细胞焦亡与肝脏疾病的相关性及中医药研究进展

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［摘要］ 细胞焦亡又称细胞炎性坏死，其形态学特征、发生及调控机制不同于凋亡、坏死等细胞死亡方式，是近年来发现并证实的一种依赖半胱氨酸天冬氨酸蛋白水解酶(Caspase)的新型程序性细胞死亡方式。研究表明，细胞焦亡与肝脏疾病发生过程密切相关，在酒精性肝病(ALD)，非酒精性脂肪性肝病(NAFLD)，肝纤维化和肝癌等病变过程中可能发挥着重要作用。细胞焦亡主要通过经典途径NOD样受体蛋白3(NLRP3)炎症小体活化Caspase-1，进而裂解效应蛋白消化道皮肤素D(GSDMD)，释放白细胞介素-18(IL-18)，白细胞介素-1β(IL-1β)等促炎细胞因子引起肝细胞炎性损伤，进而促进肝病的发生发展。临床上使用中药治疗肝脏疾病疗效独特，不良反应较低。中药干预肝脏疾病后，其阻断细胞焦亡信号通路方式为①抑制NLRP3炎症小体多蛋白复合物的组装和激活；②降低Caspase-1或Caspase-4/Caspase-5/Caspase-11的活性；③抑制GSDMD的裂解，减少IL-18和IL-1β促炎细胞因子的释放。通过这几个方面阻断焦亡信号通路，减轻肝脏炎症程度，从而发挥抗肝病作用。因此，深入研究细胞焦亡有利于认识肝脏疾病发生发展和转归中的作用，增强或抑制焦亡可能为中药防治肝病提供新策略。目前针对经典焦亡信号通路中的关键蛋白NLRP3炎症小体成为中药抗肝病靶点之一。该文简要概述了细胞焦亡与肝脏疾病的关系，对近年来中药单体、复方、有效部位和提取物的干预情况进行归纳总结，为进一步探索细胞焦亡致病机制及中药治疗肝脏疾病提供重要指导。

［关键词］ 中药；肝脏疾病；细胞焦亡；NOD样受体蛋白3(NLRP3)炎症小体
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Correlation and Traditional Chinese Medicine Intervention of Pyroptosis and Liver Diseases

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［**Abstract**］ Pyroptosis, also known as cell inflammatory necrosis, is different from apoptosis, necrosis, and other forms of cell death in morphological characteristics, occurrence, and regulatory mechanism. It is a new type of programmed cell death dependent on Caspase, which has been discovered and confirmed in recent years. Studies have shown that pyroptosis is closely related to the occurrence of liver diseases, and is critical in alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), liver fibrosis, and liver cancer. Pyroptosis causes inflammatory injury of hepatocytes to promote the occurrence and development of liver diseases by activating Caspase-1, cleaving the effector gasdermin-D (GSDMD), and releasing pro-

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inflammatory cytokines, such as interleukin-18 (IL-18) and interleukin-1β (IL-1β) mainly through the classical NOD-like receptor protein 3 (NLRP3) inflammasome pathway. Clinically, Chinese medicine in the treatment of liver diseases has unique efficacy and low side effects. In the intervention on liver diseases, Chinese medicine blocks the pyroptosis signaling pathway to relieve the liver inflammation by inhibiting the assembly and activation of NLRP3 inflammasome multiprotein complex, blunting the activity of Caspase-1 or Caspase-4/Caspase-5/Caspase-11, and inhibiting the cleavage of GSDMD to reduce the release of pro-inflammatory cytokines such as IL-18 and IL-1β. Therefore, in-depth investigation of pyroptosis facilitates unveiling its role in the occurrence, development, and prognosis of liver diseases, and the enhancement or inhibition of pyroptosis may provide a new strategy for the prevention and treatment of liver diseases by Chinese medicine. At present, NLRP3 inflammasome, a key protein in the classic pyroptosis signaling pathway, has become an anti-liver disease target of Chinese medicine. This study briefly summarized the relationship between pyroptosis and liver diseases and reviewed the intervention of monomers, compound prescriptions, effective fractions and extracts of Chinese medicine in recent years to provide important guidance for further exploring the pathogenic mechanism of pyroptosis and the treatment of liver diseases with Chinese medicine.

[**Keywords**] Chinese medicine; liver diseases; pyroptosis; NOD-like receptor protein 3 (NLRP3) inflammasome

细胞焦亡是一种依赖半胱氨酸天冬氨酸蛋白水解酶(Caspase)的炎症性细胞死亡方式,特点是炎症小体和Caspase-1或Caspase-4/Caspase-5/Caspase-11的激活,消化道皮肤素D(GSDMD)蛋白介导的细胞孔隙形成,随后细胞肿胀破裂释放出细胞内容物及炎症介质,从而启动炎症级联反应。“细胞焦亡”首次使用是在巨噬细胞中发现的一种依赖Caspase-1的细胞死亡方式[1]。细胞焦亡是人体的一种重要天然免疫反应,其中Caspase-1介导的焦亡在拮抗病原体感染和清除病原体方面至关重要[2-3]。在急慢性肝病过程中的肝细胞死亡是一个重要事件,如细胞焦亡、凋亡、坏死、自噬等导致的肝炎症损伤,不同死亡方式的重叠和串扰可向肝纤维化、肝癌发展[4-5]。细胞焦亡引起的炎症是慢性肝脏疾病的共同基础,经典焦亡途径上游的NOD样受体蛋白3(NLRP3)是活化Caspase-1的关键蛋白,在肝脏疾病发生发展过程中至关重要,抑制多种肝细胞焦亡可降低肝脏炎症[6-8]。危险相关分子模式(DAMPs)和病原相关分子模式(PAMP)能够引起肝库普佛细胞(Kupper cell),肝星状细胞(HSC)和肝实质细胞中NLRP3炎症小体高表达,NLRP3炎症小体引起的信号级联可促进肝细胞焦亡[9-10]。长期服用西药会造成胃肠道反应、药物性肝损伤等诸多不良反应,中药具有整体观、个性化、多成分协同等特点,且安全有效、价格便宜,不良反应较少,在未来具有良好的应用前景。中药通过抑制NLRP3炎症小体信介导的炎症反应,下调NLRP3炎症小体,Caspase-1,GSDMD,IL-18和IL-1β表达,作为干预慢性肝脏疾病的有效途径。目前发现许多中药可以通过调控焦亡信号通路预防肝脏疾病,通路中的关键蛋白可作为药物作用潜在靶点。本文就细胞焦亡在酒精性肝病(ALD),非酒精脂肪性肝病(NAFLD),肝纤维化和肝癌过程中的作用机制,以及中药通过下调焦亡信号通路抗肝脏疾病的研究进展进行综述。

