

蛹虫草化学成分及抗肺癌的质量标志物预测分析

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摘要: 【目的】蛹虫草具有良好的抗肺癌潜力, 本研究旨在系统预测蛹虫草抗肺癌的潜在质量标志物。【方法】通过系统梳理蛹虫草抗肺癌的研究进展, 总结已鉴定的化学成分; 整合智人肺癌微阵列数据分析与网络药理学技术, 构建“成分-靶点-通路”网络并进行分子对接分析; 结合质量标志物理论预测蛹虫草干预肺癌的潜在质量标志物。【结果】预测获得 6 类共 11 种潜在质量标志物: (1) 虫草素及虫草素类似物 O^5 -乙酰基虫草素; (2) 腺苷及腺苷类似物 N^6 -[β -(乙酰胺甲酰)氧乙基]腺苷、 N^6 -(2-羟乙基)腺苷、 N^6 -(4-甲基丁酸酯基)腺苷、5'-(3"-脱氧- β -D-呋喃核糖基)-虫草素; (3) ergosta-7,22-dien-3 β ,5 α -dihydroxy-6-one; (4) cordycepsosalt A; (5) 喷司他丁; (6) cordyrrole B。【结论】本研究基于文献整合与生物信息学方法预测了蛹虫草抗肺癌的潜在质量标志物, 所提出的作用机制和候选成分仍为有待实验验证的假说, 尚需深入研究以明确其有效性, 以期蛹虫草抗肺癌质量标准体系的建立提供参考。

关键词: 蛹虫草; 肺癌; 质量标志物; 网络药理学; 分子对接

Prediction of anti-lung cancer quality markers in *Cordyceps militaris*

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Abstract: [Objective] To examine the anti-lung cancer activity of *Cordyceps militaris* and predict

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its potential quality markers. **[Methods]** We systematically reviewed the current studies on the anti-lung cancer effects of *C. militaris* and summarized its chemical components. *Homo sapiens* lung cancer microarray data were integrated with network pharmacology to build a “component-target-pathway” network, followed by molecular docking analysis. On this basis, the potential quality markers of *C. militaris* for lung cancer treatment were predicted. **[Results]** We predicted 11 potential quality markers, which were grouped into six categories: (1) cordycepin and its analog *O*^{5'}-acetylcordycepin; (2) adenosine and its analogs, including *N*⁶-[β -(acetylcarbamoyloxy)ethyl]-adenosine, *N*⁶-(2-hydroxyethyl)-adenosine, *N*⁶-(4-methylbutyrate)-adenosine, and 5'-(3"-deoxy- β -D-ribofuranosyl)-3'-deoxyadenosine; (3) ergosta-7,22-dien-3 β ,5 α -dihydroxy-6-one; (4) cordycepinosalt A; (5) pentostatin; and (6) cordyrrole B. **[Conclusion]** This study integrates literature review and bioinformatics analysis to predict potential anti-lung cancer quality markers of *C. militaris*. The suggested mechanisms and candidate components are theoretical and need further experimental validation to confirm their effectiveness. This work offers a reference for developing a quality standard system of *C. militaris* for anti-lung cancer applications.

Keywords: *Cordyceps militaris*; lung cancer; quality markers; network pharmacology; molecular docking

肺癌是全球癌症相关死亡的首要原因, 占所有癌症类型的 12.4%, 每年新增病例约 250 万例, 死亡病例约 180 万例, 我国肺癌的发病率和死亡率均居恶性肿瘤首位^[1]。肺癌主要分为非小细胞肺癌(non-small cell lung cancer, NSCLC)和小细胞肺癌(small cell lung cancer, SCLC), 分别约占 85% 和 15%; 其中 NSCLC 分为非鳞状组织亚型(78%)和鳞状组织亚型(22%)等^[2]。目前, 顺式-二氯二氨合铂(顺铂)、吉非替尼和紫杉醇等细胞毒性化合物是肺癌的一线治疗药物, 但此类药物常抑制机体造血和免疫功能, 造成器官损伤, 并且易引发治疗抵抗和耐药性等不良反应^[3]。因此, 开发安全有效、不良反应少的新型干预策略具有重要的临床意义。

蛹虫草(*Cordyceps militaris*)为虫草属真菌, 已被国家卫生健康委批准为新资源食品(2009 年第 3 号公告, <https://www.nhc.gov.cn/sps/c100088/200903/fba61d8752a1442582ecd037aad429b7.shtml>), 并于 2014 年取消食用量限制(2014 年第 10 号公告, <https://www.nhc.gov.cn/wjw/c100175/201406/91642abf69674c4fa872b56096a1027c.shtml>)。以蛹虫草菌粉为主要成分的胶囊制剂(国药准字

Z20030035)具有补肺益肾、止咳化痰之功效, 已获批上市, 表明蛹虫草在食品和医药领域具有广阔的应用前景。研究表明, 蛹虫草特异性合成的活性成分虫草素(cordycepin)可诱导肺癌细胞凋亡, 并抑制增殖与转移^[4], 但其细胞毒性显著低于顺铂、安罗替尼和依托泊苷等化疗药物^[5]。目前, 常州市第一人民医院已开展程序性死亡受体 1 (programmed death 1, PD-1)抗体联合虫草素治疗 NSCLC 的 I 期临床试验^[6]。本文系统综述了蛹虫草化学成分抗肺癌药理作用的研究进展, 基于中药质量标志物理论, 整合智人(*Homo sapiens*)肺癌微阵列数据、网络药理学和分子对接技术, 对蛹虫草抗肺癌的潜在质量标志物进行初步预测, 以期为候选质量标志物的筛选提供参考。

