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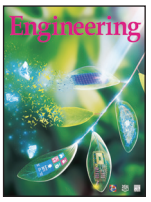

Research
Probiotics and Diseases—Review

益生菌对非酒精性脂肪性肝病疗效的研究进展

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摘要

非酒精性脂肪性肝病（NAFLD）在全球范围内的患病率高达20%~33%，已成为严重威胁人类健康的慢性肝病之一。至今为止，除了改变生活方式，改善NAFLD尚无明确的药物治疗方法。因此，找到有效、可替代的干预策略迫在眉睫。随着人们对肠道微生态在NAFLD发病机制中的重要作用的认识，益生菌防治NAFLD的研究也随之增多。NAFLD治疗中最受关注的益生菌主要包括以双歧杆菌属（*Bifidobacterium*）和乳酸杆菌属（*Lactobacillus*）为代表的传统益生菌，以及下一代新兴益生菌（NGP），如嗜黏蛋白阿克曼菌（*Akkermansia muciniphila*）和普拉梭菌（*Faecalibacterium prausnitzii*）等。本文综述了口服传统益生菌和NGP对NAFLD发生发展的影响；基于最新的动物和临床研究，阐述了益生菌直接或间接影响疾病的机制。虽然相关研究已有很多，但要全面了解益生菌、肠道微生态、NAFLD之间的具体潜在机制，仍需要深入研究，需要更多的大规模临床试验来评估益生菌治疗NAFLD的效果以及益生菌在人体内的安全性。

1. 引言

非酒精性脂肪性肝病（NAFLD）是世界上最常见的肝病之一。目前全球的发病率为20%~33%，且仍在逐年增长[1,2]。NAFLD通常被定义为：一个人在没有过量摄入酒精（女性和男性每天饮酒量分别少于20 g和30 g）、没有感染病毒、没有自身免疫或药物性肝病病史的情况下，肝组织活检标本中肝细胞脂肪浸润> 5% [3]。NAFLD包括单纯脂肪浸润（脂肪变性）以及非酒精性脂肪性肝炎（NASH）[4]。

NAFLD的发生起源于肝脏中过多的脂质堆积。人体中吸收的脂肪来源包括外周脂肪组织释放的脂肪酸（FA）、肝脏中脂肪从头合成产生的脂质以及饮食中的脂肪酸[5]。脂质主要通过脂肪酸氧化和甘油三酯（TG）分泌形成脂蛋白颗粒排出[6]。正常情况下，流入肝脏的脂质总量与肝脏的脂质处理量相同。然而，当这个平衡被打破时，就会发生NAFLD。随后，脂肪变性与其他因素，包括炎症细胞因子、脂肪因子、线粒体功能障碍、氧化应激等共同导致肝细胞损伤。如果没有得到及时且有效的治疗，NAFLD最终可能发展为肝纤维化、肝硬化甚至肝癌（这是世界上第二大常见的导致死亡的癌症）[7]。然而，目前除了建议改变生活方式，如饮食

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干预、定期锻炼身体和减肥外，还没有明确的治疗脂肪变性的药物[8]。因此，寻找改善NAFLD的有效的治疗方法是当务之急。

肠道和肝脏通过胆道和门静脉循环（被称为肠-肝轴）进行紧密的双向连接[9,10]。除了氧化应激[11]、胰岛素抵抗[12]和炎症[13]是NAFLD发病的主要诱因外，肠道微生物也起着关键的作用[14]。在正常生理条件下，肠道微生物通过促进营养物质的消化、代谢、免疫调节和屏障保护来维持肠道内的稳态，基于这些功能，肠道微生物也被称为“遗忘的器官”（forgotten organ）[15]。肠道微生物的失调会导致一系列的问题，包括有害细菌过度生长、肠道屏障通透性增加、细菌易位以及代谢物流向肝脏，从而引发和加重NAFLD [16]。

越来越多的研究结果显示，肠道微生物的调控可能是治疗NAFLD的可行的方法[17]。事实上，益生菌已显示出它们在恢复体内平衡和改善肠道微生物相关疾病中的作用[18]。本文就益生菌通过调节肠道微生物治疗NAFLD的效果进行综述。除了传统的双歧杆菌属和乳酸杆菌属，最新报道的下一代益生菌（NGP）也将被讨论。

