游离脂肪酸在代谢相关脂肪性肝病发病中的作用及其治疗研究进展

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摘要：代谢相关脂肪性肝病已是我国第一大慢性肝病，胰岛素抵抗与其发病密切相关。胰岛素抵抗使脂肪组织功能紊乱，脂解释放大量游离脂肪酸入血。肝脏是参与脂肪酸代谢的重要器官，过量的游离脂肪酸被肝脏摄取后，可通过多种途径造成肝脏脂质新生增强、脂肪酸β氧化障碍和甘油三酯合成增加，最终使甘油三酯在肝细胞中以脂滴形式蓄积而发生脂肪变性。循环中过量的游离脂肪酸可引起主要靶器官的胰岛素抵抗及肝脏炎症反应。本文从过量游离脂肪酸对肝细胞内脂质蓄积、胰岛素抵抗、炎症反应的影响以及西药和中药治疗代谢相关脂肪性肝病中脂肪酸代谢的研究进展进行综述。

关键词：游离脂肪酸；代谢相关脂肪性肝病；甘油三酯；胰岛素抵抗；棕榈酸

Research progress on the role and treatment of free fatty acids on the pathogenesis of metabolic associated fatty liver disease

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Abstract: Metabolic associated fatty liver disease has become the largest chronic liver disease in China, and insulin resistance is closely related to its pathogenesis. Insulin resistance disrupts the function of adipose tissue, and lipolysis releases a large number of free fatty acids into blood. Liver is an important organ, which is involved in fatty acid metabolism. Excessive intake of free fatty acids by liver can lead to enhanced liver lipogenesis, fatty acids β oxidative disorder and increased triglycerides synthesis through various pathways, ultimately resulting in triglycerides accumulation in hepatocytes in the form of lipid droplets and steatosis. Excessive circulation free fatty acids also cause insulin resistance in main target organs and liver inflammation. This article reviewed the effects of excessive free fatty acids on lipid accumulation, insulin resistance, and inflammatory response in hepatocytes, as well as the research progress on fatty acid metabolism in the treatment of metabolic associated fatty liver disease with Western medicine and traditional Chinese medicine.

Keywords: Free fatty acids; Metabolic associated fatty liver disease; Triglyceride; Insulin resistance; Palmitic acid

代谢相关脂肪性肝病（metabolic associated fatty liver disease，MAFLD）是排除过量饮酒和明确的肝损伤因素（如病毒性、自身免疫性及药物损伤性肝炎）引起的肝细胞内甘油三酯沉积的慢性代谢性疾病[1]，可进展为代谢相关脂肪性肝炎（metabolic associated steatohepatitis，MASH）、肝硬化甚至肝癌。随着生活方式的快速转变，中国MAFLD的总体患病率约为29.1%[2]，但MAFLD的治疗尚未引起人们的足够重视。高糖高脂饮食、肥胖、2型糖尿病、肠道菌群紊乱等是引发MAFLD的重要原因，胰岛素抵抗是关键病因。胰岛素能抑制激素敏感脂肪酶（脂肪细胞中甘油三酯分解的关键限速酶）活性，而发生胰岛素抵抗时，胰岛素失去了对脂肪动员的调控，使大量产生的游离脂肪酸释放入血，在其他细胞内异位沉积[3]。同位素标记法显示肝脏中59.0%的甘油三酯来源于血清游离脂肪酸，26.1%来源于脂质从头合成，14.9%来源于饮食中的脂肪酸[4]。由此可见，胰岛素抵抗导致脂肪组织释放的游离脂肪酸在促进肝细胞内甘油三酯的生成中起主导作用。

1 过量游离脂肪酸对肝细胞内脂质蓄积的影响

正常情况下，脂肪动员产生的长链脂肪酸入血后与白蛋白结合，经过肝细胞膜上脂肪酸转运蛋

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白（fatty acid transport protein，FATP）如FATP2、FATP4等或脂肪酸转移酶（fatty acid translocase，FAT/CD36）摄取[5]，主要由胞浆中脂肪酸结合蛋白1转输[6]到线粒体进行脂肪酸的β氧化、内质网合成甘油三酯或用于结构脂质的合成。但肝细胞不是甘油三酯的储存场所，合成后以极低密度脂蛋白（very low density lipoprotein，VLDL）的形式排出，供其他器官利用。对280例中国MAFLD患者血清游离脂肪酸的分析发现，肉豆蔻酸和棕榈酸与MAFLD风险呈正相关[7]，且胰岛素抵抗的存在能加重这种风险。近年研究表明游离脂肪酸与MAFLD进展密切相关，过量的游离脂肪酸可作用于肝细胞，使其发生脂肪变性。

