

代谢相关性脂肪性肝病的治疗研究进展

蒋春梅^{1*}, 涂舒¹, 汤建华^{2#}

¹赣南医科大学第一临床医学院, 江西 赣州

²赣州市人民医院消化内科, 江西 赣州

收稿日期: 2026年8月11日; 录用日期: 2026年9月5日; 发布日期: 2026年9月14日

摘要

代谢相关脂肪性肝病(MAFLD)已成为全球最常见的慢性肝病, 且患病人数仍在持续增加。该病早期表现为单纯性脂肪变性, 后续可逐步进展为代谢相关脂肪性肝炎、肝纤维化、肝硬化甚至肝细胞癌。MAFLD的发病机制复杂, 涉及胰岛素抵抗、脂毒性、线粒体功能障碍、炎症反应及纤维化形成等多重平行打击的交互作用。传统治疗以生活方式干预为基础, 但依从性差、减重维持困难。2024年瑞美替罗(Resmetirom)获批上市, 成为该领域首个靶向药物, 标志着MAFLD的治疗进入新阶段。此外, GLP-1受体激动剂、SGLT-2抑制剂、PPAR激动剂等药物也展现出良好的疗效。鉴于MAFLD发病机制复杂, 联合治疗将成为趋势, 通过多靶点协同, 既能提升治疗应答率又能减少药物副作用。未来治疗将向精准化、个体化和联合化方向发展。

关键词

代谢相关脂肪性肝病, 治疗, 生活方式干预, 靶向治疗, 瑞美替罗, 联合治疗

Research Progress in the Treatment of Metabolic Dysfunction-Associated Fatty Liver Disease

Chunmei Jiang^{1*}, Shu Tu¹, Jianhua Tang^{2#}

¹First Clinical Medical College, Gannan Medical University, Ganzhou Jiangxi

²Department of Gastroenterology, Ganzhou People's Hospital, Ganzhou Jiangxi

Received: August 11, 2026; accepted: September 5, 2026; published: September 14, 2026

Abstract

Metabolic dysfunction-associated fatty liver disease (MAFLD) has emerged as the most prevalent

*第一作者。

#通讯作者。

文章引用: 蒋春梅, 涂舒, 汤建华. 代谢相关性脂肪性肝病的治疗研究进展[J]. 临床医学进展, 2026, 16(9): 1543-1549.

DOI: 10.12677/acm.2026.1693194

chronic liver disease worldwide, with its affected population continuing to expand. The disease initially presents as simple steatosis, which may progressively advance to metabolic dysfunction-associated steatohepatitis (MASH), hepatic fibrosis, cirrhosis, and even hepatocellular carcinoma. The pathogenesis of MAFLD is intricate, involving the interplay of multiple parallel hits, including insulin resistance, lipotoxicity, mitochondrial dysfunction, inflammatory responses, and fibrogenesis. Conventional treatment is founded on lifestyle intervention; however, it is constrained by poor patient compliance and difficulty in sustaining weight loss. In 2024, resmetirom received regulatory approval, becoming the first targeted therapeutic agent in this field and heralding a new era in MAFLD management. Moreover, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and peroxisome proliferator-activated receptor (PPAR) agonists have also demonstrated promising efficacy. Given the complex pathogenesis of MAFLD, combination therapy is poised to become the prevailing trend; through synergistic multi-target modulation, it can enhance therapeutic response rates while mitigating adverse drug reactions. Future treatment strategies are anticipated to evolve toward precision medicine, individualized therapy, and combination regimens.

