DOI:10.3724/cbls.2026112 **CSTR**:32203.14.cbls.2026112
文章编号:1004-0374(2026)07-1241-15

运动通过重塑肠道菌群与代谢物稳态改善MAFLD的作用机制

吴鑫淼,刘 彦,胡 甜,李良鸣*,杨文琦*
(广州体育学院国家体育总局运动技战术诊断与机能评定重点实验室,广州 510500)

摘 要:代谢相关脂肪性肝病(MAFLD)已成为全球最普遍的慢性肝脏疾病,其病理机制复杂,涉及多器官交互作用。肠道菌群通过胆道、门静脉和体循环等途径,建立“肠-肝”之间的密切通讯。肠道菌群结构、代谢物以及肠道屏障完整性均影响MAFLD的发生与发展。运动是防治MAFLD的重要手段,健康效益的多器官性和安全性使其具有药物无法替代的良好效果。越来越多的证据表明,肠道菌群与代谢物是运动改善MAFLD的关键靶点。运动不仅能够调节肠道菌群的结构组成,还可重塑菌群间的互作关系,提高肠道微生态稳定性;同时,运动也可调控菌群代谢产物的生成,维持代谢物间的平衡并增强肠道屏障功能。本文就肠道菌群与代谢物失调在MAFLD发生发展中的作用进行总结,并以肠道菌群-代谢物为落脚点阐述运动对MAFLD的保护作用,以期从“肠-肝轴”的层面更好地理解MAFLD的病理机制和运动对MAFLD的防治机理。

关键词:运动;肠-肝轴;肠道菌群与代谢物;代谢功能障碍相关脂肪肝病
中图分类号:G804;Q251;R575.5 **文献标识码**:A

Research progress on the mechanism of exercise improving MAFLD by reshaping gut microbiota and metabolic homeostasis

WU Xin-Miao, LIU Yan, HU Tian, LI Liang-Ming*, YANG Wen-Qi*
(Key Laboratory of Sports Technique, Tactics and Physical Function of General Administration of Sport of China, Guangzhou Sport University, Guangzhou 510500, China)

Abstract: Metabolic-associated fatty liver disease (MAFLD) has become the most prevalent chronic liver disease globally, characterized by complex pathophysiological mechanisms involving multi-organ interactions. The gut microbiota establishes close communication between the gut and liver through pathways such as the biliary tract, portal vein, and systemic circulation. Gut microbiota composition, metabolites, and intestinal barrier integrity all influence the onset and progression of MAFLD. Exercise serves as a vital strategy for preventing and treating MAFLD. Its multi-organ health benefits and safety profile offer unparalleled advantages that cannot be replicated by pharmaceutical interventions. Growing evidence indicates that gut microbiota and metabolites are key targets for exercise-mediated improvement in MAFLD. Exercise not only modulates the structural composition of the gut microbiota but also reshapes microbial interactions and enhances gut microbial stability. Concurrently, exercise regulates the production of microbial metabolites, maintains metabolic balance, and strengthens intestinal barrier function. This article summarizes the role of dysbiosis in gut microbiota and metabolites in the development of MAFLD. It further elucidates the protective effects of exercise on MAFLD by focusing on the gut microbiota-metabolite axis, aiming to enhance our understanding of MAFLDs pathological mechanisms and the preventive and therapeutic mechanisms of exercise at the gut-liver axis level.

Key words: exercise; gut-liver axis; gut microbiota and metabolites; metabolic dysfunction-associated fatty liver disease (MAFLD)

收稿日期:2025-08-07; **修回日期**:2025-11-03
基金项目:广东省自然科学基金面上项目(2023A1515012678)
***通信作者**:E-mail:liliangming@gzsport.edu.cn (李良鸣);shuixianyuhuai@126.com (杨文琦)

代谢相关脂肪性肝病(metabolic dysfunction-associated fatty liver disease,MAFLD)已成为全球最普遍的慢性肝脏疾病,影响着全球约38.77%的人口[1-3]。MAFLD的临床分型包括:代谢相关脂肪肝(MAFLD早期阶段)、代谢相关脂肪性肝炎(metabolic dysfunction-associated steatohepatitis,MASH)、代谢相关脂肪性肝纤维化和代谢相关脂肪性肝硬化,甚至可能发展为肝癌[4]。MAFLD相关肝移植率和病死率持续上升。MAFLD的发病机制复杂,已从传统的"二次打击"学说演变为强调多系统交互作用的"多重打击"学说,其中肠道菌群与代谢物失调可通过"肠-肝轴"加重肝脏代谢紊乱、炎症反应和纤维化程度,是推动MAFLD发展的关键因素之一[5-7]。

运动是防治MAFLD的重要手段。越来越多的证据表明运动对肠道菌群-代谢物介导的生理病理效应均有积极的影响,可通过重塑肠道菌群的结构和互作网络、提高肠道微生态稳定性、调控肠道菌群代谢物和恢复肠道屏障功能等多种机制改善MAFLD。本文系统地阐述了肠道菌群-代谢物失调在MAFLD发生发展中的作用,并从改善肠道菌群失调、调控肠道菌群代谢物和修复肠道屏障受损几个方面总结了运动对MAFLD的保护机制。

1 肠道菌群-代谢物与MAFLD的关系

1.1 肠道菌群-代谢物介导"肠-肝"交流

"肠-肝轴"概念最早由Volta等[8]于1978年提出,定义为肠道与肝脏通过肝门静脉及肠系膜静脉形成的解剖学关联交互系统。随着研究的深入,现阶段"肠-肝轴"被界定为肠道与肝脏间的双向紧密调控关系,主要通过胆道、门静脉、体循环三种方式相互影响:肠道中来自宿主和微生物代谢的内源性底物(如胆汁酸(bile acids,BAs)、氨基酸等)、来自饮食和环境的外源性底物(如药物与添加剂、环境污染与毒素等)以及它们生成的产物通过门静脉转运至肝脏,参与肝脏功能和稳态的调节;而肝脏则通过释放BAs和其他生物活性介质到胆道和体循环以实现与肠道的交流[6]。肠道菌群及其代谢物是"肠-肝轴"的重要组成部分,它们介导的肠道与肝脏间的交流对于维系"肠-肝"稳态平衡至关重要。肠道菌群-代谢物稳态一旦失调,将对MAFLD等肝脏疾病的发生发展和治疗产生深远的影响[9,10]。

