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肠道菌群在代谢相关性脂肪肝病中的研究

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摘　要

代谢相关脂肪性肝病(Metabolic dysfunction-associated fatty liver disease, MAFLD)是最常见的慢性肝病，其患病率持续上升，并将成为全球最主要的健康卫生问题之一。因此，揭示NAFLD的发生机制，对诊治NAFLD有重要意义。近年来，肠道菌群作为调控宿主代谢和免疫的重要参与者之一，在MAFLD发生发展中的作用备受关注。MAFLD患者呈现显著的肠道微生态失调特征，包括菌群多样性下降、产短链脂肪酸有益菌减少及条件致病菌富集等。本文系统综述MAFLD相关的肠道菌群变化特征及相关的机制研究进展，并探讨当前研究的局限性与未来转化方向，以期为MAFLD的精准防治提供新思路。

关键词

代谢相关性脂肪肝病，肠道菌群，致病机制

Study of Gut Microbiota in Metabolic Dysfunction-Associated Fatty Liver Disease

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Abstract

Metabolic dysfunction-associated fatty liver disease (MAFLD) has emerged as the most prevalent chronic liver condition worldwide, with its incidence continuing to escalate and posing a significant global health challenge. Elucidating the underlying pathogenic mechanisms of MAFLD is therefore of great importance for improving disease management and patient outcomes. In recent years, the

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gut microbiota has garnered considerable attention as a key modulator of host metabolism and immunity, playing a pivotal role in the initiation and progression of MAFLD. Individuals with MAFLD exhibit profound intestinal dysbiosis, characterized by reduced microbial diversity, depletion of short-chain fatty acid-producing beneficial bacteria, and enrichment of opportunistic pathogens. This review systematically summarizes the alterations in gut microbiota composition associated with MAFLD and highlights recent advances in understanding the underlying mechanisms linking gut microbiota to disease pathogenesis. Additionally, we discuss current research limitations and future directions for translational applications, aiming to provide novel insights into the precision prevention and treatment of MAFLD.

Keywords

Metabolic Dysfunction-Associated Fatty Liver Disease, Gut Microbiota, Pathogenic Mechanisms

1. 引言

代谢相关脂肪性肝病(Metabolic dysfunction-associated fatty liver disease, MAFLD)是一种以肝脏脂肪过度沉积为核心病理特征，并与全身代谢功能障碍密切相关的慢性肝病，目前已成为全球范围内最常见的肝脏疾病之一[1]。近年来，MAFLD 的患病率持续攀升，全球估计已达 25%~30%，部分地区甚至超过 40%，由此导致的肝硬化、肝细胞癌及心血管事件风险显著增加，给公共卫生系统带来了沉重的疾病负担和经济压力[2]。2020 年，国际专家共识正式将沿用数十年的“非酒精性脂肪性肝病(NAFLD)”更新为“代谢相关性脂肪肝(MAFLD)”。这一命名变更不仅是对疾病认识的深化，更体现了诊疗理念的重要转变[3]。新定义摒弃了传统的“排他性”诊断逻辑(即需排除饮酒、病毒性肝炎等其他肝病)，转而采用“肯定性”诊断标准，即基于肝脏脂肪变性证据合并超重/肥胖、2 型糖尿病或代谢功能障碍指标进行阳性诊断，从而更精准地揭示了 MAFLD 作为全身代谢紊乱肝脏表现的疾病本质[4]。关于 MAFLD 的发病机制，早期提出的“二次打击”学说曾占据主导地位。该假说认为，胰岛素抵抗作为“第一次打击”诱导肝脏脂肪变性，继而通过氧化应激作为“第二次打击”触发炎症反应和肝细胞损伤，最终导致疾病进展[5]。然而，随着研究的深入，这一简化模型已难以解释 MAFLD 复杂的分子异质性和多系统受累特征。目前，“多重打击”假说已被广泛接受，用以替代过时的“二次打击”学说。该假说强调，MAFLD 的发生发展是多种因素协同作用的结果，包括肠道微生态紊乱、胰岛素抵抗、脂肪组织功能障碍、遗传与表观遗传修饰以及饮食因素等。这些因素共同导致肝脏脂肪毒性、氧化应激、线粒体功能障碍和持续性炎症，最终推动疾病从单纯脂肪变性向脂肪性肝炎、纤维化乃至肝硬化进展[6]。

据估计，人类肠道内栖息着数以万亿计的微生物，涵盖细菌、古菌、真核生物、病毒及寄生虫等多种类群[7]。作为调控宿主能量代谢、炎症反应及免疫稳态的核心枢纽，肠道菌群在代谢相关脂肪性肝病(MAFLD)发生发展中的作用日益受到关注。肠道菌群不仅参与营养物质的消化与吸收，还通过代谢产生短链脂肪酸、胆汁酸、吲哚及其衍生物、三甲胺等多种生物活性分子，借助解剖与功能上紧密相连的“肠–肝轴”与肝脏进行双向通讯。

近年来，随着研究技术的进步，除了传统的细菌，肠道真菌和病毒在 MAFLD 中的作用逐渐受到重视。研究发现白色念珠菌在 MAFLD 患者中显著富集[8]；有研究患者粪便中的真菌内部转录间隔区 2 进

行了测序，结果显示晚期 MAFLD 患者具有特定真菌组成，并对白念珠菌的系统免疫反应增强[9]。以噬菌体为主的肠道病毒在 MAFLD 的发展中发挥着重要作用，通过调控细菌种群结构和功能，间接参与肝脏炎症与代谢调控[10] [11]。Inoviridae 是一类噬菌体，能长期感染细菌宿主而不进行溶解，从而影响细菌的代谢表型，与疾病发生密切相关[12]。

肠道菌群及其代谢产物一方面可通过门静脉系统直接进入肝脏，调节肝细胞的脂质合成与氧化代谢；另一方面，当肠道屏障功能受损时，细菌及其产物(如脂多糖、肽聚糖)易位至肝脏，可激活肝内固有免疫应答，触发炎症级联反应，导致肝损伤、炎症及纤维化，从而加速 MAFLD 的进展[13]。正是这种独特的解剖位置与功能联系，使肠道菌群逐渐被揭示为连接代谢紊乱与肝脏损伤的“隐形器官”，为深入理解 MAFLD 的多重发病机制及开发靶向微生态的干预策略提供了重要视角和研究方向。

2. 肠道微生物群的生理特征及功能作用

肠道微生物群是指定植于人体消化道内种类繁多、数量庞大的微生物群落，主要包括细菌、古菌、病毒、真菌及原生生物等，其中以细菌为主导。该群落主要由专性厌氧菌构成，核心菌群包括革兰氏阳性的厚壁菌门和革兰氏阴性的拟杆菌门，此外还包含放线菌门和变形菌门等[14]。研究显示，人体肠道内微生物总数高达 10^{14} 量级，约为人体细胞总数的 10 倍，其编码的基因数量更是人类基因组的 150 倍以上，因此被称为人体的“第二基因组”[15]。作为人体最为复杂的微生态系统，肠道微生物群处于动态变化之中，其组成受饮食结构、药物使用及昼夜节律等多种因素影响，且个体间及个体自身在不同时间点的菌群构成均存在显著差异[16]。

