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Review 综述

肠道菌群在非酒精性脂肪性肝病中的研究进展

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摘　要：非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)是全球最常见的慢性肝病，其疾病进展过程复杂。肠道菌群(gut microbiota, GM)在NAFLD的发病过程中起着重要作用，肠-肝轴理论为理解GM与肝脏之间的关系奠定了理论基础。GM失调可导致免疫功能紊乱及炎症反应、肠道屏障受损和胰岛素抵抗等，从而促进NAFLD的发生与发展。此外，GM还可通过内毒素血症、短链脂肪酸代谢异常、胆汁酸和胆碱代谢异常等机制参与NAFLD的发生发展。基于GM靶向治疗NAFLD已成为当前的研究重点，包括粪便菌群移植、补充益生菌或益生元、使用中草药以及生活方式干预等。本综述主要关注GM失调状态下对NAFLD的影响，并探讨GM靶向治疗NAFLD的研究进展，为NAFLD的预防和治疗提供了最新的策略和靶点。

关键词：非酒精性脂肪性肝病；肠-肝轴；肠道菌群；肠道菌群代谢物

Research progress of gut microbiota in non-alcoholic fatty liver disease

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Abstract: Non-alcoholic fatty liver disease (NAFLD) is a common chronic liver disease around the

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world, and it has a complex disease progression. Recent studies have demonstrated that gut microbiota (GM) plays a crucial role in the pathogenesis of NAFLD. The theory of gut-liver axis provides a theoretical basis for understanding the relationship between GM and the liver. Dysbiosis of GM leads to immune dysfunction, inflammatory responses, damaged gut barrier, and insulin resistance, all of which promote the development and progression of NAFLD. Furthermore, GM can participate in the development and progression of NAFLD through endotoxemia and abnormal metabolism of short chain fatty acids, bile acids, and choline. How to mitigate NAFLD by modifying GM has become the focus of current research, and the measures include fecal microbiota transplantation, probiotics, prebiotics, Chinese herbal medicines, and lifestyle interventions. The review focuses on the impact of the pathological state of GM on NAFLD and discusses the research progress in GM-targeted therapy for NAFLD. It is expected to provide new strategies and targets for the prevention and treatment of NAFLD.

Keywords: non-alcoholic fatty liver disease; gut-liver axis; gut microbiota; gut microbiota-derived metabolites

非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)是指排除酒精等明确的肝损害因素以外，以弥漫性肝细胞大泡性脂肪病变为主要特征的临床病理综合征，全球患病率达 25.24%[1]。NAFLD 可从单纯的脂肪变性(NAFLD 的早期阶段)发展成非酒精性脂肪性肝炎(non-alcoholic steatohepatitis, NASH)，再逐渐发展为肝硬化，甚至最终形成肝癌。近年来，专家们认为 NAFLD 应由代谢相关脂肪性肝病取代，即定义为通过各种临床辅助手段检测出肝脏脂肪变性，同时具备肥胖、2 型糖尿病或机体代谢异常中任一表现[2]。微生物在自然界中无处不在，人体大多数部位也同样存在微生物，其中细菌是主要研究对象，细菌中包含常见菌与罕见菌。研究发现哈特草小螺菌(*Herbaspirillum huttiense*)、尸毒梭菌(*Clostridium cadaveris*)和缓慢爱格士氏菌(*Eggerthella lenta*)作为病原菌可引起严重血流感染，其导致的菌血症常有较高的死亡率，应引起重视[3-5]。在人类微生物群中，肠道内微生物数量非常多且在机体代谢中起重要作用[6]。肠道菌群(gut microbiota, GM)的核心菌群中芽孢杆菌门(*Bacillota*)和拟杆菌门(*Bacteroidota*)占主导地位，放线菌纲(*Actinomycetes*)和假单胞菌门(*Pseudomonadota*)等相对丰度较低。肠道与肝脏通过肠-肝轴紧密联系，共同构成一个复杂的有机整体，GM 失调通过肠-肝轴影响肝脏脂质代谢，造成脂肪在肝脏内过度堆积，引发 NAFLD。此外，GM 代谢产物如脂多糖(lipopolysaccharide, LPS)、短链脂肪酸(short chain fatty acids, SCFAs)、胆汁酸(bile acid, BA)和胆碱等在 NAFLD 发展过程中也至关重要。本文探讨了 GM 及其代谢物在 NAFLD 发病和治疗过程中的作用。

