

Integrating Network Pharmacology and Clinical Observation to Elucidate the Therapeutic Mechanisms of Yangzheng Xiaoji Decoction in Primary Liver Cancer

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Background: Primary liver cancer (PLC) is a leading cause of global cancer mortality. Yangzheng Xiaoji Decoction (YZXJD), a traditional Chinese medicine based on “Fuzheng Xiaoji” principles, is used as adjunctive PLC therapy, yet its underlying molecular mechanisms require further characterization.

Methods: Active compounds from 13 herbs were retrieved via the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database (OB $\geq$ 30%, DL $\geq$ 0.18). After identifying drug-disease target intersections, a compound-target-disease network was constructed using Cytoscape. PPI, GO, and KEGG analyses were performed. Concurrently, 40 patients with PLC were assigned, in a non-randomized prospective controlled design, to conventional therapy (control, n=20) or conventional therapy plus YZXJD (observation, n=20) for 4 weeks. Biochemical markers (AFP, AST, ALT, ALB, PT) and TCM syndrome scores were evaluated.

Results: Network pharmacology identified 195 active compounds and 135 potential therapeutic targets. PPI screening revealed 25 core targets, with GRM5, TRPA1, ADRA1D, GRIA2, and NPY2R showing the highest connectivity. GO analysis yielded 215 enriched terms, while KEGG analysis highlighted 14 pathways, notably neuroactive ligand-receptor interaction and cGMP-PKG signaling. Clinically, both groups showed within-group reductions in AST, ALT, and AFP, but under a Bonferroni-adjusted threshold ($P < 0.01$) the between-group advantage for the observation group was most clearly evident for prothrombin time (PT), which improved in the observation group while it worsened in the control group. TCM syndrome scores decreased significantly in the observation group ($P < 0.001$) but worsened in the control group ($P = 0.004$). The total effective rate was 80.0% in the observation group versus 65.0% in controls ($P = 0.048$).

Conclusion: Network pharmacology suggests that YZXJD may act against PLC through multi-component, multi-pathway mechanisms. In this preliminary, non-randomized observation, the addition of YZXJD was associated with improvements in hepatic function markers, serum AFP, and symptom burden. These findings are hypothesis-generating; the computational predictions and clinical signals require confirmation in adequately powered, randomized, and experimentally validated studies before YZXJD can be recommended for routine integration into PLC management.

Plain Language Summary: This study explores how a traditional Chinese medicine (TCM) herbal formula may help patients with primary liver cancer, a serious disease with limited treatment options. By combining modern computer-based analysis (network pharmacology) with real patient observations, we identified key active compounds in the herbal formula and the biological pathways they may influence that may help explain how it supports liver function and eases symptoms. In a small group of patients, those receiving the TCM treatment showed improvements in laboratory measures of liver function and in symptom scores compared to standard care alone. These findings suggest that TCM may offer a supportive and potentially beneficial approach in liver cancer management, working through multiple targets in the body. While the results are promising, larger and more rigorous studies are needed to confirm these effects and better understand how this treatment works.

Keywords: Yangzheng Xiaoji decoction, network pharmacology, primary liver cancer, traditional Chinese medicine, integrated Chinese and Western medicine

Introduction

Primary liver cancer (PLC) constitutes one of the most significant challenges in modern oncology, exhibiting high morbidity and mortality rates that place a substantial burden on global healthcare systems.¹ As of 2022, the World Health Organization estimated approximately 866,136 new cases of liver cancer and 758,725 associated deaths worldwide.² Within the specific context of the Chinese population, liver cancer is recognized as the fifth most common malignant tumor and the second leading cause of cancer-related mortality.^{3,4} The pathological landscape of PLC is dominated by hepatocellular carcinoma (HCC), which accounts for 75% to 85% of all cases, followed by intrahepatic cholangiocarcinoma.¹ The clinical management of PLC necessitates a multidisciplinary approach tailored to the disease stage; while early-stage interventions focus on surgical resection or liver transplantation, patients presenting with intermediate or advanced disease often require systemic drug therapies, including tyrosine kinase inhibitors, immune checkpoint inhibitors, and chemotherapy.^{5,6}

In recent years, the integration of traditional Chinese medicine (TCM) into the comprehensive treatment of PLC has gained significant attention due to its unique holistic perspective and multi-target regulatory mechanisms.⁷ Traditional interpretations of PLC categorize the disease under “liver accumulation”, “syndrome accumulation”, and “distension”, emphasizing a dynamic interplay between the deficiency of healthy qi and the accumulation of “cancer toxins” such as blood stasis, phlegm-dampness, and toxic heat.⁸ The “Fuzheng Xiaoji” principle (strengthening the body and eliminating accumulation) serves as a foundational therapeutic strategy, aiming to restore systemic homeostasis while suppressing tumor progression.⁹ Yangzheng Xiaoji Decoction (YZXJD), a formula, embodies this philosophy through a synergistic combination of 13 herbs designed to tonify deficiency and dispel evil.¹⁰ Preliminary evidence has begun to substantiate the anticancer potential of this formulation. A systematic review has summarized the antitumor activity of Yangzheng Xiaoji preparations across several malignancies,¹⁰ and experimental work in hepatocellular carcinoma has indicated that Yangzheng Xiaoji capsules may promote tumor-cell apoptosis through activation of the p53 pathway and concurrent suppression of PI3K/Akt signaling.¹¹ Nevertheless, the existing literature remains largely confined to single-component analyses or isolated experimental models, and the systems-level pharmacological basis by which the complete YZXJD formula acts against PLC, together with corroborating clinical data, has not been clearly delineated. This knowledge gap motivated the present integrative investigation.

Despite the historical and empirical success of such formulas, the biological mechanisms through which these complex multi-herb mixtures exert their effects remain largely opaque when viewed through the lens of conventional reductionist pharmacology.¹² The emergence of network pharmacology (NP) has provided a transformative methodological paradigm for interpreting TCM.¹³ First proposed by Andrew L. Hopkins in 2007, NP shifts the focus from the “one drug, one target” model to a “multi-component, multi-target, multi-pathway” framework.¹⁴ By utilizing bioinformatics, computational network science, and systems biology, NP allows for the construction of multidimensional networks that reveal the synergistic interactions between herbal ingredients and disease-related biological modules.¹⁵

This study aims to bridge the gap between ancient clinical wisdom and modern molecular biology by systematically investigating the therapeutic mechanisms of YZXJD in the treatment of PLC. By integrating high-throughput network pharmacology with a prospective controlled clinical observation, this research seeks to identify the key bioactive ingredients, core therapeutic targets, and modulated signaling pathways, while concurrently examining the clinical efficacy and safety of the decoction in a real-world patient cohort. We hypothesized that YZXJD exerts its therapeutic actions in PLC through a multi-component, multi-target, and multi-pathway mechanism predictable by network pharmacology, and that, as an adjunct to conventional therapy, it would be associated with measurable improvements in hepatic function markers, serum AFP, and traditional Chinese medicine syndrome scores relative to conventional therapy alone.

