

Network Pharmacology-based Investigation of the Mechanism of the Chaihu-Baizhu Herb Pair in Treating Liver Cancer

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Abstract: ***Objective:** To explore the potential active ingredients, targets, and signaling pathways of the Bupleuri Radix-Attractylodis Macrocephalae Rhizoma (Chaihu-Baizhu) herb pair in the treatment of liver cancer using network pharmacology, and to provide a theoretical basis for its molecular mechanism. **Methods:** Active ingredients of the Chaihu-Baizhu herb pair were retrieved from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP) with screening criteria of drug-likeness (DL) ≥ 0.18 and oral bioavailability (OB) $\geq 30\%$, and corresponding targets were obtained. Liver cancer-related targets were acquired from the GeneCards and OMIM databases. Intersection targets were identified and visualized by a Venn diagram. A “compound-target” network was constructed using Cytoscape 3.10.1 software. A protein-protein interaction (PPI) network was built via the STRING platform and Cytoscape to screen core targets. Gene Ontology (GO) functional enrichment analysis and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were performed using R 4.4.1 software. **Results:** A total of 23 potential active ingredients of the Chaihu-Baizhu herb pair were screened, corresponding to 190 targets. The intersection between liver cancer-related targets and drug targets yielded 108 common targets. Core PPI network targets included TP53, BCL2, JUN, CCND1, ESR1, and MAPK1. GO enrichment analysis showed that the key targets were primarily enriched in biological processes such as “response to oxygen levels”, “response to hypoxia”, and “response to oxidative stress”. KEGG pathway enrichment analysis identified over 120 pathways, with significantly enriched pathways including the HIF-1 signaling pathway, PI3K-Akt signaling pathway, and MAPK signaling pathway. **Conclusion:** The Chaihu-Baizhu herb pair may exert anti-liver cancer effects through active ingredients such as quercetin, kaempferol, and isorhamnetin, acting on core targets including TP53, BCL2, and MAPK1, and regulating multiple signaling pathways such as HIF-1 α /VEGF. This study provides a preliminary network pharmacology basis for the modern scientific interpretation of the “Treating liver by strengthening the spleen” theory.*

1. Introduction

Primary liver cancer is one of the most common malignant tumors in China. According to the latest data [1], there are approximately 368,000 new cases and 317,000 deaths from liver cancer in China annually, accounting for more than 42% of the global total, representing a heavy disease burden. Liver cancer has an insidious onset, and about 70%–80% of patients are already at an intermediate or advanced stage at the time of initial diagnosis, missing the optimal opportunity for surgical resection, leading to a poor prognosis [2]. Currently, modern medicine primarily employs treatment modalities such as surgical resection, ablation, interventional therapy, targeted therapy, and immunotherapy. However, these approaches are associated with significant toxic side effects, susceptibility to drug resistance, and limited applicability to specific patient populations, which considerably restrict their clinical application [3].

Traditional Chinese medicine has accumulated extensive experience in the comprehensive treatment of liver cancer. Among its key theories, the principle of “treating the liver by strengthening the spleen” originates from the Golden Chamber (Jin Gui Yao Lue), which states: “When one sees a disease of the liver, one should recognize that the liver can transmit the disease to the spleen, and therefore the spleen should be strengthened first.” This theory emphasizes that liver disease tends to affect the spleen, and treatment should focus on regulating both the liver and the spleen simultaneously, thereby treating the existing disease while preventing its further transmission [4]. The Chaihu (Bupleuri Radix)-Baizhu (Attractylodis Macrocephalae Rhizoma) herb

pair is a classic compatibility reflecting this theory: Chaihu soothes the liver and relieves stagnation, regulating liver qi to treat the root cause, while Baizhu strengthens the spleen and replenishes qi, fortifying the middle energizer to solidify the spleen. The two herbs, one for soothing and one for tonifying, jointly achieve the effects of reinforcing healthy qi and eliminating pathogenic factors. Clinically, this herb pair is commonly used as an adjuvant therapy for liver cancer of the liver depression and spleen deficiency syndrome [5]. Modern pharmacological studies have shown that components from Chaihu, such as saikosaponins and quercetin, as well as components from Baizhu, including atractylenolides and polysaccharides, exhibit activities such as inducing apoptosis of liver cancer cells, inhibiting proliferation and metastasis, and regulating immunity [6-9]. However, the synergistic effects and systemic molecular mechanisms of the Chaihu-Baizhu herb pair after its compatibility remain poorly understood.

