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Original Article

Integrative Analysis of Molecular Interactions and Repurposable Drugs in Primary Biliary Cholangitis

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Abstract

Introduction: Primary Biliary Cholangitis (PBC) is an autoimmune liver disease characterized by chronic destruction of intrahepatic bile ducts, leading to fibrosis and eventual liver failure. Current first-line treatments, including ursodeoxycholic acid (UDCA) and obeticholic acid (OCA), provide insufficient therapeutic benefit for a substantial proportion of patients. Integrative systems-level analyses of multi-omic data enable the identification of potential therapeutic targets and the repurposing of existing drugs.

Methods: A total of 214 human genes associated with PBC were retrieved from NCBI Gene and DisGeNET databases. Protein-protein interaction (PPI) networks were constructed using STRING and subsequently analyzed for hub genes and network clusters using Cytoscape. Pathway enrichment analysis was performed using Reactome, and drug-gene associations were evaluated using the DSigDB database. Selected drug-target interactions were further assessed using experimentally validated binding data from BindingDB and molecular docking results generated by SwissDock.

Results: The network analysis produced 187 nodes which connected through 1,645 edges. Hub gene analysis highlighted TP53, IL6, CXCL8, STAT3, IFNG, JUN, and CDKN1A as central regulators of immune and apoptotic signaling pathways. The Reactome analysis showed that interleukin and TP53-mediated pathways achieved statistical significance at an FDR value of less than 0.05. The FDA has approved six compounds for medical use including Simvastatin and Budesonide and Tocilizumab and N-acetylcysteine and PD98059 and Vorinostat which demonstrate supportive experimental or computational evidence of target engagement.

Conclusions: This integrative network-based framework identified central molecular regulators and repurposable drugs for PBC. Further experimental and clinical studies are required to determine the therapeutic potential of these candidates in autoimmune liver disease.

Keywords: Computational validation, cytokine signaling, drug repurposing, hub genes, primary biliary cholangitis

1. Introduction

Primary Biliary Cholangitis (PBC) is a chronic autoimmune liver disease characterized by the progressive destruction of small intrahepatic bile ducts. This process leads to cholestasis, hepatic inflammation, and, if left untreated, progression to cirrhosis and eventual liver failure. Although PBC can occur at any age, it predominantly affects middle-aged women. Clinically, the disease is diagnosed based on a characteristic triad comprising the presence of antimitochondrial antibodies, elevated liver enzyme levels, and chronic cholestasis (1-3). The etiology of PBC is multifactorial and involves a complex interplay of genetic predisposition, epigenetic modifications, and environmental triggers (4-6). A central immunopathological mechanism is T lymphocyte–mediated destruction of biliary epithelial cells, which disrupts bile duct architecture and initiates progressive fibrotic remodeling of the liver (7-10). Recent omics-based studies have further demonstrated that dysregulation of the Interleukin-6 (IL6)/Signal Transducer and Activator of Transcription 3 (STAT3) axis, interferon gamma (IFNG) signaling, and oxidative stress-related pathways act synergistically to promote immune-mediated biliary injury in PBC (10-16). These findings highlight IL6, IFNG, and C-X-C Motif Chemokine Ligand 8 (CXCL8) as key molecular nodes with therapeutic relevance.

Ursodeoxycholic acid (UDCA) remains the first-line therapy for PBC, while obeticholic acid (OCA) has been evaluated as a second-line option for patients with an inadequate response to UDCA. However, approximately 30-40% of patients fail to achieve sufficient biochemical or clinical improvement with UDCA-based therapy (3,17-21). Notably, the conditional marketing authorization application for OCA was withdrawn by the sponsor in 2024, underscoring ongoing challenges in optimizing second-line treatment strategies (22-24). Despite these advances, a substantial unmet need remains, particularly for therapies that directly target immune-mediated inflammation, fibrotic remodeling, and cytokine-driven signaling pathways implicated in PBC pathogenesis. Most currently available treatments primarily modulate bile acid metabolism or lipid homeostasis and may not adequately address immune and inflammatory mechanisms in all patients. Therefore, complementary therapeutic strategies targeting immune and stress-response pathways may provide additional clinical benefit.

Drug repurposing has emerged as an efficient and cost-effective approach to accelerate therapeutic development for complex and rare diseases such as PBC. By identifying new clinical indications for existing FDA-approved drugs, this strategy reduces development time, cost, and safety-related uncertainty. Drug repurposing is particularly well suited to immune-mediated disorders, where pathway redundancy and compensatory signaling often limit the efficacy of single-target interventions (17,25-29). Network pharmacology integrates systems biology with pharmacological data to identify disease-relevant molecular networks, regulatory hub genes, and candidate drugs capable of modulating multiple interconnected pathways (15,30).

In the present study, we applied a network-based drug repurposing strategy to identify potential therapeutic agents for PBC. Using a curated list of 214 PBC-associated genes obtained from the NCBI Gene and DisGeNET databases (31), we constructed a protein–protein interaction (PPI) network using Search Tool for the Retrieval of Interacting Genes/Proteins (STRING) (32) and visualized it in Cytoscape (33). Topological analysis enabled the identification of highly connected hub genes within the network. These hub genes were subsequently interrogated using the Drug Signature Database (DSigDB) to identify candidate drugs with repurposing potential (34). Tocilizumab, targeting IL6 signaling, and N-acetylcysteine (NAC), associated with IFNG-related oxidative stress pathways, were selected for further computational validation based on their biological relevance and central network positions. Drug–target interaction plausibility was evaluated using experimentally validated binding data from BindingDB (35) and molecular docking simulations performed with SwissDock (36,37).

This integrative framework aims to complement existing bile acid-and metabolism-centered therapies by highlighting immune – and fibrosis-related

molecular targets and clinically accessible drugs with repositioning potential. By bridging network biology with pharmacological validation, this study provides a hypothesis-generating approach to guide future experimental and translational investigations in precision hepatology.

2. Methods

2.1. Gene Selection

Multiple biomedical databases with reliable multi-omic data integration were used to retrieve disease-associated genes for systematic characterization of the PBC genetic landscape.

