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The mechanism of procyanidin B1 in the treatment of nonalcoholic fatty liver disease based on network pharmacology and molecular docking

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Abstract Non-alcoholic fatty liver disease (NAFLD), a chronic liver disorder closely associated with metabolic dysfunction, has become a significant global health challenge. In recent years, procyanidin B1 (PB1) has demonstrated potential advantages in the prevention and personalized treatment of NAFLD through multi-target and multi-pathway intervention strategies, exerting comprehensive regulatory and synergistic effects. However, its precise therapeutic mechanisms remain unclear. This study employs network pharmacology to identify key targets and potential pathways involved in the treatment of NAFLD with PB1. Additionally, molecular docking analysis is conducted to validate the reliability of these targets. The findings provide a theoretical foundation for the development of PB1 as a potential therapeutic agent for NAFLD, offering insights for future experimental and clinical research.

Keywords: Procyanidin B1; non-alcoholic fatty liver disease; network pharmacology; molecular docking

1 Introduction

Non-alcoholic fatty liver disease (NAFLD) is a prevalent chronic liver disorder with a growing global incidence, posing a significant public health concern. It is closely associated with various metabolic conditions such as central obesity, dyslipidemia, hypertension, and hyperglycemia [1]. NAFLD is characterized by excessive fat accumulation in the liver, mirroring the pathological features of alcoholic liver disease but occurring in the absence of significant alcohol intake [2]. The global prevalence of NAFLD is estimated to be approximately 30%, with projections indicating an increase to 55.7% of the adult population by 2040 [3]. In western industrialized nations, NAFLD has emerged as one of the most prevalent chronic liver diseases, among type 2 diabetes, dyslipidemia, and metabolic syndrome [4].

NAFLD progresses from benign non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH). NAFL is defined by excessive hepatic fat accumulation, with or without mild lobular inflammation, affecting more than 5% of hepatocytes in individuals with metabolic risk factors, particularly obesity and type 2 diabetes [5,6]. The progression to NASH involves hepatic lipid deposition, insulin resistance, oxidative stress, and fatty acid oxidation, leading to hepatocellular damage, diffuse lobular inflammation, and fibrosis. NASH may advance to liver cirrhosis and hepatocellular carcinoma without treatment, ultimately resulting in liver failure, choose for liver transplantation, or death [7,8]. As a result, NAFLD is a critical factor contributing to liver-related mortality.

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Proanthocyanidins have demonstrated multi-target and multi-pathway regulatory effects, offering potential advantages in the prevention and treatment of NAFLD. However, the precise mechanisms underlying their therapeutic action remain unclear and require further in-depth investigation. Network pharmacology is a powerful approach for elucidating drug mechanisms, integrating bioinformatics, network biology, and pharmacology to identify key therapeutic targets [9,10]. In this study, we employ network pharmacology to investigate the potential targets and mechanisms of procyanidin B1 (PB1) in the treatment of NAFLD. The chemical structure of procyanidin B1 is shown in Fig. 1.

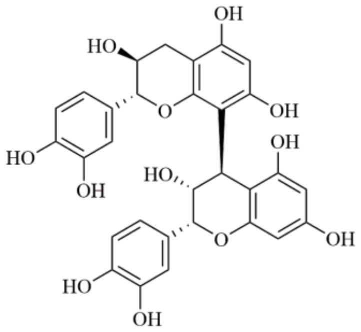


Fig. 1 Chemical structure of procyanidin B1

2 Methods

2.1 Screening of PB1 target genes

The chemical structure of procyanidin B1 was obtained from TCMSP pharmacology database (https://old.tcmsp-e.com/) by searching for the keyword "procyanidin B1" and was saved in mol2 format [11]. This file was then imported into the PharmMapper database to predict potential targets. The SMILES notation for procyanidin B1 was retrieved from the PubChem database by searching for "procyanidin B1", and subsequently employed to predict potential targets in the SwissTargetPrediction database (http://www.swisstargetprediction.ch/), with the species set to "human" [12]. Additionally, potential targets were identified using the Similarity ensemble approach database (https://sea.bkslab.org/). Targets genes were standardized using the UniProt database (https://www.uniprot.org/), with the species set to "human" [13]. After removing duplicate entries, a database of procyanidin B1 targets was compiled.

2.2 Prediction of NAFLD target genes

The keywords "non-alcoholic fatty liver disease" were systematically searched in the GeneCards database (https://www.genecards.org/) and the OMIM database (https://omim.org/). Prediction results were filtered using a relevance score > 3 in GeneCards to retain highly relevant NAFLD target genes. Duplicate entries were removed, and results from the two databases were merged.

