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Investigating the molecular mechanism of *Chelidonii Herba* against liver cancer using network pharmacology and molecular docking validation

Ming-Zhi Yang[1#], Zi-Xuan Yang[1#], Zhang Yu[1], Ju-Min Xie[1*]

[1]Hubei Key Laboratory of Renal Disease Occurrence and Intervention, Medical School, Hubei Polytechnic University, Huangshi 435003, China.

[#]These authors contributed equally to this work and are co-first authors for this paper.

[*]**Corresponding to:** Ju-Min Xie, Hubei Key Laboratory of Renal Disease Occurrence and Intervention, Medical School, Hubei Polytechnic University, No. 16 Guilin North Road, Xialu District, Huangshi 435003, China. E-mail: xiejumin@hbpu.edu.cn.

Author contributions

Ju-Min Xie conceived the study. Ming-Zhi Yang, Zi-Xuan Yang, and Zhang Yu investigated and analyzed the data. Ju-Min Xie supervised the study. Ju-Min Xie wrote and revised the manuscript. All authors read and agreed to publish the paper.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

TCM, traditional Chinese medicine; OMIM, Online Mendelian Inheritance in Man; TTD, Therapeutic Targets Database; PPI, protein-protein interaction; HCC, hepatocellular carcinoma; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; BP, biological processes; CC, cellular components; MF, molecular functions; HR, hazard ratio.

Citation

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Abstract

Background: The molecular mechanism of *Chelidonii Herba* in treating hepatocellular carcinoma was investigated using network pharmacology and molecular docking validation. **Methods:** The main active components of *Chelidonii Herba* were screened using the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform database, and the targets of these active ingredients were identified using the SwissTargetPrediction platform. Targets related to liver cancer were sourced from GeneCards, Therapeutic Targets Database, and Online Mendelian Inheritance in Man databases. Intersection targets between the active components of *Chelidonii Herba* and liver cancer were determined using the jvenn online platform. The protein interaction network was analyzed via STRING database and visualized using Cytoscape 3.9.1. Core targets were identified and further analyzed within the protein interaction network. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes enrichment analyses were conducted for the intersection targets using the DAVID database to correlate gene functions. Sankey bubble diagrams for Gene Ontology enrichment analysis and circular diagrams for Kyoto Encyclopedia of Genes and Genomes pathway enrichment analysis were generated using CNSknowall and SangerBox online platforms. Molecular docking and visualization were performed using AutoDockTools 1.5.7 and PyMOL 2.5.7 software, respectively. Overall survival and pan-cancer analysis of core targets were conducted using the GEPIA2 online platform. **Results:** Twelve active components of *Chelidonii Herba* were identified through screening. A total of 103 intersection targets and 12 core targets were found between these active constituents of *Chelidonii Herba* and liver cancer. *Chelidonii Herba* may exert its effects on liver cancer through these 12 core targets. Several signaling pathways are implicated, including chemical carcinogen-receptor activation, endocrine resistance, HIF-1 signaling pathway, and proteoglycans in cancer. **Conclusion:** *Chelidonii Herba* potentially intervenes in cancer-related signaling pathways for treating liver cancer by targeting AKT1, EGFR, and ERBB2. This action is facilitated by active ingredients such as (S)-chrysocorydaline, dihydrochelidonorubin, cryptopine, and oxysanguinarine. *Chelidonii Herba* may address liver cancer through a mechanism involving multiple components, targets, and pathways.

Keywords: *Chelidonii Herba*; liver cancer; network pharmacology; molecular docking

Introduction

Liver cancer is a highly aggressive malignancy affecting the liver, and it ranks among the most prevalent cancer types globally. It typically arises from underlying conditions such as hepatitis B virus infection, chronic liver disease, and cirrhosis. As liver disease progresses to cirrhosis, the incidence of liver cancer escalates significantly, leading to a rising annual mortality rate [1–4].

According to data from the Global Cancer Observatory in 2020, approximately 19.3 million new cancer cases and 10 million deaths occurred worldwide. Liver cancer accounted for about 906,000 new cases, representing 4.7% of all cases, and approximately 830,000 deaths, accounting for 8.3% of total cancer-related deaths [5]. In China, the situation is particularly severe, with some of the highest rates of new cases and deaths globally. In 2022 alone, China reported 4.82 million new cancer cases and 3.21 million deaths, including 430,000 new cases of liver cancer and 410,000 liver cancer-related deaths [6].

Liver cancer can be categorized into primary and secondary types. Most cases lack distinctive symptoms in the early stages and are typically detected in advanced stages. The liver plays crucial roles in various physiological, metabolic, and regulatory processes, including bile secretion, glycogen and fat-soluble vitamin storage, drug detoxification, and synthesis of plasma proteins and clotting factors [7]. Thus, pathological changes in liver tissue can significantly impact overall health.

Treatment options for liver cancer are notably limited, with primary approaches involving partial hepatectomy and liver transplantation. Unfortunately, many patients miss the window for surgical intervention due to late diagnosis and a scarcity of liver donors, among other factors. Even after surgical resection, recurrence rates remain high, leading to poor long-term prognoses [8].

The field of traditional Chinese medicine (TCM) has seen increasing utilization of Chinese herbs for cancer treatment. Compared to chemotherapy drugs, Chinese herbs are more accessible and generally associated with fewer adverse effects [9]. Given the substantial incidence and mortality rates of liver cancer, there is an urgent need for new, efficient, low-toxicity, and cost-effective treatment options.

Chelidonii Herba, a member of the poppy family, was first documented in *Materia Medica for the Relief of Famine* (Zhu Su, Ming Dynasty). The entire plant is known for its analgesic, cough-suppressing, anti-inflammatory, and detoxifying effects. Modern pharmacological studies have demonstrated that extracts and purified compounds from *Chelidonii Herba* exhibit potent antiviral, antitumor, and antibacterial properties both in laboratory and animal studies [10]. Specifically, *Chelidonii Herba* extract has shown inhibition of cancer cell proliferation and induction of apoptosis in various cancer types in vitro [11].

However, the potential of *Chelidonii Herba* in treating liver cancer and its specific molecular mechanisms remain unclear. This study employed network pharmacology methods to elucidate the interaction between active ingredients and target proteins. It constructed network diagrams linking drug components, diseases, and targets, and investigated potential pathways and mechanisms through which *Chelidonii Herba* may act in liver cancer treatment. The findings were further validated using survival curves, pan-cancer analyses, and molecular docking, aiming to provide theoretical basis for future experimental validations. The workflow was illustrated in (Figure 1).