Keywords

Metabolic Dysfunction-Associated Fatty Liver Disease, Treatment, Lifestyle Intervention, Targeted Therapy, Resmetirom, Combination Therapy

Copyright © 2026 by author(s) and Hans Publishers Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

1. 引言

代谢相关脂肪性肝病(metabolic dysfunction-associated fatty liver disease, MAFLD), 目前已成为影响全球 1/3 成年人口的第一大慢性肝病[1]。MAFLD 又称非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD), NADLD 以排除性定义为主, 2023 年国际多学会共识将其更名, 通过肯定性的诊断标准, 将疾病定义从“不是什么”转变为“是什么”, 更准确地反映了代谢紊乱驱动肝病发生的病理本质[2]。全球 MAFLD 负担持续攀升, 1990 年至 2021 年间患病人数翻倍达 13 亿, 预计 2040 年患病率将超过 55% [3] [4]。中国因饮食结构西化、久坐生活方式及人口老龄化, 发病率增速尤为显著[5]-[7]。MAFLD 的疾病谱广泛, 呈连续性进展, 从单纯性脂肪肝(可逆)发展到代谢相关性脂肪性肝炎, 进而出现肝纤维化, 最终可进展为肝硬化和肝细胞癌, 早期通过减重 $\geq 5\%$ ~10%可逆转, 同时常合并肥胖、2 型糖尿病、心血管疾病等肝外代谢异常[8]。长期以来, MAFLD 的治疗以生活方式干预为主, 但依从性差, 疗效有限。2024 年 Resmetirom 的获批打破了无药可用的僵局, 标志着 MAFLD 治疗进入靶向药物时代, GLP-1 受体激动剂、FGF21 类似物等多项药物也进入后期临床[9]。本文将就 MAFLD 的治疗展开阐述。

2. 生活方式干预: 治疗的基石

MAFLD 目前缺乏相对特异性的药物治疗, 生活方式干预仍为其核心治疗策略, 其中主要包括饮食管理和运动干预。在膳食结构层面, 地中海饮食、低碳水化合物饮食和间歇性禁食均可在不同程度上改善肝脏脂肪沉积。地中海饮食是一种以橄榄油为核心脂肪来源、以植物性食物为基底的饮食模式, 强调每餐摄入蔬菜、水果和全谷物、每日搭配坚果与乳制品、每周以鱼类、海鲜和豆类为主要蛋白质来源, 并限制红肉及甜食。可通过其富含的多酚、不饱和脂肪酸和膳食纤维, 有效改善 MAFLD 患者的胰岛素抵

抗、减少肝内脂质沉积、逆转肝脏脂肪变性并降低炎症反应,研究强调该饮食结合每周 150 分钟中等强度运动比单一药物更有效,即使体重减轻不足 5%也能显著获益,是 MAFLD 防治的核心生活方式策略[10]。低碳水化合物生酮饮食则通过抑制 DNL、促进脂肪酸氧化,可在短期快速降低肝内脂肪含量。

Chengxiang Hu 等[11]的研究表面,健康的低碳水化合物饮食(LCD)和健康的低脂肪饮食(LFD)对 MAFLD 均具有保护性作用,用 3%能量的不饱和脂肪或不饱和脂肪加植物蛋白替代碳水化合物,可分别使 MAFLD 风险降低 15%和 16%。Huafeng Chen [12]等的研究表明,间歇性禁食(隔日禁食)可通过下调肝脏中 Lrg1 基因的表达,从而抑制肝脏脂质合成减缓 MAFLD 的进展。值得注意的是,不同个体对膳食模式的反应存在异质性,需要基于代谢表型进行个体化选择。

运动干预是 MAFLD 综合管理的重要组成部分,有氧运动与抗阻训练均可降低肝内脂肪含量。有氧运动通过激活以 AMPK 为核心的能量代谢通路、SESN 家族介导的应激反应与自噬、以及 miRNA 调控的转录后修饰网络,从促进脂肪酸氧化、抑制脂肪新生、改善胰岛素抵抗、增强抗氧化能力和阻断炎症信号等多维度协同干预,从而减缓 MAFLD 的进展[13]。研究表明,有氧运动、抗阻训练和高强度间歇训练等不同运动形式对肝脂肪的降低效果相似(约 20%~30%的相对减少)[14]。