1.2 肠道菌群-代谢物失调推动MAFLD发生发展

1.2.1 宿主年龄、病程阶段和研究物种对MAFLD肠道菌群失调的影响

在健康生理情况下,肠道内各种菌群按照一定比例与宿主共生,相互受益并维持肠道生态稳定;然而,当发生MAFLD时,肠道菌群出现明显的结构失衡,且不同宿主年龄、病程阶段和物种的表现并不完全一致[11]。研究表明,出现MAFLD时,肠道菌群多样性显著降低。研究中常用α多样性和β多样性来评价肠道菌群的多样性:肠道菌群α多样性是指某一特定样本内部的菌群多样性,衡量的是样本内的菌群丰富度和均匀度;而肠道菌群β多样性是指不同样本之间的菌群组成差异,用于比较样本间的相似性或差异性[12]。人群研究显示,与健康对照组相比,MAFLD患者的肠道菌群α多样性显著降低,Shannon指数显著下降[13,14]。研究人员评估肠道菌群β多样性,MAFLD患者与健康对照组的肠道菌群组成存在显著差异[13]。动物研究亦表明,相较于正常组,MAFLD小鼠肠道菌群α多样性显著降低,β多样性发生明显改变[15]。

根据门、科、属分类,MAFLD成人患者变形菌门、埃希菌门丰度增加,放线菌门丰度下降;在科水平上,肠杆菌科、毛螺菌科、丹毒科和链球菌科增加,莱克内菌科和瘤胃球菌科减少;在属水平上,粪球菌属、真杆菌属、粪杆菌属增加,嗜胆菌属减少[16]。厚壁菌门和拟杆菌门作为肠道优势菌受到了研究人员的普遍关注,大部分研究表明在成人MAFLD患者中,厚壁菌门丰度增加,而拟杆菌门丰度下降,导致厚壁菌门/拟杆菌门(F/B)比例增加[17,18];但也有少数研究表明拟杆菌数量增加,厚壁菌门相对减少,导致研究中F/B比值降低[16]。上述不一致的研究结果可能与样本大小、年龄差异和诊断标准等因素有关。另外,在MAFLD不同病程阶段,某些菌群丰度会呈现不同的强弱特征[19];例如,当MAFLD未出现明显纤维化时,直肠真杆菌丰度增加,脆弱拟杆菌丰度降低;而发展至明显纤维化病变的MASH阶段时,直肠真杆菌丰度降低,脆弱拟杆菌丰度升高[20]。MAFLD儿童患者肠道菌群结构变化与成人患者相似,但也有其不同之处。其中最为突出的特点是成人MASH患者普雷沃氏菌丰度降低,而儿童MASH患者普雷沃氏菌丰度显著增加;此外,相较于成人患者,MAFLD儿童患者变形菌门、埃希菌门、肠杆菌门

的丰度增加比例更高[21]。儿童的肠道菌群在3岁左右才逐渐形成类似成人的稳定菌群[22]。因此,这些差异可能与儿童饮食结构、代谢发育特点、肠道菌群的发育阶段有关。在动物实验研究中也发现,MAFLD状态下的肠道菌群发生明显变化:MAFLD小鼠厚壁菌门丰度显著增加,而拟杆菌门减少,F/B比例升高[23],但拟杆菌门的变化不如其在人类患者中显著,体现了在MAFLD中人类以拟杆菌门变化为主导,而小鼠则以厚壁菌门增加为特征[24];此外,MAFLD小鼠螺旋状杆菌丰度增加,但在人类MAFLD患者中并未发现此菌有显著变化[25]。人类和实验动物MAFLD肠道菌群的差异反映了物种代谢与疾病驱动机制的差异,在研究和干预MAFLD相关肠道菌群失调时,需考虑宿主年龄、MAFLD病程阶段以及研究模型的差异性。

1.2.2 MAFLD状态下肠道菌群代谢物的改变

肠道菌群代谢产物根据其来源大致可分为3类:(1)肠道菌群分解膳食成分产生的代谢物,例如短链脂肪酸(short-chain fatty acids,SCFAs)、氧化三甲胺等;(2)宿主产生并由肠道菌群修饰的代谢物,主要以次级BAs为主;(3)肠道菌群从头合成的代谢物,例如支链氨基酸(branched-chain amino acids,BCAAs)、多胺、细菌维生素等[26]。这些代谢产物是微生物与宿主间的主要沟通媒介,并与机体一起形成肠道菌群-宿主共代谢物,在调节肠-肝之间相互作用、维持健康生理方面发挥重要的作用[27]。

SCFAs是多糖在肠道菌群作用下分解的代谢产物,其中,乙酸、丙酸和丁酸的含量在机体SCFAs中最为丰富,占比可达90%左右。SCFAs大部分在结肠上段被吸收后通过肠道组织进入门静脉,然后到达肝脏;小部分在结肠下段的乙状结肠和直肠被吸收后,通过下腔静脉进入体循环后也可至肝脏[28-31]。与健康对照人群相比,MAFLD患者某些SCFAs出现差异性变化,例如乙酸和丁酸的相对丰度有所降低,且随着MAFLD病情的加重下降幅度加大[20]。同时,在MAFLD进展至肝硬化阶段时,可测量到粪便中丙酸的绝对含量显著下降,提示肠道菌群代谢活性减弱,这可能与肝功能恶化、微生态失衡有关[32]。