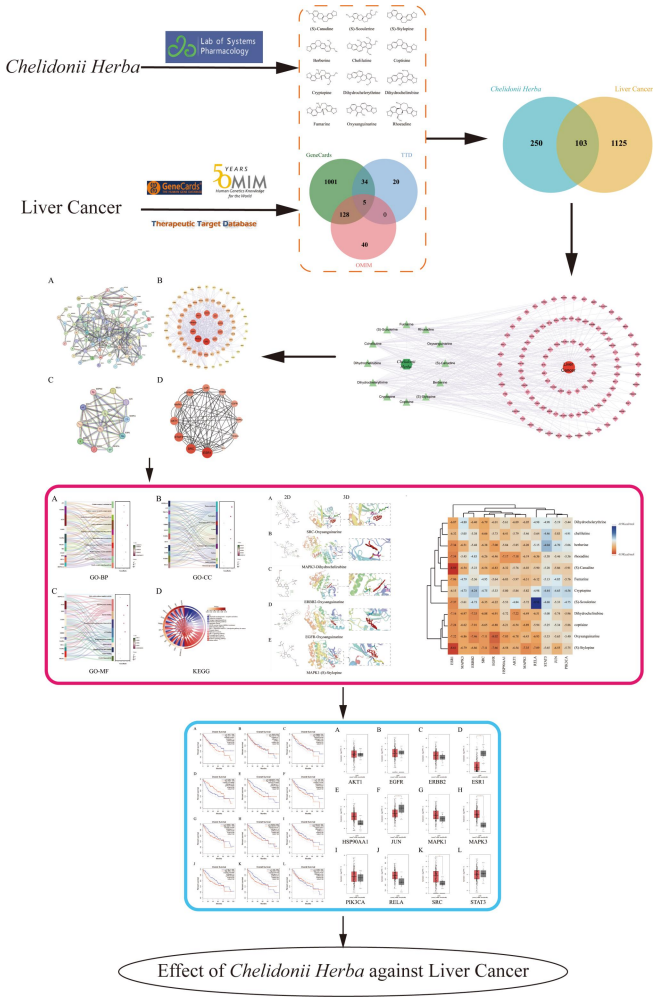

Figure 1 Flowchart of the study of *Chelidonii Herba* anti-liver cancer

Materials and methods

Active ingredients screening of *Chelidonii Herba* and target prediction

Using "*Chelidonii Herba*" as a keyword, active components were searched in the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (https://old.tcmsp-e.com/index.php) [12]. Screening criteria included oral bioavailability ≥ 20% and drug-likeness ≥ 0.1. Identified active ingredients were retrieved from PubChem [13] (https://pubchem.ncbi.nlm.nih.gov/) using their Isomeric SMILES and inputted into SwissTargetPrediction [14] (http://swisstargetprediction.ch/) to predict drug targets. The analysis focused on *Homo sapiens* species with a filter condition set to "target probability > 0.1" to obtain potential targets of *Chelidonii Herba* active ingredients.

Liver cancer targets collection

Using "liver cancer" as keywords, targets were searched in three databases: GeneCards [15] (https://www.genecards.org/), Online Mendelian Inheritance in Man (OMIM) [16] (https://www.omim.org/), and the Therapeutic Targets Database (TTD) [17] (https://db.idrblab.net/ttd/). The search criteria in GeneCards focused on relevance scores and were refined until the number of targets was reduced to below 2000. Subsequently, OMIM and the TTD database were queried to identify overlapping targets related to liver cancer. A Venn diagram was constructed using the jvenn (https://www.bioinformatics.com.cn/static/others/jvenn/example.html) platform to visualize and analyze liver cancer targets.

Chelidonii Herba-components-targets-liver cancer network construction

The active components of *Chelidonii Herba* were intersected with liver cancer targets using jvenn, resulting in identification of intersected targets. These intersection targets were sorted and then imported into Cytoscape 3.9.1 software to visualize the results. *Chelidonii Herba*-components-targets-liver cancer network was constructed using Cytoscape 3.9.1.

Protein-protein interaction (PPI) network construction and core targets screening

The intersection targets of *Chelidonii Herba*'s active components and liver cancer were uploaded to the STRING database [18] (https://cn.string-db.org/). The analysis was conducted with "*Homo sapiens*" as the selected species and a confidence level > 0.95. Non-relevant targets were excluded. The resulting TSV file was downloaded and imported into Cytoscape 3.9.1 to visualize and construct a PPI network diagram.

Within Cytoscape 3.9.1, the "analyze network" function was used to calculate and extract topological attributes, generating a gene attribute table. Targets meeting criteria such as betweenness centrality ≥ median value, closeness centrality ≥ median value, and degree ≥ twice the median value were selected as the core targets of *Chelidonii Herba* against hepatocellular carcinoma (HCC).

Gene Ontology (GO) function and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis

The core targets were imported into the DAVID database [19] (https://david.ncifcrf.gov/) for KEGG and GO enrichment analysis, focusing on "*Homo sapiens*". Data encompassed biological processes (BP), cellular components (CC), molecular functions (MF), and KEGG pathway enrichment analyses, sorted by ascending *P*-value.

GO function analysis data was imported into CNSknowall (https://cnsknowall.com/index.html#/HomePage) to make Sankey diagrams, while KEGG pathway enrichment data was imported into SangerBox (http://sangerbox.com/) to generate circular graphs.

Molecular docking and visualization

In the Uniprot database [20] (https://www.uniprot.org/), core target were searched by selecting, status "reviewed" and species "Human", and their corresponding entry numbers were copied. These entries were then imported into the RCSB Protein Data Bank database [21] (https://www.rcsb.org/) for further investigation. Species "*Homo sapiens*" was specified, with protein chosen as the Polymer Entity Type. Selection criteria included a low method value and a small number of unique ligands.

Using PyMOL 2.5.7 [22], water and residues were removed from the core target. The 2D structure of active ingredients from *Chelidonii Herba* was downloaded in SDF format from the PubChem database, and their structures were optimized using Chem 3D software. AutoDockTools 1.5.7 software was employed to hydrogenate the protein and small drug molecules, calculate charge numbers, define rigid structures, and configure parameters in the grid and docking panels for molecular docking predictions. Set the "Genetic Algorithm Parameters" in the docking panel as follows: "Number of Genetic Algorithm Runs" = 50, "Maximum Number of evals: medium" = 3,000,000, and "Maximum Number of Generations" = 30,000. The resulting docking energies were recorded and analyzed.

Molecular docking results were grouped into 12 categories based on the same target protein, and the configuration with the lowest binding energy from each group was selected for visualization using PyMOL 2.5.7. Open Babel GUI software was utilized to convert file formats before importing into PyMOL for visualization. From the 12 sets of molecular docking visualizations, 5 groups were chosen for display.

