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The Mechanism of Lycium Barbarum for Liver Cancer Treatment Was Analyzed Based on Network Pharmacology

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Abstract: Aim: The mechanism of lycium barbarum treatment liver cancer was explored based on network pharmacology. Methods: The active ingredients, action targets of Lycium barbarum and disease targets of liver cancer were searched in public database platforms TCMSP, GeneCards, DisGeNET, OMIM and TTD, and the potential target of lycium barbarum in the treatment of liver cancer was obtained by intersection of drug component target and disease target. The protein interaction network (PPI) of lycium barbarum in treating liver cancer was obtained through STRING database, and the core target was identified by Cytoscape3.9.1 software analysis. The signaling pathway of lycium barbarum on hepatocarcinoma were screened by gene ontology (GO) enrichment analysis and Genomic Encyclopedia (KEGG) pathway enrichment analysis. Results: 45 active ingredients and 430 targets of Lycium barbarum, and 6489 targets related to liver cancer were selected. There were 272 common targets of drug-disease intersection. The analysis results showed that the active components of Lycium berry mainly included δ-carotene, lano-8-enol, lano-8-ene-3beta-alcohol, 14b-pregnane, β-sitosterol, and carotenin. The core targets of lycium barbarum in the treatment of liver cancer include AKT1, TNF, EGFR, ESR1, SRC, PPARG and HSP90AA1. GO enrichment is mainly involved in biological processes such as protein phosphorylation, response to exogenous stimuli, and negative regulation of apoptosis. KEGG is mainly involved in metabolic pathway, cancer pathway, PI3K-Akt signaling pathway. Conclusions: The results of this study show that Lycium barbarum may play an important role for treatment liver cancer in protein phosphorylation, exogenous stimulus response and negative regulation of apoptosis through key targets such as AKT1, TNF, EGFR, ESR1, SRC, PPARG and HSP90AA1 in "metabolic pathway", "tumor pathway" and "PI3K-Akt signaling pathway".

Keywords: Network Pharmacology; Lycium Barbarum; Liver Cancer

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1 Introduction

Liver cancer is a malignant tumor that seriously threatens human health. There are about 905677 new cases worldwide every year, and about 830180 people die from liver cancer every year [1]. Hepatic pain is often the first symptom of liver cancer. The discussion of liver cancer in traditional chinese medicine classics can be seen in the diseases such as "fat qi", "qi accumulation" and "accumulation syndrome", which discuss the etiology and patho-

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genesis of liver cancer. Modern doctors have discussed the etiology and pathology of liver cancer, and basically agree that these diseases are liver-stagnation and spleen-deficiency, damp-heat accumulation, liver-kidney yin deficiency and qi-stagnation and blood stasis [2]. Chinese medicine believes that wolfberry taste sweet, flat, nourishing the liver and kidney, health nourishing blood, eyes calming, nourishing the lungs, phlegm, cough and so on [3]. In recent years, it has been found that wolfberry has the function of repairing liver injury, promoting liver regeneration and increasing liver weight [4]. Lycium barbarum polysaccharide (LBP) can not only play anti-cancer role by enhancing immunity and directly inhibiting tumor, but also play anti-tumor role by inducing apoptosis of cancer cells [5-7]. This study explored the mechanism for lycium barbarum in the treatment of liver cancer through network pharmacology, and provided scientific basis for the treatment of clinical related diseases.

2 Methods

2.1 Prediction and Screening of Active Ingredients and Potential Targets of Lycium Barbarum

The active ingredients of Lycium barbarum were searched through TCMSP database (https://old.tcmsp-e.com/tcmsp.php), and were screened with oral bioavailability ≥30% and drug class ≥0.18 as the conditions. Get the active ingredient with the MOLID number. The targets of effective ingredients were predicted using the Pubchem database (https://pubchem.ncbi.nlm.nih.gov/) and Swiss target prediction (http://swisstargetprediction.ch/). The gene name of the target was searched using the uniprot protein database (https://www.uniprot.org/), which of the gene source was defined as “Homo sapiens”.