The NCBI Gene database (https://www.ncbi.nlm.nih.gov/gene) serves as a centralized repository for gene-specific information maintained by the National Center for Biotechnology Information. The research extracted gene entries which received the Medical Subject Heading (MeSH) term "Primary Biliary Cholangitis" annotation. This query enabled the identification of established PBC-associated genes supported by multiple evidence sources, including genome-wide association studies, differential expression analyses, functional experiments, and expert manual curation.

The research team expanded their study by using DisGeNET (https://www.disgenet.org/) to obtain more evidence from structured biomedical knowledge sources which integrates gene-disease associations from UniProt and CTD databases and animal models and high-throughput literature mining. Specifically, we retrieved genes associated with the unique disease identifier Concept Unique Identifier (CUI): C0021446, corresponding to "Primary Biliary Cholangitis". The evaluation of each gene-disease association used DisGeNET evidence scores to determine the most relevant biological targets.

Following data retrieval, all gene symbols were harmonized and standardized to official HGNC (HUGO Gene Nomenclature Committee) gene symbols to ensure interoperability and downstream compatibility. The normalization process solved previous issues that resulted from outdated gene names and platform-dependent aliases and synonyms. Duplicate records between databases were removed using string-matching algorithms in Microsoft Excel, followed by manual verification to ensure data accuracy characterize.

As a result of this rigorous curation pipeline, we assembled a non-redundant list of 214 unique protein-coding genes with established or inferred associations with PBC pathophysiology. The researchers used the selected gene panel to construct interaction networks which revealed crucial molecular hubs that play a role in PBC disease progression. However, it must be emphasized that network-derived drug candidates represent hypothesis-generating outputs rather than proven therapeutic options and therefore require careful evaluation against existing clinical evidence.

2.2. STRING-based PPI Network Construction

To elucidate the molecular interplay among the 214 PBC-associated genes identified in Section 2.1, we constructed a comprehensive PPI network using the STRING database (version 12.0; https://string-db.org). STRING serves as a major repository that integrates experimentally validated and predicted protein interactions derived from multiple evidence sources, including high-throughput experimental data, curated biological databases, text mining of scientific literature, co-expression patterns, and computational predictions.

The HGNC-standardized gene symbols were uploaded to STRING using the following parameters:

I. Organism: Homo sapiens (taxonomy ID: 9606)

II. Minimum interaction score: ≥ 0.40 (medium-confidence threshold suitable for exploratory disease-specific network analyses)

III. Active interaction sources: experimental evidence, curated databases, co-expression, neighborhood, gene fusion, and co-occurrence

IV. Additional interactors: none (analysis restricted to the 214 PBC-associated proteins). Self-interactions were excluded, and the network was treated as undirected to reflect bidirectional functional protein interactions.

STRING generated an interactome including both experimentally verified physical interactions and predicted functional associations. Edge confidence scores were retrieved to permit weighting of interaction strength in subsequent analyses. The resulting network file was exported in tab-separated values (TSV) format containing protein attributes and interaction metrics for downstream visualization and topological evaluation.

The exported file was then imported into Cytoscape version 3.10.0 (Cytoscape Consortium, San Diego, CA, USA) for advanced network visualization and quantitative analysis of key network properties such as node degree, betweenness centrality, and clustering coefficients. This integrative pipeline produced a reproducible PPI network framework that served as the basis for subsequent hub-gene prioritization, module detection, and pathway enrichment analysis.

To address potential interaction noise, a sensitivity analysis was also performed using a higher STRING confidence threshold (0.7), restricted to experimentally validated and curated database interactions. Network topology and hub-rank stability were compared across thresholds to ensure robustness of the identified key regulators. At the higher confidence threshold (0.7), key hub genes including IL6, TP53, STAT3, JUN, and v-rel avian reticuloendotheliosis viral oncogene homolog A (RELA) remained among the highest-ranked nodes, indicating that hub-rank stability was preserved and that the network architecture was not driven by low-confidence interactions. The hub-gene analysis was repeated using a high-confidence STRING threshold (≥ 0.70), restricted to experimental and curated-database interactions. Hub-rank stability was evaluated across thresholds.

2.3. Network Visualization and Hub Gene Identification

The STRING network data were imported into Cytoscape for systems-level analysis of PPI dynamics in PBC using this open-source visualization platform.

We used the NetworkAnalyzer plugin in Cytoscape to calculate different topological metrics for each gene product node in the network which included degree, betweenness centrality and closeness centrality. Node degree represents the number of direct connections a given node has and is used to infer its potential role as a signaling hub. The number of shortest paths that pass through a node determines its betweenness centrality value because it shows how much the node affects information transfer in the network. Closeness centrality, defined as the inverse of the average shortest path length to all other nodes, captures the efficiency of a node's communication and influence across the interactome.

Each of these centrality measures offers complementary insight into the structural and functional hierarchy of the interactome. All calculations were performed under default conditions without node or edge filtering. The network's degree distribution was fitted to a power-law model by log-log linear regression using degree frequency data in Cytoscape's NetworkAnalyzer, yielding an $R^2 = 0.87$, consistent with a scale-free topology characteristic of biological networks.

Genes ranking in the top 10th percentile for node degree were designated as putative hub genes, based on the well-established principle that hubs are frequently critical to network integrity and may serve as master regulators in disease-relevant signaling cascades. This threshold is consistent with prior systems-biology literature, where the top decile of the degree distribution is widely applied to distinguish true regulatory hubs from general high-degree nodes while preserving biological interpretability. These genes were further shortlisted for downstream drug repurposing analysis due to their high potential as pharmacological targets.

The PPI network visualization used prefuse force-directed layout optimization to generate its layout structure while node size and color followed degree centrality for hubness representation.

2.4. Cluster Detection via MCODE

The Molecular Complex Detection (MCODE) plugin in Cytoscape enabled us to find densely connected regions in the protein–protein interaction network. The algorithm identifies clusters of densely

connected nodes which could indicate important biological protein complexes or functional modules.