Overall survival and pan-cancer analysis

Overall survival curves for the core targets were generated using the GEPIA2 database [23] (http://gepia2.cancer-pku.cn/#index), followed by pan-cancer analysis. On the overall survival analysis page, the gene name was inputted, "Overall Survival" was selected under "Methods", and the confidence interval was set to 95%. The horizontal axis was configured to display "Months", with the dataset selection set to liver hepatocellular carcinoma.

The survival curve was plotted, and the hazard ratio (HR) was determined. An HR > 1 indicates that high gene expression is a risk factor associated with reduced patient survival rates, while an HR < 1 signifies a protective effect where high gene expression may improve patient survival rates.

In the expression DIY page, the "Box Plot" option was selected and the gene name of the core target entered. "Subtype Filter" was clicked, and liver hepatocellular carcinoma was chosen from the "Datasets Selection". Matched The Cancer Genome Atlas normal data was selected to export the pan-cancer analysis figure.

Results

Main active ingredients of *Chelidonii Herba* and correlated targets

Twelve active ingredients from *Chelidonii Herba* were screened in the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform, and their specific information is detailed in Table 1. The molecular structures of these 12 active ingredients were obtained using Swiss Target Prediction, as illustrated in Figure 2. A total of 353 targets were identified across these twelve active ingredients after removing duplicates.

Liver cancer targets

A total of 18,680 hepatocellular carcinoma-related targets were identified in the GeneCards database, and after filtering with a median relevance score over four iterations, 1,168 targets remained. In the TTD database, 59 targets related to liver cancer were found, while the OMIM database yielded 173 liver cancer-related targets. Targets from all three databases were collected and merged using jvenn, resulting in a final set of 1,228 HCC-related targets (Figure 3A). The intersection of 353 *Chelidonii Herba* targets and 1,228 liver cancer targets yielded 103 intersected targets (Figure 3B).

"*Chelidonii Herba*-ingredients-targets-liver cancer" network construction

Chelidonii Herba, liver cancer, active ingredients, and the intersection targets of *Chelidonii Herba* and liver cancer are imported into Cytoscape 3.9.1 for visualization (Figure 3C).

PPI network construction

PPI analysis was conducted on 103 intersection targets using the STRING database. Thirty-one non-relevant targets were excluded, and the protein interaction network diagram was exported in TSV format and visualized using Cytoscape 3.9.1 software (Figure 4A). The analysis revealed a network diagram comprising 72 nodes and 442 edges. Network analysis was performed to evaluate the degree values of the intersection targets, indicating their importance. The 72 targets were ranked based on their degree values, and a protein interaction network diagram for the intersection of *Chelidonii Herba* active ingredients and liver cancer was generated (Figure 4B).

Based on core target selection criteria, 12 core targets were identified: AKT1, EGFR, ERBB2, ESR1, HSP90AA1, JUN, MAPK1, MAPK3, PIK3CA, RELA, SRC, and STAT3 (Table 2). The protein interaction network diagram for these core targets was constructed using the STRING database and Cytoscape 3.9.1 software (Figure 4C and 4D).

GO function and KEGG pathway enrichment analysis

Through GO functional analysis, we identified 145 BP, 28 CC, and 37 MF. Ten terms of BP, CC, and MF with the lowest *P*-values were selected to create Sankey bubble diagrams (Figure 5A–5C).

The BP associated with core targets predominantly include cellular responses to cadmium ions and reactive oxygen species, insulin-like growth factor receptor signaling pathways, positive regulation of transcription, and epidermal growth factor receptor signaling pathways. Regarding cellular components, core targets are primarily localized in the plasma membrane, nucleoplasm, transcription factor complexes, cytosol, and cytoplasm. Molecular functions of core targets encompass activities such as nitric-oxide synthase regulator activity, identical protein binding, enzyme binding, ATP binding, and protein phosphatase binding.

Additionally, core targets participate in 127 KEGG signaling pathways. The top 15 pathways with the smallest *P*-values were chosen to generate a circular diagram (Figure 5D). Core targets are notably enriched in pathways like chemical carcinogen-receptor activation, endocrine resistance, estrogen signaling pathway, prolactin signaling pathway, HIF-1 signaling pathway, and pathways in cancer.

Table 1 Detailed information of the active components in *Chelidonii Herba*

NO.	Name	Formula	PubChem CID	CAS ID	MW (g/mol)	OB (%)	DL
BQC1	(S)-Canadine	$C_{20}H_{21}NO_4$	21171	5096-57-1	339.42	53.83	0.77
BQC2	(S)-Scoulerine	$C_{19}H_{21}NO_4$	439654	6451-73-6	327.41	32.28	0.54
BQC3	(S)-Stylopine	$C_{19}H_{17}NO_4$	440583	84-39-9	323.37	51.15	0.85
BQC4	Berberine	$C_{20}H_{18}NO_4^+$	2353	2086-83-1	336.39	36.86	0.78
BQC5	Chelilutine	$C_{22}H_{20}NO_5^+$	443720	55950-32-8	378.43	53.55	0.87
BQC6	Coptisine	$C_{19}H_{14}NO_4$	72322	3486-66-6	320.34	30.67	0.86
BQC7	Cryptopine	$C_{21}H_{23}NO_5$	72616	482-74-6	369.45	78.74	0.72
BQC8	Dihydrochelerythrine	$C_{21}H_{19}NO_4$	485077	6880-91-7	349.41	32.73	0.81
BQC9	Dihydrochelirubine	$C_{21}H_{17}NO_5$	440589	28342-26-9	363.39	55.29	0.86
BQC10	Fumarine	$C_{20}H_{19}NO_5$	4970	130-86-9	353.40	59.26	0.83
BQC11	Oxysanguinarine	$C_{20}H_{13}NO_5$	443716	548-30-1	347.34	46.97	0.87
BQC12	Rhoeadine	$C_{21}H_{21}NO_6$	197775	2718-25-4	383.43	63.51	0.83

MW, molecular weight; OB, oral bioavailability; DL, drug-likeness.