1 细胞焦亡

细胞焦亡发生的主要标志物有炎症小体的形成,Caspase-1或Caspase-4/Caspase-5/Caspase-11的激活及GSDMD蛋白裂解。炎症小体是一种多蛋白复合物,由模式识别受体(PRR),衔接分子凋亡相关的点状蛋白(ASC)和效应分子Caspase前体(pro-Caspase-1)3部分组成,在天然免疫反应中发挥着重要作用。核苷酸结合寡聚化结构域样受体(NLRs)是一类能识别宿主来源的DAMP和PAMP的胞内PRR。参与炎症小体组装的NLRs受体蛋白包括NLRP1/3/6/7/12,核效应蛋白4(NLRC4)和神经元凋亡抑制蛋白(NAIP)等,其中NLRP3炎症小体是当前研究的最多的炎症小体[11]。细胞焦亡包括依赖Caspase-1的经典细胞焦亡和依赖Caspase-4/Caspase-5/Caspase-11非经典细胞焦亡。在经典焦亡途径中,NLRP3炎症小体是一个关键分子,由NLRP3蛋白,ASC和pro-Caspase-1组成。NLRP3炎症小体在受到胞外信号刺激后引起自身的寡聚化,然后通过ASC募集pro-Caspase-1,此时

Caspase-1酶原发生自体水解形成四聚体，最终成为具有活性的Caspase-1，进而裂解GSDMD形成含有*N*端结构域的N-GSDMD，与细胞膜上的磷脂酰肌醇结合造成细胞膜穿孔，最终释放大量炎性介质等细胞内容物引起炎症反应，导致细胞焦亡的发生；另一方面，活化的Caspase-1对pro-IL-1β和pro-IL-18的前体进行切割，形成成熟的IL-1β和IL-18并释放到细胞外，进而募集炎症细胞聚集扩大局部炎症反应，导致组织炎症损伤。在非经典焦亡途径中，Caspase-4/Caspase-5/Caspase-11可直接被脂多糖（LPS）激活，活化的Caspase-1或Caspase-4/Caspase-5/Caspase-11可使GSDMD蛋白发生剪切和多聚化，进而导致细胞肿胀，质膜溶解，染色质碎裂和促炎因子IL-1β和IL-18释放。此外，Caspase-11还可通过GSDMD诱导的膜孔使K^+外流，激活依赖NLPR3炎症小体的Caspase-1而促使细胞焦亡。

2 细胞焦亡与肝病的关系

2.1 细胞焦亡与NAFLD 目前NAFLD在全球已成为最常见的慢性疾病之一，人群患病率20%～30%，我国发病率约为5%[12]。目前研究表明NLRP3炎症小体激活导致的炎症反应促进了NAFLD的发生发展。非酒精性脂肪性肝炎（NASH）患者肝组织中NLRP3，IL-1β和IL-18表达水平显著高于健康人，提示NLRP3炎症小体参与NASH过程[13]。在高脂饮食（HFD）喂养下的野生型小鼠肝组织中嘌呤能离子通道型受体7（P2X7R），NLRP3，Caspase-1和IL-1β表达增加，肝脏炎症和脂肪变性严重，而$P2X7R^{-/-}$小鼠NASH症状明显减轻则与P2X7R介导的NLRP3炎症小体激活有关[14]。HFD可诱导小鼠肝组织中NLRP3炎症小体激活，而不饱和脂肪酸通过抑制NLRP3炎症小体活化改善NAFLD[15]。应用蛋氨酸和胆碱缺乏（MCD）饮食建立NASH小鼠模型，发现肝Kupffer细胞中NLRP3，ASC，Caspase-1和IL-1β表达增加，而$NLRP3^{(-/-)}$小鼠上述分子表达均降低，肝脏脂肪变性和炎性细胞浸润减少[16-17]。NASH小鼠肝脏NLRP3，Caspase-1和IL-1β表达升高，肝组织炎症程度加重，给予NLRP3特异性抑制剂灌胃后小鼠症状减轻[18]。此外，NAFLD细胞模型中升高的肿瘤坏死因子-α（TNF-α）可诱导NLRC4炎症小体激活，产生的IL-18和IL-1β加剧了肝内炎症反应[19]。

2.2 细胞焦亡与ALD ALD是由于长期大量饮酒导致的肝细胞结构异常和功能性障碍疾病，初期表现为单纯脂肪变形，继而发展为肝炎，肝纤维化、肝硬化，甚至肝癌。焦亡产生的炎性细胞因子可促进ALD发展，其中NLRP3炎症小体的激活与ALD发病机制密切相关。研究发现酒精性肝炎（AH）患者肝组织中NLRP3，Caspase-1，IL-1β和IL-18表达水显著高于健康人，提示NLRP3炎症小体参与了ALD病理过程[20]。酒精可上调P2X7R表达诱导NLRP3炎症小体激活，进而参与酒精性炎症反应[21]。酒精还通过上调ALD小鼠硫氧还蛋白相互作用蛋白（TXNIP）表达诱导NLRP3炎症小体活化，从而促进焦亡导致肝损伤[22]。有研究证实NLRP3炎症小体能明显增强酒精导致肝细胞自分泌尿酸和三磷酸腺苷（ATP）对肝细胞的炎症损伤和脂肪变性[23-24]。此外，Caspase-11/GSDMD非经典焦亡通路在AH中也发挥着重要作用。在AH患者和小鼠肝脏组织中Caspase-11和GSDMD表达上调，过表达的GSDMD可显著增加小鼠肝细胞死亡和炎性细胞浸润，而敲除Caspase-11基因使GSDMD活化受到抑制，肝细胞死亡率降低[25]。敲除GSDMD基因可导致Kupffer细胞炎症因子IL-1β释放减少，从而减轻小鼠酒精性脂肪肝炎[26]。

2.3 细胞焦亡与肝纤维化 肝纤维化是慢性肝损伤之后的修复过程，主要特征是细胞外基质（ECM）的合成和降解失衡，导致ECM在肝脏内的过度沉积。HSC是肝纤维化细胞的主要类型，HSC增殖和活化是肝纤维化的关键步骤。细胞焦亡与HSC活化密切相关，焦亡导致的炎症反应可促使HSC活化进而推动肝纤维化。NLRP3炎症小体在HSC活化和肝纤维化可能起到直接作用，NLRP3炎症小体持续激活能上调NLRP3基因敲入小鼠HSC活化标志物α-平滑肌肌动蛋白（α-SMA）和Ⅰ型胶原表达[27]。小鼠肝细胞焦亡释放出的NLRP3炎症小体颗粒能被HSC内吞而发生活化，从而放大和延续炎性小体驱动的纤维化形成[28]。醛固酮可通过促进NLRP3炎症小体组装和表达诱导小鼠HSC激活及肝纤维化[29]。HSC分泌促纤维化因子转化生长因子-β_1（TGF-β_1）与大肠埃希菌RNA激活NLRP3炎症小体有关[30]。此外，日本血吸虫原感染小鼠后可诱导HSC中NLRP3炎性小体激活，这可能是启动炎症反应并引起肝纤维化的早期机制[31]。上述表明细胞焦亡介导的炎症可诱导HSC活化并促进肝纤维化。