2. 肠道微生物在 NAFLD 发生发展中的致病机制

肠道微生物中的优势菌群主要来自厚壁菌门（Firmicutes）、拟杆菌门（Bacteroidetes）、放线菌门（Actinobacteria）和变形菌门（Proteobacteria）。肠道微生物的结构和组成可以被多种因素影响，如年龄、饮食、健康或者疾病。肠道微生物可通过多种机制加重NAFLD，包括改变饮食中的能量吸收能力、影响脂肪生成和短链脂肪酸（SCFA）合成途径、改变胆碱和胆汁酸代谢信号通路、增加肠道通透性和炎症，以及在肠道内产生内源性酒精[19]（图1）。

2.1. 能量吸收能力的改变

NAFLD通常与肥胖有关。动物实验已经证明了肠道微生物在获取能量（从食物中）方面的关键作用。与野生型小鼠相比，无菌小鼠在进行高脂肪饮食（HFD）后不太容易出现肥胖[20]。然而，将野生型小鼠的肠道微生物移植到无菌小鼠后，体脂质量和胰岛素抵抗均显著增加[21]。因此，肠道微生物可能有助于从食物中获取更多的能量，从而导致NAFLD的发生。

2.2. 脂肪的生成与短链脂肪酸

脂肪的从头合成是一条复杂的、高度调控的脂质代谢途径，通常在肝脏和脂肪组织中被激活。在正常情况下，脂肪的从头合成是将过量的碳水化合物转化为游离的脂肪酸，这些脂肪酸被酯化成TG，然后通过β氧化提供能量[22]。SCFA包括乙酸、丙酸和丁酸，主要由肠道微生物发酵产生。乙酸是胆固醇合成的底物，丙酸是肝脏中糖异生的底物，而丁酸被用作结肠细胞的能量底

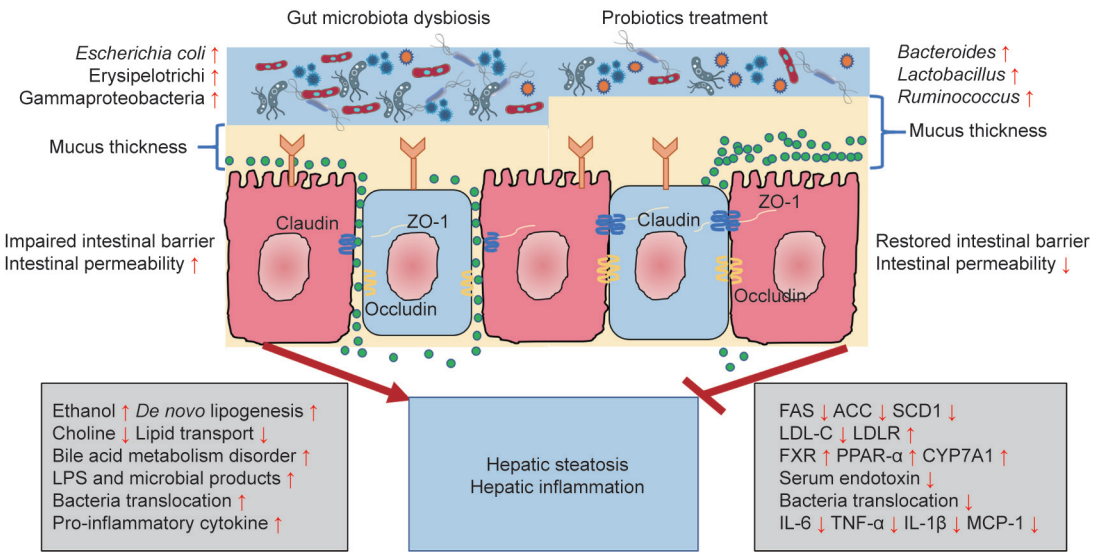

图1. NAFLD的病理机制和益生菌干预NAFLD功能。ZO-1：闭锁小带蛋白1；FAS：脂肪酸合成酶；ACC：乙酰辅酶A羧化酶；SCD1：硬脂酰辅酶A去饱和酶1；LDL-C：低密度脂蛋白胆固醇；LDLR：低密度脂蛋白受体；FXR：法尼酯X受体；PPAR：过氧化物酶体增殖物激活受体；CYP7A1：胆固醇7α羟化酶；IL：白介素；TNF：肿瘤坏死因子；MCP：单核细胞趋化蛋白。

物[23]。除了可以促进肝脏中脂肪的从头合成，SCFA还是G蛋白偶联受体GPR43和GPR41的配体，也被称为游离脂肪酸受体2和受体3。SCFA激活GPR43可以抑制脂肪的分解和脂肪细胞分化，最终导致HFD小鼠中脂肪组织的堆积[24]。