肠道微生物群具有多样化的代谢活性和重要的生理调控功能。研究表明，肠道微生物群通过与肠道相关淋巴组织相互作用，促进免疫系统的发育与成熟，在维持肠道防御功能和免疫耐受中发挥关键作用[17]。先天性淋巴细胞是 GALT 的重要组成部分，其生物学功能受肠道微生物群调控。根据表面标志和功能差异，ILC 主要分为 ILC1、ILC2、ILC3、淋巴组织诱导细胞及自然杀伤细胞五个亚群[18] [19]。微生物群及其代谢产物(如芳香烃受体配体)对 ILC3 的活化和功能维持至关重要，后者通过分泌 IL-22 维持肠道上皮屏障完整性、促进抗菌肽产生并调节组织修复[20]。此外，肠道菌群通过表观遗传机制调控 ILC1 的分化与扩增，而 ILC1 则通过其效应功能反馈调节菌群组成，在炎症应答、代谢调控和组织修复中发挥重要作用，这种精密的相互作用对维持肠道免疫稳态至关重要[21]。

肠道微生物群在调节适应性免疫方面同样发挥重要作用，主要通过协调 T 细胞和 B 细胞等多种免疫细胞的相互作用来实现[22]。不同菌群及其代谢产物可诱导 T 细胞向特定亚群分化：例如，分节丝状菌可促进 Th17 细胞分化，后者在抵御细胞外病原菌的同时参与维持肠道屏障完整性[23]；乳酸杆菌和双歧杆菌则可诱导 CD4+CD25+Foxp3+调节性 T 细胞的产生，对肠道黏膜及外周免疫系统发挥抗炎作用[24]。在 B 细胞调控方面，肠道微生物群可刺激 IL-1β 和 IL-6 等细胞因子的产生，促进原始 B 细胞在肠系膜淋巴结中分化为调节性 B 细胞[25]；同时，微生物群来源的 ATP 被转化为腺苷后，可激活 B 细胞表面的腺苷受体，促进 IgG 和 IgA 抗体的产生[26]。

综上所述，肠道微生物群与免疫系统之间的密切互动维持了对共生菌群的免疫耐受，并构筑了抵御病原体侵袭的保护屏障。一旦这种平衡被打破，可能导致免疫功能障碍及自身免疫性疾病的发生。

3. 肠道微生物群影响 MAFLD 的作用机制

代谢相关脂肪性肝病(MAFLD)与肠道菌群之间的密切关联主要通过“肠–肝轴”实现双向通讯。肠道菌群及其代谢产物经由门静脉系统持续输送至肝脏，对肝脏脂质代谢、炎症反应及纤维化进程产生深远影响；与此同时，肝脏分泌的胆汁酸等活性物质亦可反向调控肠道菌群的组成与功能。研究表明，肠

道菌群失调及其引起的肠道屏障功能损伤，是 MAFLD 发生与发展的重要病理基础。

3.1. 肠道菌群代谢物与 MAFLD 的关系

3.1.1. 短链脂肪酸

短链脂肪酸(Short-chain fatty acids, SCFAs)是一类碳原子数少于 6 的挥发性脂肪酸，主要由肠道微生物群在大肠中发酵可溶性膳食纤维和不可消化碳水化合物产生，其中以乙酸、丙酸和丁酸含量最为丰富[27]。SCFAs 可通过肝门静脉进入肝脏，为机体提供部分能量需求，是连接肠道菌群与宿主能量代谢的重要介质。研究表明，SCFAs 可通过改善肠道屏障功能、调节食欲及发挥抗炎作用，延缓代谢相关脂肪性肝病(MAFLD)的进展。

CFAs 的生物学功能主要通过激活 G 蛋白偶联受体实现。GPR41 和 GPR43 广泛表达于肠上皮细胞、肠道干细胞及肠内分泌细胞等多种细胞类型，介导 SCFAs 对肠道功能的精细调控[28]。丁酸作为 GPR41 和 GPR43 的双重激动剂，可激活丝裂原活化蛋白激酶信号通路，促进趋化因子和细胞因子的产生，参与炎症调控与肠道屏障功能的维持[29]。此外，丁酸通过 Akt/mTOR 信号通路上调紧密连接蛋白(如 claudin 家族成员)的表达，增强肠上皮细胞间的连接完整性，加固肠道屏障结构基础，从而阻止脂多糖等细菌产物易位入肝[30]；丁酸还可通过抑制组蛋白去乙酰化酶 8 活性，下调己糖激酶 2 表达，抑制线粒体呼吸，防止肠上皮细胞在炎症环境下过度死亡，维持上皮层完整性[31]。丙酸则通过刺激肠道 L 细胞分泌胰高血糖素样肽-1 和肽 YY，经肠－脑轴传递饱腹信号，减少能量摄入，改善肥胖相关的代谢紊乱[32]。

综上所述，SCFAs 特别是丁酸，不仅为机体提供能量，更通过肠－肝轴多维度调控肠道屏障、能量代谢和免疫炎症，从而缓解 MAFLD 的进展。深入理解 SCFAs 的生物学效应，对于开发以靶向菌群－肠道屏障为切入点的 MAFLD 干预策略具有重要的理论价值和临床转化前景。

3.1.2. 胆汁酸

胆汁酸由肝脏以胆固醇为原料合成并储存于胆囊中，参与多种生理与病理过程的调节。在肝脏中，胆固醇经经典途径(限速酶 CYP7A1)合成初级胆汁酸，主要包括胆酸和鹅脱氧胆酸，二者随后与甘氨酸或牛磺酸结合形成结合型胆汁酸，随胆汁分泌进入肠道。进入肠道后，肠道微生物群将远端小肠和结肠中的初级胆汁酸转化为次级胆汁酸，如脱氧胆酸和石胆酸[33]。约 95%的胆汁酸在回肠末端通过主动转运被重吸收，经门静脉返回肝脏完成肠肝循环，剩余 5%随粪便排出，以弥补每日从胆固醇新合成的损失[34]。这一精密的代谢过程不仅维持了胆汁酸池的稳态，也使肠道菌群通过对胆汁酸结构的修饰，深刻影响机体的脂质代谢与信号调控。

胆汁酸及其衍生物具有直接的抑菌活性，可通过破坏细菌细胞膜、诱导氧化应激及调节细菌基因表达等方式，塑造肠道微生态结构[35] [36]。此外，胆汁酸间接参与法尼醇 X 受体介导的抗菌防御作用。FXR 作为核激素受体家族成员，在胆汁酸肠肝循环及其从肝脏向肠道的运输过程中发挥关键调控作用。研究表明，FXR 活化可通过下调 Scd1、Dgat2 和 Lpin1 的表达，减少肝脏脂肪酸和甘油三酯合成，从而对 MAFLD 发挥治疗作用[37]；同时，FXR 还可通过抑制肝脏中多个糖异生相关基因的表达，降低血糖水平，参与葡萄糖稳态的调节[38]。Takeda-G 蛋白受体-5 是另一经典的胆汁酸受体，广泛表达于肠道、胆囊、肝脏上皮细胞及库普弗细胞[39]。TGR5 可通过促进脂肪组织褐变、诱导蛋白质解偶联、激活 PPARα 和 PGC-1α，增强线粒体氧化磷酸化和能量代谢，进而预防肥胖、2 型糖尿病及 MAFLD 的发生发展[40]。研究提示胰岛素抵抗与 NAFLD 之间存在明确的因果关系，而 TGR5 可通过抑制细胞凋亡并促进 β 细胞增殖，保护胰腺 β 细胞功能，改善胰岛素抵抗，从而缓解 MAFLD 进展[41]。