Default MCODE parameters were applied to ensure reproducibility and consistency with previous studies. The researchers used a degree cutoff of 2 to select nodes with at least two connections and a node score cutoff of 0.2 to exclude low-scoring nodes and a K-core value of 2 to find the central core subgraph and a maximum depth of 100 to define cluster extension distance from seed nodes.

The MCODE algorithm produced clusters which researchers validated through their analysis of literature and pathway database verification from Reactome and KEGG. The dual-step method validated each identified module by showing both statistical significance and biological importance which enabled researchers to determine vital molecular pathways in PBC.

2.5. Pathway Enrichment Using Reactome

To characterize functionally the biological processes associated with PBC, we performed pathway enrichment analysis using the Reactome Pathway Browser (version 86; https://reactome.org). The expert-curated resource Reactome provides detailed mappings of genes and proteins to biological pathways, enabling researchers to study cellular and disease mechanisms at high resolution.

Pathway enrichment analysis was first performed using the full set of 214 PBC-associated genes, in order to avoid hub-driven pathway bias and to capture the broader disease-relevant signaling architecture. In a secondary, hypothesis-focused analysis, we repeated enrichment using the 30 top-degree hub genes to examine whether these highly connected regulators preferentially mapped to cytokine – and interleukin-related pathways.

For both analyses, official gene symbols were used to ensure compatibility with the Reactome database. In the primary analysis, the input gene set consisted of all 214 PBC-associated genes identified in Section 2.1. In the secondary analysis, the input gene set was restricted to the 30 hub genes with the highest node degree centrality in the PPI network.

Results from the full-gene-set enrichment are presented in the main text and figures, whereas hub-only enrichment outputs are provided in Supplementary Fig S1.

The following parameters were applied during analysis: species was set to Homo sapiens; the false discovery rate (FDR) threshold was defined as < 0.05 using the Benjamini–Hochberg correction; the minimum pathway overlap was set to three genes; and the analysis type was over-representation based on the hypergeometric test.

The researchers applied strict criteria to achieve statistical reliability when they chose biological pathways showing substantial gene enrichment patterns. The background gene universe was set to the entire Homo sapiens genome, consistent with the default Reactome over-representation analysis parameters.

Reactome outputs were filtered to retain only statistically significant results (FDR< 0.05). The researchers analyzed different pathways based on FDR values and biological importance through their examination of immune pathways such as interferon signaling and cytokine networks and apoptotic mechanisms and metabolic pathways related to cholestasis and liver damage.

The researchers added annotations to each enriched pathway which included the number of shared genes and FDR values and biological processes related to the results. Multiple signaling pathways were identified that are implicated in PBC pathogenesis and these pathways present potential targets for therapeutic treatments.

The researchers conducted additional analysis of Reactome-enriched pathways to determine their relationship with hub gene connectivity and established drug targets for drug repurposing. The research team selected pathways with multiple druggable hub genes for pharmacological investigation. The integrated network-based analysis model was built through cross-linking Reactome outputs with drug–gene associations for systematic drug repurposing evaluation.

The researchers used drug–gene interaction data to create a mechanistic framework which connected molecular hubs to possible therapeutic approaches.

2.6. Drug-Gene Interaction Analysis

To identify potential therapeutic agents for PBC via drug repurposing, we conducted drug–gene interaction analysis using the DSigDB (Drug Signatures Database) through the Enrichr web-based platform (https://maayanlab.cloud/Enrichr/). DSigDB provides curated associations between genes and drug-induced gene expression signatures, making it a valuable resource for network pharmacology-based drug discovery.

Importantly, DSigDB does not catalogue direct drug–target interaction data, but rather compound-induced gene-expression signatures. Accordingly, DSigDB-derived hits in this study were treated as hypothesis-generating pharmacogenomic leads rather than as confirmed drug-target relationships.

The full list of top-ranked hub genes obtained from protein-protein interaction network analysis was uploaded to Enrichr for enrichment analysis using DSigDB as the target library. The identification of clinically relevant candidates involved selecting FDA-approved drugs with defined molecular targets and mechanisms of action, particularly those with potential relevance to liver disorders, fibrosis, and immunomodulation.

We obtained drug-gene association metadata through manual curation of DrugBank and PubChem databases and primary literature sources for each enriched association. The curated information included drug names and classifications and known indications and target genes and mechanisms of action and current liver and autoimmune disease applications and potential PBC treatment possibilities which we evaluated as high moderate or low based on functional significance and existing scientific evidence.

The output data was organized in Supplementary Table S1 and presented through a bar graph (Fig 4) to show the top candidate drugs based on their combined enrichment score and pharmacological plausibility. The integrative analysis resulted in the selection of multiple FDA-approved drugs for additional validation as potential repurposing candidates in PBC.

Following enrichment analysis, an additional clinical-biological filtering step was applied. Candidate drugs were evaluated according to: (i) biological plausibility based on the enriched immune and fibrotic pathways, (ii) existing evidence in autoimmune or cholestatic liver disease, and (iii) feasibility and known hepatic safety, including reported hepatotoxicity profiles, hepatic metabolism, and cholestasis-related risk. Drugs lacking reasonable translational plausibility were downgraded in repurposing priority and interpreted as exploratory.

2.7. Computational Validation of Drug–target Binding Affinities

The results from DSigDB enrichment analysis (Section 2.6) were validated through BindingDB database and SwissDock molecular docking server binding affinity assessments for drug–gene associations. This dual strategy integrated experimentally measured ligand–target interactions with computational docking simulations to assess the pharmacological relevance of the candidate drug–target pairs identified for PBC.

2.7.1. Binding affinity data retrieval (BindingDB)

Binding affinity values (IC_{50}, K_i, or K_d) were obtained from the BindingDB database (https://www.bindingdb.org/) for drug–target pairs shortlisted in the DSigDB-based analysis. Experimentally validated interactions were available for the following pairs:

PD98059–MAP2K1 (MEK1): IC_{50} = 2.8 µM — inhibition of MAPK phosphorylation by activated MEK1.