Network pharmacology, as an important tool in the research of traditional Chinese medicine formulas, can predict active components, action targets, and biological pathways at a systemic level, providing a theoretical basis for the “multi-component, multi-target, multi-pathway” mode of action [10]. In this study, we intend to apply network pharmacology methods to screen the active components of the Chaihu-Baizhu herb pair, predict its key targets and signaling pathways in the treatment of liver cancer, with a particular focus on analyzing its relevance to the HIF-1 α /VEGF pathway, thereby providing a foundation for subsequent experimental validation and the modern scientific interpretation of the “treating the liver by strengthening the

spleen” theory.

2. Materials and Methods

2.1 Screening of Active Ingredients and Targets of the Chaihu-Baizhu Herb Pair

Active ingredients of *Bupleuri Radix* and *Atractylodis Macrocephalae Rhizoma* were retrieved from the Traditional Chinese Medicine Systems Pharmacology Database and Analysis Platform (TCMSP, <https://tcmsp-e.com/>) [11]. Candidate active ingredients were screened using the criteria of oral bioavailability (OB) $\geq 30\%$ and drug-likeness (DL) ≥ 0.18 . The corresponding targets of each active ingredient were obtained from the TCMSP and PubChem databases. The names of target proteins were standardized into gene names using the UniProt database (<https://www.uniprot.org/>), with the species restricted to *Homo sapiens* (human).

2.2 Acquisition of Liver Cancer Disease Targets

Using the keyword “Liver cancer”, liver cancer-related targets were retrieved from the GeneCards database (<https://www.genecards.org/>) and the OMIM database (<https://omim.org/>). Duplicate targets were removed, and targets with a relevance score > 10 in the GeneCards database were selected as high-confidence disease targets.

2.3 Identification of Intersection Targets and Construction of Venn Diagram

The action targets of the Chaihu-Baizhu herb pair and the liver cancer disease targets were imported into the Venny 2.1 platform (<https://bioinfogp.cnb.csic.es/tools/venny/>) to generate a Venn diagram and obtain the common targets (intersection targets) between the drug and the disease.

2.4 Construction of the “Drug Component–Action Target” Network

The active ingredients and the intersection targets were imported into Cytoscape 3.10.1 software to construct a “compound–target” network. The Network Analyzer function of the software was used to calculate the degree of each node.

The five ingredients with the highest degree values were identified as the core potential active ingredients.

2.5 Construction of Protein-Protein Interaction (PPI) Network and Screening of Key Targets

The intersection targets were imported into the STRING database (<https://string-db.org/>) with the species set to “*Homo sapiens*” and a confidence score threshold of ≥ 0.9 (high confidence) to construct a protein-protein interaction (PPI) network. The results were exported and visualized using Cytoscape 3.10.1 software. Using the CytoNCA plugin, the core targets were identified through two rounds of screening based on the average values of parameters including betweenness centrality, closeness centrality, degree, eigenvector, local average connectivity (LAC), and network.

2.6 GO Functional Enrichment Analysis and KEGG Pathway Enrichment Analysis

The intersection targets were analyzed for Gene Ontology (GO) functional enrichment and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment using R 4.0.4 software with the “clusterProfiler” package. GO analysis encompassed three domains: biological process (BP), cellular component (CC), and molecular function (MF). The significance threshold was set at $P < 0.05$. The GO enrichment results were visualized as bar plots, and the KEGG enrichment results were displayed as bubble plots.

