite consistent with the polyherbal preparations of TCM [3]. In sharp contrast with

reductionist models of drug discovery, network pharmacology views the disease as the disintegration of a biological network, but never a malfunction of a single gene. This view is especially appropriate in complex illnesses such as chronic hepatitis B (CHB) in which immune dysregulation, viral persistence and liver tissue remodelling interact with shared pathways [4]. This review combines four network pharmacology studies that provide insights on four targets of traditional Chinese medicine used to treat CHB, which include (1) Jiawei Yinchenhao decoction (JWYCH), (2) Fructus Schisandrae (Wuweizi), (3) Ganweikang (GWK) tablets, and (4) Bupleuri Radix Scutellariae Radix pair[5]. All studies combine pharmacological modeling with molecular docking, target prediction, and pathway enrichment in providing guidance on multi-target behaviour and possible biomarkers to manage HBV both [6].

HEPATITIS B: PATHOGENESIS AND LIMITATIONS OF CURRENT THERAPIES

Hepatitis B virus (HBV) is a small, double-stranded DNA virus that can be categorized to Hepadnaviridae. It enters mainly into the cell, which is known as hepatocytes causing direct cytopathic effects and even immune mediated liver diseases. When infected, HBV reaches the nucleus and forms covalently closed circular DNA (cccDNA), and this is used as a viral reservoir and tends to perpetuate the infection hence causing chronic infection and relapses upon termination of treatment. Repeated infection during the persistent state of the infection (chronic hepatitis B, CHB) is caused by poor immune response, which is frequently manifested in T cell exhaustion and cytokine imbalance. Eventually, it can cause liver fibrosis and cirrhosis as well as hepatocellular carcinoma (HCC), especially in the presence of high viral load and chronic inflammation [7].

Today, the prevailing treatment of CHB, the most widespread agents of this group are nucleos(t)ide analogues (NAs), e.g., entecavir, tenofovir, and pegylation interferon-alpha (Peg-IFNalpha). Although these treatments are very successful in reducing replication of HBV DNA, not more than 10 percent patients directly come out of these treatments with a functional cure, meaning with the absence of HBsAg. In addition, chronic therapy has been associated with the risk of drug resistance, nephrotoxicity and bone mineral depletion necessitating the need to find alternative or adjunct type of treatment [8]. In this case, TCM offers an alternative channel. Its synergistic, multitarget effects are considered attributed to its multi-component formulations which are believed to be in tandem with the concept of biological complexity of CHB. Nevertheless, determining their exact mechanisms of actions of these polyherbal medications has been proven elusive and they therefore have not been able to find their way in the mainstream hepatology. Here, network drug magnetism comes in. Integrating computational target prediction, protein-protein interaction (PPI) mapping and enrichment analysis, it can facilitate the demystification of the mechanism of action of multi-compound and multi-target effects of TCM interventions by providing scientific credence [9, 10].

NETWORK PHARMACOLOGY: A NEW PARADIGM IN DRUG DISCOVERY

The old drug discovery paradigm has focused more on the one drug and one target principle. Although this strategy became effective in some disease fields, this method fails to deliver feasible results in disease conditions involving multiple causal factors (such as CHB which involves multiple genes, pathways, and physiological systems). In this case, network pharmacology offers the solution more in line with the systems biology approach to human diseases. Born in the year 2008, network pharmacology attempts to explain the diverse interactions of drugs with targets and disease modules through computational and experimental methods [11]. These are: compound databases (e.g., TCMSP, TCMID), target prediction resources (e.g., SEA, SwissTargetPrediction), protein-protein interaction networks (e.g., STRING) and pathway enrichment databases (e.g., KEGG, GO).

Table 1: Summary of Network Pharmacology Studies in Chronic Hepatitis B

Herbal Medicine	Model/Method	Major Bioactive Compounds	Key Targets/ Pathways	Tools Used
Jiawei Yinchenhao decoction (JWYCH)	Mouse model (AAV-HBV), Network Pharmacology + Metabolomics	Geniposide, chlorogenic acid, catechin	Bile acid, arachidonic acid, retinol metabolism	TCMSP, Cytoscape, KEGG, MetScape
Fructus Schisandrae (Wuweizi)	In silico docking and network analysis	Schisantherin A, gomisin A, schisandrin B	CYP2E1, PPARα, AMPK	STITCH, TTD, PharmGKB, STRING
Ganweikang (GWK) Tablet	Transcriptome + Network Analysis + Docking	Wogonin, ferulic acid, oleanolic acid	NF-κB, JAK-STAT, p53, MAPK	TCMSP, admetSAR, TPT network
Bupleuri Radix + Scutellariae Radix	Network Pharmacology + Molecular Docking	Quercetin, baicalein, wogonin, kaempferol	TNF, IL-6, MAPK3, JUN	Cytoscape, DAVID, KEGG, STRING