2.4 细胞焦亡与肝癌 肝癌是指来源于肝细胞和肝胆管细胞的恶性肿瘤，在肝癌的病变过程中，细胞焦亡发挥着重要调控作用。一方面，焦亡对肝癌发展起到抑制作用。据报道在肝癌患者肝组织中

雌激素受体β(ERβ)和NLRP3炎症小体的表达均显著下调,且两者表达水平呈正相关;雌激素可通过ERβ/丝裂原活化蛋白激酶(MAPK)途径激活NLRP3炎症小体抑制肝癌细胞增殖和转移[32-33]。另一方面,焦亡可能会促进肝癌的进一步发展。长链非编码RNA SNHG7增强肝癌细胞侵袭能力与抑制NLRP3,Caspase-1和IL-1β表达有关,提示抑制SNHG7表达可促进细胞焦亡而发挥抗肝癌作用[34-35]。FUN14结构域蛋白1(FUNDC1)在大多数人肝细胞癌中是一种具有特征性的有丝分裂受体,在二乙基亚硝胺(DEN)诱导的小鼠肝癌过程中,敲除FUNDC1可激活NLRP3炎症小体促进肝癌发生[36]。低氧应激下释放的核损伤相关分子高迁移率族蛋白1(HMGB1)能激活Caspase-1促进肝癌细胞侵袭和转移[37]。总之,细胞焦亡关键分子NLRP3炎症小体的活化与肝癌发病机制密切相关,通过调节细胞焦亡可为肝癌治疗提供新策略。

3 中药抗NAFLD

3.1 中药单体抗NAFLD 研究发现,水飞蓟宾[38],丹酚酸A[39]可抑制TXNIP/NLRP3炎症小体信号通路分别改善HFD诱导的NAFLD小鼠、大鼠肝脏炎症和脂肪变性。白藜芦醇[40]、芹菜素[41]通过下调NLRP3,ASC,Caspase-1,IL-1β表达阻断NLRP3炎症小体通路,从而改善HFD诱导的NAFLD小鼠肝脂肪变性和脂质蓄积。小檗碱可降低MCD饮食所致NASH小鼠肝组织中NLRP3,ASC,Caspase-1,GSDMD-N,IL-1β表达水平,抑制NLRP3炎症小体激活减轻NASH[42-43]。甘草甜素改善MCD诱导NASH小鼠肝脏脂质蓄积,其作用机制在于下调肝组织NLRP3,Caspase-1,ASC,IL-1β表达进而抑制NLRP3炎症小体活化[44]。实验表明,穿心莲内酯可通过抑制NLRP3炎症小体组装和激活减轻胆碱缺乏-氨基酸限定(CDAA)饮食诱导的小鼠NASH[45]。

3.2 中药复方和有效成分抗NAFLD 研究表明,下瘀血汤[46],复方贞术调脂颗粒[47]可抑制NLRP3炎症小体激活改善HFD诱导的NASH小鼠肝脏脂肪变性和脂质沉积,并显著降低肝组织中NLRP3,Caspase-1,ASC,IL-1β,IL-18表达水平。降脂理肝汤[48]、葛根芩连汤[49]可抑制NLRP3炎症小体表达改善HFD所致NAFLD大鼠肝脂肪变性和脂质蓄积。枸杞多糖减轻MCD诱导小鼠NASH与抑制NLRP3炎症小体信号通路有关[50]。见表1。

表1 中药抗非酒精脂肪性肝病作用机制

Table 1 Traditional Chinese medicine againsts non-alcoholic fatty live disease

药物	细胞焦亡信号通路主要分子	相关肝脏疾病	文献
水飞蓟宾	TXNIP,NLRP3,Caspase-1,IL-1β	HFD致小鼠NAFLD	[38]
丹酚酸A	TXNIP,NLRP3,ASC,Caspase-1	HFD致大鼠NAFLD	[39]
白藜芦醇,芹菜素	NLRP3,ASC,Caspase-1,IL-1β	HFD致小鼠NAFLD	[40-41]
小檗碱	NLRP3,ASC,Caspase-1,GSMDD-N, IL-1β	MCD致小鼠NASH	[42-43]
甘草甜素	NLRP3,Caspase-1,ASC,IL-1β	MCD致小鼠NASH	[44]
穿心莲内酯	NLRP3,ASC,Caspase-1,IL-1β	CDAA致小鼠NASH	[45]
下瘀血汤,复方贞术调脂颗粒	NLRP3,ASC,Caspase-1,IL-1β,IL-18	HFD诱导的NASH小鼠	[46-47]
降脂理肝汤	NLRP3,Caspase-1,IL-18,IL-1β	HFD致大鼠NAFLD	[48]
葛根芩连汤	NLRP3,ASC,caspase-1	HFD致大鼠NAFLD	[49]
枸杞多糖	NLRP3,ASC,Caspase-1,IL-1β,IL-18	MCD致小鼠NASH	[50]

4 中药抗ALD

中药单体抗ALD,研究表明,二氢槲皮素[51]、龙胆苦苷[52]可通过阻断P2X7R介导的NLRP3炎症小体信号通路改善ALD小鼠肝脏脂质堆积和脂肪变性。蓝靛果花青素减少Lieber-DeCarli饮食加慢性酒精灌胃诱导的ALD小鼠脂质堆积与抑制焦亡信号通路有关[53]。木蝴蝶素可下调NLRP3,ASC,Caspase-1,GSDMD,IL-1β和IL-18表达抑制NLRP3炎症小体活化,从而改善Lieber-DeCarli诱导的ALD小鼠肝脏脂肪蓄积和炎症[54]。芒果苷[55]、人参皂苷[56]也可通过抑制NLRP3炎症小体分别减轻大鼠、小鼠AH[55]。中药抗ALD作用情况见表2。

5 中药抗肝损伤

5.1 中药单体抗肝损伤 研究表明,灵芝酸A[57]、芒果苷[58]、汉黄芩苷[59]可通过抑制NLRP3炎症小体激活保护*D*-氨基半乳糖(*D*-Gal N)/LPS所致小鼠肝损伤,降低血清ALT,AST水平,下调肝组织中NLRP3,ASC,Caspapse-1,IL-1β表达。绿茶多酚可