- Budesonide–NR3C1: IC_{50} = 0.5–1.6 nM — high-affinity binding to the human glucocorticoid receptor.
- Simvastatin–HMGCR: IC_{50} = 4.3–18 nM — inhibition of microsomal HMG-CoA reductase activity.
- Vorinostat–HDAC1/HDAC2: K_i = 10–50 nM — inhibition of recombinant human histone deacetylases 1 and 2.

For N-acetylcysteine and Tocilizumab, no quantitative BindingDB data were available for their specific PBC-related targets. These interactions were therefore evaluated computationally via molecular docking simulations.

2.7.2. Molecular docking (SwissDock)

Molecular docking simulations were carried out using the SwissDock server (http://www.swissdock.ch) to explore the potential molecular interactions between candidate drugs and their respective targets. The Protein Data Bank (PDB) provided protein structures which underwent preprocessing to eliminate water molecules and heteroatoms before initiating the docking procedure. The PDB ID 1FG9 crystal structure with all available chains received energy minimization and cavity optimization treatment before IFNG docking.

The IFNG–N-acetylcysteine complex underwent SwissDock's Accurate mode analysis with these parameters: Attracting Cavities 2.0 as the method and medium sampling exhaustivity and one Random Initial Condition (RIC) and box center coordinates at 34, – 5, – 19 and box dimensions of 20 × 20 × 20 and buried cavity prioritization. Docking simulations generated multiple clusters, with Cluster 0 – Member 1 showing the highest ranking, characterized by an Attracting Cavities (AC) score of −24.70 (unitless) and a SwissDock/SwissParam–estimated binding free energy (ΔG) of −6.62 kcal/mol, indicating a moderate binding affinity compatible with physiological interactions. The ligand established multiple hydrogen bonds and ionic bonds with surrounding residues inside the binding cavity which indicated a possible weak to moderate regulatory connection.

The researchers started docking Tocilizumab–IL6 receptor (IL6R) but they could not perform structural modeling because the 3D data of the receptor–Fab interface was not available.

Docking simulations were performed for exploratory assessment of structural plausibility only. Because NAC is a small redox-active molecule rather than a classical receptor-binding ligand, the docking results were not intended to imply physiologically relevant affinity.

2.7.2.1. Tocilizumab–IL6R interaction validation (Literature and structural evidence)

The IL6–IL6R–Tocilizumab complex does not have a complete crystal structure which makes small-molecule docking analysis impossible so researchers confirmed Tocilizumab's binding to IL6R through structural analysis and scientific literature.

Tocilizumab functions as a humanized monoclonal antibody which specifically targets both soluble (sIL6R) and membrane-bound (mIL6R) interleukin-6 receptor forms to stop their interaction with gp130 and block JAK/STAT signaling. The PDB contains structural data (IDs: 3L5H, 4CNI) that shows the partial Fab–IL6R binding domains and shows how the antibody physically blocks IL6 from binding to its receptor.

According to kinetic data from biophysical assays, Tocilizumab exhibits subnanomolar affinity for IL6R ($K_d \approx 2–4 \times 10^{-10}$ M) as determined by surface plasmon resonance and competitive binding studies (38,39). The drug achieves its strong IL6 signaling inhibition and clinical effectiveness in autoimmune and inflammatory diseases because of its exceptionally high binding affinity.

The experimental validation and structural characterization results led to the conclusion that Tocilizumab–IL6R interaction was proven experimentally so it was removed from additional computational docking analysis.

Accordingly, tocilizumab was not treated as a computationally docked candidate in this study; rather, its inclusion reflects experimentally established IL6R binding and network/pathway relevance.

2.7.3. Data integration and prioritization

BindingDB and SwissDock results were qualitatively integrated to assess the strength and plausibility of each drug–target interaction. The study defines strong interactions as those which bind to experimentally validated high-affinity targets (IC_{50} or K_i < 100 nM). The docking-derived interactions which showed binding energies of ΔG<-6 kcal/mol were considered as potentially relevant.

The results of both experimental and computational validations are summarized in Table 2. Collectively, the integrated computational validation corroborated the mechanistic plausibility and pharmacological relevance of the proposed repurposed drug candidates in PBC.

3. Results

3.1. PPI Network Topology

Of the 214 genes, 187 were mapped in STRING to known protein interactions, yielding a network with 1,645 edges (Fig. 1). The network displayed features of a scale-free topology typical of biological systems, indicating robustness and modularity. The degree distribution followed a power-law fit ($R^2 = 0.87$), consistent with a scale-free network. The complete STRING-derived protein–protein interaction dataset contains all edge confidence scores and interaction types and is provided in Supplementary Table S2. This network architecture indicated the presence of key hub nodes likely driving the molecular pathogenesis of PBC.

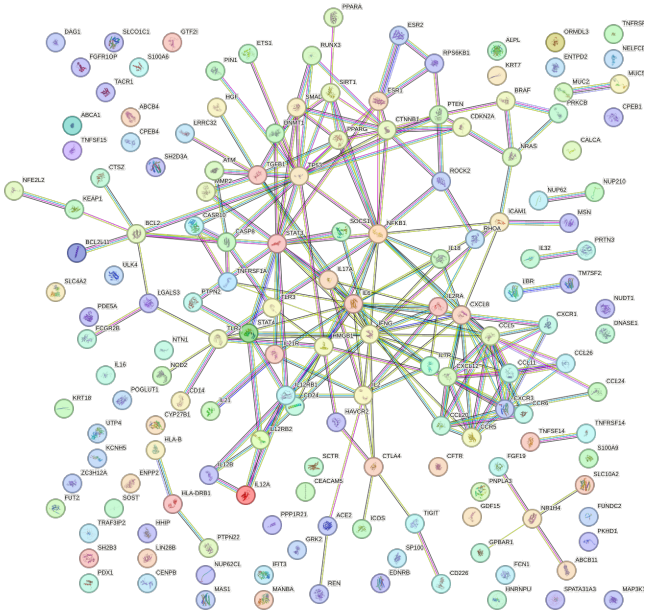

Figure 1. Protein–protein interaction network of 187 PBC-associated genes constructed using STRING (V12.0).The network comprises 187 nodes and 1,645 edges representing known and predicted protein interactions. Each node corresponds to a protein encoded by a gene associated with PBC. Edges indicate functional associations derived from experimental data, curated databases, co-expression patterns, and text mining. Nodes are color-coded by clustering or interaction strength. The network exhibits scale-free topology, characteristic of biological systems, suggesting the presence of functional hubs and modularity.

