Identification of Key Drug Targets and Molecular Mechanisms of Curcumae Rhizoma Acting on HBV-Related HCC: Weighted Correlation Network and Network Pharmacological Analyses

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1.Introduction

Hepatocellular carcinoma (HCC) is currently recognized as one of the most hard-to-treat malignancies, with the incidence increasing significantly over the last century [1–3]. According to the 2018 global tumor statistics, HCC is the 4th leading cause of cancer death at 8.2% [4]. It was reported by the National Cancer Center in 2019 that there were 370000 new cases of HCC in 2015, making it the 4th most common malignant tumor and the 2nd leading cause of tumor death in China, seriously threatening human life and health [5, 6]. About 80% of HCC in China are caused by hepatitis B virus (HBV) infection, making HBV-related HCC one of the major public health problems in China [6]. However, its pathogenesis has not yet been fully understood.

In the traditional treatment of HBV-related HCC, chronic HBV infection and liver malignancy are seen as two causally related but relatively independent aspects, and therefore, their treatment is divided into long-term aggressive antiviral therapy for HBV and interventional, targeted, and surgical treatments for HCC [7, 8]. Existing Western medicine treatment programs are generally combinatorial rather than comprehensive. Traditional Chinese medicine (TCM) treatment, due to its holistic view of the disease, can play a comprehensive role in controlling disease progression in the context of chronic HBV infection, including blocking precancerous changes, compensating for the limitations of Western medicine alone, prolonging survival, and improving quality of life [9, 10]. However, due to the high complexity of TCM mechanisms, the exploration
of drug targets and the screening of active ingredients is an important challenge at present.

Curcumae Rhizoma, bitter and acrid, could invigorate blood circulation, dispel blood stasis, regulate Qi, alleviate pain, dissolve accumulations, and alleviate pain [11, 12]. Curcumae Rhizoma has been reported to have anticancer activity against a variety of cancers, including breast cancer [13], gastric cancer [14], and colorectal cancer [15]. Curcumae Rhizoma or some of its active ingredients have been reported to have a better inhibitory effect on liver fibrosis and HCC [16, 17].

In this study, we obtained the GSE121248 dataset by searching datasets containing HCC tissues and paracancerous tissues with HBV infection in the GEO database. By bioinformatics techniques, we identified the significant modules and differentially expressed genes (DEGs) of the GSE121248 dataset. Using various databases and bioinformatics algorithms, we screened out active components of Curcumae Rhizoma, targets of HBV-related HCC, and key drug targets of Curcumae Rhizoma for the treatment of HBV-related HCC. The characteristics of these key targets were preliminary revealed. In summary, this study provides new targets and ideas for the treatment of HBV-related HCC with Curcumae Rhizoma.

2. Methods

2.1. Curcumae Rhizoma Active Ingredient Screening and Target Prediction. TCMSP is a traditional Chinese medicine database and analysis platform that could analyze the relationship among drugs, targets, and diseases, revealing the nature and potential mechanisms of TCM [18]. Curcumae Rhizoma was searched in the TCMSP database, and the chemical components were screened with oral bioavailability (OB) ≥ 30% and drug likeness (DL) ≥ 0.18%. The potential drug targets were also searched in the TCMSP database and Swiss Target Prediction database [19]. Then, the potential drug targets from the TCMSP database were imported into the UniProtKB database [20] for target gene name correction and elimination of nonhuman targets. The potential drug targets from the Swiss Target Prediction database were screened with probability > 0.

2.2. GSE121248 Dataset Collection. Gene Expression Omnibus (GEO) database [21] was utilized to search the public dataset associated with HBV-related HCC, and the GSE121248 dataset (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE121248) provided by Wang et al. [22] was downloaded via R (version 3.6.3) package of GEOquery 2.54.1 [23]. Tissues from chronic hepatitis B cancerous tissues with HBV infection in the GEO database. Euclidean distances using the ComplexHeatmap 2.2.0 package [26].

