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Research Article

Elucidating the Mechanisms of Hugan Buzure Granule in the Treatment of Liver Fibrosis via Network Pharmacology

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Objective. To holistically explore the latent active ingredients, targets, and related mechanisms of Hugan buzure granule (HBG) in the treatment of liver fibrosis (LF) via network pharmacology. *Methods*. First, we collected the ingredients of HBG by referring the TCMSP server and literature and filtered the active ingredients though the criteria of oral bioavailability ≥30% and drug-likeness index ≥0.18. Second, herb-associated targets were predicted and screened based on the BATMAN-TCM and SwissTargetPrediction platforms. Candidate targets related to LF were collected from the GeneCards and OMIM databases. Furthermore, the overlapping target genes were used to construct the protein-protein interaction network and "drug-compound-target-disease" network. Third, GO and KEGG pathway analyses were carried out to illustrate the latent mechanisms of HBG in the treatment of LF. Finally, the combining activities of hub targets with active ingredients were further verified based on software AutoDock Vina. *Results*. A total of 25 active ingredients and 115 overlapping target genes of HBG and LF were collected. Besides, GO enrichment analysis exhibited that the overlapping target genes were involved in DNA-binding transcription activator activity, RNA polymerase II-specific, and oxidoreductase activity. Simultaneously, the key molecular mechanisms of HBG against LF were mainly involved in PI3K-AKT, MAPK, HIF-1, and NF-κB signaling pathways. Also, molecular docking simulation demonstrated that the key targets of HBG for antiliver fibrosis were IL6, CASP3, EGFR, VEGF, and MAPK. *Conclusion*. This work validated and predicted the underlying mechanisms of multicomponent and multitarget about HBG in treating LF and provided a scientific foundation for further research.

1. Introduction

Liver fibrosis (LF) is a pathophysiologic wound-healing response of the liver that is occasioned by chronic hepatic damages such as viral, alcoholic, and autoimmune hepatitis [1]. Epidemiological data have disclosed that LF gradually became the public focus that gives rise to extensive morbidity and mortality [2]. LF could develop into cirrhosis without favorable intervention, which is estimated to affect more than 1 million deaths per annum, and 55% are caused by liver cirrhosis [3]. For the time being, a large number of evidence has proved that LF could be reversed with the appropriate intervention [4]. Consequently, it is extremely urgent to develop drugs with potential antiliver fibrosis activity.

Traditional Chinese Medicine (TCM) has gained wide attention in virtue of the conspicuous therapeutic effect and no obvious adverse reaction [5]. TCM also has the unique advantages of multicomponent, multitarget, and multipathway in the research field of antiliver fibrosis [6]. Therefore, further research on the material basis and the latent mechanisms of TCM is one of the ideas to develop TCM. Hugan buzure granule (HBG), a classical TCM formula, consists of Cuscuta chinensis, Chicory, Cumin, and *Apium graveolens* L.(Celery) and has been widely used in the clinical treatment of liver diseases [7]. Based on the previous research, HBG could diminish inflammatory cytokines and inhibit liver inflammatory damage and fibrosis, thereby preventing the liver from histopathological damages [8]. Due to the complex composition of HBG, it is hard to

elucidate the latent mechanisms of HBG with multitarget and multipathway by means of the conventional assessment. So, this work aims to probe active compounds, targets, and synergistic mechanisms of HBG in the treatment of LF via network pharmacology (Figure 1).

2. Materials and Methods

2.1. Screening of Active Ingredients. The ingredients of the four herbs in HBG were acquired from a comprehensive retrieval of literature and the Traditional Chinese Medicine Systems Pharmacology database and analysis platform (TCMSP, http://lsp.nwu.edu.cn/tcmsp.php) [9]. Meanwhile, the parameters for screening the bioactive ingredients were set as follows: oral bioavailability (OB) ≥30% and drug-likeness (DL) ≥0.18 [10]. Thus, the ingredients satisfying the abovementioned criteria were retained and regarded as candidate molecules of HBG for subsequent analysis. In addition, compounds with reported therapeutic effects on liver fibrosis were directly included.

2.2. Prediction and Screening of Potential Targets. The Bioinformatics Analysis Tool for Molecular mechanism of TCM (BATMAN-TCM, http://bionet.ncpsb.org/batman-tcm) and SwissTargetPrediction (http://swisstargetprediction.ch/) databases were used to identify the bioactive ingredient-associated target genes of HBG together. The targets were further screened by the criteria of the "score cutoff ≥20 and false discovery rate (FDR) <0.05" in the BATMAN-TCM database [11]. Meanwhile, the predicted active ingredient-associated target genes in SwissTargetPrediction were filtered by presetting the boundary value of "gene probability >0.7" [12]. Then, the protein names were transformed into the official symbols via the UniProt database (http://www.uniprot.org/) with the species limited to "*Homo sapiens*." LF-associated target genes were comprehensively retrieved through the Online Mendelian Inheritance in Man (OMIM, https://omim.org/) and GeneCards (https://www.genecards.org/) databases with "liver fibrosis" as the search term [13]. Finally, the potential targets of HBG against LF were identified and visualized by overlapping the above-mentioned target genes with a Venn diagram (http://bioinfogp.cnb.csic.es/tools/venny/index.html).