初级BAs在肝脏中由胆固醇转化而成,排入肠道后,在肠道菌群的作用下发生去结合、脱羟、差向异构化,形成次级BAs。次级BAs可被重吸收,经门静脉返回肝脏再利用,形成“肠-肝”循环。MAFLD状态下BAs代谢出现紊乱:由于法尼醇X受体(farnesoid X receptor,FXR)信号通路受到抑制,其对BAs合成限速酶CYP7A1的反馈性抑制减弱,导致肝脏BAs合成增加,循环和粪便中的总BAs水平升高[33];此外,促进初级BAs向次级BAs转化的肠道菌群丰度降低,次级BAs生成率降低,导致初级/次级BAs比例失调。与此同时,MAFLD状态下BAs信号通路亦存在异常:肠道菌群失调造成BAs成分发生改变,尤其是次级BAs生成减少,使FXR和G蛋白偶联胆汁酸受体1(Takeda G-protein-coupled receptor 5,TGR5/GPBAR1)信号通路均被削弱[33-35]。

肠道菌群在蛋白质代谢中也扮演着重要角色,参与芳香族氨基酸(色氨酸、苯丙氨酸)和BCAAs的代谢。色氨酸主要有三条代谢途径,包括:犬尿氨酸(kynurenines,KYN)途径、吲哚途径和5-羟色胺/褪黑激素途径。其中,KYN途径是色氨酸的主要代谢途径。当处于MAFLD状态时,色氨酸代谢发生异常。(1)KYN途径增强:具体表现为MAFLD患者粪便色氨酸水平降低而色氨酸代谢物KYN水平增加,KYN途径相关代谢酶的活性亦增强;此外,与该途径密切相关的肠道菌群柯林斯菌、不动杆菌和放线菌的丰度均有所增加。(2)吲哚途径减弱:其原因主要为产吲哚代谢物的有益菌减少(如梭菌属、乳酸杆菌等),导致吲哚及其衍生物水平降低。(3)5-羟色胺途径增强:MAFLD患者5-羟色胺标志物5-HIAA水平升高[32,36-38]。有证据提示,MAFLD时肠道菌群紊乱可促进苯丙氨酸代谢,使苯丙氨酸代谢物苯乙酸(phenylacetic acid,PAA)生成增多[39]。BCAAs包括亮氨酸、异亮氨酸和缬氨酸,是人体必需氨基酸,由于人体自身无法合成,大部分必须从食物中获取,但少部分也可由肠道微生物群合成。BCAAs在支链氨基酸转移酶(branched chain aminotransferase,BCAT)作用下可逆性地进行转氨基反应,生成支链α酮酸(branched-chain α-keto acids,BCKAs);BCKAs在支链α-酮酸脱氢酶(branched-chain α-ketoacid dehydrogenase,BCKD)复合物的催化下,不可逆地形成支链酰基辅酶A衍生物。支链酮酸脱氢酶激酶(branched chain ketoacid dehydrogenase kinase,BCKDK)和蛋白磷酸酶Mg^{2+}/Mn^{2+}依赖性1K(protein phosphatase,Mg^{2+}/Mn^{2+} dependent 1K,PPM1K)分别通过磷酸化和去磷酸化调控BCKD复合物活性。在MAFLD状态下,BCAAs代谢紊乱,循

环BCAAs水平升高[40,41]。研究提示,肠道菌群结构与功能失调可能是造成BCAAs代谢紊乱的重要原因:一方面具有BCAAs生物合成能力的肠道菌群丰度增加,促进BCAAs的合成;另一方面,肠道菌群失调可能通过诱发慢性炎症反应影响BCKDK和PPM1K的表达和活性,进而降低BCKD复合物活性,削弱BCAAs分解代谢[42]。

1.2.3 肠道菌群-代谢物失调在MAFLD发生发展中的作用

学者们利用同笼饲养和菌群移植实验逐步证实了肠道菌群失调在MAFLD发生发展中的重要作用。2012年,Henao-Mejia等[43]将健康的野生型小鼠和炎症小体相关基因敲除诱导的MAFLD易感小鼠同笼喂养,由于小鼠的食粪性,野生型小鼠也出现了肝脏脂肪变性和肥胖,初步提示肠道菌群可能在MAFLD的发生中起一定作用。在后续的研究中,越来越多的证据表明肠道菌群失调是MAFLD发生发展的重要机制。2013年,Le Roy等[44]利用高脂饮食(high-fat diet,HFD)诱导了两种模型小鼠,这两种小鼠体重的增长量相似,但其中一种小鼠表现出血糖升高和显著的炎症反应,而另一种小鼠血糖正常,炎症反应程度较轻;将这两种小鼠的粪便分别移植至无菌小鼠,无菌小鼠也对应出现了两种表型:肝脏脂肪变性高血糖小鼠与无肝脏脂肪变性正常血糖小鼠,且这两种表型小鼠的肠道菌群存在显著区别。考虑到人和小鼠肠道菌群具有一定区别,2017年,Chiu等[45]对无菌小鼠分别进行MASH患者和健康人群的粪便移植,结果显示,与健康人群粪便移植小鼠相比,移植了MASH患者粪便的小鼠肝脏脂肪变性、炎症反应程度、多灶性坏死均明显增加。2018年,Hoyles等[39]的研究也证实,将MAFLD患者粪便菌群移植至无菌小鼠,会导致被移植小鼠肝脏脂肪变性和肠道菌群出现MAFLD菌群特征。与此同时,学者们还研究了具体有益菌群干预对MAFLD的改善作用。2022年,Hu等[46]证实,给HFD小鼠口服普拉镰刀菌可明显减轻肝脏脂肪变性,降低血清丙氨酸氨基转移酶(alanine aminotransferase,ALT)和天冬氨酸氨基转移酶(aspartate aminotransferase,AST)水平,改善胰岛素抵抗等相关症状,对 MAFLD小鼠起到改善作用。2023年,Nian等[47]和Han等[48]的研究均表明,嗜黏蛋白阿克曼菌可降低肝脏脂质堆积、减少炎症细胞浸润,减轻肠道屏障功能受损程度,进而缓解HFD诱导的MAFLD。

