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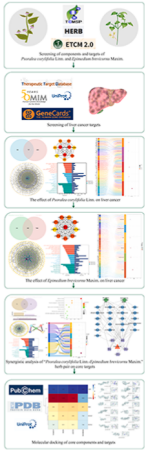
Full length article

Exploration of the mechanism of "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair in the treatment of liver cancer based on network pharmacology

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GRAPHICAL ABSTRACT



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ABSTRACT

Liver cancer treatment remains challenging, and the anti-liver cancer mechanism of the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair is unclear. This study aims to elucidate its synergistic mechanism based on network pharmacology. Network pharmacology was used to screen the active components and targets of the herb pair, construct protein–protein interaction (PPI) and "herbs-components-targets-disease" networks, perform Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses, and

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validate findings via molecular docking. A total of 221 overlapping core targets between the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair and liver cancer were identified, among which TP53, AKT1, CYP1A1, UGT1A7, and UGT1A1 were the five key nodes crucial for the synergistic effects of the herb pair. KEGG enrichment analysis showed that "Chemical carcinogenesis - receptor activation" and "Lipid and atherosclerosis" are the core pathways through which this herb pair exerts its effects. Molecular docking confirmed stable binding between core components like kaempferol and key targets such as CYP1A1, supporting the potential for this herb pair to intervene in liver cancer progression via multiple targets and pathways. This study systematically elucidates how the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair exerts anti-liver cancer effects through a multi-target and multi-pathway network, establishing a molecular mechanism framework for the synergistic intervention of liver cancer using traditional Chinese medicine herb pairs.

1. Introduction

Liver cancer is a malignant tumor that occurs in the liver and mainly includes two categories: primary liver cancer and secondary liver cancer. As a malignant tumor with a high incidence and mortality rate worldwide, liver cancer has a complex pathogenesis, rapid progression and extremely poor prognosis. It has become a major public health problem seriously threatening human health, and its incidence and mortality rates are both relatively high among malignant tumors in China. At present, the clinical treatment methods for liver cancer mainly include chemotherapy, radiotherapy and surgical resection, etc. However, there are many limitations such as frequent drug resistance, significant side effects and high treatment costs. Therefore, finding safe, effective and multi-target synergistic treatment strategies has become an urgent need in the field of liver cancer research.[1]

Traditional Chinese medicine has unique advantages such as overall regulation, multi-target, multi-pathway and low toxic and side effects in tumor treatment, and plays an important role in the comprehensive treatment of liver cancer. *Psoralea corylifolia* Linn. and *Epimedium brevicornu* Maxim., as a commonly used herb pair for "tonifying the kidney and strengthening Yang" in clinical practice, follow the traditional Chinese medical theory that "the kidney governs bone and produces marrow" and "vital qi in the body, pathogenic can not Attack". They are often used in tumor treatment to improve the patient's constitution and inhibit tumor progression.[2] Modern pharmacological research has confirmed that the main active components of *Psoralea corylifolia* Linn. (such as bavachin, isopsoralen, bakuchiol, etc.). and the core active components of *Epimedium brevicornu* Maxim. (such as icaritin, icariin, baohuoside I, etc.). can inhibit the cell cycle progression of liver cancer cells, induce tumor cell apoptosis, and simultaneously suppress the invasive and metastatic abilities of liver cancer cells. Moreover, the extracts of *Epimedium brevicornu* Maxim. and *Psoralea corylifolia* Linn. can also regulate the immune microenvironment of the body and enhance the killing effect of immune cells on tumor cells [2–6]. However, the material basis of this herb pair in the treatment of liver cancer has not yet been clarified, and the synergistic mechanisms involving multiple components, multiple targets, and multiple pathways remain insufficiently systematically analyzed, which seriously limits its clinical application and development. In addition, there is relatively little research exploring the mechanisms of the "*Psoralea corylifolia Linn.-Epimedium brevicornu Maxim.*" herb pair in the treatment of liver cancer based on network pharmacology and molecular docking methods. Based on this, this study focuses on the "*Psoralea corylifolia Linn.-Epimedium brevicornu Maxim.*" herb pair, utilizing network pharmacology methods to systematically screen potential active components within the herb pair, predict their core targets in liver cancer, construct a "herbs-components-targets-disease" regulatory network, and reveal their possible molecular mechanisms. The aim is to provide a theoretical basis for elucidating the scientific rationale of this herb pair in treating liver cancer, as well as to lay the groundwork for subsequent *in vitro* cell experiments, *in vivo* animal experiments, and the development of novel anti-tumor drugs.

2. Materials and methods

2.1. Screening of active compounds and targets of Psoralea corylifolia Linn. And Epimedium brevicornu Maxim.

The chemical components and targets of *Psoralea corylifolia* Linn. and *Epimedium brevicornu* Maxim. were collected through the Traditional Chinese Medicine Systems Pharmacology (TCMSP) Database and Analysis Platform, the HERB database, and the ETCM database. The screening criteria for the TCMSP database were oral bioavailability (OB) $\geq$ 30% and drug-likeness (DL) $\geq$ 0.18.

2.2. Screening of disease targets

Taking "liver cancer", "hepatocellular carcinoma" and "hepatoma" as the key words, the target points of liver cancer were retrieved and collected using the GeneCards Database, the Therapeutic Target Database (TDD) and the Online Mendelian Inheritance in Man (OMIM) database. The Uniprot database was used to summarize the human genes of the data, and the results were combined and the duplicate values were deleted.

2.3. Determination of the core target of "Psoralea corylifolia Linn.-Epimedium brevicornu Maxim." herb pair in the treatment of liver cancer

After identifying the target points of the active components in *Psoralea corylifolia* Linn. and *Epimedium brevicornu* Maxim., their intersections with liver cancer-related targets were analyzed to obtain the target points of *Psoralea corylifolia* Linn. and *Epimedium brevicornu* Maxim. In treating liver cancer. Cross-analyzing these two pairs identified the potential core target points of the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair for liver cancer treatment. A Venn diagram was constructed to provide the core research subjects for subsequent mechanism analysis.