2.7 Statistical Analysis

All analyses in this study were performed based on publicly available databases and software. Network topology parameter analysis was conducted using the built-in algorithms of Cytoscape. Enrichment analysis was performed using the hypergeometric test, and a P -value < 0.05 was considered statistically significant.

3. Results

3.1 Screening of Active Ingredients of the Core Drug and Their Targets, as well as Disease Targets

Table 1: Active ingredients of *Atractylodis Macrocephalae Rhizoma* (Baizhu) and *Bupleuri Radix* (Chaihu).

No.	Sources	Mol ID	Molecule Name	OB (%)	DL
1	Rhizoma (Baizhu)	MOL004718	α -spinasterol	42.98	0.76
2	Rhizoma (Baizhu)	MOL000449	Stigmasterol	43.83	0.76
3	Rhizoma (Baizhu)	MOL002776	Baicalin	40.12	0.75
4	Rhizoma (Baizhu)	MOL004653	(+)-Anomalin	46.06	0.66
5	Rhizoma (Baizhu)	MOL013187	Cubebin	57.13	0.64
6	Rhizoma (Baizhu)	MOL004702	saikosaponin c_qt	30.5	0.63
7	Rhizoma (Baizhu)	MOL004598	3, 5, 6, 7-tetramethoxy-2-(3, 4, 5-trimethoxyphenyl)chromone	31.97	0.59
8	Rhizoma (Baizhu)	MOL004624	Longikaurin A	47.72	0.53
9	Rhizoma (Baizhu)	MOL004609	Areapillin	48.96	0.41
10	Rhizoma (Baizhu)	MOL000490	petunidin	30.05	0.31
11	Rhizoma (Baizhu)	MOL000354	isorhamnetin	49.6	0.31
12	Rhizoma (Baizhu)	MOL004648	Troxerutin	31.6	0.28
13	Rhizoma (Baizhu)	MOL000098	quercetin	46.43	0.28
14	Rhizoma (Baizhu)	MOL000422	kaempferol	41.88	0.24
15	Rhizoma (Baizhu)	MOL004644	Sainfuran	79.91	0.23
16	Rhizoma (Baizhu)	MOL001645	Linoleyl acetate	42.1	0.2
17	Radix (Chaihu)	MOL000072	8 β -ethoxy atractylenolide III	35.95	0.21
18	Radix (Chaihu)	MOL000033	(3S, 8S, 9S, 10R, 13R, 14S, 17R)-10, 13-dimethyl-17-[(2R, 5S)-5-propan-2-yloctan-2-yl]-2, 3, 4, 7, 8, 9, 11, 12, 14, 15, 16, 17-dodecahydro-1H-cyclopenta [a]phenanthren-3-ol	36.23	0.78
19	Radix (Chaihu)	MOL000028	α -Amyrin	39.51	0.76

20	Radix (Chaihu)	MOL000049	3β-acetoxyatractylone	54.07	0.22
21	Radix (Chaihu)	MOL000021	14-acetyl-12-senecioid-2E, 8E, 10E-atractylentriol	60.31	0.31
22	Radix (Chaihu)	MOL000020	12-senecioid-2E, 8E, 10E-atractylentriol	62.4	0.22
23	Radix (Chaihu)	MOL000022	14-acetyl-12-senecioid-2E, 8Z, 10E-atractylentriol	63.37	0.3

3.2 Venn Diagram of Intersection Between Core Drug and Disease

The targets of the “Chaihu-Baizhu” herb pair and the disease targets of cancer pain were imported into the Venny platform, and a Venn diagram was generated, yielding a total of 108 overlapping targets.

