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基于网络药理学和分子对接技术分析茵陈治疗肝癌的潜在作用机制

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摘 要

目的：运用网络药理学和分子对接技术阐释茵陈抗肝癌的作用机制。方法：用TCMSP和UniProt数据库收集茵陈的活性成分并预测其潜在靶点。通过GeneCards、OMIM、TTD数据库筛选肝癌相关靶点。用在线软件Draw Venn Diagram将药物和疾病靶点取交集，将交集靶点导入DAVID 6.8在线数据库进行GO和KEGG分析。通过STRING数据库构建靶蛋白互作网络，用Cytoscape软件筛选关键基因，并用AutoDock Vina软件对关键靶点进行分子对接分析。结果：茵陈共筛选出13个活性成分，药物和疾病交集靶点103个，最终筛选出CDKN1A、CDK2、JUN、E2F1、RB1、TNF、IL6、CCNA2、IL1B、CXCL8 10个关键靶点，关键靶点与部分活性成分对接较好。结论：茵陈中的活性成分通过作用于CDKN1A、CDK2、CXCL8等靶点，参与调控细胞周期、机体的炎症反应以及癌症等信号通路，从而可能发挥对肝癌的治疗作用。

关键词

茵陈，肝癌，网络药理学，分子对接

Analysis of the Potential Mechanism of *Artemisiae Scopariae Herba* in the Treatment of Liver Cancer Based on Network Pharmacology and Molecular Docking Technology

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Abstract

Objective: The network pharmacology and molecular docking technology were used to elucidate the mechanism of *Artemisiae Scopariae Herba* (ASH) against liver cancer. Methods: TCMSP and UniProt databases were used to collect the active components of ASH and predict their potential targets. The target of liver cancer was screened by GeneCards, OMIM and TTD database. The intersection of drug and disease targets was obtained by online software Draw Venn Diagram, and the intersection targets were imported into David 6.8 for GO and KEGG function enrichment analysis. Construction of protein-protein interaction network through STRING database, Cytoscape software was used to screen hub genes. Molecular docking analysis of hub genes was carried out with AutoDock Vina software. Results: A total of 13 active components were screened out from ASH and 103 drug and disease intersection targets were screened. Finally, 10 hub targets including CDKN1A, CDK2, JUN, E2F1, RB1, TNF, IL6, CCNA2, IL1B and CXCL8 were screened out. The hub targets were docked well with some active components. Conclusion: The active components of ASH are involved in regulating cell cycle, inflammatory response, cancer and other signaling pathways by acting on CDKN1A, CDK2, CXCL8 and other targets, which may play a role in the treatment of liver cancer.

Keywords

***Artemisiae Scopariae Herba*, Liver Cancer, Network Pharmacology, Molecular Docking**

1. 引言

肝癌在世界最常见的癌症中排名第五，是导致癌症死亡的第三大原因，缺乏合适的早期发现的生物标志物和有限的治疗策略是高死亡率的主要原因[1]。肝细胞癌(HCC)是肝癌最常见的形式，占肝癌的90%，是男性癌症相关死亡的第二大原因，在女性中是第六大原因[2] [3] [4]。肝炎病毒，肥胖，饮食习惯，脂肪肝疾病，肝硬化等是与肝癌相关的危险因素[5] [6]。乙型和丙型肝炎病毒可引起急性和慢性感染，导致肝癌[7]。神经系统相关因子在肝癌中参与调控癌细胞的迁移、增殖和凋亡，并在治疗后的侵袭、转移和复发中发挥调节作用[8]。外泌体在多种肝脏疾病中发挥重要的作用，如病毒性肝炎、酒精性肝病、脂肪肝等，甚至参与肝纤维化的进展，最终参与肝癌的发生发展[9]。肝纤维化与肝癌死亡风险显著增加有关[10]。肿瘤微环境可影响癌细胞的存活、信号转导和转移，肝癌微环境包括与癌相关的成纤维细胞(CAFs)、肝星状细胞(HSCs)、内皮细胞、免疫细胞、生长因子、炎性细胞因子和细胞外基质蛋白[11]。

