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Identification of Therapeutic Inhibitors for Polycystic Kidney Disease Using Gene Networks and Toxicological Modeling

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Abstract

Polycystic Kidney Disease (PKD) is a advancing renal disease characterized by multiple fluid containing cysts, eventually impairing kidney structure and function. This analytics presents an analysis of disease-associated genes, potential therapeutic inhibitors, toxic, non toxic, and gene compound interaction networks. Two signature genes, *PKHD1* and *PKD1*, were identified as key genetic drivers in PKD pathogenesis. A total of twenty pharmacological inhibitors were selected for controlling this disease. Network and gene overlap analyses revealed critical regulatory nodes, including *EGFR*, *AKT1*, *JAK2*, *CTNNB1* shows promising molecular targets for drug repurposing strategies in PKD. To find inhibitors that are used to control the disease progression and generate a network that show disease related genes, compound interaction. The final merged network indicate the key regulatory nodes and potential therapeutic compounds for PKD.

Keywords: *Toxicology modeling, kidney diseases, Gene networks*

1 Introduction

Polycystic kidney disease (PKD) is a genetic disorder that causes many fluid-filled cysts to grow in your kidneys **Bais**. Unlike the usually harmless simple kidney cysts that can form in the kidneys later in life, PKD cysts can change the shape of your kidneys, including making them much larger **Ibel**. Among the genetically heterogeneous causes of PKD, mutations in *PKD1*

and *PKHD1* exhibit the strongest clinical and molecular association with disease progression **Gitomer**.

Advancement in computational biology tell us systematic identification of disease genes, therapeutic inhibitors, Toxicity of inhibitors and molecular interaction networks. This study integrates gene identification, inhibitor screening, toxicity assessment, and network-based analysis to support rational therapeutic development for PKD.

2 Methodology

2.1 Active Compound and Target Screening

To identify potential therapeutic inhibitors for Polycystic Kidney Disease (PKD), screening strategy was applied. All inhibitors shown to have relevance in renal diseases, fibrosis, inflammation, oxidative stress, and cystogenesis were collected through an extensive search of the scientific literature and biochemical databases. These include PubChem, Swiss ADME, pkcsm tool, TEST, Literature mining database.

Selection criteria included:

1. **Drug-likeness:** Lipinski's Rule of Five was applied like MW, HBD, HBA, logP using canonical SMILES.
2. **Pharmacokinetics:** ADMET properties were evaluated through Swiss ADME, focusing on high gastrointestinal absorption, BBB permeablity, and low predicted toxicity.
3. **Oral Bioavailability and Drug-Likeness:** Compounds with OB $\geq 30\%$ and DL ≥ 0.18 were retained, as reported by TCMSP.
4. **Literature Validation:** Preference was given to compounds cited across multiple databases or peer-reviewed articles to ensure reliability.
5. **Structural Diversity:** Compounds with different structures were prioritized to maximize interaction across multiple targets.

2.2 Target Screening

To identify most effective molecular targets, Venn diagrams were constructed to determine the difference between PKD-associated genes and predicted targets of the screened active compounds. These overlapping genes were considered potential therapeutic targets. Protein–protein interaction (PPI) analysis was performed using the STRING database with a minimum confidence score of 0.4. The result of protein protein interaction was visualized using

Cytoscape (version 10), allowing the determination of highly linked proteins and providing insight into the molecular interactions critical to PKD pathogenesis.

2.3 Functional Enrichment Analysis

Functional enrichment analysis of the overlapping targets was determined using the shiny go 0.85. Gene Ontology (GO) enrichment analysis was performed across three categories: Biological Process (BP), Molecular Function (MF), and Cellular Component (CC). In addition, Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway was used to identify specific genes or molecular pathways involved in disease progression.

2.4 Network Pharmacology Analysis

To elucidate the molecular mechanisms of active compounds against PKD, a compound–target interaction network was constructed using Cytoscape. In this network, nodes represented active compounds and PKD-associated target genes, while edges denoted their interactions.

2.5 Hub Gene Identification

Protein protein interaction network was analyzed using the CytoHubba plugin in Cytoscape to identify top 10 hub genes based on degree connectivity. Genes with the highest number of interactions were considered central regulators in PKD-related molecular networks. Based on network topology and biological relevance, 10 hub genes were identified: *GAPDH*, *AKT1*, *IL6*, *ALB*, *SRC*,*EGFR*,*CTNNB1*,*BCL2*, *STAT3*,*CASP3*. These genes are involved in drug transport, oxidative stress regulation, inflammatory signaling, glucose metabolism, and MAPK-mediated cell proliferation pathways. Their central roles suggest that they are key molecular targets in PKD progression and therapeutic intervention.

