

黄藤素对CCl₄致大鼠急性肝损伤的防治作用研究

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摘要

目的: 评价黄藤素(palmatine, Pal)对四氯化碳(CCl₄)诱导的大鼠急性肝损伤(ALI)的保护作用, 初步探究其潜在靶点。方法: 将48只大鼠随机分为正常对照组(NS)、模型组(CCl₄)、低剂量Pal组(Pal-L, 5 mg/kg)、中剂量Pal组(Pal-M, 10 mg/kg)、高剂量Pal组(Pal-H, 20 mg/kg)和地塞米松组(DEX, 10 mg/kg)腹腔注射5, 10, 20 mg/kg的Pal, 每天一次, 连续三天, NS组和CCl₄组的大鼠腹腔注射给予等体积的生理盐水。Pal处理组的大鼠最后一次给药1小时后, CCl₄组和Pal处理组的大鼠腹腔注射25%的CCl₄花生油溶液(3 ml/kg), NS组的大鼠腹腔注射相同体积的溶剂。各组造模后开始计时, 给予CCl₄ 24小时后处理所有大鼠, 收集血清和肝组织, 检测肺组织病理形态变化, 评估肝损伤指标ALT和氧化应激指标MDA含量。网络药理学方法初步探究黄藤素抗急性肝损伤的潜在靶点。结果: Pal预处理剂量依赖性减轻CCl₄诱导的急性肝损伤, 表现为降低血清天冬氨酸转氨酶(AST)活性, 抑制肝脏病理损伤。此外, Pal通过恢复丙二醛(MDA)水平来缓解CCl₄引发的氧化应激和炎症反应。结论: 黄藤素能够通过抑制炎症反应和氧化应激减轻急性肝损伤, STAT3可能是黄藤素发挥肝脏保护作用最具潜力的靶点。

关键词

黄藤素, 急性肝损伤, 氧化应激, 炎症, 网络药理学

Preventive and Therapeutic Effects of Berberine on Acute Liver Injury Induced by CCl₄ in Rats

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Abstract

Objective: To evaluate the protective effect of palmatine (Pal) against carbon tetrachloride (CCl₄)-induced acute liver injury (ALI) in rats, and preliminarily explore the potential targets of palmatine. **Methods:** 48 rats were randomly divided into a normal control group (NS), a model group (CCl₄), a low dose Pal group (Pal-L, 5 mg/kg), a medium dose Pal group (Pal-M, 10 mg/kg), a high dose Pal group (Pal-H, 20 mg/kg), and a dexamethasone group (DEX, 10 mg/kg). Rats in the NS and CCl₄ groups were intraperitoneally injected with 5, 10, and 20 mg/kg of Pal once a day for three consecutive days. Rats in the NS and CCl₄ groups were given equal volumes of physiological saline by intraperitoneal injection. After the last administration of 1 hour, rats in the Pal-treated groups were intraperitoneally injected with 25% CCl₄ peanut oil solution (3 ml/kg), while rats in the NS group were intraperitoneally injected with the same volume of solvent. After modeling, each group began timing, and all rats were treated with CCl₄ 24 hours later. Serum and liver tissue were collected to observe the pathological and morphological changes in lung tissue and evaluate the liver injury index ALT and oxidative stress index MDA content. Network pharmacology methods were used to preliminarily explore the potential targets of palmatine in treating acute liver injury. **Results:** Pal pretreatment attenuated CCl₄-induced acute liver injury in a dose-dependent manner, manifested by a decrease in serum aspartate aminotransferase (AST) activity and inhibition of liver pathological damage. In addition, Pal alleviates oxidative stress and inflammatory responses induced by CCl₄ by restoring malondialdehyde (MDA) levels. **Conclusion:** Palmatine can alleviate acute liver injury by inhibiting inflammatory reactions and oxidative stress. STAT3 may be the most potential target for Palmatine to exert liver protective effects.

Keywords

Palmatine, Acute Liver Injury, Oxidative Stress, Inflammation, Network Pharmacology

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1. 引言

急性肝损伤(ALI)是指在短时间内由于各种原因导致的突发性肝细胞损伤和肝功能异常。ALI 通常是由病毒感染、药物或酗酒以及摄入有毒物质引起的[1] [2]。许多化学物质会导致肝损伤,临床上构建化学性肝损伤模型主要采用四氯化碳(CCl₄) [3]、对乙酰氨基酚(APAP) [4]、酒精(Alcohol) [5]和 α -萘异硫氰酸酯(ANIT) [6]等。ALI 与肝酶的快速减少有关,其机制涉及肝细胞变性、炎症反应、活性氧(ROS)、坏死和肝细胞凋亡的复杂相互作用[7]。ALI 可诱发一系列并发症,加重其他疾病的进展,应积极预防和治疗。大多数 ALI 患者在药物治疗后恢复,但有些患者会进展为急性肝衰竭[8],死亡率很高。在预防和治疗肝病方面,许多种中药(TCM)和中药提取物如黄连、牛蒡、枸杞等已被证明对肝脏保护有效[9] [10] [11],并已广泛应用于临床实践。许多中药具有疗效好、安全性好、实用性好等优点,因此,它们在疾病治疗、预防和保健领域受到了很大的关注。