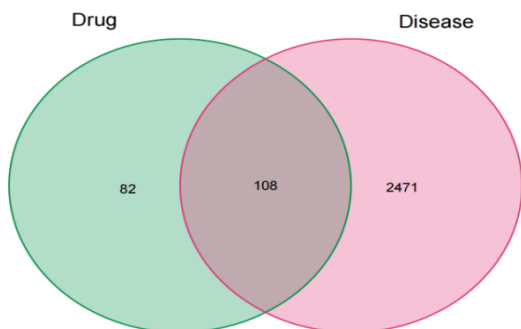


Figure 3: Intersection targets of the Chaihu-Baizhu herb pair and liver cancer

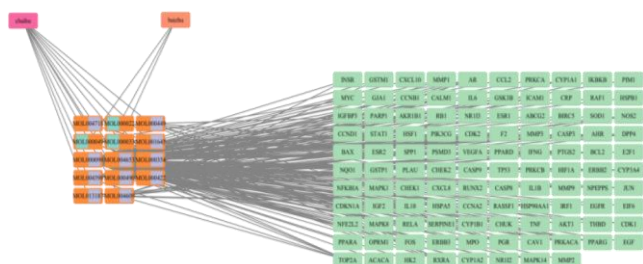


Figure 4: Intersection targets of the Chaihu-Baizhu herb pair and liver cancer

3.3 Construction of Drug Active Ingredient–Disease Target Network

The active ingredients of the drug and the effective target genes were imported into Cytoscape 3.10.1 for visualization analysis. Based on degree value, the top five compounds were selected as the potential active ingredients of the core drug for the treatment of cancer pain. These were quercetin, kaempferol, isorhamnetin, areapillin, and 3, 5, 6, 7-tetramethoxy-2-(3, 4, 5-trimethoxyphenyl) chromone.

3.4 PPI Network Construction and Screening of Key Targets

The 108 obtained intersecting targets were imported into the STRING database (<https://string-db.org/>) to construct a PPI network of the Chaihu-Baizhu herb pair for the treatment of liver cancer. The species was set to Homo sapiens, and the minimum interaction threshold was set to high confidence (0.900) to predict protein-protein interactions [12]. After constructing the PPI network and removing free proteins without interactions, the network was visualized using Cytoscape 3.10.1. Using the CytoNCA plugin, two rounds of screening were performed with the average values of betweenness centrality, closeness centrality, degree, eigenvector centrality, local average connectivity (LAC), and network centrality as the cut-off criteria. The top six proteins

ranked by degree value were identified as key targets: TP53, BCL2, JUN, CCND1, ESR1, and MAPK1.