3 Results

3.1 Evaluation of active ingredients and target screening

Inhibitors against disease are selected or evaluated based on molecular weight, bioavailability score, drug-likeness, hydrogen bond donors, and hydrogen bond acceptors through pkcsm or Swiss ADME to assess their therapeutic intervention. The results are summarized in Table 1 with their physiochemical properties.

Table 1: Physicochemical properties of selected inhibitors against disease.

Inhibitor	**Mol. Weight**	**Bioavailability**	**Drug Likeness**	**HBD**	**HBA**
Metformin	129.16	0.55	0.29	3	2
Salsalate	258.05	0.56	0.77	2	5
Oxypurinol	246.02	0.56	0.49	0	6
Benzbromarone	252.09	0.55	2.14	0	0
Niclosamide	326.99	0.55	0.25	3	4
Pioglitazone	356.12	0.55	0.94	1	5
Empagliflozin	450.14	0.55	0.49	4	7
Bosutinib	529.16	0.55	1.47	1	7
Nicotinamide	122.05	0.55	0.37	2	2
Procyclidine	287.22	0.55	0.87	1	2
Sulforaphane	257.11	0.55	0.29	0	2
Tolvaptan	448.16	0.55	0.58	2	3
Lixivaptan	473.13	0.55	0.73	1	2
Roscovitine	354.22	0.55	0.72	3	4
Nintedanib	539.25	0.55	0.67	2	7
Celastrol	450.28	0.85	0.64	2	4
Panduratin A	406.21	0.55	0.97	2	4
GSK2816126	526.31	0.55	0.93	3	4
Tamibarotene	351.18	0.85	0.48	2	3
Lixumistat acetate	375.15	0.55	0.08	5	5

3.2 Toxicity Evaluation of Selected Inhibitors

Toxicity was analyzed using molecular formulae, LD_{50} values, and toxicity classification. LD_{50} represents the median lethal dose and provides insight into compound safety. Results are shown in Table 2.

Table 2: Molecular formula, LD_{50} values, and toxicity class of selected compounds.

Molecular Formula	**LD_{50} (mg/kg)**	**Toxicity Class**
$C_4H_{11}N_5$	680	4
$C_{14}H_{10}O_5$	1190	4
$C_6H_{14}O_6S_2$	200	3
$C_{20}H_{12}$	248	3
$C_{13}H_8Cl_2N_2O_4$	500	4
$C_{19}H_{20}N_2O_3S$	1000	4
$C_{23}H_{27}ClO_7$	3000	4
$C_{26}H_{29}Cl_2N_5O_3$	849	4
$C_6H_6N_2O$	2500	3
$C_{19}H_{29}NO$	395	4
$C_6H_{11}NOS_2$	1000	4
$C_{26}H_{25}ClN_2O_3$	769	4
$C_{27}H_{21}ClFN_3O_2$	840	4
$C_{19}H_{26}N_6O$	160	3
$C_{31}H_{33}N_5O_4$	500	4
$C_{29}H_{38}O_4$	2000	4
$C_{26}H_{30}O_4$	2000	4
$C_{31}H_{38}N_6O_2$	100	3
$C_{22}H_{25}NO_3$	2500	3
$C_{15}H_{20}F_3N_5O_3$	1265	4

3.3 Identification of Common Targets Between Disease Genes and Inhibitors

Venn diagram analysis was performed to identify overlapping targets between disease-associated genes and predicted compound targets. The diagram (Figure 1) shows that 617 targets are common, representing potential key targets for further investigation in Polycystic Kidney Disease (PKD).

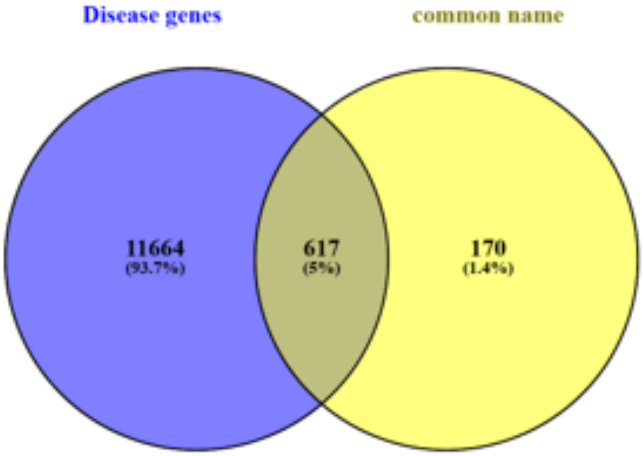


Figure 1: This figure shows the overlapping between disease-associated genes and predicted compound targets. Blue circle represents disease genes (11,664), the yellow circle represents predicted compound targets (787), and the interconnect regions (617) represents common targets.