1.1 对脂质新生的影响　肝脏利用糖进行脂质从头合成主要受2种关键转录因子调控，一类是固醇调节元件结合蛋白-1（sterol regulatory element-binding protein 1，SREBP-1），另一类是碳水化合物反应元件结合蛋白（carbohydrate response element binding protein，ChREBP）。SREBP-1是一种调控脂质新生基因的转录因子，具有2种亚型，SREBP-1a和SREBP-1c，以胰岛素诱导基因（insulin-induced gene，INSIG）-SREBP切割激活蛋白（SREBP cleavage-activating protein，SCAP）-SREBP非活化形式储存在内质网，INSIG与SCAP解离后，SREBP-SCAP从内质网易位到高尔基体，并被位点1和2蛋白酶切割，形成核形式SREBP，激活其下游靶标转录，包括乙酰辅酶A羧化酶（acetyl-CoA carboxylase，ACC）、脂肪酸合成酶（fatty acid synthetase，FAS）和硬脂酰辅酶A去饱和酶1（stearoyl-coenzyme A desaturase 1，SCD-1）[8]，将碳水化合物转化为脂肪酸。在高脂饮食诱导的MAFLD小鼠模型中，脂肪肝中神经酰胺合成酶6（ceramide synthase 6，CerS6）表达增加。用棕榈酸处理Hep3B细胞后，CerS6通过抑制INSIG-1的表达促进SREBP-1成熟，进而增加SCD-1和FAS水平[9]。游离脂肪酸通过P38丝裂原活化蛋白激酶（p38 mitogen-activated protein kinase，p38 MAPK）信号转导通路使异质性胞核核糖核蛋白A1（SREBP-1a内部核糖体进入位点的反式激活因子）从胞浆转位到核中，与SREBP-1a的内部核糖体进入位点结合，从而促进其翻译[10]。上述2种方式都是由内质网应激介导的，推测游离脂肪酸不能直接作用于SREBP1，而是通过内质网应激间接调控其表达。SREBP1c促进脂质新生除受INSIG负调控外，还受哺乳动物雷帕霉素靶点复合物1（mammalian target of rapamycin 1，mTORC1）的正向调节[11]。脂肪酸能以干扰素反应刺激因子依赖的方式促进Hep3B细胞mTORC1活化复合物的形成，且MAFLD患者肝组织中mTORC1存在高表达现象[12]。mTORC1和INSIG作为胰岛素通路蛋白激酶B（protein kinase B，PKB）的下游靶点，共同调控SREBP-1的表达[11]，上述研究表明过量游离脂肪酸可能以不依赖胰岛素的方式绕过PKB促进SREBP-1介导的脂质新生。ChREBP作为转录因子，能特异性结合于L-型丙酮酸激酶基因（L-type pyruvate kinase gene，L-PK）启动子，促进糖酵解。游离脂肪酸可通过激活腺苷酸活化蛋白激酶（adenosine monophosphate-activated protein kinase，AMPK）磷酸化$ChREBP_{Ser568}$，减弱后者DNA结合能力[13]，抑制葡萄糖诱导的L-PK转录。多不饱和脂肪酸以不依赖AMPK的方式促进ChREBP mRNA降解并抑制其核转位，下调下游L-PK和FAS基因的表达[14]。上述研究表明游离脂肪酸可能对ChREBP发挥负调控作用，而MAFLD患者肝脏的脂质从头合成增强[4]，提示在高脂饮食情况下，SREBP-1介导的脂质新生起主导作用。