1 蛹虫草中已鉴定化学成分

以“蛹虫草”“YONGCHONGCAO”“*Cordyceps militaris*”为关键词, 检索天然产物数据库[Natural Products Atlas (NPAtlas), <https://www.npatlas.org>]、中药系统药理学数据库与分析平台[Traditional Chinese Medicine Systems

Pharmacology (TCMSP), <https://www.tcm-sp-e.com>], 标准中医药数据库[Traditional Chinese Medicine Bank (TCMBank), <https://tcmbank.cn>]、中医药信息数据库[Traditional Chinese Medicine Information Database (TCM-ID), <https://bidd.group/TCMID>]、本草祖鉴(HERB, <http://herb.ac.cn>)、ETCM (<http://www.tcmip.cn/ETCM2/front>)、Web of Science、中国知网(China National Knowledge Infrastructure, CNKI)数据库, 合并去重后获得已鉴定化学成分。通过 PubChem 或 OSRA (<https://cactus.nci.nih.gov/cgi-bin/osra/index.cgi>) 获取简化分子线性输入规范(simplified molecular input line entry system, SMILES)表达式, 利用药物代谢动力学(pharmacokinetics, SwissADME, <http://www.swissadme.ch>)和 Molsoft (<https://molsoft.com/mprop>)数据库筛选口服生物利用度(oral bioavailability, OB) ≥ 0.30 、类药性(drug-likeness, DL) ≥ 0.18 、分子量 < 500 的化学成分; 随后对实验材料进行溯源分析, 排除洛伐他汀、维生素等缺乏蛹虫草合成特异性或易受培养条件影响的广谱性化合物, 最终获得 37 种化学成分, 原始数据存储在科学数据库[Science Data Bank (ScienceDB), <https://scidb.cn>], 编号为 31253.11.sciencedb.j00231.00048, 本文遴选的化合物与 ID 对应关系数据见 ScienceDB。

2 蛹虫草抗肺癌的药理作用

2.1 化学成分的药理作用

对上述 37 种化学成分进行文献检索, 发现虫草素具有明确的抗肺癌活性。虫草素的作用机制主要包括: (1) 抑制一氧化氮合酶(nitric oxide synthase, NOS)、一氧化氮(nitric oxide, NO)、细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)、糖原合成酶激酶 3 β (glycogen synthase kinase 3 β , GSK-3 β)、锌指转录因子 SLUG、B 细胞淋巴瘤/白血病-2 (B-cell lymphoma/leukemia-2, BCL-2)家族 X 蛋白(BCL-2-

associated X protein, BAX)、半胱氨酸天冬氨酸蛋白酶 3 (cysteine aspartate protease 3, CASPASE-3)、聚腺苷二磷酸核糖聚合酶[poly (ADP-ribose) polymerase, PARP]信号通路, 诱导 NSCLC 的 A549 细胞凋亡^[7]; (2) 结合表皮生长因子受体(epidermal growth factor receptor, EGFR)酪氨酸激酶活性中心, 阻断 EGFR 磷酸化, 使 H1975 细胞阻滞于 G₀/G₁ 期^[8]; (3) 下调基质金属蛋白酶(matrix metalloproteinase, MMP)-2 和 MMP-9 表达水平, 抑制 CL1-0 细胞转移^[9]; (4) 抑制酪氨酸激酶活性, 阻碍 A549 和 Calu-3 细胞增殖^[10]; (5) 上调 BAX 和活化型 CASPASE-3 表达, 同时下调 MMP-9 和 BCL-2 表达, 抑制 H1781 细胞迁移并诱导凋亡^[11]; (6) 显著抑制 SCLC 细胞在斑马鱼模型中的脑转移^[5]。此外, 虫草素可激活腺苷酸活化蛋白激酶(adenosine monophosphate-activated protein kinase, AMPK)并抑制蛋白激酶 B 通路, 在体内外 NSCLC 模型中发挥抑制增殖和诱导自噬的作用; 与顺铂联用具有协同增效作用, 且对顺铂耐药细胞仍保持显著活性^[12]。

2.2 蛹虫草的药理作用

体内外实验结果表明, 蛹虫草具有显著的抗肺癌作用: (1) 显著抑制 NSCLC 的 BALB/c 裸鼠移植瘤生长^[13]; (2) 下调黏蛋白 MUC5B 表达, 抑制 A549 细胞增殖^[14]; (3) 下调 TCTN3 表达, 抑制 Hedgehog 信号通路, 进而诱导 NSCLC 细胞自噬^[15]; (4) 下调 H-Ras 表达, 抑制顺铂耐药 A549 细胞增殖并诱导自噬^[16]; (5) 降低 Bcl-2/Bax 比值, 下调细胞周期蛋白依赖性激酶 1 (cyclin-dependent kinase 1, CDK1)/cyclin B1 表达, 诱导 NCI-H292 和 A549 细胞凋亡并抑制其增殖^[17]。

3 蛹虫草网络药理学研究

基于前述蛹虫草化学成分及药理作用的系统整理, 本研究采用网络药理学与分子对接技术筛选具有潜在抗肺癌活性的化学成分, 为质

量标志物的预测提供科学依据。

3.1 蛹虫草干预肺癌的靶点预测

将前述筛选的 37 种化学成分 SMILES 表达式分别导入 SwissTargetPrediction 数据库(<http://www.swisstargetprediction.ch>), 筛选 Probability>0 的智人靶点。设置纳入条件为“lung cancer”“*Homo sapiens*”、样本数>3, 同时包含肺癌与配对健康肺组织, 通过美国国家生物技术信息中心(National Center for Biotechnology Information, NCBI)基因表达综合数据库[Gene Expression Omnibus (GEO), <https://www.ncbi.nlm.nih.gov/geo/>]并借助 GEO2R 工具, 在每个微阵列数据集中筛选校正 P 值(P_{adjusted})<0.05 且 $|\log_2 \text{fold change}|>2$ 的肺癌与配对健康肺组织间差异表达基因(上调/下调)(图 1): GSE21933 (297/500)、GSE12236 (316/693)、GSE27262 (159/299)、GSE22863 (11/160)、GSE149507 (321/280)、GSE19804 (40/150)、GSE43458 (12/34)、GSE32665 (39/66)、GSE32863 (31/156)、GSE151103 (45/89)、GSE118370 (100/284), 合并去重后作为肺癌靶点。利用人类基因命名委员会(HUGO Gene Nomenclature Committee, HGNC)数据库(<https://www.genenames.org>)将靶点转换为正式基因名, 取化学成分与肺癌的交集靶点绘制韦恩图(图 2), 最终获得蛹虫草干预肺癌的 77 个交集靶点。