2.6. Enrichment and PPI Analysis of Key Drug Targets. Key drug targets were subjected to Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis using the clusterProfiler 3.14.3 package [28], and the top 10 entries with highest generation and P < 0.05 were visualized as bubble plots and chord diagrams. Key drug targets were uploaded to the STRING database (version 11.0) [29], and interactions with a score above 0.4 were considered significant. Then, the interactions were downloaded and visualized using Cytoscape software (version 3.8.3) [27]. The common genes in top 5 genes with highest degree and bottleneck score were detected as hub targets by cytoHubba plugin [30].

2.7. Prognostic Analysis of Hub Targets. The hub targets were entered into the KMplotter database [31] and analyzed for prognostic value based on the hepatitis virus yes subgroup and all groups. The web was established to perform univariate and multivariate survival analyses using any custom-generated data.

2.8. Active Ingredient Screening and Target Prediction. The active ingredients of Curcumae Rhizoma, including hederagenin, wenjine, and bisdemethoxycurcumin, were obtained by searching the TCMSP database and screening with OB and DL parameters (Figure 1(a), Table 1). Their molecule structure was downloaded (Figures 1(b)–1(d)).
Figure 1: Curcumae Rhizoma active ingredients. (a) The characteristics of Curcumae Rhizoma active ingredients. (b) Hederagenin molecule structure. (c) Wenjine molecule structure. (d) Bisdemethoxycurcumin molecule structure.

Table 1: Potential active compounds of Curcumae Rhizoma.

| Mol. ID   | Molecule name         | MW     | OB (%) | DL  |
|-----------|-----------------------|--------|--------|-----|
| MOL000296 | Hederagenin           | 414.79 | 36.91  | 0.75|
| MOL000906 | Wenjine               | 282.37 | 47.93  | 0.27|
| MOL000940 | Bisdemethoxycurcumin  | 308.35 | 77.38  | 0.26|
Then, 22 potential targets of hederagenin were extracted from the TCMSP database. 11 potential targets of wenjine and 68 potential targets of bisdemethoxycurcumin were predicted from the Swiss Target Prediction database.

3. Results

3.1. HBV-Related HCC Target Screening. To identify HBV-related HCC targets, we downloaded the GSE121248 dataset from the GEO database. By WGCNA analysis, a power $\beta$ of 6 was detected and 13 modules were obtained (Figures 2, 3(a)–3(c)). Among these modules, blue, brown, magenta, red, and turquoise modules were screened as important modules since they were most significantly correlated with tumor (Figure 3(d)).

Then, expression profile of the GSE121248 dataset was subjected to differential expression analysis (Figure 4(a)). The top 50 upregulated (Figure 4(b)) and downregulated (Figure 4(c)) genes were visualized.

3.2. Key Drug Targets and Their Features. To identify key drug targets of Curcuma Rhizoma in treating HBV-related HCC, we collected the overlapped genes in DEGs, genes in

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**Figure 2:** Expression profile preprocess and soft power determination. (a) The expression profile distribution of all liver samples. (b) Hierarchical clustering excluded outlier samples. (c) The soft-threshold power determined based on a scale-free $R^2$ of 0.85.
Figure 3: Continued.
Figure 3: Coexpression module identification. (a) Dynamic tree cut. (b) Module correlation. (c) WGCNA module trait correlation plot with negative correlation plotted as blue color and positive correlation plotted as red color. (d) Correlation of module membership and gene significance in blue, brown, magenta, red, and turquoise modules.

Figure 4: Continued.
Figure 4: DEGs screening on the GSE121248 dataset. (a) Volcano plot with threshold of $|\log FC| \geq 1$ and $P \text{ adjust} < 0.05$. (b) Top 50 upregulated genes. (c) Top 50 downregulated genes.

Figure 5: Continued.
**Figure 5:** Key drug targets screening and network construction. (a) Key drug targets screening. (b) Key drug target expression in the GSE121248 dataset. (c) A network of “herb-active ingredient-target-disease” interactions.