1.2 对线粒体脂肪酸β氧化的影响　线粒体相关内质网膜是线粒体和内质网间的结构连接，它通过Ⅰ型1，4，5-三磷酸肌醇受体（inositol 1，4，5-trisphosphate receptors，IP3R1）复合物依赖的机制调节从内质网到线粒体的Ca^{2+}转运。棕榈酸通过类固醇受体共激活因子激酶途径促进细胞内钙离子释放通道IP3R1的Tyr353磷酸化并增加IP3R1蛋白的稳定性，从而引起肝细胞中线粒体Ca^{2+}超载和线粒体功能障碍[15]。棕榈酸过载可使肝细胞内质网中Ca^{2+}流入线粒体中，促进谷氨酰胺作为底物合成α-酮戊二酸，随后进入三羧酸循环（添补反应）[16,17]。用棕榈酸处理H4IIEC3大鼠肝癌细胞可导致氧吸收速率加倍和线粒体通量最大化。在增加的线粒体代谢中，这种改变与脂肪酸的β氧化无关，而是通过线粒体呼吸复合物Ⅰ以谷氨酰胺作为主要燃料实现的[18]。上述研究表明，脂肪酸通过Ca^{2+}以谷氨酰胺为底物引起内质网应激，可不经过脂肪酸的β氧化利用，而是通过添补反应使三羧酸循环紊乱。一项临床试验测量了43例MAFLD患者和11例健康对照口服^{13}C标记的棕榈酸（10 mg/kg）6 h后呼出$^{13}CO_2$的累积剂量回收率（cumulative percent dose recovered，CPDR），结果表明，MAFLD患者对棕榈酸的氧化降低了27% [CPDR：（9.5 ± 2.4）%比（13.1 ± 3.7）%，P = 0.0001][19]。棕榈酸刺激HepG2细胞后，可诱导氧化磷酸化（oxidative phosphorylation，OXPHOS）复合物酶降解，且使其酶活性显著降低；还可造成线粒体DNA氧化损伤，使编码OXPHOS亚基的基因表达减少。这种作用是通过还原型辅酶Ⅱ氧化酶活化介导的[20]。在后续高脂饮食诱导的小鼠MASH模型中，OXPHOS复合物表达和活性显著降低。还原型辅酶Ⅱ氧化酶2

基因敲除的高脂饮食小鼠只有轻度脂肪变性，而无MASH[21]。正常情况下，游离脂肪酸经线粒体脂肪酸β氧化后生成酮体，分泌到血液中供肝外组织利用。过量游离脂肪酸可引起内质网应激，导致线粒体钙超载，使三羧酸循环紊乱，又影响OXPHOS复合物活性，造成游离脂肪酸在肝细胞中蓄积。

1.3 对甘油三酯合成的影响 用游离脂肪酸处理HepG2细胞可使组蛋白赖氨酸脱甲基酶7A和甘油三酯合成的关键酶甘油二脂-O-酰基转移酶（diacylglycerol acyltransferase，DGAT2）蛋白表达水平增加。进一步研究发现，组蛋白H3赖氨酸9和H3赖氨酸27在DGAT2启动子上的二甲基化富集因组蛋白赖氨酸脱甲基酶7A过表达而降低[22]。脂酰辅酶A长链合成酶3（long-chain acyl-Co A synthetase 3，ACSL3）是脂滴相关蛋白的一种，ACSL3广泛分布于大多数细胞中的脂滴表面，也是其生物合成过程中必需的酶之一[23]。油酸通过上调ACSL3蛋白表达水平使人类肝细胞系HuH7中甘油三酯蓄积[24]。禁食期间肝脏TANK结合激酶1（TANK binding kinase 1，TBK1）可被诱导产生，并维持在非磷酸化、非活性状态，使其能够作为骨架蛋白与ACSL1高亲和力结合，使后者定位于线粒体上促进脂肪酸氧化。在肥胖状态下，TBK1被激活，与ACSL1亲和力降低，后者则转移到内质网上促进脂肪酸以甘油二脂途径再酯化[25]。棕榈酸作用于肝细胞后可显著提升TBK1磷酸化水平[12,26]，表明PA可能通过TBK1/ACSL1途径促进脂质生成，但缺乏直接的证据。

