·综 述·

单味中药治疗非酒精性脂肪肝机制研究进展

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[摘要]非酒精性脂肪肝(non-alcoholic fatty liver disease,NAFLD)在全球成年人中发病率为25%,单味中药干预NAFLD的作用靶点及机制已被广泛研究。研究表明,泽泻、山楂叶黄酮等通过抑制脂肪合成的AMPK/SREBP1c/PPAR/ACC/FAS信号通路治疗NAFLD。姜黄素、紫苏油等治疗NAFLD的机制是通过调节胆固醇代谢FXR/LXR信号通路实现的。红景天苷、黄连素等通过抑制炎症及抗氧化应激相关通路起到治疗NAFLD的作用。虎杖苷、人参皂苷等治疗NAFLD的作用与自噬相关mTOR信号通路有关。绞股蓝、槲皮素等通过调节肠道菌群而人参皂苷通过延缓肝脏纤维化通路有效干预NAFLD。

[关键词]非酒精性脂肪肝;中药;信号通路;研究进展

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非酒精性脂肪肝(non-alcoholic fatty liver disease,NAFLD)是一种慢性进行性肝脏疾病,病理过程始于肝脂肪沉积,可逐渐进展为脂肪性肝炎、不可逆的肝纤维化,最终发展为肝癌。NAFLD的危害不仅局限于肝脏,还会影响多个系统导致代谢疾病、心血管疾病和慢性肾病等[1-2]。该病在全球成人中的发病率为25%[3]。在中国,NAFLD是肝功能异常的首要原因,也是第二大肝病隐患。目前,其发病机制尚未完全阐明,1998年提出的"二次打击"学说认为NAFLD的第一次打击是胰岛素抵抗引起的脂质蓄积,第二次打击是氧化应激和炎症等引起非酒精性脂肪性肝炎和纤维化的病理进程[4]。2010年提出的"多元平行打击"理论认为NAFLD发病是遗传因素、肠道菌群、胆固醇代谢、炎症等共同作用的结果[5]。目前,有关NAFLD的研究主要从抑制脂肪合成,减轻氧化应激,调节细胞能量稳态,恢复肠道微生态等分子信号通路方面展开[6]。中医将NAFLD归属于"胁痛""肝癖""积证""肥气"等病证范畴。早在《难经》中就有如"肝之积,名曰肥气,在左胁下"的描述。临床运用中药治疗NAFLD取得较好疗效,现将近年来单味中药干预NAFLD的潜在作用靶点及机制总结如下。

1 作用机制

1.1 抑制脂肪合成磷酸腺苷活化蛋白激酶/甾体调节元素结合转录因子1/过氧化物酶体增殖物活化受体/乙酰辅酶A羧化酶/脂肪酸合成酶(AMP-activated protein kinase/sterol regulatory element-binding protein 1c/peroxisome proliferator activated receptor/acetyl-CoA carboxylase/fatty acid synthase, AMPK/SREBP1c/PPAR/ACC/FAS)相关信号通路 肝脏脂肪沉积量大于肝脏质量5%时即发展为NAFLD,调控脂代谢某些关键酶活性和转录因子,可减少脂肪合成与积累。如AMPK是一种能量敏感性蛋白激酶,AMPK磷酸化增强能刺激机体分解代谢途径,同时抑制胆固醇、脂肪酸和三酰甘油(triglyceride,TG)的合成途径,降低体质量和肝脂肪含量,改善脂类水平和胰岛素抵抗[7-9]。脂代谢中的重要调控转录因子PPARγ位于调节脂肪形成转录级联的核心,上调其表达可抑制脂肪合成[10]。转录因子SREBP1c负责调控FAS和ACC,下调SREBP1c表达可抑制FAS、ACC的活性,减少脂肪合成[11]。研究[12-18]表明,泽泻、山楂叶黄酮、水飞蓟素、葛根素、黄芪甲苷Ⅳ、黄连素能通过激活AMPK磷酸化诱导SREBP1c磷酸化,下调SREBP1c、ACC、FAS等基因蛋白的表达,上调PPAR受体基因蛋白表达,从而抑制脂肪合成的相关信号通路。雷公藤红素对于脂肪合成通路具有双向调节作用[19]。

1.2 抗氧化应激与炎症相关通路 炎症和氧化应激相互依存、相互促进,贯穿于NAFLD发病的始终。NAFLD初期,炎症发生时活化的吞噬细胞在促炎因子的作用下,产生大量活性氧(reactive oxygen species, ROS)以杀灭病原体,但同时引起局部氧化应激和组织损伤,进一步激活与炎症相关的信号通路,加速炎症的发展[20]。最常见的氧化应激标记物包括一氧化氮(nitric oxide, NO)、丙二醛(ma-