2.2 Screening of Targets Related to Liver Cancer

The disease related targets were retrieved using "liver cancer" as the key word in GeneCards database (https://www.genecards.org), OMIM database (https://www.omim.org), TTD database (https://db.idrblab.net/ttd), and DisGeNET database (https://www.disgenet.org/home/). The targets related to liver cancer were obtained by integrating the gene names of the targets from the four databases and deleting duplicates. The intersection of targets as disease key targets were gotten through venny2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/) venn diagram.

2.3 Construction of "Drug-Active Ingredient-Target Network"

The "Lycium barbarum-active ingredients-target network" was constructed by using Cytoscape3.9.1 software. Lycium barbarum, its active constituents and targets were set as nodes with different shapes and colors according to the network topology parameters through summarized the information of lycium barbarum, its active ingredients and its targets.

2.4 Construction of Protein-protein Interaction (PPI) Networks and Acquisition of core Targets

Multiple proteins were selected to predict protein-protein interactions that the intersection target was imported into the STRING database (https://cn.string-db.org). The selected species was set as "Homo sapiens", and with medium confidence (0.4000), which was further visualization through resulting protein-protein interaction network introduced into Cytoscape3.9.1.

2.5 KEGG and GO Enrichment Analysis

The analysis of the gene ontology (GO) enrichment and Kyoto encyclopedia (KEGG) gene and genome signaling pathway enrichment were conducted through the intersection targets imported DAVID database (https://david.ncifcrf.gov/), and setted species as "Homo. sapiens". Among them, GO enrichment analysis was screened from three aspects: biological process, cell component and molecular function. The signal pathways with high correlation with liver cancer were selected with $P < 0.01$. The bubble chart and bar chart were drawn through the above results imported into micro sheng xin network (http://www.bioinformatics.com.cn).

3 Results

3.1 The Screening Results of Lycium Barbarum Effective Components and Targets

The active ingredients of lycium barbarum were searched in the TCMSP database, and were screened under the conditions of "oral bioavailability >=30%, chemoidoid >=0.18". 45 eligible active ingredients were found (Table 1). 430 relevant targets of active ingredients were predicted by pubChem and swiss target prediction database.

Table 1 The active ingredients of lycium barbarum

Mol ID	**Molecule Name**	**OB (%)**	**DL**
MOL010234	delta-Carotene	31.8	0.55
MOL009678	lanost-8-enol	34.23	0.74
MOL009677	lanost-8-en-3beta-ol	34.23	0.74
MOL009604	14b-pregnane	34.78	0.34
MOL000358	beta-sitosterol	36.91	0.75
MOL008173	daucosterol_qt	36.91	0.75
MOL009617	24-ethylcholest-22-enol	37.09	0.75
MOL009615	24-Methylenecycloartan-3beta,21-diol	37.32	0.8
MOL005438	campesterol	37.58	0.71
MOL009635	4,24-methyllophenol	37.83	0.75
MOL000953	CLR	37.87	0.68
MOL009620	24-methyl-31-norlanost-9(11)-enol	38	0.75
MOL009639	Lophenol	38.13	0.71
MOL009633	31-norlanost-9(11)-enol	38.35	0.72
MOL009662	Lantadene A	38.68	0.57
MOL009631	31-Norcyclolaudenol	38.68	0.81
MOL003578	Cycloartenol	38.69	0.78
MOL009640	4alpha,14alpha,24-trimethylcholesta-8,24-dienol	38.91	0.76
MOL009660	methyl (1R,4aS,7R,7aS)-4a,7-dihydroxy-7-methyl-1-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxy-1,5,6,7a-tetrahydrocyclopenta[d]pyran-4-carboxylate	39.43	0.47
MOL009653	Cycloeucalenol	39.73	0.79
MOL009646	7-O-Methylluteolin-6-C-beta-glucoside_qt	40.77	0.3
MOL001494	Mandenol	42	0.19
MOL009656	(E,E)-1-ethyl octadeca-3,13-dienoate	42	0.19
MOL001979	LAN	42.12	0.75
MOL009650	Atropine	42.16	0.19
MOL009634	31-norlanosterol	42.2	0.73
MOL009642	4alpha-methyl-24-ethylcholesta-7,24-dienol	42.3	0.78
MOL009621	24-methylenelanost-8-enol	42.37	0.77
MOL009681	Obtusifoliol	42.55	0.76
MOL009641	4alpha,24-dimethylcholesta-7,24-dienol	42.65	0.75
MOL001323	Sitosterol alpha1	43.28	0.78
MOL009644	6-Fluoroindole-7-Dehydrocholesterol	43.73	0.72
MOL009622	Fucosterol	43.78	0.76
MOL000449	Stigmasterol	43.83	0.76
MOL009618	24-ethylcholesta-5,22-dienol	43.83	0.76
MOL009665	Physcion-8-O-beta-D-gentiobioside	43.9	0.62
MOL007449	24-methylidenelophenol	44.19	0.75
MOL005406	atropine	45.97	0.19
MOL001495	Ethyl linolenate	46.1	0.2
MOL009612	(24R)-4alpha-Methyl-24-ethylcholesta-7,25-dien-3beta-ylacetate	46.36	0.84
MOL000098	quercetin	46.43	0.28
MOL009651	Cryptoxanthin monoepoxide	46.95	0.56
MOL006209	cyanin	47.42	0.76
MOL008400	glycitein	50.48	0.24
MOL009664	Physalin A	91.71	0.27