2.3 Identification of potential PB1 targets in NAFLD

procyanidin B1 target genes and NAFLD-related target genes were mapped using the Venny 2.1 online tool, and overlapping targets were identified as potential procyanidin B1 targets in NAFLD.

2.4 Construction of protein-protein interaction (PPI) network

The PPI networks visually represent protein interactions, helping to identify key nodes and elucidate potential drug action mechanisms [14]. To investigate interactions between PB1 and NAFLD-related target proteins, the STRING v.12.0 database (https://cn.string-db.org/) was used to construct a PPI network of drug-disease cross-target genes. STRING is a comprehensive platform designed for protein-protein interaction analysis and integration [15,16]. By uploading potential target genes to STRING v.12.0, with the species set to "Homo sapiens" and other parameters left as default, images and TSV format data files were exported [17].

2.5 Network construction and analysis

The v.3.10.0 was used to analyze PB1 targets among the NAFLD-related proteins identified by STRING and to visualize the interaction network. The network analysis plugin in Cytoscape was used to quantify network nodes and analyze their roles. To identify key hub genes, CytoHubba, an in-built Cytoscape plugin, was used for topological analysis. The MCC algorithm was applied to screen the top 10 core targets in the PPI network.

2.6 Gene ontology enrichment analysis

Gene Ontology (GO) enrichment analysis is a fundamental bioinformatics approach used to explore the molecular mechanisms underlying drug action. GO enrichment analysis classifies genes or proteins into three functional categories: molecular function (MF), cellular component (CC), and biological process (BP). Thereby providing insights into the molecular mechanisms of drug action and offering valuable guidance for drug development and disease treatment [14]. To identify the biological functions of potential NAFLD-related targets, target genes were input into the DAVID database in Gene Symbol format, with "Homo sapiens" selected as the species for analysis. The key MF, CC, and BP terms were analyzed and enriched. The resulting data were exported to an Excel worksheet, and the top 10 GO terms with an FDR < 0.05 were selected. A bar chart was generated using an online bioinformatics tool to visualize the enriched terms.

2.7 Kyoto encyclopedia of genes and genomes enrichment analysis

Kyoto encyclopedia of genes and genomes (KEGG) enrichment analysis was conducted using the same method as GO enrichment analysis. The top 20 KEGG pathways with FDR < 0.05 were identified and ranked. The results were visualized using a bubble chart created with an online bioinformatics tool.

2.8 Screening of differential gene targets

To identify key differential targets, an intersection analysis was performed using the Venny 2.1 online tool. The core targets obtained from PPI network topology analysis, along with the key pathway-associated targets from the GO and KEGG enrichment analysis, were compared. Overlapping genes were identified as differential gene targets of PB1, which would show therapeutic potential in the treatment of NAFLD.

2.9 Molecular docking

To further investigate the interaction between PB1 and its potential NAFLD-related targets, molecular docking analysis was conducted. The 2D structure of PB1 was retrieved from PubChem, and the 3D structures of the screened differential gene targets were obtained from the PDB (https://www.rcsb.org/). Molecular docking simulations were performed using AutoDock software to predict the optimal binding mode between PB1 and the core target proteins. The best docking conformations were selected based on binding affinity scores, and the representative optimal molecular interactions were visualized using PyMOL and LigPlot^{+} software [18].

3 Results

3.1 Screening of potential targets of procyanidin B1 for NAFLD

The mol2 format file of procyanidin B1 was retrieved from the TCMSP database. By integrating the results from SwissTargetPrediction and PharmMapper, potential targets of procyanidin B1 were obtained. These targets were then standardized using the UniProt database, and duplicates were eliminated, resulting in the identification of 932 drug action targets along with their corresponding standardized gene names. Similarly, through screening and de-duplication in the GeneCards and OMIM databases, 3334 disease-associated targets highly relevant to NAFLD were retrieved. Using the Venny 2.1 online analysis tool, 154 overlapping targets were identified as potential targets of procyanidin B1 for NAFLD treatment. A Venn diagram illustrating these intersections is shown in Fig. 2.

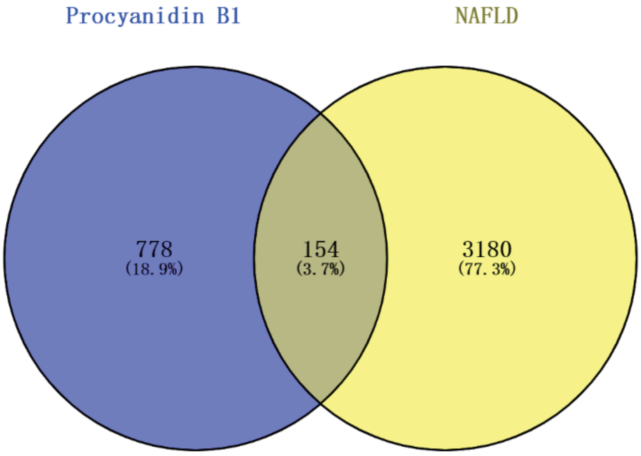


Fig. 2 Venn diagram of potential target sites of procyanidin B1 in NAFLD treatment