胆汁酸与肠道微生物群之间存在双向调控关系：肠道菌群通过其代谢酶活性塑造胆汁酸的组成与多样性，而胆汁酸则在调节肠道微生物群结构中发挥关键作用。与此同时，胆汁酸还可通过介导多种信号

通路调节宿主的新陈代谢与免疫功能。因此，靶向胆汁酸代谢及其信号通路有望成为 MAFLD 治疗的新策略。

3.1.3. 内源性乙醇

内源性乙醇是指由肠道微生物群通过发酵碳水化合物代谢产生的乙醇，作为肠道菌群与宿主代谢相互作用的重要介质之一，其在代谢相关脂肪性肝病(MAFLD)发病机制中的作用日益受到关注。研究表明，与健康人群相比，MAFLD 患者血浆中肠道菌群来源的内源性乙醇浓度显著升高[42]；肠道菌群中的高产乙醇肺炎克雷伯菌被证实可通过 2,3-丁二醇发酵途径诱导脂肪肝的发生[43]；此外，发酵乳杆菌、地中海芽孢菌及变异链球菌等其他产乙醇微生物也被认为在 MAFLD 的发生发展中发挥重要作用[44]。因此，靶向抑制产乙醇肠道微生物可能成为 MAFLD 治疗的可选策略之一。

内源性乙醇可通过多种机制破坏肠道屏障完整性。其代谢产物乙醛能够通过蛋白磷酸酶 2A 依赖性机制损害肠道上皮紧密连接，增加细胞旁通透性[45]。乙醇还可显著上调 CYP2E1、诱导型一氧化氮合酶、硝化蛋白及凋亡相关标记蛋白的表达，破坏肠道屏障功能，进而加重内毒素血症和炎症性肝损伤[46]。乙醇诱导的胃肠道通透性增加促进了更多微生物相关分子模式的易位，触发免疫应答，可能诱发肝脏炎症[47]。

除增加肠道通透性外，内源性乙醇还可影响肝脏脂质代谢及肝细胞炎症反应。在乙醇代谢为乙醛的过程中，NAD^+被消耗，导致 $NADH/NAD^+$比值升高，干扰脂肪酸氧化，进而引起肝脏脂肪变性[48]。乙醇可通过破坏肝细胞线粒体呼吸链诱导氧化应激，促进活性氧产生[49]。此外，乙醇代谢生成乙醛的过程可通过调控固醇调节元件结合蛋白 1c 和过氧化物酶体增殖物激活受体 α 的转录，影响其表达水平；同时调节免疫应答激活、内质网应激相关变异体及脂质运载蛋白水平，并降低调控蛋白 ATAT3 的活性，从而促进脂肪酸积累，推动脂肪性肝病的进展[50]。

总的来说，内源性乙醇在 MAFLD 病理机制中扮演重要角色。产乙醇菌过度增殖导致内源性乙醇水平升高，通过氧化应激、炎症激活和脂肪合成等多重途径推动 MAFLD 进展。因此，靶向产乙醇菌及其代谢通路有望成为 MAFLD 精准干预的新策略。

3.1.4. 氧化三甲胺(TMAO)

三甲胺-N-氧化物(trimethylamine N-oxide, TMAO)是三甲胺(trimethylamine, TMA)的肝脏氧化代谢产物，由含黄素单加氧酶催化生成，目前被认为是代谢综合征的潜在新型生物标志物[51]。近年来，TMAO 在代谢相关脂肪性肝病(MAFLD)发生发展中的作用受到广泛关注，其通过多种途径影响疾病进程。TMAO 可干扰肝脏脂质代谢稳态，通过抑制胆汁酸合成关键酶 CYP7A1 的表达，减少胆汁酸池容量，扰乱胆固醇代谢平衡，促进肝脏脂质沉积，从而加重 MAFLD 的脂肪变性程度[52]。此外，TMAO 可在不同层面破坏肠道屏障的结构与功能，进而激活 TLR4/MyD88/NF-κB 信号通路，并抑制 WNT/β-catenin 通路，加速 MAFLD 的进展[53]。研究表明，TMAO 可通过作用于角蛋白 17 促进肝细胞内脂质沉积及纤维化过程[54]。

多项横断面研究显示，MAFLD 患者血清 TMAO 水平显著高于健康对照人群，且与肝脏脂肪含量、肝纤维化分期及疾病严重程度呈正相关[55]；前瞻性研究进一步提示，TMAO 水平对 MAFLD 患者进展为脂肪性肝炎和肝纤维化具有一定预测价值[56]。值得注意的是，TMAO 还与 MAFLD 患者的心血管并发症风险密切相关，部分解释了 MAFLD 患者心血管事件高发的原因[57]。

综上所述，TMAO 作为肠－肝轴的关键代谢物，通过干扰脂质代谢、激活炎症反应、促进纤维化及诱导胰岛素抵抗等多重途径参与 MAFLD 的发生发展。然而，TMAO 血清水平能否作为 MAFLD 的独立生物标志物仍需更多前瞻性研究验证。

3.2. 肠道屏障通透性增加与 MAFLD 的关系

肠道屏障由机械屏障(包括肠上皮细胞及细胞间紧密连接)、免疫屏障、化学屏障和微生物屏障共同构成，其核心功能在于选择性吸收营养物质的同时，有效阻遏肠道内细菌、内毒素及其他有害代谢产物进入体循环。研究表明，代谢相关脂肪性肝病(MAFLD)患者普遍存在肠道屏障功能障碍，主要表现为紧密连接蛋白(如 ZO-1、occludin 及 claudin 家族)表达下调及分布异常，导致肠道通透性升高[58]。这一病理改变可能与高脂高糖饮食诱导的肠道微生态失调、产乙醇菌过度增殖所致局部乙醇暴露等因素密切相关。

肠道屏障受损后，病原体相关分子模式(PAMPs)更易发生易位，并通过肠道固有层及肝脏免疫细胞表面的模式识别受体(PRRs)被识别，进而触发免疫炎症反应，推动 MAFLD 的发生与发展[59]。在非酒精性肝病动物模型中，PAMPs 可通过 TLR2-NF-κB/NLRP3-Caspase-1 途径诱导肝巨噬细胞活化并向 M1 型极化，同时激活 mTOR-S6K1-SREBP-1/PPAR-α 信号通路，促使脂质代谢由甘油三酯氧化转向合成，加剧肝脏脂肪沉积[60]。此外，肠道来源的细菌 DNA、肽聚糖等成分持续进入肝脏，可进一步激活炎症小体，加重肝脏炎症损伤与氧化应激[61]。肠漏状态形成的“肠–肝轴”恶性循环——肝脏炎症导致胆汁酸分泌异常，进一步破坏肠道菌群稳态和屏障功能，形成正反馈放大效应。