2.4. Construction and analysis of protein-protein interaction (PPI) networks for core targets

Import the identified core targets into the STRING database, set the species to "*Homo sapiens*", and use a confidence score $\geq$ 0.900 as the screening criterion, while hiding isolated nodes without interactions to obtain the PPI network data of the core targets. Export this data in TSV format and import it into Cytoscape 3.10.3 software for visualization and network construction. Use the "Network Analyzer" plugin in the software to perform topological analysis of the PPI network and calculate key topological parameters such as node degree. The "Cytohubba" plugin is employed to identify key nodes and subnetworks within the PPI network.

2.5. Gene Ontology (GO) functional enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis of core targets

Import the core targets into the Metascape database, set the species to "*Homo sapiens*", and perform GO functional enrichment analysis and

KEGG pathway enrichment analysis. GO functional enrichment analysis primarily includes three dimensions: Biological Process (BP), Cellular Component (CC), and Molecular Function (MF). KEGG pathway enrichment analysis is used to identify the key signaling pathways involving the core targets.

2.6. Construction of a "herbs-components-targets-disease" regulatory network

Integrating the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair to identify key active ingredients and core targets, focusing on the "herbs-components-targets-disease" interaction relationships, a regulatory network was constructed using Cytoscape 3.10.3 software, and key topological parameters such as degree, betweenness centrality, and closeness centrality were calculated.

2.7. Molecular docking

Molecular docking technology was used to verify the binding ability of the main components of the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair with core proteins. The 3D structures of the components were obtained from the PubChem database, and the 3D structures of the main protein receptors were obtained from the UniProt database and PDB database. Subsequently, the proteins were dehydrogenated using PyMOL software, and small molecule ligands were removed from the protein receptors. Finally, molecular docking between the processed protein receptors and ligands was performed using AutoDockTools 1.5.6 software, and their binding energies were recorded.

3. Results

3.1. Screening of active components in "Psoralea corylifolia Linn.-Epimedium brevicornu Maxim." herb pair

By searching the TCMSP, ETCM, and HERB databases and removing duplicates, a total of 104 potential active ingredients of *Epimedium brevicornu* Maxim. and 74 potential active ingredients of *Psoralea corylifolia* Linn. were identified.

3.2. Collection of targets for liver cancer-related diseases

Using "liver Cancer", "hepatocellular carcinoma" and "hepatoma" as search terms, liver cancer-related targets were collected from the GeneCards, TTD, and OMIM databases. A total of 7,160 targets were retrieved from the GeneCards database, 521 from the OMIM database, and 71 from the TTD database. After merging and removing duplicates, a total of 7,538 liver cancer-related disease targets were obtained.

3.3. Effects of Psoralea corylifolia Linn. on liver cancer

3.3.1. Identification of core targets for Psoralea corylifolia Linn. in the treatment of liver cancer

A total of 1,028 targets related to *Psoralea corylifolia* Linn. were identified from the TCMSP, HERB, and ETCM databases. After consolidating and removing duplicates from liver cancer targets obtained from the GeneCards, TTD, and OMIM databases, 7,538 targets were acquired. An intersection analysis between the targets of *Psoralea corylifolia* Linn. and liver cancer-related targets revealed 727 common targets, representing the potential key targets for *Psoralea corylifolia* Linn. In the treatment of liver cancer. The Venn diagram (Fig. 1A) clearly illustrates the distribution of *Psoralea corylifolia* Linn. targets, liver cancer targets, and their overlapping targets, with the identification of these intersecting targets providing a foundation for subsequent mechanistic studies.

3.3.2. Construction and analysis of PPI network of core targets

Importing 727 core targets into the STRING database with a confidence score ≥ 0.9 and removing isolated nodes yielded a PPI network comprising 584 nodes and 2587 edges (Fig. 1B). The degree represents the number of interactions between a target and other targets. Topological analysis using Cytoscape 3.10.3 revealed an average degree value of 8.9. The MCC algorithm in CytoHubba was employed to identify and visualize the top 10 core genes: PIK3CA, PIK3CB, PIK3CD, PTPN11, JAK2, EGFR, SRC, JAK1, ERBB2, and PDGFRB (Fig. 1C). These targets play crucial regulatory roles in the PPI network and may represent core functional nodes in *Psoralea corylifolia* Linn. therapy for liver cancer.

3.3.3. GO function and KEGG pathway enrichment analysis results of core targets

To elucidate the molecular mechanism of *Psoralea corylifolia* Linn. In treating liver cancer, we performed GO and KEGG enrichment analyses on 727 candidate targets. Using $P < 0.01$ as the screening criterion, the GO functional enrichment analysis identified 2,085 significantly enriched GO terms, including 1518 BP terms, 183 CC terms, and 384 MF terms. BP terms were primarily enriched in "negative regulation of apoptotic process", "response to xenobiotic stimulus" and "lipid metabolic process", suggesting that *Psoralea corylifolia* Linn. may exert its effects by regulating apoptosis, metabolic adaptation, and stress responses in liver cancer cells. CC terms were predominantly enriched in "cytosol", "extracellular exosome" and "cytoplasmic membrane", indicating that the core target sites of psoralen are mainly distributed in intracellular functional zones and intercellular communication carriers. This may involve intracellular signaling and paracrine regulation. MF predominantly enriched in "protein kinase activity", "kinase activity" and "transferase activity", revealing that *Psoralea corylifolia* Linn. may intervene in key biological processes of liver cancer cells by regulating kinase-mediated signaling cascades. The top 10 GO entries diagram (Fig. 1D) visually presents the enrichment levels of each entry.

Using $P < 0.01$ as the screening criterion, KEGG pathway enrichment analysis identified 270 significantly enriched pathways. The Sankey diagram (Fig. 1E) displays the enrichment levels and significance scores for each pathway. The KEGG pathway enrichment analysis primarily involved "Pathways in cancer", "Lipid and atherosclerosis", "PI3K-Akt signaling pathway" and "MAPK signaling pathway". Among these, "Pathways in cancer" involved the highest number of targets, totaling 141. This suggests that this signaling pathway may be a key pathway in *Psoralea corylifolia* Linn. treatment for liver cancer. Meanwhile, classic signaling pathways such as PI3K-Akt and MAPK are crucial pathways regulating cell proliferation, apoptosis, invasion, and metastasis in the development of liver cancer. Their significant enrichment further indicates that *Psoralea corylifolia* Linn. may reshape the malignant phenotype of liver cancer cells by targeting these core signaling axes.