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londialdehyde，MDA)和CYP2E1，抗氧化剂包括谷胱甘肽(glutathione，GSH)、超氧化物歧化酶(superoxide dismutase，SOD)、过氧化氢酶(catalase，CAT)[21]。脂联素是脂肪组织表达和分泌的细胞因子，具有抗炎，增加脂肪酸β氧化，减少肝细胞内脂质累积的作用[22]。高迁移率族蛋白B1(high mobility group box-1 protein，HMGB1)可作为炎症因子和内源性损伤分子模式配体加速肝脏炎症、损伤和纤维化发生[23]。NAFLD患者的MDA、HMGB1水平均明显上升，而SOD、GSH、脂联素水平则明显下降，MDA、HMGB1及脂联素水平被认为是NAFLD发生的独立危险因素[24]。红景天苷、黄连素、虎杖苷、黄芪多糖、槲皮素、木樨草苷、人参皂苷、姜黄素、大黄酸均能降低MDA水平，提高SOD水平，其中黄连素、木樨草苷、人参皂苷还能提高GSH水平[25-35]。红景天苷、黄连素、槲皮素可降低CYP2E1水平[36-38]。泽泻上调脂联素mRNA表达，山楂叶黄酮提高血清脂联素水平[12-13]。丹参提取物抑制HMGB1核异位、乙酰化及释放，白芍总苷可下调HMGB1蛋白表达[39-40]。

沉默信息调节因子2相关酶1(sirtuin1，SIRT1)是能量代谢和氧化应激的调节因子[41]。研究[39,42-44]表明，丹参提取物丹酚酸B、木瓜提取物及发酵液、人参皂苷Rb2均可以上调SIRT1，分别激活SIRT1/HMGB1、SIRT1-FoxO1、SIRT1/AMPK通路作用于NAFLD。Nrf2作为转录因子家族成员，是氧化还原代谢和蛋白质稳态的中枢调节剂[45]。研究[26,46-48]表明，黄连素、虎杖苷、绞股蓝、姜黄素可激活Nrf2抗氧化途径，分别通过Nrf2-ARE、Keap1-Nrf2、Sirt6-Nrf2、Nrf2-FXR-LXR信号通路上调Nrf2 mRNA及蛋白的表达。TXNIP蛋白是NLRP3炎症小体激活和内皮细胞释放白细胞介素-1β所必需的蛋白，可引起炎症应激与肥胖[49]。研究[25,46,50]表明：红景天苷、丹酚酸以及虎杖苷均可以下调TXNIP/NLRP3通路，作用于NAFLD；肿瘤坏死因子(tumor necrosis factor-α，TNF-α)和白细胞介素-6(interleukin6，IL-6)是NAFLD的主要促炎细胞因子。研究[19,28,31,35,38,50-56]表明，紫苏油、丹酚酸A、丹皮酚、黄连素、虎杖苷、槲皮素、木樨草苷、姜黄素、柑桔皮提取物、大黄酸以及雷公藤红素均可以降低炎症因子TNF-α和IL-6的水平，其中部分药物还能抑制炎症因子mRNA表达，缓解NAFLD炎症。Toll样受体4(Toll-like receptor 4，TLR4)介导的信号通路可活化核因子-κB，抑制IL-1β、TNF-α等炎症因子分泌对肝星状细胞(hepatic stellate cells，HSCs)的激活[57]。而雷公藤红素、紫苏油、丹酚酸B、白芍总苷均能阻断TRL4通路，下调TLR4 mRNA和(或)蛋白的表达，有效干预肝脏疾病[39,51,58-59]。

1.3 自噬相关mTOR信号通路 自噬可通过清除过量ROS和功能障碍的线粒体，改善内质网功能，减轻氧化应激，调节炎症反应。自噬还参与细胞质脂滴的选择性降解，因此，可通过调节肝细胞自噬治疗NAFLD[60-61]。哺乳动物雷帕霉素作用靶蛋白(mammalian target of raparmycin，mTOR)是自噬过程中关键调控蛋白，营养缺乏时mTOR被迅速抑制，自噬过程激活[62]。研究[44,63-64]表明，黄连素、虎杖苷、人参皂苷Rb2均可以恢复肝细胞自噬，上调自噬标记物表达水平，抑制mTOR信号通路，减轻肝脏脂质累积和炎症。

1.4 胆固醇代谢相关FXR/LXR信号通路 肝脏是机体清除胆固醇的主要器官，在肝内广泛分布的法尼醇X受体(farnesoid X receptor，FXR)和肝X受体(liver X receptor，LXR)是调节胆固醇代谢的主要核转录因子，可调控其分解。LXR的激活具有调节胆固醇稳态，诱导抗炎和增加胰岛素敏感性的作用，抑制LXR转录活性，可以有效地减轻肝脏脂肪变性、炎症和纤维化[65-66]。FXR在肝脏和肠道中参与胆汁酸稳态和肠肝循环的调节，在糖代谢中抑制肝糖异生，促进糖原合成[67]。近年来的研究提示，FXR/LXR信号通路有望成为NAFLD治疗的重要靶点。研究[48,68-70]表明，泽泻、姜黄素、紫苏油均可以激活FXR信号通路，上调FXR表达水平，而木犀草素可抑制LXR信号通路，下调LXR表达水平，这些中药均具有改善胆固醇代谢的作用。

