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The Network Pharmacology and Multi-Omics Study on the Anti-Hepatocellular Carcinoma Effects of Zhuang Medicine Compound Tiecao Capsules

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Abstract

Objective: To elucidate the mechanism of the Zhuang medicine compound Tiecao Capsule against Hepato-Cellular Carcinoma (HCC) using network pharmacology. **Methods:** Active ingredients and their targets were collected from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) Database and literature. Disease-drug common targets were screened using GeneCards. A PPI network was constructed using STRING, and the top 30 key targets were screened using R software. Human Protein Atlas (HPA) was used to explore the protein expression levels of core targets, and Gene Expression Profiling Interactive Analysis 2 (GEPIA2) was used to analyze correlations among the targets. Gene Ontology (GO)/Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis was performed using Database for Annotation, Visualization and Integrated Discovery (DAVID). Eighteen metabolites related to liver cancer were selected from Human Metabolome Database (HMDB), and HCC-related metabolic pathways were analyzed using the metabolomics analysis platform MetaboAnalyst. Molecular docking was validated using AutoDock. Prognostic validation was performed using The Cancer Genome Atlas (TCGA) clinical data combined with Grammar of Graphics Plot 2(GGPLOT2) and Gene Expression Profiling Interactive Analysis 2 (GEPIA2). Single-cell sequencing was used to locate target expression. **Results:** 113 intersecting genes and 6 core targets (AKT1,

VEGFA, IL6, MAPK8, EGFR, SRC) were obtained. Significant correlations were found between IL6-AKT1, MAPK8-SRC, and VEGFA-EGFR; MAPK8, SRC, and VEGFA proteins were highly expressed and correlated with TNM stage and Grade, with low expression associated with better survival; bile acid and D-arginine metabolism were abnormal; SRC/VEGFA were mainly enriched in macrophages and fibroblasts. **Conclusion:** Zhuang medicine compound Tiecao Capsule may potentially inhibit the progression of hepatocellular carcinoma by targeting multiple proteins such as AKT1/VEGFA/SRC through active ingredients including quercetin and kaempferol. This proposed mechanism involves the regulation of the tumor microenvironment at both protein and metabolomic levels, and the modulation of pathways such as PI3K-AKT signaling and tumor microenvironment metabolism.

Keywords

Liver Cancer, Zhuang Medicine Compound Tiecao Capsule, Network Pharmacology, Bioinformatics

1. Introduction

Hepato-Cellular Carcinoma (HCC) is ranked among the top three malignant tumors in both incidence and mortality rates in China. Liver resection surgery is the preferred treatment for hepatocellular carcinoma patients without cirrhosis. Unfortunately, the tumor recurrence rate is high [1], accompanied by many complications, with a five-year recurrence rate reaching 70%. Currently, there are no effective adjuvant therapies to significantly reduce the recurrence rate. Liver transplantation has always been an effective means for treating liver failure and liver cancer. However, the main challenge facing liver transplantation is the shortage of donors, which may lead to malignant progression of liver cancer making patients unsuitable for transplantation, thus affecting treatment efficacy. Liver cancer immunotherapy mainly includes immunomodulators, immune checkpoint blockers, tumor vaccines, and cellular immunotherapy [2]. These treatments have certain anti-tumor effects but await validation through large-scale clinical studies. "Traditional Chinese Medicine (TCM)" has a long history in treating liver cancer in China and offers advantages such as multi-component, multi-target action, and less susceptibility to drug resistance, presenting significant research potential [3].

Zhuang medicine compound Tiecao Capsule is a modern ethnic medicine formula developed based on the traditional medication experience of the Zhuang ethnic group, combined with modern pharmacological research. It is composed of *Berchemia lineata* (Tiebaojin), *Hedyotis diffusa* (Baihuasheshecao), *Scutellaria barbata* (Banzhilian), *Scrophularia ningpoensis* (Xuanshen), *Astragalus membranaceus* (Huangqi), *Bupleurum chinense* (Chaihu), *Glycyrrhiza uralensis* (Gancao), and other Chinese herbs. The combination of these herbs works together to reduce swelling, disperse nodules, expel pathogens, and support healthy energy, demon-

strating significant clinical effects [4] [5]. Zhuang medicine compound Tiecao Capsule is widely used clinically to treat liver cancer with notable therapeutic effects. TCM compounds achieve holistic regulation and treatment of the body through multiple components and multiple targets [6]. Network pharmacology, based on systems biology theory, emphasizes the action of drugs through multiple targets and pathways, offering significant advantages for studying the multi-target therapeutic mechanisms of TCM. Furthermore, proteomics and metabolomics are used to study the effects of Zhuang medicine compound Tiecao Capsule on liver cancer. This study employs network pharmacology methods to investigate the multi-target, multi-pathway mechanism of Zhuang medicine compound Tiecao Capsule in treating liver cancer, aiming to explore the modern pharmacological effects of TCM compounds.

Notably, as an integral component of traditional Chinese medicine, Zhuang Medicine emerges from the distinctive cultural and medical heritage of the Zhuang ethnic group in Guangxi. It is characterized by its own theoretical foundations—such as the concepts of "San Dao Liang Lu" (Three Pathways and Two Routes) and "toxicity and deficiency as causes of disease"—along with extensive expertise in herbal medicine. The Zhuang medicine compound Tiecao Capsule represents a modern formulation rooted in this ethnic medical tradition. Its formula design and selection of medicinal herbs reflect the core principles of Zhuang medicine in "regulating Qi, expelling toxins, and reinforcing deficiency," demonstrating both connections and distinctions within the broader framework of TCM. In contrast to generalized TCM theories, Zhuang medicine is deeply informed by the unique worldview of the Zhuang people and the rich medicinal resources of the Lingnan region. Its theoretical framework and clinical practices exhibit strong regional and ethnic specificities, as exemplified in liver disease treatment by the frequent use of local herbs such as *Berchemia lineata* (Tiebaojin), highlighting its distinctive approach to herb selection and formula composition.

2. Materials and Methods

2.1. Collection of Compound Information and Screening of Active Ingredients for Zhuang Medicine Compound Tiecao Capsule

Potential active ingredients were screened through the following procedure: First, compound information for *Astragalus membranaceus*, *Hedyotis diffusa*, *Scutellaria barbata*, and *Scrophularia ningpoensis* was retrieved using The "TCM Systems Pharmacology (TCMSP)" (http://tcmspw.com/index.php) Database and Analysis Platform. Preliminary screening was conducted using the criteria of Oral Bioavailability (OB) ≥ 30% and Drug-Likeness (DL) ≥ 0.18 to identify potential active ingredients from each herb. Subsequently, a systematic literature search was performed in Databases such as CNKI and PubMed for pharmacological studies related to the above-mentioned herbs and their primary constituents, with a focus on their absorption, distribution, metabolism, and excretion (ADME) characteristics in human or animal models. The screening criteria included: good bioavailability demon-

strated in multiple studies, clear pharmacological activities (e.g., antitumor, anti-inflammatory, antioxidant), and confirmation of high utilization potential in in vivo experiments. By integrating database predictions with literature evidence, compounds with high bioavailability and significant bioactivity in humans were ultimately selected to ensure their suitability for subsequent network pharmacology analysis. For the remaining herbal components of the formulation not fully covered in TCMSP, such as *Berchemia lineata*, *Bupleurum chinense*, and *Glycyrrhiza uralensis*, their major compound information was obtained through literature retrieval. Target prediction was performed using the Swiss Target Prediction Database (http://www.swisstargetprediction.ch/), followed by evaluation of their ADME properties, thereby comprehensively covering all seven herbal constituents of the Tiecao Capsule formulation (*Berchemia lineata*, *Hedyotis diffusa*, *Scutellaria barbata*, *Scrophularia ningpoensis*, *Astragalus membranaceus*, *Bupleurum chinense*, and *Glycyrrhiza uralensis*) to ensure compliance with the screening criteria of high bioavailability and high activity. Ultimately, a total of 72 major compounds were identified, including 10 from *Hedyotis diffusa*, 26 from *Scutellaria barbata*, 16 from *Astragalus membranaceus*, 10 from *Scrophularia ningpoensis*, and 10 from *Berchemia lineata*, which were subsequently used for network pharmacology analysis.

2.2. Proteomics Analysis of Zhuang Medicine Compound Tiecao Capsule

To analyze the expression changes of key signaling pathway-related genes in hepatocellular carcinoma (HCC) tissues, we retrieved immunohistochemistry (IHC) staining images from the Human Protein Atlas (HPA) Database (https://www.proteinatlas.org) for six genes—AKT1, EGFR, IL6, MAPK8, SRC, and VEGFA—at the protein level in both normal liver and HCC tissues. For each gene, one representative normal tissue sample and one HCC tissue sample were selected for visualization, and their corresponding patient IDs were recorded for reference.

2.3. Prediction of Chemical Component Targets and Construction of Herb-Compound-Target Network for Zhuang Medicine Compound Tiecao Capsule

The "TCMSP Database" (http://tcmspw.com/index.php) and the "SwissTargetPrediction Database" (http://www.swisstargetprediction.ch/) were used to query the targets of the main components in Zhuang medicine compound Tiecao Capsule. The UniProt database was used to convert the obtained target names into gene names. The relationships between Chinese herbal compounds and targets were imported into Cytoscape 3.10.0 software to construct a herb-compound-target network diagram.

2.4. Prediction of Potential Therapeutic Targets and Venn Diagram Drawing for Zhuang Medicine Compound Tiecao Capsule in Treating Liver Cancer

Using the "GeneCards Database", with species set to "Homo Sapiens", relevant

target genes for liver cancer were retrieved using the keywords "Liver Cancer" and HCC. The Venny 2.1 online tool was used to map the intersection between the predicted drug targets and the disease targets, draw a "Venn Diagram", and obtain potential drug targets for Zhuang medicine compound Tiecao Capsule in treating liver cancer.

2.5. Construction of PPI Network and Screening of Core Targets

The 113 screened common targets were imported into the "STRING Database" (https://string-db.org/), with the species set to "Homo Sapiens" and a confidence score threshold greater than 0.700. Protein-Protein Interaction (PPI)network information was obtained and imported into R 4.4.1 software. The gene enrichment count value was calculated using R 4.4.1 software to screen out the core targets.

2.6. Core Target Correlation

The correlation of genes in HCC tissues was analyzed using the GEPIA2 online platform.

2.7. Target Functional Pathway Annotation Analysis

The common target genes obtained from the drug and disease were imported into R 4.4.1 software. "Gene Ontology (GO)" enrichment analysis, including "Biological Process (BP)", "Cellular Component (CC)", and "Molecular Function (MF)", and "Kyoto Encyclopedia of Genes and Genomes (KEGG)" pathway enrichment analysis were performed with a significance level set at $P < 0.05$.

2.8. Liver Cancer Metabolomics Enrichment Analysis

To explore the functional enrichment of differential metabolites in biological pathways, we used the Enrichment Analysis module in the online metabolomics analysis platform MetaboAnalyst 5.0 (https://www.metaboanalyst.ca) for pathway enrichment analysis. Eighteen metabolites related to liver cancer selected from the HMDB database were used as the input metabolite list. Homo sapiens was selected as the study species, and the SMPDB metabolite library was used for functional enrichment analysis.

2.9. Molecular Docking

Six core components were screened based on high Degree values. AutoDock software was used for flexible docking between *quercetin, kaempferol,* β*-sitosterol, wogonin, luteolin, stigmasterol* and the proteins AKT1, VEGFA, IL6, MAPK8, EGFR, and SRC.

2.10. Prognostic Analysis of Core Targets

RNAseq data (level 3) and corresponding clinical information for liver cancer were obtained from The Cancer Genome Atlas (TCGA) Database. Given that the

clinical data (such as TNM stage and Grade) are ordinal categorical variables that may not follow a normal distribution, non-parametric statistical methods were employed for the correlation analysis. Spearman's rank correlation coefficient was used to assess the relationships between core target expression levels and clinical parameters. The statistical analyses were conducted using R software package v4.0.3. Significance levels were set as *P < 0.05, **P < 0.01, and ***P < 0.001. We employed the Wilcoxon test and Kruskal-Wallis test for our analyses: the former was used to compare the mRNA expression of core targets between HCC and normal tissues, while the latter was applied to analyze the differences in the expression of these targets among HCC patients with different TNM stages (I-III) and tumor grades (1 - 4). The median expression levels of core targets in HCC tissues and normal tissues were analyzed using the GEPIA2 online platform, with parameters set as $|\log FC| \geq 1$, $P < 0.01$. The relationship between core target expression and patient overall survival was assessed using Kaplan-Meier survival analysis. The optimal cut-off value for defining high and low expression groups was set at the 50th percentile (median expression), and a log-rank test was employed to evaluate the statistical significance of differences between the survival curves, with a 95% confidence interval.