茵陈(*Artemisiae Scopariae Herba*) 也叫茵陈蒿，为菊科植物滨蒿(Artemisia scoparia Waldst. et Kit.)或茵陈蒿(Artemisia capillaris Thunb.)的地上干燥部分[12]。茵陈蒿作为传统药物广泛用于治疗肝炎、肝脏胆汁淤积、黄疸、胆囊功能障碍和消化系统疾病，对慢性乙型肝炎病毒感染和肝硬化具有抗炎作用，其主

要成分如卡青霉素和东莨菪酮对乳腺癌、前列腺癌、肺癌和肝癌均有抗肿瘤作用[13] [14]。研究发现茵陈干叶中的一种提取物比茵陈全株具有更强的抗癌活性，通过抑制 PI3K/AKT 通路抑制细胞生长并诱导线粒体介导的细胞凋亡，而 PI3K/AKT 通路上调与 HCC 预后不良有关[13]。茵陈提取物对肝炎具有一定的治疗效果，还能抑制肝癌细胞的生长、侵袭和转移，诱导细胞凋亡，起到肝保护的作用[15] [16]。

肝癌目前的治疗方案有手术治疗、局部消融、经肝动脉化疗栓塞术、放射治疗、药物治疗和免疫疗法等，但它们都有各自的缺点[17]。中医药在肝癌的治疗和预防方面都起到一定作用，包括抑制肿瘤生长、抗转移、抗炎症、诱导/降低氧化应激[18]。茵陈作为一种传统中药，具有一定的肝保护功能，有望对肝癌起到一定的治疗效果。

2. 方法

2.1. 茵陈的活性成分和作用靶点的筛选

TCMSP 数据库(https://tcmspw.com/tcmsp.php)中以“茵陈”为关键词检索其全部化学成分，活性成分的筛选条件设置为药物口服利用度(OB) ≥ 30%，类药性(DL) ≥ 0.18。活性成分的作用靶标在 TCMSP 数据库查询，将得到的靶标蛋白在 UniProt(https://www.uniprot.org/)数据库中进行规范，获得靶蛋白对应的基因名。

2.2. 肝癌疾病靶点的获取

在 GeneCards (https://www.genecards.org/)，OMIM (https://omim.org/)，TTD (http://db.idrblab.net/ttd/)数据库中输入关键词“liver cancer”，检索肝癌相关靶点，整合三个数据库的结果并去除重复。

2.3. 交集基因的获取

通过 Draw Venn Diagram (http://bioinformatics.psb.ugent.be/webtools/Venn/)将茵陈活性成分的靶点与肝癌靶点取交集，获得茵陈治疗肝癌的作用靶点，用 Cytoscape 软件构建茵陈与肝癌的“药物－成分－疾病－靶点”网络图。

2.4. GO 和 KEGG 分析

通过 DAVID 6.8 在线数据库(https://david.ncifcrf.gov/)对交集基因做 GO 和 KEGG 富集分析，设定物种为人，并用 R 软件对结果做可视化处理。

2.5. PPI 网络构建和关键基因获取

将交集基因导入 STRING 在线数据库(https://string-db.org/)，物种选择“Homo sapiens”，构建蛋白互作网络。下载蛋白互作网络结果的 TSV 格式文本并导入 Cytoscape 软件，用 cytoHubba 插件筛选排名前 10 位的关键基因。

2.6. 分子对接

用关键基因(受体)与各自在“药物－成分－疾病－靶点”网络中对应的茵陈成分(配体)进行分子对接。在 PDB 数据库(https://www.rcsb.org/)下载靶点蛋白的结构，PyMOL 软件去除溶剂分子和小分子配体，用 AutoDock 软件进行加氢等操作。从 PubChem 数据库(https://pubchem.ncbi.nlm.nih.gov/)中下载化合物 2D 结构，用 ChemOffice 软件构建 3D 结构并进行优化。用 Vina 软件对转化为*pdbqt 格式的分子和靶点进行对接，结合能 $\leq -5.0\ kJ \cdot mol^{-1}$ 表明分子与靶点对接较好。

3. 结果

3.1. 茵陈活性成分及作用靶点

茵陈活性成分共获得 13 种(表 1)，在 TCMSP 数据库种查找它们对应的靶点并在 UniProt 数据库中进行注释和校正，删除重复和没有查到对应基因名的靶点，共获得 169 个单一靶点。

