•专题报道•

# 中药复方和活性化合物调节肠道菌群治疗非酒精性脂肪肝的研究进展

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**摘要**: 非酒精性脂肪肝 (non-alcoholic fatty liver disease, NAFLD) 是最常见的慢性肝病。然而, 由于其发病机制复杂, 目前尚无正式获批的治疗药物, 寻找安全、有效的抗NAFLD药物迫在眉睫。在现代医学中, NAFLD治疗以降脂药物作为主要治疗手段, 但是, 化学药物的临床疗效也十分有限, 且存在明显的不良反应。中药以其多途径、多靶点、不良反应少等特点在NAFLD的治疗中越来越受到关注。近年来, 大量研究证据表明肠道菌群失衡在NAFLD的发生发展中起重要作用。本综述系统汇总了近些年涉及到中药复方和中药活性化合物通过调节肠道菌群治疗NAFLD的研究情况, 为进一步探索NAFLD的发病机制和运用中医药治疗NAFLD的理念提供新的参考方向。

**关键词**: 肠道菌群; 非酒精性脂肪肝; 肠−肝轴; 中药; 代谢

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# Research progress of traditional Chinese medicine formulas and active compounds in the treatment of non-alcoholic fatty liver disease by regulating gut microbiota

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**Abstract**: Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases. However, due to its complex pathogenesis, there are no officially approved drugs for NAFLD treatment currently. Therefore, it is extremely urgent to find safe and effective anti-NAFLD drugs. Nowadays, lipid-lowering drugs are the main option for NAFLD therapy, but the clinical efficacy of chemical drugs is also very limited, as well as the frequent side effects or adverse reactions. Traditional Chinese medicine (TCM) has attracted more and more attention in the treatment of NAFLD due to its unique advantages through multiple targets and pathways with few side effects. In recent years, numerous studies have demonstrated that the imbalance of gut microbiota plays an important role in the occurrence and development of NAFLD. This review systematically summarizes the experimental and clinical evidences of TCM active compounds and TCM prescription involved in the regulation of intestinal flora in the treatment of NAFLD in recent years, so as to provide a reference for further exploring the pathogenesis of NAFLD and exploring TCM treatment methods.

**Key words**: gut microbiota; non-alcoholic fatty liver disease; gut-liver axis; traditional Chinese medicine; metabolism

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非酒精性脂肪肝 (non-alcoholic fatty liver disease, NAFLD) 是临床常见慢性肝病, 按其发病进程通常包括单纯性脂肪变性、非酒精性脂肪性肝炎 (non-alcoholic steatohepatitis, NASH)、肝纤维化、肝硬化及肝细胞癌, 其全球患病率约为25%, 我国肥胖人群NAFLD发病率达70%～80%[1,2]。尽管已有多个NAFLD药物处于临床前和临床研究阶段, 但目前尚无美国食品药品管理局 (Food and Drug Administration, FDA) 批准的NAFLD药物用于临床。中医药作为中华民族传统文化瑰宝, 在长期临床实践中形成了诸多对慢性复杂性疾病具有较好疗效的经典复方, 这些复方及中药来源活性化合物是药物研发的重要资源库, 在治疗各种复杂慢性代谢性疾病如NAFLD等方面发挥了重要作用。

在NAFLD发病机制的假说中, 除了经典的“二次打击”学说外, 最新研究表明[3], NAFLD的发生发展均与肠道菌群失衡密切相关。肠道菌群参与维持人体消化道中营养物质的消化、吸收及代谢, 进而影响人体能量代谢平衡[4]。肠道菌群失衡通过影响肠黏膜屏障完整性、炎症反应、菌群代谢物如短链脂肪酸 (short-chain fatty acids, SCFA) 的生产、次级胆汁酸代谢等多个途径参与肝脏脂质代谢及机体炎症免疫反应, 最终促进NAFLD的发生发展[5]。在长期临床实践中, 中医药已被证实在NAFLD的临床治疗中具有确切疗效, 同时, 大量研究表明中医药治疗NAFLD的作用机制与调节和恢复肠道菌群平衡状态密切相关[6-10]。本综述系统检索了近年来NAFLD的中医药治疗文献, 综述了中药通过肠道菌群调节改善NAFLD的基础和临床研究进展, 为靶向肠道菌群调节治疗NAFLD的药物研发提供参考。

## 1 NAFLD的诊断与治疗现状

### 1.1 NAFLD的诊断

NAFLD是一种潜在的进行性肝病, 与肝细胞的脂质和葡萄糖代谢失调有关, 其发病常与胰岛素抵抗、脂质代谢紊乱及肠-肝轴作用等多种因素相关[1]。

NAFLD患者的临床诊断主要依靠超声波或组织病理学检查[11], 并结合生活方式及药物因素, 如是否大量饮用酒精、长期服用导致脂肪堆积的药物 (如胺碘酮、皮质类固醇、甲氨蝶呤和他莫昔芬等)、丙型肝炎病毒感染 (尤其是3型)、单基因遗传病、严重营养不良和威尔逊病[12]。目前肝穿刺活检仍是NAFLD发展阶段诊断的金标准[13], 但由于肝穿刺活检的创伤性, 大大降低了患者的依从性和可推广性。因此, 开发无创性的诊断新方法是临床NAFLD早期发现及疾病进展程度诊断的迫切需求。一些新兴的无创或低创伤性的诊断方式如新型血清生物标志物、核磁共振成像、高通量组学、FibroScan等越来越受到关注[14,15]。