2.11. Single-Cell Sequencing Analysis

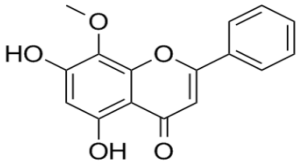
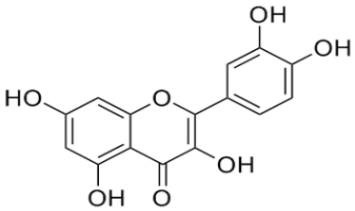
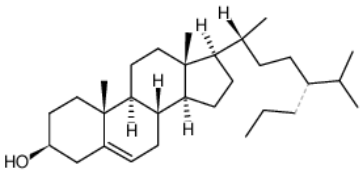
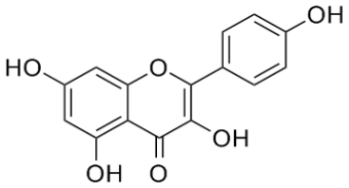
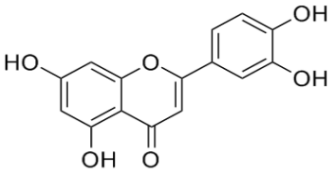
Specifically for the samples GSM8825750, GSM8825751, and GSM8825752, we used the "Seurat package" in R to filter out data with mitochondrial gene content higher than 25%. After filtering, the data were first normalized using "NormalizeData", then 2000 highly variable genes were identified using "FindVariableGenes". The harmony package was used to remove batch effects from the single-cell data. The "Seurat package" in R was used to cluster the single-cell data, and t-SNE was used to project the single cells into two dimensions. PCA was performed on the single-cell data using "RunPCA". Cell types were annotated using the SingleR package, and t-SNE was used to visualize the expression of core genes in different cell types.

3. Results

3.1. Screening of Main Active Ingredients in Zhuang Medicine Compound Tiecao Capsule

The "TCMSP Database" (http://tcmspw.com/index.php) and the "SwissTargetPrediction Database" (http://www.swisstargetprediction.ch/) were used to query the targets of the main components in Zhuang medicine compound Tiecao Capsule. Combined with literature, ADME screening was performed. Screening based on "Oral Bioavailability (OB)" ≥ 30%) and "Drug-Likeness (DL)" ≥ 0.18) yielded 72 main compounds: 10 from *Hedyotis diffusa*, 26 from *Scutellaria barbata*, 16 from *Astragalus membranaceus*, 10 from *Scrophularia ningpoensis*, and 10 from *Berchemia lineata*. Basic information for the top 5 representative active ingredients of Zhuang medicine compound Tiecao Capsule is shown in (**Table 1**).

Table 1. The basic information of the top 5 active ingredients Zhuang medicine compound Tiecao Capsule.

No.	Molecule name	OB (%)	DL	Structure
BZL13	wogonin	30.68	0.23	
A1	quercetin	46.43	0.28	
E1	beta-sitosterol	36.91	0.75	
B1	kaempferol	41.88	0.24	
BZL20	luteolin	36.16	0.25	

3.2. Construction of the Compound-Target Network for Zhuang Medicine Compound Tiecao Capsule

The targets corresponding to the 72 main compounds obtained above were predicted using the TCMSP Database. After removing duplicates, 228 action targets were obtained. The herb-compound-target network was constructed using Cytoscape 3.7.2 software, containing 981 edges and 296 nodes. Red circular nodes represent targets. The red nodes in the upper left represent active ingredients from *Hedyotis diffusa*; the purple circles at the top center represent active ingredients from *Scutellaria barbata*; the pink nodes in the upper right represent active ingredients from *Astragalus membranaceus*; the blue diamond in the center represents HCC treatment targets. In the periphery, A1 is quercetin, a common active ingredient of *Berchemia lineata*, *Hedyotis diffusa*, *Astragalus membranaceus*, and *Scutellaria barbata*; B1 is kaempferol, a common active ingredient of *Berchemia line-*

ata and *Astragalus membranaceus*; C1 is eriodictyol, a common active ingredient of Berchemia lineata and *Scutellaria barbata*; D1 is stigmasterol, a common active ingredient of *Hedyotis diffusa* and *Scutellaria barbata*; E1 is beta-sitosterol, a common active ingredient of *Hedyotis diffusa*, *Scutellaria barbata*, and *Scrophularia ningpoensis*; F1 is sitosterol, a common active ingredient of *Scutellaria barbata* and *Scrophularia ningpoensis*. Larger target nodes indicate stronger interaction relationships. This compound-target network fully reflects the multi-component, multi-target mechanism of TCM compounds in intervening diseases (**Figure 1**).

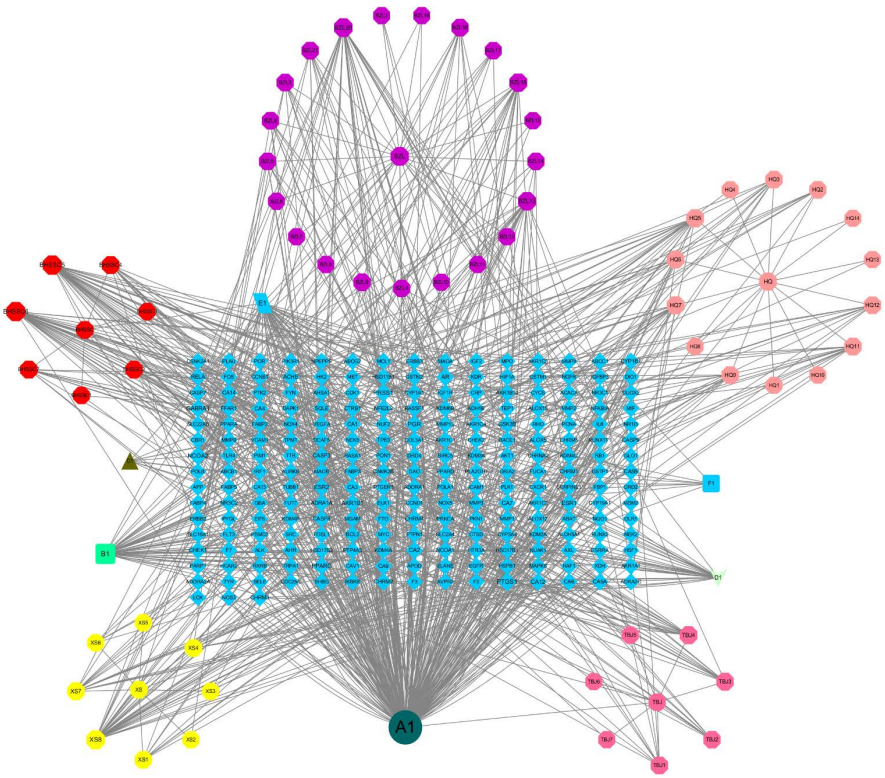


Figure 1. Zhuang medicine compound Tiecao capsule compound-target network.

3.3. Prediction of Potential Therapeutic Targets of Compound Tiecao Capsule for Liver Cancer

Relevant therapeutic targets for liver cancer were retrieved from the GeneCards database, yielding 1284 targets. Using the Venny online tool, the action targets of the main active ingredients in Compound Tiecao Capsule were mapped against the liver cancer targets, resulting in 113 intersecting targets. A "Venn diagram" was drawn (**Figure 2**).

3.4. Construction of the PPI Network for Compound Tiecao Capsule and Liver Cancer Proteins

The 113 intersecting targets obtained from the compound-disease mapping were imported into the "STRING database" (https://string-db.org/), with confidence set greater than 0.700. The TSV format file was exported and imported into R 4.0.0

software for analysis and processing. The count value was calculated, and the top 30 key targets for Compound Tiecao Capsule in treating liver cancer were screened out (see Figure 3). Based on the calculated count values, 6 core targets were screened out (see Table 2): AKT1, VEGFA, IL6, MAPK8, EGFR, SRC. We believe these core targets play key roles in the network. Through the GEPIA2 online analysis platform, we also found interactions among these core targets (Figure 4).

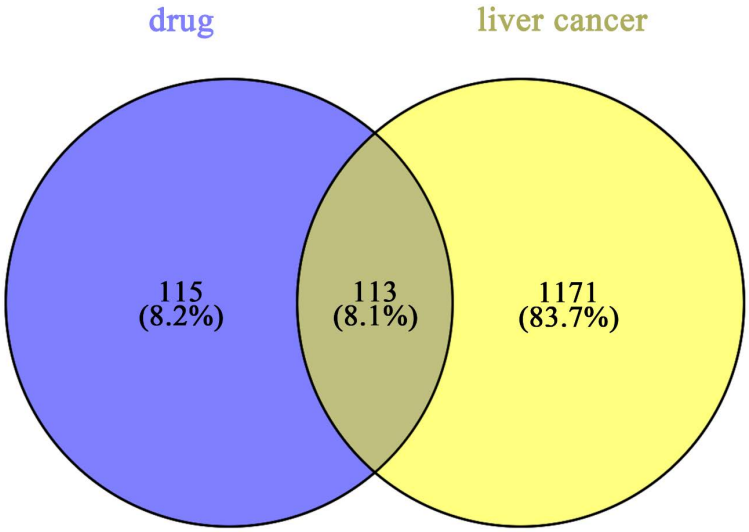


Figure 2. Zhuang medicine compound Tiecao Capsule and liver cancer target Wayne diagram.

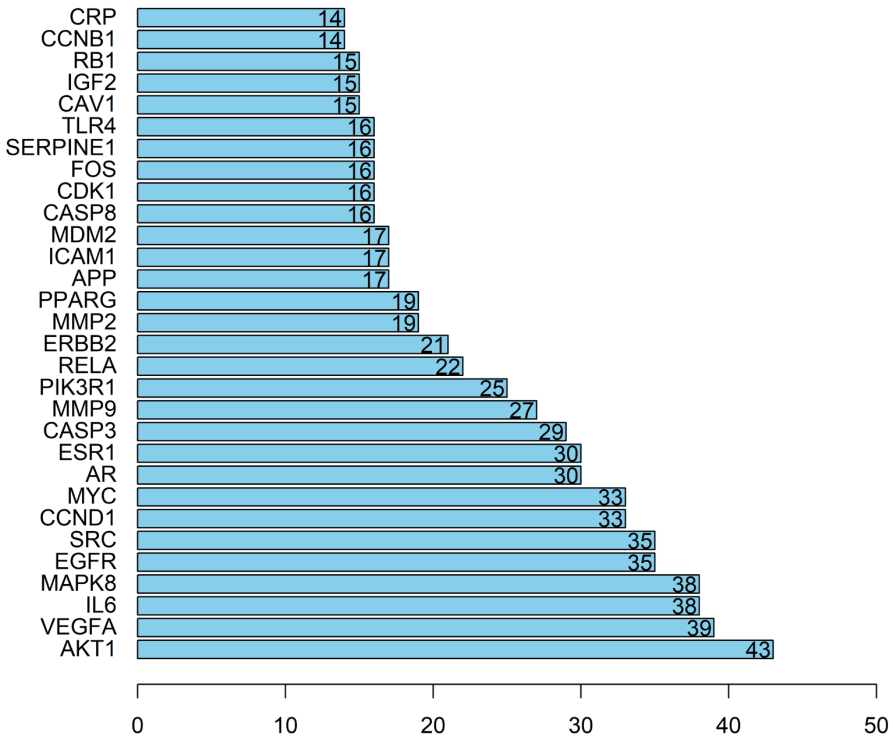


Figure 3. Interaction diagram of Zhuang medicine compound Tiecao Capsule and liver cancer protein.

Table 2. Six core targets in the PPI network of Zhuang medicine compound Tiecao Capsule.