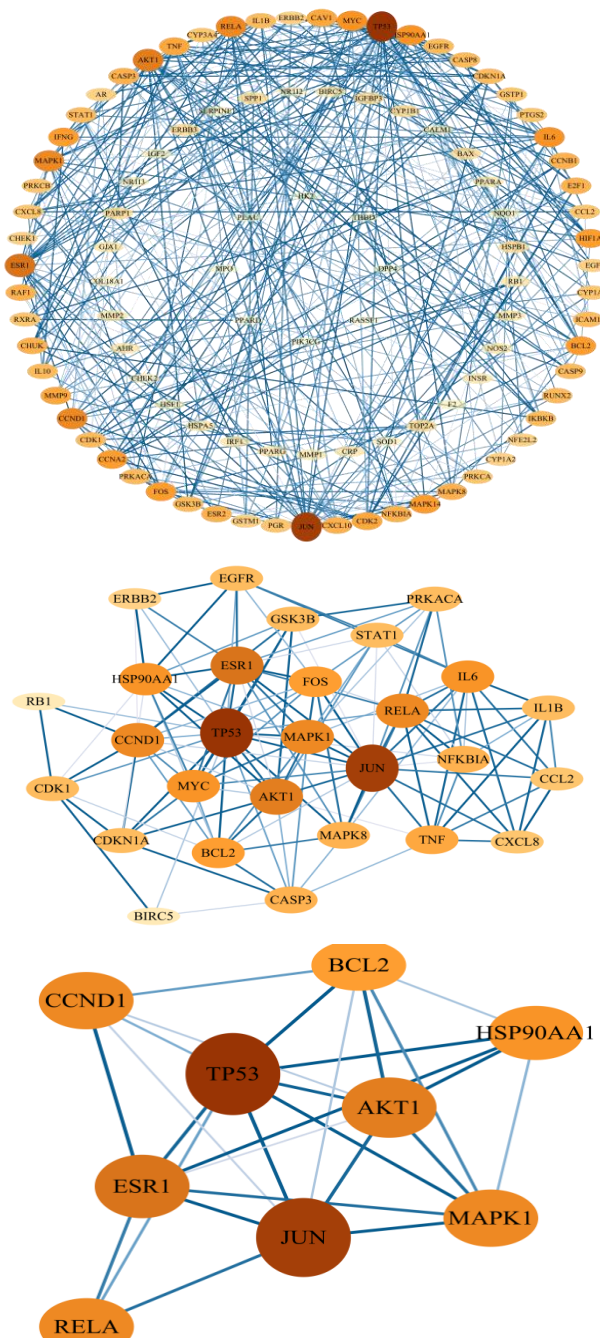


Figure 5: Protein-protein interaction (PPI) network of the Chaihu-Baizhu herb pair in the treatment of liver cancer

3.5 GO Enrichment Analysis and KEGG Pathway Enrichment Analysis

The intersecting targets of the disease and the drug were subjected to GO functional enrichment analysis and KEGG pathway enrichment analysis using R 4.4.1 software. The results of GO functional enrichment analysis were presented as bar plots, and the results of KEGG pathway enrichment analysis were presented as bubble plots.

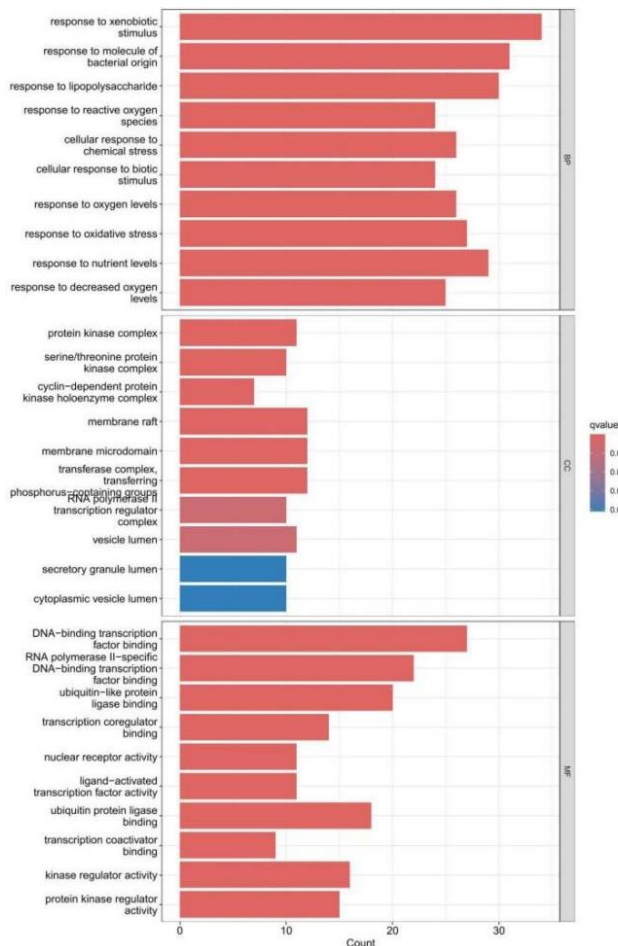


Figure 6: GO functional enrichment analysis of potential targets of the Chaihu-Baizhu herb pair in the treatment of liver cancer