This approach is ground-breaking to TCM. The network pharmacology sheds light on the mechanisms behind the actions of bioactive compounds in herbal formulas, which are assumed as a black box, in the possible mechanism of action that they appear to be associated with a multitude of therapeutic activities such as removing inflammation, immune evasion, oxidative stress, and fibrosis, all of which remain critical aspects of CHB [12].

NETWORK PHARMACOLOGY STUDIES IN HEPATITIS B

Jiawei Yinchenhao Decoction (JWYCH)

The herbal decoction combined with modified *Artemisia capillaris, Rheum palmatum, Gardenia jasminoides*, and *Atractylodes macrocephala* showed a significant effect of improving serum HBeAg levels and liver inflammation in mice model of chronic hepatitis B. The analysis of metabolomes with advanced metabolomics tool indicated 144 bioactive compounds, including geniposide, chlorogenic acid, and catechin. These chemicals were associated with significant metasthesis such as bile acid, arachidonic acid, and retinol metabolism. The combination of compound-predicted targets and metabolism profiling provided the solid evidence of the multi-pathway action of this herbal preparation [13, 14].

Fructus Schisandrae (Wuweizi)

Eight phytochemicals such as schisantherin A, gomisin A, and schisandrin B were studied as to their molecular interaction under the liver related targets. Of the oxidative stress and fatty acid metabolism-related receptors and enzymes, CYP2E1, PPARa and AMPK exhibited strong docking affinities. The resulting network of the compound-target interactions demonstrated the ability of those molecules to stimulate or inhibit several pathways at once, with a highly specific but nonetheless complex pharmacology [15].

Ganweikang (GWK) Tablets

A different polyherbal preparations, in which wogonin, ferulic acid, and ursolic acid were included, were evaluated with the help of integrated chemical profiling and network pharmacology. A total of 330 active ingredients was found and their potential influence on 199 hepatitis B related targets was examined. The analysis of enrichment indicated essential signaling pathways such as JAK-STAT, NF-kappa B, and p53. The main hub genes like AKT1, RELA, STAT1 and EP300 became central nodes in the compound-target-pathway network. These connections were also confirmed by molecular docking that depicted a systems-level treatment approach [16].

Bupleuri Radix–Scutellariae Radix Pair

A two-herb combination of the traditional treatment of liver ailments was evaluated utilizing a sequence of network analysis and molecular docking. Active compounds like quercetin, baicalein, wogonin, and kaempferol were among 37 active compounds with a strong affinity with 78 hepatitis B-related protein targets i.e. TNF, IL-6, MAPK3, and JUN. These targets are the focuses of immune modulation, inflammatory response, and apoptosis. Pathways or enrichment via functional significance included TNF signaling, MAPK signaling, cytokinecytokine receptor interaction among others that highlighted the immunological significance of the two herbs [17].

COMMON MECHANISTIC INSIGHTS ACROSS STUDIES

Even though the methodology and herbs can be changed, there are several mechanistic themes that can be seen due to the reviewed studies:

1. Multi-Component and Multi-Target Action

All formulations revealed that their active ingredients act upon multiple targets as opposed to one gene/protein. This supports the principle of network pharmacology, which holds true in accordance with the complexity in the pathogenesis of CHB.

2. Immune Modulation and Anti-Inflammation

The most important targets TNF, IL-6, MAPK3, and NF-kappa B are key points of inflammatory and antiviral immune response. Their variation with different studies indicates that these natural drugs can restore immune balance, which is the key to interrupting HBV immune disorders.

3. Oxidative Stress and Metabolic Regulation

The compounds, which act on AMPK, CYP450s, PPAR alpha, and retinoid metabolism, indicate the antioxidant property and promotes homeostasis of hepatocytes, which is essential to avoid developing disease conditions or progressing to cirrhosis or HCC.