体重管理是生活方式干预的核心。体重下降 $\geq 5\%$ 可减少肝脂肪变性, $\geq 7\%$ 可实现 MASH 消退, $\geq 10\%$ 可能进一步减轻肝纤维化程度。即使对于非肥胖的瘦型 MASLD 患者,体重减轻 3%~5%也可改善脂肪肝,然而,减重达标率的低下和长期维持困难仍是临床面临的巨大挑战[14]。

3. 药物治疗:从间接治疗到靶向治疗

3.1. GLP-1 受体激动剂

胰高血糖素样肽-1 (GLP-1)受体激动剂在 MAFLD 治疗中展现出良好前景。GLP-1 通过 cAMP/PKA、PI3K/Akt 等信号通路来调节血糖、抑制食欲、保护胰岛 β 细胞。在一项纳入 52 例经活检确诊为 MASH 患者的多中心、双盲、随机、安慰剂对照的 II 期临床试验中,证实经利拉鲁肽(1.8 mg/日皮下注射)治疗 48 周后,利拉鲁肽组有 39%的患者实现了 MASH 消退且肝纤维化无恶化,显著优于安慰剂组的 9%;同时利拉鲁肽组患者体重平均下降约 5.5 kg,肝酶(ALT)水平显著降低,胰岛素抵抗改善,且整体安全性良好[15]。

玛仕度肽(Mazdutide)作为一种 GLP-1 和 GCG 双受体激动剂,已证实在糖尿病及减重反面具有良好的效应。一项研究表明,Mazdutide 可能通过抑制内质网应激 PERK-eIF2 α -ATF4-CHOP 信号通路,下调 NF- κ B 介导的炎症反应,以及减少脂质合成关键调控因子(SREBP-1, C/EBP β , PPAR γ)的表达,从而改善血脂异常、减轻肝脏脂肪变性、降低肝损伤标志物(如 ALT、AST),并缓解炎症和氧化应激[16]。但玛仕度肽在治疗 MAFLD 方面,目前绝大部分仍在临床试验阶段。

3.2. SGLT-2 抑制剂

钠-葡萄糖协同转运蛋白 2 (sodium-dependent glucose transporters-2, SGLT-2)抑制剂包括达格列净(dapagliflozin)、恩格列净(empagliflozin)等,其在 MAFLD 治疗中的价值正受到越来越多的关注。2025 版 APASL 指南指出,达格列净、恩格列净等多种 SGLT-2 抑制剂可减少肝脏脂肪含量、改善血清转氨酶水平,同时可减轻体重[1]。一项纳入活检确诊 MASH 患者的多中心、双盲、随机、安慰剂对照试验显示,达格列净治疗(10 mg/日) 48 周后,53%的患者实现了 MASH 改善且肝纤维化未恶化,显著高于安慰剂组的 30%,MASH 缓解率和肝纤维化改善率也均显著优于安慰剂组[17]。总体上,SGLT-2 抑制剂在改善 MAFLD 及降低不良肝脏相关结局方面具有优势,但大多数研究在合并 MAFLD 的 2 型糖尿病患者中进行,仍缺乏改善肝脏炎症和纤维化的组织学证据[1]。

3.3. 过氧化物酶体增殖物激活受体(PPAR)激动剂

过氧化物酶体激活的受体(PPARs)是一种核受体转录因子,包含三种亚型,分别为 PPAR α 、PPAR β/δ 、PPAR γ ,可通过调控能量代谢、细胞发育、炎症和分化相关基因的表达,在 MAFLD 从单纯性脂肪变性进展至脂肪性肝炎、肝纤维化乃至肝细胞癌的全过程中发挥核心作用[18]。拉尼非布仑(Lanifibranor)是一种全 PPAR 激动剂。一项国际多中心 IIb 期随机、双盲、安慰剂对照临床试验(NATIVE 试验)中评估了拉尼非布仑对活动性 MASH 患者的疗效,247 名患者按 1:1:1 随机分配至每日口服 1200 mg、800 mg 或安慰剂组,治疗 24 周。结果显示,1200 mg 组 55% 的患者实现 SAF-A 评分下降 ≥ 2 分且肝纤维化未恶化,显著优于安慰剂组的 33% ($P = 0.007$); NASH 缓解率(49% vs. 22%)和纤维化改善率(48% vs. 29%)也显著更优,同时改善了血糖、血脂等代谢指标[19]。