1 肠道菌群参与 NAFLD 发病的作用机制

1.1 肠道菌群及其代谢物通过肠-肝轴参与 NAFLD 的发病

1998 年马歇尔等正式提出肠-肝轴理论，GM 及其代谢物可通过门静脉与肝细胞相互作用影响肝脏的脂质代谢，造成脂肪在肝脏内过度堆积，这种肠道与肝脏之间的双向交流称为肠-肝轴[7]。门静脉是肠-肝轴的解剖学标志，其供血占肝脏总供血量的 75%，肠道通过门静脉输送营养物质和各种调节因子进入肝脏，肝脏则分泌一些信号分子和代谢物质通过门静脉逆向作用于肠道[8]。当 GM 失调时，其组成结构及丰

度发生显著变化，同时 GM 代谢物(如 LPS、SCFAs 及 BA 等)的代谢谱也出现显著异常，这种病理改变会引发肠道屏障功能障碍，而肠道屏障功能障碍是肠-肝轴紊乱的前提[9]。上述病理过程通过破坏肠-肝轴的双向调节机制诱导免疫功能紊乱和肝脏炎症，最终参与 NAFLD 的发病进程。肠-肝轴是肠道与肝脏沟通的关键途径，在 NAFLD 发生的过程中起重要作用。

1.2 肠道菌群及其代谢物影响 NAFLD 的发生发展

1.2.1 肠道菌群失调破坏肠道屏障

GM 失调可破坏肠道屏障，导致肠道屏障受损或肠道通透性增加和细菌易位，从而诱导免疫功能紊乱和炎症反应，促进 NAFLD 的发生发展。肠-血管屏障(gut-vascular barrier, GVB)是肠道屏障的重要组成部分，研究显示大肠埃希氏菌(*Escherichia coli*) NF73-1 单独作用仅能破坏肠道上皮屏障，只有在高脂饮食协同作用下大肠埃希氏菌 NF73-1 才可进一步破坏 GVB，使得肠道内有害物质更易进入血液循环，从而加剧肝损伤，最终诱导 NAFLD 的发病，表明完整 GVB 足以防止肝损伤，这提示维护 GVB 完整性可能成为防治 NAFLD 的潜在途径[10]。Bloom 等[11]研究发现，与健康对照人群相比，肝硬化患者十二指肠中存在一些特殊菌群可增加肠道通透性，主要表现为假单胞菌科(*Pseudomonadaceae*)增多，乳杆菌属(*Lactobacillus*)、双歧杆菌属(*Bifidobacterium*)和梭菌属(*Clostridium*)减少。细菌易位是肠道通透性增加后的关键病理事件[12]，蛋白磷酸化会导致紧密连接解体及肠道通透性增加。在体外结肠炎模型中，紧密连接完整性受损诱导细菌细胞外囊泡的细胞旁易位[13]，机体内已构建一套抵御细菌易位的免疫防御系统。