3.2 PPI 网络分析

将交集靶点导入 STRING 数据库, 设置物种为“*Homo sapiens*”, 将输出的蛋白质互作网络(protein-protein interaction network, PPI)数据导入 Cytoscape 3.10.2 软件, 保留连接度大于中位数的靶点, 共筛得 36 个候选靶点, 构建 PPI 网络(图 3)。其中连接度较高的靶点主要包括白细胞介素(interleukin, IL)-6、MMP9、(prostaglandin-endoperoxide synthase 2, PTGS2)、过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptor, PPARG)、Zeste 基因增强子同源物 2

(enhancer of Zeste homolog 2, EZH2)、血管紧张素转换酶 1 (angiotensin I converting enzyme, ACE)、细胞间黏附分子 1 (intercellular adhesion molecule 1, ICAM1)、Toll 样受体 4 (Toll-like receptor 4, TLR4)、CDK1、细胞周期蛋白 A2 (cyclin A2, CCNA2)及细胞周期蛋白 B1 (cyclin B1, CCNB1)。

3.3 核心靶点的富集通路分析

利用 NCBI 数据库注释、可视化和集成发现(database for annotation, visualization and integrated discovery, DAVID)数据库对候选靶点进行京都基因与基因组百科全书(Kyoto encyclopedia of genes and genomes, KEGG)通路(图 4A)和基因本体论(gene ontology, GO)功能(图 4B)富集分析。KEGG 富集共获得 24 条通路, 其中 13 条与肺癌相关, 主要涉及癌症、细胞周期、炎症及免疫等通路。GO 分析共获得 124 项功能, 其中 30 项功能与肺癌相关, 主要包括生物过程(biological process, BP)中的细胞外基质组织(extracellular matrix organization)、有丝分裂细胞周期 G_1/G_S 和 G_2/M 期转换(G_1/G_S and G_2/M transition of mitotic cell cycle)、细胞分裂(cell division)、免疫应答(immune response)、细胞凋亡过程的正调控(positive regulation of apoptotic process)、淋巴细胞增殖(lymphocyte proliferation)、基于微管的过程调控(regulation of microtubule-based process)、信号传导及转录激活蛋白(signal transducer and activator of transcription, STAT)介导的细胞表面受体信号(cell surface receptor signaling via STAT), 及细胞组成(cellular component, CC)的纺锤体微管(spindle microtubule)、细胞外基质、微管组织中心(microtubule organizing center)、有丝分裂纺锤体(mitotic spindle)、纺锤体极(spindle pole)、外泌体(extracellular exosome)、细胞周期蛋白 A2 或 B1 与周期蛋白依赖性激酶 1 的复合体(cyclin A2 or B1-CDK1 complex)、中间体(midbody), 以