4. Pathway Convergence

In any study with enrichment analysis, the KEGG pathways that were least in number to converge are TNF, JAK-STAT, p53, MAPK, and fatty acid metabolism. This convergence has the implication that, instead of individual pharmacological effects, these herbal formulations exert a reprogramming effect on systems [18, 19, 20].

TOOLS AND METHODOLOGIES USED IN NETWORK PHARMACOLOGY

Each study involved the composition of databases, software tools and experimental validation:

Table 2: Software Tools used in Network pharmacology

Tool/Database	Purpose
TCMSP, TCMID, PubChem	Active compound identification
GeneCards, DisGeNET, OMIM	CHB-related target gene mining
STRING, Cytoscape	PPI network and network visualization
DAVID, KEGG, GO	Pathway enrichment and functional annotation
Autodock Vina, PyMOL	Molecular docking validation
MetaboAnalyst, SIMCA	Metabolomic data processing (JWYCH study)
TPT & CTP networks	Advanced network topological analysis (GWK study)

LIMITATIONS AND CHALLENGES

Although the network pharmacology provides the exciting platform to drug discovery and mechanisms, there are challenges to the approach to the disease haptic B:

1. Data Quality and Database Bias

Most of the databases available in TCM research like the TCMSP or even BATMAN-TCM are based on the predictive or inferential data. Such dataset can either not have experimental validation or have information that is out of date. Limits used to define active compounds (e.g., OB ≥ 30%, DL ≥ 0.18) tend to be arbitrary and may miss other relevant low bioavailability molecules.

2. Target Prediction Accuracy

Computational tools are capable of overpredicting targets or mispredicting targets. As well as some docking results indicate good affinity, but lack biological meaning, such as: the ability of a compound to circulate to the site of infection, be able to cross the membrane, or to be stable in vivo.

3. Species Differences

Experimental animals such as AAV-HBV mice are often employed but metabolism, immune system, and gene expression biology may vary between human and animal species and thereby diminish the translational value of results.

4. Herbal Complexity and Standardization

Herbal formulas can have hundreds of compounds, which are different according to geographical origin, season of harvest and method of processing. Representative research and the future clinical application of such formulations remain a challenge because of the lack of reproducibility.

5. Lack of Clinical Validation

Most of the studies herein reviewed are preclinical or in silico and there is little human trial data. Until robust clinical trials are performed, these findings remain hypothesis-generating not to mention useful.

6. Static Network Representation

Most network pharmacology studies generate static interaction networks that do not capture time dependent biological changes such as disease progression, treatment duration, or dynamic immune responses in CHB.

7. Lack of Dose and Concentration Consideration

Networks usually do not incorporate real pharmacological doses, tissue specific concentrations, or exposure time of compounds, which limits prediction of true therapeutic relevance.

8. Ignoring Pharmacokinetic Interactions within Formulations

Interactions among compounds in polyherbal formulations, such as synergistic absorption or metabolic competition, are rarely modeled, even though they can significantly influence efficacy. [21, 22]

FUTURE PERSPECTIVES

Despite the limitations, the field of network pharmacology holds immense promise in guiding multi-target drug development, especially for complex diseases like hepatitis B. Looking ahead:

1. Integration with Omics Technologies

Network pharmacology can better map the systems biology by mixing it with genomics, transcriptomics, proteomics and metabolomics. A good example of combination of metabolomics is the JWYCH study, which will lead to greater precision TCM.

2. AI and Machine Learning

A.I. would enhance the ability to predict targets and docking and pattern recognition in large data sets of compound with target pairs. This would also aid in an improved safety and efficacy of herbal formulations.

3. Clinical Trials and Real-World Data

Randomized controlled trials (RCTs) are urgently needed, which are designed on the basis of formulations found by network pharmacology. Also, the models can be validated

and optimized by mining data collected in the real-world setting of patients to use TCM.

4. Standardization and Regulatory Framework

To be integrated into the world healthcare system, it will be important to develop quality standards, safety profiles and manufacturing protocols of TCM herbs and formulas

5. Network Toxicology

In conjunction with efficacy, there is a need to investigate network toxicology, the possible off-target activities or herbs drug interaction, particularly when TCM is used in combination with conventional therapy of antiviral agents.