表2 中药抗酒精性肝病

Table 2 Traditional Chinese medicine againsts alcoholic liver disease

药物	焦亡信号通路相关分子	相关肝脏疾病	文献
二氢槲皮素、龙胆苦苷	P2X7R, NLRP3, Caspase-1, IL-1β	小鼠ALD	[51-52]
蓝靛果花青素	Caspase-1, IL-1β	Lieber-DeCarli+酒精诱导小鼠ALD	[53]
木蝴蝶素	NLRP3, ASC, Caspase-1, GSDMD, IL-18, IL-1β	Lieber-DeCarli诱导小鼠ALD	[54]
芒果苷	NLRP3, Caspase-1, IL-1β	大鼠AH	[55]
人参皂苷Rg_1	NLRP3, ASC, Caspase-1	小鼠AH	[56]

降低NLRP3, ASC, Caspase-1, IL-1β表达抑制NLRP3炎症小体活化，从而减轻LPS引起的小鼠肝损伤[60]。柴胡皂苷-d[61]、红景天苷[62]减轻四氯化碳(CCl_4)诱导的小鼠急性肝损伤也与抑制NLRP3炎症小体激活有关。槲皮素能抑制沉默信息调节因1(SIRT1)介导的NLRP3炎症小体激活发挥保肝作用，并显著降低异烟肼所致肝损伤大鼠肝脏中NLRP3, ASC, Caspase-1, IL-1β表达[63]。番茄红素可保护橄榄油所致小鼠肝缺血再灌注损伤，其抗肝损伤作用与抑制NLRP3炎症小体激活有关[64]。厚朴酚[65]，和厚朴酚[66]可通过抑制NLRP3炎症小体信号通路分别减轻小鼠急性酒精性肝损伤，*D*-Gal N/LPS诱导的大鼠急性肝损伤。

5.2 中药复方、提取物及有效成分抗肝损伤 研究发现，茵陈芍甘汤可通过抑制NLRP3炎症小体保护LPS所致小鼠急性肝损伤[67]。健脾理气方通过下调肝组织中NLRP3, ASC, Caspase-1, IL-18表达抑制NLRP3炎症小体活化，从而预防*D*-Gal N诱导的大鼠急性肝损伤[68]。柽柳[69]、琴叶榕提取物[70]可通过抑制NLRP3炎症小体介导的细胞焦亡改善小鼠酒精性肝损伤，降低肝脏中AST水平，并抑制NLRP3, Caspase-1和IL-1β的表达。多穗柯总黄酮干预CCl_4诱导的急性肝损伤小鼠后，肝组织中NLRP3, ASC, Caspase-1, IL-1β表达显著降低，其保肝作用在于减轻NLRP3炎症小体介导的炎症反应[71]。中药抗肝损伤总体情况见表3。

表3 中药抗肝损伤

Table 3 Traditional Chinese medicine protects against liver injury

药物	焦亡信号通路相关分子	肝脏疾病	文献
灵芝酸A，芒果苷，汉黄芩苷	NLRP3, ASC, Caspapse-1, IL-1β	*D*-Gal N/LPS诱导小鼠肝损伤	[57-58]
绿茶多酚	NLRP3, ASC, Caspase-1, IL-1β, IL-18	LPS致小鼠炎性肝损伤	[60]
柴胡皂苷d	NLRP3, ASC, Caspase-1, IL-1β	CCl_4诱导小鼠急性肝损伤	[61]
红景天苷	NLRP3, ASC, pro-Caspase-1, pro-IL-1β	CCl_4诱导小鼠急性肝损伤	[62]
槲皮素	NLRP3, ASC, Caspase-1, IL-1β	异烟肼所致大鼠肝损伤	[63]
番茄红素	NLRP3, ASC, Caspase-1, IL-1β	橄榄油所致小鼠肝缺血再灌注损伤	[64]
厚朴酚	NLRP3, Caspase-1, IL-1β	乙醇致小鼠急性肝损伤	[65]
和厚朴酚	NLRP3, ASC, pro-Caspase-1, IL-1β	*D*-Gal N/LPS诱导大鼠急性肝损伤	[66]
茵陈芍甘汤	NLRP3, Caspase-1, IL-1β	LPS所致小鼠急性肝损伤	[67]
健脾理气方	NLRP3, ASC, Caspase-1, IL-18	*D*-Gal N诱导大鼠急性肝损伤	[68]
柽柳、琴叶榕根提取物	NLRP3, Caspase-1, IL-1β	乙醇诱导小鼠肝损伤	[69-70]
多穗柯总黄酮	NLRP3, ASC, Caspase-1, IL-1β	CCl_4诱导小鼠急性肝损伤	[71]

6 中药抗肝纤维化

研究表明，五味子甲素[72]、冬凌草甲素[73]、天竺葵素[74]可阻断NLRP3炎症小体通路抑制HSC活化，逆转CCl_4诱导的大鼠肝纤维化。莪术醇能降低LPS处理HSC中NLRP3, Caspase-1, IL-1β表达，机制为抑制NLRP3炎症小体活性[75]。山姜素可抑制NLRP3炎症小体信号通路减少CCl_4诱导的肝纤维化小鼠肝脏胶原沉积[76]。熊果酸[77]，香叶木素[78]也可通过抑制NLRP3炎症小体信号通路改善CCl_4所致的大鼠肝脏炎症和纤维化。川芎嗪干预CCl_4所致肝纤维化大鼠，通过下调血小板衍生生长因子受体-β(PDGFR-β)，NLRP3, IL-1β, IL-18表达抑制PDGFR-β/NLRP3/Caspase-1信号通路，减轻肝纤维化[79]。见表4。

表4 中药抗肝纤维化

Table 4 Traditional Chinese medicine against hepatic fibrosis

药物	焦亡信号通路相关分子	相关肝脏疾病	文献
五味子甲素	NLRP3, ASC, Caspase-1, IL-1β	CCl_4诱导小鼠肝纤维化	[72]
冬凌草甲素, 天竺葵素	NLRP3, Caspase-1, IL-1β	CCl_4所致小鼠肝纤维化	[73-74]
莪术醇	NLRP3, Caspase-1, IL-1β	LPS处理的HSC	[75]
山姜素	NLRP3, ASC, Caspase-1, IL-1β, IL-18	CCl_4诱导小鼠肝纤维化	[76]
熊果酸	NLRP3, Caspase-1, IL-1β	CCl_4诱导大鼠肝纤维化	[77]
香叶木素	NLRP3, ASC, Caspase-1, IL-1β	CCl_4诱导大鼠肝纤维化	[78]
川芎嗪	NLRP3, Caspase-1, IL-1β, IL-18	CCl_4诱导大鼠肝纤维化	[79]