肠道屏障通透性增加是连接肠道微生态紊乱与肝脏损伤的核心枢纽，通过驱动内毒素入肝、激活炎症反应及促进纤维化，深刻影响 MAFLD 的疾病进展。尽管肠道屏障功能障碍在 MAFLD 发病中的地位已获广泛认可，当前研究仍存在若干局限性：肠道屏障评估方法缺乏标准化，临床常用血清标志物(如脂多糖结合蛋白、连蛋白)特异性有限，不同研究结果可比性差；此外，因果关系方向性尚存争议，屏障损伤与肝病进展形成“肠–肝轴”恶性循环，现有研究对双向反馈环路的量化解析不足；因此未来需在模型优化、方法标准化及多菌群交互研究等方面取得突破，方能推动肠道屏障靶向治疗从实验室走向临床。

4. 靶向肠道微生态的 MAFLD 治疗策略

基于“肠–肝轴”在代谢相关脂肪性肝病(MAFLD)发病机制中的核心地位，以调节肠道微生态为靶点的干预策略已成为当前研究的热点。目前，针对 MAFLD 的微生态调节疗法主要包括饮食干预、传统益生菌/合生元补充以及靶向菌群代谢物的新型制剂。

4.1. 饮食干预

饮食干预作为 MAFLD 一线治疗策略的地位已得到广泛认可，其通过直接调节肠道菌群结构和功能发挥治疗作用。地中海饮食、高蔬菜摄入，水果和坚果、谷物、橄榄油、中等比例的鱼类摄入记忆低至中度的乳制品摄入被证实可显著增加肠道菌群多样性，促进短链脂肪酸产生菌的富集，同时抑制条件致病菌的过度增殖[62] [63]。例如研究发现，在苹果中大量存在的氯素通过调控 ERK/Nrf2 途径，增强抗氧化反应，缓解氧化应激[64]；从蓝莓和葡萄中提取的翼钎被证明通过激活肝细胞中的 AMPK/mTOR 途径，促进脂肪酸代谢和分解，延缓 MAFLD 的进展[65]。此外，鹿黄酮是一种存在于蓼科植物中的主要类黄酮，通过 AMPK 信号通路缓解 MAFLD 中的氧化应激，该通路在能量稳态和应激反应中起关键作用[66]。虾红素存在于虾、螃蟹、鲑鱼、藻类及其他海洋生物中，其能够通过上调 FGF21/PGC-1α 减缓线粒体功能障碍，从而缓解 MAFLD 中的氧化应激[67]。另外，乳制品中的 α-乳白蛋白肽 Gly-Ile-Asn-Tyr (GINY)及 Asp-Gln-Trp (DQW)可能通过减少氧化应激延缓 MAFLD 的发展[68] [69]。

饮食干预虽为 MAFLD 一线基础治疗，但临床应用中面临多重挑战。首先，依从性差是最大障碍，长期严格遵循地中海饮食或低脂低糖饮食对患者生活习惯改变较大，难以持久坚持。其次，个体反应差异显著，相同饮食方案在不同患者中疗效不一，可能与遗传背景、基线菌群构成及代谢特征差异有关。再次，缺乏标准化方案，各类饮食的成分比例、干预周期及能量摄入标准尚未统一，导致研究结果可比

性差。因此，未来针对 MAFLD 患者的饮食干预需向精准化与个性化方向发展。基于营养遗传学和营养代谢组学，可根据个体基因型及菌群特征制定个性化饮食方案，提高疗效及依从性。

4.2. 益生菌及益生元

益生菌作为调节肠道微生态的经典手段，在 MAFLD 治疗中积累了丰富的临床研究证据。乳酸杆菌、双歧杆菌和杆菌可能补充肠道微生物组成，减少胃肠道内毒素血症，从而产生强烈的抗炎反应并预防 MAFLD 的发生[70]。乳杆菌属和双歧杆菌属是研究最广泛的益生菌菌株，可通过增强肠道屏障功能、调节胆汁酸代谢、抑制内毒素血症及调控肠－肝轴等多重机制，改善 MAFLD 患者的肝酶水平、胰岛素抵抗及肝脏脂肪变性[71]。在一项双盲试验中，补充含有乳酸杆菌、酸果乳杆菌、蟹状乳杆菌和双歧杆菌的益生菌配方后，MAFLD 患者的血清转氨酶水平有所下降[72]。

益生元是宿主微生物选择性利用的底物，并赋予宿主健康益处[73]。益生元主要由多糖、寡糖和非碳水化合物组成。越来越多的实验已证明益生元在治疗 MASLD 中具有显著疗效。其可以通过 PPAR-α 刺激脂肪酸氧化来减少甘油三酯的积累，并通过抑制依赖 SREBP-2 的胆固醇合成来减少胆固醇的积累[74]；此外，益生元在降低肝脏脂肪含量及升高高密度脂蛋白胆固醇方面也表现出巨大潜力[75]。

尽管益生菌及合生元在 MAFLD 治疗中展现出潜力，但其疗效异质性提示，未来研究亟需从“泛用型”向“精准化”方向转型。在未来研究中，需深入解析不同益生菌菌株的作用机制，明确其在 MAFLD 治疗中的功能分工。例如，某些乳杆菌菌株可能更擅长增强肠道屏障功能，而特定杆菌菌株可能在调节胆汁酸代谢方面更具优势。通过高通量筛选结合多组学分析，建立菌株功能图谱，将为针对不同病理环节的精准干预提供基础。同时需要开展剂量－效应研究，确定不同菌株的适宜治疗浓度，以期提高治疗效果。

4.3. 靶向代谢物的抑制

基于对菌群代谢产物在 MAFLD 中致病作用的深入认识，靶向特定代谢通路的抑制剂逐渐成为精准干预的新方向。针对靶向微生物治疗，特定益生菌株如 Lactobacillus rhamnosusGG (LGG)抑制肠道 NF-κB 信号以减少全身炎症，而其代谢产物激活 FGF21-脂联素轴以促进脂质代谢[76]，并刺激产丁酸细菌增殖以修复肠道屏障[77]；另外，多株益生菌 VSL#3 通过抑制 NF-κB 通路并下调关键脂肪生成基因 SREBP-1c 和 FAS 来缓解肝脏炎症[78]。这些发现凸显了基于微生物群的精准干预策略在 MAFLD 管理中的潜力。

5. 讨论

随着肥胖及代谢性疾病在全球范围内的日益流行，代谢相关脂肪性肝病(MAFLD)已成为一个日益严峻的公共卫生问题。除肝脏相关并发症外，MAFLD 还显著增加 2 型糖尿病、心血管疾病及慢性肾脏病的发病风险[79]。诸多干预措施，如运动及饮食调节，已被证实可有效改善 MAFLD，但其潜在机制尚未完全阐明。既往研究表明，不健康的饮食习惯及高热量摄入可加重内脏肥胖并促进异常脂质积累，从而推动 MAFLD 的发生发展[80]。

肠道微生物群与 MAFLD 密切相关，其通过递呈自身组分或代谢产物参与疾病调控。细菌内毒素、肽聚糖、细菌 DNA 及细胞外囊泡所诱发的炎症反应可能加速 MAFLD 的病理进程。MAFLD 患者常呈现肠道菌群失调及肠道屏障功能障碍，进而促进细菌组分在肝脏组织中的蓄积，诱发局部免疫应答。肠道微生物群产生的关键代谢物，包括短链脂肪酸、胆汁酸及三甲胺等，亦在 MAFLD 进展中发挥重要调节作用[81]。深入解析肠道微生物来源的效应分子如何调控宿主细胞功能，有助于阐明肝病易感性的分子机制，并为 MAFLD 的干预提供新思路。