Method

Network Pharmacology Investigation

Screening of Bioactive Ingredients and Target Prediction

To ensure methodological rigor and reproducibility, this study adhered to the international standards established in the “Network Pharmacology Evaluation Method Guidance” issued by the World Federation of Chinese Medicine Societies.¹⁶ The pharmacological material basis of YZXJD was identified by analyzing the 13 constituent herbs: *Radix Astragali* (Huangqi), *Radix Codonopsis* (Dangshen), *Rhizoma Atractylodis Macrocephalae* (Baizhu), *Poria* (Fuling), *Carapax Trionycis* (Biejia), *Paeoniae Radix Alba* (Baishao), *Rhizoma Curcumae* (Ezhu), *Agrimoniae Herba* (Xianhecao), *Ganoderma lucidum* (Lingzhi), *Radix et Rhizoma Glycyrrhizae* (Gancao), *Fritillaria thunbergii* (Zhebeimu), *Radix Scrophulariae* (Xuanshen), and *Coix Seed* (Yiyiren). It should be noted that the complete YZXJD prescription administered in the clinical component of this study comprises fifteen herbal components, as detailed in the Treatment Protocols section. The present network pharmacology analysis was conducted on the thirteen core herbs of the formula; the two remaining constituents, *Ostreae Concha* (Muli) and *Galli Gigerii Endothelium Corneum* (Jineijin), are mineral- and animal-derived substances that are not catalogued in the TCMSP database and were therefore not amenable to the in silico screening. Consequently, the computational predictions reported here pertain to these thirteen core herbs, a boundary that is revisited among the study limitations.

Chemical components were retrieved from the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database (version 2.3), which serves as a unique systems pharmacology platform capturing the relationships between drugs, targets, and diseases.¹⁷ Candidate compounds were filtered using ADME (Absorption, Distribution, Metabolism, and Excretion) parameters. To prioritize molecules with high likelihood of therapeutic activity following oral administration, the inclusion criteria were established as Oral Bioavailability (OB) $\geq 30\%$ and Drug-Likeness (DL) ≥ 0.18 .^{17,18} OB reflects the percentage of an unchanged drug dose that reaches the systemic circulation, indicating a molecule’s potential to reach the site of action, while DL assesses structural similarity to existing clinical drugs.^{17,18} The complete set of active compounds retained after this ADME-based screening, together with their corresponding OB and DL values for each constituent herb, is summarized in [Table 1](#) and presented in full in [Supplementary Table S1](#), so that the screening and filtering process can be readily traced. Targets for the screened active ingredients were obtained from the TCMSP

Table 1 Active Ingredients and Predicted Targets of the Individual Herbs of Yangzheng Xiaoji Decoction (YZXJD) Modeled in the Network Pharmacology Analysis

Herbal Component (Pinyin)	Active Ingredients (n)	Predicted Targets (n)
Astragali Radix (Huangqi)	20	444
Codonopsis Radix (Dangshen)	21	757
Atractylodis Macrocephalae Rhizoma (Baizhu)	7	200
Poria (Fuling)	15	264
Testudinis Carapax et Plastrum (Cu Biejia)	7	38
Curcumae Rhizoma (Ezhu)	3	141
Ganoderma (Lingzhi)	61	613
Paeoniae Radix Alba (Baishao)	13	243
Agrimoniae Herba (Xianhecao)	5	134
Scrophulariae Radix (Xuanshen)	9	150
Fritillariae Thunbergii Bulbus (Zhebeimu)	7	346

(Continued)

Table 1 (Continued).

Herbal Component (Pinyin)	Active Ingredients (n)	Predicted Targets (n)
Coicis Semen (Yiyiren)	9	141
Glycyrrhizae Radix (Gancao)	77	2239

Notes: Compounds were screened from the Traditional Chinese Medicine Systems Pharmacology (TCMSP) database (version 2.3) using the thresholds oral bioavailability (OB) $\geq 30\%$ and drug-likeness (DL) ≥ 0.18 . Because many compounds and targets are shared across herbs, the per-herb counts are not additive; after removal of duplicates at the formula level, the analysis retained 195 unique active compounds corresponding to 1000 unique predicted targets. The two remaining components of the clinical prescription, *Ostreae Concha* (Muli) and *Galli Gigerii Endothelium Corneum* (Jineijin), are mineral- and animal-derived substances not catalogued in TCMSP and were therefore not modeled.

and PubChem databases. All target protein names were subsequently converted into official gene symbols using the UniProt database, with the species restricted to “Homo sapiens” to ensure biological relevance to human PLC pathology.

Identification of PLC-Related Disease Targets

Disease-associated targets were aggregated through a comprehensive search of three major bioinformatics repositories: GeneCards (<https://www.genecards.org>), OMIM (Online Mendelian Inheritance in Man), and TTD (Therapeutic Target Database). The search was conducted using the keyword “primary liver cancer”. To enhance the specificity of the disease target set and minimize the impact of low-relevance associations, a median screening threshold was applied to the GeneCards relevance scores, ensuring that only targets with a strong clinical correlation to PLC were included. After the elimination of redundant entries across the databases, a finalized list of disease targets was established for further analysis.

Construction of the Compound-Target-Disease Network

The intersection between the drug-related targets and the disease-related targets was identified using a Venn diagram generated via the Weishengxin online bioinformatics platform. These intersection targets represent the potential points of molecular intervention where YZXJD components may modulate PLC progression. To visualize the global regulatory architecture, a “Drug-Ingredient-Target-Disease” network was constructed using Cytoscape version 3.9.1. Within this network, nodes represent individual herbs, active ingredients, and targets, while edges denote documented or predicted biochemical interactions. Topological analysis was performed using the NetworkAnalyzer plugin to calculate degree centrality, which identifies hub nodes that serve as critical regulatory junctions within the network.¹⁷

Construction of Protein–Protein Interaction (PPI) Network and Core Target Screening

The overlapping targets were uploaded to the STRING database (Search Tool for the Retrieval of Interacting Genes/Proteins, version 11.5; <https://www.string-db.org/>) to obtain protein–protein interaction (PPI) data. The organism was set to “Homo sapiens”, and a minimum required interaction score of 0.150 (low confidence) was applied to capture a broad spectrum of potential interactions given the exploratory nature of the network pharmacology analysis. The resulting PPI network was then imported into Cytoscape 3.9.1 in TSV format for further topological analysis. Core targets were identified by ranking nodes according to three centrality metrics: betweenness centrality (BC), closeness centrality (CC), and degree of connectivity (Degree). Targets exceeding the median values for all three parameters were selected as core therapeutic targets. All protein identifiers were standardized to official gene symbols via the UniProt database.