Table 1. Active components of *Artemisiae Scopariae Herba* (ASH)
表 1. 茵陈有效成分

Mol ID	Molecule Name	OB (%)	DL
MOL008045	4’-Methylcapillarisin	72.18	0.35
MOL008047	Artepillin A	68.32	0.24
MOL008043	Capillarisin	57.56	0.31
MOL008039	Isoarcapillin	57.4	0.41
MOL008046	Demethoxycapillarisin	52.33	0.25
MOL000354	Isorhamnetin	49.6	0.31
MOL004609	Areapillin	48.96	0.41
MOL000098	Quercetin	46.43	0.28
MOL008040	Eupalitin	46.11	0.33
MOL008041	Eupatolitin	42.55	0.37
MOL005573	Genkwanin	37.13	0.24
MOL000358	Beta-sitosterol	36.91	0.75
MOL007274	Skrofulein	30.35	0.3

3.2. 肝癌相关靶点

在 Genecards 数据库获得肝癌相关基因 16,489 个，以 relevance score > 20 筛选得到 1004 个基因。在 OMIM 数据库中得到 493 个靶点，TTD 数据库获得 13 个靶点，将三个数据库的靶点合并删除重复后剩余 1410 个与肝癌相关的基因靶点。

3.3. 药物与疾病的交集靶点

在 Draw Venn Diagram 中获得茵陈与肝癌的交集靶点 103 个(图 1)，将交集靶点导入 Cytoscape 软件构建“药物－成分－疾病－靶点”网络，其中红色代表茵陈，紫色代表肝癌，黄色代表茵陈活性成分，绿色代表靶点(图 2)。

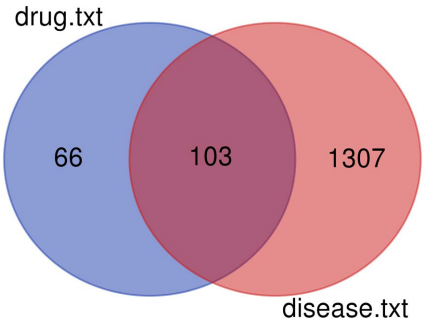

Figure 1. The intersection genes of LC and ASH
图 1. 肝癌和茵陈的交集基因

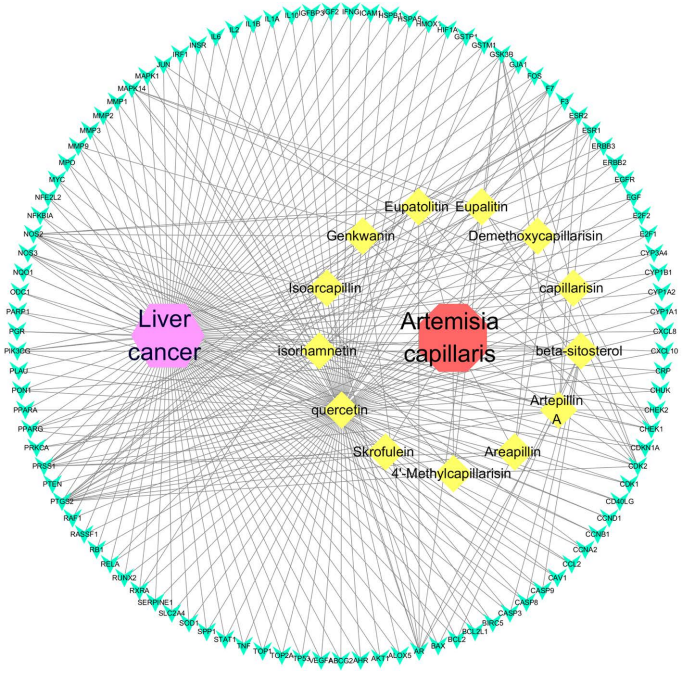

Figure 2. The “drug-component-disease-target” network
图 2. “药物－成分－疾病－靶点”网络

3.4. GO 和 KEGG 富集分析

用 DAVID6.8 对茵陈治疗肝癌的靶点做富集分析，设置 P < 0.01 和 FDR < 0.01 为界限，共获得 GO 条目 229 条，KEGG 条目 92 条。根据 P 值进行排序，用 R 软件分别对 GO 条目前 30 和 KEGG 条目前 20 做可视化分析(表 2、表 3、图 3、图 4)。