尽管肠道菌群研究为 MAFLD 防治开辟了新方向，当前领域仍面临从“相关性描述”向“机制解析”跨越的多重挑战。首先，动物模型与临床实际存在显著鸿沟——高脂饮食诱导的啮齿类模型难以模拟人类 MAFLD 数十年慢性累积的病理过程及复杂合并症背景，且种属差异导致菌群组成、免疫反应及代谢特征迥异，使得动物实验发现未必能完全转化为临床实际。其次，研究维度存在认知盲区，当前高度聚焦于肠道细菌，对真菌(如白色念珠菌)、病毒(尤其是噬菌体)在 MAFLD 中的作用知之甚少，这种“以细菌为中心”的范式可能导致对肠道微生态调控网络的片面理解。第三，干预研究转化瓶颈突出，动物实验中有效的益生菌、粪菌移植策略在临床试验中疗效参差不齐，根源在于个体间菌群基线差异、疾病分期异质性、干预方案缺乏标准化以及肠道屏障评估手段局限。未来，随着多组学技术的整合应用与人工智能算法的引入，MAFLD 的菌群研究正逐步从“相关性描述”迈向“机制解析”与“精准干预”。个体化的菌群导向治疗、工程菌作为“活体药物”等新兴策略有望突破现有治疗瓶颈，为 MAFLD 患者提供更精准、有效的防治方案。

参考文献

[1] Pipitone, R.M., Ciccioli, C., Infantino, G., La Mantia, C., Parisi, S., Tulone, A., *et al*. (2023) MAFLD: A Multisystem Disease. *Therapeutic Advances in Endocrinology and Metabolism*, **14**, Article 20420188221145549. https://doi.org/10.1177/20420188221145549

[2] Guo, Z., Wu, D., Mao, R., Yao, Z., Wu, Q. and Lv, W. (2025) Global Burden of MAFLD, MAFLD Related Cirrhosis and MASH Related Liver Cancer from 1990 to 2021. *Scientific Reports*, **15**, Article No. 7083. https://doi.org/10.1038/s41598-025-91312-5

[3] Eslam, M., Sanyal, A.J., George, J., Sanyal, A., Neuschwander-Tetri, B., Tiribelli, C., *et al*. (2020) MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. *Gastroenterology*, **158**, 1999-2014.e1. https://doi.org/10.1053/j.gastro.2019.11.312

[4] Kawaguchi, T., Tsutsumi, T., Nakano, D. and Torimura, T. (2022) MAFLD: Renovation of Clinical Practice and Disease Awareness of Fatty Liver. *Hepatology Research*, **52**, 422-432. https://doi.org/10.1111/hepr.13706

[5] Basaranoglu, M., Basaranoglu, G. and Sentürk, H. (2013) From Fatty Liver to Fibrosis: A Tale of “Second Hit”. *World Journal of Gastroenterology*, **19**, 1158-1165. https://doi.org/10.3748/wjg.v19.i8.1158

[6] Buzzetti, E., Pinzani, M. and Tsochatzis, E.A. (2016) The Multiple-Hit Pathogenesis of Non-Alcoholic Fatty Liver Disease (NAFLD). *Metabolism*, **65**, 1038-1048. https://doi.org/10.1016/j.metabol.2015.12.012

[7] Adak, A. and Khan, M.R. (2019) An Insight into Gut Microbiota and Its Functionalities. *Cellular and Molecular Life Sciences*, **76**, 473-493. https://doi.org/10.1007/s00018-018-2943-4

[8] Zhang, D., Wang, Q., Li, D., Chen, C., Lv, Y., Huang, S., *et al*. (2024) Different Fungal Signatures in ALD and MAFLD. *Frontiers in Microbiology*, **15**, Article 1510507. https://doi.org/10.3389/fmicb.2024.1510507

[9] Demir, M., Lang, S., Hartmann, P., Duan, Y., Martin, A., Miyamoto, Y., *et al*. (2022) The Fecal Mycobiome in Non-Alcoholic Fatty Liver Disease. *Journal of Hepatology*, **76**, 788-799. https://doi.org/10.1016/j.jhep.2021.11.029

[10] Barber, T.M., Hanson, P. and Weickert, M.O. (2023) Metabolic-Associated Fatty Liver Disease and the Gut Microbiota. *Endocrinology and Metabolism Clinics of North America*, **52**, 485-496. https://doi.org/10.1016/j.ecl.2023.01.004

[11] Kim, H., Nelson, P., Nzabarushimana, E., Shen, J., Jensen, J., Bhosle, A., *et al*. (2025) Multi-Omic Analysis Reveals Transkingdom Gut Dysbiosis in Metabolic Dysfunction-Associated Steatotic Liver Disease. *Nature Metabolism*, **7**, 1476-1492. https://doi.org/10.1038/s42255-025-01318-6

[12] Kwan, S., Sabotta, C.M., Cruz, L.R., Wong, M.C., Ajami, N.J., McCormick, J.B., *et al*. (2024) Gut Phageome in Mexican Americans: A Population at High Risk for Metabolic Dysfunction-Associated Steatotic Liver Disease and Diabetes. *mSystems*, **9**, e0043424. https://doi.org/10.1128/msystems.00434-24

[13] Alghamdi, W., Mosli, M. and Alqahtani, S.A. (2024) Gut Microbiota in MAFLD: Therapeutic and Diagnostic Implications. *Therapeutic Advances in Endocrinology and Metabolism*, **15**, Article 20420188241242937. https://doi.org/10.1177/20420188241242937

[14] Valdes, A.M., Walter, J., Segal, E. and Spector, T.D. (2018) Role of the Gut Microbiota in Nutrition and Health. *British Medical Journal*, **361**, k2179. https://doi.org/10.1136/bmj.k2179

[15] Fan, Y. and Pedersen, O. (2021) Gut Microbiota in Human Metabolic Health and Disease. *Nature Reviews Microbiology*, **19**, 55-71. https://doi.org/10.1038/s41579-020-0433-9

[16] Chen, Y., Zhou, J. and Wang, L. (2021) Role and Mechanism of Gut Microbiota in Human Disease. *Frontiers in Cellular and Infection Microbiology*, **11**, Article 625913. https://doi.org/10.3389/fcimb.2021.625913

[17] Jiao, Y., Wu, L., Huntington, N.D. and Zhang, X. (2020) Crosstalk between Gut Microbiota and Innate Immunity and Its Implication in Autoimmune Diseases. *Frontiers in Immunology*, **11**, Article 282. https://doi.org/10.3389/fimmu.2020.00282

[18] Shi, Z., Ohno, H. and Satoh-Takayama, N. (2021) Dietary Derived Micronutrients Modulate Immune Responses through Innate Lymphoid Cells. *Frontiers in Immunology*, **12**, Article 670632. https://doi.org/10.3389/fimmu.2021.670632

[19] Vivier, E., Artis, D., Colonna, M., Diefenbach, A., Di Santo, J.P., Eberl, G., *et al*. (2018) Innate Lymphoid Cells: 10 Years on. *Cell*, **174**, 1054-1066. https://doi.org/10.1016/j.cell.2018.07.017