黄藤素是一种天然的异喹啉生物碱,已广泛应用于制药领域。近年来,对黄藤素的药理作用进行了大量研究,包括抗癌[12]、抗菌[13]、抗病毒[14]、抗氧化[15]、抗炎[13]等。这些结果表明,黄藤素在预

防和治疗包括癌症[16][17]、心脏肥大[18]、骨质疏松症和骨关节炎[19][20]、糖尿病[21]等疾病方面具有价值。然而，黄藤素对于 CCl₄ 诱导的肝损伤是否有保护作用尚未见报道。本研究建立了 CCl₄ 诱导的大鼠肝损伤模型，评价了黄藤素对肝损伤的防治作用。

网络药理学是一门结合系统生物学和网络信息学的综合性学科，近年来在新药开发中得到了广泛的应用[22]，网络药理学旨在研究生物网络的关系，用于在系统水平上分析多组分药物对人体的作用，有助于我们找到药物有效成分的治疗靶点，提高药物的疗效，减少副作用。本研究采用网络药理学方法初步探究了黄藤素抗急性肝损伤的潜在靶点。

2. 材料和方法

2.1. 试剂

黄藤素注射液来自昆明制药集团股份有限公司产品，产品批号：14KV201-11，地塞米松注射液来自西南药业股份有限公司产品，产品批号：161006。用于测量血清和组织水平的 ALT 和 MDA 的试剂盒购自南京建成生物工程研究所(中国南京)。BCA 试剂盒购自 Beyotime Institute of Biotechnology (中国江苏)。

2.2. 动物来源与处理

SPF 级健康 SD 大鼠 48 只，雌雄各半，180~220 g，购于昆明医科大学实验动物学部[许可证号：SCXK(滇)K2020-0004]提供。大鼠在 18℃~22℃ (相对湿度 40%~60%)环境饲养，在正常照明条件下，并随意饮水。

将 48 只大鼠随机分为正常对照组(NS)、模型组(CCl₄)、低剂量 Pal 组(Pal-L, 5 mg/kg)、中剂量 Pal 组(Pal-M, 10 mg/kg)、高剂量 Pal 组(Pal-H, 20 mg/kg)和地塞米松组(DEX, 10 mg/kg)每组 8 只。NS 组和 CCl₄ 组的大鼠腹腔注射给予等体积的生理盐水，Pal 处理组的大鼠腹腔注射 5, 10, 20 mg/kg 的 Pal，每天一次，连续三天。

末次给药 1 小时后，CCl₄ 组和 Pal 处理组的大鼠腹腔注射 25%的 CCl₄ 花生油溶液(3 ml/kg)，NS 组的大鼠腹腔注射相同体积的溶剂。各组造模后开始计时，给予 CCl₄ 24 小时后处理所有大鼠，在处理前 24 小时禁食不禁水，处死前称大鼠体重，注射 1%戊巴比妥钠(30 mg/kg)麻醉大鼠，腹主动脉取血，以 1000 rpm 离心 10 分钟分离血清，用于检测血清 ALT 水平。沿腹部中线打开腹膜腔，小心分离取出肝脏，用冷盐水洗涤肝组织，部分组织用 80%中性甲醛固定进行组织病理学检查，部分组织制备匀浆用于其他指标检测。

2.3. 肝脏组织病理学分析

将肝组织样品固定在 10%中性甲醛中，用 PBS 洗涤并用酒精梯度洗脱。石蜡包埋后切成薄片。切片用二甲苯脱蜡，用酒精梯度洗脱洗脱，苏木精 - 伊红染色，再次用酒精梯度洗脱洗脱，用二甲苯澄清，加入中性树脂封片。在光显微镜下观察细胞形态的病理变化。

2.4. 肝组织 MDA 的检测

在大鼠肝组织中加入 10 倍量的生理盐水，在冰水浴中制备 10%的组织匀浆素。根据试剂盒说明书，采用酶法测定大鼠肝组织的 MDA 水平。

2.5. 血清 ALT 的检测

使用生化试剂盒测定大鼠血清中丙氨酸氨基转移酶(ALT)的活性。

2.6. 黄藤素抗 ALI 潜在靶点的获得

黄藤素的结构信息来自 PubChem 数据库(<https://pubchem.ncbi.nlm.nih.gov/>)，并将 SMILES 格式上

传至 Swiss Target Prediction 数据库(<http://www.swisstargetprediction.ch/index.php>)、pharm mapper 数据库(<http://www.lilab-ecust.cn/pharmmapper/>)中,以确定黄藤素的潜在靶点。此外,以“Acute liver injury”为关键词,利用 Gene Card 数据库(<https://genealacart.genecards.org/>)获得与 ALI 相关靶点。去除重复靶点后,黄藤素和 ALI 的共同靶点被认为是黄藤素抗 ALI 的潜在靶点。最后,绘制 Venny 图以获得交集靶点。