### 1.2 NAFLD的药物治疗

NAFLD作为包含了NASH、肝纤维化、肝硬化等在内的一组慢性肝病, 其早期诊断及干预是逆转其进展和恶化的关键。尽管NAFLD进展缓慢且早期阶段具有可逆性, 但由于对NAFLD不良预后的认识不足, 造成临床上很多NAFLD患者得不到早期诊断及有效早期干预。现阶段尚没有正式获批的NAFLD治疗药物。国际上一些具有较大潜力的药物多处于临床试验阶段, 如己酮糖激酶抑制剂、腺苷酸活化蛋白激酶 (AMP-activated protein kinase, AMPK) 激动剂、线粒体靶向药物、胰高血糖素样肽-1 (glucagon-like peptide-1, GLP-1) 类似物、生长激素类似物、脂肪从头合成 (*de novo* lipogenesis, DNL) 抑制剂、过氧化物酶体增殖激活受体 (peroxisome proliferator-activated receptor, PPAR) 激动剂、法尼醇X受体 (farnesoid X receptor, FXR) 激动剂等[16]。其中, OCA (obeticholic acid) 是鹅去氧胆酸 (chenodeoxycholic acid, CDCA) 衍生物, 具有选择性激动FXR的作用, 能显著改善NAFLD肝脏病理评分, 是治疗NASH的有效候选药物[17]。不过, OCA因激动皮肤组织中的FXR受体, 引起皮肤瘙痒的不良反应成为限制其使用的不利因素[18]。由于安全有效的治疗药物匮乏, 临床上针对NAFLD的生活方式干预仍是预防和改善NAFLD的有效策略, 如限制高热量饮食、维持低脂饮食、坚持锻炼等[19,20]。有研究指出[21,22], 减肥手术、服用抗糖尿病药物 (GLP-1调节剂等) 或减肥药物等对改善NAFLD均有一定作用。

祖国传统医学中虽无NAFLD病名, 但依据疾病特点可将其归属为传统医学中的“肝癖”“肝着”“积聚”等范畴, 现代中医治疗NAFLD多结合肥胖理论进行论治。元•朱丹溪的《丹溪治法心要》中首次提出“肥白人多痰湿”的观点, 后世医家对此也多加以引证发挥, 形成了中医学特有的理论: “肥人多痰湿”。痰、瘀是NAFLD发生发展过程中关键的病理产物与致病因素, 故“痰瘀同治”是论治之关键。现代中医治疗NAFLD多遵循“疏肝健脾, 行气利湿, 活血化瘀”的治则, 或根据病机进行方剂组合, 在临床中取得较好疗效, 且不良反应相对较小, 显示出良好的应用和开发前景[23,24]。

## 2 肠道菌群失衡与NAFLD

人体肠道微生物主要包括细菌、古生菌、病毒和真菌等数以万亿计的微生物, 其中肠道细菌是目前肠道微生态研究的主要对象。人体肠道中的4种主要细菌门是拟杆菌门 (Bacteroidetes)、厚壁菌门 (Firmicutes)、变形菌门 (Proteobacteria)、放线菌门 (Acfinobacteria)[25]。人体肠道菌群通过参与宿主的能量代谢、炎症及免疫

反应等多个方面影响人体健康[26,27]。肠道菌群失衡是促进NAFLD的重要因素[28]。Del Chierico等[29]发现, NAFLD患者的肠道菌群多样性显著低于健康对照组, 且*Ruminococcus*和*Dorea*的丰度随着NAFLD向NASH进展而增加。Wang等[30]发现, NAFLD患者的拟杆菌门丰度高于健康对照组, 而厚壁菌门的丰度低于对照组。Ye等[31]发现NAFLD模型小鼠的*Alistipes*和*Bacteroides*增加, 而*Ruminococcaceae*明显减少。进一步研究发现, 肠道菌群失衡后通过影响其代谢产物如次级胆汁酸、三甲胺、SCFA、乙醇和胆碱等来促进NAFLD的形成和进展[32-34]。微生物相关分子模式[microbial-(or pathogen-) associated molecular patterns, MAMP]和氨基酸衍生的肠道微生物代谢物在NAFLD发展中均可发挥作用[35,36]。肝脏的FXR改变也会反过来影响肠道微生物组成和功能[37]。此外, 高脂饮食(HFD)在增加能量摄入的同时, 也会改变肠道菌群平衡, 进而损害肠道屏障完整性和肠道血管屏障, 并促进细菌产物如脂多糖(lipopolysaccharide, LPS)、乙醇及三甲胺等通过门静脉进入肝脏, 加剧肝脏炎症和代谢异常[38]。

## 3　中药调节肠道菌群治疗NAFLD

中药因含极其复杂的化学成分, 治疗疾病通常具有多途径、多靶点的特征。根据临床报道, 许多经典复方具有良好的抗NAFLD作用[8-10]。肠道菌群的调节可能是中药发挥作用的重要途径, 可对中药化学成分进行代谢转化、形成次生代谢产物, 因此, 也是促进中药肠道吸收、发挥增效减毒作用的可能原因。中药发挥药效的成分通常包括生物碱、黄酮、多酚、多糖、萜类及皂苷等种类, 本综述对上述活性成分及经典复方防治NAFLD与调节肠道菌群的关系进行总结(图1)。

### 3.1　中药有效活性成分治疗NAFLD与调节肠道菌群的关系

**3.1.1　生物碱类**　小檗碱(berberine)又名黄连素, 是一种天然异喹啉类生物碱, 是传统中药黄连、黄柏的主要活性成分, 其大多数药理效应被认为与调节肠道菌群有关, 是近年研究的热点。研究表明, 小檗碱可显著降低肠道微生物多样性, 通过调节肠道菌群改善HFD诱导的代谢综合征, 包括降低肠道中厚壁菌门/拟杆菌门的相对丰度比例、降低内毒素水平、促进SCFA生成等[39,40]。Wang等[6]进一步对比了口服与注射给药方式下小檗碱对HFD动物肠道菌群的作用, 发现只有口服途径的小檗碱才能促进肠道菌群产生丁酸盐, 进而发挥降血脂和降血糖作用, 说明其作用与肠道菌群息息相关。肠道内稳态与肝脏疾病的发生关系密切, 药物改善肠道炎症的同时亦可缓解肝脏脂肪变性、增强胰