2.3. Network Construction. The Search Tool for the Retrieval of Interacting Genes/Proteins (STRING, https://string-db.org/) platform is a precomputed global resource, which could explore and build the interaction network of protein-protein [14]. In this research, the overlapping targets were input into the STRING 11.0 with species simply limited to "*Homo sapiens*" and the interaction score >0.40 to implement the analysis of protein-protein interaction (PPI). Subsequently, the PPI network of targets intersection of HBG and LF was visualized via Cytoscape 3.8.0. The top 5 target proteins were acquired as the hub targets for HBG in the treatment of LF. The complex network relationship of "drug-compound-target-disease" was visualized via using Cytoscape 3.8.0. The nodes represented the compounds, targets, and disease, while the edges represented the interactions between them in the network. Besides, the degree represented the number of edges between nodes, which was analyzed via the Network Analyzer plugin of Cytoscape.

2.4. Gene Ontology (GO) and Signaling Pathway Analyses. GO (http://www.geneontology.org) and Kyoto Encyclopedia of Genes and Genomes (KEGG, http://www.kegg.jp/pathway.html) signaling pathway analyses for overlapping targets were carried out using the Database for Annotation, Visualization, and Integrated Discovery (DAVID, https://david.ncifcrf.gov/) with the "*Homo sapiens*" setting [15]. Additionally, GO can be applied to classify and elucidate the gene functions, which was performed according to the biological processes, cellular component, and molecular function [16]. The bubble chart of the concerned GO enrichment was plotted using the OmicShare tools. Moreover, the top 20 significant signaling pathways were screened in line with the ranking of gene count. In short, the mechanisms of HBG against LF were investigated by the biological functions and related signaling pathways of the overlapping targets. An FDR <0.05 in both GO and KEGG analyses was considered significant.

2.5. Molecular Docking. AutoDock Vina software can predict the binding activities of target proteins to compounds. The molecular docking of the top 5 hub targets and the active compounds was performed using AutoDock Vina software. The energy range, exhaustiveness, and num modes were, respectively, set as "10," "20," and "100." It is generally believed that the lower the binding energy, the more stably the active compound binds to the target.

3. Results

3.1. Active Compounds of HBG. Twenty-two active ingredients in HBG with OB ≥ 30% and DL ≥ 0.18 were retrieved from the TCMSP server. Moreover, our previous studies indicated that dl-3n-butylphthalide, aesculetin, and apigenin were also regarded as active compounds in the treatment of LF [17]. In total, 25 active compounds were prepared for follow-up research, and the detailed information of them is shown in Table 1.

3.2. Target Genes Prediction. The predictive models containing BATMAN-TCM and SwissTargetPrediction platform were used to predict 132 target genes after duplicates elimination, which was associated with the 25 active ingredients of HBG. Moreover, 6376 target genes related to LF were retrieved from the GeneCards and OMIM databases. In brief, a total of 115 overlapping targets between active ingredients and LF after merging (Figure 2).

3.3. PPI Network. The PPI network was delineated via the STRING platform (Figure 3). In the PPI network, targets and relationship between targets were represented by nodes and edges. Connectivity degree, namely, is the number of lines

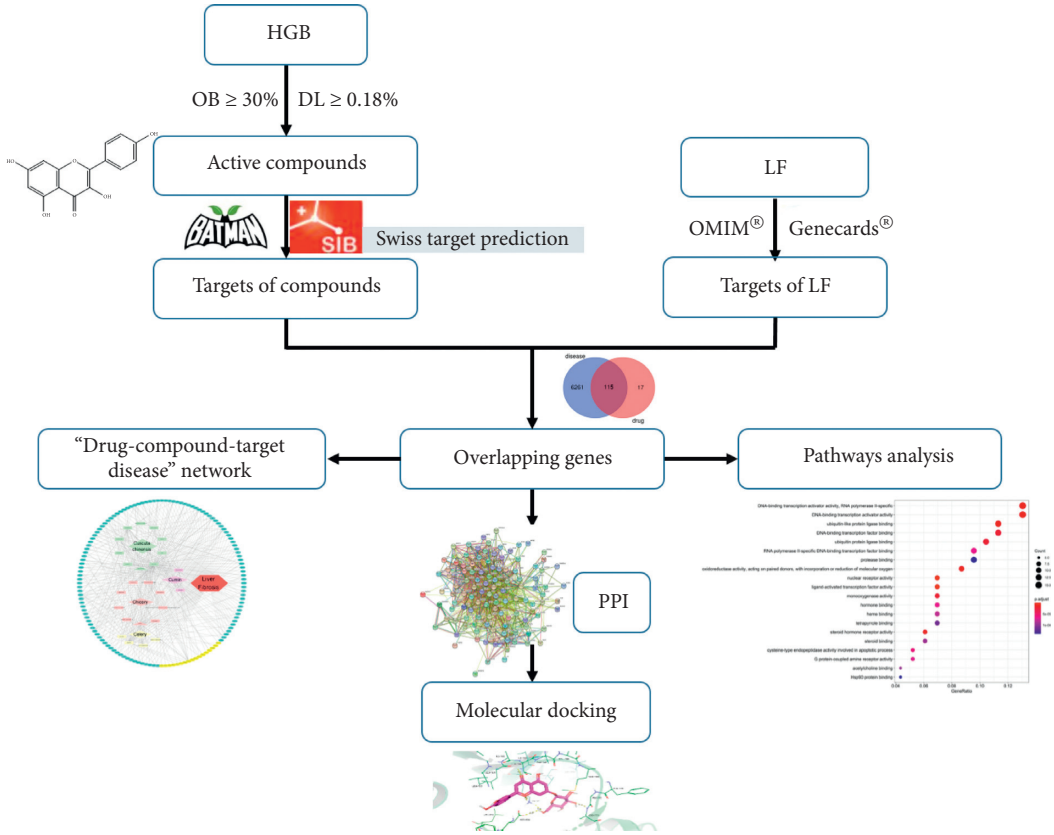

Figure 1: Flowchart of the network pharmacology of HBG in treating LF.