[20] Thaiss, C.A., Zmora, N., Levy, M. and Elinav, E. (2016) The Microbiome and Innate Immunity. *Nature*, **535**, 65-74. https://doi.org/10.1038/nature18847

[21] Constantinides, M.G. (2018) Interactions between the Microbiota and Innate and Innate-Like Lymphocytes. *Journal of Leukocyte Biology*, **103**, 409-419. https://doi.org/10.1002/jlb.3ri0917-378r

[22] Wang, X., Yuan, W., Yang, C., Wang, Z., Zhang, J., Xu, D., *et al*. (2024) Emerging Role of Gut Microbiota in Autoimmune Diseases. *Frontiers in Immunology*, **15**, Article 1365554. https://doi.org/10.3389/fimmu.2024.1365554

[23] Sano, T., Kageyama, T., Fang, V., Kedmi, R., Martinez, C.S., Talbot, J., *et al*. (2021) Redundant Cytokine Requirement for Intestinal Microbiota-Induced Th17 Cell Differentiation in Draining Lymph Nodes. *Cell Reports*, **36**, Article 109608. https://doi.org/10.1016/j.celrep.2021.109608

[24] Luckey, D., Gomez, A., Murray, J., *et al*. (2013) Bugs & Us: The Role of the Gut in Autoimmunity. *The Indian Journal of Medical Research*, **138**, 732-743.

[25] Rosser, E.C., Oleinika, K., Tonon, S., Doyle, R., Bosma, A., Carter, N.A., *et al*. (2014) Regulatory B Cells Are Induced by Gut Microbiota-Driven Interleukin-1β and Interleukin-6 Production. *Nature Medicine*, **20**, 1334-1339. https://doi.org/10.1038/nm.3680

[26] Kim, M. and Kim, C.H. (2017) Regulation of Humoral Immunity by Gut Microbial Products. *Gut Microbes*, **8**, 392-399. https://doi.org/10.1080/19490976.2017.1299311

[27] Mann, E.R., Lam, Y.K. and Uhlig, H.H. (2024) Short-Chain Fatty Acids: Linking Diet, the Microbiome and Immunity. *Nature Reviews Immunology*, **24**, 577-595. https://doi.org/10.1038/s41577-024-01014-8

[28] Li, D., Li, Y., Yang, S., Lu, J., Jin, X. and Wu, M. (2022) Diet-Gut Microbiota-Epigenetics in Metabolic Diseases: From Mechanisms to Therapeutics. *Biomedicine & Pharmacotherapy*, **153**, Article 113290. https://doi.org/10.1016/j.biopha.2022.113290

[29] Kim, M.H., Kang, S.G., Park, J.H., Yanagisawa, M. and Kim, C.H. (2013) Short-Chain Fatty Acids Activate GPR41 and GPR43 on Intestinal Epithelial Cells to Promote Inflammatory Responses in Mice. *Gastroenterology*, **145**, 396-406.e10. https://doi.org/10.1053/j.gastro.2013.04.056

[30] Yan, H. and Ajuwon, K.M. (2017) Butyrate Modifies Intestinal Barrier Function in IPEC-J2 Cells through a Selective Upregulation of Tight Junction Proteins and Activation of the Akt Signaling Pathway. *PLOS ONE*, **12**, e0179586. https://doi.org/10.1371/journal.pone.0179586

[31] Hinrichsen, F., Hamm, J., Westermann, M., Schröder, L., Shima, K., Mishra, N., *et al*. (2021) Microbial Regulation of Hexokinase 2 Links Mitochondrial Metabolism and Cell Death in Colitis. *Cell Metabolism*, **33**, 2355-2366. https://doi.org/10.1016/j.cmet.2021.11.004

[32] Psichas, A., Sleeth, M.L., Murphy, K.G., Brooks, L., Bewick, G.A., Hanyaloglu, A.C., *et al*. (2015) The Short Chain Fatty Acid Propionate Stimulates GLP-1 and PYY Secretion via Free Fatty Acid Receptor 2 in Rodents. *International Journal of Obesity*, **39**, 424-429. https://doi.org/10.1038/ijo.2014.153

[33] Winston, J.A. and Theriot, C.M. (2020) Diversification of Host Bile Acids by Members of the Gut Microbiota. *Gut Microbes*, **11**, 158-171. https://doi.org/10.1080/19490976.2019.1674124

[34] Hofmann, A.F. (2009) The Enterohepatic Circulation of Bile Acids in Mammals: Form and Functions. *Frontiers in Bioscience*, **14**, 2584-2598. https://doi.org/10.2741/3399

[35] Tremblay, S., Romain, G., Roux, M., Chen, X., Brown, K., Gibson, D.L., *et al*. (2017) Bile Acid Administration Elicits an Intestinal Antimicrobial Program and Reduces the Bacterial Burden in Two Mouse Models of Enteric Infection. *Infection and Immunity*, **85**, 14. https://doi.org/10.1128/iai.00942-16

[36] Larabi, A.B., Masson, H.L.P. and Bäumler, A.J. (2023) Bile Acids as Modulators of Gut Microbiota Composition and Function. *Gut Microbes*, **15**, Article 2172671. https://doi.org/10.1080/19490976.2023.2172671

[37] Clifford, B.L., Sedgeman, L.R., Williams, K.J., Morand, P., Cheng, A., Jarrett, K.E., *et al*. (2021) FXR Activation Protects against NAFLD via Bile-Acid-Dependent Reductions in Lipid Absorption. *Cell Metabolism*, **33**, 1671-1684.e4. https://doi.org/10.1016/j.cmet.2021.06.012

[38] Ma, K., Saha, P.K., Chan, L., *et al*. (2006) Farnesoid X Receptor Is Essential for Normal Glucose Homeostasis. *Journal of Clinical Investigation*, **116**, 1102-1109. https://doi.org/10.1172/jci25604

[39] Chiang, J.Y.L. and Ferrell, J.M. (2020) Bile Acid Receptors FXR and TGR5 Signaling in Fatty Liver Diseases and Therapy. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, **318**, G554-G573. https://doi.org/10.1152/ajpgi.00223.2019

[40] Pols, T.W.H., Noriega, L.G., Nomura, M., Auwerx, J. and Schoonjans, K. (2011) The Bile Acid Membrane Receptor TGR5 as an Emerging Target in Metabolism and Inflammation. *Journal of Hepatology*, **54**, 1263-1272. https://doi.org/10.1016/j.jhep.2010.12.004

[41] Zhang, C.H., Zhou, B.G., Sheng, J.Q., *et al*. (2020) Molecular Mechanisms of Hepatic Insulin Resistance in Nonalcoholic Fatty Liver Disease and Potential Treatment Strategies. *Pharmacological Research*, **159**, Article 104984. https://doi.org/10.1016/j.phrs.2020.104984

[42] Meijnikman, A.S., Davids, M., Herrema, H., Aydin, O., Tremaroli, V., Rios-Morales, M., *et al*. (2022) Microbiome-Derived Ethanol in Nonalcoholic Fatty Liver Disease. *Nature Medicine*, **28**, 2100-2106. https://doi.org/10.1038/s41591-022-02016-6

[43] Yuan, J., Chen, C., Cui, J., Lu, J., Yan, C., Wei, X., *et al*. (2019) Fatty Liver Disease Caused by High-Alcohol-Producing Klebsiella Pneumoniae. *Cell Metabolism*, **30**, 675-688.e7. https://doi.org/10.1016/j.cmet.2019.08.018