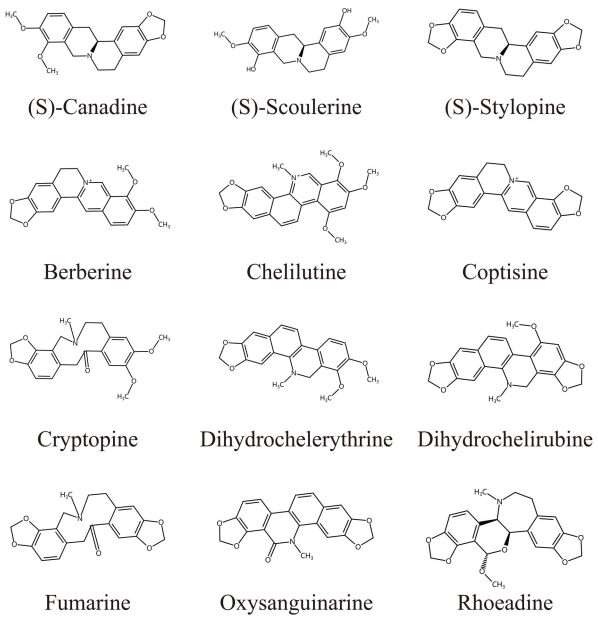

Figure 2 Molecular structure of the 12 active ingredients in *Chelidonii Herba*

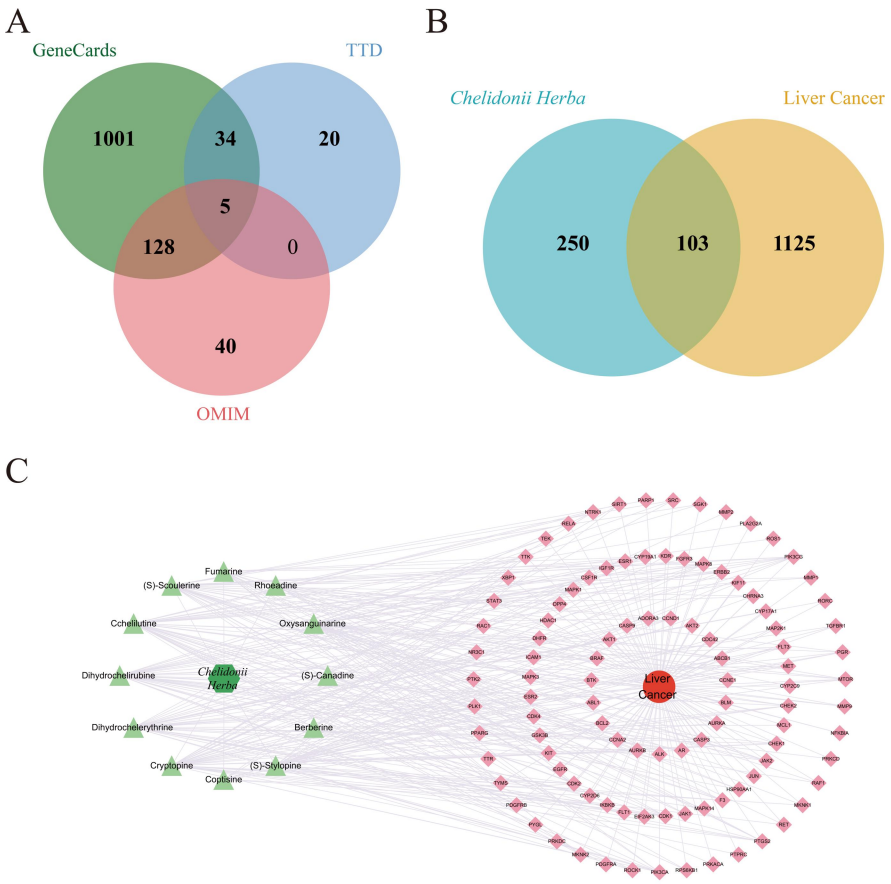

Figure 3 Targets of *Chelidonii Herba* against liver cancer. (A) Liver cancer pooled targets. (B) Intersection targets of *Chelidonii Herba* and liver cancer. (C) Network of *Chelidonii Herba*-ingredients-liver cancer. OMIM, Online Mendelian Inheritance in Man; TTD, Therapeutic Targets Database.

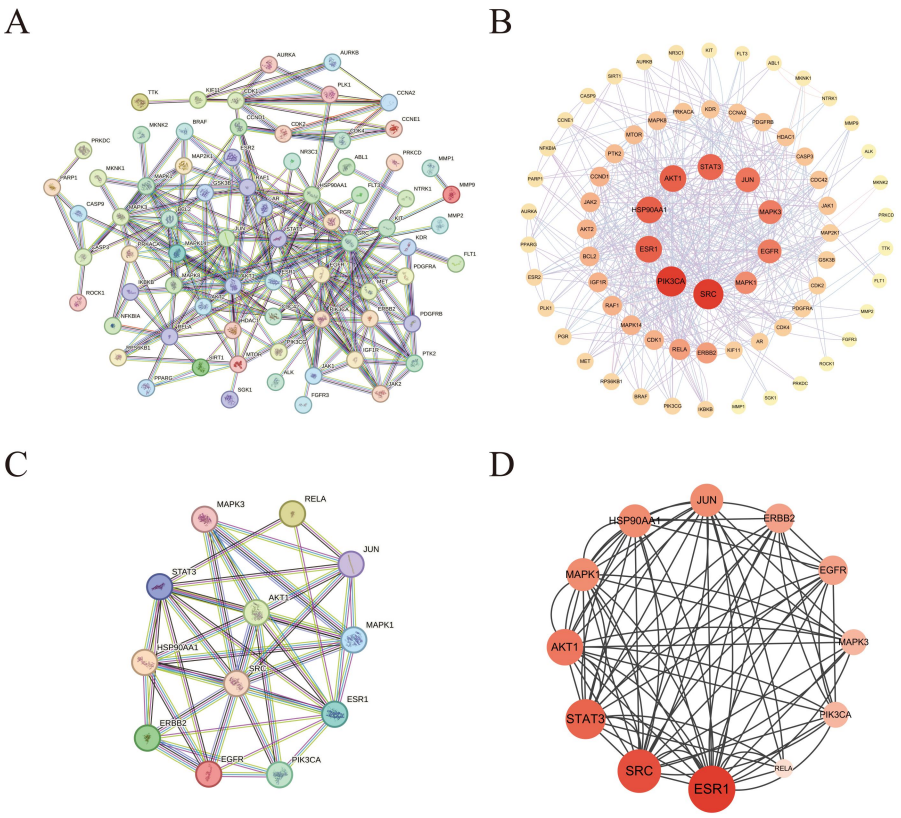

Figure 4 Protein-protein interaction network of *Chelidonii Herba*-liver cancer intersection targets and core targets. (A & B) PPI network and visualization of *Chelidonii Herba* against liver cancer. (C & D) PPI network and visualization of the core targets. PPI, protein-protein interaction.