Table 1: Detailed information for 25 active compounds of HBG.

Herb	Compound	OB (%)	DL	Degree
Celery	Dl-3n-butylphthalide	47.9	0.07	41
	Aesculetin	22.97	0.07	9
	Apigenin	23.06	0.21	47
	Luteolin	36.16	0.25	37
	Luteolin-7-o-glucoside	7.29	0.78	23
	Poriferast-5-en-3beta-ol	36.91	0.75	12
Chicory	Delphinidin	40.63	0.28	18
	Eseramine	45.89	0.31	14
	2S, 2'S-aurantiamide acetate	39.18	0.54	34
	Lactucopicrin	95.31	0.71	26
	(2R)-3-[3-(5-allyl-2-hydroxyphenyl)-4-hydroxyphenyl]propane-1, 2-diol	32.21	0.20	18
Cumin	Gitoxigenin	43.93	0.75	12
	Cyanidin 3-glucoside	58.99	0.24	17
	Ammidin	34.55	0.22	18
	Stigmasterol	43.83	0.76	31
	Sesamin	56.55	0.83	25
Cuscuta chinensis	NSC63551	39.25	0.76	23
	Isorhamnetin	49.60	0.31	37
	Beta-sitosterol	36.91	0.75	38
	Kaempferol	41.88	0.21	40
	Campest-5-en-3beta-ol	37.58	0.71	18
	Isofucosterol	43.78	0.76	12
	Matrine	63.77	0.25	11
	CLR	37.87	0.68	24
	Quercetin	46.43	0.28	31

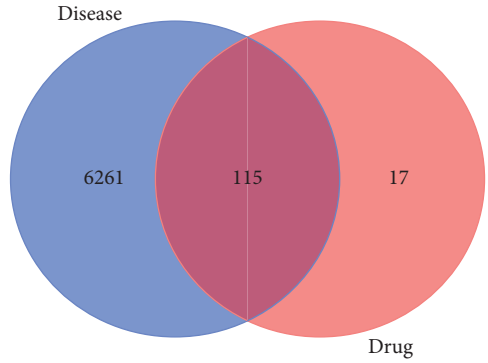

Figure 2: Venn diagram of the target genes for active ingredients and LF. Active ingredients have 132 target genes, while LF has 6376 target genes. There are 115 overlapping target genes between the two sets.

linked to a certain node. Accordingly, a target with a high connectivity degree in the PPI network might be a crucial target for the disease. The PPI network contained 114 nodes and 1160 edges. In addition, the top 5 targets were IL6 (67), CASP3 (63), EGFR (62), VEGF (61), and MAPK (60), respectively. All of these manifested the top targets coordinatively to treat LF at the molecular level. For instance, interleukin-6 (IL6) is one of the most important inflammatory cytokines. The IL6 signal pathway is involved in the regulation of profibrogenic and proinflammatory responses [18]. Additionally, the vascular endothelial growth factor (VEGF) is related the progression of LF via affecting the function of hepatic stellate cells (HSCs) [19]. Mitogen-activated protein kinase (MAPK) plays a key role in many processes of physiological and pathological such as inflammation, apoptosis, cell cycle, and growth [20]. Additionally, caspase-3 (CASP3) is activated to trigger the irreversible apoptosis [21].

3.4. "Drug-Compound-Target-Disease" Network. This work constructed a "drug-compound-target-disease" interaction network to visualize the relationship between drugs, active components, targets, and disease, and the interactions among them are represented in Figure 4. Generally, the degree of target interactions is an indicator of the potential significance of the compounds. In this research, apigenin (degree = 47), dl-3n-butylphthalide (degree = 41), and kaempferol (degree = 40) with a high connectivity degree might be the core compounds in the pharmacological effect of HBG (Table 1). The "drug-compound-target-disease" network demonstrated that multiple targets were associated with various ingredients in different herbs, which might exhibit synergistic effects or additive effects of HBG in the treating LF. It was consistent with the common characteristics of TCM, in which multicomponent and multitarget were observed.

3.5. DAVID Pathway Analysis. GO and signaling pathway analyses were performed in order to clarify the underlying mechanisms of HBG on LF. In this research, 134 GO terms and 127 signaling pathways were obtained (FDR <0.05). The top 20 terms of GO enrichment were illustrated in Figure 5, including DNA-binding transcription activator activity, RNA polymerase II-specific, ubiquitin-like protein ligase binding, and oxidoreductase activity. The signaling pathways of HBG in treating LF were mostly involved in the PI3K-AKT signaling pathway, MAPK signaling pathway, HIF-1 signaling pathway, and NF-κB signaling pathway(Table 2).