代谢物稳态的破坏是肠道菌群失调推动MAFLD进展的重要原因。在SCFAs方面,MAFLD状态下可出现乙酸、丁酸和丙酸等SCFAs含量的降低。研究表明,乙酸和丁酸具有改善MAFLD的作用[49],且被证实可恢复线粒体功能,减轻氧化应激[50]。与丁酸相比,乙酸在抑制活性氧(reactive oxygen species,ROS)生成方面作用更强,而丁酸则主要通过提高还原型谷胱甘肽的浓度增强抗氧化能力,减轻氧化应激[21,51]。此外,丁酸可有效抑制肠道炎症反应,增强肠道屏障,抑制脂多糖(lipopolysaccharide,LPS)的生成,缓解MAFLD[52,53]。除乙酸和丁酸外,丙酸也被报道具有改善MAFLD的作用。Aron-Wisnewsky等[20]的研究显示,丙酸和丁酸可激活AMPK信号通路,抑制固醇调节元件结合蛋白1c(SREBP-1c)的核转位及DNA结合能力,下调脂肪酸合成酶和乙酰辅酶A羧化酶等脂质生成关键基因的转录活性,减轻肝脏脂肪变性,改善MAFLD。

在BAs方面,MAFLD状态下机体总BAs水平增加,初级/次级BAs比例失衡,FXR和TGR5信号通路有所削减。BAs代谢与信号通路的异常均会加重MAFLD:一方面,BAs代谢失衡与肠道菌群失调相互影响形成恶性循环,加剧脂质代谢紊乱,促进胰岛素抵抗,加重炎症反应和纤维化进展,进而推动MAFLD进程[54];另一方面,FXR和TGR5信号通路的减弱会促进脂质生成、抑制脂肪酸氧化、降低胰岛素敏感性,减少能量消耗,促进NF-κB等促炎信号通路,加重炎症反应,加剧MAFLD病情进展[35,55]。

在芳香族氨基酸(色氨酸、苯丙氨酸)方面,MAFLD状态下的色氨酸代谢出现异常,研究表明异常的色氨酸代谢物可通过促进脂质蓄积、加重炎症反应、促进纤维化等多种机制推动MAFLD进程[56-60]。此外,MAFLD状态下的苯丙氨酸代谢物PAA增多,而研究表明PAA具有抑制胰岛素信号通路和促进肝脏脂肪变性的作用,在推动MAFLD发展中起到一定的作用[39]。

关于BCAAs,其在MAFLD中表现出较复杂的作用机制。部分研究表明,尽管BCAAs可减少HFD动物体重与脂肪质量,降低肝脏甘油三酯(triglyceride,TG)含量,但这是以脂肪组织的异常脂解以及其引发的高脂血症和肝脂毒性为代价的;此外,BCAAs和其代谢物BCKAs可抑制肝细胞自噬、

损害胰岛素信号并促进炎症反应,推动MAFLD进展[42,61]。但也有研究显示,BCAAs可抑制肝细胞凋亡或作用于肝星状细胞发挥抗纤维化效应[62,63],还可能通过调节肠道菌群缓解MAFLD:(1)BCAAs可促进HFD大鼠瘤胃球菌的生长和乙酸的产生,进而降低肝脏脂质积蓄[64];(2)BCAAs可增加肠道菌群多样性、促进肠道菌群重构,增加与MAFLD指标呈负相关的菌群丰度(戈登氏菌属、拟杆菌属、副拟杆菌属),降低与MAFLD呈正相关的菌群丰度(弯曲杆菌属),改善MAFLD[65]。造成上述研究结论差异的可能原因如下:首先,各研究所使用的实验模型和关注的疾病阶段不尽相同;其次,BCAAs主要通过口服的方式予以干预,对肠道菌群的影响较大,而BCAAs和肠道菌群间存在着复杂的相互作用。因此,在后续BCAAs对MAFLD作用的研究中需充分考虑肠道菌群的作用。

2 运动通过改善肠道菌群-代谢物失调减轻MAFLD

运动是MAFLD防治的主要手段。近年来,越来越多的研究表明运动可通过恢复肠道菌群稳态从而对MAFLD产生积极的影响[66-68]。首先,运动能够调节肠道菌群的多样性和结构,增强菌群间的互作网络与生态稳定性;其次,运动可影响肠道菌群的代谢产物;此外,运动还可通过肠道菌群-代谢物强化肠道屏障功能,减少LPS等促炎物质从肠道进入体循环并转移至肝脏,从而改善MAFLD (图1)。