7 中药单体和复方抗肝癌

中药可通过调节焦亡信号通路发挥抗肝癌作用。小檗碱可诱导Caspase-1介导的细胞焦亡促进肝癌HepG2细胞癌变死亡[80]。猫尾草异黄酮通过上调NLRP3, Caspase-1, IL-1β, IL-18表达激活NLRP3炎症小体, 抑制肝癌细胞生长和转移[81]。山莨菪碱通过抑制NLRP3炎症小体活化抑制小鼠肝癌移植瘤生长和转移[82]。迷迭香酸阻断波形蛋白(Vimentin)/NLRP3信号通路抑制肝癌细胞增殖[83]。木犀草苷可抑制NLRP3炎症小体激活抑制肝癌HepG2细胞增殖、侵袭和转移[84]。中药复方鳖甲煎丸通过降低DEN致肝癌大鼠NLRP3, ASC, Caspase-1, IL-1β, IL-18表达抑制NLRP3炎症小体通路, 呈剂量依耐性抑制肝癌细胞生长[85]。健脾益气方含药血清可下调Vimentin/NLRP3/Caspase-1信号通路抑制肝癌细胞增殖和侵袭能力[86]。见表5。

表5 中药抗肝癌

Table 5 Traditional Chinese medicine against liver cancer

药物	焦亡信号通路相关分子	相关肝脏疾病	文献
小檗碱	Caspase-1	肝癌HepG2细胞	[80]
猫尾草异黄酮	NLRP3, Caspase-1, IL-1β, IL-18	SMMC-7721和HuH7肝癌细胞	[81]
山莨菪碱	NLRP3, ASC, Caspase 1, IL-18, IL-1β	肝癌移植瘤小鼠	[82]
迷迭香酸	NLRP3, IL-β	肝癌HepG2细胞	[83]
木犀草苷	NLRP3, Caspase-1, IL-1β	肝癌HepG2细胞	[84]
鳖甲煎丸	NLRP3, ASC, Caspase-1, IL-1β, IL-18	DEN致大鼠肝癌	[85]
健脾益气方	Caspase-1	SMMC-7721肝癌细胞	[86]

8 展望和总结

研究证实在ALD, NAFLD, 肝纤维化和肝癌等慢性肝病病变过程, 细胞焦亡通路中相关蛋白存在异常表达, 特别是NLRP3炎症小体的表达显著增加, 表明细胞焦亡在肝脏炎症损伤、脂质沉积、纤维化和癌变过程起关键作用。细胞焦亡的致病机制比较复杂, 目前发现多数肝脏疾病发生伴随着NLRP3/Caspase-1/GSDMD通路的激活, 进而释放大量细胞内容物触发炎症级联放大, 从而促进肝脏疾病发展。肝细胞中NLRP3炎症小体的激活会造成肝组织炎症损伤和脂肪变性, 外源性刺激物和内源性损伤因子引起慢性肝损伤产生的NLRP3炎症小体可直接激活或间接激活HSC, 进而分泌大量胶原和α-SMA, 导致ECM沉积而促进肝纤维化, 最后甚至发展为肝癌。因此, 抑制细胞焦亡通路的传导可以延缓肝病进程, 这能够作为肝病治疗的潜在作用靶点。研究表明中药单体、中药提取物和中药复方可以通过抑制NLRP3炎症小体的表达调控焦亡信号通路, 进而减轻炎性细胞因子对肝细胞损害。本文归纳总结细胞焦亡信号通路和肝病之间关系及中药干预状况, 为中药治疗肝病提供新的思路。

但目前中药调控焦亡通路抗肝病研究仍存在如下问题:①多数肝脏疾病都伴随着焦亡关键分子的异常表达, 中药进行干预后, 主要通过抑制焦亡通路发挥抗肝病作用, 然而, 研究发现中药也可上调焦亡信号通路抑制肝癌细胞, 表明中药在不同肝病中对相同信号通路具有不同调节作用, 使机体内环境趋于平衡, 中药具有的这种特性仍有待深入研究。②当前中药抗肝脏疾病的细胞焦亡通路的分子机制, 大多集中在关键分子NLRP3炎症小体研究

上，对中药如何调控此关键分子机制较少。③中药和中药复方抗肝病成分复杂，较难阐明是单一成分还是多成分影响焦亡通路起到治疗作用，是抑制单一靶点还是多靶点影响焦亡信号通路发挥抗肝病作用，今后引入生物信息学及组学等先进技术可能在一定程度上阐明这一问题。

总之，中药在抗肝病发挥重要作用，本综述结论表明中药调节细胞焦亡通路治疗肝病的分子机制，但由于技术所限，当前的研究未能解决一些关键问题。在未来，随着技术的发展，比如生物信息学方法、组学等高通量技术相结合，多学科合作等研究方法和模式，将会阐明中药抗肝病的分子机制及药效物质基础。

［参考文献］

［1］ COOKSON B T, BRENNAN M A. Pro-inflammatory programmed cell death［J］. Trends Microbiol, 2001, 9(3): 113-114.

［2］ MAN S M, KARKI R, KANNEGANTI T D. Molecular mechanisms and functions of pyroptosis, inflammatory Caspases and inflammasomes in infectious diseases［J］. Immunol Rev, 2017, 277(1): 61-75.

［3］ MIAO E A, LEAF I A, TREUTING P M, et al. Caspase-1-induced pyroptosis is an innate immune effector mechanism against intracellular bacteria［J］. Nat Immunol, 2010, 11(12): 1136-1142.

［4］ SHOJAIE L, IORGA A, DARA L. Cell death in liver diseases: a review［J］. Int J Mol Sci, 2020, 21(24): 9682.

［5］ AIZAWA S, BRAR G, TSUKAMOTO H. Cell death and liver disease［J］. Gut Liver, 2020, 14(1): 20-29.

［6］ WU X, DONG L, LIN X, et al. Relevance of the NLRP3 inflammasome in the pathogenesis of chronic liver disease［J］. Front Immunol, 2017, doi: 10.3389/fimmu.2017.01728.

［7］ GUO H, XIE M, ZHOU C, et al. The relevance of pyroptosis in the pathogenesis of liver diseases［J］. Life Sci, 2019, doi: 10.1016/j.lfs.2019.02.060.

［8］ WU J, LIN S, WAN B, et al. Pyroptosis in liver disease: new insights into disease mechanisms［J］. Aging Dis, 2019, 10(5): 1094-1108.

［9］ ALMAMUN A, WU Y, JIA C, et al. Role of pyroptosis in liver diseases［J］. Int Immunopharmacol, 2020, 84: 106489. doi: 10.1016/j.intimp.2020, 106489.