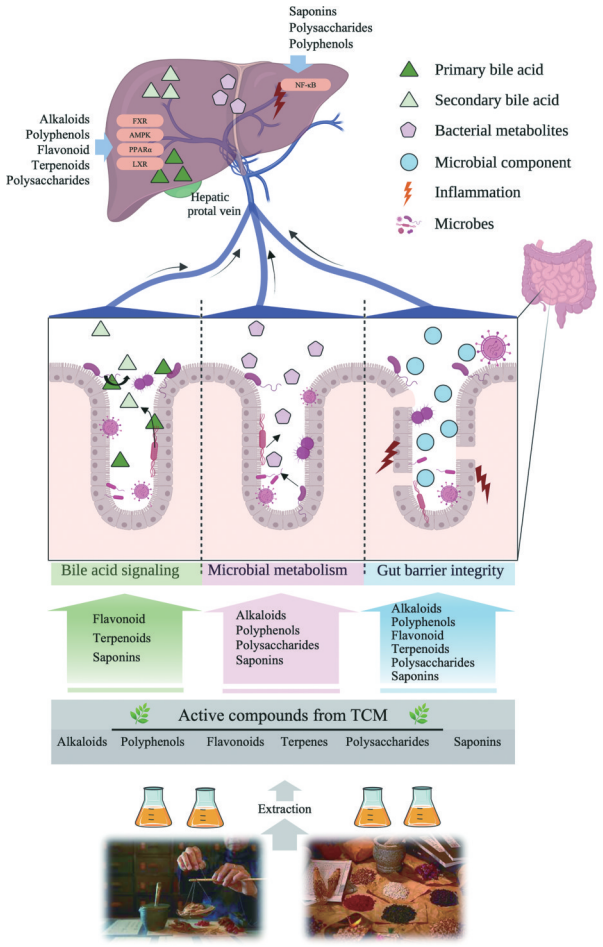


**Figure 1**　The relationship of traditional Chinese medicine (TCM) and gut-liver axis in non-alcoholic fatty liver disease (NAFLD) treatment. FXR: Farnesoid X receptor; AMPK: AMP-activated protein kinase; PPAR$\alpha$: Peroxisome proliferator-activated receptor alpha; LXR: Liver X receptor; NF-$\kappa$B: Nuclear factor kappa-B

岛素敏感性[41]。小檗碱通过减少拟杆菌等革兰阴性菌死亡, 减少LPS溶出, 抑制肠道炎症通路激活, 减轻肝纤维化[42,43]。此外, 小檗碱还可通过改变微生物介导的胆汁酸代谢和肠道FXR信号通路调节肝脏脂质代谢, 尤其是增加了肠道中牛磺胆酸(taurocholic acid, TCA)水平[44]。肠道菌群还可介导小檗碱的去甲基化和还原反应, 产生二氢小檗碱, 提高其肠道的吸收性和药效[45]。

荷叶碱(nuciferine)是荷叶中的药用成分, 具有清热降暑、减肥作用。低剂量的该类生物碱即可有效发挥降血脂作用, 并改善肝脂肪变性, 其作用靶标为过氧化物酶体增殖物激活受体-$\gamma$共激活因子-1$\alpha$ (PGC1$\alpha$)和过氧化物酶体增殖物启动受体$\alpha$ (PPAR$\alpha$)[46]。荷叶碱的结构与小檗碱相似, 且生物利用度差, 推测其也可通过调节肠道菌群发挥药效作用, 最新研究显示[47,48],

其显著升高了肠道中嗜黏蛋白阿克曼菌 (*Akkermansia muciniphila*, Akk 菌) 的丰度, 发挥其降脂作用。这不仅表明 Akk 菌的生长在治疗 NAFLD 中发挥一定作用, 更对一些口服利用度较低的中药单体而言, 肠道微生物群可能作为其疾病治疗的主要途径。

甜菜碱 (betaine) 是一种季铵型水溶性生物碱, 存在于很多天然植物中, 如枸杞、甜菜、甘蔗等[7,49]。甜菜碱对于多种肝病都具有良好的预防和治疗作用, 除可调节肝脏代谢外, 其作用也与调节肠道菌群高度相关[50,51]。HFD 喂养小鼠经甜菜碱治疗后, 80 个微生物种群发生变化, 其中属水平上的有益菌如普雷沃氏菌属、瘤胃球菌属、颤螺菌属、双歧杆菌属、阿克曼菌属、乳酸杆菌属和多尔氏菌属丰度增加, 有害菌属的沙门氏菌属和脱硫弧菌属减少。此外, 甜菜碱也可通过改变肠道菌群调节宿主 miR-378a 启动子的 DNA 甲基化水平, 改善脂质代谢[51]。甜菜碱治疗 NAFLD 作用还与抑制 TLR4/MyD88 (Toll-like receptor 4/myeloid differentiation factor 88) 通路、增加 occludin 和 ZO-1 (zonula occluden-1) 的蛋白表达、维持肠道紧密连接、减低肠上皮屏障的通透性有关, 发挥治疗肝病的作用[50]。

**3.1.2 多酚类** 白藜芦醇 (resveratrol) 是一种天然多酚类化合物, 可从决明子、虎杖等药材中获得, 是近年来研究较多的植物多酚。白藜芦醇可改变肥胖小鼠的肠道微生物组成, 包括降低苏黎世杆菌科、厚壁门菌、毛螺菌科、阿克曼菌的相对丰度, 升高拟杆菌属、副杆状菌属的相对丰度, 产生有益菌群代谢物如 4-羟基苯乙酸和 3-羟基苯丙酸; 将白藜芦醇喂养的健康供体小鼠的粪便进行移植, 可使肥胖小鼠的葡萄糖稳态得到改善[52-55]; 保持肠道屏障的完整[56], 改善宿主代谢; 调控十二指肠 AMPK-SIRT 轴和迷走神经元肠−大脑神经元轴, 以扭转肥胖和糖尿病大鼠的代谢综合征[57]。不过, 尽管大量实验研究表明白藜芦醇具有改善 NAFLD 功效, 但临床试验结果并不一致, 临床中还没有足够证据证明其可治疗脂肪肝, 因此是否具有治疗 NAFLD 的作用还有待深入探究[58,59]。