2.7. PPI 网络构建

为了找到黄藤素治疗 ALI 潜在靶点之间相互作用关系,我们通过 String11.0 数据库(<https://www.string-db.org/>),构建 PPI 的网络图。并将数据输入 Cytoscape 3.8.2 软件进行分析。网络图里的节点(nodes)表示靶点蛋白,边(edges)意味着蛋白相互之间存在的作用。在网络中程度值(degree)代表一个节点和另外的节点连接数量,程度值分数越高表明该节点越重要。

2.8. 数据分析

数据表示为平均值 \pm SD,使用 SPSS 17.0 统计软件行实验数据分析,并通过 GraphPad Prism v6.0 软件绘制柱状图。组间比较采用单因素方差分析(ANOVA)和 q 检验。 $P < 0.05$ 被认为差异具有统计学意义。

3. 结果

3.1. 黄藤素对 CCl_4 诱导急性肝损伤大鼠肝组织病理形态的影响

正常对照组大鼠肝组织结构正常, CCl_4 模型对照组大鼠肝组织有片状肝细胞坏死,坏死区边缘有大量气球样变性,同时伴有大量炎症细胞浸润;地塞米松组大鼠肝组织有弥漫性气球样变性和少量肝细胞坏死;Pal 低剂量组大鼠肝组织有片状肝细胞坏死,坏死区边缘有气球样变性,伴有炎症细胞浸润;Pal 中剂量组大鼠肝组织有局灶性肝细胞坏死,坏死区边缘可见气球样变性;Pal 高剂量组大鼠肝组织结构基本正常,局部有急性炎症细胞浸润和点状气球样变性,见图 1。

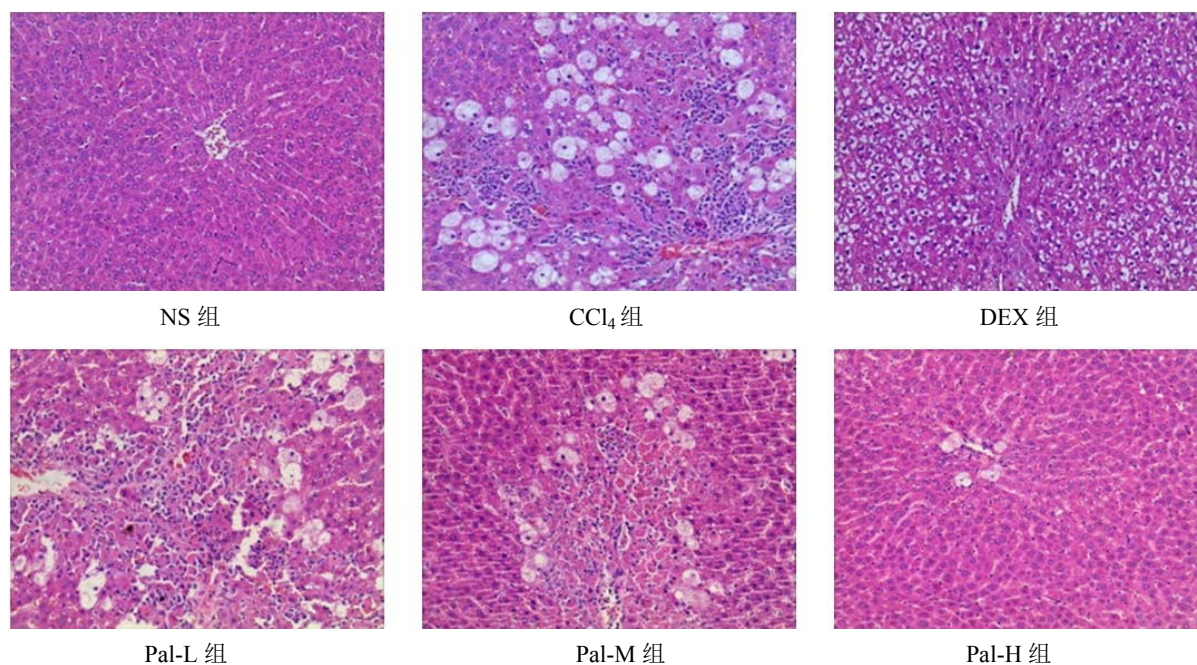


Figure 1. Pathological morphology of liver tissue ($\times 200$)

图 1. 肝组织病理形态($\times 200$)