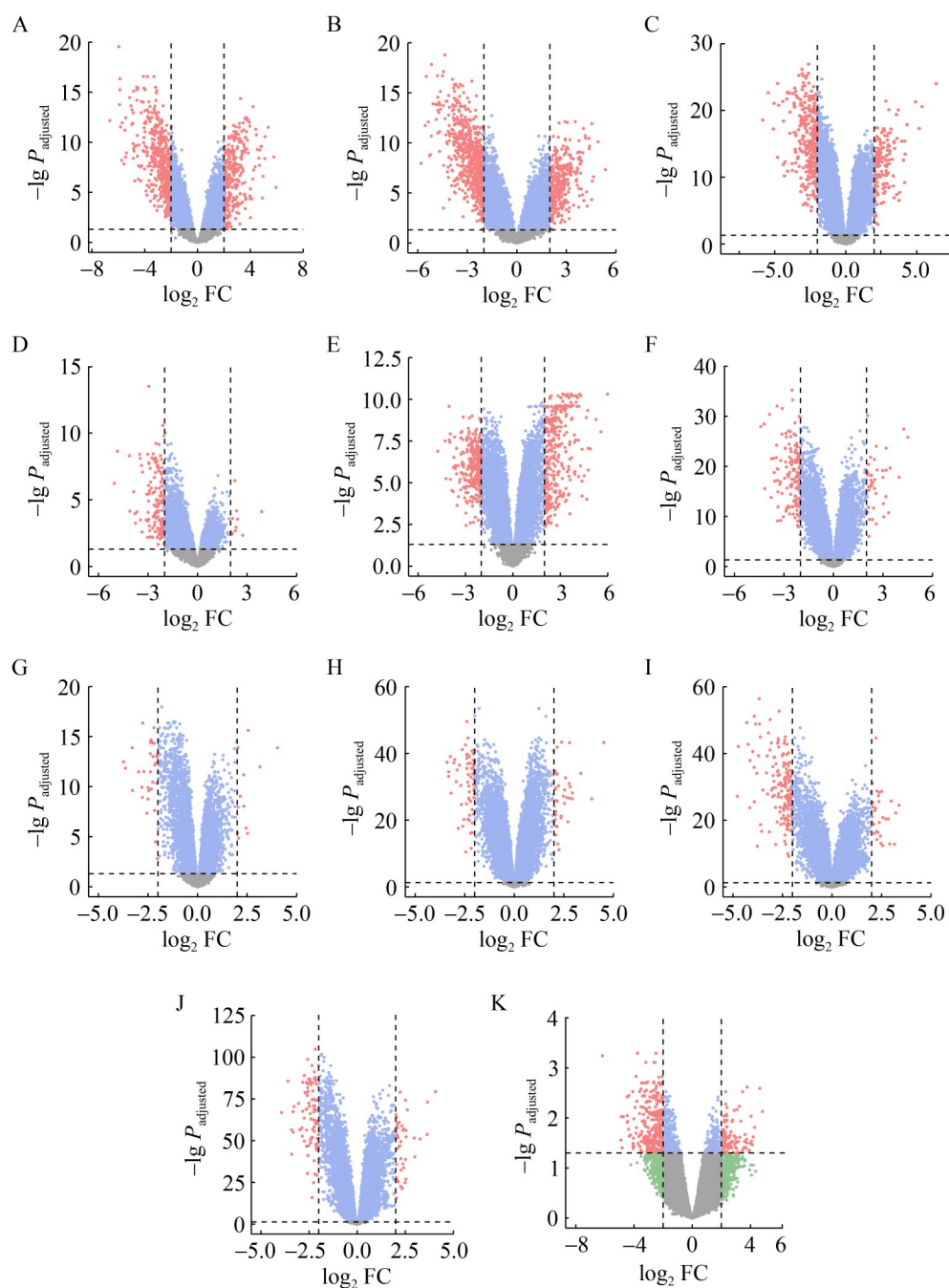


图1 微阵列数据分析火山图(肺癌组织对比配对健康肺组织)

Figure 1 Volcano plot of microarray data analysis (lung cancer tissues versus paired healthy lung tissues). A: GSE21933; B: GSE12236; C: GSE27262; D: GSE22863; E: GSE149507; F: GSE19804; G: GSE43458; H: GSE32665; I: GSE32863; J: GSE151103; K: GSE118370. Axes show adjusted P -values and $\log_2$ fold change (FC). Vertical dashed lines indicate $|\log_2 \text{FC}|=2$, and the horizontal dashed line represents the significance threshold at $-\lg 0.05$. Each circle denotes a gene; Red circles represent significantly upregulated ($\log_2 \text{FC}>2$) or downregulated ($\log_2 \text{FC}<-2$) genes in lung cancer tissues.

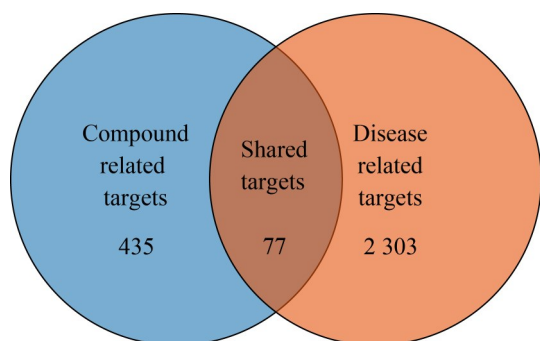


图2 蛹虫草化学成分介导干预肺癌的靶点
Figure 2 Targets of bioactive compounds from *Cordyceps militaris* for lung cancer intervention.

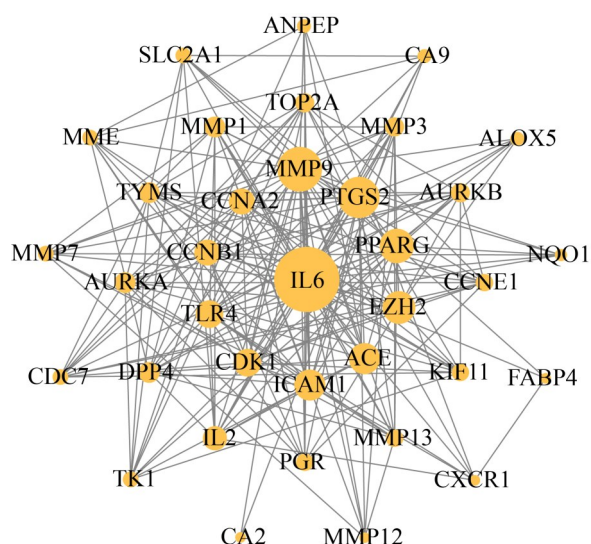


图3 蛹虫草候选靶点的PPI网络
Figure 3 PPI network of key targets of *Cordyceps militaris*. Each node represents a target, and node diameter corresponds to connectivity; Larger nodes indicate stronger interaction potential; Gray lines represent interactions between targets.

及分子功能(molecular function, MF)的金属和丝氨酸内肽酶活性(metallopeptidase and serine-type activity)、周期蛋白依赖性激酶调节活性(CDK regulator activity)、胶原结合(collagen binding)、丝氨酸蛋白激酶活性(protein serine kinase activity)、蛋白激酶结合(protein kinase binding)功能。

3.4 蛹虫草“成分-靶点-通路”网络构建

对图 3 数据进行拓扑分析, 筛选与肺癌关联的核心靶点。整合核心靶点对应的化学成分与通路信息, 导入 Cytoscape 3.10.2 软件, 构建“成分-靶点-通路”网络(图 5)。其中具有蛹虫草合成特异性的虫草素(C18)、喷司他丁(C23)、cordycepsisalt A (C31)、*O*⁵-乙酰基虫草素(C48)、5'-(3''-脱氧-β-D-呋喃核糖基)-虫草素(C4)、ergosta-7, 22-dien-3β, 5α-dihydroxy-6-one(C36)、*N*⁶-(4-甲基丁酸酯基)腺苷(C2)、*N*⁶-[β-(乙酰胺甲酰)氧乙基]腺苷(C47)及 cordyrrole B (C14)被筛选为核心成分, 可作为蛹虫草干预肺癌的潜在质量标志物候选, 对应核心靶点。