3.4 Protein-Protein Interaction (PPI) Network and Hub Genes

By using STRING database , protein protein interaction (PPI) was constructed by uploading the selected target genes (Fig. 2). This database construct a network to visualizes nodes and edges, representing proteins and their interactions that contribute to the progression of the disease. To identify the top 10 genes within this network, the CytoHubba plugin in Cytoscape was applied.

The analysis revealed the top 10 hub genes based on degree centrality. This genes play an important role in controlling the disease progression.

Table 3: 10 hub genes identified from the PPI network (ranked by degree centrality).

Gene Name	Degree Value
GAPDH	560
AKT1	554
IL6	524
ALB	466
SRC	458
STAT3	446
EGFR	442
CTNNB1	434
BCL2	406
JAK2	400

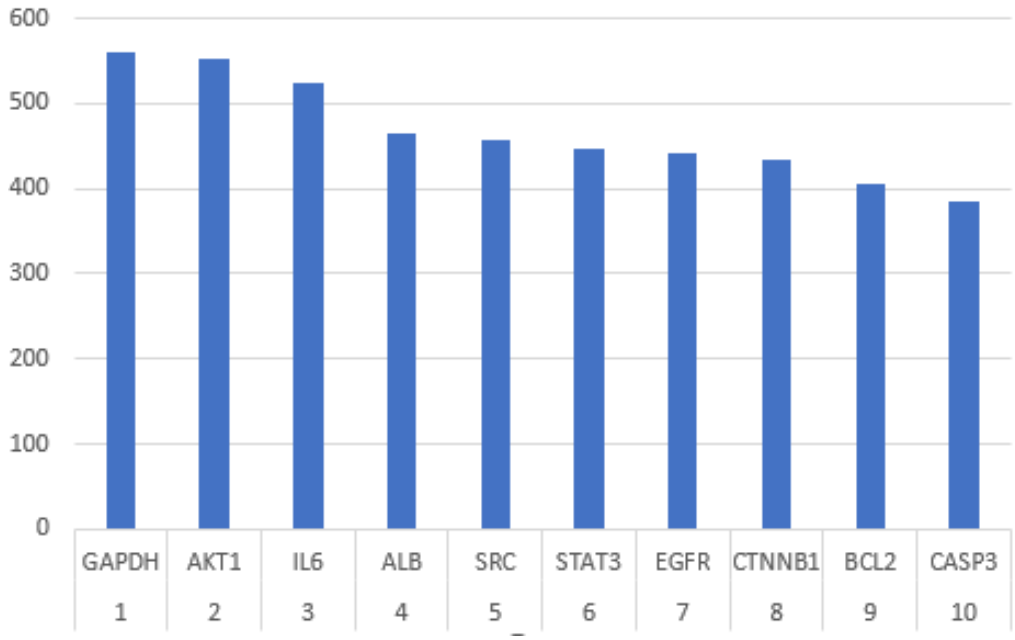
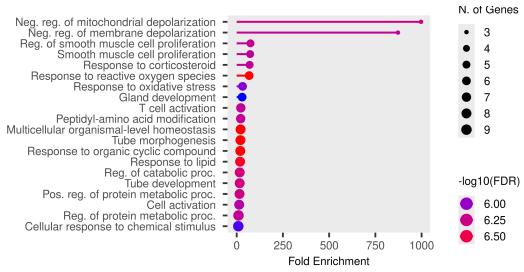


Figure 2: 10 hub genes identified by using CytoHubba degree ranking method. The bar graph shows the highest degree values of genes in the PPI network.

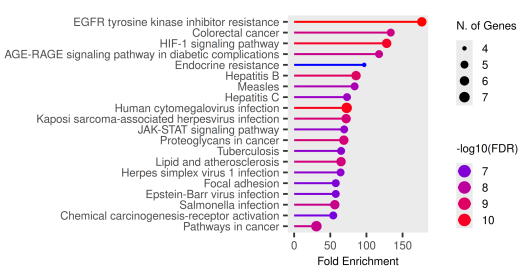
3.5 Gene Ontology and Pathway Enrichment Analysis

Biological relevance of target genes were identified, Gene Ontology (GO) and KEGG pathway enrichment analyses were performed. The enrichment results provide insight into the molecular mechanisms and signaling pathways potentially involved in disease progression.