3.2. 黄藤素对 CCl₄ 诱导急性肝损伤大鼠组织氧化应激指标 MDA 的影响

与正常组比较, CCl₄ 模型组 MDA 水平明显升高, 差异有统计学意义($P < 0.001$); 与 CCl₄ 模型组比较, 黄藤素各剂量组、地塞米松组的 MDA 有所下降, 差异有统计学意义($P < 0.001$), 见图 2。

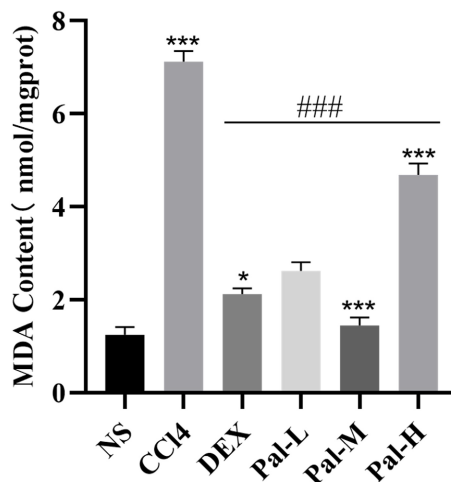


Figure 2. The effect of Palmatine on MDA levels. Compared with the NS group, * $P < 0.05$, *** $P < 0.001$, and compared with the CCl₄ group, ### $P < 0.001$

图 2. 黄藤素对肝组织 MDA 的影响。与 NS 组比较, * $P < 0.05$, *** $P < 0.001$, 与 CCl₄ 组比较, ### $P < 0.001$

3.3. 黄藤素对 CCl₄ 诱导急性肝损伤大鼠生化指标 ALT 的影响

与正常组比较, CCl₄ 模型组、黄藤素各剂量组的血清中 ALT 的活性明显升高($P < 0.001$), 表明 CCl₄ 致大鼠肝损伤造模成功。而与 CCl₄ 模型组比较, 黄藤素各剂量组和地塞米松组血清中 ALT 活性都明显下降($P < 0.001$), 有统计学意义; 说明黄藤素对 CCl₄ 致急性肝损伤有一定治愈作用。见图 3。

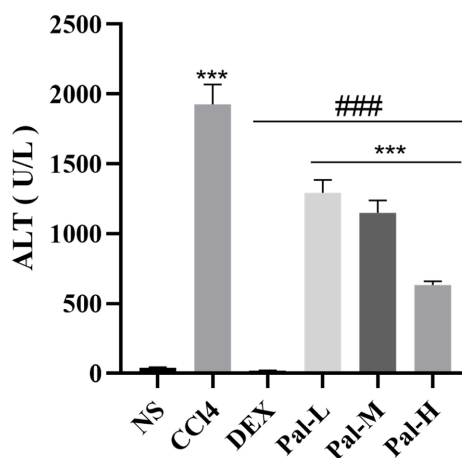


Figure 3. The effect of Palmatine on alanine aminotransferase levels compared with NS group, *** $P < 0.001$, compared with CCl₄ group, ### $P < 0.001$

图 3. 黄藤素对丙氨酸转氨酶水平的影响。与 NS 组比较, *** $P < 0.001$, 与 CCl₄ 组比较, ### $P < 0.001$

3.4. 黄藤素抗 ALI 靶点的获取和筛选结果

我们通过 Swiss Target Prediction、pharm mapper 数据库, 去重后共预测得到 227 个黄藤素目标靶点。同时, 以“Acute liver injury”为关键词, 在 GeneCard 数据库检索筛选后共检索出 2077 个 ALI 相关靶点。经韦恩图取交集共得到 67 个黄藤素治疗 ALI 的交集靶点(图 4B)。随后, 利用 STRING 数据库构建了蛋白-蛋白相互作用(PPI)网络分析(图 4C)。结果发现, 共有 67 个节点, 403 条边, 平均度值为 12。继而将 TSV 格式数据文件导入 Cytoscape 3.8.2 软件, 得到 20 个核心靶点, 包括度值排名前 10 的潜在靶点依次为 STAT3, ALB, MMP9, CCND1, MTOR, ERBB2, CDC42, MDM2, CDK4 与 PIK3CB(图 4D)。