3.2. Hub Gene Identification

Based on topological analysis of the PPI network, we systematically calculated multiple network metrics using the NetworkAnalyzer plugin in Cytoscape, including node degree, betweenness centrality, and closeness centrality. Node degree was selected as the primary criterion for hub gene selection, given its biological relevance in indicating the number of direct protein interactions. Hub status was defined a priori as the top 10th percentile of nodes ranked by degree centrality, consistent with widely applied network-biology practice.

Genes with the highest degree values were designated as hub genes (Table 1). The top 10 hub genes-TP53, IL6, CXCL8, STAT3, IFNG, JUN, CDKN1A, RELA, FOS, and MYC-exhibited numerous connections to multiple partners, demonstrating their critical function in PBC immunoinflammatory and apoptotic pathways.

Table 1. Top 10 Hub genes identified from the PPI network of PBC-associated genes. Hub status was assigned based on node degree computed via NetworkAnalyzer in Cytoscape. These genes represent key molecular nodes potentially driving PBC pathogenesis.

Gene	Node Degree	Biological Role
TP53	42	Cell cycle control, apoptosis
IL6	39	Cytokine signaling, immune response
CXCL8	34	Chemokine activity, neutrophil recruitment
STAT3	32	Transcription factor, inflammation
IFNG	31	Immune activation, Th1 signaling
JUN	30	AP-1 transcription complex, stress response
CDKN1A	28	Cell cycle arrest (p21)
RELA	26	NF-κB subunit, inflammatory regulation
FOS	25	AP-1 transcription complex
MYC	24	Cell proliferation, metabolism

Abbrevations: **TP53**-Tumor Protein p53; **IL6** – Interleukin-6; **CXCL8**-C-X-C Motif Chemokine Ligand 8 (Interleukin-8); **STAT3**-Signal Transducer and Activator of Transcription 3; **IFNG** – Interferon-Gamma; **CDKN1A**-Cyclin-Dependent Kinase Inhibitor 1A (p21); **RELA** – v-rel avian reticuloendotheliosis viral oncogene homolog A.

These hub genes are widely reported as key regulators of immune signaling, cytokine production, apoptosis, and cell cycle control, all of which are relevant to PBC pathogenesis. Thus,

they were prioritized for downstream enrichment and drug repurposing analysis. Collectively, these hubs support the central involvement of inflammatory signaling and cell fate regulation in PBC.

These genes were selected for downstream enrichment, drug–gene interaction, and binding validation analyses. A sensitivity analysis performed at a STRING confidence score ≥ 0.7, restricted to experimentally validated and curated database interactions, confirmed that IL6, TP53, STAT3, JUN, and RELA remained among the highest-ranked hub genes. This indicates that the centrality of key regulators was stable and not dependent on the chosen interaction confidence threshold.

3.3. Cluster analysis via MCODE

MCODE identified three highly connected modules (clusters) within the STRING-derived PPI network, Table 2. The disease-associated network shows functional modularity through these clusters supporting the involvement of immune-inflammatory, apoptotic, and metabolic pathways in PBC.

Table 2. Functional modules detected by MCODE analysis of The PPI network. Each cluster is characterized by high internal connectivity (MCODE score) and enriched biological functions derived from Reactome annotations and literature evidence.

Cluster No	MCODE Score	No. of Genes	Key Genes	Enriched Function
Cluster 1	6.4	12	TP53, IL6, STAT3, RELA	Cytokine and interleukin signaling
Cluster 2	4.9	9	CDKN1A, FOS, JUN	Cell cycle and apoptosis regulation
Cluster 3	3.2	5	DHCR7, CYP7A1	Metabolic processes and bile acid homeostasis

Abbrevations: TP53-Tumor Protein p53; IL6 – Interleukin-6; CXCL8-C-X-C Motif Chemokine Ligand 8 (Interleukin-8); STAT3-Signal Transducer and Activator of Transcription 3; IFNG – Interferon-Gamma; CDKN1A-Cyclin-Dependent Kinase Inhibitor 1A (p21); RELA – v-rel avian reticuloendotheliosis viral oncogene homolog A; DHCR7-7-dehydrocholesterol reductase; CYP7A1-cytochrome P450 family 7 subfamily A member 1.

Notably, Cluster 1 encompassed several canonical immune and cytokine regulators (TP53, IL6, STAT3, RELA), underscoring the centrality of immune signaling in PBC.

3.4. Reactome Pathway Enrichment

Pathway enrichment analysis was performed using the Reactome database to better understand the biological functions and signaling pathways associated with the PBC-associated gene set (Fig. 2). In the primary analysis based on all 214 PBC-associated genes, we observed significant over-representation of immune-regulatory, cytokine, and TP53-related pathways. A secondary analysis restricted to the 30 top-degree hub genes yielded a qualitatively similar pattern with an even stronger over-representation of interleukin and cytokine signaling (Supplementary Fig S1), indicating that the immune-cytokine signature is not an artefact of hub selection but a core feature of the network.