2.1 运动调节肠道菌群结构、重构菌群互作网络、提高肠道微生态稳定性, 改善MAFLD

Cheng等[67]的人群研究表明,与非运动组相

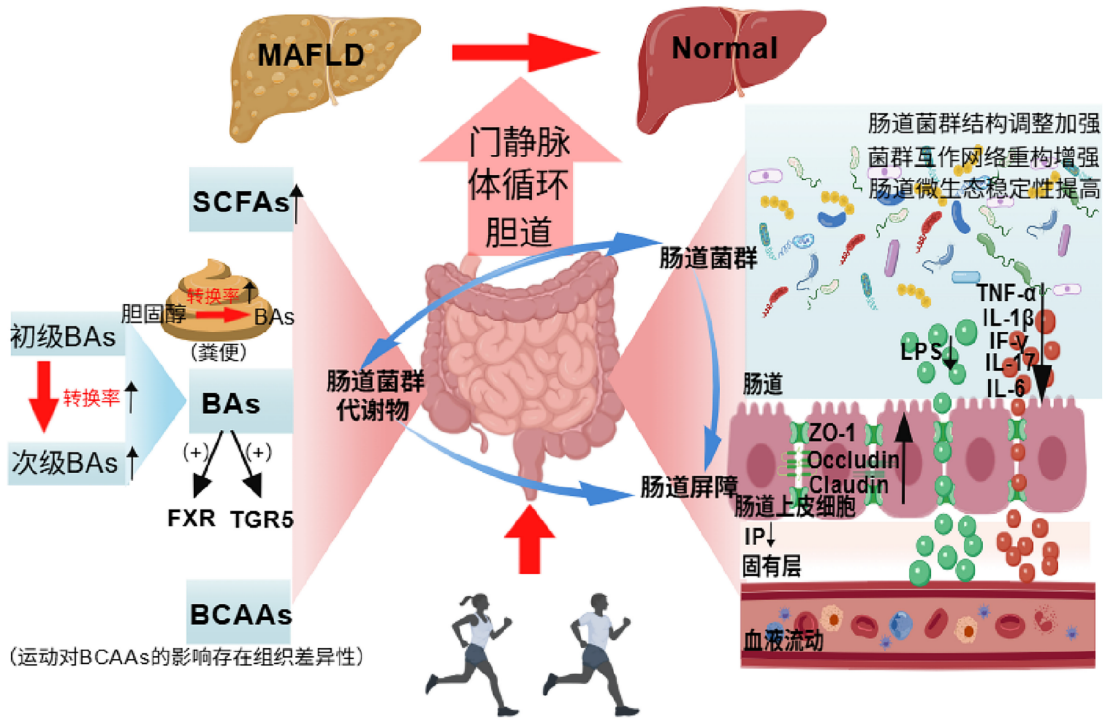

图1 运动通过调节肠道菌群及其代谢物和肠道屏障改善MAFLD

"↑"表示升高,"↓"表示降低,"+"表示激活。短链脂肪酸(short-chain fatty acids,SCFAs);支链氨基酸(branched-chain amino acids,BCAAs);胆汁酸(bile acids,BAs);肠道通透性(intestinal permeability,IP);紧密连接蛋白(ZO-1、Claudin、Occludin);脂多糖(lipopolysaccharide,LPS);肿瘤坏死因子α(tumor necrosis factor-α,TNF-α);干扰素γ(interferon-γ,IFN-γ);白介素-1β(interleukin-1β,IL-1β);白介素-6(interleukin-6,IL-6);白介素-17(interleukin-17,IL-17)。

Figure 1 Exercise improves MAFLD by regulating gut microbiota, metabolites, and the intestinal barrier

"↑" indicates an increase, "↓" indicates a decrease, and "+" indicates activation. Short-chain fatty acids (SCFAs); Branched-chain amino acids (BCAAs); Bile acids (BAs); Intestinal permeability (IP); Tight junction proteins (ZO-1, Claudin, Occludin); Lipopolysaccharide (LPS); Tumor necrosis factor-α (TNF-α); Interferon-γ (IFN-γ); Interleukin-1β (IL-1β); Interleukin-6 (IL-6); Interleukin-17 (IL-17).

比，有氧运动（持续8.6个月，每周2~3次，每次30~60 min，60%~75%的VO_2max）干预可上调MAFLD患者肠道菌群α多样性。Imdad等[69]的动物实验结果显示，渐进式跑台运动（12周，每周5天，每次训练1 h，中等强度）能显著改变HFD小鼠肠道菌群β多样性。然而，有研究表明，肥胖女性受试者在耐力运动（6周，每周3次，每次训练60 min）干预后，其肠道菌群的α多样性和β多样性均未发生显著变化[70]。同样，一项12 周个体化高强度间歇训练（high-intensity interval training，HIIT）研究也表明，虽然运动可以降低MAFLD患者肝内脂质含量，但对肠道菌群α和β多样性没有显著影响[68]。上述结果的不一致性可能与运动类型、运动强度及研究模型等因素有关。

运动已被证实可从多个层面调节肠道菌群，改善MAFLD。在MAFLD状态下，肠道菌群在门、纲、属层面会发生改变，而运动则起到调节作用：在门层面，运动显著减少厚壁菌门相对丰度并增加拟杆菌门相对丰度，抑制HFD诱导的F/B比率升高；此外，运动还可下调变形菌门的比例[24,66]。拟杆菌具有减轻炎症反应、维持肠道屏障和激活FXR受体调节BAs代谢的作用[71]。运动下调F/B比率有利于抑制炎症反应，减少肝脏脂质聚集，进而改善MAFLD。在纲层面，运动上调α-变形菌纲和β-变形菌纲的相对丰度；在属层面，运动上调杜氏杆菌属、副拟杆菌属和瘤胃球菌属的相对丰度，下调梭菌属和粪便拟杆菌属的相对丰度[66,67]。杜氏杆菌属是改善MAFLD的关键菌属。已有研究表明，有氧运动通过FGF21上调杜氏杆菌属丰度，进而减轻MAFLD的脂质积累，改善MAFLD[72]。

了解单一菌种的变化已不能满足当下的研究需要，越来越多的研究人员着眼于宏观层面，对菌群间的相互作用和肠道微生态进行评估，他们发现运动可重塑菌群互作网络并增强肠道微生态稳定性。Csader等[68]利用宏基因组学分析了12周HIIT对MAFLD患者肠道菌群的影响，结果显示：运动使菌群产生了18个新的正关联和17个新的负关联，表明运动改变了菌群间的互作关系。Cheng等[67]对MAFLD患者进行了8.6个月的运动干预，并采用共丰富组（co-abundance group，CAG）对微生物生态系统中的群落结构进行分析；该研究定义了35个CAG，并以此构建了微生物共现网络，发现运动能够提高肠道微生态系统稳定性。以上研究结果表明，运动对MAFLD患者肠道菌群的积极影响不仅是改变单一结构，更是提高整个菌群网络系统的稳定性。