Table 2 Core target protein information

Target	Uniprot entry	Protein names	RCSB PDB ID	Method
JUN	P05412	Transcription factor Jun	1JNM	X-RAY DIFFRACTION
SRC	P12931	Proto-oncogene tyrosine-protein kinase Src	1O43	X-RAY DIFFRACTION
AKT1	P31749	RAC-alpha serine/threonine-protein kinase	1UNQ	X-RAY DIFFRACTION
HSP90AA1	P07900	Heat shock protein HSP 90-alpha	1UYL	X-RAY DIFFRACTION
PIK3CA	P42336	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform	2ENQ	SOLUTION NMR
MAPK3	P27361	Mitogen-activated protein kinase 3	4QTB	X-RAY DIFFRACTION
STAT3	P40763	Signal transducer and activator of transcription 3	6NJS	X-RAY DIFFRACTION
RELA	P04206	Transcription factor p65	6QHL	X-RAY DIFFRACTION
ESR1	P03372	Estrogen receptor	7BAA	X-RAY DIFFRACTION
ERBB2	P04626	Receptor tyrosine-protein kinase erbB-2	7PCD	X-RAY DIFFRACTION
EGFR	P00533	Epidermal growth factor receptor	8A27	X-RAY DIFFRACTION
MAPK1	P28482	Mitogen-activated protein kinase 1	8AOJ	X-RAY DIFFRACTION

PDB, Protein Data Bank.

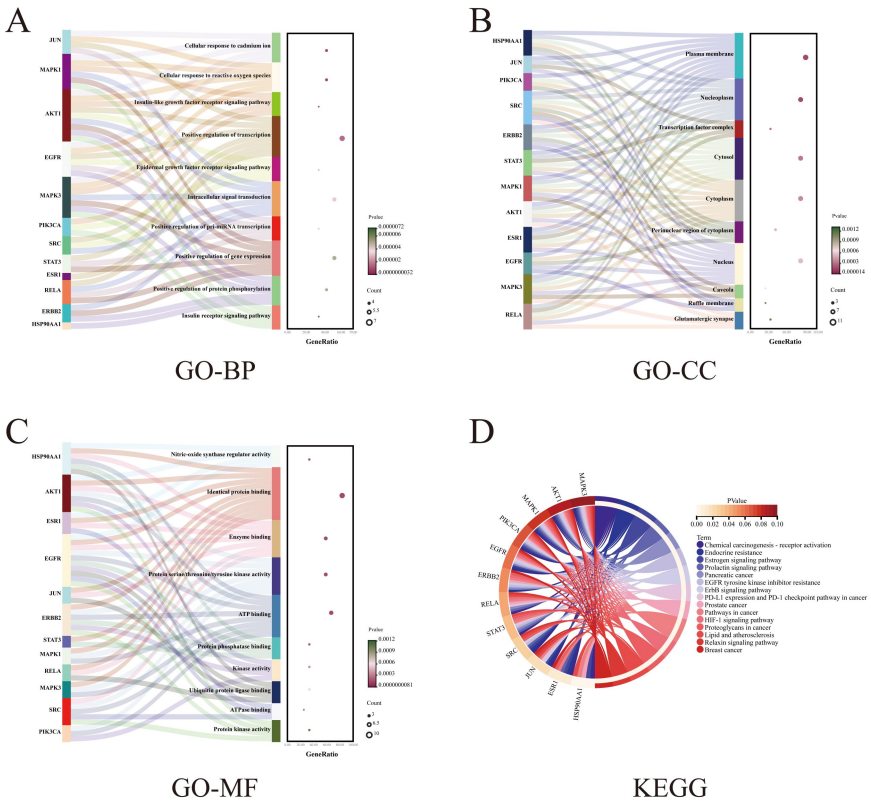

Figure 5 GO function and KEGG enrichment analysis of targets in *Chelidonii Herba* against liver cancer. (A) BP enrichment analysis. (B) CC enrichment analysis. (C) MF enrichment analysis. (D) KEGG enrichment analysis. GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; BP, biological processes; CC, cellular components; MF, molecular functions.

Molecular docking and visualization

Twelve active components and 12 core targets of *Chelidonii Herba* were screened, yielding a total of 144 molecular docking and binding results. Heat maps were generated based on their binding energy values (Figure 6). Within each binding group, pairs with the lowest binding energies were selected for visualization. Ultimately, SRC-Oxysanguinarine, MAPK3-Dihydrochelirubine, ERBB2-Oxysanguinarine, EGFR-Oxysanguinarine, and MAPK1-(S)-Stylopine were chosen for display (Figure 7) (Table 3).

Overall survival and pan-cancer analysis

The 12 core targets were analyzed using the GEPIA2 database to generate overall survival curves and conduct pan-cancer analyses. The survival curve indicates that AKT1, HSP90AA1, JUN, MAPK1, MAPK3, PIK3CA, RELA, and SRC have risk ratios greater than 1, while EGFR's ratio equals 1, and ERBB2, ESR1, and STAT3 have ratios less than 1 (Figure 8).

Pan-cancer analysis revealed that compared to the normal control, AKT1, ERBB2, HSP90AA1, MAPK1, MAPK3, PIK3CA, RELA, and SRC were up-regulated in the HCC group, with MAPK3 and SRC showing significant up-regulation. Conversely, EGFR, ESR1, JUN, and STAT3 were down-regulated, with ESR1 and JUN significantly decreased (Figure 9).