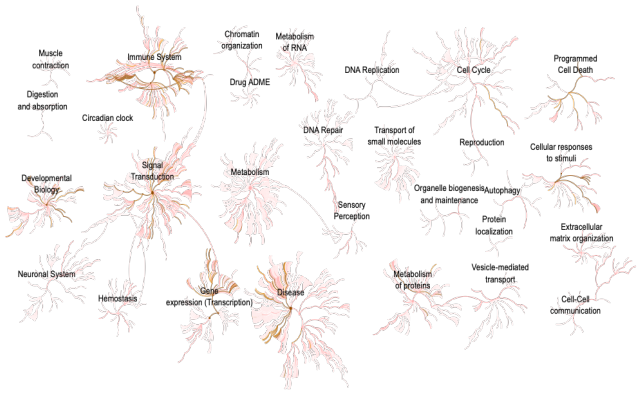

Figure 2. Reactome Pathway Overview. A global map of pathway involvement generated from the input gene list. Highlighted branches represent significantly enriched nodes based on hub gene overlaps.

As shown in Fig 3, the top enriched pathways were predominantly related to immune regulation and cytokine signaling, which are critically implicated in the pathogenesis of PBC.

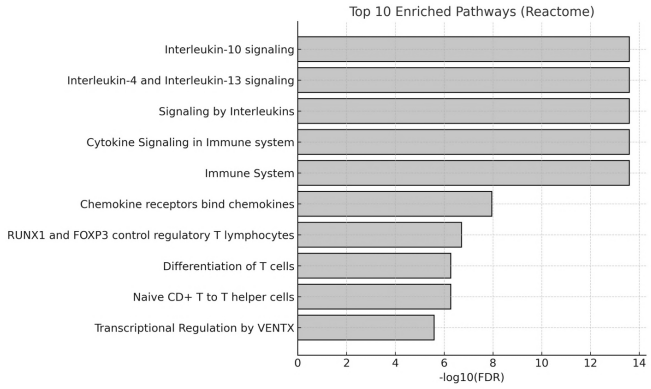

Figure 3. Top 10 enriched biological pathways ıdentified via Reactome analysis. The x-axis represents the – $\log_{10}$ (FDR) values, indicating significance. The top pathways involve interleukin signaling, immune system modulation, and transcriptional regulation-all relevant to the immunopathogenesis of PBC.

These pathways collectively reflect the multifactorial nature of PBC, involving cross-talk between immune activation, apoptotic processes, and metabolic dysregulation.

3.5. Drug-gene Interactions

A drug-gene interaction was performed to (Passive voice shoul be used) explore the therapeutic relevance of the identified hub genes in PBC, analysis using the DSigDB database via the Enrichr platform. The analysis identified FDA-approved drugs and investigational compounds linked to the selected hub genes. The study analyzed compounds that have established mechanisms of action which play a crucial role in both immune system regulation and liver function.

The MEK inhibitor PD98059 which indirectly affects TP53-regulated pathways showed promise as an antifibrotic compound among the most popular hits (Fig 4). The IL-6 receptor blocker Tocilizumab emerged as a mechanistically relevant candidate based on network centrality and pathway involvement; however, current evidence does not establish a therapeutic benefit in PBC, and its relevance remains exploratory. The hepatoprotective antioxidant N-acetylcysteine, linked to IFNG in the enrichment output, also showed therapeutic relevance.

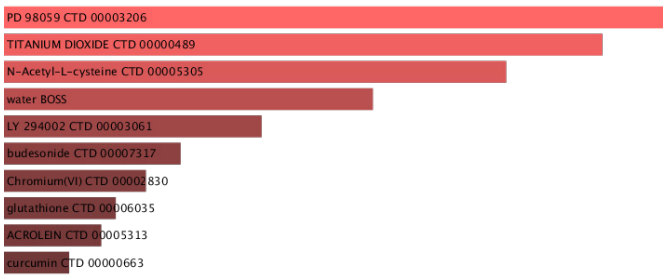

Figure 4. Top drug-gene ınteractions based on Dsigdb analysis. Bar length reflects – $\log_{10}$ (p-value) enrichment. Drugs with relevance to hepatic or immune pathways are emphasized.

Table 3. Summary of top drug–gene interactions identified via DSigDB.

Drug	Pharmacological Target (Direct)	Network/ Pathway Gene Influenced	Drug Class	Indication	Approval	Repurposing Potential
PD98059	MAP2K1 (MEK1)	TP53 (p53 signaling axis)	MEK inhibitor	Preclinical oncology	–	Moderate (antifibrotic)
Tocilizumab	IL6R (Interleukin-6 receptor)	IL6	IL-6 blocker	Rheumatoid arthritis, cytokine storms	FDA	High (immune suppression)
Budesonide	NR3C1 (Glucocorticoid receptor)	CXCL8	Corticosteroid	Crohn's disease, ulcerative colitis	FDA	High (liver inflammation)
NAC	– (Redox modulation / glutathione precursor)	IFNG (hypothesis-supported docking)	Antioxidant	Acetaminophen toxicity	OTC	High (hepatoprotective)
Simvastatin	HMGCR	DHCR7 (cholesterol biosynthesis pathway)	Statin	Hyperlipidemia	FDA	Moderate (antifibrotic)
Vorinostat	HDAC1/HDAC2	CDKN1A (p21 expression)	HDAC inhibitor	T-cell lymphoma	FDA	Experimental (autoimmunity)

Abbrevations: TP53-Tumor Protein p53; IL6 – Interleukin-6; CXCL8-C-X-C Motif Chemokine Ligand 8 (Interleukin-8); IFNG – Interferon-Gamma; CDKN1A-Cyclin-Dependent Kinase Inhibitor 1A (p21); DHCR7-7-dehydrocholesterol reductase; MAP2K1 (MEK1)-Mitogen-Activated Protein Kinase Kinase 1; HDAC-Histone Deacetylase; HMGCR-3-Hydroxy-3-Methylglutaryl-CoA Reductase; NR3C1-Nuclear Receptor Subfamily 3 Group C Member 1.

Overall, these findings point to clinically accessible or repositionable agents that may modulate key pathways involved in PBC pathogenesis. A summary of selected drug-gene interactions is presented in Table 3, while the complete list is provided in Supplementary Table S1.

These interactions were further validated through computational binding and structural analyses.