3.6. Molecular Docking. The top 5 hub targets in the PPI network were docked with the active ingredients (Table 3, Figure 6). The binding energy (affinity) was selected as the group representative. It was usually considered that the value of binding energy represented the binding activity between a compound and a certain protein, and the lower the binding energy, the more stably the active compound binds to the target. The results showed that the binding ability between EGFR and luteolin-7-o-glucoside was the best in all, followed by MAPK and sesamin, CASP3, IL6, and luteolin-7-o-glucoside, and VEGF and delphinidin. In total, the molecular docking revealed that the active compounds of HBG had good binding activities to key targets. The dotted yellow line in Figure 6 represents hydrogen bonds.

4. Discussion

LF is regarded as a crucial pathological procedure in the development of cirrhosis or hepatocellular carcinoma, with complicated formation procedures and molecular mechanisms, so the effective treatment of LF still confronts great challenges [22]. Although the preceding studies have carried out primary research on HBG, the scientific material basis and molecular mechanisms in the treatment of LF have still not been systematically illuminated. Hence, a new analytical method is needed which could link the HBG to its target genes with the purpose of proving its relationships with the observed biological efficacy. Due to the intricate compounds in HBG and the diverse target genes *in vivo*, this work explored the material basis and mechanisms of HBG via network pharmacology. The systematic and holistic characteristic of network pharmacology is identical with the integral view of TCM [23]. It can illustrate the underlying mechanisms of HBG in treating LF via using existing

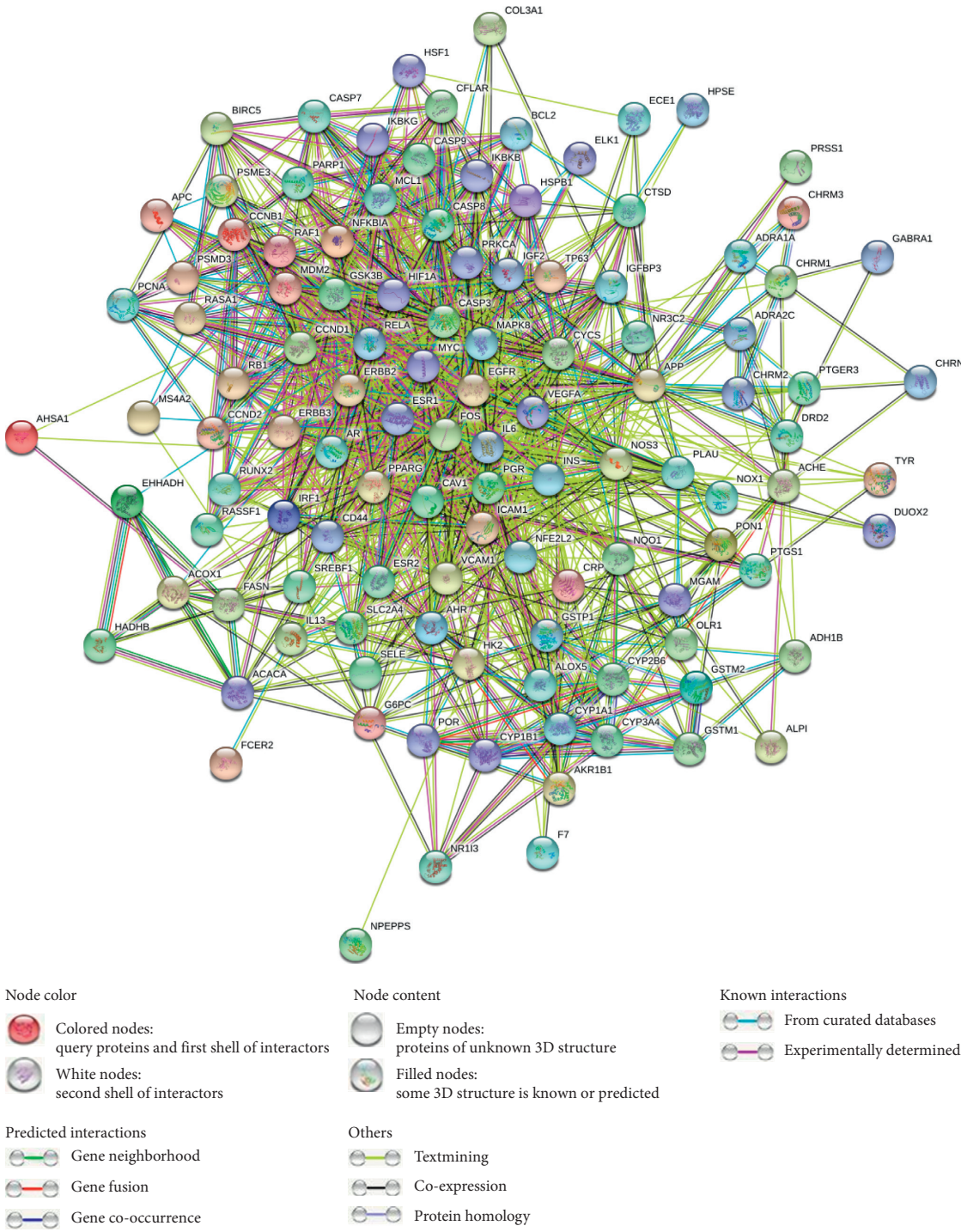

Figure 3: PPI network of targets intersection of LF and HBG.

databases and network analysis platforms. In the present study, 25 bioactive ingredients, 115 latent targets, and 127 related signaling pathways in HBG were predicted by network pharmacological analysis. Among them, IL6, CASP3, EGFR, VEGF, and MAPK were hub target genes of HGB in treating LF. Simultaneously, the key molecular mechanisms of HBG against LF were mainly involved in PI3K-AKT, MAPK, HIF-1, and NF-κB signaling pathways.