1.2.2 肠道菌群失调诱导免疫功能紊乱及炎症反应

肝硬化患者肠道内菌群多样性下降，表现为大肠埃希氏菌和肺炎克雷伯氏菌(*Klebsiella pneumoniae*)等有害菌增多，长链多尔氏菌(*Dorea longicatena*)和普氏栖粪杆菌(*Faecalibacterium prausnitzii*)等有益菌减少[14]，从而诱导机体免疫功能紊乱并加剧肝脏炎症反应。研究证实在 NASH 小鼠模型中，敲除 *TLR4* 基因可抑制鸟嘌呤核苷酸结合蛋白 G(i) 亚基 α 抑制剂 2 [guanine nucleotide-binding protein G(i) subunit alpha-2, GNAI2]表达，促进过氧化物还原酶 1-肿瘤坏死因子受体相关因子 6 (peroxiredoxin 1-tumor necrosis factor receptor-associated factor 6, PRDX1-TRAF6)复合物和过氧化物还原酶 1-甘油磷酸二酯酶磷酸结构域 5 (peroxiredoxin 1-glycerophosphodiester phosphodiesterase domain-containing 5, PRDX1-GDPD5)复合物形成，减轻 NASH 中的肝脏炎症反应和脂质积累，而敲除 *ARRB1* 基因后不仅体内生长分化因子 15 (growth differentiation factor 15, GDF15)的成熟与分泌受影响，且 GDF15 过表达对 NASH 的改善作用消失，导致小鼠炎症症状加重[15-16]。NAFLD 患者 GM 失调会导致 LPS 等病原体相关分子模式进入循环系统，激活肝脏免疫细胞，同时增加辅助性 T 细胞 1 (helper T cell 1, Th1)的比例，降低 Th2 的比例，使 Th1/Th2 失衡，加剧炎症反应[17]。

1.2.3 肠道菌群失调引起胰岛素抵抗

GM 失调是导致胰岛素抵抗(insulin resistance, IR)的重要原因之一。研究表明小鼠体内 GM 失调、肠道屏障被破坏且黏膜免疫反应改变，导致肠道炎症反应及肠道通透性增加，进而诱导 IR 发生。维生素 K 可通过调节 GM 改善肝脏 IR，双歧杆菌属(*Bifidobacterium*)在其中发挥重要作用[18]。GM 失调时会减少紧密连接蛋白表达，使肠道屏障受损，从而引发 LPS 入血激活炎症反应并抑制自噬，同时 SCFAs 水平下降直接干扰胰岛素信号，导致 IR[19]。IR 是大部分代谢性疾病的基本病理变化，在 NAFLD 患者群体中也存在 IR 水平升高的情况[20]，表明 IR 在 NAFLD 进程中起关键推动作用。Xue 等[21]研

究发现，IR 可通过诱导肝脏脂质代谢紊乱导致肝内甘油三酯过度积蓄，同时激活肝脏糖异生通路并增强其代谢过程，最终增加 NAFLD 的发病风险，且 TyG-WC、TyG-WHtR 和 TyG-BMI 作为新型复合指标突破了传统 IR 指标的局限性，在 IR 评估及 NAFLD 早期诊断中均展现显著优势。NAFLD 作为银屑病的一种常见共病，与 IR 和各种炎症途径密切关联，银屑病患者全身炎症和代谢紊乱会加剧 IR 和肝脂肪变性[22]。因此通过针对银屑病的治疗干预可有效缓解 IR，为 NAFLD 的治疗提供新的治疗策略。

1.2.4 内毒素血症与 NAFLD

内毒素的主要成分是来自革兰氏阴性菌细胞壁上的 LPS，GM 失调可引发肠道通透性增加并致使产 LPS 的细菌数量显著增多，同时过量 LPS 会损害肠道上皮细胞，进而导致大量 LPS 自肠道释放进入血液循环，最终诱发内毒素血症。人体内埃希氏菌属(*Escherichia*)和肠杆菌科(*Enterobacteriaceae*)等过度生长会使门静脉中 LPS 增加，引起炎症反应，从而导致肝脏损伤，最终发展为 NAFLD[23]。Nier 等[24]研究发现，NAFLD 患者外周血中的细菌内毒素水平是健康对照组的 2 倍，且肝脏脂肪变性严重程度与细菌内毒素水平呈正相关。Fei 等[25]研究显示，NAFLD 患者体内含有丰富的大肠埃希氏菌和肺炎克雷伯氏菌，其产生的 LPS 活性较高，可显著促进 NAFLD 和相关代谢紊乱。LPS 诱导肝脏炎症受到 Toll 样受体 4 (Toll-like receptor 4, TLR4)通路的调节，且持续性 LPS 刺激可触发机体内毒素耐受[26]，表明可通过调节内毒素血症来缓解其诱导的 NAFLD 进展。