3.2 Target Screening Results of Liver Cancer

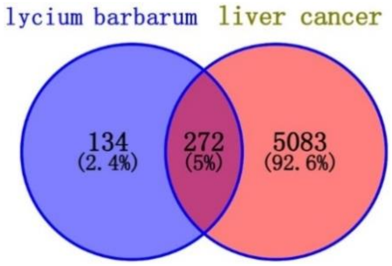

Figure 1 Venn diagram of lycium-liver cancer

The related targets of liver cancer were searched using “liver cance r” as the keyword in multiple databases, including 4500 in Genecards database, 1395 in DisGeNET database, 519 in OMIM database, and 75 in TTD database. 6489 targets related to liver cancer were obtained that integrated the targets of above four databases and removed duplicates. 272 key targets of lycium barbarum on liver cancer were obtained by drawing venn diagram.

3.3 Construction of "Wolfberry - Active Ingredients-Target Network"

The network of lycium barbarum-active Ingredients- related target were constructed through lycium barbarum, and its effective components, and related target information imported into Cytoscape3.9.1 software. The network is composed of 427 nodes and 460 edges through visual analysis, which of nodes represent various component proteins, and edges represent certain relationships between component proteins. Among them yellow represents wolfberry, green represents the active ingredient of wolfberry, and orange represents the gene target (Figure 2).