姜黄素 (curcumin) 是从中药姜黄、郁金、莪术等根茎中提取的天然多酚类物质, 因其广泛的药理活性 (如抗氧化、抗炎、抗菌、抗病毒等) 受到广泛关注[60]。在一项临床随机安慰剂对照研究中发现, 姜黄素可显著改善 NAFLD[61]。姜黄素改善 NAFLD 的途径主要是通过中断瘦素信号传导、提高胰岛素敏感性、抗氧化应激、激活 FXR 和 LXR 信号通路等[62-66]。除肝脏外, 肠道亦是姜黄素主要的代谢部位, 因此其与肠道微生物群的双向作用也受到关注。在治疗 NAFLD 过程中, 姜黄素可通过调节肠道菌群组成改善 HFD 诱导的大鼠代谢内毒素血症、肠道炎症, 减轻肝脂肪变性[67]。姜黄素可通过调节普雷沃氏菌属和拟杆菌属细菌的丰度, 改善宿主代谢[68]。另一方面, 肠道菌群也会对姜黄素进行去甲基化、还原、羟基化和乙酰化反应, 产生比姜黄素原型具有更强药理活性和生物利用度的代谢产物。与姜黄素相比, 二甲氧基姜黄素具有更强的体内稳定性和更佳的抗炎特性[69,70]。这些由肠道菌群转化的姜黄素代谢物具有巨大开发潜力, 肠道菌群对中药化学成分代谢转化形成的新化合物是寻找中药活性成分的重要来源。

原儿茶酸 (protocatechuic acid) 是一种酚酸类化合物, 在中药中具有广泛分布。研究表明, 原儿茶酸具有改善 NAFLD 作用, 其作用机制包括调节脂质代谢、葡萄糖代谢、氧化应激、肠道菌群及褐色脂肪功能等[71]; 可通过肠道菌群代谢为花青素中的 *O*-*β*-葡萄糖苷, 作为花青素等多酚的主要代谢产物之一[72]。最新研究发现[73], 原儿茶酸可有效调节血浆脂质, 防止肝脏胆固醇和脂质的积累, 并揭示这种效应是通过调节肠道菌群组成、增加肠道菌群代谢产生 SCFA 和胆汁酸的排泄来介导的, 说明原儿茶酸治疗 NAFLD 与肠道菌群调节的关系密切。不过, 目前相关研究还较少, 原儿茶酸调节肠道菌群与其改善 NAFLD 形成之间的关系有待进一步研究。

**3.1.3 黄酮类** 木犀草素 (luteolin) 是一种天然黄酮化合物, 存在于全叶青兰、辣椒、野菊花、金银花、紫苏等中草药中, 具有显著的抗氧化、抗炎、抗菌及抗肿瘤活性[73-75]。研究发现木犀草素可通过恢复肠黏膜屏障完整性, 调节肠−肝轴缓解大鼠的 NAFLD[76]。与 HFD 喂养大鼠相比, 饮食中添加木犀草素可增加动物肠道菌群的多样性, 增加肠细胞 ZO-1 表达, 降低肠黏膜通透性, 降低血浆 LPS 水平, 抑制 TLR4/NF-*κ*B 通路, 提示木犀草素的抗炎作用可能与调节肠道菌群相关[76,77]。

黄芩苷 (baicalin) 是中药黄芩的主要活性成分, 对肝脏和肠道有保护作用。黄芩苷主要通过介导氧化应激和炎症引起的细胞凋亡和免疫反应途径发挥药理作用[78]。研究发现, PI3K/Akt/NRF2 (phosphoinositide 3-kinase/protein kinase B/nuclear factor erythroid 2-related factor 2)、Keap-1、NF-*κ*B 和 HO-1 (heme oxygenase 1) 是黄芩苷发挥调节氧化应激的靶点[79,80], IL-6、IL-1*β*、TNF-*α* (tumor necrosis factor-*α*)、MIP-2 (macrophage inflammatory protein 2)、MIP-1*α*、TGF-*β*1 (transforming growth factor beta 1)/Smads、STAT3 (signal transducer and activator of transcription 3) 和 NF-*κ*B 是黄芩苷减缓炎症、胆汁淤滞和肝纤维化的可能靶标[81-83]。此外, 黄芩苷还能增加肠道菌群产生的 SCFA, 调节肠道菌群

介导的次级胆汁酸, 调控Gpbar1 (TGR5)、FXR胆汁酸受体等方式发挥NAFLD防治作用[80]。

水飞蓟宾 (silybin) 是从水飞蓟种子的种皮中提取所得的一种黄酮木脂素类化合物, 在各种类型肝脏疾病中表现出较好的保护作用[84]。水飞蓟宾可通过调节Sirtuin 1/AMPK[85]、激活FXR信号等途径改善NAFLD[86]。研究表明, 水飞蓟宾对HFD诱导的肠道菌群改变具有恢复作用, 而且可对肠道菌群代谢物 (如SCFA和次级胆汁酸) 的生成产生显著影响[87]。不过, 该研究还发现其对一些已知的有益细菌表现出一定抑制作用, 如*Alloprevotella*和*Lactobacillus*。因此, 水飞蓟宾改变肠道菌群与其改善NAFLD的关系还需更深入的研究。

**3.1.4　萜类**　齐墩果酸 (oleanolic acid) 是女贞子的果实中分离获得的萜类化合物, 可通过调控LXR$\alpha$和PXR抑制脂肪生成[88]。齐墩果酸衍生物可通过激活AMPK通路改善NAFLD[89]。最新报道指出[90], 齐墩果酸可通过降低厚壁菌门/拟杆菌门比率, 增加产生丁酸盐的细菌丰度, 重塑HFD喂养大鼠肠道菌群的组成, 并通过肠-肝轴介导的抗炎、抗氧化作用, 发挥减肥及抗NAFLD作用。

灵芝酸A (ganoderic acid A) 是从灵芝中提取的三萜类化合物, 具有广泛的药理作用[91-94]。Liu等[95]研究发现灵芝酸A还可调节肠道菌群, 增加肠道中细菌代谢产生的SCFAs水平, 并促进胆汁酸通过粪便排泄等途径改善NAFLD, 提示其改善NAFLD作用与调节肠道菌群组成及功能高度相关。相关机制还需进一步研究。