1.2.5 短链脂肪酸代谢异常与 NAFLD

SCFAs 是 GM 来源的重要代谢产物，其可通过肝门静脉抵达肝脏，为肝细胞提供能量，主要成分有乙酸盐、丙酸盐和丁酸盐，其中丁酸盐是公认的免疫系统调节剂[27]。Hong 等[28]研究显示，与高脂饮食组相比，补充黄芪多糖的小鼠体内普通脱硫弧菌(*Desulfovibrio vulgaris*)明显富集，其可通过高效产生乙酸盐提升体内 SCFAs 水平，从而改善 NAFLD。NAFLD 患者肠道内产 SCFAs 的瘤胃球菌科(*Ruminococcaceae*)和栖粪杆菌属(*Faecalibacterium*)丰度降低[23]，导致 SCFAs 水平降低和肠道屏障受损，进而促进 NAFLD 的发生发展。Yoon 等[29]研究表明，补充双歧杆菌可升高体内 SCFAs 水平，从而抑制炎症反应减轻 NAFLD。SCFAs 不仅可作为信号分子结合 G 蛋白偶联受体调节肝脏脂质代谢，还可参与其他信号通路。例如，SCFAs 激活腺苷酸活化蛋白激酶 [adenosine 5′-monophosphate (AMP) -activated protein kinase, AMPK]信号通路，抑制肝脏脂肪酸合成和脂肪堆积[30]，多通路协同作用共同调控肝脏脂质代谢。

1.2.6 胆汁酸代谢异常与 NAFLD

BA 代谢是一个复杂的肠肝循环过程，在 NAFLD 发生发展中发挥重要作用。BAs 分为初级和次级，其中部分 BAs 在 GM 作用下被转化为次级 BAs，大部分 BAs 在末端回肠通过肠肝循环被重吸收[31]。胆酸(cholic acid, CA)等初级 BAs 经过 GM (如梭菌属等)的 7α-脱羟基作用生成脱氧胆酸，然后脱氧胆酸再分别与甘氨酸或牛磺酸结合可形成甘氨脱氧胆酸(glycodeoxycholate, GDCA)和牛磺脱氧胆酸(taurodeoxycholic acid, TDCA)。肝纤维化是 NAFLD 发展过程中的关键病理阶段，相较于其他 BAs，GDCA 和 TDCA 在激活肝星状细胞方面更有效，可观察到纤维化相关标记物表达显著上调[32]。多数 BAs 通过激活法尼酯 X 受体(farnesoid X receptor, FXR)诱导其下游效应器 SHP 发挥作用，从而抑制顶端钠依赖性 BA 转运体功能和细胞色素 P450 酶活性，通过调控胆汁酸的合成和肠道上皮对其的摄取量来维持 BA 代谢平衡[33]。CA 作为 FXR 的强效激活剂可通过 FXR 信号通路上调紧密连接蛋白的表达，从而增强肠道屏障功能并抑制 LPS 移位[34]。相比之下，高浓度 GDCA 可能导致肠道内 CA 水平

显著下降，不仅削弱 FXR 介导的肠道屏障保护机制及 BA 稳态调节，同时还可加剧肝脏炎症反应和纤维化进程，最终推动 NAFLD 的发生发展。研究发现 NAFLD 患者血清 TDCA 水平显著升高，提示肝脏中可能存在 CA 过度合成，且 TDCA 可与 FXR 特异性结合影响 BA 代谢，表明可通过调节 CA 代谢或 FXR 信号通路改善 NAFLD；研究数据中 TDCA 浓度的第 3 个三分位数与 NAFLD 患病风险显著增加相关，这提示 TDCA 可作为 NAFLD 诊断或进展评估的潜在生物标志物[35]。