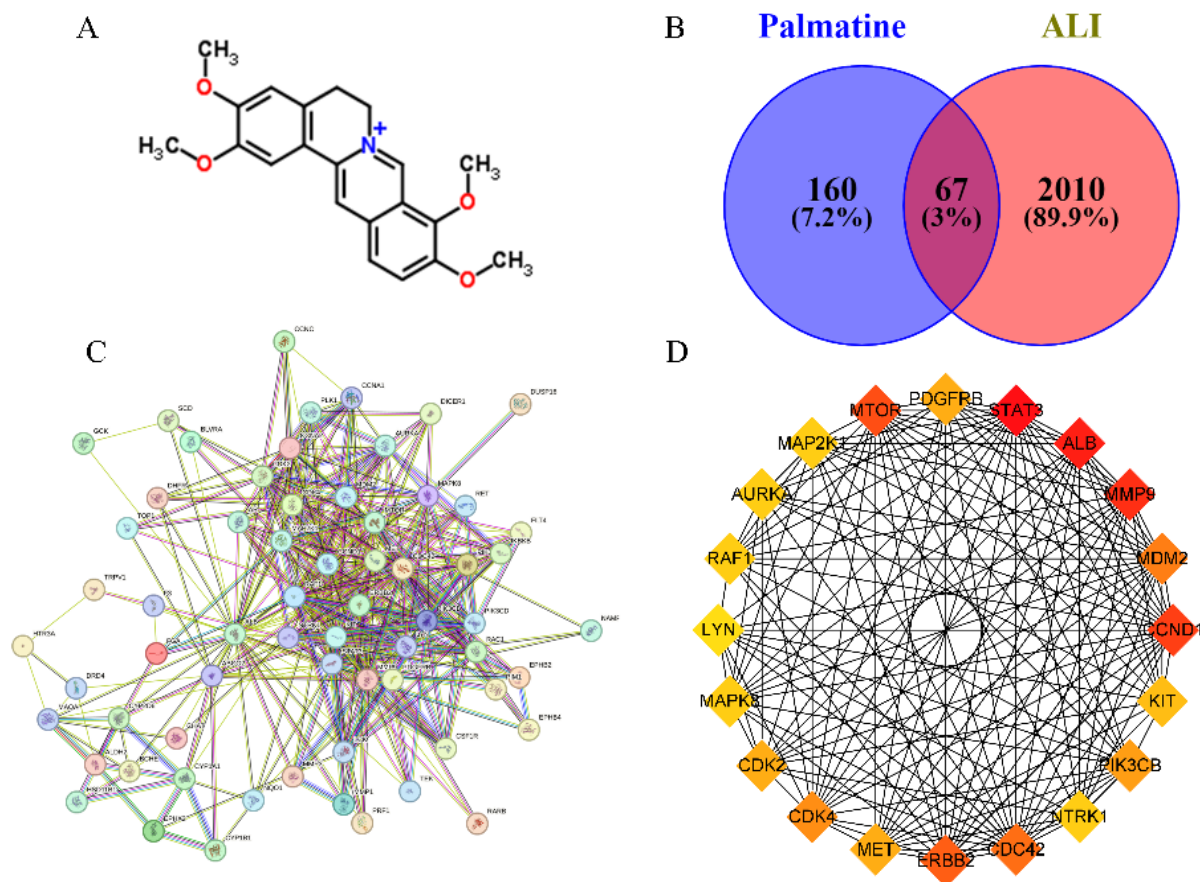


Figure 4. Target screening and PPI network analysis of Huangtensu and ALI. (A) The molecular structure formula of berberine. (B) Venn diagram of Huangtensu and ALI targets. (C) PPI network analysis of Huangtensu against ALI. (D) Core target PPI network diagram

图 4. 黄藤素与 ALI 的相关靶点筛选及 PPI 网络分析。(A) 黄藤素的分子结构式。(B) 黄藤素与 ALI 靶点的韦恩图。(C) 黄藤素抗 ALI 的 PPI 网络分析。(D) 核心靶点 PPI 网络图

4. 讨论

肝脏疾病是临床常见病, 全球肝病负担沉重, 估计每年死亡人数刚刚超过 100 万[23]。黄藤素是一种天然异喹啉生物碱, 是从防己科植物黄藤 *Fibraurea recisa* Pierre. 干燥藤茎提取的[24] [25]。近年来, 关于黄藤素的药理作用进行了大量研究, 包括其抗炎、抗氧化应激、神经保护、抗菌、抗病毒和抗肿瘤活性。此外, 黄藤素已被证明在多种肝脏疾病中起保护作用, 研究发现, 黄藤素通过调节细胞因子反应和抑制细胞凋亡来减轻 GalN/LPS 诱导的肝损伤[26]。黄藤素还可通过减轻代谢紊乱和重新平衡肠道微生物群发

挥抗肝纤维化作用[27]。然而,尚不清楚黄藤素是否对 CCl₄ 诱导的急性肝损伤具有肝保护作用。CCl₄ 诱导的急性肝损伤主要表现为急性肝组织炎症和肝细胞变性坏死。本研究发现,黄藤素进行预处理 3 天可有效减轻 CCl₄ 诱导的大鼠急性肝损伤程度,减轻肝组织炎症反应和肝细胞变性坏死。