［10］ MEHAL W Z. Constitutive NLRP3 activation: too much of a bad thing［J］. Hepatology, 2014, 59(3): 761-763.

［11］ ZHONG Y, KINIO A, SALEH M. Functions of NOD-like receptors in human diseases［J］. Front Immunol, 2013, doi: 10.3389/fimmu.2013.00333.

［12］ AL-DAYYAT H M, RAYYAN Y M, TAYYEM R F. Non-alcoholic fatty liver disease and associated dietary and lifestyle risk factors［J］. Diabetes Metab Syndr, 2018, 12(4): 569-575.

［13］ MITSUYOSHI H, YASUI K, HARA T, et al. Hepatic nucleotide binding oligomerization domain-like receptors pyrin domain-containing 3 inflammasomes are associated with the histologic severity of non-alcoholic fatty liver disease［J］. Hepatol Res, 2017, 47(13): 1459-1468.

［14］ BLASETTI FANTAUZZI C, MENINI S, IACOBINI C, et al. Deficiency of the purinergic receptor 2X(7) attenuates nonalcoholic steatohepatitis induced by high-fat diet: possible role of the NLRP3 inflammasome［J］. Oxid Med Cell Longev, 2017, doi: 10.1155/2017/8962458.

［15］ SUI Y H, LUO W J, XU Q Y, et al. Dietary saturated fatty acid and polyunsaturated fatty acid oppositely affect hepatic NOD-like receptor protein 3 inflammasome through regulating nuclear factor-kappa B activation［J］. World J Gastroenterol, 2016, 22(8): 2533-2544.

［16］ PAN J, OU Z, CAI C, et al. Fatty acid activates NLRP3 inflammasomes in mouse Kupffer cells through mitochondrial DNA release［J］. Cell Immunol, 2018, doi: 10.1016/j.cellimm.2018.08.006.

［17］ CAI C, ZHU X, LI P, et al. NLRP3 deletion inhibits the non-alcoholic steatohepatitis development and inflammation in kupffer cells induced by palmitic acid［J］. Inflammation, 2017, 40(6): 1875-1883.

［18］ MRIDHA A R, WREE A, ROBERTSON A A B, et al. NLRP3 inflammasome blockade reduces liver inflammation and fibrosis in experimental NASH in mice［J］. J Hepatol, 2017, 66(5): 1037-1046.

［19］ CHEN Y, MA K. NLRC4 inflammasome activation regulated by TNF-α promotes inflammatory responses in nonalcoholic fatty liver disease［J］. Biochem Biophys Res Commun, 2019, 511(3): 524-530.

［20］ PENG Y, FRENCH B A, TILLMAN B, et al. The inflammasome in alcoholic hepatitis: Its relationship with Mallory-Denk body formation［J］. Exp Mol Pathol, 2014, 97(2): 305-313.

［21］ LE DARÉ B, VICTONI T, BODIN A, et al. Ethanol upregulates the P2X7 purinergic receptor in human macrophages［J］. Fundam Clin Pharmacol, 2019, 33

(1): 63-74.

[22] HEO M J, KIM T H, YOU J S, et al. Alcohol dysregulates miR-148a in hepatocytes through FoxO1, facilitating pyroptosis via TXNIP overexpression [J]. Gut, 2019, 68(4): 708-720.

[23] PETRASEK J, IRACHETA-VELLVE A, SAHA B, et al. Metabolic danger signals, uric acid and ATP, mediate inflammatory cross-talk between hepatocytes and immune cells in alcoholic liver disease [J]. J Leukoc Biol, 2015, 98(2): 249-256.

[24] BAI X, SUN S S, ZHOU J Y. Role of NLRP3 inflammasome in the pathogenesis of alcoholic liver disease[J]. Zhonghua Gan Zang Bing Za Zhi, 2019, 27(7): 567-571.

[25] KHANOVA E, WU R, WANG W, et al. Pyroptosis by Caspase 11/4-gasdermin-*D* pathway in alcoholic hepatitis in mice and patients [J]. Hepatology, 2018, 67(5): 1737-1753.

[26] LUAN J, CHEN W, FAN J, et al. GSDMD membrane pore is critical for IL-1β release and antagonizing IL-1β by hepatocyte-specific nanobiologics is a promising therapeutics for murine alcoholic steatohepatitis [J]. Biomaterials, 2020, doi: 10. 1016/j. biomaterials.

[27] INZAUGARAT M E, JOHNSON C D, HOLTMANN T M, et al. NLR family pyrin domain-containing 3 inflammasome activation in hepatic stellate cells induces liver fibrosis in mice [J]. Hepatology, 2019, 69(2): 845-859.

[28] GAUL S, LESZCZYNSKA A, ALEGRE F, et al. Hepatocyte pyroptosis and release of inflammasome particles induce stellate cell activation and liver fibrosis [J]. J Hepatol, 2021, 74(1): 156-167.

[29] LI Y, ZHANG Y, CHEN T, et al. Role of aldosterone in the activation of primary mice hepatic stellate cell and liver fibrosis via NLRP3 inflammasome [J]. J Gastroenterol Hepatol, 2020, 35(6): 1069-1077.

[30] WANG H, LIU S, WANG Y, et al. Nod-like receptor protein 3 inflammasome activation by Escherichia coli RNA induces transforming growth factor beta 1 secretion in hepatic stellate cells [J]. Bosn J Basic Med Sci, 2016, 16(2): 126-131.

[31] MENG N, XIA M, LU Y Q, et al. Activation of NLRP3 inflammasomes in mouse hepatic stellate cells during Schistosoma J. infection [J]. Oncotarget, 2016, 7(26): 39316-39331.

[32] WEI Q, MU K, LI T, et al. Deregulation of the NLRP3 inflammasome in hepatic parenchymal cells during liver cancer progression [J]. Lab Invest, 2014, 94(1): 52-62.

[33] WEI Q, GUO P, MU K, et al. Estrogen suppresses hepatocellular carcinoma cells through ERβ-mediated upregulation of the NLRP3 inflammasome [J]. Lab Invest, 2015, 95(7): 804-816.

[34] CUI H, ZHANG Y, ZHANG Q, et al. A comprehensive genome-wide analysis of long noncoding RNA expression profile in hepatocellular carcinoma [J]. Cancer Med, 2017, 6(12): 2932-2941.

[35] CHEN Z, HE M, CHEN J, et al. Long non-coding RNA SNHG7 inhibits NLRP3-dependent pyroptosis by targeting the miR-34a/SIRT1 axis in liver cancer [J]. Oncol Lett, 2020, 20(1): 893-901.