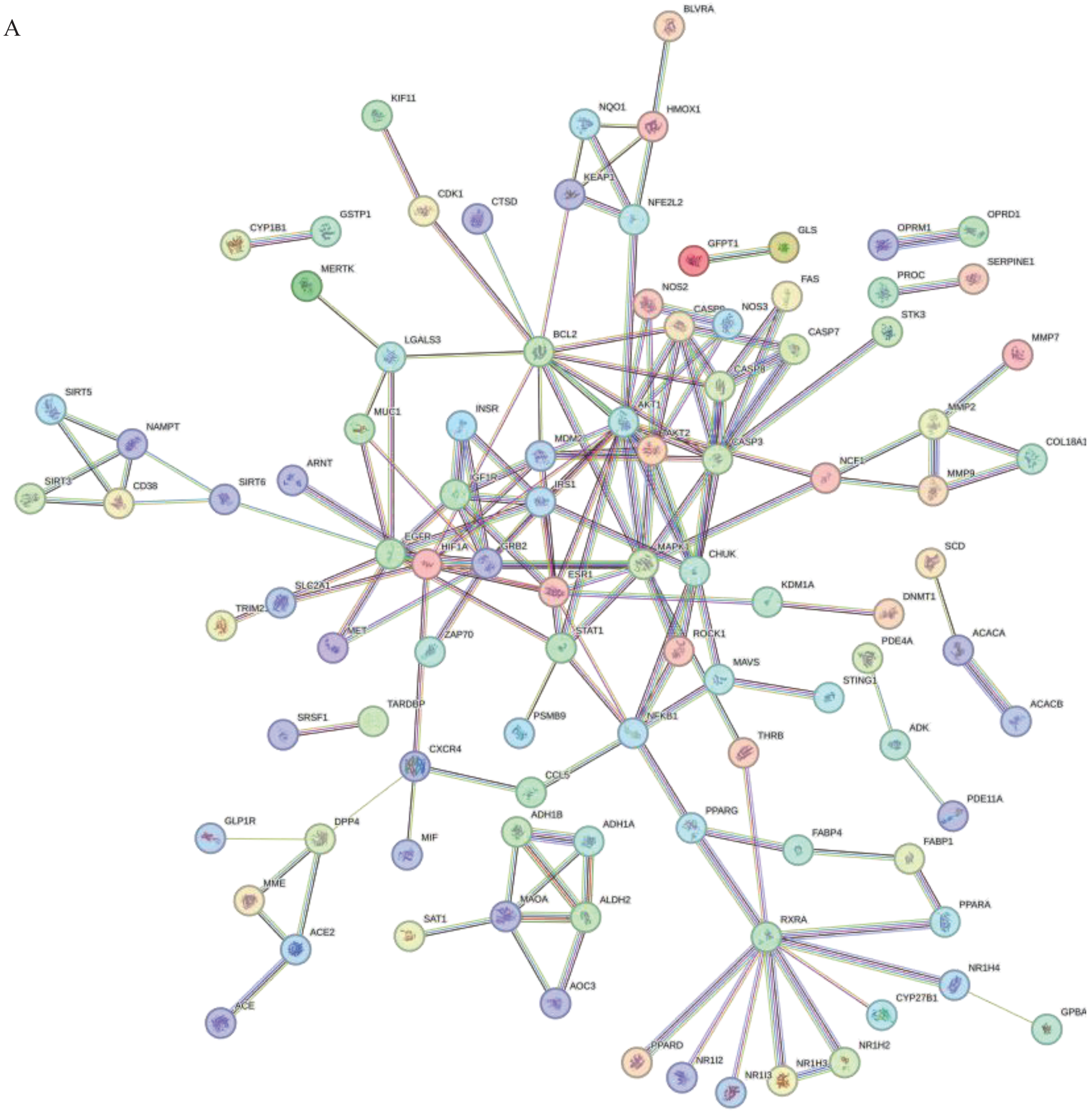
3.2 Construction and analysis of PPI network of potential targets

The PPI network constructed using the STRING database was used to analyze the 154 drug-disease intersection gene targets. The PPI network diagram (Fig. 3A) comprises 154 nodes and 161 edges, representing interactions between drug and disease-associated target genes. The STRING network data were imported into Cytoscape software, where the network analysis plugin was used to calculate node connectivity based on degree centrality. Each node in the network represents a target gene, with larger nodes indicating higher degree values, signifying their greater biological importance (Fig. 3B). To identify key hub genes, the CytoHubba plugin in Cytoscape was applied using the MCC algorithm. The top 10 core targets identified were AKT1, BCL2, MAPK1, MDM2, AKT2, HIF1A, ESR1, CASP3, CASP9 and IRS1, suggesting their critical role in the network (Fig. 3C).

