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Curcumin and Nonalcoholic Fatty Liver Disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic liver disease in the world; the prevalence of NAFLD in different populations is 25% - 45%; due to the global increase in obesity and diabetes prevalence, NAFLD is on the rise. NAFLD ranges from clinically benign hepatic steatosis to non-alcoholic fatty liver disease (NASH), an intermediate disease, to cirrhosis and even liver failure and death. Considering the high prevalence of NAFLD and its adverse impact on patients' quality of life, curcumin is *Curcuma longa* L., a bioactive polyphenol pigment in turmeric. In recent decades, more and more studies have shown that curcumin plays an important role in the treatment of liver diseases and has become an increasingly interesting research object. It has significant protective and therapeutic effects on non-alcoholic fatty liver diseases through a variety of cellular and molecular mechanisms. This article mainly reviews curcumin treatment of nonalcoholic fatty liver disease.

Keywords

Curcumin, Nonalcoholic Fatty Liver, Lipid, Oxidative Stress, Inflammation, Apoptosis, Autophagy, Hepatic Stellate Cell

姜黄素与非酒精性脂肪肝疾病

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摘　要

非酒精性脂肪性肝病(non alcohol fatty liver disease, NAFLD)是全球最常见的慢性肝病，NAFLD在不同人群中的患病率在25%~45%之间，由于全球肥胖症和糖尿病患病率的增加，NAFLD呈上升趋势。NAFLD的范围从临床上最良性的肝脂肪变性，到非酒精性脂肪肝(NASH) (一种中间病变)，再到肝硬化甚至肝功能衰竭和死亡。姜黄素(curcumin)是姜黄(*Curcuma longa* L.)是姜黄中具有生物活性的多酚类色素。近几十年来，越来越多的研究表明姜黄素在肝脏疾病的治疗中起着重要作用，已成为人们越来越感兴趣的研究对象，它通过多种细胞和分子机制对非酒精性脂肪肝疾病具有显著的保护和治疗作用。本文主要针对姜黄素治疗非酒精性脂肪肝进行综述。

关键词

姜黄素，非酒精性脂肪肝，脂质，氧化应激，炎症，凋亡，自噬，肝星状细胞

1. 引言

姜黄素[1,7-双(4-羟基-3-甲氧基苯基)-1,6-庚二烯 3,5-二酮]是从姜黄根中提取的一种天然黄色多酚。姜黄根是一种生长在世界热带和亚热带地区的植物，在许多亚洲国家广泛用于食品制备。姜黄素具有抗炎、抗氧化、抗病毒和清除氧自由基、降低血脂、保护肾脏、预防癌症和抗癌等作用[1] [2] [3] [4]。姜黄素的使用在许多国家的传统医学中已经有数百年的历史。近年来发现，姜黄素在治疗肝脏疾病方面表现出了非常好的前景[5]。考虑到 NAFLD 的高患病率和对患者生活质量的不利影响，本文主要目的是总结姜黄素在治疗非酒精性脂肪肝脏疾病中的作用，并着重针对姜黄素治疗非酒精性脂肪肝的药物作用及机制进行综述。

2. 姜黄素对非酒精性脂肪肝病的作用机制

非酒精性脂肪肝的标志是由于酒精滥用以外的其他因素导致的肝脏脂肪堆积。胰岛素抵抗已被认为是 NAFLD [6]及其相关共病(包括中央型肥胖、2 型糖尿病和代谢综合征)发病机制的关键触发因素。NAFLD 的治疗主要取决于其严重程度，无论是否治疗，NAFLD 在特定人群中都可能发展为纤维化和肝硬化，并且随着年龄的增长、糖尿病和肥胖症的增加，其风险也会增加[7] [8] [9]。因此，寻找有效、安全控制 NAFLD/NASH 的治疗药物具有重要意义。目前，通过临床研究及特殊动物模型研究，对 NAFLD 发病机制的认识取得一定的进展[10]。最被接受的理论是 Day 和 James [5]提出的“双击假说”。“第一个打击”是脂肪变性的发展，长期营养过剩导致脂质代谢失调，并在肝脏中引发游离脂肪酸(FFAs)和甘油三酯的积累。在“第二次打击”中，脂肪变性由于氧化应激、线粒体功能障碍和炎症细胞因子而发展为炎症和纤维化，导致肝细胞炎症和坏死，激活肝细胞纤维化。姜黄素可以改善胰岛素抵抗和高甘油三酯血症，姜黄素还可以通过对抗氧化应激及炎性反应，降低肝细胞凋亡水平，诱导变性肝细胞自噬，阻止 HSC 活化和促进 HSC 调亡，影响 ECM 的合成和代谢起到治疗非酒精脂肪性肝病的作用[11]。