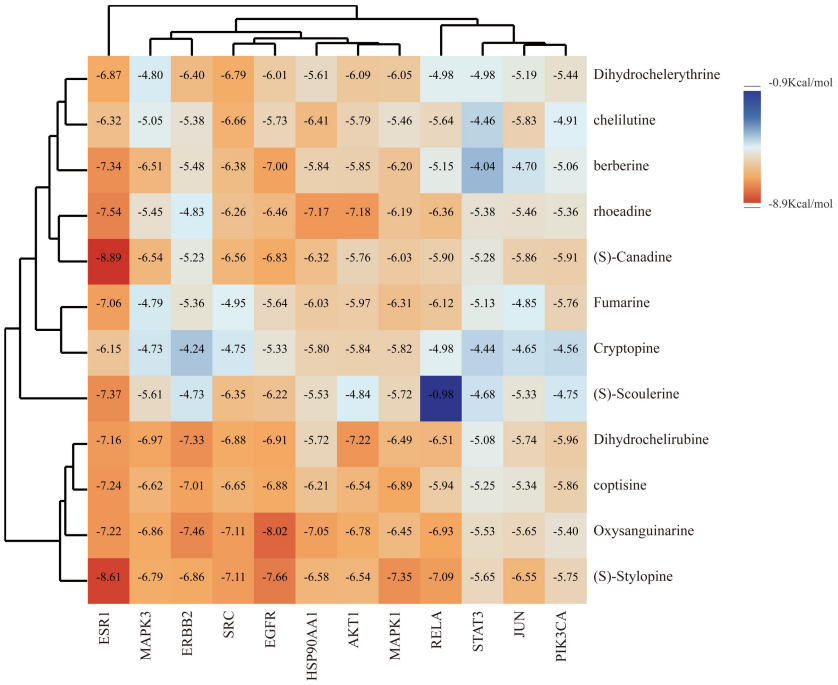

Figure 6 Heat map of binding energy

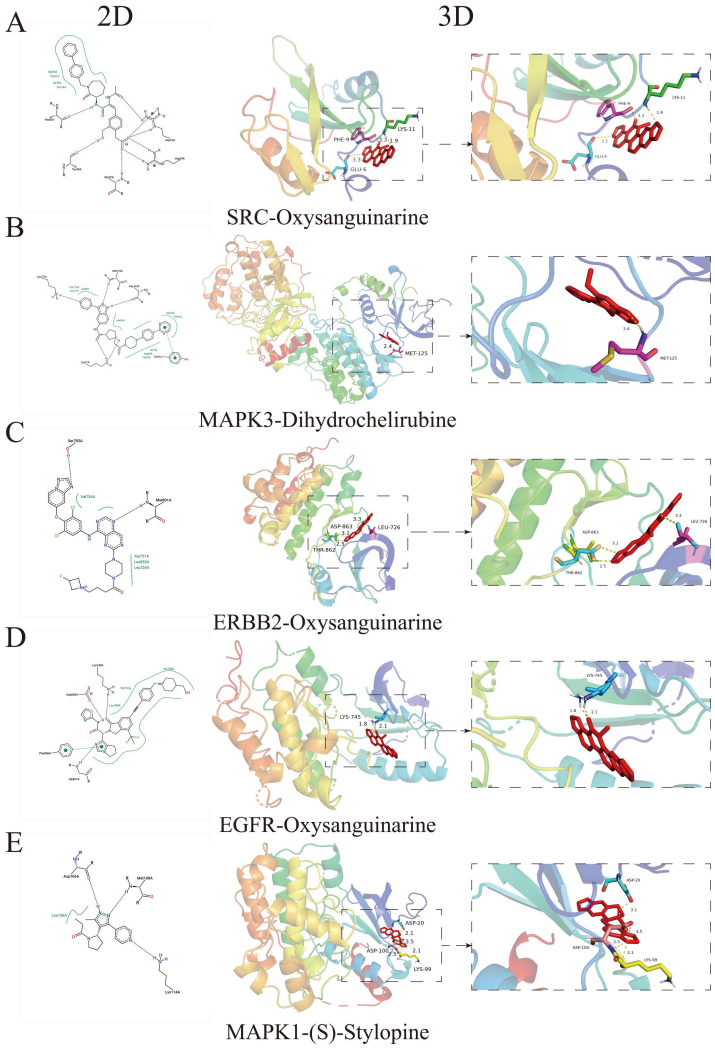

Figure 7 Molecular docking and visualization of *Chelidonii Herba* active ingredients-core targets. (A) SRC-Oxysanguinarine. (B) MAPK3-Dihydrochelirubine. (C) ERBB2-Oxysanguinarine. (D) EGFR-Oxysanguinarine. (D) MAPK1-(S)-Stylopine.

Table 3 Grid box parameter settings

Combination	Grid				
	Current Total Grid Pts per map	Spacing (angstrom)	Center Grid Box: x	Center Grid Box: y	Center Grid Box: z
SRC-Oxysanguinarine	2016125	0.481	10.745	19.23	19.962
MAPK3-Dihydrochelirubine	2048383	0.914	44.329	38.765	73.25
ERBB2-Oxysanguinarine	2016125	0.575	2.245	–13.102	–16.917
EGFR-Oxysanguinarine	2048383	0.725	10.063	–6.553	–16.126
MAPK1-(S)-Stylopine	2048383	0.697	–1.574	5.45	38.042