3.4. THR- β 激动剂

THR- β 在肝脏高度表达,参与调节肝脏脂质代谢和炎症[20]。瑞美替罗(Resmetirom)是一种口服、肝脏靶向的选择性甲状腺激素受体 β (THR- β)激动剂,在 MAFLD/MASH 治疗领域取得了突破性进展。通过选择性激活肝脏 THR- β 受体,促进脂肪酸氧化、降低肝脏脂肪生成和胆固醇代谢,同时避免对心脏和骨骼的副作用[21]。一项国际多中心 3 期随机、双盲、安慰剂对照临床试验显示,954 名经非侵入性检查确诊的 MAFLD 患者,随机分配至每日口服 Resmetirom 80 mg、100 mg 或安慰剂组,治疗 52 周。结果显示,治疗 16 周时,100 mg 组肝脏脂肪含量较基线降低 45.1%,80 mg 组降低 41.4%,均显著优于安慰剂组的 6.5% ($P < 0.0001$),且该效果持续至 52 周;同时 Resmetirom 显著降低了 LDL-C、载脂蛋白 B、甘油三酯等致动脉粥样硬化脂质水平,改善了 ALT、AST、GGT 等肝损伤标志物,肝脏体积平均缩小 23% [22]。

瑞美替罗已于 2024 年 3 月获得 FDA 批准,成为首个获批用于治疗伴有中度至晚期肝纤维化的非肝硬化 MAFLD/MASH 患者的药物。

4. 联合治疗策略

MAFLD 的发病机制涉及胰岛素抵抗、脂毒性、炎症反应及纤维化重塑等多条复杂通路,MASH 单药治疗的组织学应答率普遍低于 32%,单一靶点药物难以全面覆盖。联合治疗的核心优势在于多靶点协同覆盖 MAFLD 的复杂病理网络,故联合治疗成为提高疗效的必然方向。其策略主要包括:提高应答率(将代谢类药物与抗炎或抗纤维化药物联用,覆盖更多病理通路)、最大化治疗反应(同时实现纤维化改善与 MASH 消退)、减少不良反应(如通过降低药物剂量或联用他汀、贝特类药物来减轻瘙痒、低密度脂蛋白升高及高甘油三酯血症等副作用),以及与降糖药(如 GLP-1 激动剂、SGLT-2 抑制剂)联用以兼顾肝脏与代谢结局[23]。基于 MAFLD 多重打击学说,联合用药方案可进一步细化为几条互补路径。在代谢调节与抗炎的协同方面,GLP-1 受体激动剂(如利拉鲁肽、司美格鲁肽)与 FXR 激动剂(如奥贝胆酸)或 CCR2/5 拮抗剂的联用颇具前景——前者通过减重和改善胰岛素抵抗纠正代谢紊乱,后者则调节胆汁酸代谢并抑制肝脏炎症小体激活,Alkhoury 等开展的 II 期开放标签试验显示,108 例 MASH(F2-F3)患者接受司美格鲁肽联合 cilofexor(FXR 激动剂)或 firsocostat 治疗 24 周后,在肝脂肪、肝酶及纤维化指标上的改善均优于司美格鲁肽单药,且安全性良好,为 MASH 联合治疗提供了初步临床证据[24]。对于已出现显著纤维化(F2~F3)的患者,代谢调节与抗纤维化的协同更为关键。THR- β 激动剂瑞美替罗(Resmetirom)联合 PPAR 泛激动剂,旨在直接改善 MASH 的组织学特征。瑞美替罗(Resmetirom)通过选择性激活肝脏 THR- β 受体促进脂肪酸氧化、降低脂质合成;PPAR 泛激动剂则同时激活 PPAR $\alpha/\beta/\gamma$,调控脂质代谢、抗炎及抗纤维化,两者机制互补,有望协同实现 MASH 消退与纤维化逆转,但目前尚缺乏直接联合用药的临床或临床