2.3. 胆碱和胆汁酸代谢的改变

胆碱在脂质代谢中扮演着重要的作用，尤其在极低密度脂蛋白的产生和肝脏中脂质运输的过程中。胆碱可以促进肝细胞中的脂质运输，从而防止肝脏中的异常脂质堆积[25]。因此，肝脏脂肪变性的实验模型通常采用胆碱缺乏的饮食诱导。事实上，膳食中的胆碱含量影响了与NAFLD发展有关的γ-变性菌和产芽孢菌的组成及丰度[26]。此外，肠道微生物能够将胆碱转化为三甲胺氧化物，从而导致肝脏炎症和损伤，加重NAFLD[27]。

胆汁酸是在肝细胞中由胆固醇合成而来，并由肠道微生物代谢。在胃肠道中，初级胆汁酸能够促进脂溶性食物的消化吸收，维持肠道屏障，防止细菌易位[28,29]。此外，胆汁酸可以激活法尼酯X受体（FXR）以及G蛋白偶联胆汁酸受体1（TGR5），从而通过这些内源性受体，调节脂质和糖代谢以及能量消耗[30]。

2.4. 肠道通透性增加及炎症产生

肠道和肝脏通过肠-肝轴进行沟通，而肠-肝轴由肠道、肝脏和肠道屏障组成。紧密连接蛋白，包括闭锁小带蛋白1（ZO-1）、闭合蛋白（occludin）、封闭蛋白（claudin），连接肠上皮细胞和维持肠道屏障的完整性[31]。肠道屏障功能障碍和肠道微生物失调在肝脏疾病的病理生理学中起着重要作用[32]。事实上，与脂肪变性的儿童相比，患脂肪性肝炎的儿童的肠道通透性更高，这表明不同阶段的NAFLD的肠道通透性水平也不同[33]。

小肠细菌过度生长和炎症是导致NAFLD肠道通透性增高的主要原因。小肠细菌过度生长的定义为：近端空肠吸出物中的细菌浓度等于或者超过每毫升1×10^5菌落形成单位（CFU），而正常浓度低于1×10^4 CFU·mL^{-1}[34]。小肠细菌过度生长还可以诱导细菌从肠腔移位至门静脉循环，从而导致肝脏损伤[35]。脂多糖（LPS）是革兰氏阴性菌细胞膜的主要成分，可以被Toll样受体4识别（TLR4）。LPS可以刺激巨噬细胞和单核细胞产生促炎症细胞因子和促纤维化的细胞因子（如TNF-α、IL-8），且会激发肝脏中中性粒细胞和单核细胞的募集，从而导致肝脏损伤和全身炎症[36]。

2.5. 内源性酒精的产生

尽管根据定义，被诊断为NAFLD的患者没有摄入过量的酒精，但研究发现患有NASH的儿童和青少年，在没有经常接触酒精性饮料及食物的情况下，其血清中酒精浓度升高。肠道中产酒精的细菌（如大肠杆菌）丰度的增加被认为是内源性酒精的来源[37]。肠道微生物产生的酒精可以通过激活甾醇调节元件结合蛋白1（SREBP-1），增加肝脏中脂肪的生成，从而导致脂肪变性[38]。此外，酒精还会破坏肠道屏障，导致细菌易位增加及肝脏炎症的产生[39]。

3. 益生菌和益生菌的功能

联合国粮食与农业组织（FAO）和世界卫生组织（WHO）将益生菌定义为“活的微生物，当给予足够的剂量时会给宿主的健康带来好处”[40]。最常用的益生菌，即传统益生菌，主要是双歧杆菌属（*Bifidobacterium*）和乳酸杆菌属（*Lactobacillus*）。随着培养方法的改进，下一代测序技术和生物信息学方法的发展，一类名为NGP的新型益生菌已经被发现，包括嗜黏蛋白阿克曼菌（*Akkermansia muciniphila*）[41,42]、普拉梭菌（*Faecalibacterium prausnitzii*）[43]，以及脆弱拟杆菌（*Bacteroides fragilis*）[44]。由于大多数的益生菌是由胃肠道内的共生细菌组成，因此通常不需要额外的补充。然而，在啮齿动物NAFLD模型和NASH患者中均检测到双歧杆菌数量减少[37,45]。益生菌对人体的影响，包括肠道微生物群的改变、肠道屏障功能的改善、黏膜和上皮的竞争黏附性增加，以及肠道相关淋巴系统的调节[46]（图1）。许多研究已经证明益生菌对NAFLD动物模型和患者均有有效的治疗效果（表1 [47–57]和表2 [58–71]）。