GO 可视化分析显示交集靶点主要富集在生物过程(BP)中，涉及对血管生成，炎症反应，基因表达，转录，细胞增殖与凋亡等过程的调控，以及对一些化合物和特殊环境的应答反应。

KEGG 可视化分析显示交集靶点涉及癌症通路，膀胱癌、前列腺癌、胰腺癌、小细胞肺癌等癌症，乙型和丙型肝炎，TNF、HIF-1、p53 信号通路，Toll 样受体信号通路等。

Table 2. GO enrichment analysis
表 2. GO 富集分析

GO-term	Gene counts	P-value
enzyme binding	29	1.43E−24
positive regulation of transcription from RNA polymerase II promoter	37	2.19E−19
response to drug	23	6.69E−18
negative regulation of apoptotic process	26	1.99E−17
positive regulation of transcription, DNA-templated	27	3.21E−17
identical protein binding	29	3.33E−15
protein binding	91	5.82E−15
cellular response to hypoxia	14	1.85E−14
extracellular space	35	2.19E−14

Continued

positive regulation of gene expression	19	2.36E−14
transcription factor binding	19	8.67E−14
extrinsic apoptotic signaling pathway in absence of ligand	10	3.63E−13
angiogenesis	17	3.77E−13
cellular response to organic cyclic compound	11	2.14E−12
response to toxic substance	12	3.52E−12
positive regulation of nitric oxide biosynthetic process	10	3.73E−12
cellular response to lipopolysaccharide	13	3.87E−12
positive regulation of angiogenesis	13	4.78E−12
response to estradiol	12	7.57E−12
aging	14	2.17E−11

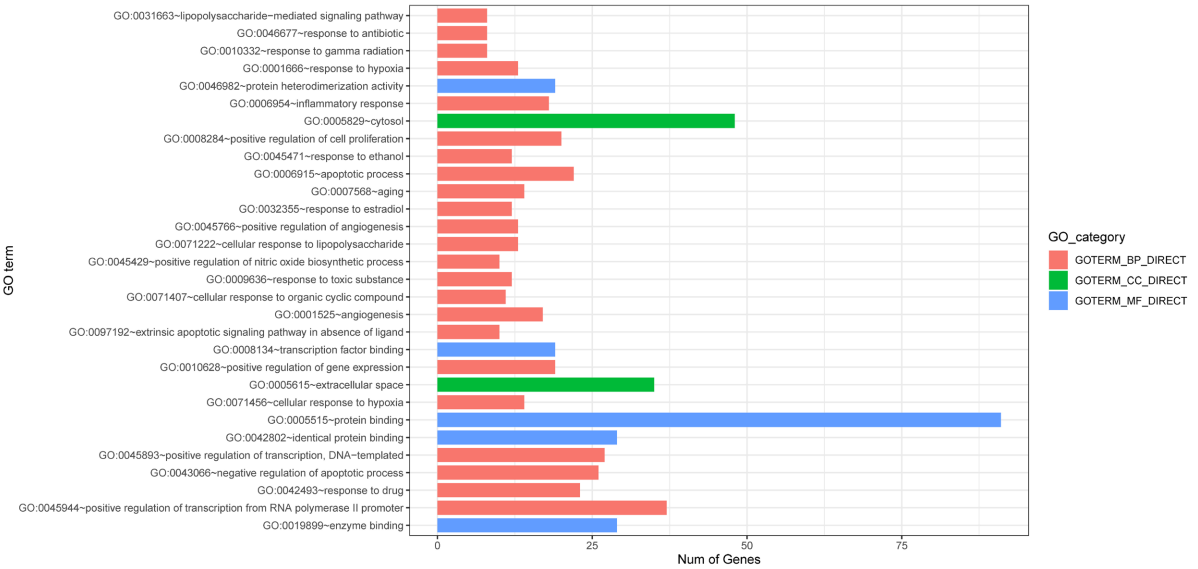

Figure 3. Histogram of GO enrichment analysis
图 3. GO 富集分析柱状图

Table 3. Enrichment analysis of KEGG pathway
表 3. KEGG 通路富集分析

Pathway	Gene counts	P-value
Pathways in cancer	45	9.82E−30
Hepatitis B	31	6.98E−28
Bladder cancer	18	9.06E−22
Prostate cancer	22	6.38E−21
Pancreatic cancer	18	8.42E−18
Small cell lung cancer	19	5.11E−17
Chagas disease (American trypanosomiasis)	20	1.20E−16