[36] LI W, LI Y, SIRAJ S, et al. FUN14 Domain-containing 1-mediated mitophagy suppresses hepatocarcinogenesis by inhibition of inflammasome activation in mice [J]. Hepatology, 2019, 69(2): 604-621.

[37] YAN W, CHANG Y, LIANG X, et al. High-mobility group box 1 activates Caspase-1 and promotes hepatocellular carcinoma invasiveness and metastases [J]. Hepatology, 2012, 55(6): 1863-1875.

[38] ZHANG B, XU D, SHE L, et al. Silybin inhibits NLRP3 inflammasome assembly through the NAD(+)/SIRT2 pathway in mice with nonalcoholic fatty liver disease [J]. Faseb J, 2018, 32(2): 757-767.

[39] DING C, ZHAO Y, SHI X, et al. New insights into salvianolic acid A action: regulation of the TXNIP/NLRP3 and TXNIP/ChREBP pathways ameliorates HFD-induced NAFLD in rats [J]. Sci Rep, 2016, doi: 10. 1038/srep28734.

[40] YANG S J, LIM Y. Resveratrol ameliorates hepatic metaflammation and inhibits NLRP3 inflammasome activation [J]. Metabolism, 2014, 63(5): 693-701.

[41] LV Y, GAO X, LUO Y, et al. Apigenin ameliorates HFD-induced NAFLD through regulation of the XO/NLRP3 pathways [J]. J Nutr Biochem, 2019, doi: 10. 1016/j. jnutbio. 2019. 05. 015.

[42] VIVOLI E, CAPPON A, MILANI S, et al. NLRP3 inflammasome as a target of berberine in experimental murine liver injury: interference with P2X7 signalling [J]. Clin Sci (Lond), 2016, 130(20): 1793-1806.

[43] MAI W, XU Y, XU J, et al. Berberine inhibits nod-like receptor family pyrin domain containing 3 inflammasome activation and pyroptosis in nonalcoholic steatohepatitis via the ROS/TXNIP axis

[J]. Front Pharmacol, 2020, doi: 10.3389/fphar.2020.00185.

[44] YAN T, WANG H, CAO L, et al. Glycyrrhizin alleviates nonalcoholic steatohepatitis via modulating bile acids and Meta-inflammation [J]. Drug Metab Dispos, 2018, 46(9): 1310-1319.

[45] CABRERA D, WREE A, POVERO D, et al. Andrographolide ameliorates inflammation and fibrogenesis and attenuates inflammasome activation in experimental non-alcoholic steatohepatitis [J]. Sci Rep, 2017, 7(1): 3491.

[46] 吴柳, 杨广越, 张洁, 等. 下瘀血汤下调NLRP3改善高脂饮食诱导小鼠非酒精性脂肪性肝炎[J]. 中国中西医结合杂志, 2020, 40(10): 1202-1208.

[47] CHEN Y, HE X, YUAN X, et al. NLRP3 inflammasome formation and activation in nonalcoholic steatohepatitis: therapeutic target for antimetabolic syndrome remedy FTZ [J]. Oxid Med Cell Longev, 2018, doi: 10.1155/2018/2901871.

[48] 尹抗抗, 聂娟, 唐标. 降脂理肝汤抑制NLRP3炎症小体活化减轻高脂饮食诱导的大鼠非酒精性脂肪肝病[J]. 中国免疫学杂志, 2020, 36(22): 2716-2720.

[49] YUQI Y, HAITAO Z, DIAN Y, et al. Gegen qinlian decoction ameliorates nonalcoholic fatty liver disease in rats oxidative stress, inflammation, and the NLRP3 signal axis [J]. Evid-Based Compl Alt Med, 2021, doi: 10.1155/2021/6659445.

[50] XIAO J, WANG F, LIONG E C, et al. Lycium barbarum polysaccharides improve hepatic injury through NFkappa-B and NLRP3/6 pathways in a methionine choline deficient diet steatohepatitis mouse model [J]. Int J Biol Macromol, 2018, 120(Pt B): 1480-1489.

[51] ZHANG Y, JIN Q, LI X, et al. Amelioration of alcoholic liver steatosis by dihydroquercetin through the modulation of AMPK-dependent lipogenesis mediated by P2X7R-NLRP3-inflammasome activation [J]. J Agric Food Chem, 2018, 66(19): 4862-4871.

[52] LI X, ZHANG Y, JIN Q, et al. Liver kinase B1/AMP-activated protein kinase-mediated regulation by gentiopicroside ameliorates P2X7 receptor-dependent alcoholic hepatosteatosis [J]. Br J Pharmacol, 2018, 175(9): 1451-1470.

[53] ZUO A, WANG S, LIU L, et al. Understanding the effect of anthocyanin extracted from *Lonicera caerulea* L. on alcoholic hepatosteatosis [J]. Biomed Pharmacother, 2019, doi: 10.1016/j.biopha.2019.109087.

[54] KAI J, YANG X, WANG Z, et al. Oroxylin a promotes PGC-1α/Mfn2 signaling to attenuate hepatocyte pyroptosis via blocking mitochondrial ROS in alcoholic liver disease [J]. Free Radic Biol Med, 2020, doi: 10.1016/j.freeradbiomed.2020.03.031.

[55] LI M, WU C, GUO H, et al. Mangiferin improves hepatic damage-associated molecular patterns, lipid metabolic disorder and mitochondrial dysfunction in alcohol hepatitis rats [J]. Food Funct, 2019, 10(6): 3514-3534.

[56] YANG C, HE X, ZHAO J, et al. Hepatoprotection by ginsenoside Rg_1 in alcoholic liver disease [J]. Int Immunopharmacol, 2021, doi: 10.1016/j.intimp.2020.107327.

[57] 卫昊, 张新玥. 灵芝酸A对*D*-氨基半乳糖/脂多糖诱导小鼠肝损伤的保护作用[J]. 南京中医药大学学报, 2019, 35(4): 432-435.

[58] PAN C W, PAN Z Z, HU J J, et al. Mangiferin alleviates lipopolysaccharide and *D*-galactosamine-induced acute liver injury by activating the Nrf2 pathway and inhibiting NLRP3 inflammasome activation [J]. Eur J Pharmacol, 2016, doi: 10.1016/j.ejphar.2015.12.006.

[59] GAO Y Z, ZHAO L F, MA J, et al. Protective mechanisms of wogonoside against Lipopolysaccharide/*D*-galactosamine-induced acute liver injury in mice [J]. Eur J Pharmacol, 2016, doi: 10.1016/j.ejphar.2016.02.040.

[60] WANG D, ZHANG M, WANG T, et al. Green tea polyphenols prevent lipopolysaccharide-induced inflammatory liver injury in mice by inhibiting NLRP3 inflammasome activation [J]. Food Funct, 2019, 10(7): 3898-3908.