4. 传统益生菌在 NAFLD 治疗中的作用

4.1. 体内研究

降低肝脏内TG被认为是减缓NAFLD的有效途径之一[72]。几项体内研究表明，益生菌可以有效降低脂肪含量，从而治疗脂肪性肝病（简称脂肪肝）。通过HFD诱导、基因修饰或者多种干预措施组合可以建立NAFLD动物模型，这些方法在之前的文献[73]中已被

表1 传统益生菌在动物实验中显示出改善NAFLD的作用

Probiotic strains	Treatment results	References
L. plantarum NCU116	ALT ↓, AST ↓, lipogenesis (FAS, ACC, and SCD1) ↓, fatty acid oxidation (PPARs, PGC1α, and CPT1α) ↑	[47]
Lactic bacteria	Serum lipid levels ↓, CYP7A1 ↑, FXR ↑, PPAR-α ↑, PPAR-γ ↓, occluding ↑, ZO-1 ↑	[48]
LGG	Hepatic fat content ↓, TG ↓, cholesterol ↓, CYP7A1 ↑	[49]
L. reuteri GMNL-263	Liver fibrosis ↓, TGF-β ↓, LDLR ↑, CYP7A1 ↑	[50]
L. johnsonii BS15	Hepatic steatosis ↓, ALT ↓, TG ↓, TNF-α ↓, *Lactobacillus* spp. ↑, Enterobacteriaceae ↑	[51]
L. paracasei N1115	Hepatic steatosis ↓, TNF-α ↓	[52]
L. paracasei	Hepatic steatosis ↓, ALT ↓, TLR4 ↓, TNF-α ↓, MCP-1 ↓, PPAR-γ ↓, intestinal permeability ↓, M2 Kupffer cell ↑	[53]
Saccharomyces boulardii	Liver index ↓, AST ↓, endotoxin ↓, TNF-α ↓, occludin ↑, *Escherichia coli* ↓, *Bacteroides* ↑	[54]
Symbiter	Lobular inflammation ↓, IL-1 ↓, IL-10 ↑	[55]
Lactobacillus, *Bifidobacterium*	Free FA ↓, TG ↓, ALT ↓, fecal butyrate ↑, GPR109a ↑, IL-1β ↓, IL-18 ↓	[56]
Compound probiotics	TC ↓, TG ↓, Free FA ↓, ALT ↓, LPS ↓, IL-1β ↓, IL-18 ↓, colonic SCFAs ↑, GPR43 ↑, *Ruminococcus* ↑, *Veillonella* ↓	[57]

L.: *Lactobacillus*; LGG: *L. rhamnosus* GG; ALT: alanine aminotransferase; AST: aspartate aminotransferase; FAS: fatty acid synthetase; ACC: acetyl-coenzyme A carboxylase; SCD1: stearoyl coenzyme A desaturase 1; PPAR: peroxisome proliferator-activated receptor; PGC1α: PPAR-γ coactivator 1α; CPT: carnitine palmitoyltransferase ; CYP7A1: cholesterol 7α-hydroxylase; FXR: farnesoid X receptor; ZO-1: zonula occluden-1; TG: triglyceride; TGF: transforming growth factor; LDLR: low density lipoprotein receptor; TNF: tumor necrosis factor; TLR: toll-like receptor; MCP: monocyte chemotactic protein; FA: fatty acid; GPR: G-protein-coupled receptor; IL: interleukin; TC: total cholesterol; LPS: lipopolysaccharide; SCFA: short chain fatty acid.