3.3 Gene ontology functional analysis

The intersection target genes were subjected to GO enrichment analysis using the DAVID database. With FDR < 0.05 as the screening criterion, 156 entries for biological processes (BP), 21 entries for cellular components (CC), and 92 entries for molecular functions (MF) were obtained. The top 10 most enriched terms in each category, ranked by -log10 (FDR) were visualized as bar charts (Fig. 4).

Fig. 4 demonstrates that the potential targets of procyanidin B1 for NAFLD are primarily involved in various BP, MF, and CC. The BP analysis indicates that these genes participate in the negative regulation of apoptosis, positive regulation of RNA polymerase II transcription, negative regulation of gene expression, positive regulation of DNA-template transcription, and response to insulin receptor signaling pathways. The MF analysis highlights their roles in protein binding, nuclear receptor activity, zinc ion binding, sequence-specific DNA binding, transcription coactivator binding, enzyme binding, peptidase activity, and transcription coregulator binding. Meanwhile, the CC analysis shows that these genes are associated with the cytoplasmic matrix, extracellular vesicles, receptor complexes, nucleoplasm, RNA polymerase II transcription regulatory complexes, cytoplasm, chromatin, protein-containing complexes, and mitochondria. The GO enrichment analysis suggests that these targets are predominantly involved in intercellular signaling modulation, suppression of inflammatory responses, enhancement of liver metabolic function, and protecting hepatocytes from damage, thereby exerting therapeutic effects against NAFLD.