This research manifested that apigenin, 3-n-butylphthalide, and kaempferol might be the pivotal compounds in the pharmacological effect of HBG. Our previous research has indicated that apigenin could mitigate liver inflammation and fibrosis in rats by MAPK, PI3K/AKT, HIF-1, and eNOS signaling pathways [24]. Moreover, the preceding study has revealed that 3-n-butylphthalide, aesculetin, and quercetin could decrease the synthesis of the hepatic extracellular matrix (ECM) to alleviate LF via regulating proliferation and apoptosis of hepatic HSCs [17]. Besides, it has been reported that kaempferol might restrain the proliferation of liver cancer HepG2 cells by deactivating

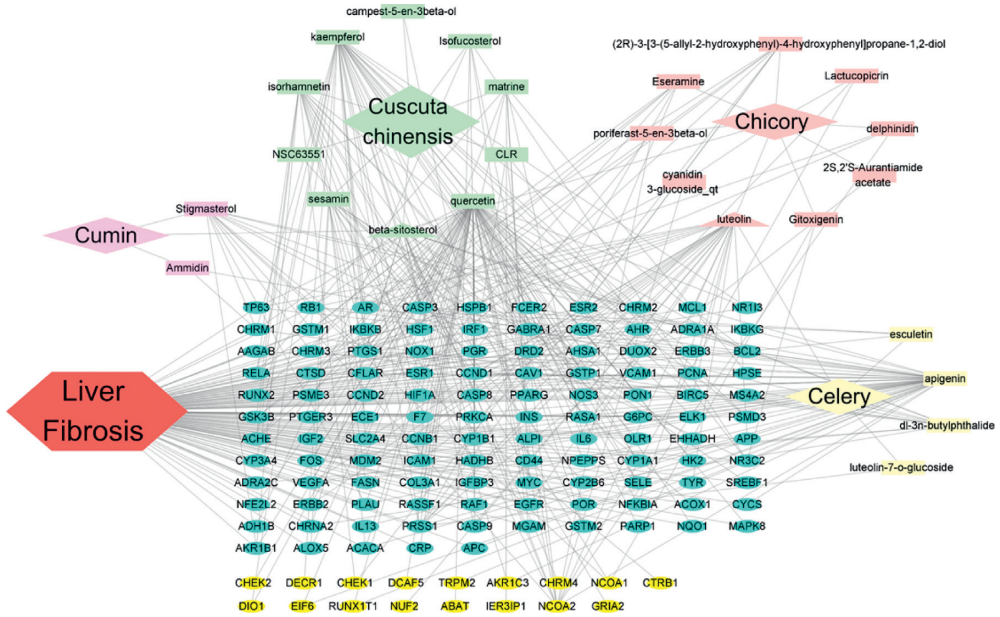

Figure 4: Network of the drug, active ingredients, targets, and LF. Red hexagon, LF; diamond, drug; rectangle, active compounds; and oval, targets.