**3.1.5　植物多糖**　黄芪多糖 (*Astragalus* polysaccharides) 是来源于中药黄芪的多糖类化合物, 具有调节免疫、降脂、降糖等作用[96]。研究发现, $\gamma$黄芪多糖对NAFLD的治疗作用与调控宿主代谢及肠道菌群密切相关[97]。Hong等[98]研究发现黄芪多糖可显著调节HFD喂养小鼠的肠道菌群结构, 利用宏基因组学分析发现, 其显著富集了HFD喂养小鼠肠道脱硫弧属细菌丰度, 其中*Desulfovibrio vulgaris*是最具代表性的, 进一步研究发现该菌不仅能产硫化氢, 而且可大量产生乙酸, 进而改善HFD喂养小鼠的糖脂代谢, 抑制NAFLD形成, 提示黄芪多糖可能是一类活性较好的益生元, 对于代谢性疾病的防治具有较好的研究潜力。

枸杞多糖 (*Lycium barbarum* polysaccharide) 作为枸杞的主要活性成分, 被认为是一种新型益生元, 具有通过调节肠道菌群、改善NAFLD的作用[99], 可上调SIRT1表达和脱乙酰酶活性, 减轻HFD诱导的肝脂肪变性[100], 并通过NF-$\kappa$B和NLRP3/6途径改善肝损伤[101]。最新研究表明[102], 枸杞多糖能恢复肠道菌群、改善肠屏障及抑制肝脏炎症等, 改善NAFLD。

MDG-1是从中药麦冬提取的多糖中分离的$\beta$-*D*-果聚糖, 具有促进非糖尿病和糖尿病小鼠肠道益生菌如乳酸菌和双歧杆菌的作用, 同时减少有害菌如大肠杆菌和链球菌[103]。MDG-1通过调节肠-肝轴抑制NAFLD的发展[104], 还具有调节PPAR$\alpha$和PPAR$\gamma$作用, 降低小鼠血脂水平[105], 以及通过PI3K/Akt途径降血糖等[106]。因此, MDG-1改善NAFLD的作用可能与调节肠道菌群有关, 但肠道菌群的调节作用在其防治NAFLD作用中的贡献度及肠道菌群变化是否参与其对肝脏糖脂代谢的调控尚不清楚。

灵芝多糖 (*Ganoderma* polysaccharide) 是从灵芝中提取的多糖类化合物, 具有广泛的生物活性, 对NAFLD具有确切的改善作用[107]。赖信志团队[108]对灵芝多糖治疗NAFLD作用进行了深入研究, 发现灵芝多糖对HFD诱导的NAFLD模型具有显著改善作用, 且该作用依赖于对HFD喂养动物肠道菌群的调节, 其机制主要与降低机体炎症、改善肠屏障、降低代谢性内毒素等有关。相似的研究报道也表明, 灵芝多糖调控肠道菌群组成, 增加有益菌丰度, 改善脂肪肝[109]。

**3.1.6　皂苷类**　TSG (2,3,5,4'-tetrahydroxy-stilbene-2-*O*-$\beta$-*D*-glucoside) 是何首乌的有效成分之一, 可通过改善SIRT5依赖的线粒体功能, 减轻肝脂肪变性[110], 也可通过调控肠-肝轴、TLR4/NF-$\kappa$B通路, 改善NAFLD[111,112]。此外, TSG改善NAFLD作用还与恢复肠道菌群平衡、增加肠道黏膜ZO-1的蛋白表达、改善肠黏膜屏障功能、降低血清LPS含量, 以及抑制炎症有关[111,113]。

三七总皂苷 (*Panax notoginseng* saponins, PNS) 是中药三七中的主要活性成分, 具有降低血脂、减轻肝脏脂质积累等作用[114,115]。Xu等[116]以HFD诱发的肥胖小鼠和*ob/ob*小鼠为研究对象, 发现PNS治疗后动物肠道菌群代谢产物SCFA含量增加、TLR4下调、肠漏得到改善等, 因此PNS防治NAFLD作用可能是通过肠道菌群参与的肠-肝轴途径实现。

甘草酸二铵 (diammonium glycyrrhizinate) 是甘草根提取物的主要成分, 具有抗炎、保肝功效。研究表明甘草酸二铵通过上调IRS-1和IRS-2的磷酸化提高胰岛素敏感性, 改善NAFLD[117], 也可通过调节胆汁酸及抑制炎症等缓解肝脏脂肪变性, 还可通过调节肠道菌群和恢复肠道屏障防治NAFLD[118,119]。

冬青皂苷 (ilexhainanoside) 从苦丁茶中提取, 具有抗炎保肝的作用, 其抗NAFLD作用也与调节肠道菌群及肠屏障密切相关, 包括降低厚壁菌门/拟杆菌门比例, 降低*Desulfovibrio*相对丰度, 增加*Akkermansia*相

对丰度, 上调肠道ZO-1和occludin蛋白的表达, 改善肠道屏障等[120]。

上述各类中药有效成分防治NAFLD的作用与调节肠道菌群组成或功能、肠−肝轴、肠道菌群代谢物(SCFA及胆汁酸)、肠屏障完整性及肝脏TLR4介导的炎症信号通路等有关, 常见的中药有效成分防治NAFLD与调控肠道菌群的关系总结见表1[44,45,47,48,51,55,57,67,76-78,87-90,95-98,101,104,108,110-112,116,118,119]。