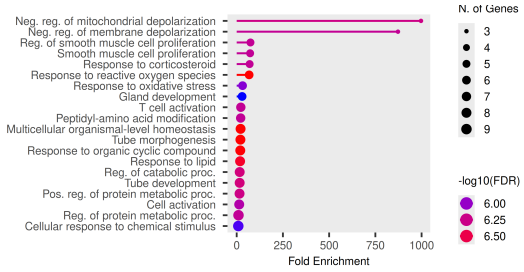
GO Biological Process (BP) analysis revealed significant enrichment of genes associated with apoptosis regulation, transcriptional regulation, and programmed cell death. KEGG pathway analysis demonstrated that the shared targets participate in multiple key signaling pathways, highlighting their functional importance. Furthermore, GO Cellular Component (CC) analysis indicated that the proteins encoded by these genes are predominantly localized in intracellular compartments such as the nucleus and cytosol. GO Molecular Function (MF) analysis revealed enrichment in activities such as protein kinase binding and transcription factor interaction.



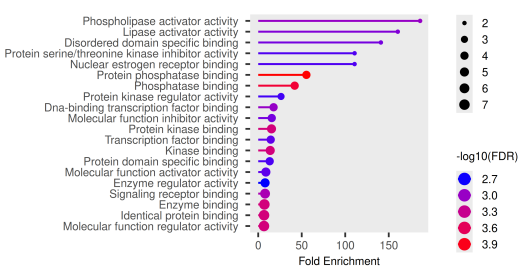
(a) Biological Process



(b) KEGG Pathway Enrichment



(c) Cellular Component



(d) Molecular Function

Figure 3: Functional enrichment analysis of the shared target genes. (a) Biological Process enrichment. (b) KEGG pathway enrichment analysis. (c) Cellular Component annotation. (d) Molecular Function annotation.

3.6 Interaction Networks Build

A compound target pathway interaction network was build using Cytoscape to visualize the multi-target therapeutic mechanism against Polycystic Kidney Disease (PKD). In this network, nodes represent bioactive compounds, PKD associated target genes, and enriched signaling pathways, while edges indicate their interactions. Hub targets were highlighted based on higher connectivity, indicating their central regulatory roles within the network. The dense interconnections illustrate the synergistic and multi-component nature of the therapeutic strategy in PKD

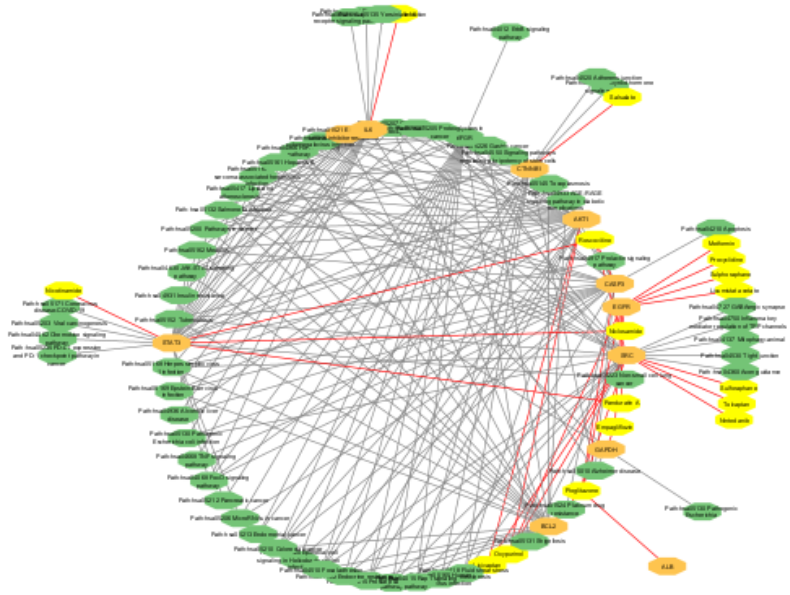


Figure 4: Compound target pathway interaction network for Polycystic Kidney Disease (PKD).

4 Conclusion

This study provides the first systematic exploration of Polycystic Kidney Disease using an integrated network pharmacology. A total 10 hub genes were identified, including AKT1, EGFR, BCL2, CASP3, SRC, CTNNB1, GAPDH, IL6, ALB, STAT3 which are functionally involved in controlling disease progression.By integrating data from multiple databases and constructing a protein-protein interaction network from STRING database, we highlighted potential therapeutic targets that could guide future drug development and intervention strategies.Targeting these genes could lead to novel therapeutic strategies and improved patient outcomes.

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