1.2.7 胆碱代谢异常与 NAFLD

胆碱可通过多种途径调节肝脏脂肪代谢，其中 GM 参与胆碱向三甲胺(trimethylamine, TMA)转化，之后 TMA 通过门静脉循环到达肝脏形成氧化三甲胺(trimethylamine oxide, TMAO)。梭菌属可促进胆碱向 TMAO 转化，而 NAFLD 患者体内梭菌属相对丰度较高，导致胆碱过度转化为 TMAO，表明 NAFLD 患者体内 TMAO 水平较高且缺乏胆碱[36]。人体内大部分胆碱主要依赖饮食摄入，部分胆碱在体内可通过氧化反应转化为甜菜碱。Chen 等[37]研究发现给予 NAFLD 小鼠甜菜碱干预后，小鼠肝功能恢复且病理表现明显改善，提示甜菜碱可通过激活成纤维细胞生长因子 10 (fibroblast growth factor 10, FGF10)/AMPK 信号通路预防 NAFLD。体内胆碱缺乏会导致甜菜碱生成不足，而甜菜碱补充能显著改善 NAFLD，表明体内胆碱缺乏可能通过减少甜菜碱合成促进 NAFLD 的发生和发展。

1.3 肠道菌群及其代谢产物与 NAFLD 的关联

GM 失调与 NAFLD 的关联已被多项临床研究证实。例如，NAFLD 患者存在 GM 失调，表现为芽孢杆菌门/拟杆菌门比值(*Bacillota*/*Bacteroidetes*, *F/B*)失调，有益菌(如双歧杆菌等)丰度减少，有害菌(如大肠埃希氏菌、肺炎克雷伯氏菌等)丰度增加，进而诱导机体免疫功能紊乱及炎症反应[23-24,38]；GM 失调使肠道屏障受损，导致外周血 LPS 水平升高，同时 SCFAs 水平下降且 BA 代谢异常，进而诱导肝脏脂质代谢紊乱，最终引发 NAFLD[23-24,29]。动物模型的研究为 GM 失调与 NAFLD 的关联提供了关键性机制证据，运用动物模型可控制变量，从而更直接地观察到 GM 失调带来的变化。例如，将肥胖患者的阴沟肠杆菌(*Enterobacter cloacae*) B29、大肠埃希氏菌 PY102 和肺炎克雷伯氏菌 A7 移植至无菌小鼠，在高脂饮食协同作用下显著诱导小鼠 NAFLD，小鼠表现为体内 GM 失调且肝脏脂肪变性，外周血中 LPS 水平升高及机体产生炎症反应[25]。更多有关肠道菌群代谢物参与 NAFLD 病理机制的动物模型研究信息详见表 1。

2 基于 GM 靶向治疗 NAFLD 的方法

NAFLD 治疗是一个综合性的复杂过程。随着研究的不断深入，发现 GM 失调在 NAFLD 发病机制中扮演重要角色，提示其可能成为潜在治疗靶点。基于 GM 靶向治疗 NAFLD 是近年来的重点研究方向，通过调节 GM 失调可有效改善 NAFLD[40]，具体方法包括粪便菌群移植(fecal microbiota transplantation, FMT)、补充益生菌/益生元、使用中草药或方剂治疗以及生活方式干预等。

2.1 粪便菌群移植

FMT 作为一种新型的微生态治疗手段，通过将健康人粪便中的功能菌群移植到患者肠道内，旨在重建新的肠道 GM 平衡，达到治疗疾病的目的。Witjes 等[41]开展的双盲试验显示，与自体 FMT 组相比，同种异体 FMT 组的受试者其肝脏中与脂质代谢和炎症相关的基因表达出现了显著差异。在 Xue 等[42]进行的另一项双盲试验中，相比口服益生菌组，同种异体 FMT 组

表1 肠道菌群代谢物参与NAFLD发生发展

Table 1 Gut microbiota-derived metabolites are involved in the development and progression of nonalcoholic fatty liver disease