Gene Ontology (GO) Functional Enrichment and KEGG Pathway Enrichment Analyses

The potential therapeutic targets were subjected to Gene Ontology (GO) functional annotation and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses using the Database for Annotation, Visualization, and Integrated Discovery (DAVID, <https://david.ncicrf.gov/>). GO analysis encompassed three domains: biological process (BP), cellular component (CC), and molecular function (MF). A significance threshold of $P < 0.05$ was applied to filter enriched terms. The top ten enriched terms for each GO domain, ranked by ascending P -value, were selected for

visualization. KEGG pathway results were further processed and visualized using the Bioinformatics online analysis and visualization platform (<http://www.bioinformatics.com.cn/>) to generate enrichment bubble plots.

Clinical Study

Study Design and Patient Enrollment

This prospective, non-randomized controlled clinical study enrolled patients with primary liver cancer who were admitted to the Department of Hepatobiliary, Pancreatic, and Spleen Surgery at the Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine between September 2020 and December 2024. The study protocol was approved by the Institutional Ethics Committee (approval number: YJS2022220507), and written informed consent was obtained from all participants prior to enrollment. A total of 40 patients meeting both the Western medicine and Traditional Chinese Medicine (TCM) diagnostic criteria for primary liver cancer were enrolled and assigned to one of two groups according to whether the YZXJD formula was incorporated into the patient's treatment regimen, rather than through a formal randomization procedure: the observation group (ZY group, $n = 20$), receiving conventional Western medicine treatment combined with YZXJD, and the control group (CG group, $n = 20$), receiving conventional Western medicine treatment alone. Because group assignment was not randomized and neither the participants nor the outcome assessors were blinded, the present investigation is most appropriately characterized as a short-term, prospective controlled pilot study, and its findings should be interpreted within this framework.

Diagnostic Criteria

Western medicine diagnosis of primary liver cancer was established in accordance with the "Guidelines for the Diagnosis and Treatment of Primary Liver Cancer (2019 Edition)" issued by the National Health Commission of the People's Republic of China. The diagnostic criteria included: (1) a documented history of hepatic cirrhosis with serological evidence of hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection; (2) characteristic imaging findings of PLC, defined as arterial-phase hyperenhancement followed by washout in the portal venous and/or equilibrium phases—for intrahepatic nodules ≤ 2 cm in diameter, at least two independent imaging modalities were required to demonstrate this pattern, whereas nodules > 2 cm required confirmation by at least one modality; (3) sustained elevation of serum alpha-fetoprotein ($\text{AFP} \geq 400 \mu\text{g/L}$ for ≥ 1 month or $\geq 200 \mu\text{g/L}$ for ≥ 2 months) after exclusion of pregnancy, active hepatitis, and other AFP-producing tumors; or (4) histopathological confirmation via liver biopsy or surgical specimen. A diagnosis of PLC was established when any two of the first three criteria were fulfilled, or when histopathological confirmation alone was obtained.

TCM syndrome differentiation was performed with reference to the "Guiding Principles for Clinical Research of New Chinese Medicines",¹⁹ and each patient's syndrome was quantitatively scored. The total TCM syndrome score was calculated as the sum of individual symptom scores assigned during clinical evaluation.

Inclusion Criteria

Patients were eligible for inclusion if they met all of the following criteria: confirmed diagnosis of PLC per both the Western medicine and TCM diagnostic standards described above; age between 18 and 75 years, regardless of sex; a Karnofsky Performance Status (KPS) score > 50 and an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) score < 2 ; disease onset within the preceding 5 years; patients who were not candidates for surgical resection or who declined surgery; and provision of written informed consent.

Exclusion Criteria

Patients were excluded if any of the following conditions were present: severe dysfunction of vital organs including the heart, brain, lung, or kidney, or serious primary diseases of the hematopoietic system; a documented history of allergy to any component of the study medications; inability to provide informed consent due to psychiatric illness or cognitive impairment; pregnancy or lactation; concurrent enrollment in other clinical trials that could potentially confound the efficacy or safety assessments of this study; or any condition deemed by the investigator to render the patient unsuitable.

for participation, such as anticipated poor compliance or an estimated survival of insufficient duration to complete the treatment course.

Treatment Protocols

Conventional Western medicine treatment (both groups): All patients received standardized supportive care comprising continuous monitoring of vital signs, bed rest, supplemental oxygen via nasal cannula as indicated, and analgesic therapy when necessary. Fluid and electrolyte balance was maintained with attention to acid–base homeostasis and microcirculatory support to prevent complications. Patients with confirmed viral hepatitis received appropriate antiviral therapy with rationally selected agents (such as entecavir or tenofovir disoproxil fumarate). For patients with advanced-stage disease not amenable to surgical intervention, systemic therapy with immune checkpoint inhibitors and/or targeted agents was administered as clinically indicated (for example, a programmed cell death protein-1 [PD-1] inhibitor in combination with a tyrosine kinase inhibitor such as sorafenib or lenvatinib). Additional symptomatic interventions were provided as warranted by individual clinical circumstances. Because the conventional regimen was individualized according to each patient's disease stage, hepatic reserve, and viral status in accordance with the aforementioned national guidelines, the specific agents and dosages were not strictly uniform across all participants; this pragmatic, guideline-directed variation reflects routine clinical practice and is acknowledged as a source of heterogeneity within the control condition.

YZXJD (observation group only): In addition to the conventional treatment described above, patients in the ZY group received YZXJD, a formula devised by Chief Physician Ding Xianqun, designated as one of the “Fourth Cohort of Renowned TCM Practitioners in Guizhou Province”. The prescription comprised the following components: Astragali Radix 20 g, Codonopsis Radix 20–30 g, Atractylodis Macrocephalae Rhizoma (stir-fried) 15 g, Poria 15 g, Testudinis Carapax et Plastrum processed with vinegar (decocted first) 15 g, Ostreae Concha (decocted first) 30 g, Curcumae Rhizoma 10 g, *Gallus gallus domesticus* Endothelium Corneum (stir-fried) 15 g, Ganoderma 20 g, Agrimoniae Herba 30 g, Paeoniae Radix Alba 15 g, Scrophulariae Radix 15 g, Fritillariae Thunbergii Bulbus 15 g, Coicis Semen (stir-fried) 20 g, and Glycyrrhizae Radix 6 g. All herbal materials were authenticated and quality-controlled by the Department of Traditional Chinese Medicine Pharmacy at the Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine. The decoction was prepared by an automated TCM decocting machine at the hospital pharmacy and dispensed as individual 200 mL vacuum-sealed packets. Patients were instructed to take one packet orally three times daily at approximately 08:00, 14:00, and 18:00 hours. The treatment duration was 4 weeks (28 days) for both groups, with clinical assessments performed at baseline (admission) and at the end of the treatment period.