前证据,是未来值得探索的方向[25]。双重代谢通路的协同同样值得探索。Lee 等人在 2 型糖尿病合并 MAFLD 患者中开展了一项 24 周随机对照试验,发现吡格列酮联合恩格列净在降低肝脏脂肪含量(MRI-PDFF)和肝脏硬度(MRE)方面具有协同效应,联合组实现肝脏脂肪减少 $\geq 30\%$ 且硬度降低 $\geq 20\%$ 的患者比例达 50%,显著优于单药组;同时联合治疗避免了吡格列酮单药所致的皮下脂肪堆积,最大程度减少了内脏脂肪并显著升高脂联素水平,提示 PPAR- γ 激动剂与 SGLT2 抑制剂可通过互补机制协同改善肝脏脂肪变性及纤维化[26]。然而,联合治疗仍面临诸多挑战:药物间相互作用、不良反应叠加、个体化用药方案制定以及长期安全性数据缺乏等。

5. 总结与展望

代谢相关性脂肪性肝病作为全球第一大慢性肝病,其治疗策略正经历从单一生活方式干预向多元化靶向治疗的深刻转变。但生活方式干预仍是治疗的基石,地中海饮食、低碳水化合物饮食及规律运动可有效改善肝脂肪沉积,但临床实践中减重达标比例偏低且长期依从性欠佳,构成制约疗效的重要瓶颈。2024 年瑞美替罗(Resmetirom)获批标志着 MAFLD 进入靶向药物时代,作为首个治疗代谢功能障碍相关脂肪性肝炎的 THR- β 激动剂,可显著降低肝脏脂肪含量并改善纤维化。此外,GLP-1 受体激动剂、SGLT-2 抑制剂及 PPAR 激动剂等也展现出良好的肝脏组织学改善效果。鉴于 MAFLD 发病机制复杂,单药应答率有限,联合治疗已成为必然趋势,通过多靶点协同覆盖病理通路、提高疗效并减少不良反应。同时,非侵入性诊断技术的进步也为治疗决策提供了关键支撑:FIB-4 和 VCTE 适用于基层筛查和分层,MRE、ELF 和 MRI-PDFF 则为靶向治疗的选择和疗效监测提供了精确工具,人工智能驱动的多参数评分有望在未来实现治疗反应的个体化预测[27]-[29]。

展望未来,MAFLD 的临床管理将逐步趋于精准化与联合化,但仍面临诸多关键挑战。肠道菌群在 MAFLD 治疗中的角色有待深入阐明,菌群通过 SCFAs、胆汁酸代谢物和细菌胞外囊泡等调控肝-肠轴,益生菌、益生元及粪菌移植等微生态干预策略在改善肝酶、血脂及炎症指标方面已积累一定证据,但其与靶向药物的协同效应值得进一步探索[30]-[32]。针对特定纤维化通路的药物研发是突破现有疗效瓶颈的关键,建立能够预测不同药物反应的生物标志物模型是实现精准医疗的前提,基于基因组学、蛋白质组学、代谢组学及肠道菌群特征的多组学整合模型,有望识别出对特定药物或联合方案高应答的亚群患者[33]。此外,新药上市后的卫生经济学影响不容忽视。以 Resmetirom 为例,其年治疗费用约为 19,011 美元,卫生经济学评估显示在当前价格下增量成本效果比(ICER)约为 140,134 美元/QALY,高于 10 万美元/QALY 的常规支付意愿阈值,提示需通过真实世界研究进一步验证长期获益并探索基于价值的定价策略,以确保药物可及性与医疗系统可持续性的平衡[34]。唯有在循证医学、精准诊断和卫生经济学三重维度上协同推进,方能真正改善 MAFLD 患者的远期预后。