[44] Mbaye, B., Magdy Wasfy, R., Borentain, P., Tidjani Alou, M., Mottola, G., Bossi, V., *et al*. (2023) Increased Fecal Ethanol and Enriched Ethanol-Producing Gut Bacteria *Limosilactobacillus fermentum*, *Enterocloster bolteae*, *Mediterraneibacter gnavus* and Streptococcus Mutans in Nonalcoholic Steatohepatitis. *Frontiers in Cellular and Infection Microbiology*, **13**, Article 1279354. https://doi.org/10.3389/fcimb.2023.1279354

[45] Dunagan, M., Chaudhry, K., Samak, G. and Rao, R.K. (2012) Acetaldehyde Disrupts Tight Junctions in Caco-2 Cell Monolayers by a Protein Phosphatase 2A-Dependent Mechanism. *American Journal of Physiology-Gastrointestinal and Liver Physiology*, **303**, G1356-G1364. https://doi.org/10.1152/ajpgi.00526.2011

[46] Cho, Y., Yu, L., Abdelmegeed, M.A., Yoo, S. and Song, B. (2018) Apoptosis of Enterocytes and Nitration of Junctional Complex Proteins Promote Alcohol-Induced Gut Leakiness and Liver Injury. *Journal of Hepatology*, **69**, 142-153. https://doi.org/10.1016/j.jhep.2018.02.005

[47] Díaz, L.A., Arab, J.P., Louvet, A., Bataller, R. and Arrese, M. (2023) The Intersection between Alcohol-Related Liver Disease and Nonalcoholic Fatty Liver Disease. *Nature Reviews Gastroenterology & Hepatology*, **20**, 764-783. https://doi.org/10.1038/s41575-023-00822-y

[48] Meijnikman, A.S., Nieuwdorp, M. and Schnabl, B. (2024) Endogenous Ethanol Production in Health and Disease. *Nature Reviews Gastroenterology & Hepatology*, **21**, 556-571. https://doi.org/10.1038/s41575-024-00937-w

[49] Fromenty, B. and Roden, M. (2023) Mitochondrial Alterations in Fatty Liver Diseases. *Journal of Hepatology*, **78**, 415-429. https://doi.org/10.1016/j.jhep.2022.09.020

[50] Seitz, H.K., Bataller, R., Cortez-Pinto, H., Gao, B., Gual, A., Lackner, C., *et al*. (2018) Alcoholic Liver Disease. *Nature Reviews Disease Primers*, **4**, Article No. 16. https://doi.org/10.1038/s41572-018-0014-7

[51] Bestavashvili, A., Glazachev, O., Ibragimova, S., Suvorov, A., Bestavasvili, A., Ibraimov, S., *et al*. (2023) Impact of Hypoxia-Hyperoxia Exposures on Cardiometabolic Risk Factors and TMAO Levels in Patients with Metabolic Syndrome. *International Journal of Molecular Sciences*, **24**, Article 14498. https://doi.org/10.3390/ijms241914498

[52] Tan, X., Liu, Y., Long, J., Chen, S., Liao, G., Wu, S., *et al*. (2019) Trimethylamine N-Oxide Aggravates Liver Steatosis through Modulation of Bile Acid Metabolism and Inhibition of Farnesoid X Receptor Signaling in Nonalcoholic Fatty Liver Disease. *Molecular Nutrition & Food Research*, **63**, Article 19000257. https://doi.org/10.1002/mnfr.201900257

[53] Nian, F., Chen, Y., Xia, Q., Zhu, C., Wu, L. and Lu, X. (2024) Gut Microbiota Metabolite Trimethylamine N-Oxide Promoted NAFLD Progression by Exacerbating Intestinal Barrier Disruption and Intrahepatic Cellular Imbalance. *International Immunopharmacology*, **142**, Article 113173. https://doi.org/10.1016/j.intimp.2024.113173

[54] Nian, F., Zhu, C., Jin, N., Xia, Q., Wu, L. and Lu, X. (2023) Gut Microbiota Metabolite TMAO Promoted Lipid Deposition and Fibrosis Process via KRT17 in Fatty Liver Cells *in Vitro*. *Biochemical and Biophysical Research Communications*, **669**, 134-142. https://doi.org/10.1016/j.bbrc.2023.05.041

[55] León-Mimila, P., Villamil-Ramírez, H., Li, X.S., Shih, D.M., Hui, S.T., Ocampo-Medina, E., *et al*. (2021) Trimethylamine N-Oxide Levels Are Associated with NASH in Obese Subjects with Type 2 Diabetes. *Diabetes & Metabolism*, **47**, Article 101183. https://doi.org/10.1016/j.diabet.2020.07.010

[56] Li, X., Hong, J., Wang, Y., Pei, M., Wang, L. and Gong, Z. (2021) Trimethylamine-N-Oxide Pathway: A Potential Target for the Treatment of MAFLD. *Frontiers in Molecular Biosciences*, **8**, Article 733507. https://doi.org/10.3389/fmolb.2021.733507

[57] Thomas, M.S. and Fernandez, M.L. (2021) Trimethylamine N-Oxide (TMAO), Diet and Cardiovascular Disease. *Current Atherosclerosis Reports*, **23**, Article No. 12. https://doi.org/10.1007/s11883-021-00910-x

[58] Chakaroun, R., Massier, L. and Kovacs, P. (2020) Gut Microbiome, Intestinal Permeability, and Tissue Bacteria in Metabolic Disease: Perpetrators or Bystanders? *Nutrients*, **12**, Article 1082. https://doi.org/10.3390/nu12041082

[59] Shaker, M.E. (2022) The Contribution of Sterile Inflammation to the Fatty Liver Disease and the Potential Therapies. *Biomedicine & Pharmacotherapy*, **148**, Article 112789. https://doi.org/10.1016/j.biopha.2022.112789

[60] Zhang, Y., Jiang, W., Xu, J., Wu, N., Wang, Y., Lin, T., *et al*. (2020) *E. coli* NF73-1 Isolated from NASH Patients Aggravates NAFLD in Mice by Translocating into the Liver and Stimulating M1 Polarization. *Frontiers in Cellular and Infection Microbiology*, **10**, Article 535940. https://doi.org/10.3389/fcimb.2020.535940

[61] Yang, G., Lee, H.E. and Lee, J.Y. (2016) A Pharmacological Inhibitor of NLRP3 Inflammasome Prevents Non-Alcoholic Fatty Liver Disease in a Mouse Model Induced by High Fat Diet. *Scientific Reports*, **6**, Article No. 24399. https://doi.org/10.1038/srep24399

[62] Zeng, X., Varady, K.A., Wang, X., Targher, G., Byrne, C.D., Tayyem, R., *et al*. (2024) The Role of Dietary Modification in the Prevention and Management of Metabolic Dysfunction-Associated Fatty Liver Disease: An International Multidisciplinary Expert Consensus. *Metabolism*, **161**, Article 156028. https://doi.org/10.1016/j.metabol.2024.156028

[63] Tian, T., Zhang, J., Xie, W., Ni, Y., Fang, X., Liu, M., *et al*. (2022) Dietary Quality and Relationships with Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) among United States Adults, Results from NHANES 2017-2018. *Nutrients*, **14**, Article 4505. https://doi.org/10.3390/nu14214505