Outcome Measures and Assessment Methods

Clinical symptoms and signs: Symptoms were systematically observed and documented from the time of admission through the treatment period, including abdominal distension, abdominal pain, loss of appetite, nausea, vomiting, insomnia, xerostomia (dry mouth), and bitter taste. Fatigue levels and their changes were also monitored throughout the study period.

Biochemical and tumor markers: Serum levels of AFP, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and albumin (ALB), along with prothrombin time (PT), were measured at admission (baseline) and at the end of the 4-week treatment period. All laboratory analyses were performed by the Clinical Laboratory Department of the Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine using standardized automated analytical methods.

TCM syndrome scoring: A quantitative TCM syndrome scoring system was employed, in which each symptom was graded on a four-point ordinal scale: absent (0 points), mild (1 point), moderate (2 points), and severe (3 points). The total TCM syndrome score was calculated as the sum of all individual symptom scores and was assessed at both baseline and post-treatment time points.

Clinical efficacy evaluation: Therapeutic efficacy was assessed according to the criteria established by the State Administration of Traditional Chinese Medicine of the People's Republic of China. Responses were classified into four categories based on the percentage reduction in total TCM syndrome score: complete remission (CR), defined as a score reduction $\geq 90\%$ with resolution or near-resolution of clinical signs and TCM symptoms; partial remission (PR), defined as a score reduction $\geq 70\%$ but $< 90\%$ with marked symptomatic improvement; stable disease (SD), defined as a score reduction $\geq 30\%$ but $< 70\%$ with partial symptomatic improvement; and progressive disease (PD), defined as a score

reduction < 30% with worsening or no improvement in signs and symptoms. The total effective rate was calculated as the combined proportion of patients achieving SD, PR, or CR.

Statistical Analysis

All clinical data were collected and organized using Microsoft Excel. Statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were first tested for normality using the Shapiro–Wilk (S–W) test. Normally distributed measurement data were expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$) and analyzed using paired-sample *t*-tests for within-group comparisons. Non-normally distributed data were expressed as median with interquartile range [M (P25, P75)] and analyzed using the Wilcoxon signed-rank test for paired samples. For between-group comparisons, the change from baseline (defined as the post-treatment value minus the pre-treatment value) was derived for each biochemical marker and compared between the observation and control groups using the independent-samples *t*-test or the Mann–Whitney *U*-test, as dictated by the distribution of the data. Categorical data were analyzed using the rank-sum test or the chi-square (χ^2) test, as appropriate. A two-sided $P < 0.05$ was considered statistically significant for all comparisons. To mitigate the inflation of the type I error rate arising from the simultaneous testing of the five biochemical markers (AFP, AST, ALT, ALB, and PT), a Bonferroni correction was applied to this family of comparisons, yielding an adjusted significance threshold of $P < 0.01$ (0.05 divided by 5).

Results

Network Pharmacology Findings

Active Compounds and Targets of YZXJD

Systematic screening of the 13 constituent herbs of YZXJD through the TCMSP database yielded a total of 195 active ingredients satisfying the pharmacokinetic criteria ($OB \geq 30\%$ and $DL \geq 0.18$), corresponding to 1000 predicted molecular targets. The distribution of active compounds and targets across individual herbs is summarized in Table 1. Notably, Glycyrrhizae Radix (Gancao) contributed the largest number of active ingredients and associated targets, followed by Ganoderma (Lingzhi) and Codonopsis Radix (Dangshen), reflecting the multi-component nature of this formulation (Table 1).

Disease Target Identification

Comprehensive retrieval from three disease-related databases identified 17,469 targets from GeneCards, 555 from OMIM, and 1 from TTD. Following the removal of duplicate entries and application of median-based relevance score filtering for GeneCards data, a refined set of 8735 PLC-associated disease targets was obtained.

Identification of Potential Therapeutic Targets

Intersection analysis of the 1000 drug-related targets with the 8735 PLC disease targets yielded 135 overlapping genes, which were visualized in a Venn diagram (Figure 1A). These 135 intersecting targets represent the putative molecular targets through which YZXJD may exert therapeutic effects against PLC. The compound–target–disease network was subsequently constructed and visualized in Cytoscape 3.9.1 (Figure 1B). Topological analysis of this network ranked the compounds by degree value, revealing that 7-acetoxy-2-methylisoflavone, mandelonitrile, astragalopterin, licoisoflavone, and 7-methoxy-2-methylisoflavone were among the top five compounds with the highest target connectivity.

PPI Network Construction and Core Target Screening

The 135 overlapping targets were submitted to the STRING database for PPI analysis. The resultant PPI network comprised 134 nodes (proteins) and 994 edges (interactions), with an average node degree of 14.8 (Figure 2A). Following topological analysis using betweenness centrality (BC), closeness centrality (CC), and degree of connectivity, 25 core targets were identified (Figure 2B). The top five core targets ranked by degree value were metabotropic glutamate receptor 5 (*GRM5*, degree = 50), transient receptor potential cation channel subfamily A member 1 (*TRPA1*, degree = 44), alpha-1D adrenergic receptor (*ADRA1D*, degree = 42), glutamate ionotropic receptor AMPA type subunit 2 (*GRIA2*, degree = 41), and neuropeptide Y receptor type 2 (*NPY2R*, degree = 41), as presented in Table 2.

Table 2 Topological Parameters of the Five Highest-Ranked Core Targets of YZXJD Against Primary Liver Cancer

Gene Symbol	Gene Name	UniProt ID	BC	CC	Degree
GRM5	Metabotropic glutamate receptor 5	P41594	655.45	0.0041	50
TRPA1	Transient receptor potential cation channel subfamily A member 1	O75762	857.64	0.0041	44
ADRA1D	Alpha-1D adrenergic receptor	P25100	468.65	0.0039	42
GRIA2	Glutamate ionotropic receptor AMPA type subunit 2	P42262	402.32	0.0039	41
NPY2R	Neuropeptide Y receptor type 2	P49146	657.82	0.0039	41

Notes: Core targets were identified from the protein–protein interaction network by selecting nodes that exceeded the median values of all three centrality metrics; 25 core targets were obtained in total, of which the five with the highest degree are shown here. Closeness centrality values are shown to four significant figures (full precision: GRM5 0.004098, TRPA1 0.004082, ADRA1D 0.003891, GRIA2 0.003891, NPY2R 0.003861).