In summary, the enrichment features of the aforementioned GO functional entries and KEGG pathways collectively reveal that *Psoralea corylifolia* Linn. treatment for liver cancer may involve multidimensional molecular mechanisms. These mechanisms include regulating cell survival and metabolic balance, interfering with kinase-mediated signaling, and targeting core cancer pathways. This provides clear target and pathway directions for subsequent validation studies.

3.4. Effects of Epimedium brevicornu Maxim. On liver cancer

3.4.1. Identification of core targets for the treatment of liver cancer by Epimedium brevicornu Maxim.

This study first retrieved 466 target genes associated with *Epimedium brevicornu* Maxim. From three major databases: TCMSP, HERB, and ETCM. Subsequently, an intersection mapping analysis was performed between these *Epimedium brevicornu* Maxim. targets and liver cancer-related targets. The results revealed 335 shared targets, which were defined as the potential core targets for *Epimedium brevicornu* Maxim.'s intervention in liver cancer. A Venn diagram (Fig. 2A) visually illustrates

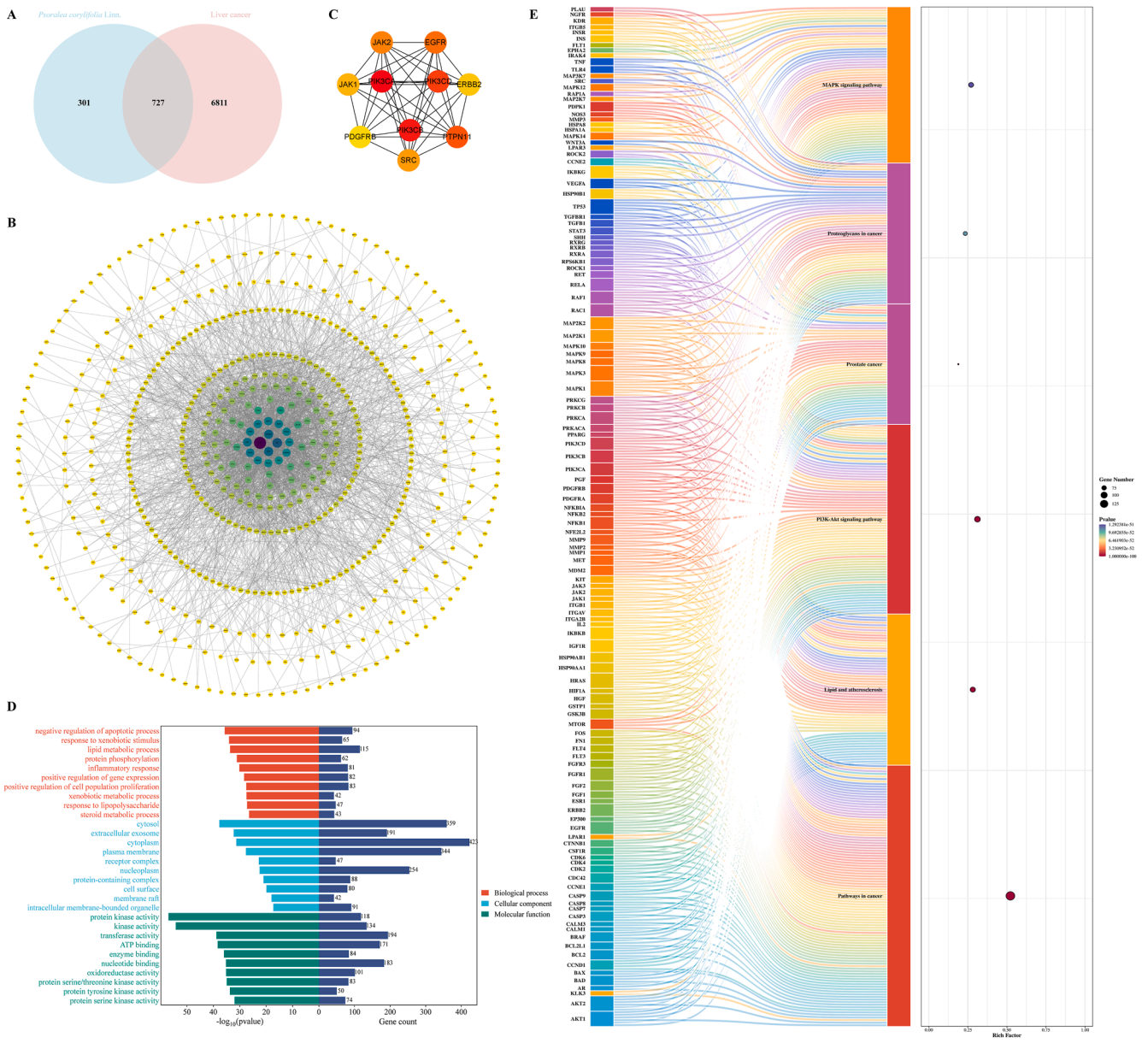


Fig. 1. Screening and analysis of overlapping targets between *Psoralea corylifolia* Linn. and liver cancer. (A) Venn diagram of overlapping targets between *Psoralea corylifolia* Linn. and liver cancer. (B) PPI network of overlapping targets (node size and color intensity positively correlated with degree). (C) Top 10 hub targets identified by the CytoHubba plugin. (D) GO analysis results of potential targets. (E) Sankey diagram showing the key KEGG pathways and related genes of targets overlapping between *Psoralea corylifolia* Linn. and liver cancer.

the quantitative relationships and distribution patterns among *Epimedium brevicornu* Maxim. targets, liver cancer disease targets, and their overlapping targets. The identification of this overlapping target set establishes a crucial foundation for subsequent in-depth analysis of molecular mechanisms.

3.4.2. Construction and analysis of PPI network of core targets

Uploading 335 core targets to the STRING database with a confidence threshold $\geq$ 0.9 and removing isolated nodes yielded a PPI network comprising 285 nodes and 1380 edges (Fig. 2B). Topological analysis using Cytosccape 3.10.3 software yielded an average degree of 9.8. These nodes play pivotal regulatory roles in the PPI network and are presumed to be core functional nodes underpinning *Epimedium brevicornu* Maxim.'s anti-liver cancer effects. Using the MCC algorithm in the CytoHubba plugin, the top 10 core genes were screened and visualized: CYP1A1, UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, and AKR1C3 (Fig. 2C).