表2 传统益生菌在NAFLD临床治疗中的应用

Probiotic strains	Treatment results	References
L. acidophilus	ALT ↓, AST ↓	[58]
L. bulgaricus, S. thermophilus	ALT ↓, AST ↓	[59]
L. acidophilus La5, *B. lactis* Bb12	ALT ↓, AST ↓, LDL-C ↓	[60]
L. acidophilus, L. rhamnosus, L. paracasei, P. pentosaceus, B. lactis, B. breve	Total body fat ↓, IHF ↓, TG ↓, TC ↓, TNF-α ↓	[61]
Symbiter	IL-6 ↓, IL-8 ↓, TNF-α ↓, IL-1β ↓, IFN-γ ↓	[62]
L. casei, L. acidophilus, L. rhamnosus, L. bulgaricus, *B. breve*, *B. longum*, *S. thermophilus*	Insulin ↓, insulin resistance ↓, TNF-α ↓, IL-6 ↓	[63]
L. acidophilus, *L. bulgaricus*, *B. lactis*, *S. thermophiles*	Ammonia levels↓	[64]
L. rhamnosus GG	TNF-α ↓, endotoxin ↓, Enterobacteriaceae ↑, Ruminococcaceae ↑	[65]
L. reuteri (synbiotic)	Steatosis ↓, body weight ↓, BMI ↓, waist circumference ↓	[66]
B. longum (synbiotic)	Steatosis ↓, AST ↓, TNF-α ↓, serum endotoxin ↓	[67]
L. casei, *L. rhamnosus*, *L. acidophilus*, *B. longum*, *B. breve*	Serum concentrations of leptin ↓, insulin ↓, HOMA-IR ↓	[68]
Protexin	ALT ↓, AST ↓, cholesterol ↓, TG ↓, BMI ↓	[69]
L. acidophilus, *L. rhamnosus*, *B. lactis*, *B. bifidum*	ALT ↓, AST ↓, TG ↓, waist circumference ↓, cholesterol ↓	[70]
VSL#3	BMI ↓, steatosis ↓, GLP-1 ↓, aGLP-1 ↑	[71]

S.: *Streptococcus*; *B.*: *Bifidobacterium*; *P.*: *Pediococcus*; ALT: alanine amino transferase; AST: aspartate aminotransferase; LDL-C: low-density lipoprotein cholesterol; IHF: intrahepatic fat; TG: triglyceride; TC: total cholesterol; TNF: tumor necrosis factor; IL: interleukin; IFN: interferon; BMI: body mass index; HOMA-IR: homeostasis model assessment of insulin resistance; VSL#3: generic name of *Bifidobacterium*, *Lactobacillus*, and *Streptococcus*; GLP: glucagon-like peptide; aGLP: activated GLP.

提到。一项针对HFD诱导的大鼠NAFLD的研究表明，经植物乳杆菌（*Lactobacillus plantarum*）NCU116治疗5周后，大鼠体内的脂肪堆积水平降低，肝功能恢复；可能的作用机制包括上调脂肪分解和脂肪酸氧化相关基因的表达以及下调脂肪的从头合成[47]。另一项研究表明，口服鼠李糖乳杆菌GG（*L. rhamnosus* GG, LGG）和植物乳杆菌WCFS1（*L. plantarum*, WCFS1），通过上调参与肝脏胆固醇代谢相关的基因CYP7A1，可降低血清TG、总胆固醇（TC）、游离脂肪酸和肝脏脂肪储存水平[48]。另一项研究也表明，单独服用LGG也可以降低肝脏脂肪含量，上调CYP7A1 [49]。此外，还有研究证明，高脂饲料饲养的仓鼠补充热灭活的罗伊氏乳杆菌（*L. reuteri*）GMNL-263（Lr263）可以改善脂质和胆固醇代谢功能，从而可能改善肝脏健康[50]。

炎症是加重NAFLD病情的另一个主要原因。因此，降低肝脏的促炎反应对治疗NAFLD具有重要的意义。一种基于约氏乳杆菌（*L. johnsonii*）BS15的制剂已经被证明可以通过降低肠道通透性、改变肠道微生物组成、降低血清中LPS水平、下调肝脏炎症因子（如TNF-α），来保护HFD喂养的NAFLD小鼠免于肝脏脂肪变性和肝细胞凋亡[51]。另一项研究表明，口服副干酪乳杆菌（*L. paracasei*）N1115可以减轻HFD诱导的肝脏脂肪变性和炎症因子TNF-α的释放，从而减缓肝硬化的发展[52]。在另一项研究中，副干酪乳杆菌治疗通过抑制促炎M1 Kuffer细胞的应答以及抗炎M2反应，可以显著降低促炎细胞因子TNF-α和MCP1的表达水平[53]。此外，布拉氏酵母菌（*Saccharomyces boulardii*）的干预可以改善HFD诱导的NAFLD大鼠的肝脏脂肪变性，降低TNF-α的表达[54]。含有14种益生菌的Symbiter也被证明可以显著降低IL-1的表达水平，而提高IL-10的表达水平 [55]。