Abbreviations: BC, betweenness centrality; CC, closeness centrality; Degree, degree of connectivity.

adenylate cyclase-inhibiting G protein-coupled receptor signaling pathway, neuropeptide signaling pathway, chemical synaptic transmission, G protein-coupled receptor signaling pathway, and regulation of postsynaptic membrane potential. Among CC terms, the targets were predominantly localized to the plasma membrane, presynaptic membrane, postsynaptic membrane, neuronal projections, and GABAergic synapses. The MF domain analysis revealed significant

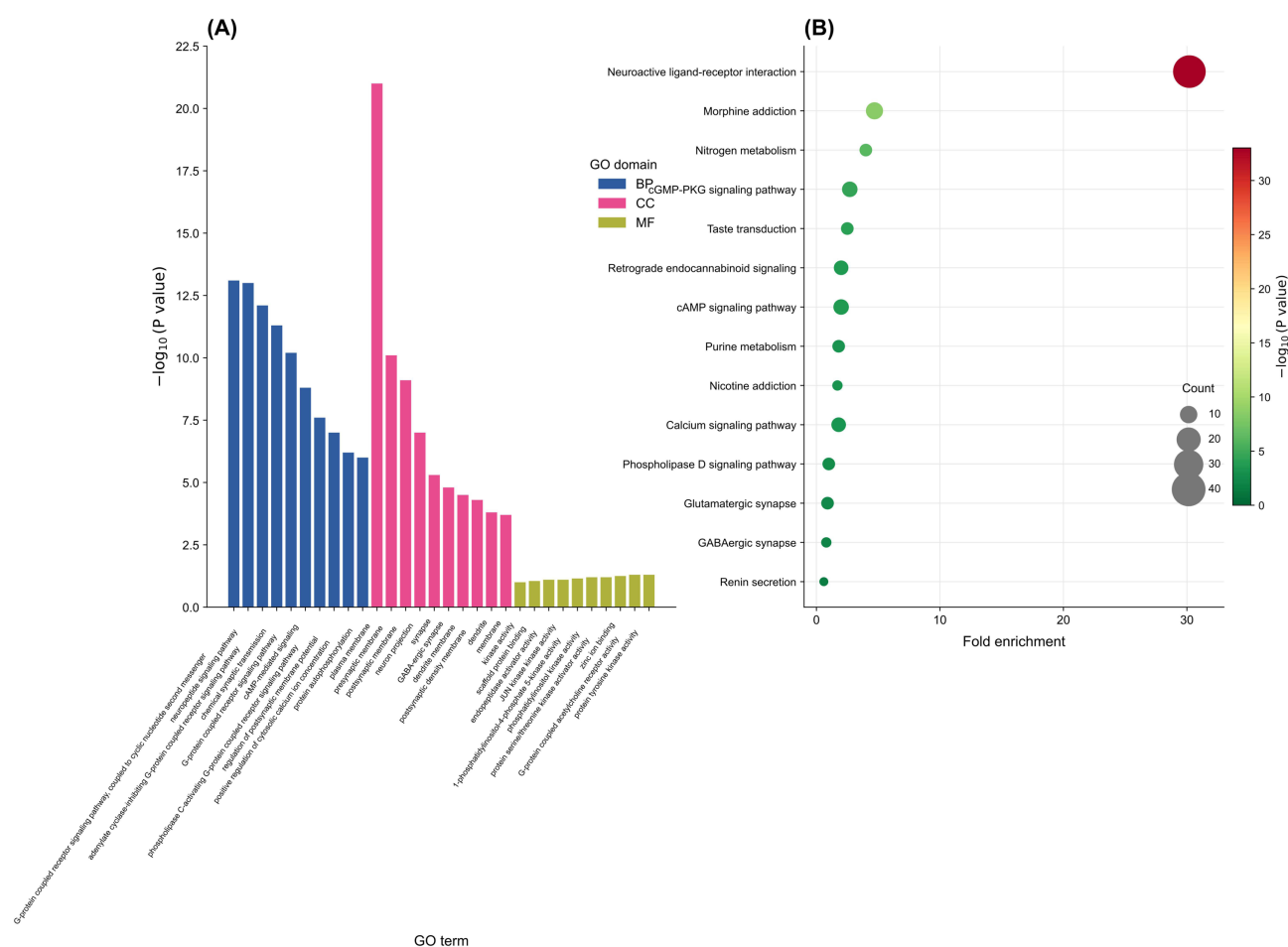


Figure 3 Functional enrichment analysis of the 135 potential therapeutic targets. **(A)** Gene Ontology (GO) enrichment analysis showing the top ten significantly enriched terms ($P < 0.05$) across three functional domains: biological process (BP), cellular component (CC), and molecular function (MF). **(B)** Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment bubble plot displaying the 14 significantly enriched signaling pathways.

enrichment in G protein-coupled receptor activity, kinase binding, scaffold protein binding, endopeptidase activator activity, JUN kinase activity, and protein tyrosine kinase activity (Figure 3A).

KEGG pathway enrichment analysis identified 14 significantly enriched signaling pathways. The most prominently enriched pathways included neuroactive ligand–receptor interaction, morphine addiction, nitrogen metabolism, and the cGMP–PKG signaling pathway, suggesting that YZXJD may exert its therapeutic effects through modulation of multiple interconnected signaling cascades (Figure 3B).