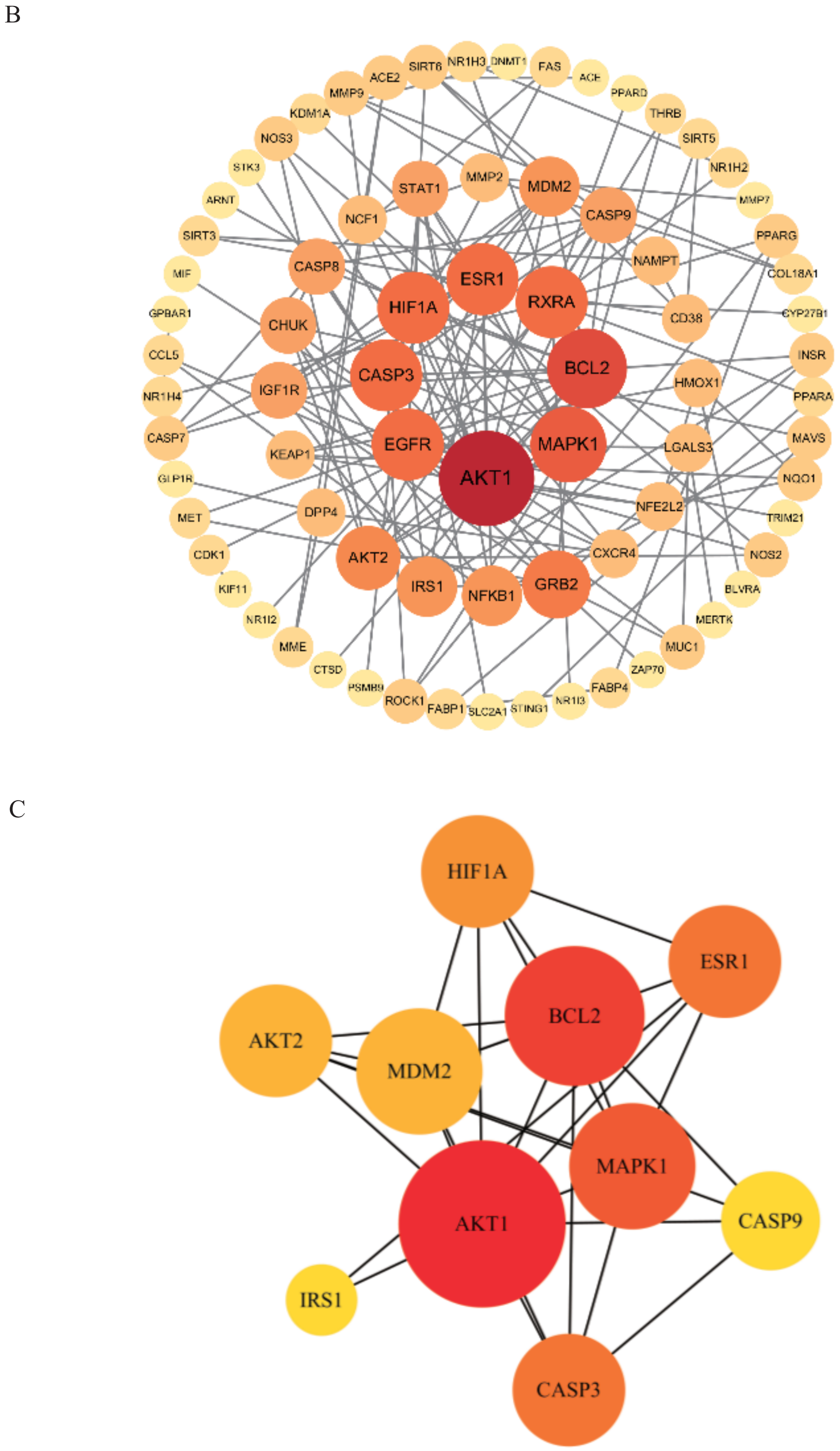


Fig. 3 PPI network analysis. A - PPI network of targets generated by STRING 12.0; B - PPI network diagram of potential targets; C - PPI network diagram of key targets