益生菌还可以通过产生SCFA来改善NAFLD。肠道代谢物SCFA，包括乙酸、丙酸和丁酸，是脂质代谢和肠道免疫的关键调节因子[74]。其中，丁酸和丙酸被认为是抗肥胖的，而乙酸是促肥胖的。丁酸在维持肠道生态平衡及降低肠道通透性方面起着重要作用，可能会阻止内毒素的释放[18]。研究表明，乳酸杆菌和双歧杆菌联合使用可显著提高粪便中丁酸的水平，并导致GPR109a表达下调，从而抑制全身肥胖和炎症[56]。GPR109a是SCFA的受体，在脂肪细胞、肝细胞及结肠细胞中表达，主要由丁酸激活[75]。另一项研究显示，由6株乳酸杆菌和3株双歧杆菌组成的复合益生菌可以上调SCFA受体GPR43的表达，而GPR43可以抑制脂质沉积和慢性代谢性炎症[57]。

4.2. 临床试验

许多的随机临床试验（RCT）已经开展，用于评价益生菌对NAFLD的治疗效果。益生菌的疗效高度依赖于其组成的菌株以及其他的添加物。一项涉及30例患者的RCT结果显示，口服嗜酸乳杆菌（*L. acidophilus*）一个月后，患者的谷丙转氨酶（ALT）和谷草转氨酶（AST）活性显著降低，其中部分患者消化不良的症状得到缓解[58]。ALT和AST水平是判断脂肪肝患者炎症和肝细胞损伤的重要指标。然而，大多数治疗NAFLD的随机对照实验使用了含有两种或者两种以上菌株的配方，从而获得协同效应。Aller等[59]进行了一项RCT实验，用于评价由保加利亚乳杆菌（*L. bulgaricus*）和嗜热链球菌（*Streptococcus thermophiles*）组成的混合菌对28例NAFLD患者的疗效，结果显示治疗后ALT和AST水平降低。另一项RCT研究结果表明，服用含有嗜酸乳杆菌La5（*L. acidophilus* La5）和乳双歧杆菌Bb12（*Bifidobacterium lactis* Bb12）的益生菌酸奶可以降低肝酶水平、血清中TC水平以及低密度脂蛋白胆固醇水平（LDL-C）[60]。而在最近的一项研究中，68名患有NAFLD的肥胖患者随机接受混合益生菌[共含有6种，即嗜酸乳杆菌、鼠李糖乳杆菌、副干酪乳杆菌、戊糖片球菌（*Pediococcus pentosaceus*）、乳双歧杆菌、短双歧杆菌（*B. breve*）]或安慰剂治疗12周，结果表明混合益生菌可降低体重、体脂、肝内脂肪和TG水平，但对ALT、AST、葡萄糖、胰岛素及LPS水平无影响[61]。另一项对72例2型糖尿病和NAFLD患者进行的RCT研究结果显示，利用多株益生菌Symbiter联合治疗30 d可显著降低血浆中促炎细胞因子水平，尤其是IL-6、IL-8、TNF-α、IL-1β和IFN-γ [62]。另一项对42例NAFLD患者的RCT研究显示，补充多株益生菌可显著降低TNF-α和IL-6水平[63]。另外，有研究结果显示，服用益生菌后，肝硬化患者的任何测量参数都没有显著差异[64]。然而另一项对肝硬化患者的RCT研究显示，LGG可降低内毒素和TNF-α水平，同时减少肠杆菌科（Enterobacteriaceae）的数量，增加梭状芽胞杆菌（Clostridiales Incertae Sedis）XIV的数量 [65]。

益生元和合生元是另外两种被关注的补充剂（由于具有潜在的减轻肝损伤的有益效果）。益生元的定义为：一种选择性发酵的成分，可导致胃肠道内微生物的组成和（或）活性发生特定变化，从而有益于宿主健康[76]；而合生元则是益生菌与食物成分或膳食补充剂（即益生元）的结合。50名被诊断为NASH的患者服用由罗伊氏乳杆菌和菊粉组成的合生元后，肝脂肪变性程度降低，与NASH相关的代谢参数也降低，包括体重、BMI及血清尿酸水平[66]。另一项针对NASH患者的RCT研究，评估了服用含有低聚果糖的长双歧杆菌（*B. longum*）的合生元以及改变生活方式24周后的治疗效果，结果显示与单一改变生活方式相比，服用合生元和改变生活方式可显著降低TNF-α、血清AST水平、血清内毒素、脂肪变性和NASH活性指标[67]。此外，关于益生菌与生活方式改变或者与药物联合使用的治疗效果也有相关研究。Behrouz等[68]研究了89例NAFLD患者使用益生菌的效果，这些益生菌包括干酪乳杆菌、鼠李糖乳杆菌、