1.4 对VLDL分泌的影响 血浆游离脂肪酸是肝脏VLDL-甘油三酯合成的主要底物，研究显示高脂饮食诱导的MAFLD大鼠血浆中利用游离脂肪酸新合成的VLDL低于正常大鼠 [（46.8 ± 2.3）%比（57.2 ± 4.5）%]，但差异无统计学意义（$P = 0.0569$）[27]。一项早期研究指出，尽管MAFLD患者血中游离脂肪酸浓度较正常人高，但血中由游离脂肪酸转化的甘油三酯反而减少 [（25.1 ± 2.9）%比（52.8 ± 6.2）%；$P < 0.01$]，来源于肝脏的脂质从头合成却增加了约3倍 [（14.9 ± 2.7）%比（4.6 ± 1.1）%；$P < 0.01$][28]。后续类似研究进一步表明，MAFLD患者血浆中肝脏脂质新生来源的VLDL-甘油三酯增加了2～3.5倍 [（23.2 ± 7.9）%比（10.1 ± 6.7）%，$P < 0.001$）；（10.9 ± 1.7）%比（38.5 ± 2.0）%，$P < 0.01$）][29,30]。上述研究表明，血中游离脂肪酸再酯化占MAFLD患者分泌的VLDL-甘油三酯百分比仍高于脂质新生[4,28]，甚至与健康人相比有降低趋势，但通过肝细胞脂质从头合成分泌的VLDL-甘油三酯显著增强，是MAFLD患者糖脂代谢紊乱的标志。这种作用可能是通过内质网应激增强肝脏SREBP介导的脂质新生[31]及减弱脂肪酸的β氧化[32]实现的。

2 过量游离脂肪酸对胰岛素抵抗的影响

胰岛素抵抗是其靶向组织对高生理胰岛素水平反应性降低的状态，主要发生在肝脏、骨骼肌和脂肪组织。胰岛素与受体结合后，通过级联反应激活PKB。在骨骼肌中，PKB将葡萄糖转运蛋白4储存囊泡转移到胞膜来促进葡萄糖摄取，还可负调控糖原合酶激酶3β及糖原磷酸化酶促进糖原合成。此外，在肝脏中，PKB还可抑制叉头框蛋白O1（forkhead box protein O1，FoxO1）介导的糖异生基因表达[33]。Meta分析显示，MAFLD和MASH患病人群中2型糖尿病的发病率分别为65.04%和31.55%[34]。使用质子磁共振波谱分析发现，MAFLD患者肝脏饱和脂肪酸所占分数与肝脏脂质新生程度呈正相关，并与肝胰岛素敏感性呈负相关[35]。在原代小鼠肝细胞中，过量的游离脂肪酸使多磷酸肌醇激酶表达减少，抑制下游PKB磷酸化而产生胰岛素抵抗[36]。棕榈酸刺激HepG2细胞后，磷酸化组学显示其选择性抑制胰岛素信号通路：调控糖原合成的关键靶点PKB$_{(S473)}$、糖原合酶激酶3β和调控糖异生的关键靶点FoxO1磷酸化显著下降。胰岛素刺激下，p-FoxO1由静息状态下定位的细胞核转移到胞浆中，失去对糖异生基因的转录活性。免疫荧光显示棕榈酸处理后继用胰岛素，FoxO1仍滞留于胞核中[37]。腺苷三磷酸（adenosine triphosphate，ATP）敏感性钾通道作为葡萄糖感受器能启动胰岛素的分泌。在慢性棕榈酸刺激下，胰岛β细胞膜上ATP敏感性钾通道表达减少，并以半胱氨酸蛋白酶3途径凋亡[38]。饱和脂肪酸刺激人肌小管后，能以Toll样受体4（Toll-like receptor 4，TLR4）依赖的方式诱导产生粒细胞集落刺激因子，作用于脂肪细胞和肌小管后产生胰岛素抵抗[39]，且可改变原本表达在肌小管细胞膜上的葡萄糖转运蛋白4，使之滞留于核周储存室[40]。上述研究证明游离脂肪酸对胰岛素抵抗的主要靶器官（肝脏、胰腺、肌肉和脂肪组织）均有脂毒性，可抑制胰岛素通路磷酸化，造成其对葡萄糖的利用障碍。

3 过量游离脂肪酸对炎症反应的影响

12例体态偏瘦且糖耐量正常的个体以30 ml/h低剂量静脉注射游离脂肪酸48 h后，TLR4表达显著增加，炎症信号通路c-Jun氨基末端激酶（c-Jun N-terminal kinase，JNK）和p38 MAPK磷酸化水平升高，TLR4表达和p38 MAPK磷酸化水平与外周胰岛素抵抗直接相关[41]。在40例无糖尿病MAFLD患者中，可溶性CD163（反映巨噬细胞活动）与血中游离脂肪酸水平和脂肪组织胰岛素抵抗密切相关[42]。体外实验表明，暴露于棕榈酸的人巨噬细胞可溶性CD163分泌增加[42]。MAFLD患者肝细胞可分泌一种富含棕榈酸和硬脂酸等饱和脂肪酸的外泌