Continued

TNF signaling pathway	20	2.10E−16
HIF-1 signaling pathway	19	5.10E−16
Non-small cell lung cancer	16	5.57E−16
Influenza A	22	1.65E−14
Proteoglycans in cancer	23	2.55E−14
Colorectal cancer	15	7.84E−14
Toxoplasmosis	18	1.09E−13
Hepatitis C	19	2.06E−13
p53 signaling pathway	15	2.49E−13
Chronic myeloid leukemia	15	7.18E−13
Toll-like receptor signaling pathway	17	9.02E−13
Glioma	14	3.44E−12
HTLV−I infection	23	3.57E−12

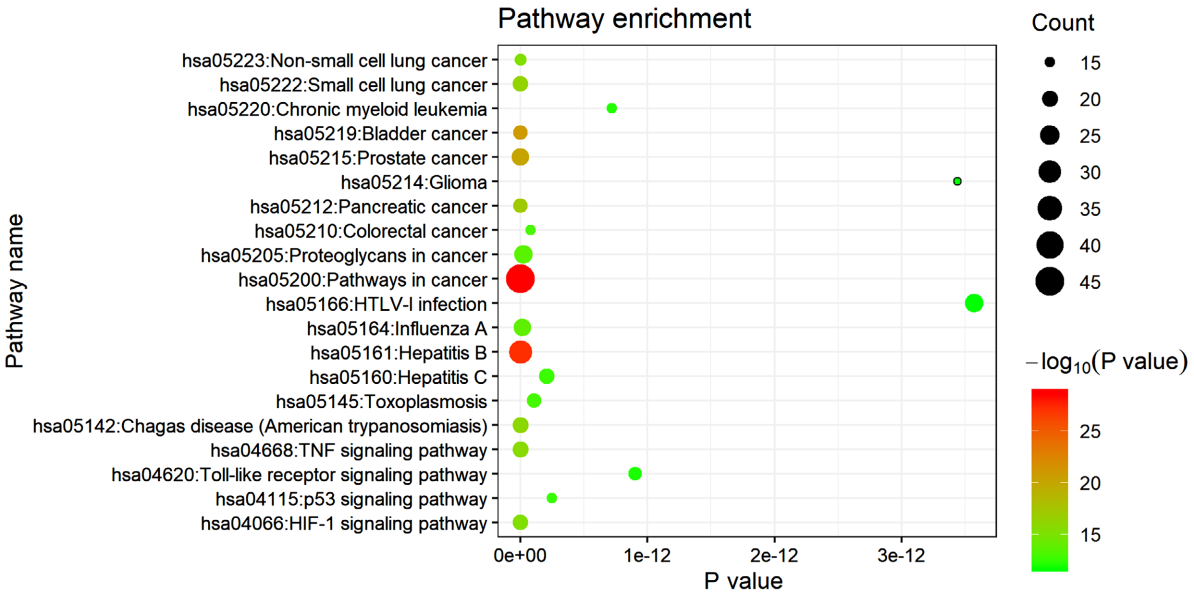

Figure 4. Bubble chart of KEGG analysis
图 4. KEGG 分析气泡图

3.5. PPI 网络和关键基因

将茵陈治疗肝癌的靶点导入 STRING，设定置信度高于 0.95 并删除没有联系的靶点，得到蛋白互作网络(图 5)。将 TSV 格式文本导入 Cytoscape 软件，用 cytoHubba 插件根据 MCC 算法筛选 10 个关键基因，分别为 CDKN1A、CDK2、JUN、E2F1、RB1、TNF、IL6、CCNA2、IL1B、CXCL8 (图 6)。