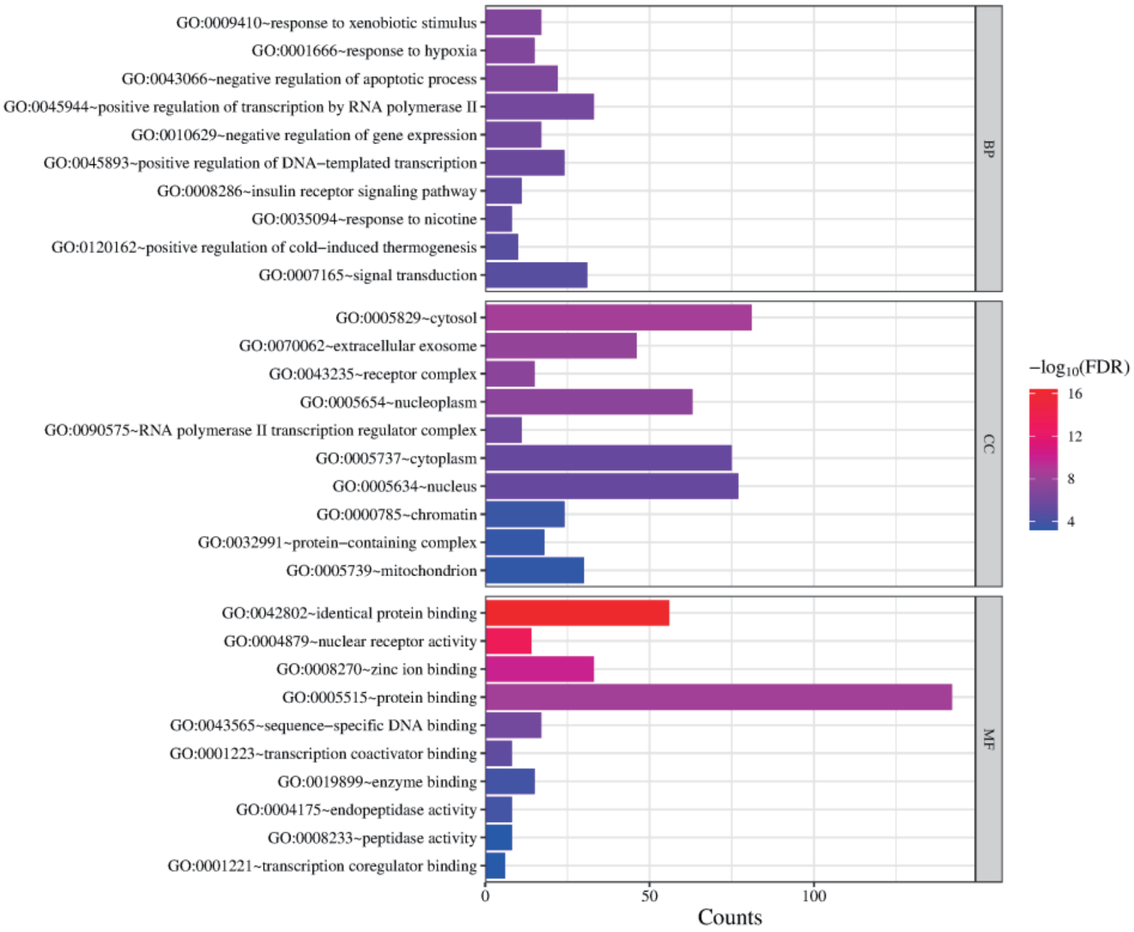


Fig. 4 GO enrichment analysis of potential targets

3.4 KEGG pathway enrichment analysis

To elucidate the potential mechanism underlying PB1's effects on NAFLD, KEGG pathway enrichment analysis was performed using the David database. Using FDR < 0.05 as the threshold, a total of 115 enriched pathways were identified. The top 20 pathways, ranked by FDR values from low to high, were selected as primary mechanisms of action (Fig. 5). These NAFLD-related pathways predominantly involve lipid metabolism and atherosclerosis, HIF-1 signaling pathway, hepatitis C, alcoholic liver disease, cancer pathways, chemical carcinogenesis - receptor activation, non-alcoholic fatty liver disease, insulin resistance, apoptosis, hepatitis B, and PPAR signaling pathway, etc. The results indicate that procyanidin B1 ameliorates NAFLD through multiple mechanisms, including promoting fatty acid oxidation and degradation, improving insulin resistance, inhibiting the expression of inflammatory factors, and enhancing antioxidant capacity.

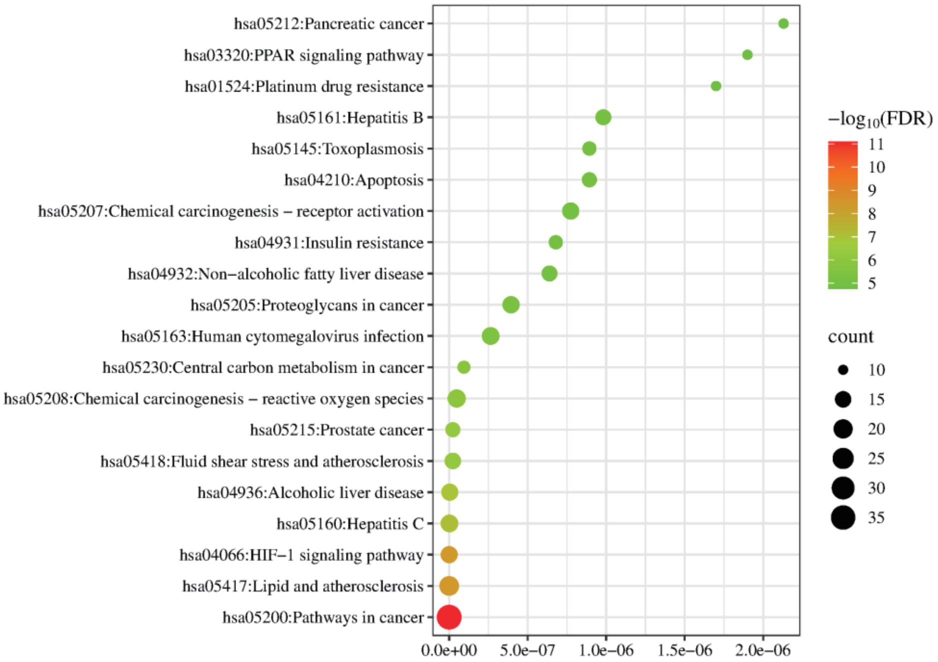


Fig. 5 KEGG pathway enrichment analysis of potential targets

3.5 Screening of differential gene targets

The Venn diagram analysis revealed a notable overlap among targets derived from PPI network topology analysis, KEGG and GO analysis. By identifying the intersection of these datasets using the Venny 2.1 online tool, it is speculated that three differential gene targets, AKT1, AKT2 and IRS1, serve as potential regulators of PB1's therapeutic effects on NAFLD (Fig. 6).

3.6 Molecular docking

In this study, the three-dimensional structures of AKT1 (PDB ID: 7nh5), AKT2 (PDB ID: 3d0e) and IRS1 (PDB ID: 1qqg) were retrieved from the PDB database. Among the three molecular docking results between the receptor protein and the ligand, AKT1 has the lowest binding energy. Using PyMol and LigPlot^{+} software, the most representative optimal conformation during the molecular docking process was presented. Both three-dimensional and two-dimensional binding conformations were displayed, with the three-dimensional conformation located on the far left and middle of the figure, and the two-dimensional conformation on the far right (Fig. 7A-C). In the 3D conformation diagram, the ligands and amino acid residues connected by hydrogen bonds are marked. In the 2D conformation diagram, green dashed lines represent hydrogen bonds, and red eyelash symbols indicate hydrophobic interactions. These images show stable hydrogen bond structures, with four hydrogen bonds established between procyanidin B1 and AKT1 connecting amino acid residues such as Leu78, Lys183 and Gln59 in AKT1, four hydrogen bonds established between procyanidin B1 and AKT2 connecting amino acid residues such as Thr444 and Leu155 in AKT2, and five hydrogen bonds established between procyanidin B1and IRS1 connecting amino acid residues such as Lys81 and His82 in IRS1.