[61] CHEN Y, QUE R, LIN L, et al. Inhibition of oxidative stress and NLRP3 inflammasome by saikosaponin-D alleviates acute liver injury in carbon tetrachloride-induced hepatitis in mice [J]. Int J Immunopathol Pharmacol, 2020, doi: 10.1177/2058738420950593.

[62] ZHANG X, KUANG G, WAN J, et al. Salidroside protects mice against CCl_4-induced acute liver injury via down-regulating CYP2E1 expression and inhibiting NLRP3 inflammasome activation [J]. Int Immunopharmacol, 2020, doi. 10.1016/j.intimp.2020.106662.

[63] ZHANG Y, QU X, GAO H, et al. Quercetin attenuates NLRP3 inflammasome activation and apoptosis to protect INH-induced liver injury via regulating SIRT1 pathway [J]. Int

Immunopharmacol, 2020, doi: 10.1016/j.intimp.2020.106634.

[64] XUE R, QIU J, WEI S, et al. Lycopene alleviates hepatic ischemia reperfusion injury via the Nrf2/HO-1 pathway mediated NLRP3 inflammasome inhibition in Kupffer cells [J]. Ann Transl Med, 2021, 9(8): 631.

[65] LIU X, WANG Y, WU D, et al. Magnolol prevents acute alcoholic liver damage by activating PI3K/Nrf2/PPARγ and inhibiting NLRP3 signaling pathway [J]. Front Pharmacol, 2019, doi: 10.3389/fphar.2019.01459.

[66] 李琛,戴晨希,阚建英. 和厚朴酚对*D*-氨基半乳糖/脂多糖诱导的急性肝损伤大鼠NLRP3炎症通路及肝细胞自噬的影响[J]. 热带医学杂志,2021,21(2):148-151,74.

[67] 俞佳,周垚,厉瑶,等. 茵陈芍甘汤对内毒素性急性肝损伤小鼠NLRP3炎症小体的影响[J]. 中华中医药学刊,2015,33(11):2734-2737.

[68] 岳紫晨,音金萍,陈玲玲,等. 健脾理气方通过下调NLRP3炎症小体的活化防治内毒素性急性肝损伤大鼠[J]. 中药药理与临床,2020,36(1):168-173.

[69] WANG Z D, ZHANG Y, DAI Y D, et al. Tamarix chinensis Lour inhibits chronic ethanol-induced liver injury in mice [J]. World J Gastroenterol, 2020, 26(12): 1286-1297.

[70] 冯会婷,戴卫波,白莎莎,等. 基于细胞焦亡探讨琴叶榕提取物对急性酒精性肝损伤的保护机制[J]. 中国实验方剂学杂志,2020,26(13):125-131.

[71] 刘晓东,温雯静,赵志军. 多穗柯总黄酮对四氯化碳致小鼠急性肝损伤的保护作用[J]. 医药导报,2020,39(12):1626-1630.

[72] 王肖辉,周霖,杜秋争,等. 五味子甲素对四氯化碳诱导小鼠肝纤维化的保护作用及其机制研究[J]. 中国药房,2020,31(22):2725-2730.

[73] LIU D, QIN H, YANG B, et al. Oridonin ameliorates carbon tetrachloride-induced liver fibrosis in mice through inhibition of the NLRP3 inflammasome [J]. Drug Dev Res, 2020, 81(4): 526-533.

[74] SHI Y S, LI X X, LI H T, et al. Pelargonidin ameliorates CCl_4-induced liver fibrosis by suppressing the ROS-NLRP3-IL-1β axis via activating the Nrf2 pathway [J]. Food Funct, 2020, 11(6): 5156-5165.

[75] 郑洋,杨妍琪,宗晓轲,等. 莪术醇对肝星状细胞NLRP3炎症小体作用的实验研究[J]. 时珍国医国药,2021,32(1):58-60.

[76] ZHU Z, HU R, LI J, et al. Alpinetin exerts anti-inflammatory, anti-oxidative and anti-angiogenic effects through activating the Nrf2 pathway and inhibiting NLRP3 pathway in carbon tetrachloride-induced liver fibrosis [J]. Int Immunopharmacol, 2021, doi. 10.1016/j.intimp.2021.107660.

[77] 黄晨恺,甘达凯,张望,等. 熊果酸对肝纤维化大鼠NOX2/ROS/NLRP3炎性小体活化的影响[J]. 基础医学与临床,2018,38(4):485-491.

[78] 崔东娟,刘涛,赵艳红. 香叶木素降低NLRP3炎性小体活性缓解CCl_4诱导的肝损伤大鼠肝纤维化[J]. 中国免疫学杂志,2019,35(5):555-559.

[79] WU X, ZHANG F, XIONG X, et al. Tetramethylpyrazine reduces inflammation in liver fibrosis and inhibits inflammatory cytokine expression in hepatic stellate cells by modulating NLRP3 inflammasome pathway [J]. IUBMB Life, 2015, 67(4): 312-321.

[80] CHU Q, JIANG Y, ZHANG W, et al. Pyroptosis is involved in the pathogenesis of human hepatocellular carcinoma [J]. Oncotarget, 2016, 7(51): 84658-84665.

[81] ZHANG Y, YANG H, SUN M, et al. Alpinumisoflavone suppresses hepatocellular carcinoma cell growth and metastasis via NLRP3 inflammasome-mediated pyroptosis [J]. Pharmacol Rep, 2020, 72(5): 1370-1382.

[82] LI P, LIU Y, HE Q. Anisodamine suppressed the growth of hepatocellular carcinoma cells, induced apoptosis and regulated the levels of inflammatory factors by inhibiting NLRP3 inflammasome activation [J]. Drug Des Devel Ther, 2020, 14: 1609-1620.

[83] 郑艳侠,姚杨,苏杰,等. 迷迭香酸通过Vimentin/NLRP3影响人肝癌HepG2细胞的增殖及凋亡[J]. 中国药理学通报,2018,34(10):1380-1384.

[84] FAN S H, WANG Y Y, LU J, et al. Luteoloside suppresses proliferation and metastasis of hepatocellular carcinoma cells by inhibition of NLRP3 inflammasome [J]. PLoS One, 2014, 9(2): e89961.

[85] 冯明辉,贺松其,黄松泽,等. 鳖甲煎丸对二乙基亚硝胺诱导的大鼠肝癌的抑制作用及机制[J]. 南方医科大学学报,2020,40(8):1148-1154.

[86] 卓少元,谢金玲. 健脾益气方含药血清下调Vimentin蛋白水平对人肝癌细胞SMMC-7721的影响[J]. 时珍国医国药,2017,28(1):55-59.

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