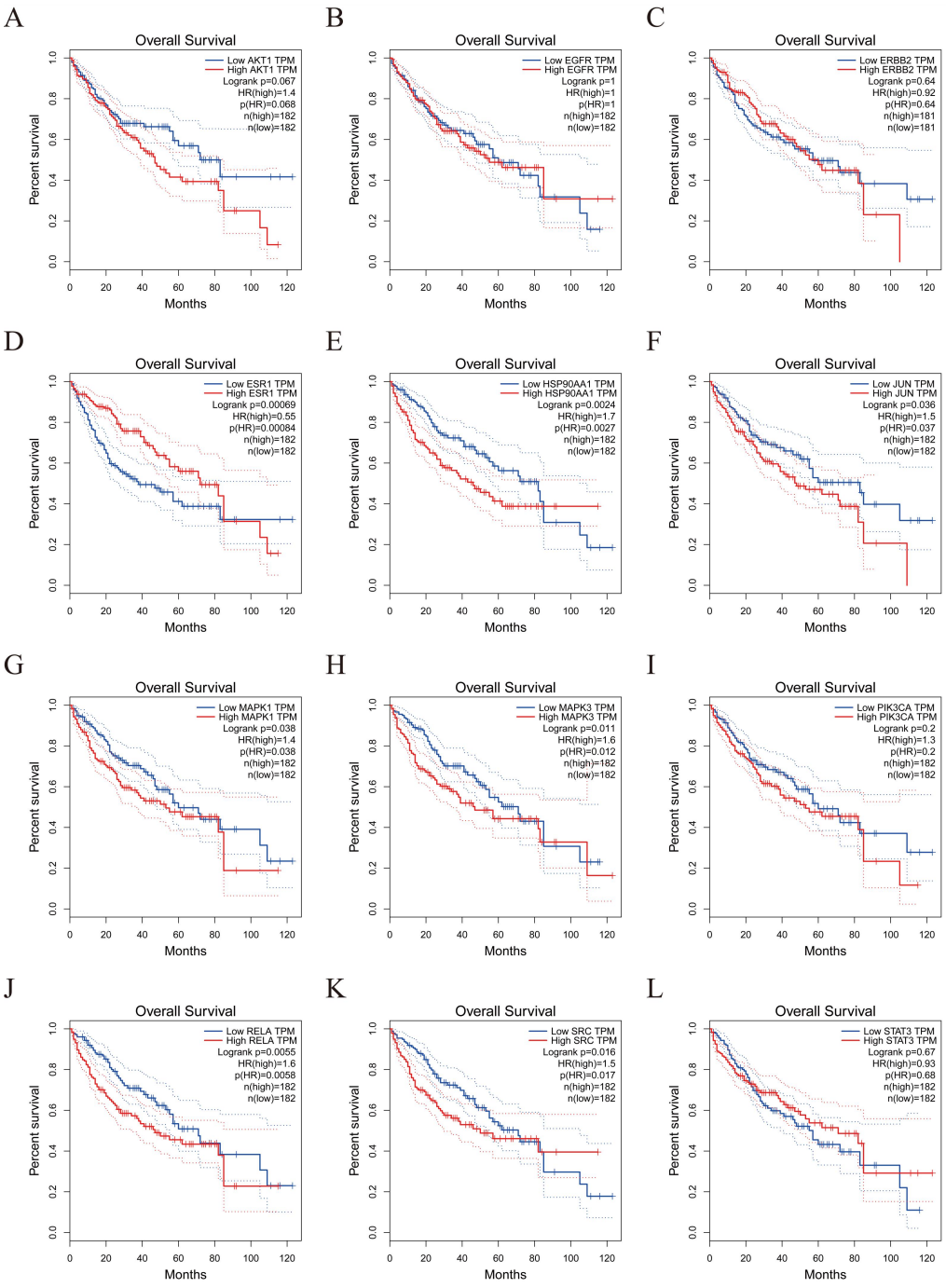

Figure 8 Overall survival curve of 12 core targets. (A) AKT1, (B) EGFR, (C) ERBB2, (D) ESR1, (E) HSP90AA1, (F) JUN, (G) MAPK1, (H) MAPK3, (I) PIK3CA, (J) RELA, (K) SRC and (L) STAT3. HR, hazard ratio.

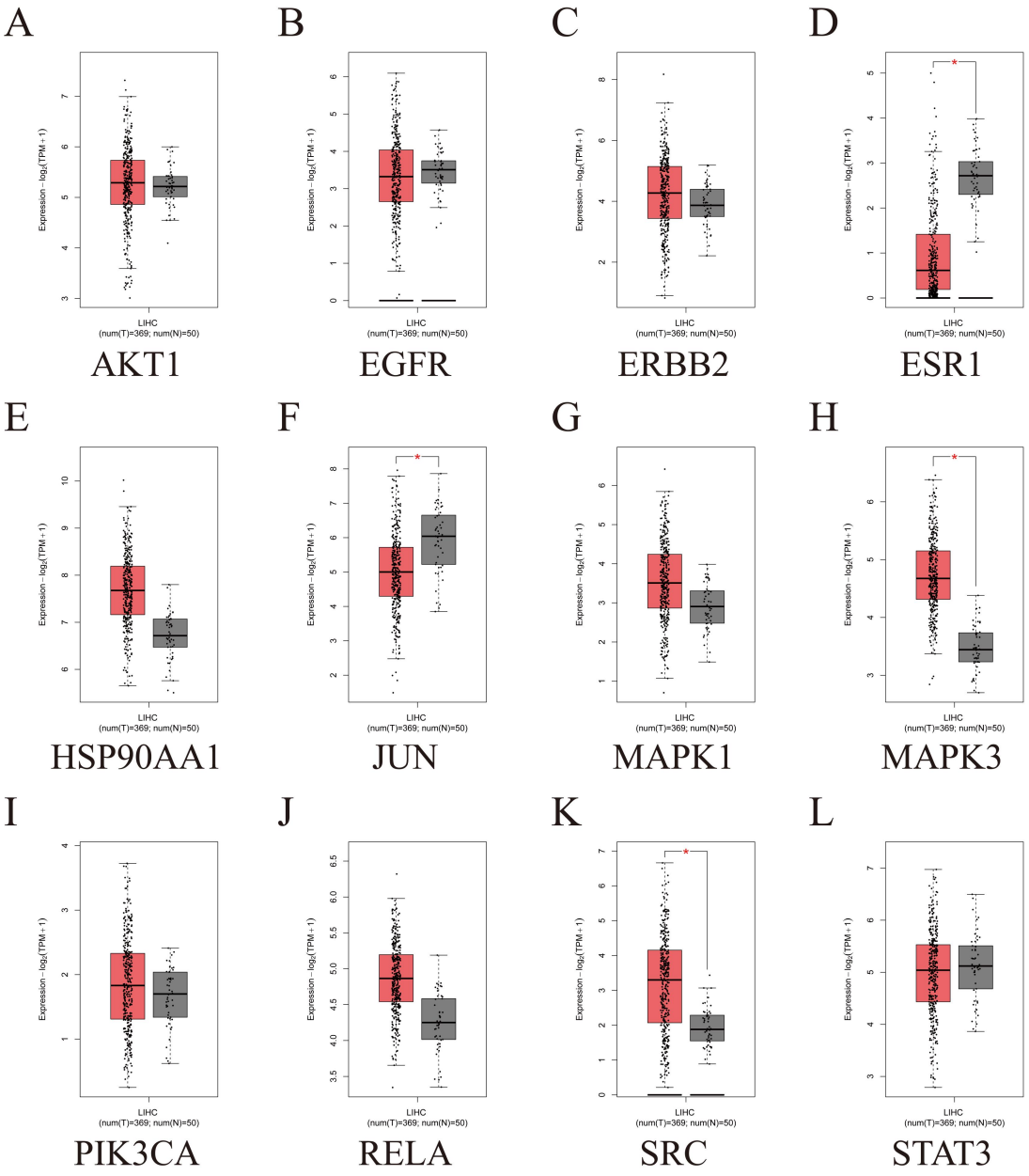

Figure 9 Pan-cancer analysis of 12 core targets. (A) AKT1, (B) EGFR, (C) ERBB2, (D) ESR1, (E) HSP90AA1, (F) JUN, (G) MAPK1, (H) MAPK3, (I) PIK3CA, (J) RELA, (K) SRC and (L) STAT3. LIHC, liver hepatocellular carcinoma.

Discussion

Liver cancer ranks among the most prevalent malignant tumors, characterized by rapid growth and high mortality, and represents a heterogeneous malignancy among known tumors [24]. It frequently develops in genetically predisposed individuals exposed to risk factors, particularly those with cirrhosis, a major determinant in up to 90% of liver cancer cases [25]. Given that cirrhosis is often asymptomatic, early detection of liver cancer remains challenging [26].

Current radical treatments for liver cancer include hepatectomy, liver transplantation, ablation, radiofrequency ablation combined with arterial chemoembolization, and radiation. However, these treatments have variable efficacy. Liver transplantation is considered the definitive treatment option, with 5-year and 10-year survival rates in Asian countries reported at 70% and 50%, respectively, and a 5-year recurrence rate of 10%–15% [27].