**Table 1** TCM effective parts for prevention and treatment of NAFLD. SD: Sprague-Dawley; HFD: High-fat diet; ACEA: Arachidonyl-20-chloroethylamide hydrate; AM630: 6-Iodopravadoline; i.p.: Intraperitoneal injection; FMT: Fecal microbiota transplantation; CB: Cannabinoid receptor; TLR4: Toll-like receptor-4; FASN: Fatty acid synthase; LPS: Lipopolysaccharide; SIRT: Sirtuin; MDG-1: A *β*-*D*-fructan polysaccharide extracted from the roots of *Ophiopogon japonicus*

| Category | Compound name | Main source | Experimental subject | Experimental design | Modulation target | Ref. |
|---|---|---|---|---|---|---|
| Alkaloid | Berberine | *Coptis chinensis* Franch., *Phellodendron chinense* Schneid., *Berberis soulieana* Schneid. | Wild-type and gut-specific FXR knockout mice with C57BL/6J background; male SD rat | Fed with HFD, at the same time, berberine 150 mg·kg$^{-1}$·d$^{-1}$ was administered continuously for 8 weeks; HFD was fed for 16 weeks, and berberine 150 mg·kg$^{-1}$·d$^{-1}$ was administered continuously from the second week | Bile acid metabolism, ileal FXR signaling pathway, gut microbiota structure; intestinal flora structure (Bacteroidetes, Firmicutes), intestinal mucosal damage | [44, 45] |
| | Lotusine | *Nelumbo nucifera* Gaertn. | Male SD rat | HFD for 6 weeks, at the same time, 7.5 and 15 mg·kg$^{-1}$·d$^{-1}$ of lotusine were administered by gavage continuously | *Akkermansia muciniphila* | [47, 48] |
| | Betaine | *Lycium barbarum* L. | Female Kunming mice | HFD with 1% betaine diet for 23 weeks | miR-378a/YY1 regulates axis, short-chain fatty acids, and gut microbiota structure | [51] |
| Polyphenol | Resveratrol | *Cassia obtusifolia* L., *Polygonum cuspidatum* Sieb. et Zucc. | Male SD rat; male C57BL/6J mice | HFD fed concurrently with resveratrol 50, 100 mg·kg$^{-1}$·d$^{-1}$ for 6 weeks, then with or without ACEA, AM630 i.p. for 4 weeks; Resveratrol 300 mg·kg$^{-1}$·d$^{-1}$ continuous intragastric administration and FMT experiment were carried out during HFD feeding | CB1 and CB2 in the distal colon, gut microbiota structure, gut barrier; intestinal metabolic pathways (4-hydroxyphenylacetic acid, 3-hydroxyphenylpropionic acid), intestinal oxidative pathway | [55, 57] |
| | Curcumin | *Curcuma longa* L. | Male SD rat | Curcumin administration of curcumin 200 mg·kg$^{-1}$·d$^{-1}$ for 12 weeks on HFD | Metabolic endotoxin, intestinal inflammatory pathways, intestinal mucosal barrier, and intestinal flora structure | [67] |
| | Luteolin | *Lonicera japonica* Thunb., *Chrysanthemum morifolium* Ramat., *Schizonepeta tenuifolia* Briq., *Prunella vulgaris* L. | Wistar rat | HFD for 8 weeks, 25, 50 and 100 mg·kg$^{-1}$·d$^{-1}$ of luteolin were continuously administered at the same time | TLR4, intestinal flora structure (*Lactobacillus*, *Bifidobacterium*, *Desulfovibrio*, etc.), intestinal mucosal barrier | [76, 77] |
| Flavonoid | Baicalin | *Scutellaria baicalensis* Georgi | Male C57BL/6 mice | HFD for 15 weeks, 200 mg·kg$^{-1}$·d$^{-1}$ of baicalin was administered continuously at the same time | Short-chain fatty acid metabolism, gut microbiota structure | [78] |

Continued

| Category | Compound name | Main source | Experimental subject | Experimental design | Modulation target | Ref. |
|---|---|---|---|---|---|---|
| | Silybin | *Silybum marianum* (L.) Gaertn. | Male C57BL/6 mice | HFD for 8 weeks, concurrently with silybin 100 or 300 mg·kg$^{-1}$·d$^{-1}$ by gavage | Short-chain fatty acids, bile acids, and gut microbiota structure | [87] |
| | Oleanolic acid | *Ligustrum lucidum* Ait. | Male SD rat | HFD for 12 weeks, 25, 50 or 100 mg·kg$^{-1}$·d$^{-1}$ oleanolic acid by gavage for 8 weeks | TLR4-related pathways, gut microbiota structure, and intestinal mucosal barrier | [88-90] |
| | Ganoderma A | *Ganoderma lucidum* (Leyss. ex Fr.) Karst. | Male SD rat | HFD for 4 weeks, 20, 40 mg·kg$^{-1}$·d$^{-1}$ ganoderma A by gavage for 2 weeks | Short-chain fatty acids, bile acids, intestinal flora | [95] |
| | *Astragalus* polysaccharide | *Astragalus membranaceus* (Fisch.) Bge. var. mongholicus (Bge.) Hsiao | Male C57BL/6J mice | Adding or not adding *Astragalus* polysaccharide HFD for 12 weeks; mice in different groups were caged for 8 weeks | FASN, CD36, short-chain fatty acid metabolism, gut microbiota structure (*D. vulgaris*) | [96-98] |
| | Wolfberry polysaccharide | *Lycium barbarum* L. | Male SD rat | HFD for 18 weeks, starting from the 10th week, 50 mg·kg$^{-1}$·d$^{-1}$ *Lycium barbarum* polysaccharide was administered by gavage for 8 weeks | LPS/TLR4/NF-$\kappa$B signaling pathway, SIRT, bile acids, gut microbiota structure | [101] |
| Terpene | MDG-1 | *Ophiopogon japonicus* (L. f) Ker-Gawl. | Male C57BL/6J mice | After 8 weeks of HFD diet feeding, 2‰, 4‰ and 8‰ MDG-1 treatments were administered, respectively | Intestinal flora, "gut-liver axis" structure | [104] |
| | *Ganoderma lucidum* polysaccharide | *Ganoderma lucidum* (Leyss. ex Fr.) Karst. | C57BL/6N mice | HFD for 2 months, and gavage of *Ganoderma lucidum* polysaccharide aqueous extract with 2%, 4%, and 8% mass concentration at the same time; and FMT experiment | Intestinal flora structure, intestinal mucosal barrier | [108] |
| Plant polysaccharide | 2,3,5,4-Tetrahydroxystilbene-2-*O*-$\beta$-*D*-glucoside | *Polygonum multiflorum* Thunb. | Male and female SD rats | HFD for 12 weeks, and the drug was administered at 12, 24, and 48 mg·kg$^{-1}$·d$^{-1}$ at the same time | TLR4/NF-$\kappa$B pathway, gut microbiota structure, gut mucosal barrier, "gut-liver axis" | [111, 112] |
| | *Panax notoginseng* saponins | *Panax notoginseng* (Burk.) F. H. Chen | *ob/ob* mice and C57BL/6J mice | HFD for 4 weeks, ginsenoside 800 mg·kg$^{-1}$·d$^{-1}$ was re-gavage for 4 weeks | TLR4, short-chain fatty acid, "gut-liver axis" | [116] |
| | Diammonium glycyrrhizinate | *Glycyrrhiza uralensis* Fisch. | C57BL/6J mice | HFD for 14 weeks, concurrently with intraperitoneal injection of diammonium glycyrrhizinate (150 mg·kg$^{-1}$) every other day | Intestinal flora structure, intestinal mucosal barrier | [118, 119] |
| | Wintergreen saponins | Kudingcha | C57BL/6 mice | HFD for 14 weeks, concurrently with diammonium glycyrrhizinate 60, 120, 240 mg·kg$^{-1}$·d$^{-1}$ intragastric administration | Pro-inflammatory cytokines, intestinal flora structure, intestinal mucosal barrier | [110] |