Clinical Observation Results

Comparison of Biochemical Markers and Tumor Indicators Between Groups

Baseline demographic and clinical characteristics were comparable between the ZY group and the CG group. Following 4 weeks of treatment, serum levels of AFP, AST, ALT, ALB, and PT were evaluated in both groups. In the ZY group, AFP levels demonstrated a declining trend from baseline, whereas the CG group showed no statistically significant change in AFP across the treatment period. To formally assess the relative treatment effect rather than within-group change alone, the magnitude of change from baseline was compared between the two groups for each marker; the corresponding between-group statistics are presented in Table 3. Within-group hepatocellular injury markers improved in both groups, with reductions in AST and ALT observed under conventional therapy alone and under YZXJD-supplemented therapy alike. After Bonferroni correction for the five biochemical comparisons (adjusted threshold $P < 0.01$), the addition of YZXJD was associated with a clear between-group advantage for prothrombin time (PT), which improved in the ZY group while it worsened in the CG group. The between-group difference in the change of ALT favoured the ZY group in direction but did not reach the Bonferroni-adjusted threshold of significance, and the change in AST did not differ significantly between groups. ALB declined modestly in both groups with no significant inter-group

Table 3 Comparison of Serum AFP, ALB, AST, ALT, and PT Within Each Group Before and After Treatment, and Between-Group Comparison of the Change from Baseline

Panel A. Within-Group Values Before and After Treatment							
Group	n	Time Point	AFP (ng/mL)	ALB (g/L)	AST (U/L)	ALT (U/L)	PT (s)
CG group	20	Before treatment	—	37.70 (32.93, 41.80)	54.50 (36.75, 71.75)	37.50 (22.50, 74.75)	11.61 ± 1.46
CG group		After treatment	—	33.35 (31.65, 37.95)	34.00 (25.50, 49.00)	33.50 (22.00, 47.00)	12.36 ± 1.91
ZY group	20	Before treatment	47.75 (3.40, 826.95)	40.70 (35.25, 44.10)	60.50 (38.75, 84.38)	37.30 (27.00, 48.25)	12.08 ± 1.46
ZY group		After treatment	25.12 (2.27, 379.32)	36.90 (32.03, 42.25)	44.75 (26.25, 61.50)	24.75 (13.75, 35.75)	11.11 ± 1.18
Panel B. Between-Group Comparison of the Change from Baseline (Δ = Post-Treatment – Pre-Treatment)							
Marker	Test	Test Statistic	P value†				
AFP	Wilcoxon (within ZY)*	Z = -1.93	0.053				
ALB	Mann–Whitney U	U = 208.0, Z = 0.22	0.839				
AST	Mann–Whitney U	U = 214.0, Z = 0.38	0.715				
ALT	Mann–Whitney U	U = 177.0, Z = -0.62	0.543				
PT	Independent-samples t (Welch)	t = -7.22, df = 38	< 0.001				

Notes: Non-normally distributed variables (AFP, ALB, AST, ALT) are expressed as median (P25, P75) and were analysed within groups using the Wilcoxon signed-rank test; PT was normally distributed and is expressed as mean ± standard deviation and analysed using the paired-sample t-test. AFP was not measured in the control (CG) group within the present dataset and is therefore shown as “—” for that group. † A Bonferroni-adjusted significance threshold of $P < 0.01$ (0.05 divided by the five biochemical markers) applies to this family of comparisons. The Mann–Whitney U-test was used for non-normally distributed change scores; the independent-samples t-test (Welch's correction for unequal variances) was used for the normally distributed change in PT. * For AFP, the CG group did not contribute serial measurements within the present dataset, so a formal between-group comparison of the change from baseline is not feasible; the within-group Wilcoxon signed-rank test for AFP in the ZY group is therefore reported in this row. After Bonferroni correction, only the between-group difference in the change of PT reaches statistical significance, with the ZY group showing an improvement (mean $\Delta \approx -0.97$ s) while the CG group worsened (mean $\Delta \approx +0.75$ s). The between-group differences for AST, ALT, and ALB do not reach the adjusted threshold, although the directions of change for ALT and AFP favour the ZY group.

Abbreviations: AFP, alpha-fetoprotein; ALB, albumin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; PT, prothrombin time.

difference. Detailed values for all biochemical parameters in both groups before and after treatment, together with the between-group comparisons of the change from baseline, are presented in [Table 3](#).

Comparison of TCM Syndrome Scores Before and After Treatment

The Shapiro–Wilk normality test indicated that the TCM syndrome score data in both groups deviated from a normal distribution; therefore, the Wilcoxon signed-rank test was employed for within-group comparisons. In the CG group, the TCM syndrome score increased from a median of 5.30 (IQR: 3.00–7.00) at baseline to 6.65 (IQR: 4.00–9.00) after treatment ($Z = -2.853$, $P = 0.004$), indicating a statistically significant worsening of TCM symptom burden in the control group.

Conversely, in the ZY group, the TCM syndrome score decreased from a median of 4.95 (IQR: 2.25–7.00) at baseline to 3.95 (IQR: 2.50–5.75) after treatment ($Z = -3.497$, $P < 0.001$), demonstrating a statistically significant reduction in symptom severity following treatment with YZXJD combined with conventional therapy. These findings are detailed in [Table 4](#).

Comparison of Clinical Efficacy Between Groups

Clinical efficacy evaluation revealed that neither group achieved complete remission (CR) during the 4-week treatment period. In the CG group, 7 patients (35.0%) attained partial remission, 6 (30.0%) demonstrated stable disease, and 7 (35.0%) experienced progressive disease, yielding a total effective rate of 65.0% (13/20). In the ZY group, 11 patients (55.0%) achieved partial remission, 5 (25.0%) had stable disease, and 4 (20.0%) exhibited progressive disease, yielding a total effective rate of 80.0% (16/20). The ZY group demonstrated a statistically superior clinical response compared with the CG group ($Z = -1.321$, $P = 0.048$), as presented in [Table 5](#).

Table 4 Comparison of TCM Syndrome Scores Within Each Group Before and After Treatment

Group	n	Before Treatment	After Treatment	Z	P
CG group	20	5.30 (3.00, 7.00)	6.65 (4.00, 9.00)	-2.853	0.004
ZY group	20	4.95 (2.25, 7.00)	3.95 (2.50, 5.75)	-3.497	< 0.001

Notes: Values are expressed as median (P25, P75). Within-group changes were analysed using the Wilcoxon signed-rank test. The TCM syndrome score increased (worsened) in the CG group and decreased (improved) in the ZY group. The post-treatment interquartile range for the ZY group has been corrected to (2.50, 5.75); the previously reported lower quartile of 4.50 was a transcription error inconsistent with the median of 3.95.

Abbreviation: TCM, traditional Chinese medicine.

Table 5 Comparison of Clinical Efficacy Between the Two Groups [n (%)]

Group	n	CR	PR	SD	PD	Total Effective
CG group	20	0	7 (35.0)	6 (30.0)	7 (35.0)	13 (65.0)
ZY group	20	0	11 (55.0)	5 (25.0)	4 (20.0)	16 (80.0)

Notes: Clinical efficacy was compared between groups using the rank-sum test across the ordinal response categories ($Z = -1.321$, $P = 0.048$). The corresponding effect size, calculated as $r = |Z|/\sqrt{N}$ with $N = 40$, was 0.21, indicating a small effect. Because the P value lies close to the 0.05 threshold and each group comprised only 20 patients, this result should be interpreted with caution. The total effective rate is the combined proportion of patients achieving SD, PR, or CR.