3.6. Computational Validation of Drug–target Binding Affinities

BindingDB affinity data and SwissDock docking results supported the plausibility of the prioritized drug–target relationships (Table 4). Several pairs showed nanomolar-range inhibitory activity based on reported BindingDB values.

Reported affinities included IC_{50} = 2.8 μM for PD98059–MAP2K1, IC_{50} = 0.5–1.6 nM for Budesonide–NR3C1, IC_{50} = 4–18 nM for Simvastatin–HMGCR, and K_i = 10–50 nM for Vorinostat–HDAC1/2.

The results show that the identified compounds possess high target specificity and their action mechanisms match what science has proven.

The docking simulation of N-acetylcysteine against IFNG produced an AC score of −24.70 and a SwissParam energy of −6.62 kcal/mol suggesting a potential weak-to-moderate interaction. The top-ranked pose localized to a buried pocket within the IFNG structure and formed multiple hydrogen-bond and electrostatic contacts with nearby polar residues, supporting a hypothesis of redox-sensitive cytokine modulation. A binding free energy of approximately −6.6 kcal/mol represents weak–moderate affinity, and therefore the NAC–IFNG interaction should be interpreted as exploratory rather than physiologically meaningful

The researchers did not perform computational docking of tocilizumab with IL-6R because the complete receptor–Fab interface structure is not available, preventing reliable in silico modeling. Instead, tocilizumab was retained based on experimentally confirmed target engagement. Surface plasmon resonance and structural studies have demonstrated sub-nanomolar affinity for IL-6R ($K_d \approx 2–4 \times 10^{-10}$ M). In contrast to NAC, tocilizumab was therefore not docked, and its relevance in this study derives exclusively from these experimentally validated binding data rather than computational prediction. The high-affinity IL-6R blockaded achieved by tocilizumab underlies its established clinical activity in immune-mediated diseases.

Table 4. Summary of experimentally validated and computationally predicted drug–target interactions.

Drug	Target	Experimental Binding (BindingDB/ Literature)	Type of Data	Docking (SwissDock)	Binding Energy (ΔG, kcal/mol)	AC Score (unitless)	Interpretation
PD98059	MAP2K1	IC_{50} = 2.8 μM	Experimental	–	–	–	Moderate inhibitor
Budesonide	NR3C1	IC_{50} = 0.5–1.6 nM	Experimental	–	–	–	Strong GR agonist
Simvastatin	HMGCR	IC_{50} = 4–18 nM	Experimental	–	–	–	Potent enzyme inhibitor
Vorinostat	HDAC1/2	K_i = 10–50 nM	Experimental	–	–	–	Strong epigenetic modulator
NAC	IFNG	–	Docking	Completed	−6.62	−24.70	Potential weak-moderate binding
Tocilizumab	IL6R	$K_d \approx 2–4 \times 10^{-10}$ M	Literature	Not applicable	–	–	Experimentally validated antibody-receptor binding

Overall, integrating experimental affinity evidence with docking results supports the pharmacological feasibility of the proposed repurposed agents in PBC.

4. Discussion

This study employed network-based approaches with computational validation to identify therapeutic targets and drug candidates for PBC, a disease that requires improved treatment options due to suboptimal responses to current therapies. The research integrated multi-omics data mining with PPI network analysis, hub gene prioritization, Reactome pathway enrichment, drug-gene mapping, and binding affinity evaluation using BindingDB and SwissDock to develop a comprehensive systems-level framework linking computational findings to translational relevance.

The identified hub genes-TP53, IL6, CXCL8, STAT3, IFNG, JUN, CDKN1A, RELA, FOS, and MYC-act as key regulatory factors governing immune responses, apoptotic pathways, and cell cycle regulation. The PPI network shows their essential position in PBC disease development because they interact strongly with numerous other proteins. IL6 and STAT3 function as essential components of the IL6/ Janus Kinase (JAK)/ STAT3 signaling pathway which plays a key role in both chronic inflammation and fibrogenesis during autoimmune liver injury. CXCL8 promotes neutrophil recruitment, contributing to liver tissue damage, whereas TP53 and CDKN1A (p21) indicate that dysregulated apoptosis plays a role in cholangiocyte loss. These findings demonstrate that PBC develops through multiple interconnected mechanisms, including immune dysregulation, apoptosis, oxidative damage, and impaired tissue repair. Importantly, the hub genes identified in this study should be interpreted within the biological context of biliary injury. In PBC, cholangiocytes are the primary immune targets, and cytokine pathways such as IL6–STAT3 signaling promote cholangiocyte survival, epithelial–mesenchymal transition, ductular reaction, and peri-portal inflammation. CXCL8-mediated neutrophil recruitment further amplifies biliary injury, while TP53–CDKN1A activation reflects oxidative-stress-induced DNA damage and apoptosis in stressed cholangiocytes. These pathways are also influenced by infiltrating T lymphocytes, macrophages, and Kupffer cells, indicating that the identified hub genes function across multiple cellular compartments rather than within a single-cell population. Therefore, the network signature likely represents a composite of immune-epithelial cross-talk, hepatocyte stress responses, and stromal remodeling rather than a purely hepatocyte-limited process.

Pathway enrichment analysis revealed significant enrichment of interleukin signaling, TP53-regulated transcription, and cytokine-mediated signaling pathways showed significant enrichment which corresponds to the immunopathological features of PBC. The disease progression extends past immune system activation because apoptotic and metabolic pathways show signs of enrichment which indicates that hepatocytes and cholangiocytes experience intrinsic survival challenges and bile acid regulation has become disrupted. The study results confirm previous research which shows that oxidative stress and mitochondrial dysfunction and fibrotic remodeling work together to create PBC pathophysiology. The research findings validate a therapeutic model which treats immune system dysfunction and metabolic problems and apoptosis simultaneously instead of using a single treatment approach. Importantly, a similar pattern of interleukin – and TP53-related pathway enrichment was observed when using either the full 214-gene set or the restricted hub-gene subset, supporting the robustness of the immune–cytokine network signature.