3.4.3. GO function and KEGG pathway enrichment analysis results of core targets

To elucidate the molecular mechanisms underlying *Epimedium brevicornu* Maxim.'s intervention in liver, GO functional enrichment and KEGG pathway enrichment analyses were conducted on 335 candidate targets. The GO functional enrichment analysis yielded 1547 significantly enriched entries across three dimensions: BP, CC, and MF, with 1,172, 145, and 230 entries respectively. The top 10 enriched GO entries are shown in Fig. 2D. Within the BP dimension, core enrichments included "positive regulation of transcription by RNA polymerase II", "positive regulation of gene expression" and "negative regulation of apoptotic process", suggesting *Epimedium brevicornu* Maxim. may exert its effects by regulating gene transcription and apoptosis in liver cancer cells. CC dimension showed enrichment in "protein-containing

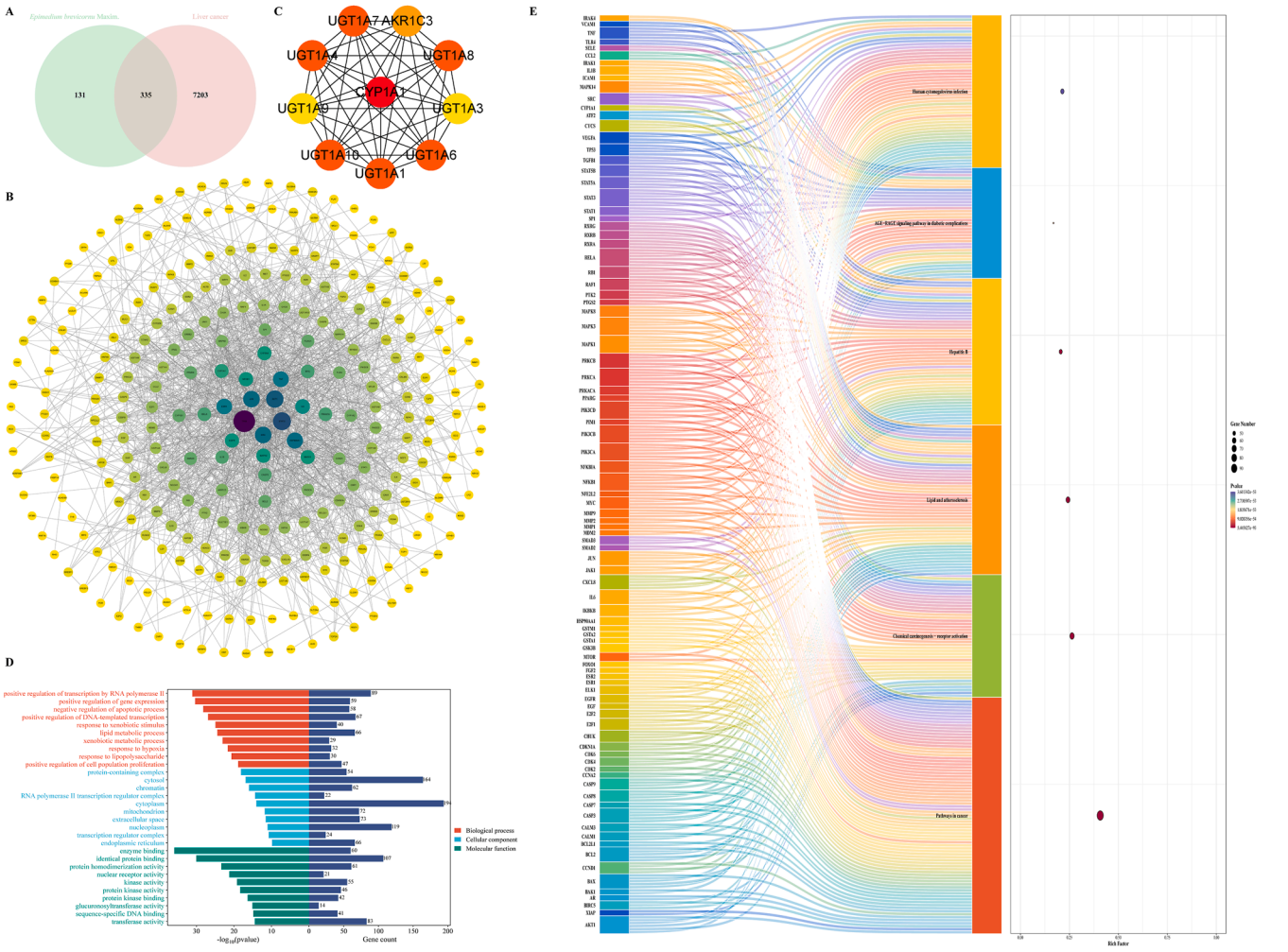


Fig. 2. Screening and analysis of overlapping targets between *Epimedium brevicornu* Maxim. and liver cancer. (A) Venn diagram of overlapping targets between *Epimedium brevicornu* Maxim. and liver cancer. (B) PPI network of overlapping targets (node size and color intensity positively correlated with degree). (C) Top 10 hub targets identified by the CytoHubba plugin. (D) GO analysis results for potential targets. (E) Sankey diagram illustrating key KEGG pathways and associated genes for targets intersecting *Epimedium brevicornu* Maxim. and liver cancer.

complex", "cytosol" and "chromatin", suggesting its core targets are localized within intracellular functional complexes and genetic regulatory regions, potentially participating in intracellular signaling and gene expression regulation; MF predominantly enriched in "enzyme binding", "identical protein binding" and "protein homodimerization activity" reveals that *Epimedium brevicornu* Maxim. may intervene in signal transduction of key biological processes in liver cancer cells by regulating protein-protein interactions and dimerization.