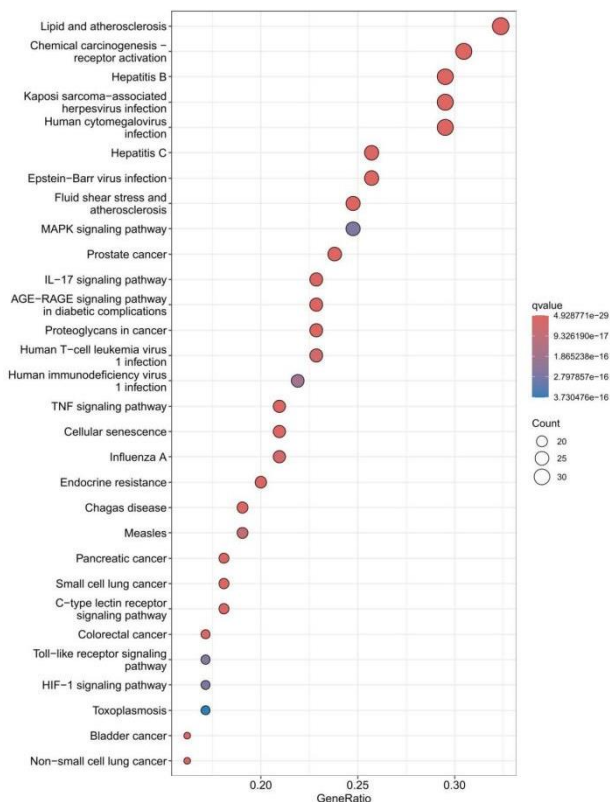


Figure 7: KEGG signaling pathway enrichment analysis of the Chaihu-Baizhu herb pair in the treatment of liver cancer

GO enrichment analysis showed that the potential targets of the Chaihu-Baizhu herb pair were significantly enriched in a series of biological processes and molecular functions closely related to the tumor hypoxic microenvironment. In terms of biological processes, the targets were highly concentrated in terms such as “response to oxygen levels”, “response to decreased oxygen levels”, and “response to oxidative stress”. Regarding molecular functions, they were significantly enriched in “DNA-binding transcription factor binding” and “transcription coregulator binding”. These results collectively suggest that the action of this herb pair may directly intervene in the core cellular response to hypoxic stress and subsequent transcriptional regulation.

KEGG pathway enrichment analysis further provided direct pathway-level evidence supporting the above inference. The analysis revealed that the “HIF-1 signaling pathway” was significantly enriched. This pathway serves as a core bridge linking cellular hypoxia sensing to malignant tumor progression, and its downstream key effector molecule VEGF is the most important factor driving tumor angiogenesis. Notably, although multiple pathways related to inflammation and cancer were also enriched, the HIF-1 pathway, due to its central hub role in integrating upstream signals and shaping the tumor hypoxic microenvironment, as well as its strong cross-validation with the “hypoxia response” terms in the GO analysis, stands out as the most promising scientific clue for elucidating the mechanism of action of the herb pair.

4. Discussion

Hepatocellular carcinoma (HCC) is a malignant tumor caused by multiple etiologies and is one of the most common causes of cancer-related death worldwide [13]. Currently, surgical resection, ablation, interventional therapy, targeted therapy, and immunotherapy are the main treatment modalities; however, they are associated with significant toxic side effects, susceptibility to drug resistance, and limited applicability to specific patient populations. In traditional Chinese medicine (TCM), HCC is generally considered to be of the “liver depression with spleen deficiency” pattern. The theory of “treating the liver by strengthening the spleen” originates from the Golden Chamber (Jin Gui Yao Lue), which states: “When one sees a disease of the liver, one must recognize that the liver will transmit its pathology to the spleen; therefore, the spleen should be strengthened first.” This principle emphasizes that liver disease tends to affect the spleen, and treatment should regulate both the liver and the spleen simultaneously. The Chaihu (Bupleuri Radix)-Baizhu (Atractylodis Macrocephalae Rhizoma) herb pair represents a classic compatibility of this theory: Chaihu soothes the liver and relieves stagnation, while Baizhu strengthens the spleen and replenishes qi. Together, they are clinically used as an adjuvant therapy for HCC patients with the pattern of liver depression and spleen deficiency. Nevertheless, the multi-component, multi-target molecular mechanisms of this herb pair remain poorly understood.