3.5 核心成分与核心靶点的分子对接预测分析

从蛋白数据库(Protein Data Bank, PDB)获取核心靶点及其内源配体的晶体复合物结构, 其他无复合物结构的靶点则采用特异性抑制剂, 如 CXC 趋化因子受体 1 (CXC chemokine receptor 1, CXCR1)采用 Reparixin。按表 1 设置网格参数, 对核心成分与核心靶点进行分子对接, 绘制结合自由能热图(图 6A), 结果显示所有核心成分与核心靶点的结合自由能均低于阈值-5 kJ/mol, 且接近对照(control), 提示存在潜在结合可能性; 其中 C48、C31 和 C14 与核心靶点的结合自由能均低于对照。研究已证实虫草素能显著下调肺癌细胞中 MMP9 的表达水平^[9,11], 因此利用 PyMOL 软件进行可视化预测, 结果显示虫草素与 MMP9 之间存在 7 条氢键作用(图 6B), 该复合体的结合自由能略高于对照但仍低于-5 kJ/mol。综上所述, 这些核心成分可为蛹虫草干预肺癌的候选质量标志物筛选提供参考。

4 蛹虫草干预肺癌的质量标志物预测分析

依据质量标志物提出原则^[20], 预测分析蛹

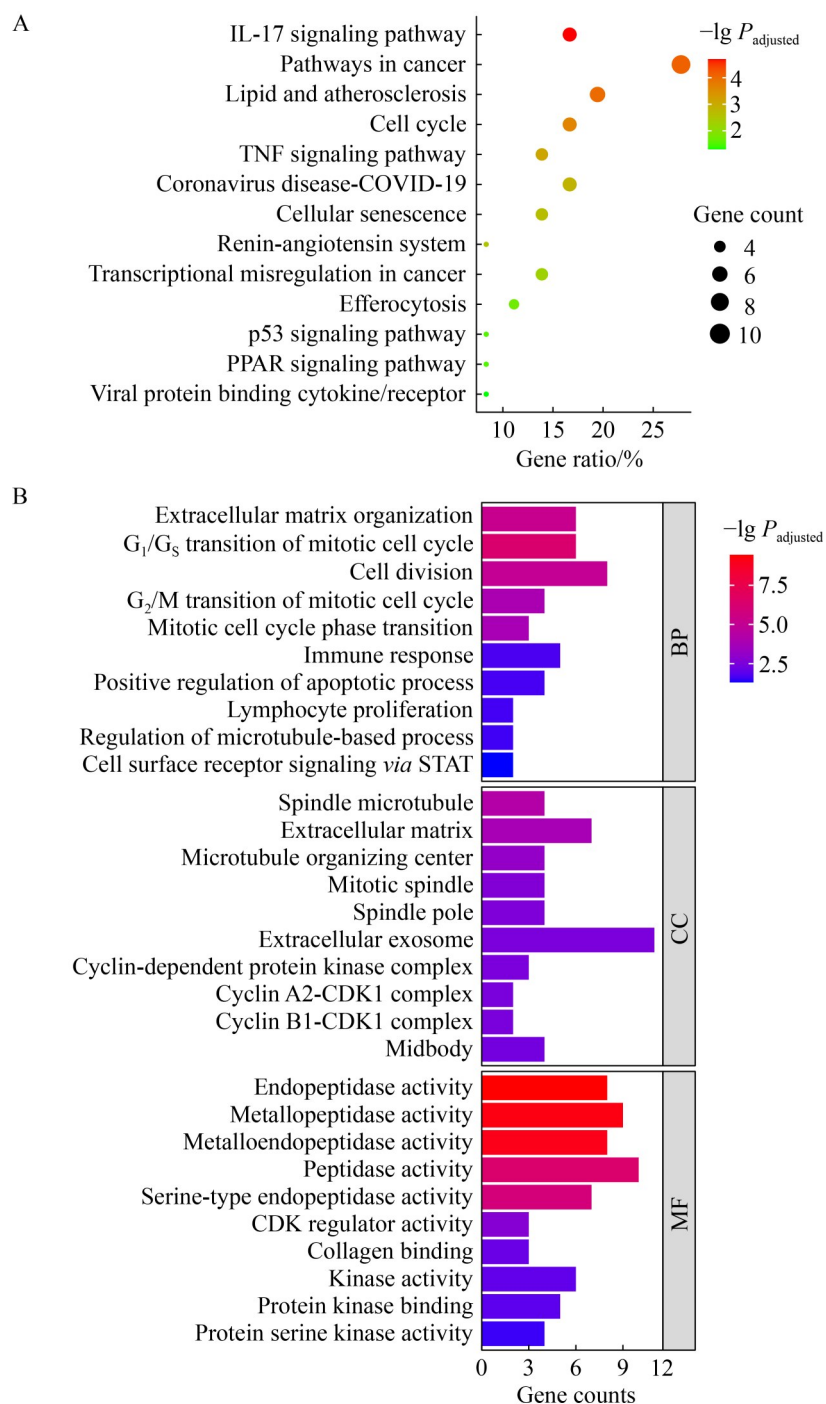


图4 KEGG和GO通路富集分析

Figure 4 KEGG and GO pathway enrichment analyses. A: KEGG; B: GO. The left vertical axis represents biological pathways, and the horizontal axis shows the percentage or number of enriched genes in each pathway. Each bubble denotes an enriched gene set, with its diameter proportional to the number of genes. Bubble and bar colors reflect $-\lg P_{\text{adjusted}}$, indicating enrichment reliability, with red representing higher reliability. BP, CC, and MF denote biological processes, cellular components, and molecular functions, respectively.