### 3.2　中药复方治疗NAFLD与调节肠道菌群的关系

《黄帝内经》云“饮食自倍, 脾胃乃伤”, NAFLD患者从中医角度分析常是过食肥甘, 导致脾失健运, 水谷精微不能转化为营卫气血, 反为痰浊膏脂, 痰浊内生, 蕴而化热。而且NAFLD发病常与肝脾二脏相关, 两者相互影响, 相互转变。NAFLD以痰瘀互结为基本病机, 并责之肝脾肾三脏, 常见证型有湿热蕴结、肝郁脾虚和肝肾不足, 或相互间夹。因此中医学认为,

NAFLD治疗以疏肝健脾、祛湿化痰、活血化瘀为主。研究发现[121], NAFLD治疗的复方中以微寒、苦味、归肝经药物为主, 治法以疏肝健脾、利水渗湿、活血化瘀为主, 兼以化痰、消食、清热、理气等为辅, 与中医基础理论较为吻合。

**3.2.1 四妙方** 四妙方源自清代张秉承的《成方便读》, 由黄柏、苍术、薏苡仁、牛膝按照质量比2∶1∶2∶1组成, 具有清热利湿功效, 是一种降尿酸的经典中医方剂。现代药理学研究发现四妙方还可用于防治NAFLD, 含有生物碱、挥发油、甾酮类和皂苷类等化学成分, 其中小檗碱、*β*-蜕皮甾酮等可能为该方剂的药效物质基础[8]。Han等[122]指出, 在喂食高糖HFD的小鼠中, 四妙方减轻了肝脏脂肪变性, 降低了体重增长和脂质含量, 提高了对胰岛素敏感性及葡萄糖耐受性。从机制上看, 四妙方下调了肝脏中脂质代谢和促炎细胞因子代谢有关基因的表达, 更重要的是, 其显著改变了肠道菌群的组成和丰度, 尤其是增加*Akkermansia muciniphila*的丰度特别明显。上述结果表明四妙方发挥抗NAFLD的作用与重塑肠道菌群、增加肠道中*Akkermansia muciniphila*的丰度具有高度的相关性, 提示四妙方可通过调控肠-肝轴改善NAFLD。

**3.2.2 苓桂术甘汤** 苓桂术甘汤出自《金匮要略》, 由茯苓、桂枝、白术、甘草组成, 临床试验表明, 其可用于治疗脾阳虚型NAFLD[123,124], 研究发现其可通过调节Thrsp-Srebp1[125]、TRAF3、NF-*κ*B、TLR4通路[126], 抑制STING介导的巨噬细胞炎症, 改善HFD诱导的肝脏脂质沉积[127]。研究表明[128], 苓桂术甘汤可逆转由HFD诱发的肠道菌群结构的改变, 回调*Fusobacteria*、*Actinobacteria*、*Elusimicrobia*、*Candidatus Shapirobacteria*的丰度, 增加肠道中产生丁酸盐的细菌的丰度, 增加脂肪酸氧化并抑制脂质生物合成, 从而改善NAFLD。

**3.2.3 祛湿化瘀方** 祛湿化瘀方由茵陈、虎杖、片姜黄、栀子、田基黄5味中药组成, 是临床上治疗湿热蕴结型NAFLD常用经验方。方中茵陈、栀子配伍取自《伤寒论》中茵陈蒿汤。茵陈清热利湿退黄, 栀子清利三焦, 二者为清热化湿要药, 清热之效强。临床研究发现, 祛湿化瘀方可明显改善NAFLD的各项指标和中医证候[9]。机制研究发现, 祛湿化瘀方可能通过抑制MAPK通路磷酸化、增强PPAR-*γ*和p-p65的入核和增强肝星状细胞 (HSCs) 编程来发挥抗脂肪变性和纤维化的保肝作用[129]; 通过AMPK途径抑制肝脏脂质积累[130], 改善NAFLD。进一步研究表明, 祛湿化瘀方中的有效成分栀子苷和绿原酸可通过改善肠道屏障功能、恢复结肠黏膜完整性、促进肠道中调节性T细胞诱导的微生物发挥抗NASH作用[131,132]。此外, 茵陈蒿汤临床上也用于治疗NAFLD[133]。动物实验证实, 茵陈蒿汤改善NAFLD作用与改变模型大鼠厚壁菌门、拟杆菌门、放线菌门及变形菌门丰度失调有关[10]。

**3.2.4 大黄泽泻汤** 大黄泽泻汤源于中医名方泽泻汤, 通过改善NAFLD大鼠肠道菌群结构, 降低致病菌和升高有益菌的比例, 减少肠道TLR4的配体LPS的产生, 下调TLR4信号通路, 改善肠黏膜屏障紧密连接蛋白的表达及分布, 降低肠黏膜屏障通透性, 减少致病菌及其代谢产物由门静脉入肝, 达到改善肝脏炎症及脂质沉积的作用[134]。