1.5 抗肝纤维化相关通路 NAFLD持续进展会导致肝脏纤维化，活化的HSCs是胶原的关键生产者，增加HSC凋亡可延缓肝脏纤维化[71]。人参皂苷Rh1能降低HSC-T6活力并加速其凋亡，下调HSCs活化标记物α-平滑肌肌动蛋白(α-smooth muscle actin，α-SMA)表达水平，降低促纤维化及细胞外基质蛋白表达水平，延缓肝脏纤维化进程[72]。

1.6 调节肠道微生物 肠道菌群为药物治疗NAFLD的新思路与靶点，肠道菌群紊乱时有害细菌和内毒素增加，可通过影响肠道屏障功能、TLR信号传导、胆碱代谢、胆汁酸合成和氨基酸的产生，促进NAFLD发生与进展[73-74]。动物实验研究[38,51,75-77]表明，绞股蓝、紫苏油、黄连素、槲皮素、

砂仁挥发油均能有效调节肠道菌群，改变细菌丰度，促进优势菌群生长，改善肠黏膜屏障完整及通透性，有效减少有害细菌及菌群产物易位。这与中医所说的“肝与大肠相通”的理论不谋而合，肝脏借道大肠可降泄浊气，而肝疏泄功能的正常是保证大肠顺利降浊的前提。反之，当大肠因菌群失调无法顺利降浊时，肝脏的疏泄功能也必然受到影响，肝失疏泄日久，肝内污浊累积成病。中药可通过改善菌群结构，提高大肠的降浊能力以优化肝脏的疏泄功能，从而发挥抗NAFLD的作用。

2 中药有效改善NAFLD生化指标

临床研究表明，转氨酶水平升高对诊断NAFLD有重要价值，早期积极降低转氨酶水平有可能逆转脂肪肝的发生[78]。临床常规检测天冬氨酸氨基转移酶(aspartate aminotransferase，AST)及谷氨酸氨基转移酶(alanine transaminase，ALT)反映肝功能状况；检测低密度脂蛋白胆固醇(low density lipoprotein cholesterin，LDL-C)、高密度脂蛋白胆固醇(high density lipoprotein cholesterin，HDL-C)、TG、总胆固醇(total cholesterol，TC)可反映体内脂肪代谢状况。实验研究表明：能降低AST、ALT、TG、TC、LDL-C，升高HDL-C的单味中药或其有效成分有黄连素、黄芪多糖、槲皮素、白芍总苷、泽泻、人参皂苷[26,29,59,68,76,79-81]；降低AST、ALT、TG、TC的单味中药或其有效成分有紫苏、红景天苷、木樨草苷、大黄酸、葱白提取物、姜黄素[25,31,35,55,69,82]；仅降低AST、ALT的中药有丹参、绞股蓝[39,75]；仅降低TG、TC的单味中药或其有效成分是虎杖、雷公藤红素、砂仁、柑桔皮提取物、葛根[15,46,56,77,83]。

3 从中医理论探讨中药防治NAFLD机制

NAFLD发病率的增加与现代生活方式和饮食习惯密切相关。中医学认为，嗜食肥甘油腻易导致脾胃运化受损，湿浊内停，日久酿生湿热，加之生活压力增加，现代人多忧思恼怒而致肝气郁结，克犯脾胃，使其失于运化，滋生痰浊内蕴肝体，患病日久及肾，气化失司，易形成气滞血瘀，瘀血与痰又互结于肝脏，最终病入血分。因此，痰、湿、浊、瘀、热为NAFLD主要病理因素，临床常见的证型以湿浊内停证、肝郁脾虚证、湿热蕴结证、痰瘀互结证、脾肾两虚证为主[84]。治疗上应注重肝脾同治，调节中焦气机以促进水津布散，对于痰湿为患应化痰除湿、标本兼顾，久病有瘀应理血散结，内有郁热应酌加凉药。常用中药黄芪、人参、白芍等可助脾运化，红景天、丹参、山楂能活血化瘀祛脂，砂仁、虎杖、槲皮等化湿利湿，大黄、黄连、黄芩等清热燥湿。从中医角度来看，这些中药提取物种类虽不同，但都被证实有效，这与NAFLD中医病机密切相关。

4 展望

NAFLD病位虽在肝脏，但可能是全身代谢障碍在局部的具体体现。当前，学者从抑制炎症和氧化应激，调节肠道菌群等多方面、多角度探索阐明不同单味中药干预NAFLD的机制，取得一定成果，但也存在不足。首先，研究大多基于动物实验探讨单味中药干预NAFLD的机制，对于人体微环境下单味中药作用机制及临床疗效有待进一步深入。其次，结合中医证型观察中药组分干预机制和靶点的研究甚少，有待延续中药方证相关思想，开拓新视野。综上，今后应在总结药物治疗靶点和作用机制的基础上，进一步优化治疗方案，探索更高效的治疗方法。

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