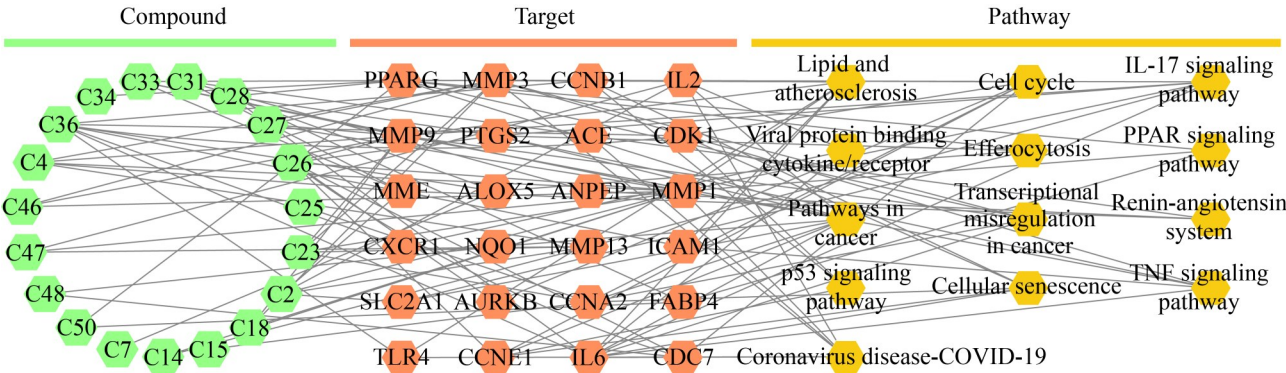


图5 蛹虫草干预肺癌“成分-靶点-通路”网络

Figure 5 “Compound-target-pathway” network for intervening lung cancer. Compound IDs are consistent with those in ScienceDB, and the same applies to the following content. Gray lines represent interactions among compounds, targets, and pathways. PPAR represents peroxisome proliferator-activated receptor.

表1 分子对接中核心靶点的网格参数

Table 1 Grid parameters of core targets in molecular docking

Core targets	Size (x/y/z)	Centre coordinates (x/y/z)	Core targets	Size (x/y/z)	Centre coordinates (x/y/z)
IL-2	30/48/34	0.84/14.03/−5.36	TLR4	80/94/118	13.64/4.53/52.74
IL-6	34/50/36	−6.60/−13.74/−1.58	ACE	36/44/50	40.31/32.91/47.02
MME	45/45/45	22.99/−46.51/16.13	ANPEP	36/38/46	107.22/18.09/21.40
MMP1	44/44/36	27.13/42.73/−2.07	CDC7	39/39/39	21.19/19.11/58.46
MMP3	30/30/52	−0.06/50.67/55.06	ICAM1	60/76/90	11.22/−3.83/−0.99
MMP9	30/36/36	19.45/−17.02/21.21	CDK2-CCNA2	39/39/39	−12.26/7.56/34.33
MMP13	36/36/36	9.99/16.59/19.68	CDK1-CCNB1	45/45/49	29.00/−71.54/184.67
NQO1	38/58/64	17.77/−9.99/−3.56	CXCR1	51/51/80	105.40/101.74/127.46
SLC2A1	38/42/38	580.80/−25.64/280.55	ALOX5	50/40/50	34.16/66.12/38.16

NQO1: NAD(P)H quinone dehydrogenase 1; SLC2A1: Solute carrier family 2 member 1; ANPEP: Alanyl aminopeptidase; CDC7: Cell division cycle 7; ALOX5: Arachidonate 5-lipoxygenase.

虫草干预肺癌的质量标志物，为建立蛹虫草功能食品和药品质量标准提供参考。

4.1 不同基源的质量标志物预测分析

虫草素与喷司他丁为蛹虫草的标志性成分。研究表明，子实体中虫草素含量显著高于菌丝体，且以活体蚕蛹培育的子实体中虫草素含量显著高于其他培养基^[21]；喷司他丁则仅存在于子实体中^[22]。上述差异可作为区分蛹虫草有性型(子实体)与无性型(菌丝体)基源的参考依据。此外，不同产地蛹虫草子实体中虫草素、腺苷及麦角甾醇含量存在显著差异^[23]。高效液相色谱

谱指纹图谱分析显示，不同来源菌株育成的子实体均可检出虫草素、*N*⁶-(2-羟乙基)-腺苷(即本文化合物 C51)、腺苷及麦角甾醇等特征性成分^[24]，提示 *N*⁶-(2-羟乙基)-腺苷、腺苷及麦角甾醇可作为潜在质量标志物。