Target Gene	English full name	Degree Value
AKT1	RAC-alphaserine	43
VEGFA	Vascular endothelial growth factor A	39
IL6	Interleukin 6	38
MAPK8	Mitogen-activated protein kinase 8	38
EGFR	Epidermal growth factor receptor	35
SRC	roto-oncogene tyrosine-protein kinase Src	35

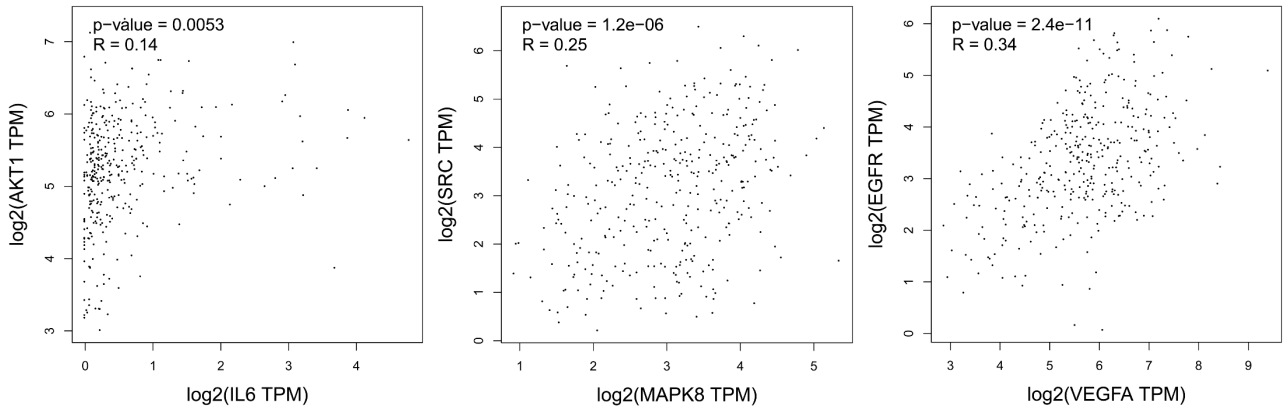


Figure 4. Relationship between six core targets in the PPI network of Zhuang medicine compound Tiecao Capsule.

3.5. GO Biological Function Annotation of Common Action Targets

GO enrichment analysis was performed on the 113 common action targets using R 4.4.1 software. Results were retained based on the criterion $P \leq 0.01$, and the top 20 entries were visualized for each category, resulting in **Figure 5**. The vertical axis represents the target information participating in the enrichment analysis, and the horizontal axis represents the number of enriched terms. **Figure 5(A)** shows the main targets enriched in biological processes, including cellular response to oxidative stress, response to steroid hormone, cellular response to reactive oxygen species, regulation of apoptotic signaling pathway, extrinsic apoptotic signaling pathway, negative regulation of apoptotic signaling pathway, etc. **Figure 5(B)** shows that the enriched cellular component terms for the action targets mainly involve vesicle lumen, membrane raft, membrane microdomain, secretory granule lumen, membrane region, cytoplasmic vesicle lumen, protein kinase complex, serine/threonine protein kinase complex, chromosome region, basal plasma membrane, etc. **Figure 5(C)** shows that the molecular functions of the action targets are mainly concentrated in protein tyrosine kinase activity, transmembrane receptor protein kinase activity, transcription factor-activity, etc.

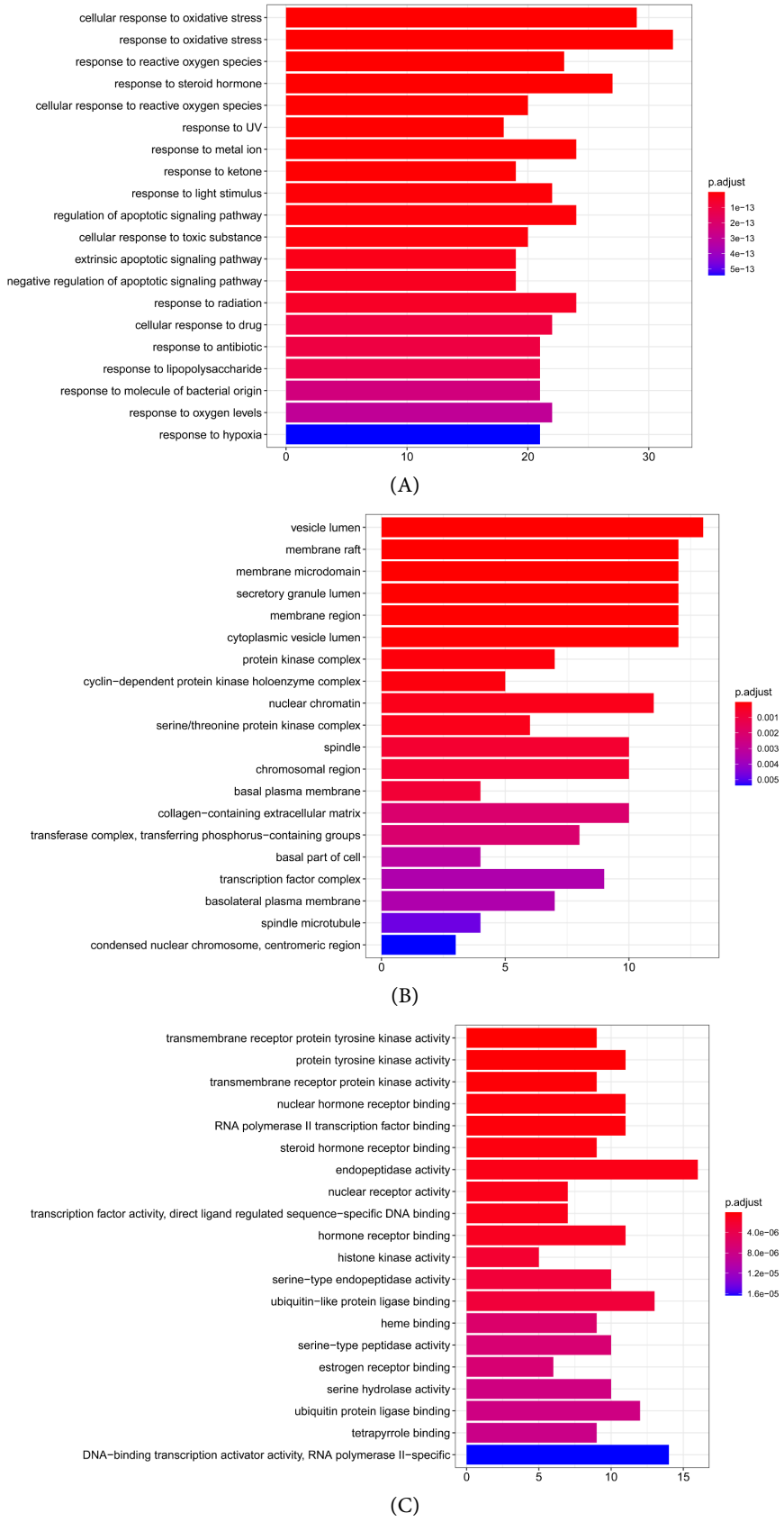


Figure 5. GO function enrichment BP (A), CC (B), MF (C) results.

3.6. KEGG Pathway Enrichment Analysis

KEGG enrichment analysis was performed on the 113 common targets using R language. Results were retained based on $P < 0.01$. Visualization was processed using Cytoscape 3.7.2 software, as shown in Figure 6. The main pathways involved include Prostate cancer, Proteoglycans in cancer, Hepatitis B, Endocrine resistance, EGFR tyrosine kinase inhibitor resistance, Kaposi sarcoma-associated herpesvirus infection, Human cytomegalovirus infection, Apoptosis, PI3K-Akt signaling pathway, AGE-RAGE signaling pathway in diabetic complications. Additionally, key pathways such as Colorectal cancer and C-type lectin receptor signaling pathway were included.

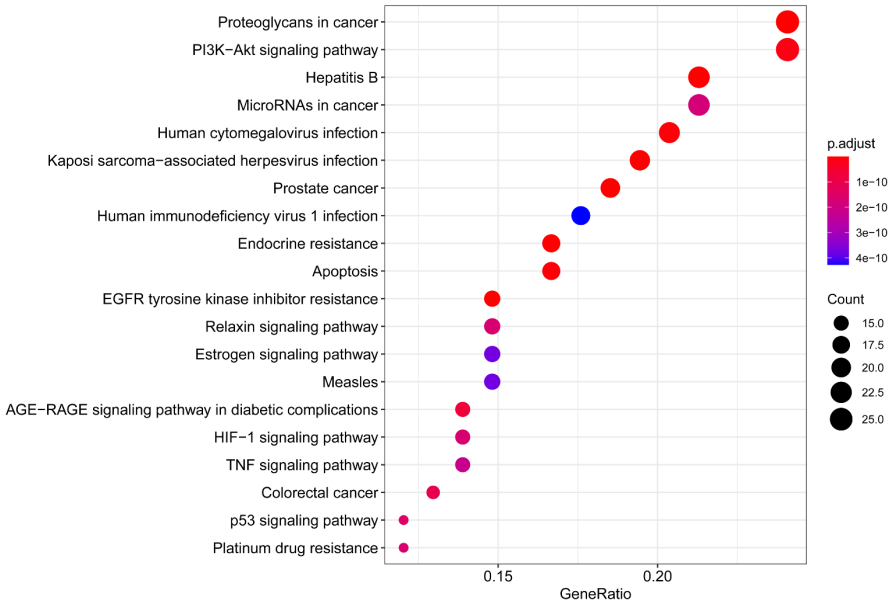


Figure 6. KEGG channel enrichment results.

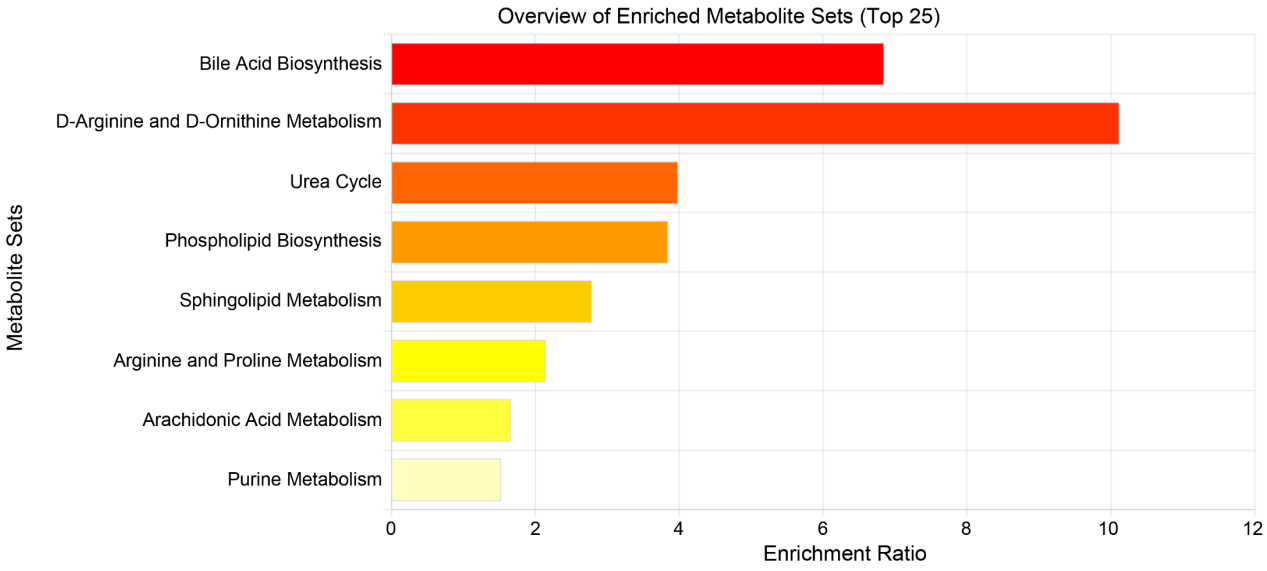
3.7. Enrichment Analysis of Liver Cancer-Related Metabolic Pathways

Pathways such as Bile Acid Biosynthesis and D-Arginine and D-Ornithine Metabolism were significantly enriched, suggesting they may play important roles in the metabolic regulation of liver cancer. Furthermore, functional associations (gray lines) exist between the Urea Cycle and Arginine and Proline Metabolism, suggesting potential biological synergistic mechanisms (Table 3).