嗜酸乳杆菌、长双歧杆菌和短双歧杆菌。与单纯的生活方式改变相比，益生菌和益生元的补充加上生活方式的改变对血糖参数及瘦素水平影响更大。此外，益生菌也被用于与药物联合使用，从而提高治疗效果。Shavakhi等[69]发现，在NASH患者中，联合使用益生菌与二甲双胍对肝脏ALT水平的改变效果比单一使用二甲双胍更好。

关于益生菌对儿童NAFLD的有益作用的RCT也取得了一些进展。一项针对64名患有NAFLD的肥胖儿童的RCT研究显示，通过补充含有嗜酸乳杆菌、鼠李糖乳杆菌、乳双歧杆菌和双歧杆菌的益生菌胶囊可以降低ALT、AST、胆固醇和TG的水平[70]。另一项针对NAFLD儿童患者的RCT研究显示，服用VSL#3（双歧杆菌、乳酸杆菌和链球菌）可降低BMI、提高GLP-1水平、激活胰高血糖素样肽1（aGLP-1）水平[71]。尽管RCT研究已经证实了益生菌对NAFLD治疗的有益效果，但对其潜在的作用机制尚未完全了解。

5. NGP 在 NAFLD 治疗中的潜在益处

除了传统的益生菌，NGP作为治疗NAFLD的潜在益生菌也受到了关注[77]。NGP包括嗜黏蛋白阿克曼菌[41,42]、普拉梭菌[43]、单行拟杆菌（*Bacteroides uniformis*）[78]、解木聚糖拟杆菌（*Bacteroides xylanisolvens*）[79]、脆弱拟杆菌[44]、霍氏真杆菌（*Eubacterium hallii*）[80]、丙酸菌属（*Propionibacterium*）[81]以及梭菌属IV、XIVa和XVIII [82]的一些成员，其中一些菌已经被证明对治疗NAFLD有改善作用。

5.1. 嗜黏蛋白阿克曼菌

肠道黏液层由不含细菌的内层和共生菌定植的外层组成，其主要成分为一些细菌（如嗜黏蛋白阿克曼菌）可降解的氨基酸和低聚糖[41]。嗜黏蛋白阿克曼菌是一种黏蛋白降解菌，是人类肠道微生物中含量最丰富的单一物种之一，占细菌总数的0.5%~5.0% [83]。虽然该菌种没有被应用于食物和制药工业的历史，但已有研究证实嗜黏蛋白阿克曼菌在肠道中的丰度与代谢性疾病，如肥胖和NAFLD存在负相关的关系[84–86]。与野生型小鼠相比，NAFLD小鼠中嗜黏蛋白阿克曼菌的丰度显著降低，而导致该菌丰度提高的干预措施可以改善代谢参数[86]。使用益生元（如低聚果糖）可以恢复嗜黏蛋白阿克曼菌的丰度，缓解相关的疾病紊乱[87,88]。虽然嗜黏蛋白阿克曼菌治疗不会显著改变由饮食诱导的肥胖小鼠的肠道微生物的组成，但可以逆转HFD诱导的代谢紊乱，包括脂肪质量增加、代谢性内毒素血症、脂肪组织炎症和胰岛素抵抗，这表明其具有可能用于预防或治疗肥胖及相关代谢紊乱性疾病的潜力[87]。也有研究发现，嗜黏蛋白阿克曼菌及其主要的代谢产物（丙酸和乙酸）可以影响宿主脂质代谢相关的基因表达及其表观激活与沉默[89]。此外，使用嗜黏蛋白阿克曼菌作为益生菌的一个意想不到的优势是，与使用活菌相比，巴氏灭菌处理后的嗜黏蛋白阿克曼菌对饮食诱导的小鼠代谢紊乱所产生的有益作用与使用活菌相似，这可能是因为嗜黏蛋白阿克曼菌外膜上存在大量高度丰富的蛋白质[90,91]。