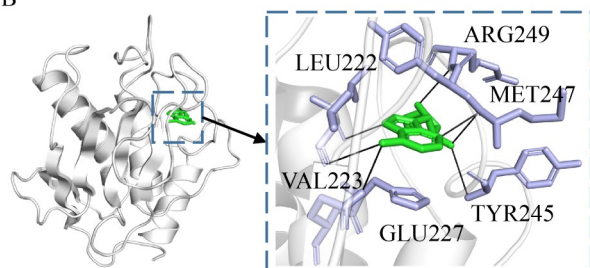
4.2 基于中药理论和药效关联性的预测分析

中医理论认为，肺癌属“肺肾两虚”之证，主要因“正气不足、久病缠绵、耗伤正气、致痰湿、瘀血”等病理产物积聚而成瘤。故治当“扶

A

	IL-2	IL-6	MME	MMP1	MMP3	MMP9	MMP13	NQO1	SLC2A1	TLR4	ACE	ANPEP	CDC7	ICAM1	CDK2-CCNA2	CDK1-CCNB1	CXCR1	ALOX5
C48	-8.90 (0.05)	-9.01 (0.31)	-11.76 (0.41)	-10.11 (0.03)	-11.44 (0.02)	-12.18 (0.01)	-11.93 (0.01)	-8.83 (0.14)	-10.09 (0.06)	-8.14 (0.31)	-10.46 (0.25)	-10.99 (0.33)	-10.70 (0.09)	-8.01 (0.02)	-10.41 (0.01)	-10.58 (0.03)	-9.15 (0.04)	-11.32 (0.01)
C47	-5.79 (0.12)	-5.84 (0.24)	-8.33 (0.15)	-7.60 (0.24)	-8.19 (0.32)	-8.68 (0.13)	-8.79 (0.10)	-6.76 (0.17)	-8.51 (0.29)	-6.26 (0.19)	-7.70 (0.27)	-8.63 (0.13)	-7.74 (0.37)	-5.84 (0.23)	-7.49 (0.13)	-7.66 (0.15)	-6.82 (0.31)	-7.51 (0.21)
C36	-6.69 (0.19)	-6.50 (0.03)	-8.64 (0.21)	-7.68 (0.02)	-9.72 (0.65)	-8.82 (0.06)	-8.65 (0.02)	-7.62 (0.15)	-10.86 (0.32)	-7.44 (0.27)	-10.39 (0.04)	-10.04 (0.01)	-7.56 (0.18)	-6.37 (0.20)	-8.58 (0.18)	-8.13 (0.49)	-8.73 (0.09)	-8.74 (0.85)
C31	-9.75 (0.02)	-9.11 (0.01)	-11.77 (0.01)	-11.41 (0.01)	-12.34 (0.02)	-12.68 (0.02)	-12.57 (0.01)	-9.27 (0.04)	-10.56 (0.02)	-9.42 (0.15)	-11.81 (0.01)	-11.68 (0.02)	-10.96 (0.03)	-9.11 (0.03)	-11.46 (0.01)	-10.86 (0.13)	-12.76 (0.01)	-12.03 (0.01)
C23	-5.41 (0.01)	-5.63 (0.07)	-7.61 (0.15)	-6.60 (0.15)	-7.11 (0.44)	-7.66 (0.37)	-7.52 (0.11)	-6.60 (0.01)	-7.57 (0.02)	-6.36 (0.02)	-7.32 (0.10)	-7.89 (0.01)	-6.97 (0.05)	-5.68 (0.04)	-7.07 (0.02)	-7.24 (0.03)	-6.50 (0.00)	-6.99 (0.08)
C18	-5.35 (0.08)	-5.03 (0.07)	-7.70 (0.01)	-6.72 (0.09)	-7.78 (0.20)	-8.18 (0.28)	-7.95 (0.02)	-6.19 (0.04)	-7.33 (0.01)	-6.12 (0.21)	-7.04 (0.00)	-7.73 (0.03)	-7.03 (0.02)	-5.34 (0.27)	-7.64 (0.02)	-7.75 (0.01)	-6.59 (0.01)	-7.43 (0.39)
C14	-9.25 (0.07)	-9.28 (0.28)	-12.68 (0.01)	-11.46 (0.02)	-13.43 (0.01)	-13.81 (0.05)	-13.84 (0.01)	-10.74 (0.12)	-11.74 (0.02)	-9.32 (0.15)	-11.72 (0.05)	-11.75 (0.23)	-11.59 (0.01)	-8.59 (0.02)	-11.87 (0.02)	-12.47 (0.13)	-10.44 (0.03)	-12.35 (0.01)
C4	-5.89 (0.02)	-6.00 (0.15)	-8.67 (0.74)	-7.38 (0.28)	-9.22 (0.25)	-8.74 (0.05)	-8.58 (0.17)	-6.59 (0.23)	-8.57 (0.36)	-6.87 (0.27)	-7.91 (0.19)	-8.78 (0.03)	-7.32 (0.61)	-5.79 (0.31)	-8.21 (0.02)	-8.36 (0.08)	-6.81 (0.27)	-8.20 (0.08)
C2	-5.64 (0.11)	-5.28 (0.15)	-7.99 (0.14)	-6.92 (0.13)	-7.84 (0.11)	-8.40 (0.15)	-8.77 (0.09)	-6.38 (0.14)	-8.35 (0.17)	-5.92 (0.21)	-7.57 (0.19)	-8.33 (0.17)	-7.40 (0.27)	-5.56 (0.14)	-7.71 (0.20)	-7.87 (0.12)	-6.38 (0.23)	-7.69 (0.23)
Control	-7.80 (0.31)	-5.01 (0.69)	-7.35 (0.07)	-7.27 (0.21)	-9.44 (0.05)	-8.74 (0.53)	-8.42 (0.11)	-8.36 (0.45)	-9.75 (0.06)	-5.27 (0.08)	-7.46 (0.15)	-7.77 (0.11)	-9.76 (0.01)	-5.16 (0.52)	-8.21 (0.01)	-9.45 (0.02)	-6.47 (0.11)	-7.44 (0.75)
PDB ID	1M48	1ALU	6SUK	1CGL	1HY7	4XCT	5B5O	1D4A	5EQG	2Z65	1O86	4FYR	6YA6	5MZA	7ACK	4Y72	-	6N2W
Binding energy/(kJ/mol)																		
-5 -6 -8 -10 -12 -14																		