丙氨酸氨基转移酶(ALT)主要存在于肝细胞浆内,只要有 1%的肝细胞被破坏,就可以使血清酶增高一倍,因此 ALT 是反映肝功能的重要指标之一。本研究发现,四氯化碳诱导急性肝损伤时,大鼠血清 ALT 水平明显升高,而黄藤素能够明显降低四氯化碳诱导的急性肝损伤大鼠血清 ALT 水平,表明黄藤素具有肝细胞保护作用。

STAT3 被发现是白细胞介素 6 (IL-6)激活的急性期反应因子(APRF)复合物的组成部分[28],该复合物在刺激肝脏中先天免疫介质的表达中起着至关重要的作用[29]。STAT3 是 JAK/STAT 信号通路的重要成员。近年来,多项研究证明,STAT3 与各种因素引起的肝损伤的发生发展密切相关[30][31]。研究表明,STAT3 在氧化应激反应中发挥关键作用,FTY720 可以通过调节 JAK2/STAT3 信号通路减少肝损伤,能够抑制氧化应激,以减少肝细胞死亡和肝脏中嗜中性粒细胞的浸润[32]。

大量研究表明,氧化应激参与急性肝损伤的发生发展[33],袁等人证实五味子酸性多糖通过抑制 CYP2E1 蛋白的表达,进而减轻乙醇诱导的氧化应激损伤[34]。当归多糖改善了脂质过氧化和氧化应激,抑制肝细胞凋亡发挥抗肝纤维作用[35]。本研究发现,黄藤素可明显降低急性肝损伤大鼠肝组织 MDA 的水平,表明黄藤素能够抑制急性肝损伤时肺组织发生氧化应激。

我们采用网络药理学方法对黄藤素抗急性肝损伤的潜在靶点进行了预测,结果发现,排名前 10 的潜在靶点依次为 STAT3, ALB, MMP9, CCND1, MTOR, ERBB2, CDC42, MDM2, CDK4 与 PIK3CB。

5. 结论

综上所述,本研究表明黄藤素能够通过抑制炎症反应和氧化应激减轻急性肝损伤,STAT3 可能是黄藤素发挥肝脏保护作用最具潜力的靶点,后续有待在实验中进一步验证。

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参考文献

- [1] Oh, I.S. and Park, S.H. (2015) Immune-Mediated Liver Injury in Hepatitis B Virus Infection. *Immune Network*, **15**, 191-198. <https://doi.org/10.4110/in.2015.15.4.191>
- [2] Allard, J., Le Guillou, D., Begriche, K. and Fromenty, B. (2019) Drug-Induced Liver Injury in Obesity and Nonalcoholic Fatty Liver Disease. *Advances in Pharmacology*, **85**, 75-107. <https://doi.org/10.1016/bs.apha.2019.01.003>
- [3] Long, X., Wang, P., Zhou, Y., et al. (2022) Preventive Effect of *Lactobacillus plantarum* HFY15 on Carbon Tetrachloride (CCl₄)-Induced Acute Liver Injury in Mice. *Journal of Food Science*, **87**, 2626-2639. <https://doi.org/10.1111/1750-3841.16171>
- [4] Niu, B., Lei, X., Xu, Q., et al. (2022) Protecting Mitochondria via Inhibiting VDAC1 Oligomerization Alleviates Ferroptosis in Acetaminophen-Induced Acute Liver Injury. *Cell Biology and Toxicology*, **38**, 505-530. <https://doi.org/10.1007/s10565-021-09624-x>
- [5] Liu, R., Hao, Y.T., Zhu, N., et al. (2023) Walnut (*Juglans regia* L.) Oligopeptides Alleviate Alcohol-Induced Acute Liver Injury through the Inhibition of Inflammation and Oxidative Stress in Rats. *Nutrients*, **15**, Article 2210. <https://doi.org/10.3390/nu15092210>
- [6] Cai, J., Wu, J., Fang, S., et al. (2022) Cultured Bear Bile Powder Ameliorates Acute Liver Injury in Cholestatic Mice via Inhibition of Hepatic Inflammation and Apoptosis. *Journal of Ethnopharmacology*, **284**, Article ID: 114829. <https://doi.org/10.1016/j.jep.2021.114829>