参考文献

- [1] Eslam, M., Fan, J.G., Yu, M.L., Wong, V.W., Cua, I.H., Liu, C., *et al.* (2025) The Asian Pacific Association for the Study of the Liver Clinical Practice Guidelines for the Diagnosis and Management of Metabolic Dysfunction-Associated Fatty Liver Disease. *Hepatology International*, **19**, 261-301. <https://doi.org/10.1007/s12072-024-10774-3>
- [2] Gofton, C., Upendran, Y., Zheng, M. and George, J. (2023) MAFLD: How Is It Different from NAFLD? *Clinical and Molecular Hepatology*, **29**, S17-S31. <https://doi.org/10.3350/cmh.2022.0367>
- [3] Wang, Y., Huang, X., Ye, S., Li, T., Huang, Y., Cheryala, M., *et al.* (2025) Global Burden of Metabolic-Associated Fatty Liver Disease: A Systematic Analysis of Global Burden of Disease Study 2021. *Chinese Medical Journal*, **138**, 2947-2954. <https://doi.org/10.1097/cm9.0000000000003517>
- [4] Le, M.H., Yeo, Y.H., Zou, B., Barnet, S., Henry, L., Cheung, R., *et al.* (2022) Forecasted 2040 Global Prevalence of Nonalcoholic Fatty Liver Disease Using Hierarchical Bayesian Approach. *Clinical and Molecular Hepatology*, **28**, 841-850. <https://doi.org/10.3350/cmh.2022.0239>