体，通过内体途径被库普弗细胞吸收，库普弗细胞通过TLR4促进JNK磷酸化、核因子κB（nuclear factor kappa-B，NF-κB）核转位、白细胞介素-6（interleukin-6，IL-6）等炎症因子表达及免疫细胞在肝实质的渗入。极化后的库普弗细胞能抑制肝细胞PKB_{473}和PKB_{308}磷酸化，诱导肝细胞发生胰岛素抵抗[43]。游离脂肪酸刺激库普弗细胞后可分泌肿瘤坏死因子-α，作用于肝细胞后引起脂肪变性[44]。棕榈酸诱导肝细胞脂毒性损伤后，分泌的骨桥蛋白可通过p-局部黏着斑激酶/NF-κB通路促进巨噬细胞的激活和迁移[45]。上述研究表明，巨噬细胞在游离脂肪酸引起的炎症中起关键作用，且肝小叶炎症和胰岛素抵抗强烈相关[46]，因此炎症反应可加剧胰岛素抵抗。此外，游离脂肪酸构成比棕榈油酸/棕榈酸与MAFLD患者外周血程序性死亡受体$1^{+}CD4^{+}$ T细胞含量呈负相关，同时代表免疫激活的$CD25^{+}CD45^{+}CD4^{+}$ T细胞量增加，表明游离脂肪酸可调节外周血T细胞谱向促炎方向发展[47]。亚油酸可参与中性粒细胞外陷阱的形成，而后者是加重巨噬细胞炎症反应的起始因素，且亚油酸代谢与MASH进展高度相关[48]。提示游离脂肪酸活化的$CD4^{+}$ T细胞和中性粒细胞也参与了MASH患者肝脏炎症微环境的形成。

4 西药治疗 MAFLD 中脂肪酸代谢进展

研究表明，J147以激活$AMPK_{\alpha\text{-}Thr172}$抑制脂肪酸合成限速酶$ACC1_{Ser79}$磷酸化的方式抑制小鼠肝细胞和血浆中游离脂肪酸含量，同时增加游离脂肪酸β氧化产物乙酰辅酶A和ATP水平[49]。SREBP强效抑制剂25-HL能与INSIG结合，促进INSIG和SCAP滞留在内质网，抑制SREBP活化。在MASH小鼠模型中，25-HL能降低血和肝脏胆固醇和甘油三酯水平，增强胰岛素敏感性，通过下调脂质生成基因缓解肝脏脂肪沉积和气球样变性、炎症及纤维化[50]。奥贝胆酸能抑制FATP5对长链脂肪酸的吸收，显著减轻甘油三酯在高脂饮食饲养的人源化FATP5小鼠肝脏中的积累[51]。在一项Ⅰb期临床试验中，AMPK激动剂PXL770能降低MAFLD患者肝脏脂质从头合成和血浆甘油三酯水平，改善糖耐量和胰岛素抵抗[52]。一项Ⅱa期临床试验中，MAFLD患者联合应用ACC抑制剂PF-05221304和DGAT2抑制剂PF-06865571，肝脏脂肪较安慰剂对照降低44.6%[53]。Aramchol是SCD1的部分抑制剂，Aramchol虽然未能显著降低MASH患者肝脏甘油三酯水平（95%*CI*：−6.4～0.2，$P = 0.066$），但对肝组织学与丙氨酸氨基转移酶水平有改善作用[54]。FAS抑制剂TVB-2640和FT-4101[55]均能抑制MAFLD患者肝脏脂质从头合成和脂肪沉积，前者还能降低血中促炎性脂毒素，改善肝功能、血脂和纤维化[56,57]。综上，西药对游离脂肪酸诱导的MAFLD新药临床研究多集中在抑制ACC、FAS和SCD1等脂质新生方面（表1）。