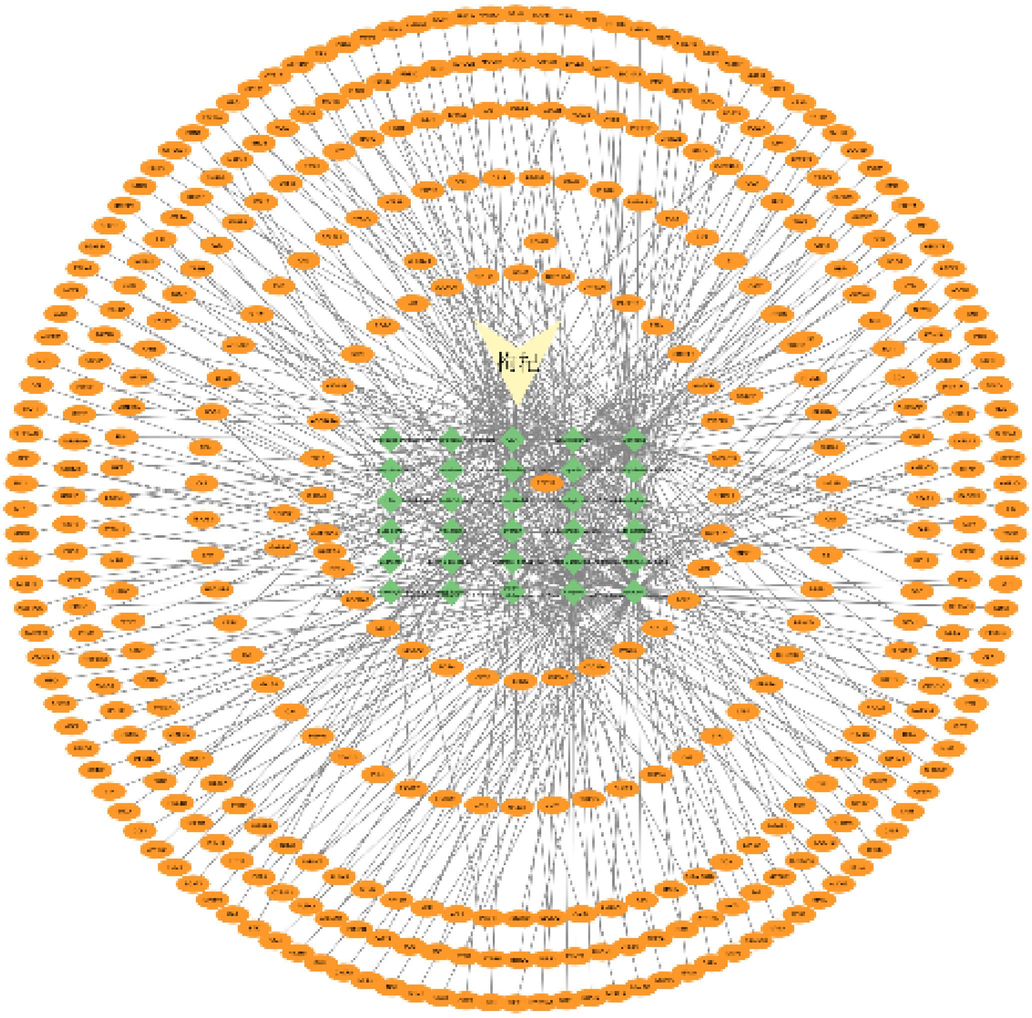

Figure 2 The network lycium barbarum - active constituents - target

3.4 Construction of Protein-Protein Interaction Network

272 intersection targets were imported into the STRING database to generate the protein interaction network of lycium barbarum on liver cancer (Figure 3). The network constructed by Cytoscape3.9.1 software shows 271 nodes and 3650 edges. Nodes are the target proteins, and edges represent the relationship between each target. PPI is further optimized (Figure 4) after analyzing the degree value of network nodes, in which red represents the relevant targets with large degree value, green represents the relevant targets with small degree value, and the size of the graph is arranged according to the size of the degree value. The larger the graph is, the larger the degree value is, and the greater the correlation is. It can be seen that the highest degree value is ABCB1, two gene proteins with degree value greater than 120 are MMP2 and NR3C1, and four gene proteins with degree value greater than 100 are MDM2, MAPK3, KDR and EGFR. These targets are considered to be important targets of Lycium berry for liver cancer, and the following is the network topology of im-