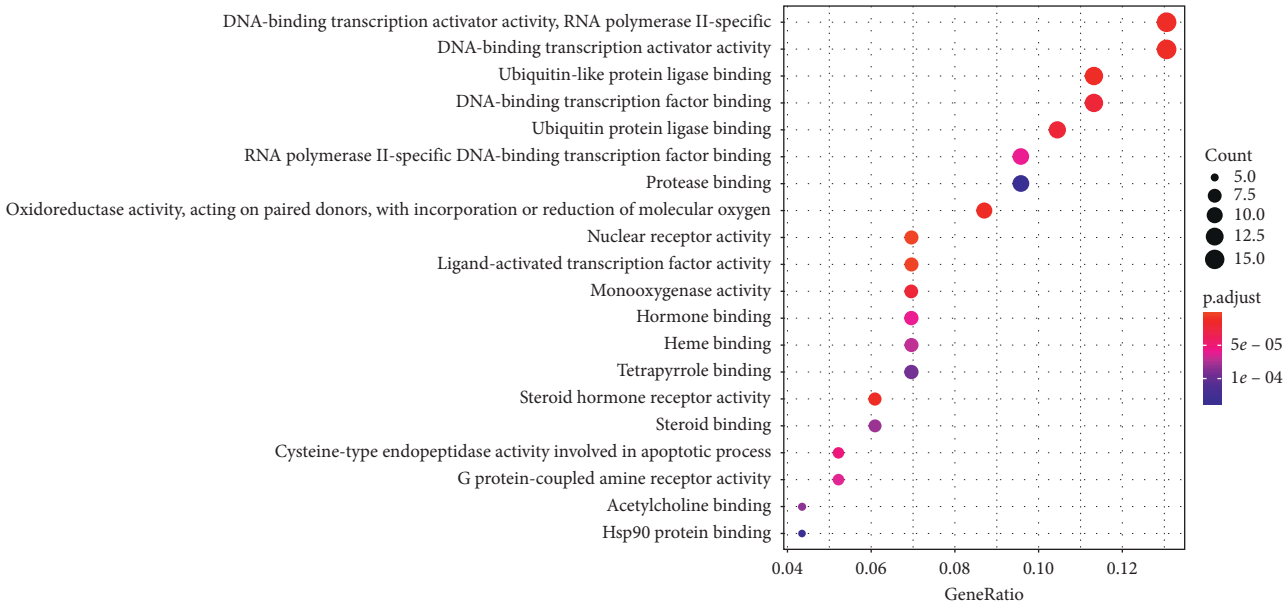

Figure 5: The bubble chart for GO analysis of the overlapping targets.

the PI3K/AKT signaling pathway [25]. In conclusion, multiple components of HBG might synergistically ameliorate LF.

Hub targets are closely interconnected with nodes in a PPI network, which proved that they have highly correlation in a certain disease. Simultaneously, IL6, CASP3, EGFR, VEGF, and MAPK were predicted as hub targets which possessed high connection degree in the PPI network. It suggested that HBG has the characteristics of multicomponent and multitarget in treating LF. IL6 is a profibrogenic and proinflammatory cytokine which can accelerate the occurrence of LF via increasing the deposition of ECM [26]. Several studies have demonstrated the rise of IL6 with the exacerbation of LF, which has a positive correlation with the ECM levels of hyaluronic acid, laminin, type IV collagen, and phase of LF, manifesting that the raise of the IL6 level could give rise to the development of LF [27]. The activation of CASP3 is regarded as the irreversible stage of apoptosis. Meanwhile, it has been found that the drug can mitigate LF by antagonizing the caspase receptor or suppressing the expression of key proteins in caspase, thereby preventing the cascade reaction of hepatocyte apoptosis [28]. Furthermore,

Table 2: KEGG analysis of the overlapping targets (top 20).

Name of pathways	Count	FDR	Enriched genes
PI3K-AKT signaling pathway	24	$4.47E-10$	BCL2, CHRM1, VEGFA, MYC, GSK3B, MDM2, EGFR, ERBB2, G6PC, MCL1, IL6, ERBB3, RELA, NOS3, IKBKG, CCND1, INS, IKBKB, CASP9, RAF1, IGF2, CHRM2, CCND2, PRKCA
MAPK signaling pathway	18	$6.39E-10$	VEGFA, MYC, EGFR, ERBB2, RASA1, CASP3, ELK1, ERBB3, FOS, RELA, HSPB1, IKBKG, INS, IKBKB, MAPK8, RAF1, IGF2, PRKCA
HIF-1 signaling pathway	15	$3.06E-09$	BCL2, VEGFA, EGFR, ERBB2, IL6, RELA, HIF1A, NOS3, INS, HK2, PRKCA, CFLAR, CASP8, ICAM1, VCAM1
NF-κB signaling pathway	11	$3.09E-09$	BCL2, NFKBIA, RELA, IKBKG, IKBKB, CFLAR, PLAU, PARP1, ICAM1, VCAM1, EGFR
Hepatitis B	10	$5.34E-09$	BCL2, MYC, NFKBIA, IL6, CASP3, ELK1, FOS, RELA, CYCS, BIRC5
Hepatitis C	10	$4.98E-08$	MYC, GSK3B, EGFR, NFKBIA, CASP3, RELA, CYCS, IKBKG, CCND1, MAPK8
TNF signaling pathway	9	$5.95E-08$	NFKBIA, IRF1, SELE, CASP7, IL6, CASP3, FOS, RELA, RB1
Hepatocellular carcinoma	9	$3.38E-07$	GSTP1, NFE2L2, MYC, GSK3B, EGFR, ELK1, NQO1, CCND1, GSTM1
Ras signaling pathway	8	$4.74E-07$	VEGFA, EGFR, RASA1, ELK1, RELA, RASSF1, IKBKG, INS
FoxO signaling pathway	7	$5.18E-07$	CCNB1, MDM2, EGFR, G6PC, IL6, SLC2A4, CCND1
Insulin signaling pathway	7	$1.19E-06$	INS, IKBKB, MAPK8, SREBF1, FASN, RAF1, HK2
Focal adhesion	7	$1.42E-06$	BCL2, VEGFA, GSK3B, EGFR, ERBB2, ELK1, CAV1
Pancreatic cancer	6	$1.76E-06$	VEGFA, EGFR, ERBB2, RELA, IKBKG, CCND1
IL-17 signaling pathway	6	$2.50E-06$	GSK3B, NFKBIA, IL6, CASP3, FOS, RELA
VEGF signaling pathway	6	$5.57E-06$	VEGFA, NOS3, HSPB1, CASP9, RAF1, PRKCA
p53 signaling pathway	5	$9.47E-06$	CCNB1, BCL2, MDM2, IGFBP3, CASP3
Relaxin signaling pathway	5	$2.26E-05$	VEGFA, EGFR, NFKBIA, COL3A1, FOS
Calcium signaling pathway	5	$3.86E-05$	CHRM1, ADRA1A, EGFR, ERBB2, CHRM3
cAMP signaling pathway	4	$6.05E-05$	FOS, RELA, MAPK8, ACOX1
AMPK signaling pathway	4	$9.76E-05$	INS, SREBF1, FASN, PPARG