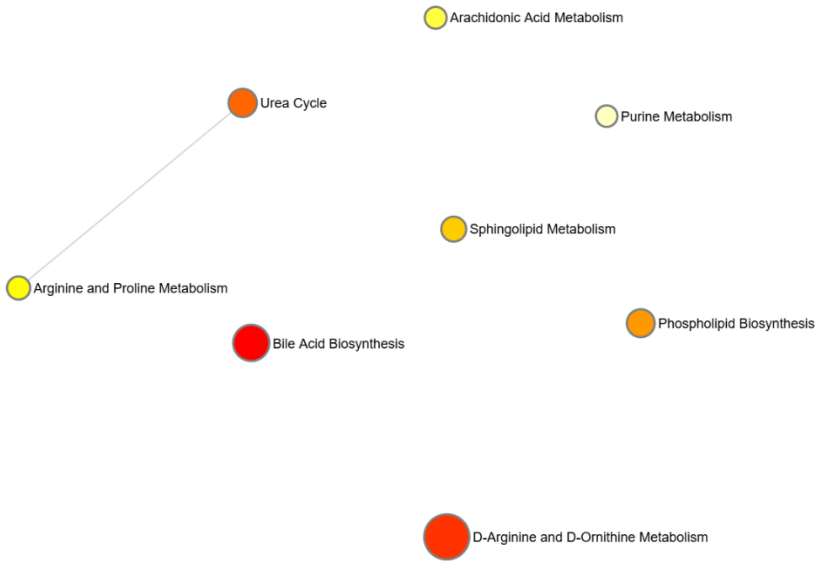
Results of metabolite set enrichment analysis based on the MetaboAnalyst 5.0 platform. (Figure 7, part A): Enrichment of 18 liver cancer-related metabolites at the metabolic pathway level. The horizontal axis represents the enrichment ratio, reflecting the concentration of metabolites in the corresponding metabolic pathway; color from light yellow to dark red indicates increasing enrichment degree. (Figure 7, part B): Metabolic pathway enrichment network diagram. Nodes represent significantly enriched metabolic pathways; color from light yellow to dark red indicates increasing enrichment degree; node size represents the enrichment ratio (Figure 7).

Table 3. Hepatocellular carcinoma (HCC)-related metabolites and their HMDB IDs.

Metabolite Name	HMDB ID
1-Methyladenosine	HMDB0003331
Glycodeoxycholic acid	HMDB0000631
Glycochenodeoxycholic acid-3-sulfate	HMDB0002497
Lysophosphatidylethanolamine (20:0/0:0)	HMDB0011511
Sphingosine-1-phosphate	HMDB0000277
Taurocholic acid	HMDB0000036
Taurodeoxycholic acid	HMDB0000896
Chenodeoxycholic acid	HMDB0000518
Lysophosphatidylcholine (16:0/0:0)	HMDB0010382
Lysophosphatidylcholine (18:0/0:0)	HMDB0010384
Hyocholic acid	HMDB0000467
Stercobilinogen	HMDB0004157
Urobilin	HMDB0004160
Arabinofuranose	HMDB0012325
D-Xylitol	HMDB0002917
Hypoxanthine	HMDB0000157
Thromboxane A2	HMDB0001452
Urea	HMDB0000294



(A)



(B)

Figure 7. Metabolite set enrichment analysis results based on MetaboAnalyst 5.0 platform.

3.8. Construction of Main Target-Pathway Network

Based on P value ranking, the top 20 pathways and related target information from the "KEGG enrichment analysis" were imported into Cytoscape 3.7.2 software to draw a pathway-target network diagram, as shown in **Figure 8**. Pink V-shapes

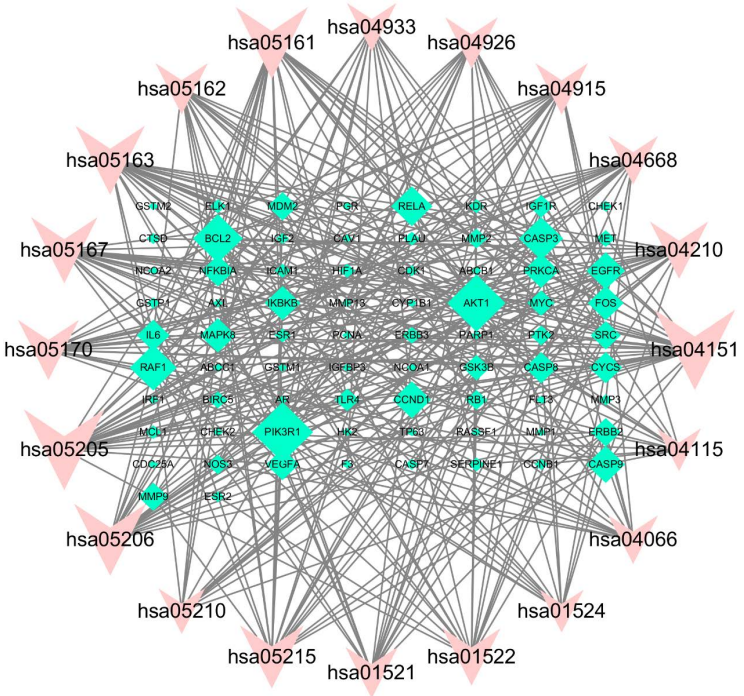


Figure 8. The main target of Zhuang medicine compound Tiecao Capsule-pathway diagram.

represent pathways, and green diamonds represent targets. Nodes are sorted by degree value; higher degree indicates greater target centrality. As core targets in the target-pathway network, they also play key roles in disease treatment. The GEPIA2 database was used to validate the expression differences of core targets in HCC tissues and normal tissues. It was found that the median mRNA expression levels of MAPK8, SRC, and VEGFA were higher in HCC tissues than in normal tissues, while the median mRNA expression levels of AKT1, EGFR, and IL6 were lower in HCC tissues than in normal tissues (Figure 9).

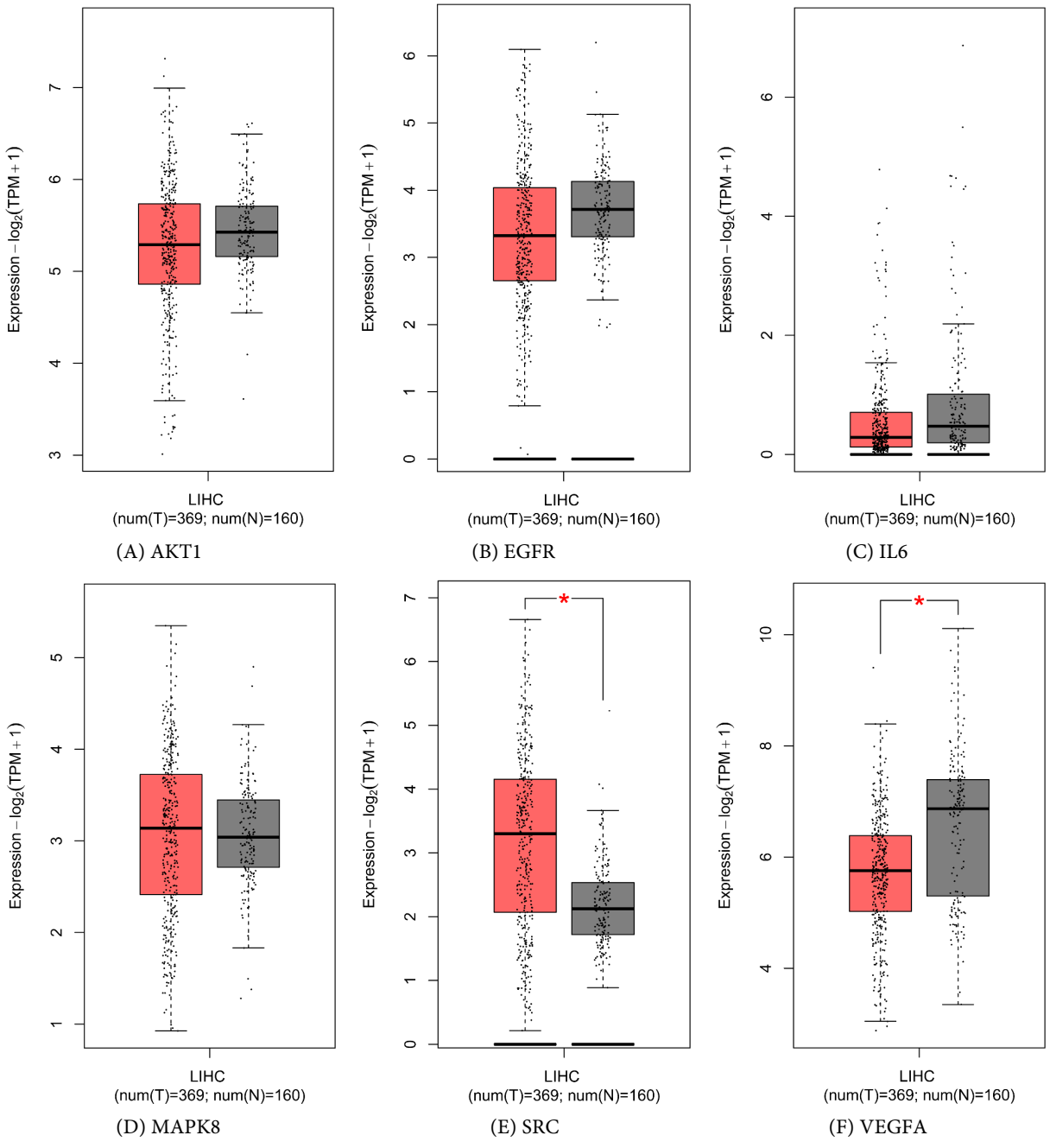


Figure 9. mRNA expression levels of core target in HCC and normal liver tissues.

3.9. Immunohistochemistry of Zhuang Medicine Compound Tiecao Capsule

At the protein expression level, the immunohistochemistry results were consistent with the transcriptome results, judged by the staining intensity. The protein expression levels of MAPK8, SRC, and VEGFA were higher in liver cancer tissues than in normal liver tissues, while the protein expression levels of AKT1, EGFR, and IL6 were lower in liver cancer tissues than in normal liver tissues (Figure 10).

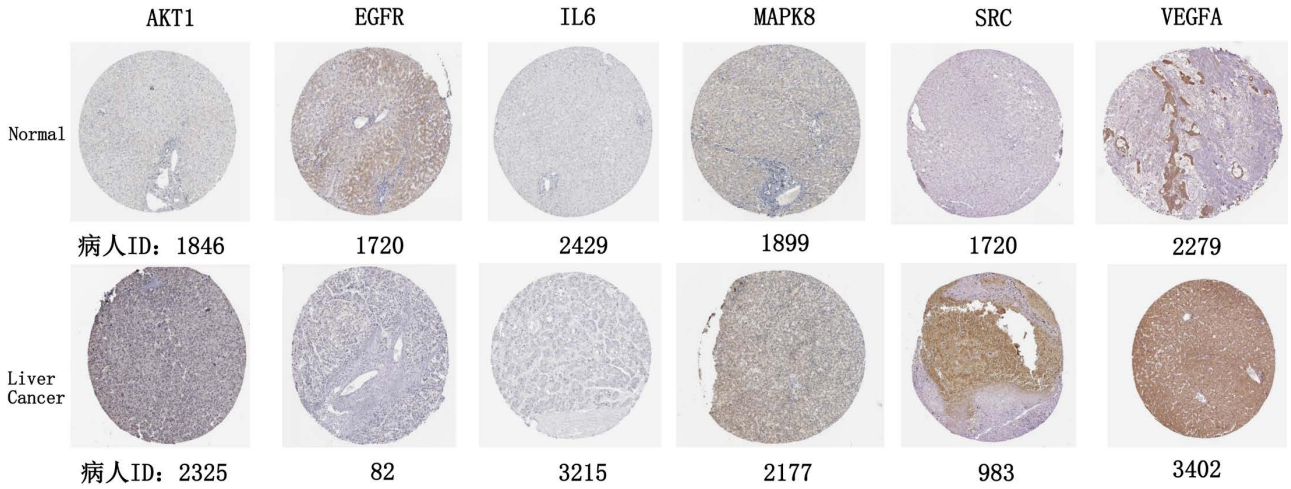


Figure 10. Immunohistochemical staining results.

3.10. Molecular Docking

The results showed that the molecular docking binding energies were all less than −5.0 kcal/mol, indicating good binding between each core target protein and the components, as shown in (Figure 11, Figure 12). Overall, SRC had the best binding affinity with the other components, followed by VEGFA and EGFR. Their stable binding may play an important role in the treatment of liver cancer by Zhuang medicine compound Tiecao Capsule.