肠道菌群代谢物 Gut microbiota-derived metabolites	动物模型 Animal models	机制 Mechanism	参考文献 References
脂多糖 Lipopolysaccharide	HFD (小鼠) HFD (mice)	GM失调，LPS水平升高，LBP-CD14复合物激活LPS-TLR4通路，引起炎症反应，诱导NAFLD Dysregulation of GM leads to elevated LPS levels. The LBP-CD14 complex activates the LPS-TLR4 pathway, triggering inflammatory responses and inducing NAFLD	[25]
胆汁酸 Bile acids	HFD (小鼠) HFD (mice)	GM失调，BA肠肝循环紊乱，FXR信号通路受影响，导致肝脏脂质代谢异常并诱导炎症反应等，促进NAFLD发展 Dysregulation of GM disrupts the enterohepatic circulation of BAs, which impairs FXR signaling pathway. It leads to aberrant hepatic lipid metabolism and inflammatory responses, thereby driving the progression of NAFLD	[31]
三甲胺 Trimethylamine	MCD (小鼠) MCD (mice)	GM失调，小鼠体内脱铁杆菌纲(*Deferribacteres*)和支原体门(*Mycoplasmatota*)相对丰度增加，导致肝脏内TMAO水平升高，促进NAFLD发展 Dysregulation of GM induces an increased relative abundance of *Deferribacteres* and *Tenericutes* in mice, which elevates hepatic TMAO levels, thereby driving the progression of NAFLD	[36]
铁 Iron	MCD (小鼠) MCD (mice)	铁超载抑制肠道缺氧诱导因子(hypoxia inducible factor, HIF)-2α活性、间接促进谷胱甘肽过氧化物酶(glutathioneperoxidase, GPx) 4表达，加重肝脏IR严重程度，引起肝细胞炎症，诱导NAFLD Iron overload inhibits HIF-2α activity in the gut and indirectly promotes GPx4 expression, thereby exacerbating hepatic IR severity, which triggers hepatocellular inflammation responses and ultimately induces the development of NAFLD	[39]

HFD：高脂饮食；MCD：甲硫氨酸胆碱缺乏饮食。

HFD: High fat diet; MCD: Methionine choline deficient.

受试者体内某些细菌丰度与健康者无异。Maestri 等[43]研究显示，NAFLD 患者经 FMT 治疗后肝脏脂肪减少，促炎细胞因子降低，体内有益菌丰度增加，且对瘦型 NAFLD 患者治疗效果更加明显。FMT 需要严格筛查供体且谨慎选择合适给药途径，同时移植的粪便实现成分标准化较困难，在未来的研究中还需进行更深层次的探索[44]。FMT 作为一种创新疗法为 NAFLD 的治疗提供了全新策略，具有潜在临床应用价值。

2.2 补充益生菌/益生元

益生菌是一类对人体有益的活性微生物，可作为肠道微生态调节剂，通过调节 GM 平衡和改善肠道屏障受损等影响 NAFLD 的发展[45]。Li 等[46]研究显示，高脂饮食小鼠补充多形拟杆菌(*Bacteroides thetaiotaomicron*)可降低小鼠体内 *F*/*B* 比率，恢复肠道内部平衡，多形拟杆菌还可增加肝脏叶酸水平和多不饱和脂肪酸比例，调节肝脏脂质代谢，从而改善 NAFLD。相较于传统益生菌，新一代益生菌(next-generation probiotics, NGP)的有益效果更为明显，补充嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*)等 NGPs 可增强肠道屏障功能，调节肝脏抗氧化通路，减轻肝脏炎症，从而有效缓解 NAFLD，值得注意的是，大多数 NGPs 的临床应用仍处于研究初期阶段[47]。卵形拟杆菌(*Bacteroides ovatus*)也属于 NGP，可通过调节肠道免疫功能和代谢来减轻 NAFLD 症状[48]。益生元是一类不被宿主