2.1. 抗脂质

肝细胞中脂质的异常积累(5%或更高)通常被称为脂肪变性。大泡脂肪变性形成为非酒精性脂肪性肝炎(NASH)病灶发展的有利环境。姜黄素已被证明可以减少高脂饮食啮齿类动物肝细胞内的脂质储存，有助于减少线粒体功能障碍和氧化应激引起的肝脏损伤。Rao 等[12]报道了姜黄素的降血脂活性的初步数据，结果显示，与只喂食胆固醇的大鼠相比，同时喂食胆固醇和姜黄素的大鼠肝脏胆固醇含量较低。随后，Asai 和 Miyazawa [13]研究表明，补充 1.0 g 姜黄素/100 g 饲料的雄性 Sprague-Dawley 大鼠与未补充姜黄素的对照组大鼠相比，其肝脏三酰基甘油和胆固醇浓度显著降低。这可以解释姜黄素在体内具有降血脂作用。Rukkumani 等[14] [15]评估了姜黄素及其合成类似物在酒精诱导和高脂肪饮食肝损伤雄性大鼠模型中的肝保护和降血脂的作用。在这两个实验中，姜黄素被证明可以减轻肝脏的组织病理学变化，并降低肝脏组织中胆固醇、甘油三酯的水平。最近，Jang 等人[16]研究表明，在仓鼠高脂饮食中补充姜黄素可以降低循环脂质的水平和肝脏脂质的水平。姜黄素也已被证明能够显著抑制关键蛋白质的表达和活动参与新陈代谢，如肝蛋白酪氨酸磷酸酶 1 B (PTP1B)，姜黄素还能够降低 LOX-1 的表达，阻断细胞外 OX-LDL 进入造血干细胞，从而阻止其活化[17]。很明显，姜黄素具有降血脂作用，可阻止脂肪酸在肝细胞中积累，这是各种代谢失衡导致最终导致 NASH 的结果。尽管姜黄素在动物模型中的抗脂质作用有积极的研究结果，但在临床实践中探讨姜黄素抗脂质作用的研究较少[18] [19] [20]。

2.2. 降低氧化应激

氧化应激是脂肪肝第二次打击的重要原因，它在脂肪肝的形成和发展过程中起着非常重要的作用。而非酒精性肝硬化往往伴随着氧化应激的增加。活性氧(ros)对组织具有很强的破坏性，是由分子氧在氧化过程中形成的中间产物，并且 Ros 可以通过氧化大分子引起损伤[21]。活性氧(ROS)水平过高，活性氧的产生和降解不平衡可导致蛋白质、脂质降解。活性氧(ROS)还参与肝纤维化发生，并参与缺血、再生、坏死和凋亡的过程。氧化应激还可加重胰岛素抵抗，激活多种炎性细胞因子，损伤细胞核 DNA 并诱导细胞凋亡的发生，被认为是 NAFLD 由单纯脂肪变性向 NASH 发展的最关键环节[22]。SOD 是重要抗氧化酶，它可以清除机体自由基；T-AOC 可代表生物体内抗氧化剂的总体水平；GSH-Px 能催化过氧化物还原生成无毒羟基化合物，保护细胞不受过氧化物的损害[22]；MAD 是自由基与脂质过氧化反应的最终产物。它们都是衡量细胞氧化应激水平的重要指标[23]。姜黄素具有抗氧化活性，通过影响氧化应激的多个过程和信号传导通路有效清除肝细胞内过多的活性氧自由基，调节体内氧化应激酶的活性。有研究发现，高脂饮食大鼠通过姜黄素干预后，血清中 SOD、T-AOC、GSH-Px 均有明显的升高，MAD 降低，表明姜黄素能增强非酒精性脂肪肝大鼠肝脏抗氧化活性，抑制自由基生成，降低氧化应激水平[24]。姜黄素还可以通过干扰 HSC 上胰岛素信号通路，诱导胱氨酸连接酶的表达合成谷胱甘肽，减轻了胰岛素诱导的肝脏的氧化应激[25]。