studies have shown that the downstream signal pathways of the epidermal growth factor receptor (EGFR) were activated in HSCs when the liver was damaged and the phosphorylation levels of AKT, Smad, and Cyclin D1 were upregulated, promoting the increase of ECM and accelerating the generation of LF [29]. Additionally, the VEGF plays a vital role in the pathological progress of fibrogenesis. Recent publications have indicated that the level of serum VEGF was increased via activated HSCs after CCl_4 intervention, which was related to the development of LF [30, 31]. MAPK is an indispensable protein that keeps the balance between anti-inflammatory and proinflammatory responses. Studies have reported that suppression of MAPK alleviated LF by repression of inflammatory factors [32]. These findings indicated the potential antifibrosis activity of hub targets of HBG in LF.

According to the KEGG metabolic pathway analysis, the PI3K-AKT, MAPK, HIF-1, and NF-κB signaling pathways were mainly involved in treating LF with HBG. With the study of a great deal of literature, the phosphatidylinositol 3 kinase/protein kinase B (PI3K/AKT) signaling is closely linked to the activation, proliferation, and ECM deposition of HSCs [33, 34]. Simultaneously, acceleration of ECM deposition is related to all sorts of fibrosis diseases via the stimulated PI3K/AKT pathway. Conversely, blocking of the PI3K/AKT pathway in HSCs can decrease fibrosis factors, collagen synthesis, and ECM deposition [35]. The mitogen-activated protein kinase family (MAPKs) cascade primarily containing p38 MAPK, JNK, and ERK can regulate elementary cellular signals including proliferation, apoptosis, differentiation, and inflammation [36, 37]. The activation of p38 MAPK, JNK, and ERK could accelerate the release of proinflammatory factors which further exacerbate LF [38, 39]. Meanwhile, several studies have manifested that interruption of the MAPK pathway alleviated LF via diminishing the expression of inflammatory factors [40]. Hypoxia is inevitable in the local microenvironment during liver injury and secondary inflammatory reaction [41]. Hypoxiainducible factor 1 (HIF-1) consisted of oxygen-regulated HIF-1α subunit and HIF-1β subunit, which activates a great many of hypoxia responsive factors to adapt to the hypoxic microenvironment [42]. Another study reported that HIF-1α might ameliorate LF via regulating expression of genes for angiogenesis and collagen synthesis [43]. Nuclear transcription factor-kappa B (NF-κB) is a pivotal transcription factor, which could govern inflammatory response by taking part in the activation procedure of inflammatory and macrophages cells [44, 45]. Interestingly, it has been well reported that suppression of the NF-κB pathway and changed regulation of NF-κB-dependent gene transcription

Table 3: Docking results of the top 5 hub targets with active compounds.

No.	Compound	Affinity (kJ·mol^{-1})				
		IL6	CASP3	EGFR	VEGF	MAPK
1	Dl-3n-butylphthalide	−5.4	−5.2	−6.4	−5.3	−8.5
2	Esculetin	−6.0	−5.1	−7.2	−5.3	−6.7
3	Apigenin	−6.4	−6.4	−8.2	−6.8	−9.0
4	Luteolin	−6.6	−6.8	−8.4	−7.1	−8.9
5	Luteolin-7-o-glucoside	−7.5	−7.6	−10.0	−7.2	−9.2
6	Poriferast-5-en-3beta-ol	−5.5	−6.7	−8.2	−5.7	−7.7
7	Beta-sitosterol	−5.7	−6.4	−9.1	−5.8	−7.7
8	Delphinidin	−6.6	−6.6	−8.7	−7.4	−8.5
9	Eseramine	−7.1	−6.5	−7.6	−6.1	−8.1
10	2S, 2'S-aurantiamide acetate	−6.6	−7.0	−9.0	−6.2	−7.8
11	Lactucopicrin	−6.0	−8.0	−9.2	−6.3	−7.9
12	(2R)-3-[3-(5-allyl-2-hydroxyphenyl)-4-hydroxyphenyl]propane-1, 2-diol	−6.2	−6.6	−8.0	−6.0	−8.1
13	Gitoxigenin	−6.2	−6.8	−8.5	−6.0	−7.2
14	Cyanidin 3-glucoside	−6.4	−6.1	−8.5	−7.3	−8.6
15	Ammidin	−6.0	−6.1	−8.2	−6.7	−8.0
16	Stigmasterol	−6.2	−6.6	−8.5	−6.9	−8.0
17	Sesamin	−7.2	−7.3	−9.7	−7.1	−9.5
18	NSC63551	−6.4	−7.2	−9.3	−5.9	−8.3
19	Isorhamnetin	−6.5	−6.7	−8.3	−6.8	−8.8
20	Kaempferol	−6.4	−6.4	−8.0	−6.7	−8.8
21	Campest-5-en-3beta-ol	−6.1	−6.1	−9.1	−5.5	−7.5
22	Isofucosterol	−5.8	−6.5	−9.5	−5.8	−7.9
23	Matrine	−5.7	−6.0	−6.7	−5.5	−7.4
24	CLR	−5.3	−6.3	−7.8	−5.8	−7.3
25	Quercetin	−6.5	−6.8	−8.5	−7.2	−8.5