**Table 2:** Potential targets of active compounds of Curcumae Rhizoma in HBV-related HCC.

| Gene symbol | Protein name                                      | logFC  | Degree | Bottleneck |
|-------------|--------------------------------------------------|--------|--------|------------|
| TOP2A       | DNA topoisomerase 2-alpha                        | 3.261963 | 4      | 1          |
| ESR1        | Estrogen receptor                                | −2.27525 | 7      | 9          |
| CDK1        | Cyclin-dependent kinase 1                        | 2.029494 | 4      | 1          |
| CYP2C19     | Cytochrome P450 2C19                             | −1.72843 | 1      | 1          |
| PTGS2       | Prostaglandin G/H synthase 2                     | −1.62828 | 3      | 2          |
| SERPINE1    | Plasminogen activator inhibitor 1                | −1.55996 | 2      | 1          |
| ADH1C       | Alcohol dehydrogenase 1C                         | −1.4645  | 0      | 0          |
| AURKA       | Aurora kinase A                                  | 1.381586 | 3      | 1          |
| HSD17B2     | 17-Beta-hydroxy steroid dehydrogenase type 2     | −1.15057 | 1      | 1          |
| LYZ         | Lysozyme C                                       | 1.128273 | 0      | 0          |
| PRKDC       | DNA-dependent protein kinase catalytic subunit   | 1.029811 | 3      | 1          |

**Table 3:** Enriched GO-BP and KEGG terms of potential targets.

| Ontology | ID       | Description                              | GeneRatio | BgRatio | P value  | P adjust | Q value  | Genes | Count | Zscore |
|----------|----------|------------------------------------------|-----------|---------|----------|----------|----------|-------|-------|--------|
| BP       | GO: 0044774 | Mitotic DNA integrity checkpoint          | 4/11      | 106/18670 | 3.14e−07 | 1.88e−04 | 9.49e−05 | TOP2A/CDK1/AURKA/PRKDC | 4     | 2      |
| BP       | GO: 0048511 | Rhythmic process                          | 5/11      | 295/18670 | 4.07e−07 | 1.88e−04 | 9.49e−05 | TOP2A/ESR1/CDK1/SERPINE1/PRKDC | 5     | 0.447213595 |
| BP       | GO: 0031570 | DNA integrity checkpoint                   | 4/11      | 157/18670 | 1.52e−06 | 4.10e−04 | 2.07e−04 | TOP2A/CDK1/AURKA/PRKDC | 4     | 2      |
| BP       | GO: 0007093 | Mitotic cell cycle checkpoint              | 4/11      | 165/18670 | 1.85e−06 | 4.10e−04 | 2.07e−04 | TOP2A/CDK1/AURKA/PRKDC | 4     | 2      |
| BP       | GO: 0007623 | Circadian rhythm                          | 4/11      | 208/18670 | 4.65e−06 | 4.10e−04 | 2.07e−04 | TOP2A/CDK1/SERPINE1/PRKDC | 4     | 1      |
### Table 3: Continued.