2.3. 减少炎症反应

在肝脏中，NF-κB 可以调节多种炎症因子的表达。激活后，通过增加 TNF-α、IL-6、IL-1 等炎症因子的表达水平，参与肝脏的炎症反应过程。是 NAFLD 发展的重要机制[26]。研究发现，NAFLD 大鼠 TNF-α 和 IL-6 的表达明显高于正常对照组，在炎症细胞中诱导炎症反应，加重肝细胞损伤[27]。大量体外研究表明姜黄素具有强大的抗氧化和抗炎作用，这可能是其在慢性肝病中的保护作用的原因。姜黄素能下调非酒精性脂肪肝细胞中的多种炎症相关信号通路活性和基因转录，抑制趋化因子和炎症介质的释放，减少炎症细胞的增殖和活化。AFRIN 等[28]研究发现，姜黄素降低 NASH 小鼠 IFNβ-γ 和 IL-1β 诱导蛋白等促炎因子的表达，并且 HMGB1、NF-κB 的转录表达也明显下降，说明姜黄素通过抑制 HMGB1，NF-κB

的转录，延缓 NASH 进程。

2.4. 抑制细胞凋亡

细胞凋亡被认为是程序化细胞的一种形式死亡和各种过程的主要组成部分，如平衡细胞再生和消除，免疫功能系统等等。诱导细胞凋亡后，细胞出现皱缩，DNA 损伤，染色质凝聚，膜起泡，以及体内凋亡小体的碎裂和发育核等形态变化。NAFLD 肝脏中的饱和脂肪酸和游离胆固醇等诱导肝细胞凋亡。PCNA、caspase-3、caspase-8、caspase-9、Bax 和 Bcl-2 基因是细胞增殖和凋亡相关途径的关键因子，凋亡水平由 Bcl-2 和 Bax 蛋白表达水平的比值决定[29]。实验表明，姜黄素治疗后肝组织中的 Bcl-2 表达水平增高而 Bax 表达水平降低，说明姜黄素通过激活 Bcl-2 并抑制 Bax 表达，增加 Bcl-2/Bax 比值抑制 NAFLD 大鼠肝细胞凋亡[24]。Li [30]等同时证实姜黄素可上调对乙酰氨基酚(APAP)所致小鼠急性肝损伤模型中凋亡相关基因 Bcl-2/Bax 的比值。降低肝细胞凋亡水平。因此，姜黄素能显著改善 NAFLD 肝细胞凋亡。