3.6. 分子对接结果

选取 PPI 网络中排名前 10 位的核心基因与它们在“药物－成分－疾病－靶点”网络中对应的成分进行分子对接，结果显示靶点与其对应的成分均对接良好，其中 JUN 与槲皮素对接最好(表 4)。槲皮素与

JUN 活性位点 ARG-270、LYS-273、LEU-274 形成疏水相互作用，与 SER-269、ARG-270 形成氢键，与 ARG-270 形成 π-阳离子相互作用(图 7)。

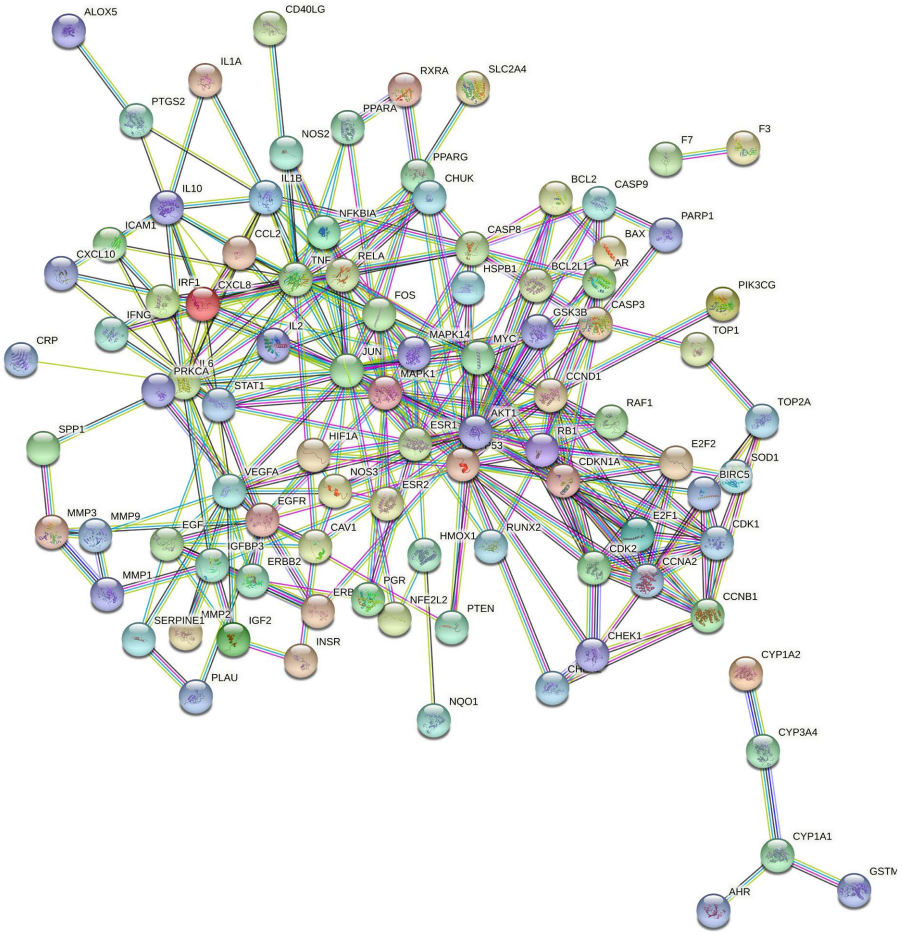

Figure 5. PPI network
图 5. PPI 网络

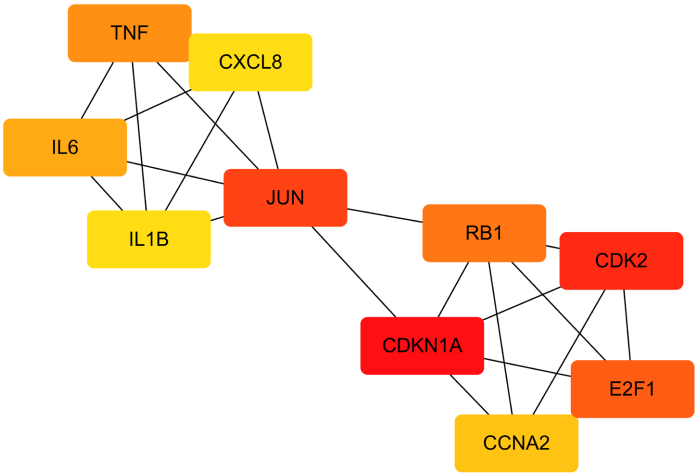

Figure 6. Hub gene
图 6. 关键基因

Table 4. Molecular docking
表 4. 分子对接

靶点	成分	结合能/kJ·mol^{-1}
CDKN1A	quercetin	−5.7
CDK2	isorhamnetin	−7.6
	Eupalitin	−7.2
	Eupatolitin	−7.7