5 中药有效成分治疗 MAFLD 中脂肪酸代谢的研究

岩黄连生物总碱能以AMPK/SREBP1通路抑制脂肪酸的合成，改善MAFLD小鼠肝脏脂质沉积和糖耐量[58]。穿心莲内酯能改善高脂饮食喂养的小鼠糖脂代谢紊乱，减轻肝脏脂肪变性，这种作用是通过抑制肝脏FATP2介导游离脂肪酸吸收实现的[59]。研究发现黄连素能通过多种途径缓解小鼠脂质代谢紊乱：①抑制脂肪酸吸收（脂肪酸结合蛋白1，CD36）、脂质生成（SCD1，AMPK/ACC）和改善β氧化（肉毒碱棕榈酰基转移酶1A）；②减轻线粒体肿胀和减少线粒体DNA拷贝数，促进线粒体融合等[60]。泽泻醇B对CD36的特异性抑制可减少游离脂肪酸的吸收，MASH小鼠肝脏甘油三酯减少28.1%。CD36的抑制能降低JNK/NF-κB磷酸化水平和活性氧的产生，降低肿瘤坏死因子-α和IL-6等炎症因子的表达[61]，进一步改善肝功能和纤维化。苦茶碱作为去乙酰化酶-3的激活剂，通过脱乙酰化提高长链酰基辅酶A脱氢酶的活性，促进线粒体对长链酰基肉碱代谢，由此改善MAFLD小鼠脂肪酸β氧化，抑制IL-6、IL-1β、环氧合酶-2炎症介质的表达和库普弗细胞的浸润[62]。雷公藤甲素作为$AMPK_{Thr172}$的变构激活剂，可提高$ACC\text{-}1_{Ser79}$磷酸化，降低SREBP-1、SCD-1和FAS表达，抑制脂质生成；还可上调过氧化物酶体生长因子活化受体α和肉毒碱棕榈酰基转移酶1A的表达，促进脂肪酸β氧化，显著改善MASH小鼠肝脏炎症、气球样变和纤维化[63]。以上结果提示中药有效成分能通过抑制脂肪酸的新生和吸收、促进脂肪酸β氧化等途径改善MAFLD糖脂代

表1　临床在研药物对游离脂肪酸代谢的影响

药物	靶点	疗效	不良反应或不足
PXL770	AMPK激动剂	降低血中甘油二脂和甘油三酯水平、抑制肝脏脂质从头合成、改善糖耐量和胰岛素敏感性	腹泻、恶心和头痛眩晕等
PF-05221304＋PF-06865571	ACC抑制剂＋DGAT2抑制剂	显著降低肝脏脂肪、改善纤维化，不升高肝酶和血脂水平	安全性良好但对肝纤维化改善的结果是从大鼠模型中获得的
Aramchol	SCD1部分抑制剂	降低肝酶水平，不加重肝纤维化	安全性良好但对肝脏脂质的降低不及预期
FT-4101	FAS抑制剂	抑制肝脏脂质从头合成及脂肪变性	安全性良好但对肝功能和糖脂代谢无改善
TVB-2640	FAS抑制剂	降低肝脏脂肪、护肝降脂、提高胰岛素敏感性和抗纤维化	头痛、外周水肿、皮疹和上呼吸道感染等

谢紊乱的相关症状，但目前研究多集中在细胞实验和动物实验，缺乏相应的临床数据。

6 总结与展望

MAFLD患者肝脏存在代谢重编程，即脂肪酸β氧化降低[19]和脂质从头合成增强[28-30]现象，糖脂代谢障碍主导了疾病的进程，而游离脂肪酸介导的内质网应激似乎起关键作用[31,32]。游离脂肪酸的脂毒性还可引起炎症反应（NF-κB和JNK途径）和外周组织的胰岛素抵抗，低程度的慢性炎症反应又能加剧胰岛素抵抗。针对MAFLD患者肝脏代谢重编程，有研究纳入了10例MAFLD患者，经过2周低碳水化合物高蛋白饮食，肝脏脂质从头合成降低79.8%，反映β氧化的β-羟丁酸增加了4.9倍，在体质量保持不变的情况下肝脏脂肪减少43.8%[64]。因此，合理的饮食结构对MAFLD的综合治疗具有重要作用。药物干预方面，脂质新生抑制剂在MAFLD临床试验中虽然展现出了良好的效果，但均存在不同程度的不良反应[52-57]。虽然相关研究对泽泻醇B（祛湿类中药有效成分的代表）[56]和苦茶碱（清热药有效成分的代表）[57]改善脂肪酸代谢的具体药理学机制进行了较深入的阐释，且在动物实验中也取得了较理想的效果，但尚没有应用于临床后的相关数据。从中药中挖掘治疗MAFLD的有效成分并应用于临床将是一项有益的探索。

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