2.5. 促进肝细胞自噬

自噬是一种细胞过程，通过吞噬多余的细胞器和蛋白质，在细胞质中形成双膜自噬体，然后与溶酶体结合以进行降解。正常水平的自噬是对维持正常的肝脏功能有着非常重要的作用。然而，过度的自噬会破坏正常蛋白质和细胞器[31]。因此，自噬能促进细胞存活，也能导致细胞死亡。在 NAFLD 中，通过清除损伤的细胞器或累积的多余的蛋白质聚集物等来维持细胞内环境的稳态从而降低对细胞的损伤的过程称为自噬。研究表明，高脂饮食小鼠肝组织自噬活性增加，而通过自噬抑制剂抑制肝细胞自噬后反而促进了细胞凋亡。说明在脂肪酸诱导的肝细胞损伤过程中，自噬对肝细胞起保护作用[32]-[44]。还有研究证实，姜黄素能诱导肝癌、乳腺癌、结肠癌和肺癌等肿瘤细胞的自噬[42] [43] [44] [45]。近年来的研究已阐明串扰凋亡与自噬的关系。有一些相交的蛋白质调节细胞凋亡和自噬，如结果研究已确定抗凋亡蛋白 bcl-2 和促凋亡蛋白 Bim 为相互作用伙伴。另外，自噬也受许多其他信号的调节，例如哺乳动物的目标雷帕霉素(mTOR)和 AMP 活化蛋白激酶(AMPK)作出回应营养素，生长因子和能量压力。据报道，姜黄素似乎激活了许多细胞过程 JNK1 和 AMPK 信号通路，进而调节各种细胞凋亡和自噬细胞。目前，姜黄素诱导非酒精性脂肪性肝病细胞自噬机理仍需进一步研究。

2.6. 阻止肝星状细胞活化

非酒精性脂肪性肝炎(NASH)是一种晚期非酒精性脂肪性肝病，通常与肥胖和/2 型糖尿病有关。大约三分之一的 NASH 中存在肝纤维化。肝纤维化可进一步发展为肝硬化甚至肝细胞癌，导致肝衰竭、门脉高压甚至死亡。肝星状细胞(hepatic Stellate cells, HSC)激活是肝纤维化发展过程中的关键环节。因此，有效抑制 HSC 的活化，促进 HSC 的凋亡清除，从而减少以胶原纤维为主的细胞外基质的沉积，对逆转肝纤维化在非酒精性疾病治疗中具有重要意义。近年来，多项研究发现，姜黄素在抑制 HSC 激活，促进 HSC 凋亡清除方面有重要作用。研究证实姜黄素可以抑制 HSC 的活化和增殖，在 G2/M 期抑制细胞周期，诱导 HSC 凋亡，并具有剂量－时间依赖性[46]。Lin 等[47]以大鼠 HSC-T6 细胞系为研究对象，发现姜黄素在 TGF-β 刺激后抑制 HSC-T6 细胞中 SMA 的表达和胶原沉积，说明其具有抗纤维化作用。然而，姜黄素浓度的增加引起了不同的效应，因为它们诱导了 HSC-T6 细胞凋亡。因此，姜黄素在这一水平上通过不同的剂量依赖机制发挥其肝保护作用。抑制 HSC 活化、增殖，可以从细胞因子及其信号转导途径进行调控，也可以通过清除肝细胞及内皮细胞损伤坏死时释放的氧化刺激因子，如氧自由基和炎性细胞因子等环节来进行。姜黄素通过下调 PDGF-βR，EGFR 和 TGF-β 并且诱导 PPAR-γmRNA 水平抑制 HSC 的活化和增殖，导致细胞外基质胶原蛋白的产生减少，保护肝脏不发生纤维化[48] [49]。研究发现，姜黄素

可以干扰胰岛素受体 IRS-PI3k-AKT 信号通路，抑制 GLUT4 膜转位从而抑制 HSC 活化[50] [51]。自然杀伤细胞(NK 细胞)在 HSC 的清除中也起着重要作用。KINGER 等[52]发现，姜黄素可以促进 HSC 衰老，改善主要组织相容性复合体 I 相关基因 A 和 NK 细胞活性，例如，UL16 连接蛋白配体表达对 NK 细胞中 HSC 的老化敏感，并促进 HSC 老化的清除。

3. 小结

综上所述，姜黄素通过以上多种作用机制起到治疗非酒精性脂肪肝病作用，它可能成为预防和治疗非酒精性脂肪肝的有效药物。然而其确切机制仍需进一步探索。但目前姜黄素在调控脂变肝细胞的作用机制报道甚少。因此，今后应进一步扩大从脂变细胞自噬这一视角明确姜黄素保护肝细胞的作用机制，为非酒精性脂肪性肝病防治寻找新的治疗靶点。

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