	capillarisin	−7.0
	4'-Methylcapillarisin	−7.5
	Demethoxycapillarisin	−7.7
	Artepillin A	−6.9
JUN	beta-sitosterol	−7.3
	quercetin	−9.4
E2F1	quercetin	−8.4
RB1	quercetin	−8.2
TNF	quercetin	−8.7
IL6	quercetin	−7.8
CCNA2	isorhamnetin	−7.7
IL1B	quercetin	−8.0
CXCL8	quercetin	−6.8

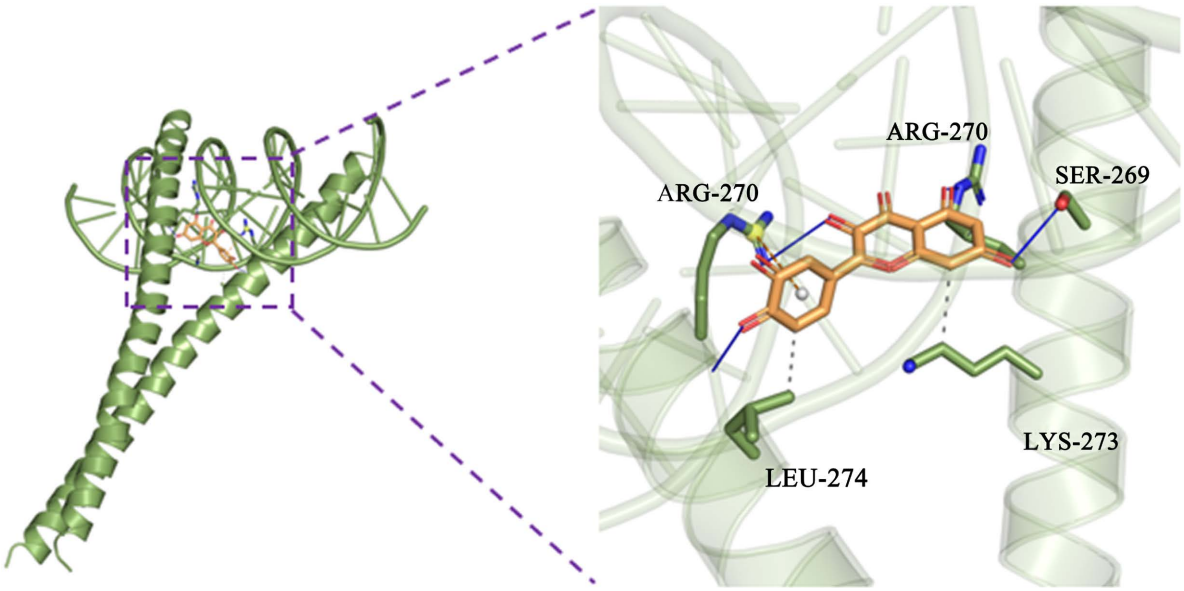

Figure 7. Molecular docking of quercetin and JUN
图 7. 槲皮素与 JUN 分子对接

4. 讨论

本研究中，我们共获得茵陈的 13 种有效成分，它们属于黄酮类、色原酮类和植物甾醇类化合物。黄酮类化合物可以调节几乎所有参与癌变的关键过程，包括细胞凋亡、增殖、血管生成和转移进展，触发