- [5] Le, M.H., Le, D.M., Baez, T.C., Wu, Y., Ito, T., Lee, E.Y., *et al.* (2023) Global Incidence of Non-Alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis of 63 Studies and 1,201,807 Persons. *Journal of Hepatology*, **79**, 287-295. <https://doi.org/10.1016/j.jhep.2023.03.040>
- [6] Zhou, F., Zhou, J., Wang, W., Zhang, X., Ji, Y., Zhang, P., *et al.* (2019) Unexpected Rapid Increase in the Burden of NAFLD in China from 2008 to 2018: A Systematic Review and Meta-Analysis. *Hepatology*, **70**, 1119-1133. <https://doi.org/10.1002/hep.30702>
- [7] Zhou, J., Zhou, F., Wang, W., Zhang, X., Ji, Y., Zhang, P., *et al.* (2020) Epidemiological Features of NAFLD from 1999 to 2018 in China. *Hepatology*, **71**, 1851-1864. <https://doi.org/10.1002/hep.31150>
- [8] Kanwal, F., Shubrook, J.H., Younossi, Z., Natarajan, Y., Bugianesi, E., Rinella, M.E., *et al.* (2021) Preparing for the NASH Epidemic: A Call to Action. *Diabetes Care*, **44**, 2162-2172. <https://doi.org/10.2337/dci21-0020>
- [9] Administration U.S. Food and Drug Administration (FDA) (2024) FDA Approves First Treatment for Patients with Liver Scarring Due to Fatty Liver Disease. <https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-patients-liver-scarring-due-fatty-liver-disease>
- [10] Xiao, Y., Zhang, X., Yi, D., Qiu, F., Wu, L., Tang, Y., *et al.* (2023) Mediterranean Diet Affects the Metabolic Outcome of Metabolic Dysfunction-Associated Fatty Liver Disease. *Frontiers in Nutrition*, **10**, Article ID: 1225946. <https://doi.org/10.3389/fnut.2023.1225946>
- [11] Hu, C., Huang, R., Li, R., Ning, N., He, Y., Zhang, J., *et al.* (2023) Low-Carbohydrate and Low-Fat Diet with Metabolic Dysfunction-Associated Fatty Liver Disease. *Nutrients*, **15**, Article No. 4763. <https://doi.org/10.3390/nu15224763>
- [12] Chen, H., Zhang, S., Xie, W., Shen, J. and Liang, H. (2026) Intermittent Fasting Ameliorates MAFLD by Downregulating Lrg1: Insights from Bulk RNA Sequencing and Functional Verification. *Frontiers in Endocrinology*, **17**, Article ID: 1754251. <https://doi.org/10.3389/fendo.2026.1754251>
- [13] Zhang, W., Hu, Y., Zou, F., Ding, L. and Jiang, M. (2025) Unlocking the Benefits of Aerobic Exercise for MAFLD: A Comprehensive Mechanistic Analysis. *Journal of Translational Medicine*, **24**, Article No. 63. <https://doi.org/10.1186/s12967-025-07535-7>
- [14] Romero-Gómez, M., Zelber-Sagi, S. and Trenell, M. (2017) Treatment of NAFLD with Diet, Physical Activity and Exercise. *Journal of Hepatology*, **67**, 829-846. <https://doi.org/10.1016/j.jhep.2017.05.016>
- [15] Armstrong, M.J., Gaunt, P., Aithal, G.P., Barton, D., Hull, D., Parker, R., *et al.* (2016) Liraglutide Safety and Efficacy in Patients with Non-Alcoholic Steatohepatitis (LEAN): A Multicentre, Double-Blind, Randomised, Placebo-Controlled Phase 2 Study. *The Lancet*, **387**, 679-690. [https://doi.org/10.1016/s0140-6736\(15\)00803-x](https://doi.org/10.1016/s0140-6736(15)00803-x)
- [16] Gan, L., Duan, L. and Zheng, X. (2026) Mazdutide Ameliorates Metabolic Dysfunction-Associated Steatotic Liver Disease by Modulating Endoplasmic Reticulum Stress, Improving Lipid Metabolism and Alleviating Inflammation. *Pharmaceuticals*, **19**, Article No. 371. <https://doi.org/10.3390/ph19030371>
- [17] Lin, J., Huang, Y., Xu, B., Gu, X., Huang, J., Sun, J., *et al.* (2025) Effect of Dapagliflozin on Metabolic Dysfunction-Associated Steatohepatitis: Multicentre, Double Blind, Randomised, Placebo Controlled Trial. *BMJ*, **389**, e083735. <https://doi.org/10.1136/bmj-2024-083735>
- [18] Qiu, Y.Y., Zhang, J., Zeng, F.Y. and Zhu, Y.Z. (2023) Roles of the Peroxisome Proliferator-Activated Receptors (PPARs) in the Pathogenesis of Nonalcoholic Fatty Liver Disease (NAFLD). *Pharmacological Research*, **192**, Article ID: 106786. <https://doi.org/10.1016/j.phrs.2023.106786>
- [19] Francque, S.M., Bedossa, P., Ratzl, V., Anstee, Q.M., Bugianesi, E., Sanyal, A.J., *et al.* (2021) A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH. *New England Journal of Medicine*, **385**, 1547-1558. <https://doi.org/10.1056/nejmoa2036205>
- [20] Suvarna, R., Shetty, S. and Pappachan, J.M. (2024) Efficacy and Safety of Resmetirom, a Selective Thyroid Hormone Receptor- β Agonist, in the Treatment of Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD): A Systematic Review and Meta-Analysis. *Scientific Reports*, **14**, Article No. 19790. <https://doi.org/10.1038/s41598-024-70242-8>
- [21] Keam, S.J. (2024) Resmetirom: First Approval. *Drugs*, **84**, 729-735. <https://doi.org/10.1007/s40265-024-02045-0>
- [22] Harrison, S.A., Taub, R., Neff, G.W., Lucas, K.J., Labriola, D., Moussa, S.E., *et al.* (2023) Resmetirom for Nonalcoholic Fatty Liver Disease: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial. *Nature Medicine*, **29**, 2919-2928. <https://doi.org/10.1038/s41591-023-02603-1>
- [23] Dufour, J., Caussy, C. and Loomba, R. (2020) Combination Therapy for Non-Alcoholic Steatohepatitis: Rationale, Opportunities and Challenges. *Gut*, **69**, 1877-1884. <https://doi.org/10.1136/gutjnl-2019-319104>
- [24] Alkhouri, N., Herring, R., Kabler, H., Kayali, Z., Hassanein, T., Kohli, A., *et al.* (2022) Safety and Efficacy of Combination Therapy with Semaglutide, Cilofexor and Firsocostat in Patients with Non-Alcoholic Steatohepatitis: A Randomised, Open-Label Phase II Trial. *Journal of Hepatology*, **77**, 607-618. <https://doi.org/10.1016/j.jhep.2022.04.003>