运动是MAFLD防治的重要手段，对MAFLD的改善效果也具有明显的个体差异性。“运动响应”的关键因素对于MAFLD等慢病的运动防治具有重要的意义。现阶段越来越多的证据显示，肠道菌群的结构、互作以及功能是“运动响应”的重要影响因素。上述Csader等[68]还比较了运动响应者（12周运动干预后肝内脂质降低）和运动非响应者（12周运动干预后肝内脂质并未发生改变）肠道菌群结构、互作以及功能上的不同：在菌群结构方面，尽管两者肠道菌群α和β多样性未发生明显改变，但与运动非响应者相比，运动响应者多形拟杆菌相对丰度降低，粪便拟杆菌相对丰度升高；在菌群互作方面，响应者菌群互作形成16个新的关联，而18个原有的关联消失；在菌群功能方面，他们对菌群模块、功能和临床参数进行了关联分析，结果表明响应者菌群网络可分解为与不同临床指标相关的3个模块，在这3个模块中对临床指标影响最大的菌群分别是多雷拟杆菌（模块1）、粪拟杆菌和解纤维素拟杆菌（模块2）以及粪便拟杆菌和光冈链杆菌（模块3），它们与L-谷氨酸和L-谷氨酰胺的合成、甲醇氧化、甲基柠檬酸循环、异型乳酸发酵和嘧啶脱氧核糖核苷酸生物合成等微生物通路相关，影响AST、TG和饱和脂肪酸等临床参数。其中，甲醇氧化和丙氨酸发酵通路与临床改善相关性最高。多尔拟杆菌和粪便拟杆菌与甲醇氧化通路呈负相关，提示它们可能通过抑制该通路促进代谢健康。这项研究表明，菌群结构、互作关系和菌群功能可能是造成MAFLD患者运动响应和非响应的原因之一。与此相似，Liu等[73]发现运动响应者肠道菌群的SCFAs合成及BCAAs分解功能增强，SCFAs有益代谢产物增加，而非响应者则无上述菌群功能及代谢产物变化；把“运动响应者”与“非响应者”的粪菌分别移植给经抗生素处理的HFD肥胖小鼠，研究发现仅接受“响应者”菌群的小鼠葡萄糖耐量、肝脏胰岛素敏感性出现改善，肝脂质沉积减少，而接受“非响应者”菌群的小鼠无此效应，从而证明了能否实现运动的健康效应与肠道菌群的功能性密切相关。

关于运动对MAFLD肠道菌群多样性影响的研

究虽然未取得一致的结果,但绝大多数的研究显示运动可通过调节肠道菌群改善MAFLD(表1)。基于现代技术的发展,对于运动如何改善MAFLD肠道菌群可从以下两方面深入探讨:一是从微观的层面阐明受运动调控的对MAFLD产生积极作用的具体菌群和机制,二是从宏观的层面研究运动对菌群生态系统的作用。同时,还应考虑到运动强度、运动类型、运动持续时间、MAFLD病程阶段等因素的影响。

2.2 运动调节肠道菌群代谢物改善MAFLD

运动已被证实可调节MAFLD相应肠道菌群代谢物,目前相关研究主要集中于SCFAs、BAs和BCAAs。

2.2.1 运动调节SCFAs生成

在正常生理条件下,运动促进乙酸、丙酸和丁酸等SCFAs的生成。这些SCFAs在调节能量代谢和全身免疫反应中发挥关键作用[77]。在MAFLD状态下,肠道菌群失调导致SCFAs水平发生改变,主要表现为粪便和血清中乙酸和丁酸水平降低。SCFAs失衡反过来又可加重炎症反应、氧化应激和肝脏脂质的蓄积,促进MAFLD的发展[49,78]。目前大部分研

表1 运动调节MAFLD肠道菌群组成

Table 1 Exercise modulates the composition of the gut microbiome in patients with MAFLD