KEGG pathway enrichment analysis identified 243 significantly enriched pathways, with the enrichment levels and significance of each pathway visually represented via Sankey diagrams (Fig. 2E). Core enriched pathways primarily included "Pathways in cancer", "Chemical carcinogenesis - receptor activation", "PI3K-Akt signaling pathway", "Lipid and atherosclerosis" and "AGE-RAGE signaling pathway in diabetic complications". Among them, the number of candidate targets for "Pathways in cancer" ranks first, confirming that this pathway may be a central hub through which *Epimedium brevicornu* Maxim. regulates the occurrence and development of liver cancer.

Collectively, the core features of the above GO functional enrichment terms and KEGG pathways collectively point to multidimensional molecular mechanisms underlying *Epimedium brevicornu* Maxim.'s therapeutic effects against liver cancer: regulating liver cancer cells by modulating gene transcription and apoptosis balance, intervening in intracellular protein interactions and signaling pathways, and targeting core cancer pathways and associated regulatory networks. These enrichment analysis results provide clear candidate targets and pathway research directions for subsequent validation of *Epimedium brevicornu* Maxim.'s anti-liver cancer targets and in-depth mechanism studies.

3.5. Synergistic analysis of "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair on core targets

3.5.1. Construction and analysis of PPI network of core targets

A cross-comparison of the target proteins for *Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim. in liver cancer treatment ultimately identified 221 common core targets (Fig. 3A). These targets were imported into the STRING database to construct a PPI network, which was subsequently imported into Cytoscape 3.10.3 software for further analysis. This PPI network consists of 178 nodes and 651 edges. Through topological analysis, the average degree is 7.3, the average value of betweenness centrality is 0.014, and the average value of closeness centrality is 0.298 (Fig. 3B). The top five core targets selected based on the MCC algorithm were TP53, AKT1, CYP1A1, UGT1A7, and UGT1A1 (Fig. 3C).

3.5.2. GO function and KEGG pathway enrichment analysis results of core targets

To elucidate the molecular mechanism by which the "*Psoralea*

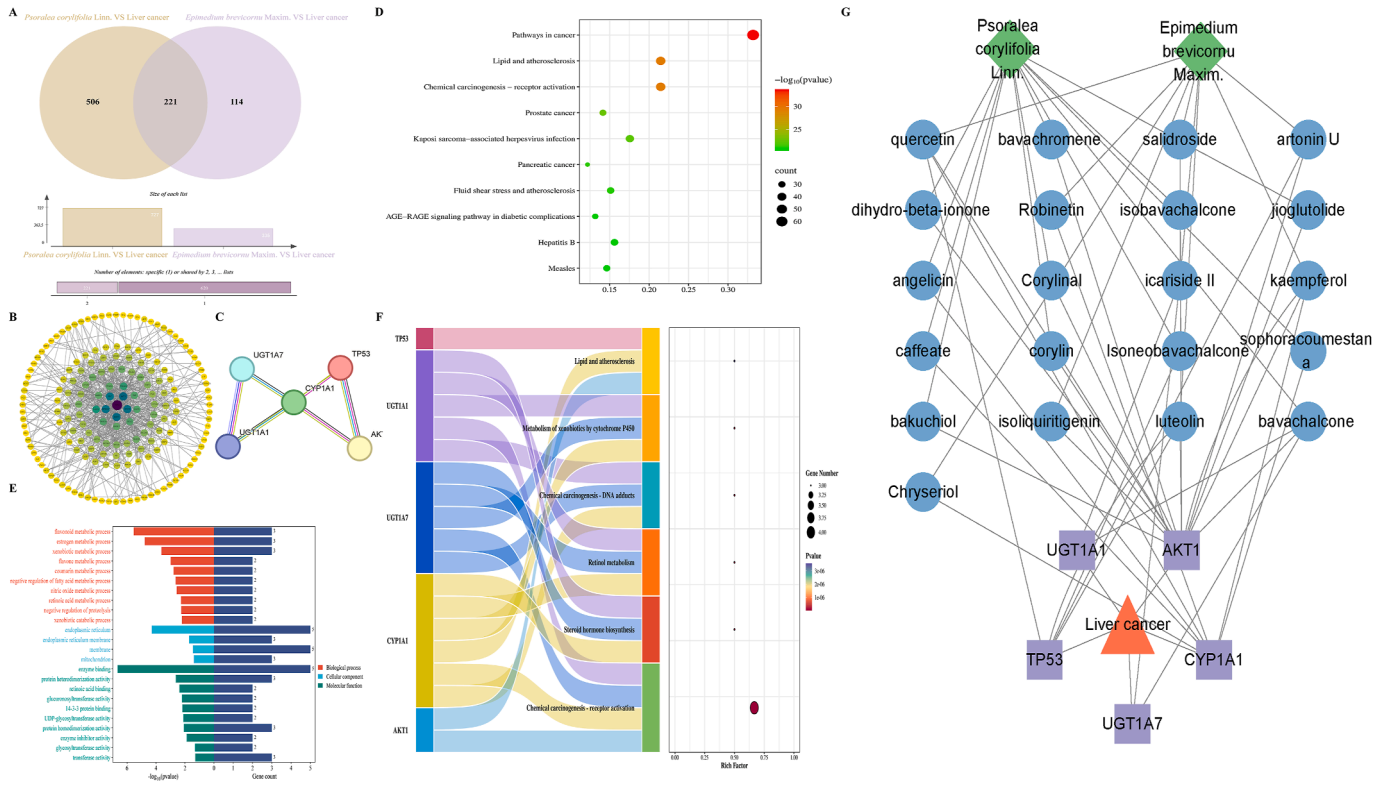


Fig. 3. Comprehensive analysis of the core targets of the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair. (A) Venn diagram of the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair overlapping with liver cancer targets, accompanied by a statistical bar chart showing the number of targets for each disease. (B) The PPI network diagram of the 221 intersection targets of the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair. (C) The PPI network of the core targets of the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair. (D) Bubble plot of KEGG enrichment analysis of 221 intersection targets. (E) The bar chart of GO enrichment analysis of the core target. (F) Sankey diagram of KEGG pathway enrichment analysis for the common core targets of the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair and liver cancer. (G) "herbs-components-targets-disease" regulatory network diagram. Nodes of different colors and shapes represent drugs (green diamonds), active ingredients (blue circles), core targets (purple squares), and diseases (red triangles), with edges indicating the interactions among them.

corylifolia Linn.-*Epimedium brevicornu* Maxim." herb pair regulates the progression of liver cancer, a KEGG pathway enrichment analysis was conducted on the 221 common core targets obtained through the above collaborative screening. The enrichment results were classified into three categories based on the degree of association with liver cancer and functional characteristics: Core anti-liver cancer pathways: "Pathways in cancer", "Chemical carcinogenesis - receptor activation" and "Hepatitis B"; Metabolism and inflammation microenvironment regulation pathways: "Lipid and atherosclerosis", "AGE-RAGE signaling pathway in diabetic complications" and "Fluid shear stress and atherosclerosis"; Other tumor and infection-related pathways: "Prostate cancer", "Kaposi sarcoma-associated herpesvirus infection", "Prostate cancer" and "Measles" (Fig. 3D).