- [7] Yang, Z., Zhang, J., Wang, Y., *et al.* (2021) Caveolin-1 Deficiency Protects Mice against Carbon Tetrachloride-Induced Acute Liver Injury through Regulating Polarization of Hepatic Macrophages. *Frontiers in Immunology*, **12**, Article 713808. <https://doi.org/10.3389/fimmu.2021.713808>
- [8] Zhang, X., Kuang, G., Wan, J., *et al.* (2020) Salidroside Protects Mice against CCl₄-Induced Acute Liver Injury via Down-Regulating CYP2E1 Expression and Inhibiting NLRP3 Inflammasome Activation. *International Immunopharmacology*, **85**, Article ID: 106662. <https://doi.org/10.1016/j.intimp.2020.106662>
- [9] Feng, Y., Wang, N., Ye, X., *et al.* (2011) Hepatoprotective Effect and Its Possible Mechanism of *Coptidis rhizoma* Aqueous Extract on Carbon Tetrachloride-Induced Chronic Liver Hepatotoxicity in Rats. *Journal of Ethnopharmacology*, **138**, 683-690. <https://doi.org/10.1016/j.jep.2011.09.032>
- [10] Xiang, W., Wei, J., Lv, L., *et al.* (2023) *Arctium lappa* L. Root Polysaccharides Ameliorate CCl₄-Induced Acute Liver Injury by Suppressing Oxidative Stress, Inflammation and Apoptosis. *Natural Product Research*. <https://doi.org/10.1080/14786419.2023.2272287>
- [11] Huang, J., Bai, Y., Xie, W., *et al.* (2023) *Lycium barbarum* Polysaccharides Ameliorate Canine Acute Liver Injury by Reducing Oxidative Stress, Protecting Mitochondrial Function, and Regulating Metabolic Pathways. *Journal of Zhejiang University-SCIENCE B*, **24**, 157-171. <https://doi.org/10.1631/jzus.B2200213>
- [12] Zhang, X., Su, K., Liu, Y., *et al.* (2021) Small Molecule Palmatine Targeting Musashi-2 in Colorectal Cancer. *Frontiers in Pharmacology*, **12**, Article 793449. <https://doi.org/10.3389/fphar.2021.793449>
- [13] Cheng, J.J., Ma, X.D., Ai, G.X., *et al.* (2022) Palmatine Protects against MSU-Induced Gouty Arthritis via Regulating the NF- κ B/NLRP3 and Nrf2 Pathways. *Drug Design, Development and Therapy*, **16**, 2119-2132. <https://doi.org/10.2147/DDDT.S356307>
- [14] Ho, Y.J., Lu, J.W., Huang, Y.L. and Lai, Z.Z. (2019) Palmatine Inhibits Zika Virus Infection by Disrupting Virus Binding, Entry, and Stability. *Biochemical and Biophysical Research Communications*, **518**, 732-738. <https://doi.org/10.1016/j.bbrc.2019.08.120>
- [15] Okechukwu, P.N., Ekeuku, S.O., Chan, H.K., Eluri, K. and Froemming, G.R.A. (2021) Palmatine Inhibits Up-Regulation of GRP78 and CALR Protein in an STZ-Induced Diabetic Rat Model. *Current Pharmaceutical Biotechnology*, **22**, 288-298. <https://doi.org/10.2174/1389201021666200730124208>
- [16] Grabarska, A., Wroblewska-Luczka, P., Kukula-Koch, W., *et al.* (2021) Palmatine, a Bioactive Protoberberine Alkaloid Isolated from *Berberis cretica*, Inhibits the Growth of Human Estrogen Receptor-Positive Breast Cancer Cells and Acts Synergistically and Additively with Doxorubicin. *Molecules*, **26**, Article 6253. <https://doi.org/10.3390/molecules26206253>
- [17] Liu, X., Zhang, Y., Wu, S., *et al.* (2020) Palmatine Induces G2/M Phase Arrest and Mitochondrial-Associated Pathway Apoptosis in Colon Cancer Cells by Targeting AURKA. *Biochemical Pharmacology*, **175**, Article ID: 113933. <https://doi.org/10.1016/j.bcp.2020.113933>
- [18] Yuan, Y., Peng, W., Liu, Y., *et al.* (2017) Palmatine Attenuates Isoproterenol-Induced Pathological Hypertrophy via Selectively Inhibiting HDAC2 in Rats. *International Journal of Immunopathology and Pharmacology*, **30**, 406-412. <https://doi.org/10.1177/0394632017742225>
- [19] Jie, L., Ma, Z., Gao, Y., *et al.* (2023) The Mechanism of Palmatine-Mediated Intestinal Flora and Host Metabolism Intervention in OA-OP Comorbidity Rats. *Frontiers in Medicine*, **10**, Article 1153360. <https://doi.org/10.3389/fmed.2023.1153360>
- [20] Ekeuku, S.O., Pang, K.L. and Chin, K.Y. (2020) Palmatine as an Agent against Metabolic Syndrome and Its Related Complications: A Review. *Drug Design, Development and Therapy*, **14**, 4963-4974. <https://doi.org/10.2147/DDDT.S280520>
- [21] Nwabueze, O.P., Sharma, M., Balachandran, A., *et al.* (2022) Comparative Studies of Palmatine with Metformin and Glimepiride on the Modulation of Insulin Dependent Signaling Pathway *in Vitro*, *in Vivo* & *ex Vivo*. *Pharmaceuticals*, **15**, Article 1317. <https://doi.org/10.3390/ph15111317>
- [22] Hopkins, A.L. (2008) Network Pharmacology: The Next Paradigm in Drug Discovery. *Nature Chemical Biology*, **4**, 682-690. <https://doi.org/10.1038/nchembio.118>
- [23] Mokdad, A.A., Lopez, A.D., Shahraz, S., *et al.* (2014) Liver Cirrhosis Mortality in 187 Countries between 1980 and 2010: A Systematic Analysis. *BMC Medicine*, **12**, Article No. 145. <https://doi.org/10.1186/s12916-014-0145-y>
- [24] Pereira, J.F., De Sousa Neves, J.C., Fonteles, A.A., *et al.* (2023) Palmatine, a Natural Alkaloid, Attenuates Memory Deficits and Neuroinflammation in Mice Submitted to Permanent Focal Cerebral Ischemia. *Journal of Neuroimmunology*, **381**, Article ID: 578131. <https://doi.org/10.1016/j.jneuroim.2023.578131>
- [25] Tarabasz, D. and Kukula-Koch, W. (2020) Palmatine: A Review of Pharmacological Properties and Pharmacokinetics. *Phytotherapy Research*, **34**, 33-50. <https://doi.org/10.1002/ptr.6504>
- [26] Lee, W.C., Kim, J.K., Kang, J.W., *et al.* (2010) Palmatine Attenuates D-Galactosamine/Lipopolysaccharide-Induced