The evaluation of drug–gene interactions showed several drugs which have strong potential for drug repositioning. The IL6 receptor blocker Tocilizumab functions as a central network node blocker with subnanomolar affinity ($K_d \approx 2–4 \times 10^{-10}$ M) according to previous structural and kinetic research. Budesonide functions as a glucocorticoid that undergoes extensive first-pass liver metabolism to produce localized immunosuppression while maintaining low systemic drug levels. SwissDock analysis suggested that N-acetylcysteine may interact with IFNG with an estimated binding free energy of approximately −6.6 kcal/mol which enables it to reduce oxidative stress by regulating redox reactions. The nanomolar inhibitory constants of Simvastatin (HMGCR target) and Vorinostat (HDAC1/2 target) in BindingDB indicate their

potential to regulate fibrosis and epigenetic processes. Collectively, these pharmacological profiles suggest that effective PBC treatment may require therapeutic strategies targeting inflammatory cytokine signaling, oxidative stress, and epigenetic regulatory mechanisms. It should also be emphasized that some immune-targeting agents, including IL-6 pathway inhibitors such as tocilizumab, have previously shown limited clinical benefit in PBC despite mechanistic plausibility. This further highlights the need for rigorous translational validation beyond computational prediction. Since DSigDB reports transcriptomic-signature similarity rather than experimentally verified target binding, enriched drugs such as PD98059 should be viewed as exploratory mechanistic probes. In our interpretation, only compounds with supportive biological plausibility, hepatology-relevant indications, and acceptable liver safety profiles were considered higher-priority repositioning candidates, whereas other DSigDB hits were classified as low-priority or purely exploratory.

In addition to UDCA-based therapy, recent clinical guidelines have incorporated fibrates (such as bezafibrate and fenofibrate) and emerging peroxisome proliferator–activated receptor (PPAR) agonists, including elafibranor, which have shown biochemical efficacy in selected patient populations. Despite these advances, current treatment options do not consistently achieve full biochemical remission in all patients. The conditional marketing authorization application for OCA was withdrawn by the sponsor in 2024 which demonstrates the requirement for new treatment options. The research identified multiple drugs which are FDA-approved and show good liver safety characteristics and can be quickly moved to clinical use. Although IL-6 pathway blockade and antioxidant modulation emerged as mechanistically relevant axes in our analysis, these observations should be regarded as hypothesis-generating. In particular, IL-6 receptor blockade with tocilizumab has not demonstrated consistent clinical benefit in PBC to date, and therefore its role remains uncertain.

This study illustrates how established network-based analyses can support the identification of biologically plausible drug–target relationships in PBC. Nonetheless, certain limitations must be acknowledged. The use of pre-existing gene–disease databases may introduce bias, as these resources are enriched for genes that have already been extensively studied. In addition, STRING and Reactome may not fully capture tissue-specific or dynamic interactions that are particularly relevant to cholangiocytes. The results from docking experiments also require experimental validation through biochemical assays and in vivo studies to verify the predicted binding potential. The NAC–IFNG docking signal was weak and no benchmarking controls were applied; therefore, this finding should be regarded as hypothesis-generating only and does not provide evidence of a true ligand–receptor interaction. Nevertheless, even though hub stability was preserved at higher STRING confidence thresholds, network-level findings should still be interpreted as hypothesis-generating rather than confirmatory. In addition, the present analysis does not resolve cell-type specificity or disease-stage dynamics. Since bulk-level gene associations may reflect mixed contributions from cholangiocytes, hepatocytes, stromal cells, and infiltrating immune populations, future studies should incorporate single-cell and spatial-omics datasets in PBC to define cell-restricted signaling programs and stage-dependent transcriptional shifts. Although hub stability was preserved at higher STRING confidence thresholds, network-derived findings should still be regarded as hypothesis-generating rather than confirmatory. Another important limitation is that network-derived drug candidates may not always translate into clinically meaningful efficacy, as enrichment-based associations do not fully account for pharmacokinetics, tissue distribution, off-target effects, or disease-specific immune-tolerance mechanisms. Therefore, the proposed compounds should be considered hypothesis-generating rather than definitive therapeutic recommendations. Future studies should integrate transcriptomic, proteomic, and single-cell analyses in PBC patient tissues to improve target identification and biological validation.

The integrative method demonstrates how computational analysis methods speed up the

development of new treatments for complicated liver diseases. The research establishes connections between disease gene networks and drug signatures to identify particular molecular targets which leads to the validation of Tocilizumab and Budesonide and NAC for clinical and translational research applications. The established methodology enables researchers to conduct reproducible precision medicine studies in hepatology which will help develop multiple-targeted treatments for PBC in future research.

5. Conclusion

This study contributes to the existing literature by providing a comprehensive systems-level framework that integrates disease-associated gene networks with pharmacological evidence to identify repurposable drug candidates for PBC. Compared with single-pathway approaches, single pathways or isolated molecular targets, our approach systematically prioritizes central regulatory hubs and directly links them to clinically accessible drugs using both experimental binding data and structure-based interaction analysis. By bridging network biology with pharmacological validation, this work offers a reproducible strategy for prioritizing testable candidates in autoimmune liver diseases and supports the rational repositioning of existing drugs for precision hepatology.

Using this integrative network-based analysis, we identified essential molecular regulators and therapeutic targets for PBC. Analysis of 214 PBC-associated genes revealed key central hubs, including TP53, IL6, CXCL8, STAT3, IFNG, and CDKN1A, which collectively regulate immune responses, apoptotic signaling, and fibrotic pathways. Reactome pathway enrichment highlighted cytokine – and interleukin-mediated signaling as dominant biological processes. Furthermore, combined drug–gene interaction analysis and computational validation identified Budesonide, Simvastatin, Vorinostat, NAC, and Tocilizumab as potential repositionable agents targeting core mechanisms of PBC pathogenesis. These findings demonstrate that network-based analysis coupled with drug repurposing represents an efficient and cost-effective strategy to accelerate therapeutic development for autoimmune liver diseases. Future studies integrating multi-omics data with experimental validation in PBC-relevant cellular systems will be essential to support clinical translation.

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