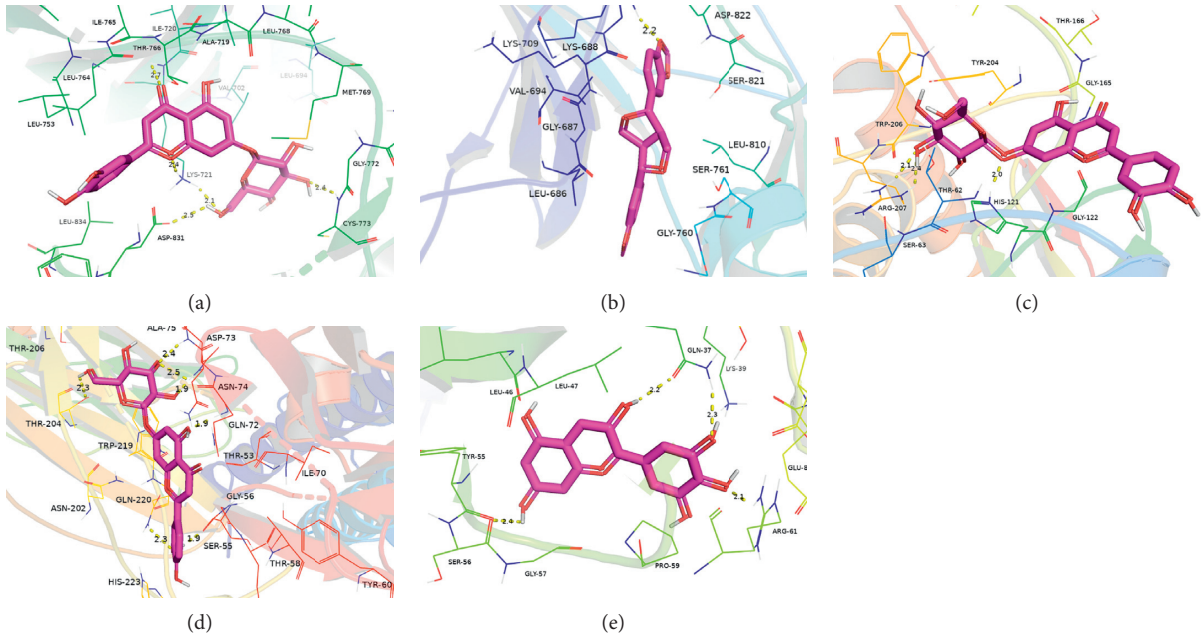

Figure 6: The molecular docking of the compound target. (a) EGFR and luteolin-7-o-glucoside. (b) MAPK and sesamin. (c) CASP3 and luteolin-7-o-glucoside. (d) IL6 and luteolin-7-o-glucoside. (e) VEGF and delphinidin.

can induce HSCs apoptosis which may further mitigate the severity of LF [46]. HBG also mitigated LF through PDGF, TNF, VEGF, and IL-17 signaling pathways in addition to the abovementioned main signaling pathways. The platelet-derived growth factor (PDGF) is a ubiquitous cytokine that promotes cell activation, division, and proliferation and plays an important role in the development of LF [47]. The tumor necrosis factor (TNF) pathway is associated with cell apoptosis, survival, and inflammation [48]. The VEGF, the most potent angiogenesis cytokine, plays a crucial role in the

pathological process of fibrogenesis [49]. As a characteristic cytokine, Interleukin-17 (IL-17) regulates the local or systemic inflammatory response [50]. In summary, it was further proved that multicomponent and multitarget of HBG could participate cooperatively in regulating multiple metabolic pathways, such as PI3K-AKT, MAPK, HIF-1, NF-κB, PDGF, TNF, VEGF, and IL-17 signaling pathways, thereby exerting anti-inflammatory and antifibrotic effects.

Several limitations existed in the prediction of active ingredients and underlying mechanisms for HBG via network pharmacology. First, network pharmacology cannot reflect the influence of herb compatibility interaction in prescription. Second, the screening of OB and DL of compounds also had limitations, only preserved the information of TCMSP, yet had no regard for other bioactive compounds in treating LF. Third, the active components selected were not necessarily the drug components actually absorbed into the body after oral administration. Consequently, it requires to be verified in follow-up pharmacological experiments to further development of HBG.

5. Conclusions

This work firstly explored the active components, potential targets, and mechanisms of HBG against LF based on a systematical perspective by network pharmacology-molecular docking. In this work, 25 active ingredients, 115 crucial targets, and 127 related signaling pathways in HBG were predicted. Among them, IL6, CASP3, EGFR, VEGF, and MAPK were hub targets of HGB in treating LF. Simultaneously, the key molecular mechanisms of HBG against LF were mainly involved in PI3K-AKT, MAPK, HIF-1, and NF-κB signaling pathways. It unfolded the characteristics of multicomponent, multitarget, and multipathway in HBG for the treatment of LF. In brief, this work broadens the line of thought for further pharmacological research.

Data Availability

The data used to support the findings of this study are available from the authors.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

Authors' Contributions

Yi Zhu and Ming Qiao contributed equally to this work.

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