- Fulminant Hepatic Failure in Mice. *Food and Chemical Toxicology*, **48**, 222-228.
<https://doi.org/10.1016/j.fct.2009.10.004>
- [27] Qin, J., Luo, Z., Wang, Q., *et al.* (2023) Integrating Metabonomics and Metagenomics Sequencing to Study the Anti-Liver Fibrosis Effects of Palmatine in *Corydalis saxicola* Bunting. *Journal of Ethnopharmacology*, **315**, Article ID: 116666. <https://doi.org/10.1016/j.jep.2023.116666>
- [28] Zhong, Z., Wen, Z. and Darnell Jr., J.E. (1994) Stat3: A STAT Family Member Activated by Tyrosine Phosphorylation in Response to Epidermal Growth Factor and Interleukin-6. *Science*, **264**, 95-98.
<https://doi.org/10.1126/science.8140422>
- [29] Hillmer, E.J., Zhang, H., Li, H.S. and Watowich, S.S. (2016) STAT3 Signaling in Immunity. *Cytokine & Growth Factor Reviews*, **31**, 1-15. <https://doi.org/10.1016/j.cytogfr.2016.05.001>
- [30] Yao, W., Li, H., Luo, G., *et al.* (2017) SERPINB1 Ameliorates Acute Lung Injury in Liver Transplantation through ERK1/2-Mediated STAT3-Dependent HO-1 Induction. *Free Radical Biology and Medicine*, **108**, 542-553.
<https://doi.org/10.1016/j.freeradbiomed.2017.04.011>
- [31] Li, M., Zhang, X., Wang, B., *et al.* (2018) Effect of JAK2/STAT3 Signaling Pathway on Liver Injury Associated with Severe Acute Pancreatitis in Rats. *Experimental and Therapeutic Medicine*, **16**, 2013-2021.
<https://doi.org/10.3892/etm.2018.6433>
- [32] He, X., Kang, K., Pan, D., Sun, Y. and Chang, B. (2022) FTY720 Attenuates APAP-Induced Liver Injury via the JAK2/STAT3 Signaling Pathway. *International Journal of Molecular Medicine*, **49**, Article No. 67.
<https://doi.org/10.3892/ijmm.2022.5123>
- [33] Ruart, M., Chavarria, L., Camprecios, G., *et al.* (2019) Impaired Endothelial Autophagy Promotes Liver Fibrosis by Aggravating the Oxidative Stress Response during Acute Liver Injury. *Journal of Hepatology*, **70**, 458-469.
<https://doi.org/10.1016/j.jhep.2018.10.015>
- [34] Yuan, R., Tao, X., Liang, S., *et al.* (2018) Protective Effect of Acidic Polysaccharide from *Schisandra chinensis* on Acute Ethanol-Induced Liver Injury through Reducing CYP2E1-Dependent Oxidative Stress. *Biomedicine & Pharmacotherapy*, **99**, 537-542. <https://doi.org/10.1016/j.biopha.2018.01.079>
- [35] Cao, P., Sun, J., Sullivan, M.A., *et al.* (2018) *Angelica sinensis* Polysaccharide Protects against Acetaminophen-Induced Acute Liver Injury and Cell Death by Suppressing Oxidative Stress and Hepatic Apoptosis *in Vivo* and *in Vitro*. *International Journal of Biological Macromolecules*, **111**, 1133-1139.
<https://doi.org/10.1016/j.ijbiomac.2018.01.139>