-
- [25] Zhou, X., Fan, Q., Byrne, C.D., Targher, G., Muthiah, M.D., Huang, D.Q., *et al.* (2026) Combination Therapies for Metabolic Dysfunction-Associated Steatohepatitis: Challenges and Opportunities. *Gut*, **75**, 815-825. <https://doi.org/10.1136/gutjnl-2025-337431>
- [26] Lee, M., Hong, S., Cho, Y., Rhee, H., Yu, M.H., Bae, J., *et al.* (2025) Synergistic Benefit of Thiazolidinedione and Sodium-Glucose Cotransporter 2 Inhibitor for Metabolic Dysfunction-Associated Steatotic Liver Disease in Type 2 Diabetes: A 24-Week, Open-Label, Randomized Controlled Trial. *BMC Medicine*, **23**, Article No. 266. <https://doi.org/10.1186/s12916-025-04017-x>
- [27] Dawod, S. and Brown, K. (2024) Non-Invasive Testing in Metabolic Dysfunction-Associated Steatotic Liver Disease. *Frontiers in Medicine*, **11**, Article ID: 1499013. <https://doi.org/10.3389/fmed.2024.1499013>
- [28] Castera, L., Rinella, M.E. and Tsochatzis, E.A. (2025) Noninvasive Assessment of Liver Fibrosis. *New England Journal of Medicine*, **393**, 1715-1729. <https://doi.org/10.1056/nejmra2403308>
- [29] Newsome, P.N., Sasso, M., Deeks, J.J., Paredes, A., Boursier, J., Chan, W., *et al.* (2020) FibroScan-AST (FAST) Score for the Non-Invasive Identification of Patients with Non-Alcoholic Steatohepatitis with Significant Activity and Fibrosis: A Prospective Derivation and Global Validation Study. *The Lancet Gastroenterology & Hepatology*, **5**, 362-373. [https://doi.org/10.1016/s2468-1253\(19\)30383-8](https://doi.org/10.1016/s2468-1253(19)30383-8)
- [30] Zhang, B., Zhao, J., Jiang, M., Peng, D., Dou, X., Song, Y., *et al.* (2022) The Potential Role of Gut Microbial-Derived Exosomes in Metabolic-Associated Fatty Liver Disease: Implications for Treatment. *Frontiers in Immunology*, **13**, Article ID: 893617. <https://doi.org/10.3389/fimmu.2022.893617>
- [31] Yang, X., Wang, J., Qi, X., Hou, M., Liu, M., Xiao, Y., *et al.* (2025) HLF and PPAR α Axis Regulates Metabolic-Associated Fatty Liver Disease through Extracellular Vesicles Derived from the Intestinal Microbiota. *iMeta*, **4**, e70022. <https://doi.org/10.1002/imt2.70022>
- [32] 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>
- [33] Bourganou, M.V., Chondrogianni, M.E., Kyrou, I., Flessa, C., Chatzigeorgiou, A., Oikonomou, E., *et al.* (2025) Unraveling Metabolic Dysfunction-Associated Steatotic Liver Disease through the Use of Omics Technologies. *International Journal of Molecular Sciences*, **26**, Article No. 1589. <https://doi.org/10.3390/ijms26041589>
- [34] Le, P., Dasarathy, S., Herman, W.H., Adekunle, O.A., Tran, H.T., Criswell, V., *et al.* (2025) Value-Based Pricing of Resmetirom for Metabolic Dysfunction-Associated Steatotic Liver Disease. *JAMA Network Open*, **8**, e2517122. <https://doi.org/10.1001/jamanetworkopen.2025.17122>