Abbreviations: CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

Discussion

This study employed a combined network pharmacology and clinical observation approach to explore the potential molecular mechanisms and preliminary clinical efficacy of YZXJD in the treatment of primary liver cancer (PLC). The following discussion integrates the study findings with existing literature across theoretical, methodological, and clinical dimensions.

Modern medical understanding of PLC emphasizes epidemiological risk factors such as chronic viral hepatitis (HBV/HCV infection) and aflatoxin exposure, as well as molecular aberrations in signaling pathways including PI3K/AKT/mTOR and PD-1/PD-L1 that drive tumor initiation and progression.^{20,21} Clinical management follows a stage-dependent strategy integrating surgery, locoregional ablation, targeted therapy, and immunotherapy. While these approaches have improved survival outcomes, they are frequently associated with hepatotoxicity, drug resistance, and adverse effects that limit their long-term tolerability.^{22,23}

In contrast, TCM categorizes PLC within the domains of “Ganji” (liver accumulation), “Zhengji” (abdominal masses), and “Guzhang” (tympanites). The core pathogenesis is conceptualized as a dynamic interplay between internal factors (deficiency of vital qi, emotional disturbance) and external factors (pathogenic invasion, dietary irregularity), culminating in qi stagnation, blood stasis, phlegm-dampness accumulation, and toxic heat that coalesce to form “cancer toxin”—a pattern of concurrent deficiency and excess.^{24,25} This integrative pathogenesis framework complements the lesion-focused intervention strategy of Western medicine. In the present study, the addition of YZXJD to standard Western medical treatment was designed to improve the patient’s internal milieu, alleviate symptoms, and enhance treatment tolerance through holistic regulation, reflecting the synergistic potential of integrated Chinese and Western medicine in comprehensive liver cancer management.²⁶

TCM compound formulations are characterized by multi-component, multi-target, and multi-pathway synergistic actions, which pose substantial challenges for mechanistic elucidation using conventional reductionist approaches.²⁷ Network pharmacology, with its systems-level analytical framework, aligns closely with the holistic philosophy and syndrome-based treatment principles of TCM, offering a powerful methodology for deciphering the complex pharmacology of herbal formulations.¹² In this study, systematic screening through the TCMSMP database identified 195 active compounds and 135 potential therapeutic targets shared between YZXJD and PLC. GO functional enrichment and KEGG pathway analyses revealed that these targets are primarily involved in G protein-coupled receptor signaling, neuropeptide signaling, and regulation of postsynaptic membrane potential at the biological process level, with enrichment in pathways such as neuroactive ligand–receptor interaction, nitrogen metabolism, and cGMP–PKG signaling. This multi-target, multi-pathway profile is consistent with findings reported in network pharmacology studies^{28–30} of other TCM formulations, and provides a bioinformatics-based scientific hypothesis for the mechanism of action of YZXJD. The analysis further suggests that the Fuzheng (vital qi-supporting) components of the formulation may predominantly modulate immune and metabolic targets, whereas the Xiaoji (accumulation-resolving) components may more directly influence cell proliferation and apoptosis pathways, offering molecular-level support for the compatibility rationale of this prescription.

The composition of YZXJD is closely aligned with the core pathogenesis of PLC, characterized in TCM as “deficiency of vital qi with mutual accumulation of toxin and blood stasis”. *Astragali Radix* and *Codonopsis Radix* serve as the sovereign (Jun) herbs, powerfully tonifying qi and supporting vital energy; modern pharmacological studies have confirmed their immunomodulatory, antioxidant, and hepatoprotective properties.^{11,31} *Atractylodis Macrocephalae Rhizoma* and *Poria* function as ministerial (Chen) herbs, strengthening the spleen and resolving dampness to protect digestive function. *Testudinis Carapax et Plastrum* (processed with vinegar), *Ostreae Concha*, and *Curcumae Rhizoma* serve as assistant (Zuo) herbs; studies have demonstrated their capacity to inhibit tumor cell proliferation and metastasis.^{32,33} *Scrophulariae Radix* and *Coicis Semen* contribute heat-clearing and detoxifying effects, *Paeoniae Radix Alba* nourishes blood and soothes the liver, *Agrimoniae Herba* provides hemostatic and detoxifying actions, and *Ganoderma* tonifies qi while exerting reported anti-tumor effects. *Glycyrrhizae Radix* harmonizes the actions of all components as the envoy (Shi) herb.³⁴ The clinical observations in this study showed that patients receiving the combined treatment demonstrated favorable trends in hepatic function markers (ALT and AST), a reduction in serum AFP levels, and improvement in coagulation function (PT), suggesting that YZXJD may exert comprehensive therapeutic

effects through multiple channels, including attenuation of hepatocellular damage, suppression of tumor activity, amelioration of hypercoagulability, and immunomodulation.