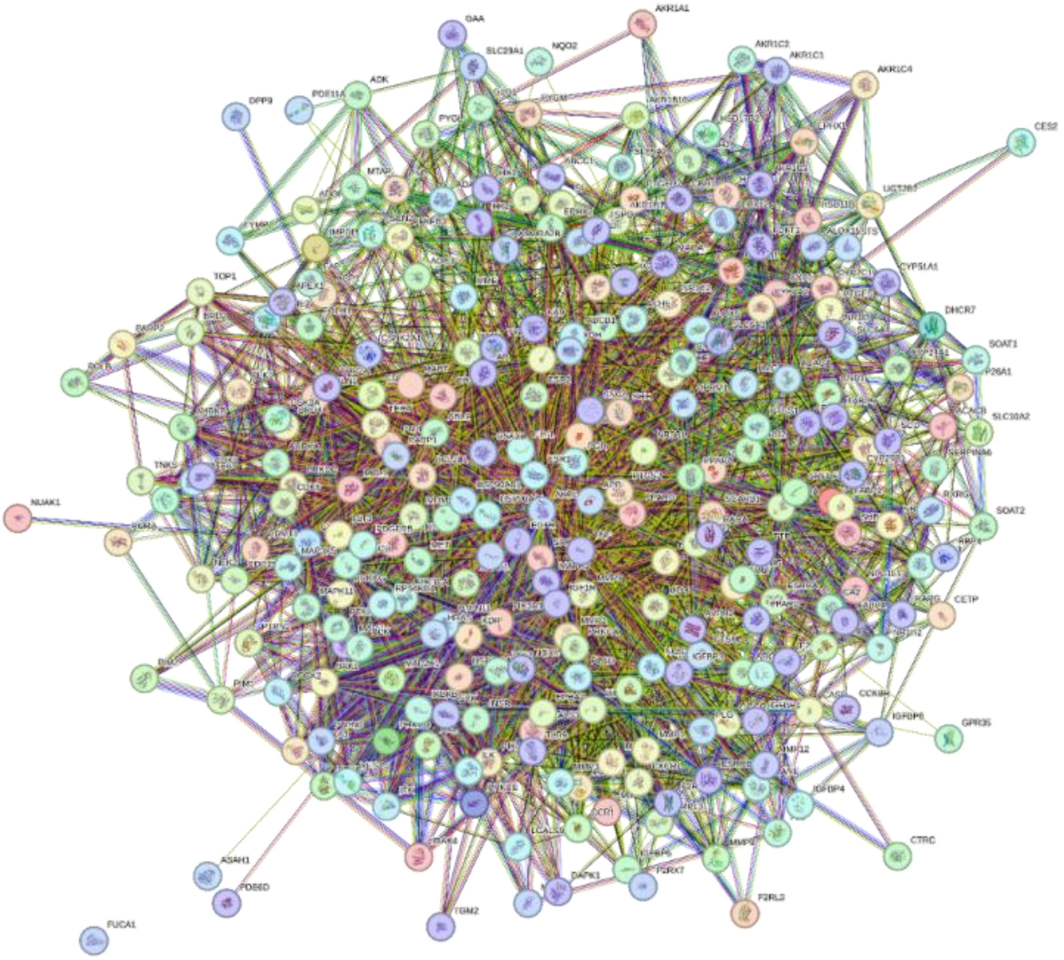

Figure 3 Protein interaction network of Lycium-liver cancer

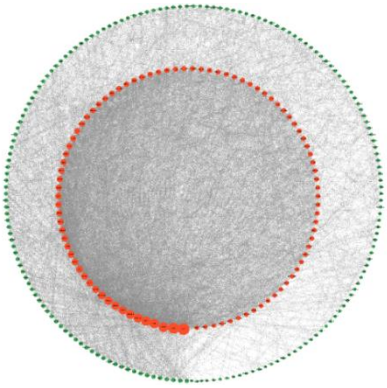

Figure 4 Optimization of lycium-liver cancer protein interaction network

portant targets (Table 2).

Table 2 The top ten targets and parameters of lycium barbarum action on liver carcinoma

name	**Betweenness unDir**	**Closeness unDir**	**Degree unDir**
ABCB1	891.4123615	0.001988072	154
MMP2	574.5089352	0.002020202	141
NR3C1	407.4300921	0.001968504	120
MDM2	613.7669084	0.002083333	117
MAPK3	1493.731448	0.002202643	116
KDR	470.8802974	0.002057613	109
EGFR	3965.792621	0.002364066	105
HMGCR	1087.297755	0.001976285	93
KIT	323.9944631	0.00203252	93
GSK3B	904.4437259	0.00210084	93

3.5 The Results of KEGG and GO Enrichment Analysis

272 intersection targets were imported into DAVID database for analysis. KEGG enrichment analysis showed 170 pathways. 149 pathways were selected according to P<0.01, which include metabolic pathways, cancer pathways, PI3K-Akt signaling pathway, chemical carcinogenic-receptor activation, and etc. The top 20 KEGG signal paths were selected according to count value to draw bubble diagram (Figure 5). The color of the bubble is related to the P-value, and the smaller the P-value, the redder the bubble color, and the stronger the correlation; and the larger the value, the larger the bubble.

GO enrichment analysis yielded 1110 items. Among them, there were 795 biological processes, 96 cell components and 219 molecular functions. A total of 361 samples were obtained according to P<0.01. The biological process mainly involves protein phosphorylation, response to exogenous stimuli and negative regulation of apoptosis. The cell components mainly involve cytoplasm, cytoplasm, plasma membrane, exosome, nucleus, karyoplasm and so on. The molecular functions mainly involve tyrosine kinase activity, protein kinase activity, ATP binding, enzyme binding, zinc ion binding and so on.