Subsequently, GO functional enrichment and KEGG pathway enrichment analyses were performed on five key core targets. The GO functional enrichment analysis yielded 37 significantly enriched entries. As shown in Fig. 3E, the BP were mainly enriched in the "flavonoid metabolic process", "estrogen metabolic process" and "xenobiotic metabolic process", suggesting that the herb pair may exert their effects on liver cancer cell physiology by modulating metabolism-related pathways. CC were primarily enriched in subcellular structures such as the "endoplasmic reticulum", "endoplasmic reticulum membrane" and "membrane", indicating that the core targets of the herb pair are concentrated in key regions of substance synthesis and signal transduction. MF were mainly characterized by "enzyme binding", "protein heterodimerization activity" and "retinoic acid binding", revealing that the herb pair may exert biological effects by regulating protein interactions and ligand binding.

KEGG pathway enrichment analysis identified six significantly enriched pathways, with their enrichment levels and statistical significance shown in Fig. 3F. The core enriched pathways included "Chemical carcinogenesis - receptor activation", "Steroid hormone biosynthesis", "Retinol metabolism", "Chemical carcinogenesis - DNA adducts", "Metabolism of xenobiotics by cytochrome P450" and "Lipid and atherosclerosis". Based on the aforementioned results, it was found that the 5 core hub targets (such as TP53, AKT1, etc.) are all the intersectional regulatory nodes of the core pathways and metabolic pathways. For instance, AKT1 not only participates in the regulation of cell proliferation in the "Pathways in cancer" pathway, but also mediates the regulation of lipid metabolism in the "Lipid and atherosclerosis" pathway, suggesting that the core targets are the "key link" for the multi-pathway synergy of this herb pair. They can represent the overall pathway characteristics and focus on the core of the synergy mechanism. Additionally, the 221 intersectional targets regulated by the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair for liver cancer and the further screened 5 core targets are all enriched in "Chemical carcinogenesis - receptor activation" and "Lipid and atherosclerosis". The "Chemical carcinogenesis - receptor activation" pathway may block the receptor activation pathways of exogenous carcinogens, interrupt downstream pro-carcinogenic signaling, and directly inhibit the malignant transformation of hepatocytes. The enrichment of the "Lipid and atherosclerosis" pathway indicates that the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair can also exert a synergistic effect by regulating lipid metabolism and improving metabolic disorders. This result suggests that the "Chemical carcinogenesis - receptor activation" and "Lipid and atherosclerosis" pathways might be the key

pathways through which this herb pair exerts its anti-liver cancer effect.

3.5.3. *Construction and analysis of "herbs-components-targets-disease" regulatory network*

By integrating active ingredients and core targets, a "herbs-components-targets-disease" regulatory network was constructed (Fig. 3G). This network comprises a total of 29 nodes and 57 edges. Topological analysis showed an average degree of 3.9, an average betweenness centrality of 0.049, and an average closeness centrality of 0.43. Among them, kaempferol, bavachalcone, quercetin, and luteolin have degree values above the average, indicating that they are the core active ingredients in the network. AKT1, CYP1A1, TP53, and other hub targets are connected to multiple active ingredients, suggesting that the herb pair may exert its anti-liver cancer effects by acting on these hub targets through these core ingredients in a synergistic manner.

3.6. *Analysis of molecular docking results*

Molecular docking analysis was performed on the core active components and hub targets of the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair obtained from the "herbs-components-targets-disease" regulatory network. Among these, 15 "component-target" combinations exhibited binding energies ≤ -7.0 kcal/mol, indicating strong binding activity (Fig. 4A), which suggests that these core components have a high binding affinity for their corresponding targets. The "component-target" combinations with strong binding activity are shown in Fig. 4B. The results indicate that kaempferol has the strongest binding energy with CYP1A1. Furthermore, CYP1A1 demonstrated the most favorable binding activity, showing the most advantageous binding conformation among multiple target genes, providing molecular-level evidence for the herb pair's anti-liver cancer effects through these component-target interactions.

4. Discussion

Liver cancer, as one of the most lethal malignant tumors worldwide, involves complex pathogenic mechanisms including uncontrolled cell proliferation, apoptosis inhibition, abnormal angiogenesis, and immune microenvironment dysregulation. Clinical treatment still faces severe challenges such as high drug resistance and poor prognosis.[7,8] Traditional Chinese medicine, with its core advantages of "holistic regulation and multi-target intervention", demonstrates unique value in adjunctive cancer therapy. *Psoralea corylifolia* Linn. and *Epimedium brevicornu* Maxim., as a classic herb pair, have been used together for a long time. Modern pharmacological studies have confirmed that each herb possesses anti-tumor activity individually.[4,9] However, the molecular mechanisms underlying their synergistic treatment of liver cancer remain unclear. This study systematically analyzed the molecular mechanisms of the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair in treating liver cancer through network pharmacology techniques, considering aspects such as bioactive components, core targets, and signaling pathways, providing a theoretical basis for subsequent experimental validation and clinical applications.