| Ontology | ID     | Description                              | GeneRatio | BgRatio | P value   | P adjust | Q value   | GenelID                          | Count | Zscore |
|----------|--------|------------------------------------------|-----------|---------|-----------|----------|-----------|----------------------------------|-------|--------|
| BP       | GO: 0000075 | Cell cycle checkpoint                     | 4/11      | 216/18670 | 5.40e–06  | 4.10e–04 | 2.07e–04 | TOP2A/CDK1/AURKA/PRKDC           | 4     | 2      |
| BP       | GO: 0018105 | Peptidyl-serine phosphorylation           | 4/11      | 299/18670 | 1.95e–05  | 1.00e–03 | 5.04e–04 | CDK1/PTG52/AURKA/PRKDC           | 4     | 1      |
| BP       | GO: 0007568 | Aging                                    | 4/11      | 321/18670 | 2.57e–05  | 0.001    | 5.78e–04 | CDK1/PTG52/SERPINE1/PRKDC        | 4     | 0      |
| BP       | GO: 0018209 | Peptidyl-serine modification              | 4/11      | 322/18670 | 2.60e–05  | 0.001    | 5.78e–04 | CDK1/PTG52/AURKA/PRKDC           | 4     | 1      |
| BP       | GO: 0045930 | Negative regulation of mitotic cell cycle | 4/11      | 338/18670 | 3.15e–05  | 0.001    | 6.68e–04 | CDK1/PTG52/SERPINE1/PRKDC        | 4     | 2      |
| KEGG     | hsa05204 | Chemical carcinogenesis                   | 3/11      | 82/8076   | 1.57e–04  | 0.008    | 0.006    | CYP2C19/PTG52/ADH1C              | 3     | −1.73205081 |
| KEGG     | hsa04913 | Ovarian steroidogenesis                   | 2/11      | 51/8076   | 0.002     | 0.044    | 0.035    | PTG52/HSD17B2                   | 2     | −1.41421356 |
| KEGG     | hsa00590 | Arachidonic acid metabolism               | 2/11      | 63/8076   | 0.003     | 0.044    | 0.035    | CYP2C19/PTG52                   | 2     | −1.41421356 |
| KEGG     | hsa00982 | Drug metabolism-cell cycle checkpoint     | 2/11      | 71/8076   | 0.004     | 0.044    | 0.035    | CYP2C19/ADH1C                   | 2     | −1.41421356 |
| KEGG     | hsa04115 | p53 signaling pathway                     | 2/11      | 73/8076   | 0.004     | 0.044    | 0.035    | CDK1/PRKDC                      | 2     | 0      |

### Figure 6: Continued.
important modules, and predicted targets (Figure 5(a)).

These genes were screened as key drug targets, including TOP2A, ESR1, CDK1, CYP2C19, PTGS2, SERPINE1, ADH1C, AURKA, HSD17B2, LYZ, and PRKDC (Table 2).

Moreover, the expression levels of key drug targets were analyzed (Figure 5(b)). Then, a network of "herb-active ingredient-target-disease" interactions was constructed (Figure 5(c)).

To characterize the key drug targets, we performed GO and KEGG enrichment analyses (Table 3). The results depicted that the key drug targets mainly involved in the rhythmic process, mitotic DNA integrity checkpoint, DNA integrity checkpoint, mitotic cell cycle checkpoint, circadian rhythm, cell cycle checkpoint, peptidyl-serine phosphorylation, aging, peptidyl-serine modification, and negative regulation of mitotic cell cycle (Figure 6(a)).

Besides, some cellular component (CC) terms were also enriched, such as chromosomal region, spindle microtubule, mitotic spindle, nuclear chromosome, telomeric region, centriole, chromosome, telomeric region, midbody, microtubule organizing center part, protein-DNA complex, and condensed chromosome (Figure 6(b)). In terms of molecular function (MF), key drug targets participated in protein serine/threonine kinase activity, histone kinase activity, oxidoreductase activity, acting on the CH–OH group of donors, heme binding, tetrapyrrole binding, and oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen (Figure 6(c)).

Moreover, the involved pathways included chemical carcinogenesis, ovarian steroidogenesis, arachidonic acid metabolism, drug metabolism–cytochrome P450, etc. (Figure 6(d)).
and p53 signaling pathway (Figure 6(d)). Combining logFC, the GO-biological process (BP) and KEGG enrichment results are shown in Figures 6(e) and 6(f).

Meanwhile, the key drug targets were subjected to PPI analysis (Figure 7(a)). In Cytoscape software, degree and bottleneck algorithm identify top 5 genes, respectively (Figures 7(b) and 7(c)). The common genes were ESR1 and PTGS2 under two algorithms. Based on the two hub targets, a network of “herb-active ingredient-target-disease” interactions was simplified (Figure 7(d)).

### 3.3. Hub Target Verification.

The hub targets, ESR1 and PTGS2, were uploaded to the KMplotter database, and the
Figure 8: Prognostic analysis of hub targets. ESR1 expression was associated with overall survival probability (a) and disease-specific survival probability (b) in liver cancer patients with hepatitis virus. ESR1 expression was associated with overall survival probability (c) and disease-specific survival probability (d) in liver cancer patients.
prognostic analysis showed that ESR1 might be a tumor suppressor gene in HBV-related HCC (Figure 8).