Draw a bar chart (Figure 6) by ranking the first 10 of each item on the basis of count value. The horizontal coordinate is the count value, and the vertical coordinate is the path name. The color of the bar chart is related to the P value, and the smaller the P value, the redder the bar color, and the stronger the correlation.

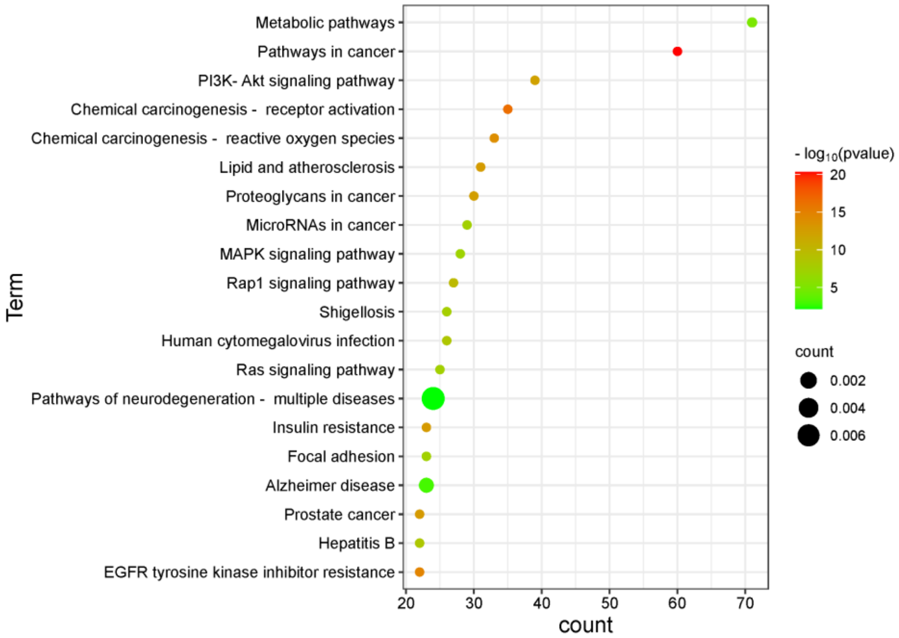

Figure 5 Top 20 KEGG enrichment signaling pathways of Lycium barbarum for hepatocarcinoma

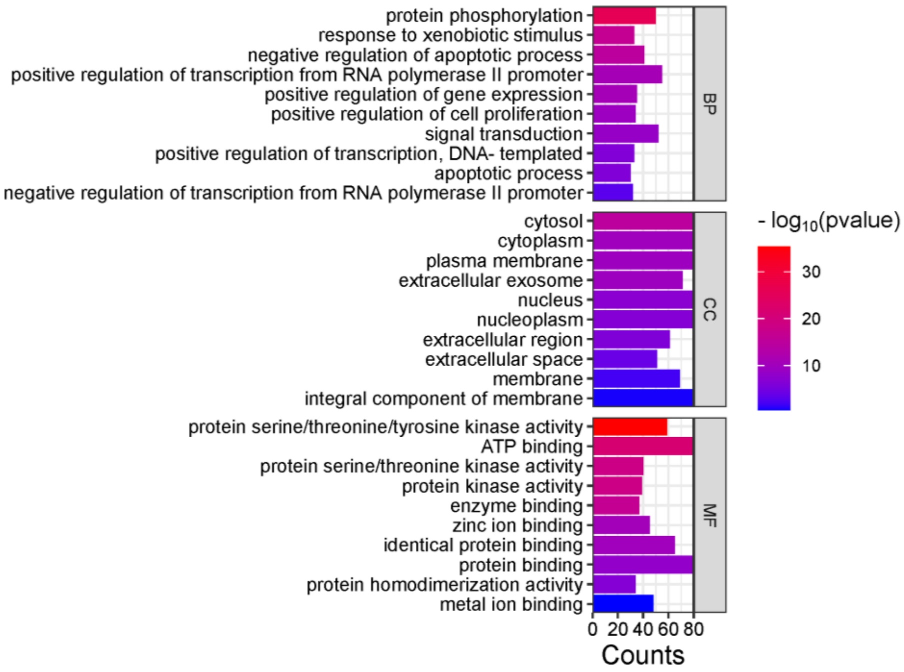

Figure 6 Top 10 CG enrichment signaling pathways of Lycium barbarum therapy for liver cancer