Research indicates that dysregulation of NF-κB, JUN, and JAK-STAT signaling pathways in primary liver cancer triggers inflammatory responses, hepatocyte proliferation, and promotes hepatocellular carcinoma development [28, 29].

Chelidonii Herba, a TCM documented in several texts including *Sichuan Traditional Chinese Medicine*, *Common Chinese Herbs of the North*, and *Chinese Medicinal Materials*, is a perennial herb known for its medicinal properties. The entire plant is utilized for its analgesic, antitussive, diuretic, detoxifying, and other therapeutic effects, reflecting a longstanding history of medicinal use. Modern pharmacological research has identified its potential efficacy in treating various cancers.

As medical standards advance, the exploration of anti-cancer agents derived from TCM like *Chelidonii Herba* holds significant scientific value. Investigating *Chelidonii Herba*'s molecular mechanisms in hepatocellular carcinoma treatment using network pharmacological methods can delineate precise molecular targets and signaling pathways. This approach is crucial for guiding future experimental validations and enhancing therapeutic strategies for hepatocellular carcinoma with *Chelidonii Herba*.

The primary active components of *Chelidonii Herba* include

chelidonine, coptisine, cryptopine, dihydrochelidonine, dihydrochelidonine, and oxysanguinarine. Among these, coptisine exhibits diverse pharmacological effects, including anticancer, anti-metabolic diseases, anti-inflammatory diseases, and anti-gastrointestinal diseases. According to its pharmacokinetics, the liver serves as the primary site of coptisine metabolism [30]. Coptisine is abundant in various herbs such as corydalis and coptis.

Coptisine induces mitochondrial damage by generating excess reactive oxygen species and eliminates damaged mitochondria through the mitochondrial autophagy pathway, ultimately causing death in hepatoma Hep3B cells due to excessive mitochondrial autophagy [31]. Research has shown that coptisine can inhibit the viability of SMMC7721, HepG2, and BEL7402 cells in human HCC cell lines, while not affecting LO2 cells in normal liver cell lines [32].

Through PPI analysis, 12 core targets were identified. The main associated targets of (S)-corydaline, (S)-Scoulerine, dihydrochelirubine, cryptopin, and oxysanguinarine, were identified. It is concluded that the mechanism of action of *Chelidonii Herba* in treating liver cancer is multi-component and multi-targeted. Among these core targets, PIK3CA is implicated in various cancers. Circ-ZEB1 promotes PIK3CA expression by suppressing miR-199a-3p, potentially influencing hepatocellular carcinoma proliferation and apoptosis [33].

The cell signaling pathways implicated in these core targets primarily include chemical carcinogen-receptor activation, endocrine resistance, estrogen signaling pathway, HIF-1 signaling pathway, and proteoglycans in cancer, among others. These pathways suggest that *Chelidonii Herba* may exert its effects in treating liver cancer by modulating multiple biological pathways. Core targets such as JUN, PIK3CA, AKT1, and MAPK3 play pivotal roles across these pathways.

Proteoglycans are widely distributed in the extracellular matrix, cell surfaces, and intracellular secretory particles. Their glycosaminoglycan chains interact with numerous regulatory molecules and signaling pathways. Research indicates that proteoglycans undergo changes during the progression of liver cancer [34]. Additionally, studies highlight the unmatched structural and functional diversity of proteoglycans, enabling them to serve as critical mediators in interactions between tumor cells and the host microenvironment. Proteoglycans directly facilitate the organization and dynamic remodeling of this environment, significantly influencing tumor progression [35].

In molecular docking, a lower binding energy indicates a stronger interaction between the target protein and the ligand, and vice versa. Specifically, EGFR-Oxysanguinarine exhibits a binding energy of –8.02 kcal/mol, with two hydrogen bonds formed between the target protein and the ligand at relatively short distances of 1.8 Å and 2.1 Å. These findings suggest a tight binding affinity between EGFR and oxysanguinarine, underscoring the involvement of *Chelidonii Herba*'s active ingredient in targeting crucial intracellular pathways for liver cancer treatment.

In overall survival and pan-cancer analyses, the hazard ratios of AKT1, HSP90AA1, MAPK1, MAPK3, PIK3CA, RELA, and SRC were found to be greater than 1, indicating up-regulation across various cancer types. Conversely, the hazard ratios of ESR1 and STAT3 were less than 1 in the survival curve, suggesting downregulation in pan-cancer analysis. These genes play pivotal roles in liver cancer by modulating the expression of AKT1, HSP90AA1, MAPK1, MAPK3, PIK3CA, RELA, and SRC, while promoting ESR1 and STAT3 expression, thereby presenting potential therapeutic targets for liver cancer treatment. These core targets hold promise as key molecules for targeted liver cancer therapy.

Cirrhosis represents a significant risk factor for liver cancer, serving as a predominant precursor to the disease. Timely identification of cirrhosis has been shown to be crucial for enhancing liver cancer prognosis, especially among high-risk populations. This identification facilitates adequate screening and early cancer diagnosis, enabling patients to potentially benefit from effective treatments [36, 37]. Statistical analyses indicate that monitoring for liver cancer is associated with early detection, treatment, and improved patient survival rates in those with cirrhosis [38]. Numerous studies and statistical findings underscore the heightened susceptibility of cirrhosis patients to liver cancer, emphasizing the importance of enhanced monitoring and timely detection.

Regrettably, intensified cirrhosis surveillance alone does not cure liver cancer. Traditional Chinese medicine has long been employed in cancer prevention, treatment, and as an adjunct therapy, boasting advantages such as low toxicity, strong specificity, and high efficacy [39]. The judicious use of TCM represents a promising new frontier in modern medical practice. *Chelidonii Herba*, widely utilized in folk medicine for various ailments including cancer, has emerged as a focal point in research aimed at uncovering its mechanisms in liver cancer treatment [40].

This study utilized predictions from a database of TCM and diseases, along with network pharmacological analysis, to theoretically confirm that *Chelidonii Herba* could treat liver cancer. However, due to issues such as incomplete data and limited database analysis results, these predictions require validation through relevant in vitro experiments and clinical trials.

Conclusion

In this study, network pharmacology was employed to investigate the active components of *Chelidonii Herba* and their shared targets in liver cancer. Through GO gene function enrichment analysis, KEGG signaling pathway analysis, molecular docking verification, survival curve analysis, and pan-cancer analysis, it was elucidated that *Chelidonii Herba* exhibits potential in treating liver cancer through a multi-component, multi-target, and multi-pathway approach. Literature reviews confirmed the association between cirrhosis and liver cancer incidence, offering theoretical insights for subsequent experimental validation.

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