[64] Chhimwal, J., Goel, A., Sukapaka, M., Patial, V. and Padwad, Y. (2022) Phloretin Mitigates Oxidative Injury, Inflammation, and Fibrogenic Responses via Restoration of Autophagic Flux in *in Vitro* and Preclinical Models of NAFLD. *The Journal of Nutritional Biochemistry*, **107**, Article 109062. https://doi.org/10.1016/j.jnutbio.2022.109062

[65] Shen, B., Wang, Y.L., Cheng, J.Q., Peng, Y., Zhang, Q.L., Li, Z., *et al*. (2023) Pterostilbene Alleviated NAFLD via AMPK/mTOR Signaling Pathways and Autophagy by Promoting Nrf2. *Phytomedicine*, **109**, Article 154561. https://doi.org/10.1016/j.phymed.2022.154561

[66] Liu, Y., Sun, Z., Dong, R., Liu, P., Zhang, X., Li, Y., *et al*. (2024) Rutin Ameliorated Lipid Metabolism Dysfunction of Diabetic NAFLD via AMPK/SREBP1 Pathway. *Phytomedicine*, **126**, Article 155437. https://doi.org/10.1016/j.phymed.2024.155437

[67] Ni, Y., Nagashimada, M., Zhuge, F., Zhan, L., Nagata, N., Tsutsui, A., *et al*. (2015) Astaxanthin Prevents and Reverses Diet-Induced Insulin Resistance and Steatohepatitis in Mice: A Comparison with Vitamin E. *Scientific Reports*, **5**, Article No. 17192. https://doi.org/10.1038/srep17192

[68] Chen, H., Ma, Y.F., Qi, X.F., Tian, J.J., Ma, Y., *et al*. (2023) *α*-Lactalbumin Peptide Asp-Gln-TRP Ameliorates Hepatic Steatosis and Oxidative Stress in Free Fatty Acids-Treated HepG2 Cells and High-Fat Diet-Induced NAFLD Mice by Activating the PPAR*α* Pathway. *Molecular Nutrition & Food Research*, **67**, e2200499. https://doi.org/10.1002/mnfr.202200499

[69] Chen, H., Qi, X.F., Guan, K.F., *et al*. (2023) Tandem Mass Tag-Based Quantitative Proteomics Analysis Reveals the Effects of the *α*-Lactalbumin Peptides GINY and DQW on Lipid Deposition and Oxidative Stress in HepG2 Cells. *Journal of Dairy Science*, **106**, 2271-2288. https://doi.org/10.3168/jds.2022-22511

[70] Xue, L., He, J.T., Gao, N., Lu, X.L., Li, M., Wu, X.K., *et al*. (2017) Probiotics May Delay the Progression of Nonalcoholic Fatty Liver Disease by Restoring the Gut Microbiota Structure and Improving Intestinal Endotoxemia. *Scientific Reports*, **7**, Article No. 45176. https://doi.org/10.1038/srep45176

[71] Narem, R.S.R., Mathakala, V., Sallabathula, S.T., Peddiboyina, V.L. and Palempalli, U.M.D. (2026) Probiotics as Emerging Adjuncts in Metabolic Associated Fatty Liver Disease Therapy—A Systemic Review. *BMC Gastroenterology*, **26**, Article No. 156. https://doi.org/10.1186/s12876-026-04618-7

[72] Wong, V.W., Wong, G.L., Chim, A.M., Chu, W.C., Yeung, D.K., Li, K.C., *et al*. (2013) Treatment of Nonalcoholic Steatohepatitis with Probiotics. A Proof-of-Concept Study. *Annals of Hepatology*, **12**, 256-262. https://doi.org/10.1016/s1665-2681(19)31364-x

[73] Gibson, G.R., Hutkins, R., Sanders, M.E., Prescott, S.L., Reimer, R.A., Salminen, S.J., *et al*. (2017) Expert Consensus Document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) Consensus Statement on the Definition and Scope of Prebiotics. *Nature Reviews Gastroenterology & Hepatology*, **14**, 491-502. https://doi.org/10.1038/nrgastro.2017.75

[74] Zhao, W., Guo, M., Feng, J., Gu, Z., Zhao, J., Zhang, H., *et al*. (2022) Myristica Fragrans Extract Regulates Gut Microbes and Metabolites to Attenuate Hepatic Inflammation and Lipid Metabolism Disorders via the AhR-FAS and NF-*κ*B Signaling Pathways in Mice with Non-Alcoholic Fatty Liver Disease. *Nutrients*, **14**, Article 1699. https://doi.org/10.3390/nu14091699

[75] Wu, J., Chen, X., Qian, J. and Li, G. (2024) Clinical Improvement Effect of Regulating Gut Microbiota on Metabolic Dysfunction-Associated Steatotic Liver Disease: Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Clinics and Research in Hepatology and Gastroenterology*, **48**, Article 102397.

https://doi.org/10.1016/j.clinre.2024.102397

[76] Liu, Q., Liu, Y., Li, F., Gu, Z., Liu, M., Shao, T., *et al*. (2020) Probiotic Culture Supernatant Improves Metabolic Function through FGF21-Adiponectin Pathway in Mice. *The Journal of Nutritional Biochemistry*, **75**, Article 108256. https://doi.org/10.1016/j.jnutbio.2019.108256

[77] Zhao, C., Liu, L., Liu, Q., Li, F., Zhang, L., Zhu, F., *et al*. (2019) Fibroblast Growth Factor 21 Is Required for the Therapeutic Effects of Lactobacillus Rhamnosus GG against Fructose-Induced Fatty Liver in Mice. *Molecular Metabolism*, **29**, 145-157. https://doi.org/10.1016/j.molmet.2019.08.020

[78] Jena, P.K., Sheng, L., Li, Y. and Wan, Y.Y. (2020) Probiotics VSL#3 Are Effective in Reversing Non-Alcoholic Steatohepatitis in a Mouse Model. *Hepatobiliary Surgery and Nutrition*, **9**, 170-182. https://doi.org/10.21037/hbsn.2019.09.07

[79] Fang, J., Yu, C., Li, X., Yao, J., Fang, Z., Yoon, S., *et al*. (2022) Gut Dysbiosis in Nonalcoholic Fatty Liver Disease: Pathogenesis, Diagnosis, and Therapeutic Implications. *Frontiers in Cellular and Infection Microbiology*, **12**, Article 997018. https://doi.org/10.3389/fcimb.2022.997018

[80] Gao, Y., Zhang, W., Zeng, L., Bai, H., Li, J., Zhou, J., *et al*. (2020) Exercise and Dietary Intervention Ameliorate High-Fat Diet-Induced NAFLD and Liver Aging by Inducing Lipophagy. *Redox Biology*, **36**, Article 101635. https://doi.org/10.1016/j.redox.2020.101635

[81] Ma, C., Bao, Y., Hereid, S., Zhang, H., Bai, X., Bai, Q., *et al*. (2025) Mechanistic Elucidation of Tricholoma Mongolicum Polysaccharides in Treating MAFLD via Regulation of the Gut Microbiota-Metabolite-Ferroptosis Axis: A Multi-Omics Perspective. *Journal of Agricultural and Food Chemistry*, **73**, 17040-17056. https://doi.org/10.1021/acs.jafc.5c05877