In this network pharmacology study, we predicted the main active components and potential mechanisms of the Chaihu-Baizhu herb pair in treating liver cancer. According to the drug component-disease target network diagram, the top five effective components ranked by degree value were

quercetin, kaempferol, isorhamnetin, areapillin, and 3, 5, 6, 7-tetramethoxy-2-(3, 4, 5-trimethoxyphenyl) chromone. Research has shown that quercetin, a flavonoid compound, can inhibit tumor proliferation by suppressing the NF- κ B and PI3K/Akt signaling pathways [15, 16]. Kaempferol and isorhamnetin, also belonging to the flavonoid class, possess anti-inflammatory, antioxidant, and anti-tumor activities, and exert their anticancer effects by regulating pathways such as MAPK and PI3K/Akt [17, 18]. The synergistic action of components such as areapillin constitutes the material basis for the “hepatosplenic harmonization” effect of the Chaihu-Baizhu herb pair in treating liver cancer [19].

PPI network analysis identified the top six protein genes ranked by node degree value: TP53, BCL2, JUN, CCND1, ESR1, and MAPK1. Among these, TP53 is an important tumor suppressor gene and one of the most frequently mutated genes in human tumors, participating in cell cycle arrest, DNA repair, and apoptosis induction; its loss of function is a landmark event in hepatocarcinogenesis [20]. BCL2, as a core member of the anti-apoptotic protein family, helps liver cancer cells evade apoptosis by inhibiting the release of cytochrome c from the mitochondria [21]. CCND1 (Cyclin D1) is a key regulator of the G1/S phase transition of the cell cycle, and its overexpression drives aberrant cell proliferation [22]. MAPK1 (ERK2) plays a critical role in the MAPK signaling pathway; its activation promotes tumor cell proliferation and inhibits apoptosis [23]. JUN is the expression product of the proto-oncogene c-Jun. Within the nucleus, it forms the transcription factor AP-1 in combination with FOS, participating in the regulation of cell proliferation, differentiation, and epithelial-mesenchymal transition [24]. The role of ESR1 (estrogen receptor α) in liver cancer is relatively complex; it may function in specific liver cancer subtypes by influencing processes such as cell proliferation and apoptosis [25]. These targets suggest that the Chaihu-Baizhu herb pair may exert anti-liver cancer effects by interfering with cell cycle regulation and inducing apoptosis.

Pathway enrichment analysis indicated that the therapeutic effect of the Chaihu-Baizhu herb pair on liver cancer may involve the HIF-1 signaling pathway, PI3K-Akt signaling pathway, MAPK signaling pathway, and others. Among these, the HIF-1 signaling pathway is particularly noteworthy. Hypoxia is a core feature of the liver cancer microenvironment. Under hypoxic conditions, HIF-1 α is stably expressed and translocates into the nucleus, activating downstream target genes such as VEGF, thereby promoting tumor angiogenesis and providing nutritional support for the growth, invasion, and metastasis of liver cancer [26]. In the GO enrichment analysis of this study, biological processes such as “response to decreased oxygen levels” and “response to oxidative stress” were highly significant, mutually validating the HIF-1 pathway results. In the context of traditional Chinese medicine theory, the metabolic disorders and energy deficits corresponding to “spleen deficiency” may provide the pathological soil for the formation of the tumor hypoxic microenvironment, while the HIF-1 α /VEGF pathway serves as the key engine driving angiogenesis within this microenvironment. Thus, the Chaihu-Baizhu herb pair may treat liver cancer through multi-target and multi-pathway mechanisms, among which regulating the HIF-1 α /VEGF

pathway may be one of its core mechanisms.

5. Summary

In summary, this study employed a network pharmacology approach to analyze the active components of the core Chaihu-Baizhu herb pair, including quercetin, kaempferol, and isorhamnetin. The findings suggest that these components may exert anti-liver cancer effects by modulating the HIF-1 signaling pathway, the PI3K-Akt signaling pathway, and key targets such as TP53, BCL2, and MAPK1. This provides a preliminary network pharmacology basis for the modern scientific interpretation of the “treating the liver by strengthening the spleen” theory. However, the specific mechanisms require further validation through in vitro cellular experiments and in vivo animal models.

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