The screening of active components forms the foundation of this study. Through searches of the TCMSP, ETCM, and HERB databases, this study ultimately identified 104 potential active components of *Epimedium brevicornu* Maxim. and 74 potential active components of *Psoralea corylifolia* Linn., which constitute the material basis for the anti-liver cancer effects of these herbs. Subsequent analyses of the "herbs-components-targets-disease" regulatory network indicated that kaempferol, bavachalcone, quercetin, luteolin, among others, are the core active components within the network, with their degree values all above the average. Existing studies have confirmed that kaempferol can induce autophagy and apoptosis in liver cancer cells by activating the AMPK signaling pathway.[10] Bavachalcone can alleviate liver injury in mice by inhibiting inflammation and oxidative stress responses.[11] Quercetin

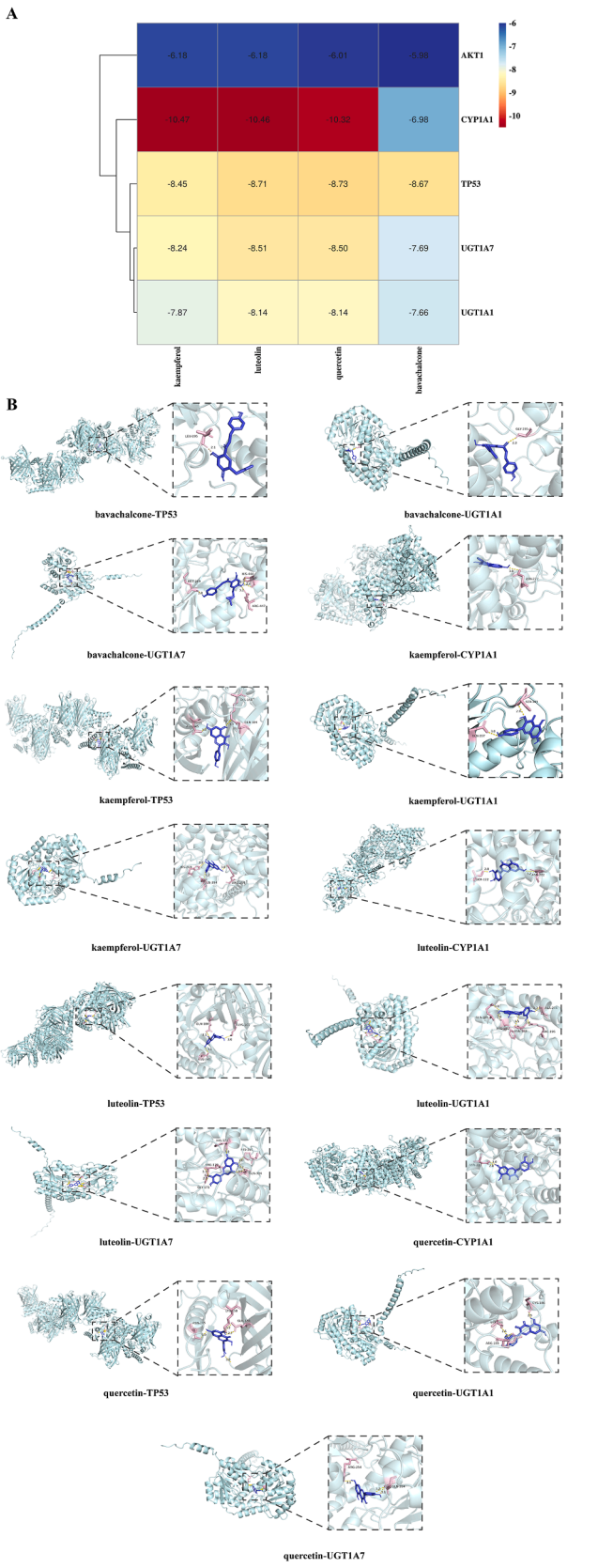


Fig. 4. Molecular docking pattern diagram. (A) Heatmap of binding affinity between core components and corresponding targets. (B) Molecular docking diagram of "component-target" combinations with strong binding.

plays a key role in liver cancer development, involving signaling pathways such as hTERT, MEK1/ERK1/2, Notch, Wnt/β-catenin, PI3K/Akt, and inflammatory NF-κB. It can regulate multiple mechanisms to induce cell cycle arrest and apoptosis, and is considered a novel potential anti-liver cancer candidate compound.[12–14] Luteolin can induce apoptosis in liver cancer cells by targeting key molecules such as AKT1 and SRC.[15] The synergistic effects of these core components may constitute an important material basis for the anti-liver cancer efficacy of the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair, providing candidate targets for subsequent precise validation of active components.

The identification and analysis of core targets are key to elucidating the mechanisms of drug action. In this study, intersection analysis was used to obtain 727 core targets for *Psoralea corylifolia* Linn. In the treatment of liver cancer and 335 core targets for *Epimedium brevicornu* Maxim. In the treatment of liver cancer. Further screening identified 221 core targets for their synergistic action, suggesting that the herb pair may exert therapeutic effects through multi-target synergistic regulation. PPI network analysis showed that the core targets of *Psoralea corylifolia* Linn. alone were primarily PIK3CA, PIK3CB, EGFR, and SRC, which are largely involved in kinase-mediated signaling processes. The core targets of *Epimedium brevicornu* Maxim. alone were concentrated in CYP1A1 and the UGT1A family (UGT1A1, UGT1A3, etc.), which are mostly associated with drug metabolism and detoxification of exogenous substances. The core targets for the synergistic action of the herb pair were TP53, AKT1, CYP1A1, UGT1A7, and UGT1A1. TP53, as a classic tumor suppressor gene, may undergo mutations in liver cancer, and its loss of function can lead to uncontrolled cell proliferation.[16] AKT1, a key molecule in the PI3K-Akt signaling pathway, is closely associated with liver cancer invasiveness when hyperactivated.[15] The active components of this herb pair may inhibit pathway activation by targeting AKT1, thereby hindering liver cancer progression. Additionally, CYP1A1 and members of the UGT1A family are involved in the metabolic activation and detoxification of exogenous carcinogens, and abnormal expression can affect the malignant transformation of hepatocytes.[17,18] Molecular docking results showed that kaempferol exhibited the strongest binding activity with CYP1A1, indicating favorable binding affinity, providing molecular-level evidence that the herb pair may exert its effects through a "component-target" interaction.