发表年份	研究对象	运动方式	运动对肠道菌群的影响	参考文献
2019	雄性Wistar大鼠经6周HFD诱导构建的早期肥胖-MAFLD模型	F:5天/周,持续5周 I:中等强度(约65%~70% VO_2max) T:60 min/次 Type:跑台有氧运动	门:疣微菌门↓、厚壁菌门↓ 纲:芽孢杆菌纲↓ 属:副拟杆菌属↑、拟杆菌属↑、黄杆菌属↑、嗜碱杆菌属↑、梭状芽孢杆菌属↓	Carbajo-Pescador等[66]
2021	雄性Sprague-Dawley大鼠经10周HFD诱导构建的MAFLD模型	F:5天/周,持续8周 I:中等强度(约65%~70% VO_2max) T:60 min/次 Type:跑台有氧运动	门:拟杆菌门↑、变形菌门↓、厚壁菌门↓	Gao等[24]
2022	115名经活检证实的MAFLD合并糖尿病前期患者	F:3次/周,为期8.6个月 I:中等强度(约65%~70% VO_2max) T:30~60 min/次 Type:有氧运动为主(如快走、慢跑、骑自行车)+抗阻运动辅助(如哑铃、弹力带训练)	纲:α-变形菌纲↑、β-变形菌纲↑ 属:杜氏杆菌属↑、副拟杆菌属↑、瘤胃球菌属↑、拟杆菌属↑、梭菌属↓	Cheng等[67]
2023	39名经活检证实的MAFLD患者	F:3次/周,持续12周 I:中等强度(约55%~75% VO_2max) T:45~60 min/次 Type:有氧运动(如步行、慢跑,为患者可耐受的常见类型)	种:粪便拟杆菌↑、粪球菌↑、甲酸生成多尔氏菌↑、艾森贝格氏菌↑、产气普雷沃菌↑、乳酸乳球菌↑、纤维分解拟杆菌↑、多形拟杆菌↓、嗜酸乳杆菌↓	Csader等[68]
2023	8周龄雄性C57BL/6J小鼠经18周HFD诱导构建的肥胖-MAFLD模型	F:5次/周,持续18周 I:中等强度(约65%~75% VO_2max) T:60 min/次 Type:跑台有氧运动	属:杜氏杆菌属↑	Ye等[72]
2024	*APOE*3-Leiden.CETP*雄性小鼠经12周高脂-高胆固醇饮食诱导构建的MAFLD模型	F:5次/周,持续8周 I:中等强度(约65%~70% VO_2max) T:60 min/次 Type:跑台有氧运动	科:毛螺菌科↑ 属:理研菌属↑ 种:嗜黏蛋白阿克曼菌↑	Kovynev等[74]
2025	*APOE*3-Leiden.CETP*雄性小鼠经12周高脂-高胆固醇饮食诱导构建的MAFLD模型	F:5次/周,持续12周 I:中等强度(约65%~70% VO_2max) T:60 min/次 Type:跑台有氧运动	属:毛螺菌属↑、瘤胃球菌属↑ 种:嗜黏蛋白阿克曼菌↑	Kovynev等[75]
2025	8周龄雄性C57BL/6J小鼠经16周HFD诱导构建的MAFLD模型	F:5次/周,持续8周 I:中等强度(约65%~75% VO_2max) T:60 min/次 Type:递增负荷跑台有氧运动	门:厚壁菌门↓ 属:异杆菌属↑、纤维杆菌属↓、普雷沃菌属↓、奈瑟菌属↓、链球菌属↓ 种:嗜黏蛋白阿克曼菌↑	Zhang等[76]

注:"↓"表示菌群的相对丰度降低,"↑"表示菌群的相对丰度增加;MAFLD,metabolic dysfunction-associated fatty liver disease,代谢功能障碍相关脂肪肝病;F,frequency,频率;I,intensity,强度;T,time,时间;Type,类型。

Note: "↓" indicates a decrease in the relative abundance of a microbial community, while "↑" indicates an increase; Metabolic dysfunction-associated fatty liver disease (MAFLD); Frequency (F); Intensity (I); Time (T).

究表明,运动可提高MAFLD等肥胖相关慢病状态下SCFAs的含量,这是运动改善MAFLD的机制之一。Gao等[24]的研究证实,有氧运动(连续8周,每周5次,每次30 min, 60%~70% VO_2max)在显著减少HFD小鼠肝脏TG、总胆固醇(total cholesterol,TC)的同时,明显提高粪便乙酸、丁酸、戊酸水平。与此一致,Yu等[79]的研究也显示,有氧运动(为期8周,每周5次,每次60 min, 60% VO_2max)可显著提高HFD小鼠粪便丁酸水平。然而,Allen等[80]的研究表明,每周3次、每次30~60 min、强度从中等(60%心率储备)到高强度(75%心率储备)、持续6周的有氧运动可提高正常体重人群粪便SCFAs水平,对肥胖人群(BMI>30 kg·m^{-2})SCFAs却无显著影响。Carbajo-Pescador等[66]亦报道运动促进正常饮食大鼠SCFAs生成,HFD则会削弱该作用。由此可见,BMI和饮食状况会影响运动对SCFAs的作用。运动对肥胖和正常体重MAFLD患者的SCFAs生成是否有不同作用,利用运动提高SCFAs水平防治MAFLD是否需考虑饮食因素,这些问题都有待进一步研究。研究发现,运动提高SCFAs水平的主要原因是运动增加了相应的产SCFAs菌群的丰度,如嗜黏蛋白阿克曼菌和肠杆菌是产生丁酸的必要菌群[75,81]。运动还能促进其他产SCFAs菌群,如拟杆菌属、毛螺菌属和罗斯氏菌属的生长[82]。此外,运动时肌肉产生的乳酸可通过体循环进入肠道,在肠道中被丙酸杆菌和韦荣氏球菌等菌群转化为丙酸或其他SCFAs,这一转化过程不仅减少肠道中乳酸的积累,还促进丙酸等SCFAs的产生[83,84]。如前文所述,运动增加的乙酸、丁酸等SCFAs具有抑制炎症反应、减轻氧化应激和抑制脂质合成的作用,有助于防治MAFLD。

2.2.2 运动调节BAs代谢

急性运动干预可降低正常人群循环总BAs以及去氧胆酸、牛磺去氧胆酸、甘氨去氧胆酸等次级BAs水平[85,86]。不同运动方式对BAs的作用也不尽相同。Morville等[87]比较了急性抗阻运动和急性耐力运动对血浆BAs的影响,结果表明抗阻运动下调初级BAs胆酸、鹅去氧胆酸和熊去氧胆酸水平,而耐力运动下调初级BAs牛磺鹅去氧胆酸,上调DCA。目前长期运动对正常人BAs的影响尚未阐明,有待进一步研究。

在MAFLD状态下,肝脏和粪便总BAs含量增加;而且由于肠道菌群发生改变,尤其是促进初级BAs向次级BAs转化的肠道菌群丰度降低,导致BAs代谢谱发生改变,初级BAs向次级BAs的转换率明显降低[88]。此外,BAs FXR和TGR5信号通路被抑制。肠道菌群失调、BAs代谢紊乱和BAs信号通路异常相互影响[89],加重MAFLD病情。运动被证实有助于调节MAFLD BAs水平。Shi等[90]分析了8周有氧运动、抗阻运动和有氧联合抗阻运动对MAFLD患者BAs水平的影响,其研究结果显示:有氧运动在改善MAFLD的同时可上调总BAs水平,并上调血清初级BAs TCA、甘氨鹅去氧胆酸、甘胆酸和次级BAs UDCA、牛磺熊去氧胆酸水平;抗阻运动并未表现出对BAs的明显影响;有氧联合抗阻运动可上调BAs TCA、UDCA、TUDCA水平。Babu等[91]则报道12周HIIT显著降低MAFLD患者脂肪组织和尿液中的BAs水平。上述研究结果提示,不同类型的运动对机体不同组织BAs水平的影响并不相同。