6. Dynamic and Time Series Network Modeling

Future studies can integrate temporal data to model how compound target interactions evolve during different stages of CHB and treatment.

7. Personalized Network Pharmacology

Incorporating patient specific genomic, transcriptomic, and immunological data could enable individualized herbal or combination therapies.

8. Integration with Single Cell Technologies

Single cell RNA sequencing data could help reveal cell specific targets and pathways affected by herbal compounds in hepatocytes, immune cells, and stellate cells.

9. Modeling Herb Drug Interactions

Network pharmacology can be expanded to predict interactions between TCM formulations and conventional antiviral drugs, improving combination therapy safety.

10. Linking Network Outputs to Clinical Biomarkers

Future research should aim to associate network predicted targets with measurable biomarkers to improve clinical relevance.

11. Regulatory Acceptance through Standardized Frameworks

Developing standardized pipelines for network pharmacology analysis may support regulatory evaluation of TCM based therapies. [23, 24]

CONCLUSION

Network pharmacology is a revolutionary means toward drug discovery, especially that of complex, chronic disease such as hepatitis B. Based on the four studies reviewed of the most significant JWYCH, Wuweizi, Ganweikang, and Bupleuri-Scutellariae TCM shows multi-pathway therapeutic potential that includes immune modulation, inflammation and oxidative stress, and metabolic dysregulation. Such limitations as database bias, insufficient clinical validation, and standardization of herbs have yet to diminish, but the incorporation of computational modeling, molecular docking, and high throughput omics platforms is fast transforming the landscape. Our move into the future of individualized and integrative medicine can be seen in the dawn of network pharmacology as the next evolution of wisdom and science convergence to safer, more effective, and holistic interventions to treat hepatitis B.

References

1. World Health Organization. *Hepatitis B*. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b (2024).
2. Christensen PB. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *The Lancet. Gastroenterology & Hepatology*. 2018; 3 (6) :383–403 . Available from: https://doi.org/10.1016/s2468-1253(18)30056-6
3. Terrault NA, Bzowej NH, Chang K, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology*. 2016; 63 (1) :261-283 . Available from: https://doi.org/10.1002/hep.28156
4. Li J, Lu C, Jiang M, Niu X, Guo H, Li L, *et al*. Traditional Chinese Medicine-Based Network Pharmacology Could Lead to New Multicompound Drug Discovery. *Evidence-Based Complementary and Alternative Medicine*. 2012; 2012 :1-11 . Available from: https://doi.org/10.1155/2012/149762
5. Li S, Zhang B. Traditional Chinese medicine network pharmacology: theory, methodology and application. *Chinese Journal of Natural Medicines*. 2014; 11 (2) :110-120 . Available from: https://doi.org/10.3724/sp.j.1009.2013.00110
6. Xu X, Liu J, Li X, Feng Q, Su Y. Integrated network pharmacology and metabolomics to study the potential mechanism of Jiawei Yinchenhao decoction in chronic hepatitis B. *Heliyon*. 2024; 10 (16) :e36267 . Available from: https://doi.org/10.1016/j.heliyon.2024.e36267
7. Pan S, Zhou S, Gao S, Yu Z, Zhang S, Tang M, *et al*. New Perspectives on How to Discover Drugs from Herbal Medicines: CAM's Outstanding Contribution to Modern Therapeutics. *Evidence-Based Complementary and Alternative Medicine*. 2013; 2013 :1-25 . Available from: https://doi.org/10.1155/2013/627375
8. Xu J, Su S, Chen CY, Gao J, Cao ZM, Guan JL, *et al*. Mechanisms of Ganweikang Tablets against Chronic Hepatitis B: A Comprehensive Study of Network Analysis, Molecular Docking, and Chemical Profiling. *BioMed Research International*. 2023; 2023 (1) . Available from: https://doi.org/10.1155/2023/8782892
9. Long P, Xia Y, Yang Y, Cao J. Network-based pharmacology and molecular docking exploring the "Bupleuri Radix-Scutellariae Radix" mechanism of action in the viral hepatitis B treatment. *Medicine*. 2022; 101 (48) :e31835 . Available from: https://doi.org/10.1097/md.0000000000031835
10. Angeli P, Bernardi M, Villanueva C, Francoz C, Mookerjee RP, Trebicka J, *et al*. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *Journal of Hepatology*. 2018; 69 (2) :406-460 . Available from: https://doi.org/10.1016/j.jhep.2018.03.024
11. Yousfi N, Hattaf K, Tridane A. Modeling the adaptive immune response in HBV infection. *Journal of Mathematical Biology*. 2011; 63 (5) :933-957 . Available from: https://doi.org/10.1007/s00285-010-0397-x
12. WHO. *Hepatitis B key facts*. 2023. https://www.who.int/news-room/fact-sheets/detail/hepatitis-b
13. Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *PsycEXTRA Dataset*.