4 Discussion

In this study, the mechanism of liver cancer was treated using Lycium barbarum through network pharmacology predicting, and 272 intersection targets of drugs and diseases were obtained, corresponding to 45 kinds of active ingredients of Lycium barbarum. It mainly includes delta-Carotene, lanost-8-enol, lanost-8-en-3beta-ol, 14b-pregnane, beta-sterol (beta-s) itosterol, daucosterol_qt, etc. The main chemical components of Lycium barbarum are polysaccharides, flavonoids, anthocyanins, alkaloids, etc [8]. Lycium barbarum polysaccharide has pharmacological effects such as immune regulation, anti-aging, anti-tumor, anti-radiation, etc [9-14]. Anthocyanins have pharmacological effects such as lowering blood pressur and anti-inflammatory [15-18], β-sitosterol has a protective effect on chronic alcoholism and has broad clinical application prospects in the treatment of alcohol-induced liver damage [19], and betaine has pharmacological effects such as anti-fatigue, liver and kidney protection [20-22]; Carotenoids also have significant protective effects on hepatocytes and liver [23].

Intersection targets include AKT1, TNF, EGFR, ESR1, SRC, PPARG and HSP90AA1, among them AKT1 can inhibit autophagy and related to the occurrence of liver cancer [24-27]. In the early stage of liver cancer, TNF and EGFR can promote the development of tumor by promoting the proliferation of elliptical cells (liver stem cells) [28-30]. and hepatocyte-specific EGFR activity acts as a key player in the crosstalk between parenchymal and non-parenchymal hepatic cells, promoting the pro-inflammatory response activated during cholestatic injury and therefore contributing to the pathogenesis of cholestatic liver disease [31]. These intersection targets are highly likely to be the key targets for the treatment of liver cancer by lycium barbarum.

According to the above analysis, in the KEGG enrichment analysis of the intersection target of Lycium berry and liver cancer, the abnormal expression of PI3K-Akt signaling pathway is an important factor in the occurrence of liver cancer. The activated PI3K/Akt signaling pathway can exert anti-inflammatory, anti-oxidative stress, anti-apoptosis and autophagy regulatory effects through downstream related targeted pathways and proteins, thereby alleviating liver injury. Therefore, the regulation of PI3K/Akt signaling pathway is expected to be an effective targeted pathway for clinical prevention and mitigation of liver injury [32-34].

Studies have shown that Lycium barbarum polysaccharide can significantly reduce tumor infection through the PI3K-AKT pathway and increase the apoptosis rate of tumors and inhibit the inflammatory effect of macrophages, exert anti-inflammatory activity, reduce the inflammatory response of cells, and then inhibit the proliferation of cancer cells, thus achieving the purpose of anti-inflammatory and anti-tumor [35-37].

Among the Go-enriched molecular functions, the activity of tyrosine kinase is highly correlated with the treatment of liver cancer by lycium barbarum. Abnormally activated tyrosine kinase can evade immune surveillance by regulating other signal networks such as nucleic acid innate immunity, thereby indirectly promoting the occurrence and development of tumors [38, 39].

In summary, based on network pharmacology, this study analyzed the active ingredients of Lycium barbarum and the intersection targets of Lycium barbarum in the treatment of liver cancer, revealing the network interaction of multi-components, multi-targets and multi-pathways of Lycium barbarum in the treatment of liver cancer, and obtained key targets such as AKT1, TNF, EGFR, ESR1, SRC, PPARG and HSP90AA1. It provides reference data for subsequent studies, but due to the limitations of network pharmacology, further experimental verification should be carried out if clinical treatment is needed.

5 Conclusions

This study shows that Lycium barbarum may play an important role for treatment liver cancer in protein phosphorylation, exogenous stimulus response and negative regulation of apoptosis through key targets such as AKT1, TNF, EGFR, ESR1, SRC, PPARG and HSP90AA1 in "metabolic pathway", "tumor pathway" and "PI3K-Akt signaling pathway".

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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