上述中药复方对于NAFLD具有明确防治效果, 且其作用都可能与肠道菌群的调节有关, 二者关系总结见表2[10,122,128-132,134]。

## 4 总结与展望

NAFLD是最常见的慢性肝病, 目前尚无正式获批的治疗药物。中医药治疗NAFLD具有多层次、多途径、多靶点的特点。中药中的活性化合物或中药复方对NAFLD的改善作用显著, 且不良反应小, 中医药的优势和开发前景突显。肠道菌群失衡与众多疾病的发生发展密切相关, 靶向肠道菌群的调节已成为疾病防治的重要策略之一。传统中药大多以口服为主, 肠道菌群和药物间的相互作用往往是中药药效得以发挥的关键。首先, 中药活性成分到达肠道后可通过促进有益菌增殖和/或抑制病原菌生长, 增加有益菌群代谢物 (如SCFA、次级胆汁酸等代谢产物) 的生成, 调节由疾病引发的肠道菌群紊乱, 使其肠道微生态平衡, 从而发挥防治疾病的作用。另一方面, 肠道菌对中药的代谢和转化是影响中药药效和毒性的重要途径。中药发挥防治NAFLD不仅通过调节脂质生成通路、下调炎症通路、提高胰岛素敏感性、修复线粒体功能等发挥药效。近年来越来越多的研究指出, 中药可调节肠道菌群、胆汁酸的生成, 通过肠-肝轴等途径发挥治疗NAFLD的作用。

虽然肠道菌群是当前中药作用机制研究的热点领域和崭新的切入点, 不过在一些情况下, 肠道菌群的变化也可能只是中药干预机体后的结果, 而并不是其发挥药效的途径。根据本课题组[135]所提出的中药、肠道菌群与人体系统三者之间互作的三种模式假说, 未来中药复方药效机制的阐释需更多关注肠道菌群在中药发挥药效作用中所扮演的真实角色, 以及肠道菌群所影响的宿主代谢对于疾病发生发展或药效发挥中所起到的实际贡献度, 而不是简单认为肠道菌群的变化一定是中药发挥作用的关键。在研究方法上, 除可通过FMT、无菌小鼠、抗生素干预等方式探明肠道菌群参与中药药效的作用, 还需结合更多高通量的组学技术

**Table 2**　Complex traditional Chinese medicine treatment of NAFLD with regulation of intestinal flora related statistics. ACLY: ATP citrate lyase; FAS: Fatty acid synthesis; ACC: Acetyl-CoA carboxylase; SCD-1: Stearoyl-CoA desaturase-1; IL-1$\beta$: Interleukin-1$\beta$; NLRP-3: Nucleotide-binding and oligomerization domain-like receptor family pyrin domain-containing 3; GLP: Glucagon-like peptide

| Name | Composition of TCM | Experimental subject | Experimental design | Modulation target | Ref. |
|---|---|---|---|---|---|
| Simiao Formula | *Phellodendron chinense* Schneid., *Atractylodes lancea* (Thunb.) DC., *Achyranthes bidentata* Bl., *Coix lachryma-jobi* L. var. ma-yuen (Roman) Stapf | Male C57BL/6 mice | HFD for 16 weeks, 10 and 20 $g\cdot kg^{-1}\cdot d^{-1}$ were administered by gavage at the same time | Fatty acid metabolism (ACLY, FAS, ACC, SCD-1), inflammation (IL-1$\beta$, NLRP-3), insulin secretion pathway, gut microbiota composition (*e.g.* Akk bacteria) | [122] |
| Linggui Zhugan Decoction | *Poria cocos* (Schw.) Wolf, *Atractylodes macrocephala* Koidz. *Glycyrrhiza uralensis* Fisch., *Cinnamomum cassia* Presl | Male C57BL/6 mice | For 16 weeks of HFD, Linggui Zhugan Decoction was administered by gavage, and FMT was performed every 3 days | Restore the structure of intestinal flora and increase the abundance of butyrate produces bacteria | [128] |
| Qushi Huayu Decoction | *Artemisia scoparia* Waldst. et Kit., *Polygonum cuspidatum* Sieb. Et Zucc., *Grangea maderaspatana* (L.) Poir., *Gardenia jasminoides* Ellis, *Curcuma longa* L. | Male SD rat | After 6 weeks of HFD diet feeding, 0.47 $g\cdot 100\ g^{-1}\cdot d^{-1}$, 0.93 $g\cdot 100\ g^{-1}\cdot d^{-1}$ Qushi Huayu Decoction treatments were administered for 4 weeks, respectively | AMPK, GLP, intestinal flora structure and intestinal permeability, improve intestinal barrier function and restore colonic mucosal damage | [129-132] |
| Yinchenhao Decoction | *Artemisia scoparia* Waldst. et Kit., *Gardenia jasminoides* Ellis, *Rheum palmatum* L. | Male SD rat | NAFLD rat model was established after HFD for 16 weeks, and Yinchenhao Decoction 3.6 $g\cdot kg^{-1}\cdot d^{-1}$ was administered continuously for 2 weeks | Glycerophospholipid metabolism, purine metabolism and glutathione metabolism; intestinal flora | [10] |
| Dahuang Zexie Decoction | *Rheum palmatum* L., *Atractylodes macrocephala* Koidz., *Panax ginseng* C. A. Mey. | Male SD rat, male C57BL/6 mice | The rat model of NAFLD was established after 16 weeks of HFD, and Rhubarb Zexie Decoction (5 $g\cdot kg^{-1}$) was given for 4 weeks and FMT was given for 8 weeks | Intestinal flora structure—the proportion of pathogenic bacteria decreased and the proportion of beneficial bacteria increased; the intestinal TLR4 signaling pathway decreased the permeability of the intestinal mucosal barrier | [134] |

如宏基因组学、宏代谢组学、宏转录组学及具有实现跨组学数据整合分析能力的生物信息学等, 从而能在肠道菌群组成和功能及肠道菌群与宿主代谢之间互作关系等角度系统揭示中药、肠道菌群与人体互作的确切关系与机制。

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