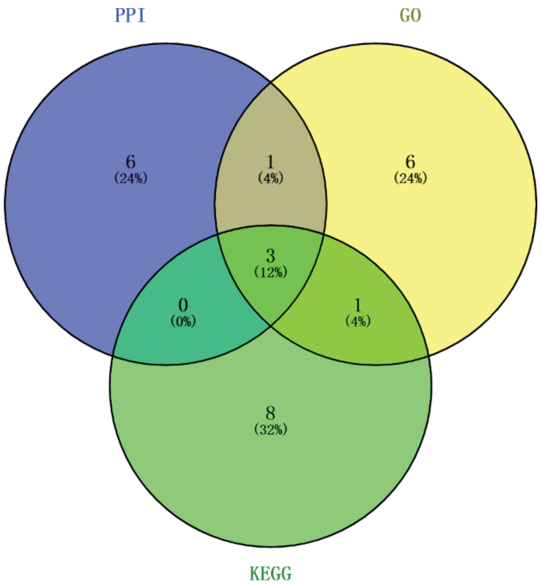


Fig. 6 Differential gene targets of procyanidin B1 in NAFLD treatment

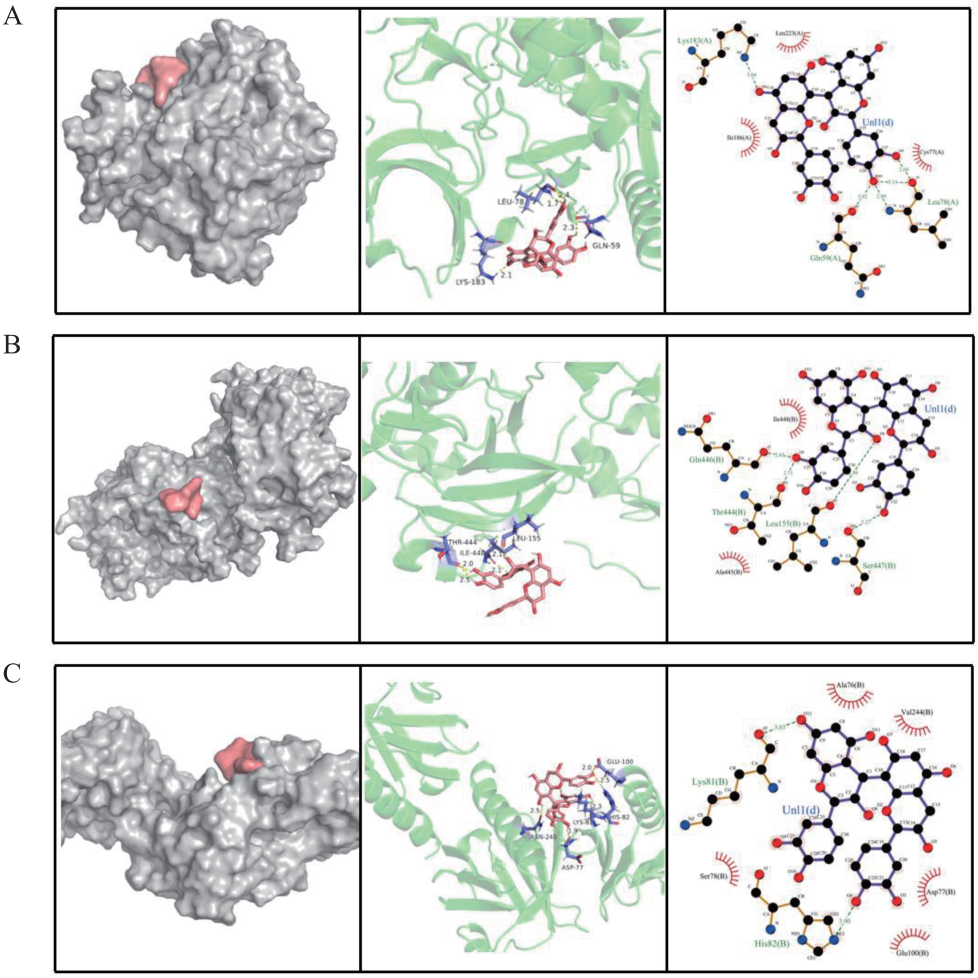


Fig. 7 Molecular docking. A - Schematic diagram of molecular docking of AKT1 and procyanidin B1; B - Schematic diagram of molecular docking of AKT2 and procyanidin B1; C- Schematic diagram of molecular docking of IRS1 and procyanidin B1

4 Discussion

With NAFLD emerging as a significant global health challenge, research on its pathogenesis and potential therapeutic strategies has garnered extensive attention from the scientific community [19]. Recent studies have demonstrated that NAFLD involves multiple complex mechanisms, including inflammasome activation, insulin resistance, intestinal imbalance and liver cell fibrosis, etc [20,21]. Despite the absence of highly specific and efficacious pharmacological treatments for NAFLD, proanthocyanidins have attracted increasing interest due to their multi-pathway synergistic therapeutic effects and relatively low side effects [22-24]. However, current research has yet to establish a comprehensive multi-pathway and multi-target model to elucidate the precise therapeutic mechanism of NAFLD.