5.2. 拟杆菌

拟杆菌属（*Bacteroides*）属于拟杆菌门，是人类肠道微生物拟杆菌目中数量最多的一种[92]。拟杆菌属都是专性厌氧菌，在结肠黏液层中高度富集，大多数都对20%胆盐具有抗性[93]。拟杆菌最广为人知的特性之一是其强大的多糖降解系统。拟杆菌可以分解多种目标多糖，尤其是非消化性膳食纤维，产生大量的SCFA（主要是乙酸和丙酸）[94]。被吸收的SCFA可以诱导脂质生成，这与NAFLD的发生有关[95]。Gauffin Cano等[78]已经证实，在HFD喂养的小鼠中，单行拟杆菌CECT 7771株可以通过降低肝脏和血清中的胆固醇水平来降低体重，减轻脂肪变性。因此，还需要进一步探索将拟杆菌属用作益生菌用于治疗NAFLD的潜力。

5.3. 普拉梭菌

普拉梭菌是肠道共生菌，约占主要肠腔微生物的4% [96]。由于普拉梭菌可以产生丁酸，而丁酸的缺乏与克罗恩病有关，因此推测其可能有利于延缓NAFLD的进展[97]。根据最近的一项研究[98]发现，肥胖的糖尿病患者在减轻体重之后，普拉梭菌的丰度会增加。而另一项研究[99]则发现，肝脏脂肪含量> 5%与低丰度的普拉梭菌及增加的脂肪组织炎症有关，与体重无关。虽然在肥胖和非肥胖人群的粪便中普拉梭菌的丰度没有显著差异（$p = 0.082$），但是在男性和女性之间却存在差异，这表明区分性别可能对未来该菌种的研究很重要[100]。普拉梭菌的多样性也可能在宿主的炎症过程中发挥作用。一项研究表明，患有和不患有2型糖尿病的肥胖患者之间的普拉梭菌不同，这可能是由表观遗传调控、线粒体β氧化、葡萄糖敏感性和肥胖症而导致的胰岛素抵

抗所产生的差异[101,102]。阐明不同菌株之间的功能差异是该菌种制成益生菌制剂的关键。普拉梭菌ATCC 27766的治疗已经被证明可以改善小鼠的肝脏健康，减少脂肪组织炎症，表明该菌种的存在可能与增强线粒体呼吸、改变肠道微生物组成和维持肠道屏障完整性有关[103]。一项基于小鼠回肠类器官的体外实验模型的研究比较了嗜黏蛋白阿克曼菌和普拉梭菌对细胞代谢和生长相关的基因转录的影响，发现与嗜黏蛋白阿克曼菌相比，普拉梭菌对较少基因的转录有影响[89]。

5.4. 罗氏菌属

罗氏菌属（*Roseburia*）属于厚壁菌门梭状芽胞杆菌科XIV，包括5个菌种，即肠道罗氏菌（*R. intestinalis*）、人罗氏菌（*R. hominis*）、食葡糖罗氏菌（*R. inulinivorans*）、粪便罗氏菌（*R. faecis*）以及盲肠罗氏菌（*R. cecicola*）[104]。和普拉梭菌一样，罗氏菌也可以通过分解不能消化的碳水化合物来产生SCFA，尤其是丁酸[105]。研究表明，SCFA通过GPR及一系列的与细胞凋亡和先天性免疫相关的通路，发挥抗炎的功效。丁酸是结肠上皮细胞主要的能量来源，通过抑制NF-κB的激活来抑制黏膜中促炎症细胞因子的表达[106]。如上所述，由于炎症是脂肪肝向脂肪性肝炎发展的主要原因之一，由此可以推断，罗氏菌在预防NAFLD发展方面有较好的应用前景。事实上，一项研究已表明，补充甲壳素多糖纤维可显著减缓HFD小鼠的体重增加，并增加了罗氏菌的丰度[107]。然而，对于其在NAFLD治疗中的有效性，仍然需要进一步的研究来验证。

6. 结论

由于缺乏批准的药物，迫切需要有效的治疗策略来预防NAFLD的发生和发展。肠道微生物已经被证明是NAFLD发病的重要影响因素之一。许多体内研究和临床试验研究已经报道了通过给予传统的商业益生菌来调节肠道微生物，而益生菌治疗NAFLD的有效性也已经被证实。调节脂质代谢、减少肝脏脂肪的堆积、恢复肠道微生物稳态、修复肠道屏障以及缓解炎症是益生菌缓解NAFLD的可能机制。传统的益生菌主要由乳酸杆菌和双歧杆菌组成，但最近的研究表明，制剂不应局限于这些属的菌株。NGP（如阿克曼菌）在治疗NAFLD方面显示出巨大的潜力。然而，在益生菌临床应用之前，还需要进一步的研究来提供充分的理论依据，同时也需要更多的研究来证明新型益生菌优于传统益生菌。

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Compliance with ethics guidelines

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