B



C

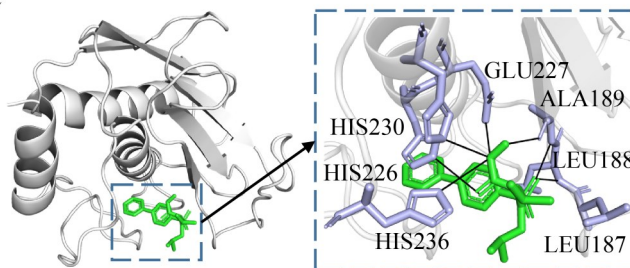


图6 蛹虫草核心成分与核心靶点的分子对接结果

Figure 6 Docking results between core compounds and core targets in *Cordyceps militaris*. A: Binding free energies; B: Cordycepin-MMP9 complex; C: N73-MMP9 complex. Panel A displays binding free energies, with the vertical axis showing core component IDs, endogenous ligands, and PDB IDs, while the upper horizontal axis indicates core targets; Colored blocks represent binding free energy [mean (SD)], where red signifies lower values. Panels B and C highlight the local hydrogen bonding of the complexes. Core components and targets were preprocessed in Discovery Studio 2019, including hydrogenation, residue repair, etc. Docking was performed using AutoDock Vina 1.2.5 in Dockey software^[18], with ten independent runs and nine conformations per component-target pair. The binding free energy, used as the evaluation metric, was derived from intermolecular interactions including hydrogen bonding, hydrophobic effects, and others, employing empirical weighting from AutoDock Vina^[19].

正”以增强免疫力，“祛邪”以抑制肿瘤生长。《新华本草纲要》记载，蛹虫草归肺、肾经，味甘、性平，具补肺益肾、止咳化痰之功，此亦

为蛹虫草菌粉胶囊(国药准字 Z20030035)的主治功效。体外研究表明，蛹虫草代谢产物虫草素与腺苷可显著下调 IL-6、IL-1 β 及肿瘤坏死因子

α (tumor necrosis factor- α , TNF- α)的表达水平,抑制人肺上皮细胞 BEAS-2B 炎症反应^[25]。此外,基于百令胶囊补肺益肾功效的成分图谱分析,腺苷被认为具有补肺益肾作用^[26]。综上所述,虫草素与腺苷可作为蛹虫草抗肺癌的潜在质量标志物。

4.3 基于成分可测的质量标志物预测分析

成分可测性是质量标志物筛选的重要依据。目前,色谱法为中药有效成分定量检测的主要手段,可为质量标准制定提供科学依据。已有研究采用高效液相色谱法同时测定蛹虫草中虫草素、腺苷及麦角甾醇的含量。色谱-质谱联用技术可实现已知及未知化合物的全面分析,有研究联合超高效液相色谱-质谱与气相色谱-质谱技术,分析蛹虫草子实体干品在6个月冷藏过程中的风味物质变化,结果显示差异代谢物以有机酸和核苷类化合物为主,其中腺苷含量下降71.5%,而虫草素未被纳入差异代谢物^[27],提示虫草素在贮藏过程中稳定性较好。因此,虫草素可作为可靠性较高的潜在质量标志物。

5 总结与展望

本文系统梳理了蛹虫草抗肺癌的国内外研究进展,目前已证实蛹虫草及其活性成分虫草素在体外和体内均具有抗肺癌功效,虫草素是蛹虫草抗肺癌的重要质量标志物候选,但仍需通过临床试验进一步验证。在此基础上,借助网络药理学等多种生物信息学分析手段并整合已鉴定化合物,本文预测筛选了蛹虫草抗肺癌的候选质量标志物:(1)虫草素及虫草素类似物 O^5 -乙酰基虫草素;(2)腺苷及腺苷类似物 N^6 -[β -(乙酰胺甲酰)氧乙基]腺苷、 N^6 -(2-羟乙基)腺苷、 N^6 -(4-甲基丁酸酯基)腺苷、5'-(3"-脱氧- β -D-呋喃核糖基)-虫草素;(3) ergosta-7,22-dien-3 β ,5 α -dihydroxy-6-one;(4) cordycepinosalt

A;(5) 喷司他丁;(6) cordyrolle B。上述化合物可为抗肺癌候选质量标志物的筛选提供参考,但仍需更多实验验证其有效性。

本文网络药理学与分子对接结果存在以下局限性:(1)虽本文总结的成分均源自文献报道的蛹虫草内源性组分,但部分成分可能来源于培养基质或受培养条件影响;(2)本文选取的微阵列数据虽具有代表性,但差异表达基因与肺癌的相关性受组织样本异质性影响,部分靶点可能具有组织特异性,因此GO和KEGG富集分析中存在一定非特异性通路;(3)网络药理学主要依赖文献、数据库及分子对接模拟进行理论预测,对成分有效性及靶点特异性缺乏实验验证,尚需结合其他预测方法及实验技术加以补充;(4)分子对接基于模拟算法预测成分与靶点的结合模式,仍需通过体内外实验进一步验证;(5)本研究为基于文献整合与生物信息学分析的预测性研究,所提出的作用机制和候选成分仍属于有待实验验证的假说,尚需深入研究以明确其有效性。

蛹虫草兼具食用和药用价值,应用领域广泛,但目前尚缺乏完备的质量评价体系及国家标准。未来需继续扩充蛹虫草的质量标志物,深入探究其有效性、安全性和药理作用机制,进而推动蛹虫草产业的高质量发展。

作者贡献声明

秦鹏:研究方案的制定,文献检索与遴选,微阵列数据筛选,网络药理学分析,分子对接,数据统计与分析,初稿撰写与返修;王治业:创新点与研究思路的提出,文献数据的一致性检查,微阵列数据质量审查,网络药理学分析,分子对接,初稿与返修稿件的审查。

作者利益冲突公开声明

作者声明不存在任何可能会影响本文所报告工作的已知经济利益或个人关系。

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