2009; 58 (RR-4) :1–207 . Available from: https://doi.org/10.1037/e537722009-001

14. Ghany MG, Buti M, Lampertico P, Lee HM. Guidance on treatment endpoints and study design for clinical trials aiming to achieve cure in chronic hepatitis B and D: Report from the 2022 AASLD-EASL HBV-HDV Treatment Endpoints Conference. *Hepatology*. 2023; 78 (5) :1654-1673 . Available from: https://doi.org/10.1097/hep.0000000000000431
15. Zhang X, Zhao Y, Zhang M, Pang X, Xu J, Kang C, *et al*. Structural Changes of Gut Microbiota during Berberine-Mediated Prevention of Obesity and Insulin Resistance in High-Fat Diet-Fed Rats. *PLoS ONE*. 2012; 7 (8) :e42529 . Available from: https://doi.org/10.1371/journal.pone.0042529
16. Li S, Zhang B, Zhang N. Network target for screening synergistic drug combinations with application to traditional Chinese medicine. *BMC Systems Biology*. 2011; 5 (Suppl 1) :S10 . Available from: https://doi.org/10.1186/1752-0509-5-s1-s10
17. Wang Y, Zhang S, Li F, Zhou Y, Zhang Y, Wang Z, *et al*. Therapeutic target database 2020: enriched resource for facilitating research and early development of targeted therapeutics. *Nucleic Acids Research*. 2019; 48 (D1) :D1031–D1041 . Available from: https://doi.org/10.1093/nar/gkz981
18. Ru J, Li P, Wang J, Zhou W, Li B, Huang C, *et al*. TCMSP: a database of systems pharmacology for drug discovery from herbal medicines. *Journal of Cheminformatics*. 2014; 6 (1) :13 . Available from: https://doi.org/10.1186/1758-2946-6-13
19. Zhou Y, Zhou B, Pache L, Chang M, Khodabakhshi AH, Tanaseichuk O, *et al*. Metascape provides a biologist-oriented resource for the analysis of systems-level datasets. *Nature Communications*. 2019; 10 (1) :1523 . Available from: https://doi.org/10.1038/s41467-019-09234-6
20. Liu J, Liu J, Tong X, Peng W, Wei S, Sun T, *et al*. Network Pharmacology Prediction and Molecular Docking-Based Strategy to Discover the Potential Pharmacological Mechanism of Huai Hua San Against Ulcerative Colitis. *Drug Design, Development and Therapy*. 2021; Volume 15 :3255-3276 . Available from: https://doi.org/10.2147/dddt.s319786
21. Scannell JW, Bosley J. When Quality Beats Quantity: Decision Theory, Drug Discovery, and the Reproducibility Crisis. *PLOS ONE*. 2016; 11 (2) :e0147215 . Available from: https://doi.org/10.1371/journal.pone.0147215
22. Project of the ABIM Foundation, ACP–ASIM Foundation, European Federation of Internal Medicine. Medical Professionalism in the New Millennium: A physician Charter. *Annals of Internal Medicine*. 2002; 136 (3) :243-246 . Available from: https://doi.org/10.7326/0003-4819-136-3-200202050-00012
23. Liu J, Liu J, Tong X, Peng W, Wei S, Sun T, *et al*. Network Pharmacology Prediction and Molecular Docking-Based Strategy to Discover the Potential Pharmacological Mechanism of Huai Hua San Against Ulcerative Colitis. *Drug Design, Development and Therapy*. 2021; Volume 15 :3255-3276 . Available from: https://doi.org/10.2147/dddt.s319786
24. Seyhan AA. Lost in translation: the valley of death across preclinical and clinical divide – identification of problems and overcoming obstacles. *Translational Medicine Communications*. 2019; 4 (1) . Available from: https://doi.org/10.1186/s41231-019-0050-7