消化吸收，但能被有益菌分解吸收并促进肠道内益生菌活性和增进机体健康的物质，如低聚糖、果胶和环糊精等[49]。菊粉是最常见益生元之一，可促进乳酸菌等有益菌增殖，缓解肝脏脂肪沉积并调节脂质代谢，从而改善肥胖相关的 NAFLD[50]。NAFLD 患者补充益生菌或益生元后，可有效改善 GM 失调并抑制炎症反应，从而达到治疗 NAFLD 的目的。目前临床治疗上常将其与其他治疗手段联合使用。

2.3 中草药与中医方剂治疗

中草药可调节 NAFLD 患者体内 GM 平衡，保护肝脏，其活性成分主要包括黄酮类化合物、萜类或生物碱等。例如，三萜类糖苷化合物人参皂苷通过增多副拟杆菌属(*Parabacteroides*)和阿克曼氏菌属(*Akkermansia*)等有益细菌丰度以及降低螺杆菌属(*Helicobacter*)等有害菌丰度减轻炎症，调节高脂饮食诱导的 GM 失衡，从而对 NAFLD 产生积极影响[51]。黄酮类化合物川陈皮素可增多粪便拟杆菌(*Bacteroides stercoris*)和干酪乳酪杆菌(*Lacticaseibacillus casei*)的丰度，调节肉豆蔻酸代谢，改善高脂高糖诱导的 NAFLD[52]。中医方剂学是在中医理论指导下将中草药按照一定原则配伍组合形成的具有治疗作用的方剂，有助于缓解 NAFLD 症状。例如，大柴胡汤可增加拟杆菌属(*Bacteroides*)和乳杆菌属等有益菌丰度，降低肠杆菌科等有害菌丰度，从而影响代谢通路[53]；苓桂术甘汤可增加乳酸菌丰度，改善 IR，缓解 BA 代谢紊乱，对 NAFLD 有良好治疗效果[54]。中医通过多靶点、多途径的综合作用，显著改善 NAFLD 患者 GM 失调，从而有效缓解患者的临床症状，在 NAFLD 治疗中具有独特的优势。

2.4 生活方式干预

高脂饮食是诱导 NAFLD 的重要因素，长期高脂饮食会显著改变 GM 组成结构和丰度，增加肥胖人群 NAFLD 的发生率。因此合理调整饮食习惯可降低 NAFLD 发病风险，如多摄入含酚酸[55]和大豆皂苷[56]的蔬菜、水果或谷物以及富含芝麻素和木脂素的芝麻[57]等。有氧运动如快走、跑步和游泳等可抑制高脂饮食诱导的脂肪积累并降低体重，通过改善 GM 失调和降低内毒素血症起到积极防治 NAFLD 的作用[58]。健康饮食联合有氧运动具有改善 *F/B* 比例失衡、提高患者 GM 多样性和改善 IR 等作用，通过改善 GM 失调靶向治疗 NAFLD。生活方式干预是 NAFLD 治疗的基石，既可有效预防 NAFLD 向更严重的肝病发展，又可改善 NAFLD 患者的预后。

3 总结与展望

GM 及其代谢物与 NAFLD 的发生发展和治疗密切相关，其在 NAFLD 病理过程中发挥复杂的双向调控作用：一方面，GM 失调通过破坏肠道屏障、诱导免疫功能紊乱和肝脏炎症反应及诱发 IR 等多重机制驱动 NAFLD 进展；另一方面，GM 代谢物(如 SCFAs)通过调控机体免疫应答和炎症反应、改善肠道通透性等途径减轻肝脏脂肪累积及炎症损伤，从而缓解 NAFLD。近年来，大量研究认为基于 GM 靶向治疗的策略(如 FMT、益生菌、益生元、中医药和生活方式干预等)可有效改善 NAFLD，尤其是 FMT 作为一种新型治疗策略展现出显著的临床疗效及机制优势。目前，改善 GM 失调已成为 NAFLD 治疗的重要研究方向，随着研究的深入，有望进一步揭示 GM 与 NAFLD 之间的具体作用机制，提高 NAFLD 患者治疗的有效性，为临床治疗提供新的靶点和方法。

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