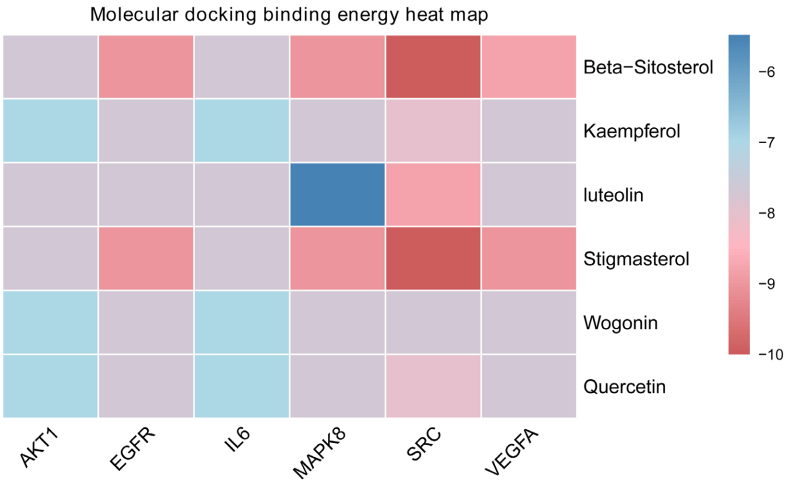


Figure 11. Molecular docking binding energy heat map.

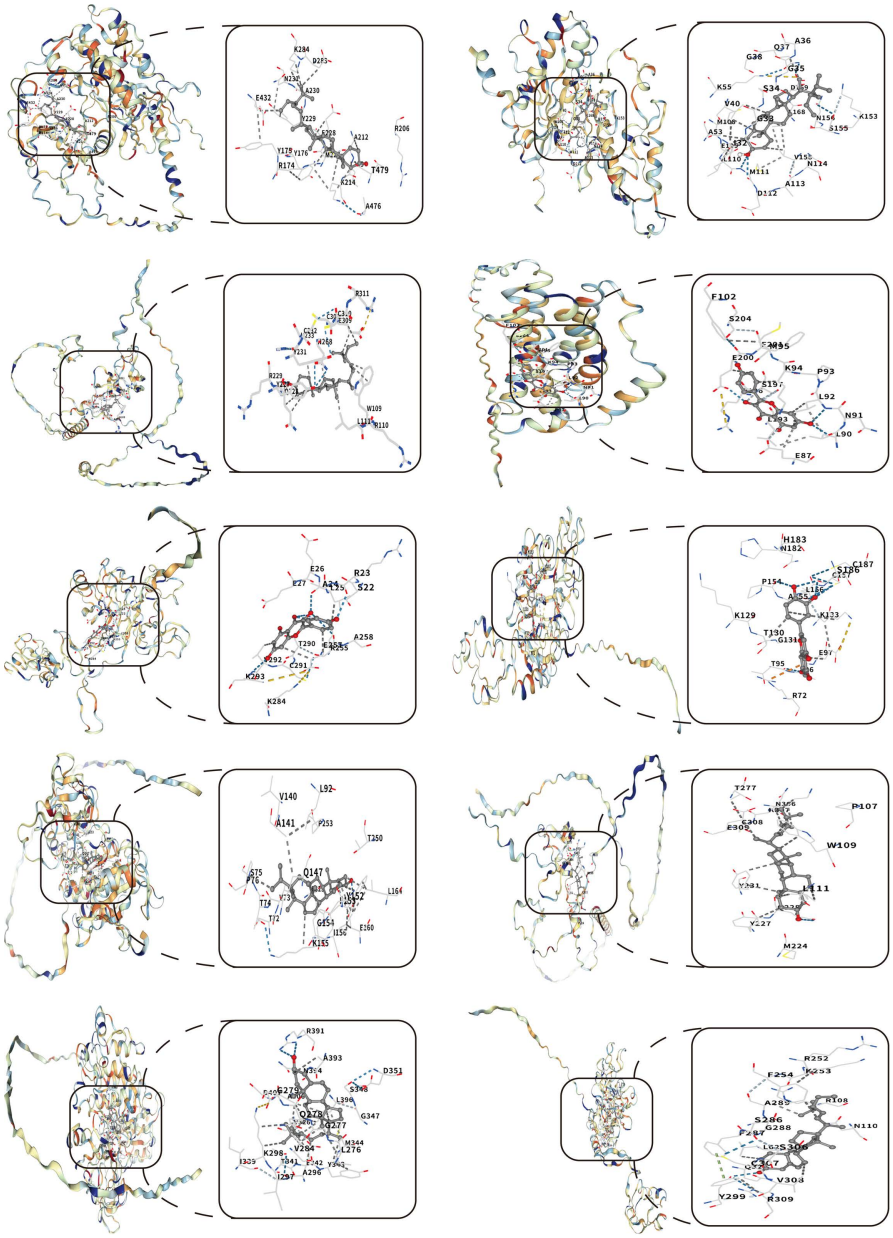


Figure 12. Core target and active ingredient docking.

3.11. Prognostic Analysis

Our study found that the expression levels of MAPK8, SRC, VEGFA, AKT1, and IL6 were positively correlated with the TNM stage (Figure 13(A), G1: TNM Stage I, G2: TNM Stage II, G3: TNM Stage III) and Grade (Figure 13(B), G1: Grade1, G2: Grade2, G3: Grade3, G4: Grade4) of liver cancer patients, while SRC showed no significant correlation with TNM stage or Grade. Prognostic analysis showed that low expression of SRC and VEGFA affected the overall survival of patients, and patients with low gene expression had higher survival rates than those with high gene expression ($P < 0.05$), which was statistically significant. In contrast, the expression of MAPK8, AKT1, EGFR, and IL6 showed no significant correlation

with patient overall survival (Figure 14).

3.12. Single-Cell Sequencing Analysis

Cells with mitochondrial gene content greater than 25% were removed from the single-cell data (Figure 15(A)). After removal, The Pearson correlation coefficient was calculated to assess the relationship between the number of detected genes and the number of unique molecular identifiers (UMIs) per cell, revealing a strong positive correlation (R = 0.91) (Figure 15(B)). The harmony package was used to remove batch effects, and t-SNE plots before and after batch removal were drawn (Figure 15(C), Figure 15(D)). The top 2000 highly variable genes were identified (Figure 15(E)) for "PCA analysis". The top 20 "Principal Components (PCs)" were selected for "cluster analysis" (Figure 16). Using a resolution of 1, 22 clusters were obtained (Figure 17(A), Figure 17(B)). These clusters were annotated using the SingleR package and labeled as NK cells, Monocytes, T cells, Macrophages, Fibroblasts, and Tissue_stem_cells (Figure 17(C)). We found that SRC and VEGFA genes were expressed more prominently in Macrophages and Fibroblasts, but their expression was not significant in T cells (Figure 17(D)).

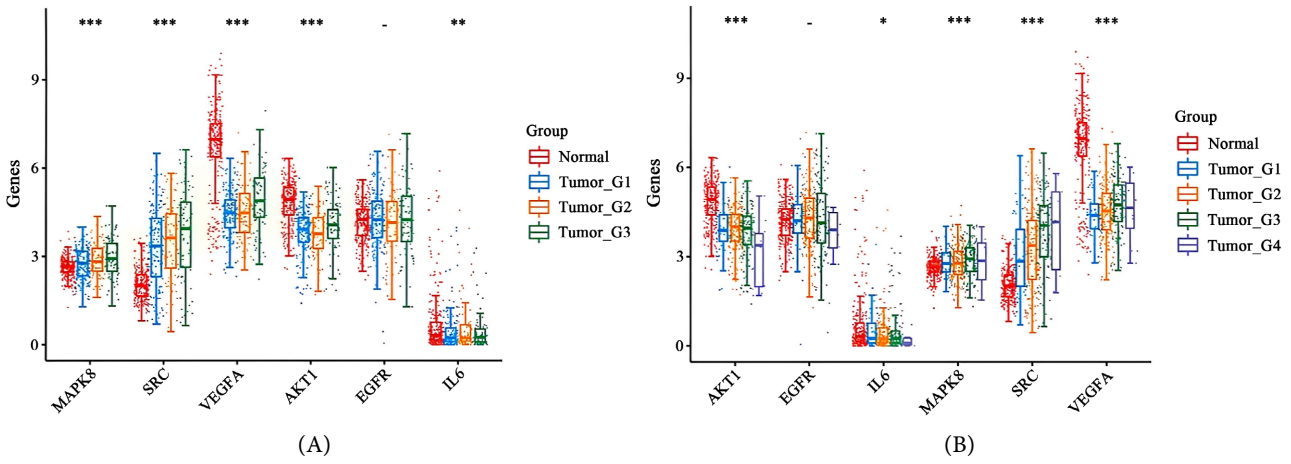
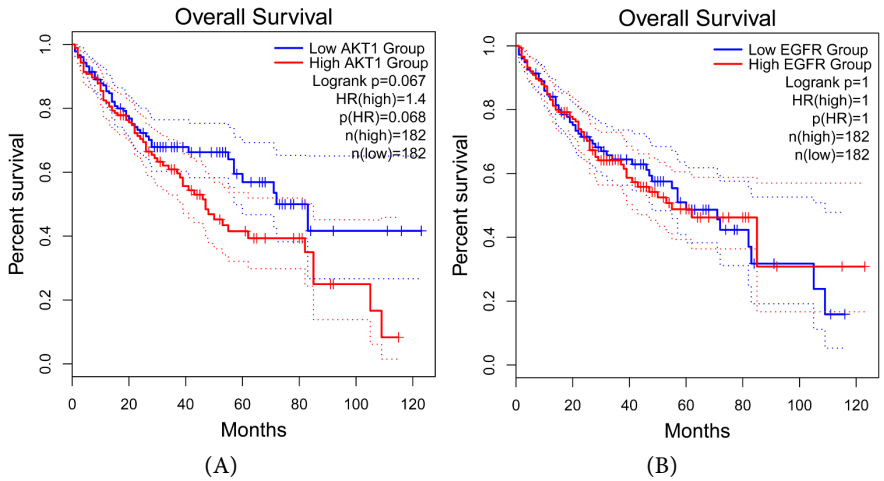


Figure 13. The expression of core targets affecting the overall survival of patients.