4. Discussion

Globally, there are nearly 887000 deaths per year from HBV infection-related diseases, of which HBV-related HCC accounts for about 38% [32]. In China, the proportion of HCC caused by HBV is as high as 84% [32]. Research on the molecular mechanisms of HBV-related HCC development is still emerging, but there is still a lack of effective biomarkers for targeted therapy. In this study, 11 key drug targets of Curcumae Rhizoma for the treatment of HBV-related HCC were identified through a combination of data mining and network pharmacology analysis, and these key targets were characterized. This study provided new targets and ideas for the treatment of HBV-related HCC with Curcumae Rhizoma.

Through the TCMSP database and Swiss Target Prediction database, we obtained three potential active ingredients of Curcumae Rhizoma, including hederagenin, wenyjine, and bisdemethoxycurcumin. Hederagenin reportedly mediated cytotoxicity to cancers via multipathways, for example, hederagenin inhibits proliferation and promotes apoptosis of cervical cancer CaSki cells by blocking the STAT3 pathway [33]. Hederagenin saponin extraction offers great potential as an antibiotic cancer drug via the mitochondrial pathway [34]. By impairing autophagy, hederagenin induced ROS accumulation, potentiating the cytotoxicity of cisplatin and paclitaxel to lung cancer cells [35]. According to Liu et al., hederagenin displayed potent antitumor activities against human HCC HepG2 cell line [36]. Bisdemethoxycurcumin has antitumor effects exerted through a multimechanistic mode of action [37]. For example, bisdemethoxycurcumin sensitizes nonsmall cell lung cancer cells to icotinib [38]. It enhances α-PD-L1 antibody-mediated immune responses against bladder cancer [39]. It induces glioblastoma cell apoptosis [40]. Besides, it could cause a decrease in HCC cell viability and an increase in apoptosis [41, 42].

In terms of pathogenesis, GO-BP enrichment analysis suggested that the 11 key drug targets screened were involved in cell cycle checkpoint, DNA integrity checkpoint, and peptidyl-serine modification, all of which were associated with the development, progression, and metastasis of HCC [43–45]. The KEGG pathway enrichment results indicated that the p53 signaling pathway and arachidonic acid metabolism are enriched, which was supported by recent findings. HBV reportedly induce the abnormal lipid metabolism and activate Tregs through arachidonic acid signaling [46]. Hepatocytes with p53 inhibition escape death and senescence, becoming HCC progenitors [47]. Curcumae Rhizoma might play roles in treatment of HBV-related HCC via these biological processes and pathways.

In PPI analysis, we screened out ESR1 as a hub target. A recent study showed that ESR1 could inhibit HCC worsening [48]. ESR1 was lowly expression in liver tissues from chronic hepatitis B induced HCC in the GSE121248 dataset. Low ESR1 expression correlated with poor overall survival and disease specific survival in liver patients, no matter whether they had hepatitis virus infection. Besides, the study by Shuying Dai et al. implied that bisdemethoxycurcumin has a good affinity with ESR1 [49]. Curcumae Rhizoma, modulating ESR1, could be a potential therapeutic agent against HBV-related HCC.

Although there are some limitations in this study, such as fewer Curcumae Rhizoma active ingredients and fewer HBV-related HCC dataset, making the findings somewhat one-sided, we used bioinformatics to screen out the key drug targets of HBV-related HCC, which will lay an important foundation for subsequent research on the therapeutic targets of HBV-related HCC with Curcumae Rhizoma.

5. Conclusion

Based on WGCNA and network pharmacological analysis, our results illustrated that Curcumae Rhizoma might work through regulating multitargets and multipathways in HBV-related HCC. Therefore, it is suggested that we can refer to these relevant mechanisms in the future research of Curcumae Rhizoma on clinically treating HBV-related HCC. In addition, ESR1 and PTGS2 modulators are also deserved to be validated by further clinical and animal models of HBV-related HCC.

Data Availability

The data used to support this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors’ Contributions

Mengyuan Zhao and Yun Fu contributed equally to this study.

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