细胞周期阻滞，促进肿瘤抑制基因的表达[19] [20]。此外，黄酮类化合物还具有抗菌、抗病毒特性，对人工诱导的肝损伤具有潜在的保护作用[20]。色原酮类化合物具有抗菌、抗氧化、抗病毒、抗肿瘤活性，对炎症性疾病、癌症、神经退行性疾病、传染病等疾病都起到一定的作用，对肝代谢酶也有作用[21] [22]。植物甾醇可以影响宿主系统，通过提高对癌症的免疫应答识别来实现抗肿瘤反应，同时也表现出直接抑制肿瘤生长的特性，包括减少细胞周期进程、诱导细胞凋亡和抑制肿瘤转移[23]。植物甾醇的摄入还可以减少肝脏炎症，具有保肝的作用[24]。

PPI 网络显示茵陈抗肝癌的作用靶点并非单独起作用，而是一个复杂的网络，根据 PPI 结果最终筛选出 10 个关键基因，分别为 CDKN1A、CDK2、JUN、E2F1、RB1、TNF、IL6、CCNA2、IL1B、CXCL8。CDKN1A 别名 P21，可以促进细胞周期阻滞，在阻止细胞增殖中起重要作用[25]。研究表明，p21 既可以作为致癌基因，也可以作为肿瘤抑制因子，作为肿瘤抑制因子的作用依赖于 NF-kB，此外 p21 还对 DNA 损伤具有保护作用[26]。CDK2 在细胞分化和凋亡中发挥关键作用，经常在人类肿瘤中过度表达，而大多数正常组织低表达，有药理证据表明 CDK2 过表达导致细胞周期调控异常，与癌细胞的过度增殖直接相关[27] [28]。CDK2 mRNA 在原发性肝细胞癌组织中表达显著增加，在肝癌细胞的侵袭和转移中发挥作用[29]。

JUN 基因编码核内重要的癌蛋白，Jun 家族主要有 Jun B、c-Jun、Jun D 3 类，在原发性肝细胞癌组织中，核内转录基因 Jun D 表达产物的表达强度明显增高[30]。转录激活因子 E2F1 参与细胞周期调控、凋亡、衰老、DNA 损伤反应等多种细胞信号通路和生物学过程，通过影响多种信号通路调控多种癌症进展[31]。晚期肝癌患者的肿瘤中，E2F1 基因剂量有轻微但显著的增加[32]。

肿瘤抑制基因 RB1 编码细胞周期的负调控因子，是多种类型癌症的肿瘤抑制因子，包括肝癌[33]。RB1 在肝细胞癌中经常失活导致了肿瘤的多样性和染色体不稳定性，pRb 蛋白在细胞周期调控中起着关键作用，尤其是在 S-G2 转化过程中，还调控参与细胞分化、凋亡、DNA 损伤反应、衰老的几种下游通路[34]。TNF-α 编码一种促炎细胞因子，在炎症性自身免疫性疾病和恶性疾病的发病机制中有一定作用，也被证实能促进肝癌的生长、侵袭和转移，并与肝癌患者的临床预后相关，TNF-α 在肝脏修复和保护肝脏免受慢性损伤中发挥关键作用[35]。IL-6 影响肝癌的增殖，并在肝癌的发生和复发中起重要作用，也可通过激活 STAT3 影响肝癌细胞的增殖、凋亡、侵袭和转移[36]。

细胞周期蛋白 A2 (CCNA2)通过促进 S 期的进入和进展来调控细胞周期，在缺乏 CCNA2 的情况下，肿瘤细胞增殖受损[37] [38]。IL-1B 诱导大量生长因子和血管生成因子，促进肿瘤生长和转移，细菌或病毒感染在肝癌的致癌过程中起重要作用，血浆中 IL1b 的浓度在感染或炎症患者升高[39] [40]。CXCL8 改变了肝癌中 miRNA 的表达谱，促进肝癌细胞的转移和生存[11]。越来越多的研究表明 CXCL8 及其受体在多种类型的人类癌症中过表达，包括结直肠癌、前列腺癌、宫颈癌和非小细胞肺癌，在肝癌组织中高表达，与非肝癌组织相比，CXCL8 的上调与临床分期和肿瘤浸润密切相关[41]。

5. 结论

综上所述，本研究以茵陈为研究对象，通过网络药理学和分子对接方法对茵陈治疗肝癌的有效成分、作用靶点、分子机制进行了初步预测，为今后肝癌的治疗提供了一定的理论指导。

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