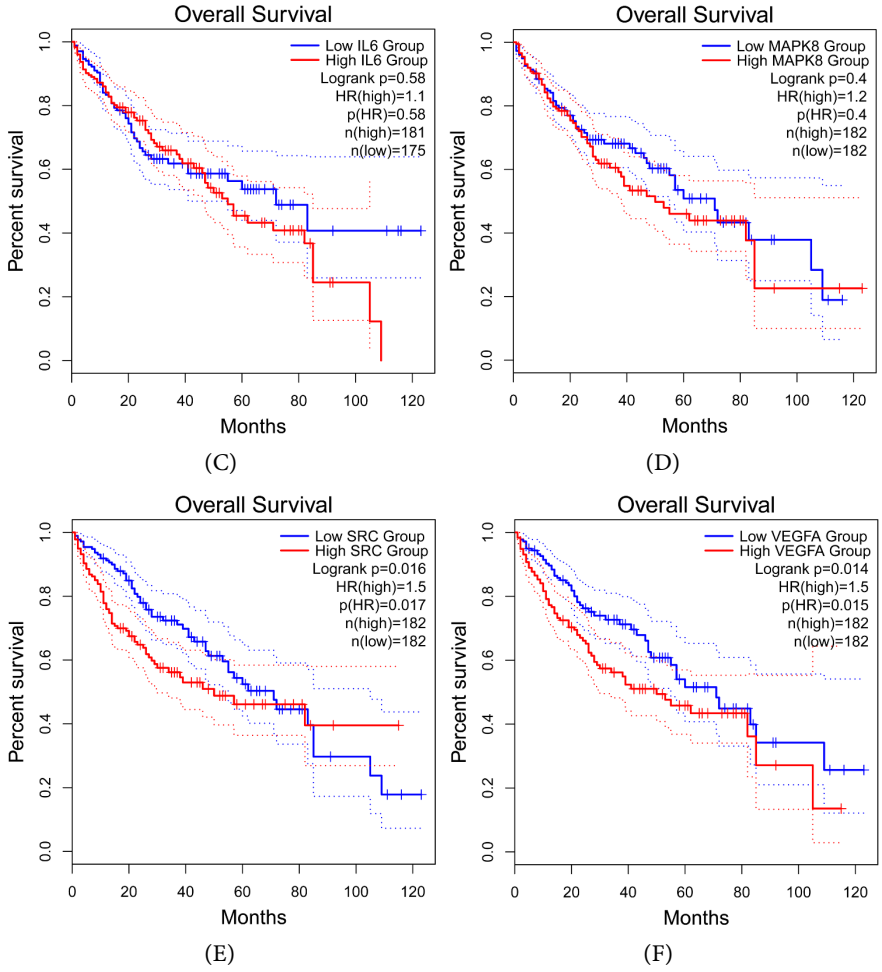
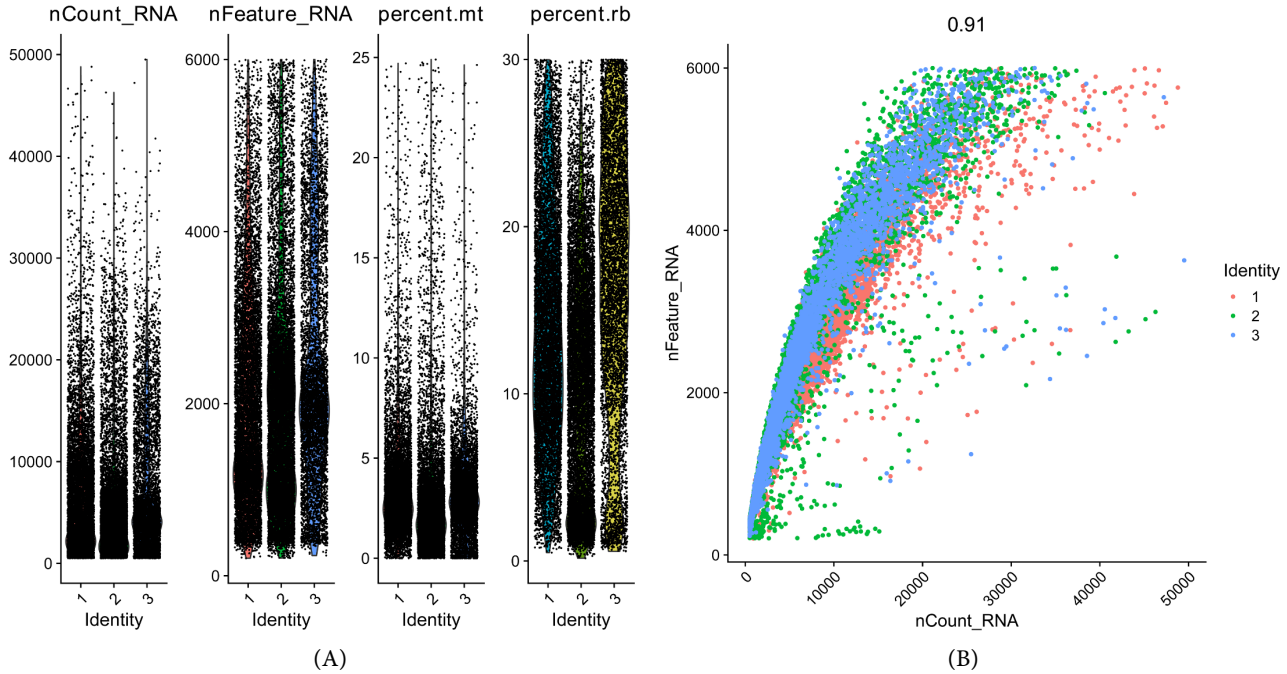
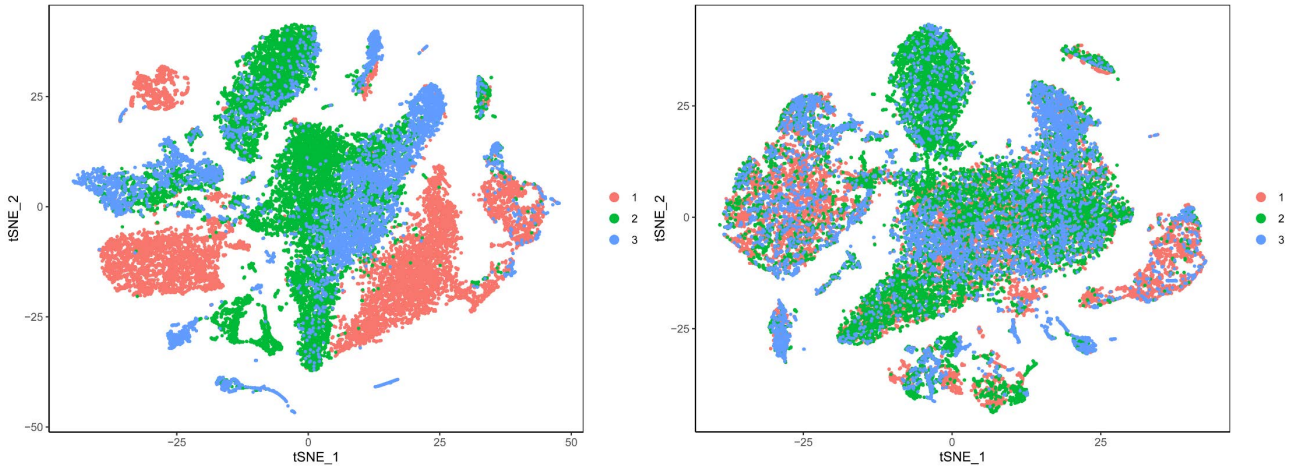
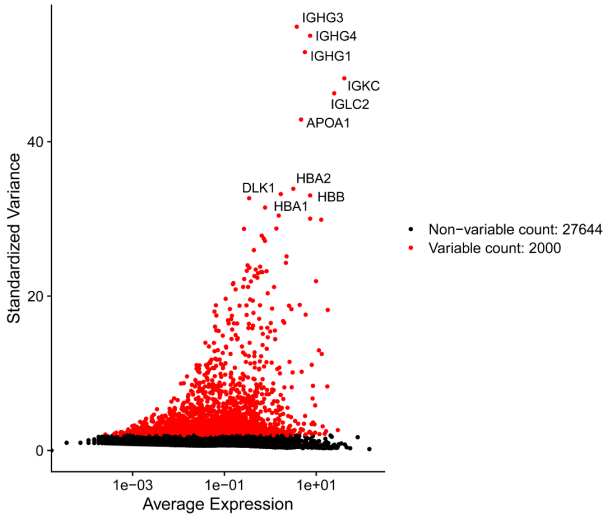


Figure 14. Relationship between expression of core target and TNM stage and grade.



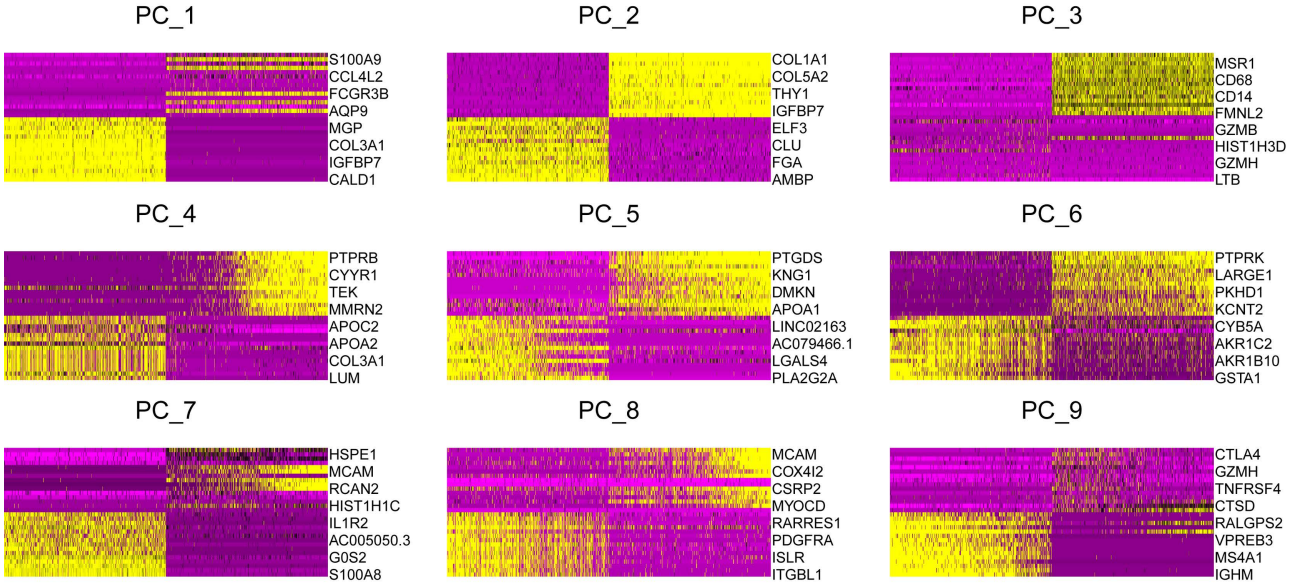


(C) (D)



(E)

Figure 15. Single-cell data cleaning and processing.