GO function and KEGG pathway enrichment analyses further revealed the molecular mechanisms by which the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair exerts therapeutic effects against liver cancer. GO functional enrichment for *Psoralea corylifolia* Linn. alone indicated that its core targets are mainly involved in biological processes such as "negative regulation of apoptotic process", "response to xenobiotic stimulus" and "lipid metabolic process" primarily localized in subcellular structures such as the cytoplasm and extracellular vesicles, exerting molecular functions including protein kinase activity and transferase activity. KEGG pathway analysis showed significant enrichment in "Pathways in cancer", "Lipid and atherosclerosis", "PI3K-Akt signaling pathway" and "MAPK signaling pathway". Among these, the PI3K-Akt and MAPK signaling pathways are critical in liver cancer development, and their abnormal activation can promote tumor cell proliferation and inhibit apoptosis,[19,20] suggesting that *Psoralea corylifolia* Linn. may modulate the malignant phenotype of liver cancer cells by targeting these pathways. For *Epimedium brevicornu* Maxim. alone, GO functional enrichment focused on biological processes such as "positive regulation of transcription by RNA polymerase II", "positive regulation of gene expression" and "negative regulation of apoptotic process", with core targets localized in regions including protein-containing complexes and chromatin, functioning through enzyme binding and protein homodimerization activity. KEGG pathway analysis similarly showed enrichment in core pathways such as "Pathways in cancer" and "PI3K-Akt signaling pathway", indicating that *Epimedium brevicornu* Maxim. may intervene in liver cancer progression through multiple pathways, including regulation of gene transcription and signal transduction.

The enrichment characteristics of the core target set of the single herb were compared with those of the 221 common targets of the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herbal pair. The results showed that they had intersections in core pathways (such as Lipid and atherosclerosis, etc.), and the number of targets enriched by the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair was also higher than that of the single herb, suggesting that the compatibility of the herb pair is not simply the superposition of targets, but rather through the synergistic effect of active components, it enhances the targeted regulatory ability of the core oncogenic pathways and expands the anti-liver cancer action dimension. Next, the target sites of the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair were further screened and enriched analyzed. The GO functional enrichment of the synergistic effects of the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair indicates that its core targets are primarily involved in the "flavonoid metabolic process", "estrogen metabolic process" and "xenobiotic metabolic process", mainly localized in critical areas such as the endoplasmic reticulum and cell membrane, exerting their effects through enzyme binding and protein heterodimerization activities. The KEGG pathway enrichment is notably concentrated in "Chemical carcinogenesis - receptor activation", "Steroid hormone biosynthesis", "Retinol metabolism", "Chemical carcinogenesis - DNA adducts", "Metabolism of xenobiotics by cytochrome P450" and "Lipid and atherosclerosis" pathways. Among these, the "Chemical carcinogenesis - receptor activation" pathway contains the largest number of targets. This pathway can inhibit hepatocellular malignancy by blocking the receptor activation of exogenous carcinogens and interrupting downstream pro-cancer signaling, suggesting that it may be a key pathway through which the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair exerts its anti-liver cancer effects. Notably, *Psoralea corylifolia* Linn. and *Epimedium brevicornu* Maxim. Individually are enriched in core pathways such as "Pathways in cancer" and "PI3K-Akt signaling pathway", whereas the herb pair further concentrates on metabolism-related pathways. This suggests that the two herbs may act through a "complementary synergy": *Psoralea corylifolia* Linn. and *Epimedium brevicornu* Maxim. exert individual effects by regulating signaling and drug metabolism-related targets, respectively, while their combination enhances anti-liver cancer effects by modulating metabolic processes. This finding confirms the synergistic advantage of the herb pair in traditional Chinese medicine.

This study systematically analyzed the multi-component, multi-target, and multi-pathway synergistic mechanisms of the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair in the treatment of liver cancer through network pharmacology methods. However, certain limitations still exist: First, the screening of active components and targets in this study was based on existing databases, which may have led to the omission of some active components or targets, and the metabolic transformation of the drug components *in vivo* was not considered. Second, network pharmacology analysis provides predictive results, and the interactions between core components and targets, as well as the regulatory mechanisms of key pathways, still require further validation through *in vitro* cell experiments and *in vivo* animal experiments. Finally, this study did not consider the impact of the compatibility ratio of the herb pair on the content and efficacy of active components, and the mechanistic differences under different compatibility ratios still need to be further explored.

In summary, this study predicts through network pharmacology analysis that the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair may exert anti-liver cancer effects through core active components such as kaempferol, bavachalcone, quercetin, and luteolin, targeting key hubs including TP53, AKT1, and CYP1A1, and regulating crucial pathways such as "Chemical carcinogenesis - receptor activation" and the "Lipid and atherosclerosis". These effects are mediated through multiple mechanisms, including modulation of metabolic processes, signal transduction, and apoptosis. The findings of this study

provide a scientific basis for the clinical application of the "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair and lay a foundation for subsequent experimental research and the development of novel anti-tumor drugs.

5. Conclusions

By combining network pharmacology with molecular docking, this study systematically explored the potential molecular mechanisms of "*Psoralea corylifolia* Linn.-*Epimedium brevicornu* Maxim." herb pair in the treatment of liver cancer. These findings provide new insights into the synergistic regulatory effects of this herb pair on the pathogenesis of liver cancer, thereby laying a theoretical foundation for the subsequent development of anti-liver cancer drugs based on the key components or targets of this herb pair.

CRediT authorship contribution statement

Meijun Yue: Writing – original draft, Visualization, Software, Methodology, Formal analysis, Conceptualization. **Naiqiu Lin:** Supervision, Investigation. **Shiqi Jia:** Software, Formal analysis. **Qiong Gu:** Methodology. **Guohui Li:** Writing – review & editing, Supervision. **Chunyu Li:** Writing – review & editing, Supervision, Software.

Informed consent statement

Not applicable.

Institutional review board statement

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Data availability

The additional data supporting the manuscript are available from the corresponding author upon request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

The following abbreviations are used in this manuscript:

PPI	protein–protein interaction
GO	Gene Ontology
KEGG	Kyoto Encyclopedia of Genes and Genomes
TCMSP	Traditional Chinese Medicine Systems Pharmacology
TDD	Therapeutic Target Database
OMIM	Online Mendelian Inheritance in Man
OB	oral bioavailability
DL	drug-likeness
BP	Biological Process
CC	Cellular Component
MF	Molecular Function

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