Network pharmacology is an effective strategy for predicting and evaluating drug-target interactions and pathway mechanisms from a systems perspective, providing a promising research approach for precise prevention and treatment of diseases [25]. By integrating systems network analysis with pharmacological principles, network pharmacology enables a holistic investigation of drug targets and their associated pathways at the molecular level, thereby enhancing our understanding of the intricate interactions between key molecular targets. In this study, we employed network pharmacology to identify differential gene targets and potential key pathways involved in the therapeutic action of PB1 in NAFLD, providing a scientific basis for further elucidation of its underlying mechanisms.

We identified 932 procyanidin B1-related drug targets by utilizing databases such as SwissTargetPrediction and PharmMapper, and then selected 3334 NAFLD-related disease targets from GeneCards and OMIM databases. The intersection of these datasets, as analyzed through the Venny 2.1 online tool, yielded 154 potential targets for procyanidin B1 in the treatment of NAFLD. CytoHubba analysis of the PPI network for these 154 targets revealed that AKT1, BCL2, MAPK1, MDM2, AKT2, HIF1A, ESR1, CASP3, CASP9, and IRS1 were likely key targets, serving as the first criterion for differential gene target selection. Further functional enrichment analyses, including GO enrichment and KEGG pathway analysis, were performed on the identified targets. The GO enrichment analysis highlighted the strong correlation between procyanidin B1-mediated biological processes and the insulin receptor signaling pathway, leading to the selection of 11 key targets associated with this process as the second criterion for differential gene target identification. These targets included IRS1, AKT2, INSR, PDK4, MAPK1, AKT1, GRB2, MERTK, MET, EGFR, and IGF1R. Additionally, KEGG pathway analysis indicated that procyanidin B1's therapeutic effects on NAFLD might be closely linked to the insulin resistance signaling pathway. Given that numerous endocrine and metabolic disorders are characterized by altered insulin sensitivity during disease progression [26]. And epidemiological studies have established a strong correlation between hepatic steatosis and insulin resistance (IR) in NAFLD [27]. IR has been recognized as a central pathological factor in NAFLD. IR contributes to NAFLD pathogenesis by promoting excessive fatty acid influx into adipose tissue while impairing lipolysis, thereby increasing the transport of free fatty acids to the liver and stimulating de novo lipogenesis [28,29]. Consequently, 12 targets implicated in this pathway—IRS1, NOS3, AKT2, NR1H2, INSR, GFPT1, SLC2A1, NR1H3, AKT1, PPARA, ACACB, and NFKB1—were selected as the third criterion for differential gene target identification.

Next, through Venny 2.1, integrating the results of PPI network topology analysis, GO enrichment analysis and KEGG pathway analysis, three key differential gene targets, AKT1, AKT2 and IRS1, were screened out. These targets may play a key role in the treatment of NAFLD with PB1.

To further verify the accuracy and reliability of network pharmacology in predicting the target sites of procyanidin B1, this study conducted verification analysis through molecular docking methods to reveal the binding stability of procyanidin B1 with the three key differential gene target proteins AKT1, AKT2 and

IRS1. The docking results of AKT1 showed the lowest binding energy, indicating that the interaction between AKT1 and procyanidin B1 was the most stable. RAC-alpha serine/threonine-protein kinase (AKT1), as a core member of the Akt family, plays an important role in processes such as cell apoptosis, cell proliferation, lipolysis in adipose tissue, liver inflammation and liver fibrosis [30-32].

5 Conclusion

In this study, key targets related to the treatment of NAFLD were predicted using a bioinformatics approach, as well as the GO and KEGG signaling pathways of their intervention. This study identified key targets related to insulin signaling pathways, apoptosis, and inflammatory responses using target screening, PPI network analysis, GO enrichment analysis, KEGG pathway enrichment analysis, and molecular docking experiments. The key targets AKT1, AKT2, and IRS1 may play a crucial role in its therapeutic effects. procyanidin B1 might improve insulin resistance, promote fatty acid decomposition, and inhibit inflammatory factor expression. These findings provide a theoretical basis for PB1 as a potential therapeutic drug for NAFLD. These findings provide a theoretical basis for its further development and application of procyanidin B1. However, the specific mechanism and material basis should be confirmed in vivo and in vitro.

Acknowledgments

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