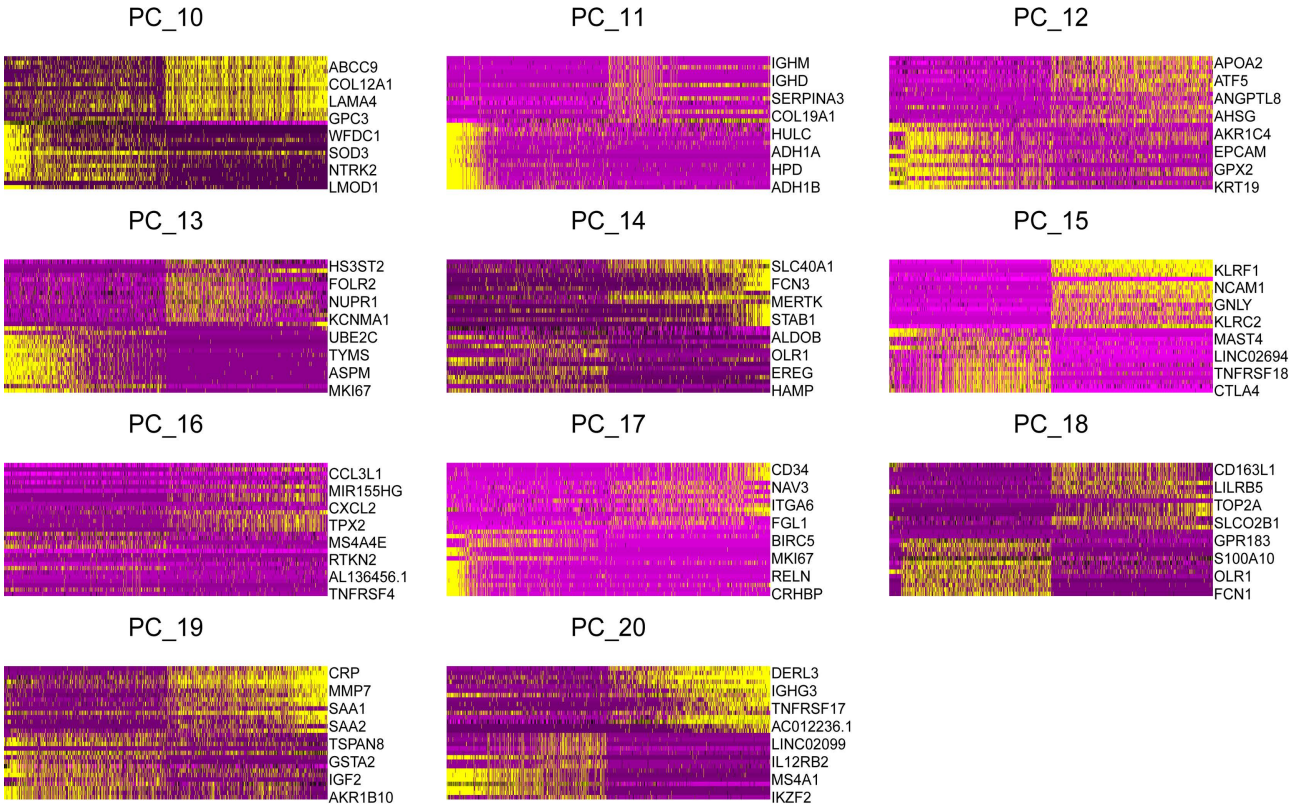
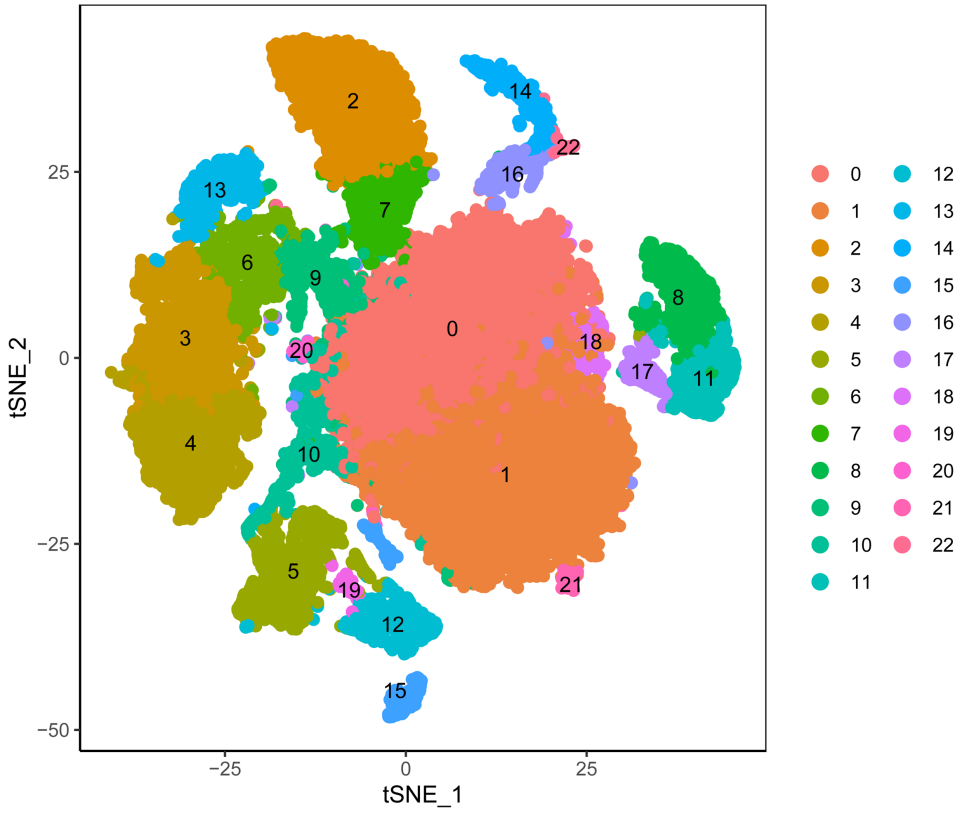
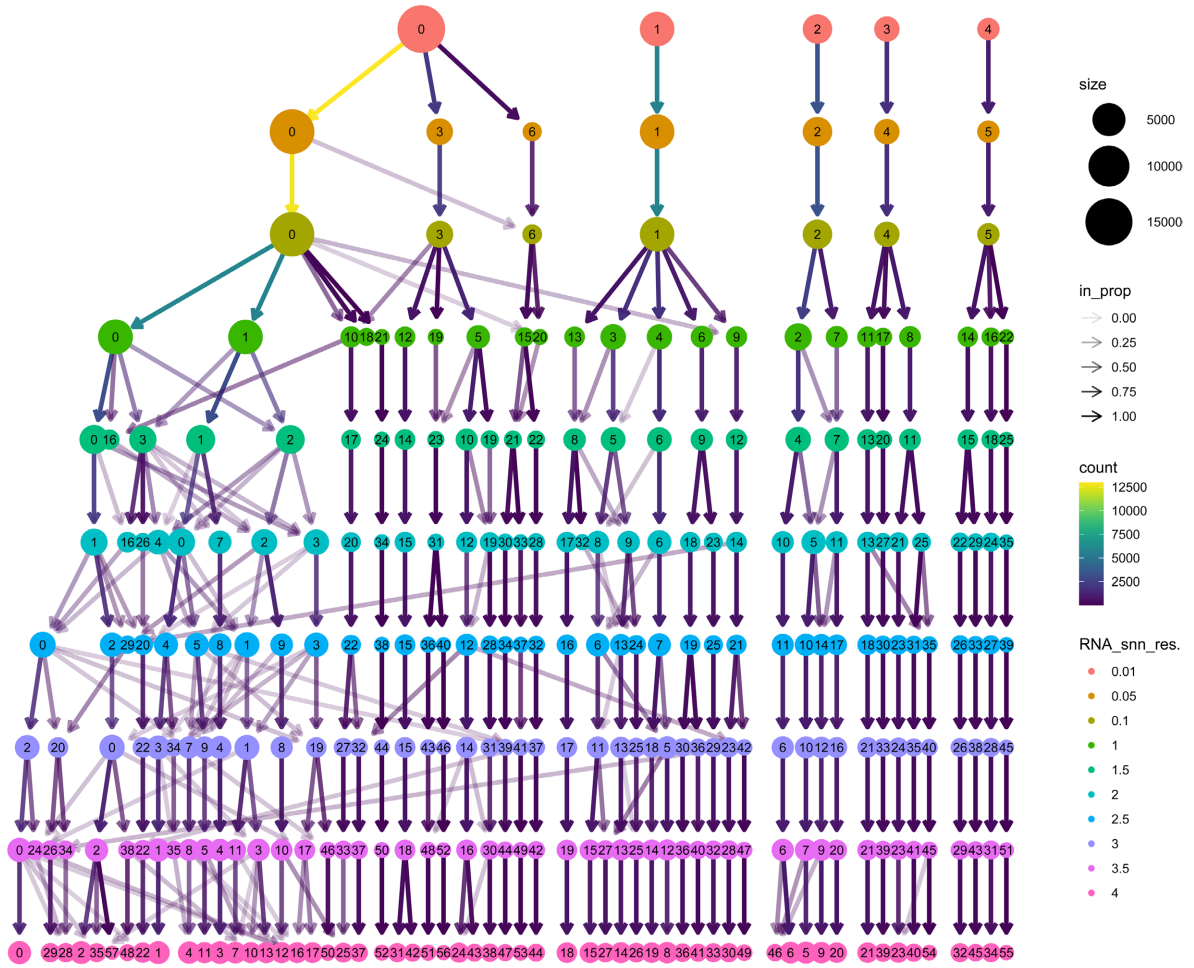


Figure 16. Scree plot of the top 20 Principal Components (PCs) for single-cell clustering.



(A)


size
5000
10000
15000
in_prop
0.00
0.25
0.50
0.75
1.00
count
12500
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7500
5000
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RNA_snn_res.
0.01
0.05
0.1
1
1.5
2
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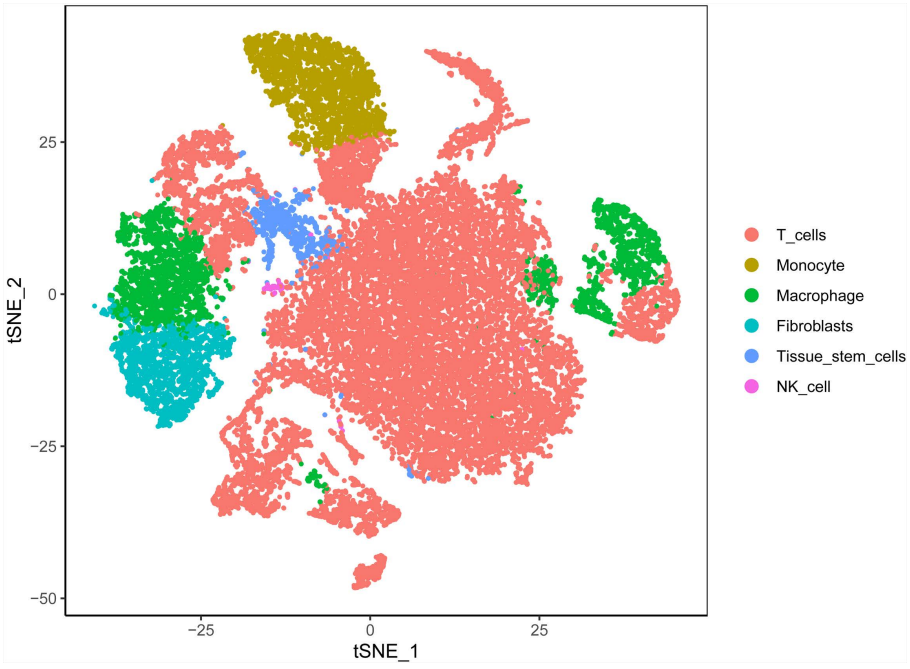
3
3.5
4

(B)


tSNE_2
tSNE_1
25
0
−25
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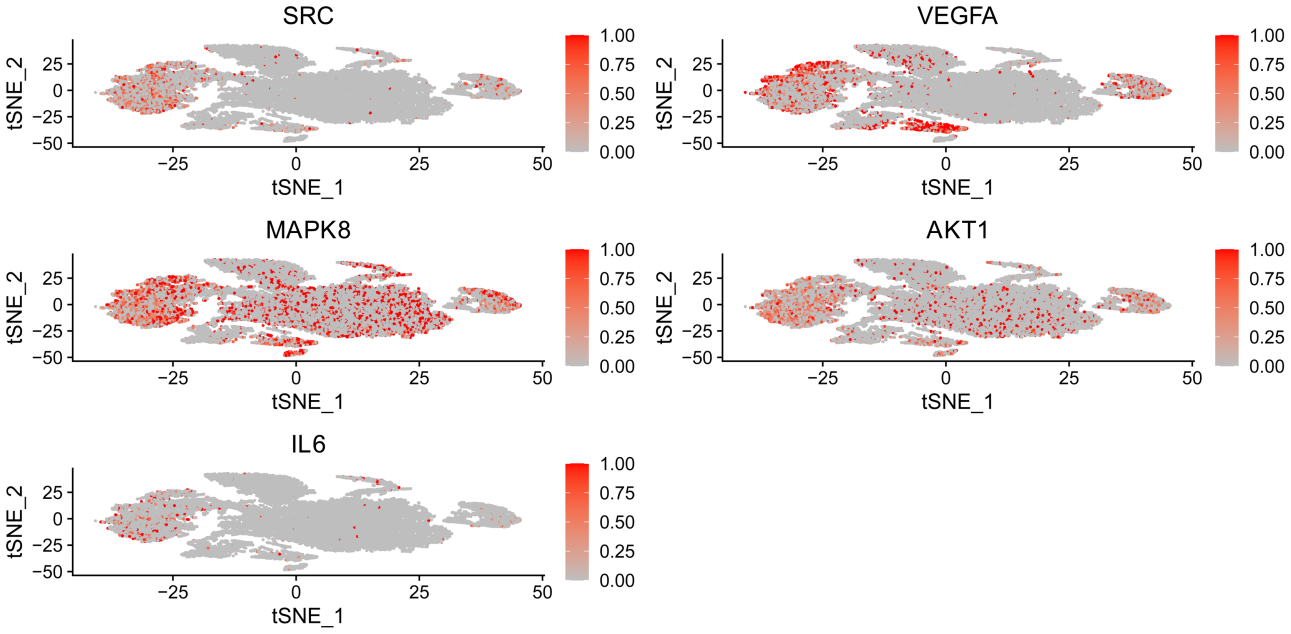
−25
0
25
T_cells
Monocyte
Macrophage
Fibroblasts
Tissue_stem_cells
NK_cell

(C)



(D)

Figure 17. Analysis of core gene expression levels at the single-cell level.

4. Discussions

"Hepato-Cellular Carcinoma (HCC)" is a primary malignant tumor of the liver caused by multiple inducing factors. Liver cancer cells are highly complex, and current Western medicine treatments have not achieved satisfactory results. Traditional Chinese medicine can regulate the balance of Yin and Yang in the body, offers flexible combinations, abundant resources, and fewer side effects, providing significant advantages in treating tumors [7].

Through network analysis, we identified the top six active components in the Zhuang medicine compound Tiecao Capsule based on Degree value, including quercetin, kaempferol, β-sitosterol, wogonin, luteolin, and stigmasterol. These components exert anti-hepatocellular carcinoma effects through multiple synergistic pathways.