This study integrates network pharmacology prediction with preliminary clinical observation to systematically explore the potential molecular mechanisms and clinical applicability of YZXJD in PLC treatment. The network pharmacology analysis identified key active compounds, including 7-acetoxy-2-methylisoflavone, mandelonitrile, astragalopterin, licoisoflavone, and 7-methoxy-2-methylisoflavone, along with core targets such as *GRM5*, *TRPA1*, *ADRA1D*, *GRIA2*, and *NPY2R*, which operate through pathways including neuroactive ligand–receptor interaction, morphine addiction, nitrogen metabolism, and the cGMP–PKG signaling pathway. These core targets warrant cautious interpretation. *GRM5*, *TRPA1*, *ADRA1D*, *GRIA2*, and *NPY2R* are predominantly recognized for their roles in neuronal and neuroactive signaling, and none of them currently has a firmly established, well-characterized function in hepatocarcinogenesis. Their emergence in the present analysis should therefore be regarded as hypothesis-generating rather than confirmatory. One plausible explanation is that these receptors were prioritized in part because the neuroactive ligand–receptor interaction pathway is heavily represented in the source databases, and in part because a growing literature suggests that neurotransmitter and neuropeptide signaling may participate in tumour–nerve crosstalk and in the modulation of the hepatic tumour microenvironment. In the absence of direct experimental confirmation in liver cancer models, however, the specific contribution of these targets to the antitumour activity of YZXJD remains speculative and requires dedicated validation. Clinical observation demonstrated that, compared with the CG group receiving conventional Western medicine alone, the ZY group supplemented with YZXJD showed within-group reductions in AST, ALT, and AFP, an improvement in PT, and a higher total effective rate (80.0% vs 65.0%). When the change from baseline was compared formally between groups under a Bonferroni-adjusted threshold ($P < 0.01$), the between-group advantage was most clearly evident for PT, which improved in the ZY group while it worsened in the CG group; the between-group difference in the change of ALT favoured the ZY group in direction but did not reach the adjusted threshold, and the change in AST and ALB did not differ significantly between groups. These results should therefore be interpreted as encouraging but preliminary, in keeping with the small sample size and the non-randomized, unblinded design of the present pilot. Taken together, the computational and clinical components of this study may be integrated only with caution. The network pharmacology analysis indicates that YZXJD acts in a multi-component, multi-target manner, and the hub targets and pathways identified are broadly relevant to processes governing hepatocellular injury and repair. At the clinical level, the reductions in AST and ALT are compatible with improved hepatocellular integrity, the decline in AFP is consistent with attenuated tumour activity, and the improvement in PT suggests a beneficial effect on hepatic synthetic and coagulation function. While it is tempting to map individual predicted targets directly onto these biochemical changes, the present data do not permit such precise attribution; the predicted mechanisms are best viewed as candidate explanations that future target-level experiments will need to test. These observations are broadly consistent with the existing literature on Yangzheng Xiaoji and on integrative Chinese and Western medicine in primary liver cancer. A systematic review of the anticancer potential of Yangzheng Xiaoji has documented activity across multiple tumour types,¹⁰ and meta-analytic evidence indicates that adding Traditional Chinese Medicine to conventional targeted therapy can improve outcomes in patients with primary liver cancer.²⁶ More broadly, Traditional Chinese Medicine has been reported to modulate the hepatic tumour microenvironment and has remained an active focus of liver-cancer research.^{24,25} Mechanistically, our multi-target predictions accord with network pharmacology and experimental studies of related Xiaoji-type and Fuzheng formulations, which have similarly converged on immune- and apoptosis-related signalling, including the JAK/STAT/PD-L1 axis.^{29,30} The present study extends this body of work by linking, within a single investigation, an in silico mechanistic prediction for YZXJD to concurrently collected clinical biochemical outcomes; nevertheless, differences in formulation, patient population, and analytical methodology across these studies preclude direct quantitative comparison.

However, several important limitations should be acknowledged. First, the network pharmacology findings represent computational predictions, and the exact bioactive components and key targets require further validation through in vitro cell-based experiments and in vivo animal models. Second, the clinical observation was limited by a small sample size ($n = 40$), a relatively short observation period (4 weeks), and a non-randomized design, all of which constrain the generalizability of the conclusions. Third, the absence of a placebo control and blinding introduces potential bias.

Fourth, because group assignment was determined by whether YZXJD was incorporated into care rather than by randomization, the study is susceptible to selection and confounding bias, and the conventional regimen itself was not strictly uniform across participants. Fifth, no a priori power or sample-size calculation was performed, so the study may have been underpowered to detect modest between-group differences, and the multiplicity of biochemical comparisons was addressed only by a conservative Bonferroni adjustment. Sixth, part of the efficacy assessment relied on TCM syndrome scores, which are inherently subjective and, in an unblinded setting, vulnerable to observer expectation. Seventh, overall survival and other long-term oncological endpoints were not captured within the four-week observation window. Finally, the network pharmacology analysis modelled the thirteen core herbs of the formula rather than all fifteen administered constituents, so the *in silico* predictions describe a defined subset of the clinical prescription. Collectively, these considerations reinforce that the present findings are preliminary and hypothesis-generating.

Future research should address these limitations through several approaches: conducting large-sample, multi-center, prospective randomized controlled trials (RCTs) with adequate blinding to rigorously evaluate long-term efficacy and safety; employing metabolomics, proteomics, and other omics technologies to elucidate the specific mechanisms by which YZXJD modulates the tumor microenvironment; and investigating its synergistic effects and toxicity-attenuating potential when combined with conventional chemotherapy, targeted therapy, or immunotherapy.

In conclusion, YZXJD, guided by the “Fuzheng Xiaoji” therapeutic principle, demonstrates multi-component, multi-target, and multi-pathway characteristics as revealed by network pharmacology analysis, and preliminary clinical observation suggests that it may confer benefits in improving liver function, reducing AFP levels, and modulating coagulation status in PLC patients. This study provides a foundational basis for the further development and clinical application of YZXJD, and underscores the potential value of the integrated Chinese and Western medicine model in the management of complex diseases such as liver cancer. Subsequent studies should focus on deepening mechanistic understanding and strengthening clinical evidence to advance toward more precise and individualized therapeutic strategies. It must be emphasized that the mechanistic relationships proposed here are derived from computational predictions and must be validated by *in vitro* and *in vivo* studies before any firm conclusions regarding the molecular basis of YZXJD can be drawn.

Clinical Trial Registration

This prospective clinical observation was not registered in a public clinical trials registry prior to its commencement, which we acknowledge as a limitation; retrospective registration of the study is currently being pursued.

Data Sharing Statement

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request. The network pharmacology data were derived from publicly accessible databases including TCMSP (<https://old.tcmsp-e.com/tcmsp.php>), GeneCards (<https://www.genecards.org>), OMIM (<https://omim.org>), TTD (<https://db.idrblab.net/ttd/>), STRING (<https://string-db.org>), and DAVID (<https://david.ncifcrf.gov/>).

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study protocol was reviewed and approved by the Institutional Ethics Committee of the Second Affiliated Hospital of Guizhou University of Traditional Chinese Medicine (Approval No. YJS2022220507). All procedures involving human participants were performed in compliance with the ethical standards of the institutional research committee and applicable national regulations.

Consent for Publication

All participants provided consent for the publication of anonymized data collected during this study. No personally identifiable information is included in this manuscript.

Informed Consent

Written informed consent was obtained from all individual participants included in this study prior to enrollment. Participants were fully informed about the study objectives, procedures, potential risks and benefits, and their right to withdraw from the study at any time without any consequence to their ongoing medical care.

Author Contributions

Shengbo Yang: Conceptualization, study design, network pharmacology analysis, and drafting of the original manuscript. Rui Liu: Data curation, software operation, statistical analysis, result verification, and visualization. Shuai Wen, Ya Wang, and Nan Tai: Clinical case observation, patient data collection, and implementation of clinical protocols. Jie Tian: Supervision, resource acquisition, funding administration, and critical revision and final approval of the manuscript. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship: each made substantial contributions to the conception or design of the work, or to the acquisition, analysis, or interpretation of the data; each took part in drafting the work or revising it critically for important intellectual content; each gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and each agreed to be accountable for all aspects of the work, ensuring that questions relating to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Disclosure

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 manuscript.

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