Quercetin, also known as quercetin, is a polyhydroxy flavonoid widely distributed in nature. It is commonly found in the stems, bark, flowers, leaves, and fruits of various plants, often in the form of glycosides, and exhibits broad anticancer, antioxidant, and anti-inflammatory activities. Studies have shown that quercetin regulates the expression of cyclins Cyclin D1 and Cyclin E, reduces the proportion of G1 phase cells, and induces cell cycle arrest at the G2/M phase, thereby inhibiting the occurrence and progression of liver cancer [8].

Kaempferol is a flavonoid compound that can be isolated from various vegetables and fruits. It possesses anti-inflammatory, antioxidant, anticancer, antidiabetic, and cardioprotective effects. Its anti-liver cancer mechanism primarily involves downregulating the expression of the pro-oncogenic miR-21, upregulating the tumor suppressor gene PTEN, and inhibiting the activation of the

PI3K/AKT/mTOR signaling pathway, thereby effectively suppressing the proliferation, migration, and invasion of liver cancer HepG2 cells [9].

β-Sitosterol is found in many plants and has pharmacological effects such as expectorant, antitussive, serum cholesterol-lowering, tissue repair, and antitumor properties. It exerts its anti-liver cancer effects by interfering with the cell cycle progression and inducing apoptosis. This component can arrest human liver cancer SMMC-7721 cells in the G2/M phase, while inhibiting proliferation and activating apoptotic pathways, achieving dual suppression of liver cancer cell growth [10].

Wogonin is derived from the Lamiaceae plant *Scutellaria baicalensis* and has anticancer, antispasmodic, and diuretic effects. As a main active ingredient of *Scutellaria baicalensis*, it exerts anti-liver cancer effects by regulating apoptosis-related signaling pathways. It promotes apoptosis of liver cancer cells by inhibiting the activation of the NF-κB/Bcl-2 signaling pathway, demonstrating its potential as a therapeutic agent for HCC [11].

Luteolin is a natural flavonoid compound. Traditional Chinese Medicine attributes various pharmacological activities to it, such as antitumor, anti-inflammatory, antiviral, and anti-allergic effects, and it is often used in TCM to treat hypertension and inflammatory diseases. It inhibits liver cancer progression through multi-target actions. By inhibiting the activity of various protein kinases, it interferes with the proliferation, metastasis, and angiogenesis of cancer cells. Experimental studies have confirmed that luteolin has a significant growth inhibitory effect on Hep-G2 cells [12].

Stigmasterol is a phytosterol abundant in soybeans. It induces tumor cell death by activating the mitochondrial apoptosis pathway. This component downregulates the expression of anti-apoptotic molecules, such as Bcl-2 and XIAP in a dose-dependent manner, while activating the caspase cascade, ultimately leading to apoptosis of liver cancer cells [13].

By constructing the PPI network of Compound Tiecao Capsule and liver cancer proteins, we screened six core action targets: AKT1, VEGFA, IL6, MAPK8, EGFR, and SRC. It is well known that tumors are often accompanied by inflammation, and cytokines play a potential role in promoting the occurrence and development of liver cancer [14]. Interleukin-6 (IL-6) can stimulate hepatocytes to synthesize acute-phase proteins, induce inflammatory responses, promote cell proliferation and angiogenesis, and downregulate apoptosis and oxidative stress [15], making it a promoting factor in the development and progression of liver cancer. VEGFA is an important regulator of angiogenesis metabolism, can induce endothelial cell proliferation, promote cell migration, inhibit apoptosis, and induce vascular permeability. Research data prove that VEGFA plays a tumor-suppressing role in HCC; inhibiting VEGFA expression in hepatocellular carcinoma by upregulating RUNX1 suppresses cancer cell proliferation and migration [16]. The active ingredients in Zhuang medicine compound Tiecao Capsule that act on VEGFA include quercetin, baicalein, and luteolin. In liver cancer, phosphorylated AKT is highly

expressed and often indicates poor prognosis, suggesting that AKT may be another important target for the prevention and treatment of liver cancer [17]. AKT1 is a member of the AKT family. Studies have shown that targeting AKT1 can inhibit the growth of HCC [16]. Epidermal Growth Factor Receptor (EGFR) is the expression product of the proto-oncogene c-erbB-1 (HER-1). High expression of EGFR can promote the occurrence and development of liver cancer and is positively correlated with its invasiveness. Targeted inhibition of EGFR reduces the invasiveness of liver cancer cells accordingly. Compounds acting on the EGFR target include: quercetin and luteolin. MAPK8 is an important member of the MAPKs family. It can be phosphorylated and activate the transcription factor Activator Protein-1 (AP-1), thereby activating the expression of a series of downstream genes, regulating cell proliferation, differentiation, survival, death, inflammation, and other pathological processes [18].

This study is the first to explore how miR-433-3p regulates the occurrence and development of liver cancer cells by targeting MAPK8 in HCC. The compound in Compound Tiecao Capsule that acts on the MAPK8 target is: kaempferol. SRC kinase was the first discovered proto-oncogene [19]. It belongs to the non-receptor tyrosine kinase family (SFKs) and shows abnormal expression in various tumors. SRC kinase can be activated by overexpression or phosphorylation, participating not only in the occurrence and development of various tumor cells but also closely related to tumor invasion and metastasis. The mechanism by which SRC promotes tumor metastasis may involve its impairment of E-cadherin-mediated intercellular adhesion, facilitating tumor metastasis. Restoring c-SRC activity can reconstruct this damage, inhibit cell migration and invasion, and reverse the c-Src-regulated invasive phenotype. The compound in Compound Tiecao Capsule that acts on the SRC target is: quercetin.

Our analysis suggests that Compound Tiecao Capsule may exert therapeutic effects against liver cancer through multiple signaling pathways. According to the GO enrichment results, the primary mechanisms potentially involve response to lipopolysaccharide, lipopolysaccharide-mediated signaling pathway, positive regulation of nitric oxide biosynthetic process, immune response, response to glucocorticoid, and positive regulation of chemokine biosynthesis, among others. At the protein expression level, immunohistochemistry results were consistent with transcriptomic findings: the protein expression levels of MAPK8, SRC, and VEGFA were higher in liver cancer tissues compared to normal liver tissues, whereas the protein expression levels of AKT1, EGFR, and IL6 were lower in liver cancer tissues. Quercetin, one of the main active components of Zhuang medicine Compound Tiecao Capsule, has been reported in previous studies to potentially control inflammation development by influencing the expression of antioxidant proteins via the NF-κB and Nrf-2/ARE signaling pathways, downregulating the expression of NF-κB/p65 and ICAM-1, and inhibiting the release of inflammatory factors. Another major mechanism through which Zhuang medicine Compound Tiecao Capsule may exert its efficacy is the positive regulation of nitric oxide (NO) biosynthe-

sis. Studies have indicated that NO can exert significant cytotoxic effects during infection and inhibit various DNA and RNA viruses. This mechanism may involve acting on the Th1/Th2 balance system, inducing the expression of IL-4 and IL-12 while suppressing the expression of IL-2 and IFN-γ. Therefore, the positive regulation of NO production is also proposed as one of the potential antiviral mechanisms of the compounds in Zhuang medicine Compound Tiecao Capsule. From the perspective of metabolic pathway network structure, the connection between the urea cycle and amino acid metabolism suggests the possible reactivation of nitrogen metabolism and ammonia excretion mechanisms in tumor tissues. Meanwhile, the significant enrichment of bile acid and phospholipid metabolism implies a potential regulatory role of liver lipid metabolism in the tumor microenvironment, which aligns with previous conclusions regarding metabolic abnormalities in liver cancer research. Based on KEGG pathway enrichment analysis, the key pathways involved may mainly include Endocrine resistance, EGFR tyrosine kinase inhibitor resistance, Apoptosis, and the PI3K-Akt signaling pathway. Targets in the Endocrine resistance pathway include EGFR, SRC, AKT1, BCL2, and MAPK8; the EGFR tyrosine kinase inhibitor resistance pathway includes EGFR, SRC, AKT1, BCL2, VEGFA, and IL6; the Apoptosis pathway includes AKT1, BCL2, and MAPK8; and the PI3K-Akt signaling pathway includes EGFR, AKT1, BCL2, VEGFA, and IL6. All of these are targets of the key components. These findings demonstrate the potential advantage of synergistic regulation through multi-component, multi-target, and multi-pathway actions of Zhuang medicine Compound Tiecao Capsule in the prevention or treatment of liver cancer.

The high expression of SRC and VEGFA genes in macrophages and fibroblasts suggests that these two genes may primarily participate in innate immunity and stromal cell-mediated biological processes, such as tissue repair, angiogenesis (VEGFA-driven neovascularization), and inflammation regulation (microenvironment modulation by macrophages). In contrast, the low expression in T cells indicates that their immune functions may be less dependent on this pathway [20]. The observed expression differences may be associated with chronic inflammation, fibrosis, or aberrant stromal-immune interactions within the tumor microenvironment. These findings further suggest that targeting the SRC/VEGFA pathway may allow for selective regulation of the pathological functions of macrophages and fibroblasts [21], thereby potentially inhibiting fibrosis or tumor angiogenesis while preserving the anti-tumor or anti-infection activity of T cells. This study provides a new potential direction for the treatment strategy of hepatocellular carcinoma.

In summary, this study utilized a network pharmacology approach to identify the main active components and potential targets of Zhuang medicine Compound Tiecao Capsule, and analyzed its multi-target, multi-pathway mechanism of action in treating liver cancer. From the compound-target network, we screened six important active components. Through Venn diagram analysis, we obtained 113 effective targets, and from the PPI protein interaction network, we identified six

core targets: AKT1, VEGFA, IL6, MAPK8, EGFR, and SRC. GO and KEGG pathway enrichment analyses revealed that the five key compounds in Zhuang medicine Compound Tiecao Capsule—quercetin, kaempferol, wogonin, β-sitosterol, and luteolin—primarily exert their anti-liver cancer effects by regulating these six core targets, in conjunction with pathways such as the PI3K-Akt signaling pathway, cancer-related pathways (e.g., Prostate cancer, Proteoglycans in cancer), C-type lectin receptor signaling pathway, MAPK signaling pathway, and TNF signaling pathway.

The findings from this network pharmacology and multi-omics study offer valuable insights for future clinical translation. The identification of core targets such as SRC and VEGFA—which are not only highly expressed in HCC tissues but also correlate with TNM stage, tumor grade, and patient survival—suggests their potential as therapeutic targets or biomarkers for patient stratification. For instance, patients with high SRC or VEGFA expression might benefit from combination therapies that include SRC inhibitors (e.g., dasatinib) or anti-angiogenic agents (e.g., sorafenib). Moreover, the multi-target and multi-pathway characteristics of Zhuang medicine Compound Tiecao Capsule support its potential use as an adjunct therapy to enhance the efficacy of conventional treatments and reduce drug resistance. The enrichment of SRC and VEGFA in macrophages and fibroblasts further highlights the role of the tumor microenvironment in HCC progression, indicating that modulating stromal-immune crosstalk could be a promising therapeutic direction. Future studies validating these targets in preclinical models and clinical cohorts will help translate these findings into personalized treatment strategies for HCC.

Despite the systematic approach employed in this study, several limitations should be acknowledged. Firstly, as an in silico analysis based on network pharmacology and molecular docking, the findings and mechanistic insights we obtained are predominantly predictive. The reliability of these predictions is inherently dependent on the coverage and accuracy of the underlying public databases (e.g., TCMSP, GeneCards, STRING). Secondly, the complex multi-component, multi-target nature of Zhuang medicine Compound Tiecao Capsule poses a challenge for comprehensively elucidating its precise pharmacological interactions. The synergistic effects among the numerous active ingredients require further experimental investigation. Therefore, while this study provides valuable hypotheses and a solid foundation, the proposed anti-HCC mechanisms necessitate rigorous validation through future in vitro and in vivo experiments to confirm the bioactivity, efficacy, and safety of the identified compounds and their interactions with the core targets.

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Author Contributions

Shuhan Wang: Writing—review & editing, Writing—original draft, Software, Investigation, Formal analysis, Data curation, Conceptualization. Yongle Li: review & editing, Software, Investigation, Formal analysis, Data curation. Zhenzhen Ren: Investigation, Formal analysis, Data curation. Xiaomei Xie: review & editing. Rong He: review & editing. Lihe Jiang: Conceptualization, Supervision, Methodology, Writing—review & editing, Visualization, Software, Resources, Funding acquisition, Formal analysis.

Conflicts of 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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