现阶段,关于运动如何调控BAs代谢仍未完全阐明,但已取得部分研究结果;动物研究显示,运动可增加BAs的分泌和粪便排泄[92,93]。机体过剩的胆固醇可转化为BAs随粪便排出体外,提高BAs的分泌和粪便排泄可能是运动降低胆固醇水平改善MAFLD的重要机制。值得注意的是,由于运动促进BAs的粪便排泄,机体可能增加BAs的合成以维持BAs量的平衡,但目前关于运动对BAs合成的影响存在分歧。部分研究表明,运动通过上调BAs合成限速酶CYP7A1的表达增加BAs的合成[94-96]。然而,其他研究显示,运动对BAs合成关键基因CYP7A1、CYP8B1和CYP27A1的表达并无显著影响[93,97]。对于运动是否调控BAs合成仍需进一步研究,在研究时需考虑运动类型、运动时间、膳食等因素的影响。除了增加BAs的分泌和排泄外,运动还可改变BAs的代谢谱。Carbajo-Pescador等[66]利用HFD诱导MAFLD模型,发现与HFD无运动组相比,HFD运动组小鼠粪便代谢物(BAs、SCFAs和氨基酸等)出现明显异质性。Ortega-Santos等[98]的研究则表明,运动可上调促进初级BAs向次级BAs转化的关键菌瘤胃球菌的丰度,进而升高次级BAs的浓度。大部分次级BAs属于疏水性BAs,较难被重吸收,容易随粪便排泄。综上所述,运动可通过促进疏水性次级BAs的生成,增加BAs的粪便排泄,进而促使胆固醇转化为BAs排出体外,降低机体胆固醇含量,这可能是运动减轻MAFLD的重要机制。

运动已被证实可减轻MAFLD状态下BAs信号通路异常,恢复BAs-FXR/TGR5通路的激活。研究表明,运动增强FXR和TGR5通路的激活主要依靠以下机制。(1)优化肠道菌群,改变BAs池的组成和比例:不同BAs对FXR的活化作用并不相同,在MAFLD状态下,对FXR有激活作用的CDCA水平升高,而对FXR起拮抗作用的DCA水平下降,使FXR信号通路处于抑制状态[54]。运动可调整MAFLD菌群结构进而影响BAs的组成。尽管现阶段有关运动对CDCA的影响仍无明确定论,但已有证据显示,运动可降低DCA水平[85]。这提示运动可能通过调节肠道菌群优化Bas中FXR激动剂/拮抗剂的比例,进而解除对FXR信号通路的抑制。另一方面,运动使具有更高胆汁盐水解酶和羟基类固醇脱氢酶活性的菌群丰度增加,增强了初级BAs向次级BAs转化的能力[98]。次级Bas石胆酸和DCA是TGR5的强效激动剂,次级BAs生成的增多促进了TGR5信号通路的激活。(2)促进FXR和TGR5的表达:多项研究表明长期运动不但增加健康状态下FXR的表达,还提高MAFLD、糖尿病等慢性代谢性疾病状态下FXR的水平[99-101]。已有研究表明,急性运动促进TGR5的表达[102],而长期运动对MAFLD状态下TGR5表达的影响仍有待进一步研究。鉴于FXR和TGR5信号通路可改善糖脂代谢和减轻炎症反应,运动可能通过BAs-FXR/TGR5通路改善MAFLD。

2.2.3 运动调节BCAAs水平

已有研究提示运动或可通过调节肠道菌群BCAAs代谢改善MAFLD。Shi等[103]分析了中等强度运动(12个月快走,每周5天,每次30 min, 45%~55%的最大心率)和高中强度交替运动(前6个月慢跑、后6个月快走,慢跑为65%~80%的最大心率)MAFLD患者循环BCAAs水平和肝脏脂质含量的关系,发现循环BCAAs(尤其是亮氨酸和缬氨酸)下降幅度越大,肝脏脂质含量下降幅度也越大,且BCAAs水平变化与肝脂质含量变化的关联强度在不同运动组间并无差异,这提示不同强度的运动均可通过改善BCAAs代谢减轻MAFLD。Babu等[91]则报道,12周的HIIT可显著上调MAFLD患者脂肪组织亮氨酸水平,且脂肪组织亮氨酸水平的提高与腰围的减少呈正相关。值得注意的是,Vanweert等[104]的研究显示,渐进式有氧和阻力运动相结合(持续12周,每周3次,每次30~60 min)可降低MAFLD患者肝脏脂质含量,但对循环BCAAs水平并无显著影响。上述研究在运动对MAFLD BCAAs水平的影响、BCAAs水平的变化与临床指标的关联方面未取得一致的结果,可能与BCAAs组织效应的差异性、运动类型和剂量的区别有一定关系。Liu等[73]还发现,与运动非响应者相比,运动响应者肠道菌群BCAAs的分解功能增强;此外,仅接受"响应者"菌群的小鼠出现糖脂代谢改善。这提示运动或可通过改善肠道菌群功能,促进BCAAs分解,进而减轻MAFLD。因此,运动对肠道菌群代谢物BCAAs的调节机制及其在改善MAFLD中的作用仍需进一步研究,且需考虑运动类型、组织效应等因素的影响。

2.3 运动增强肠道屏障功能改善MAFLD

肠道屏障由机械屏障(肠道黏膜上皮细胞、细胞间紧密连接和黏液层)、化学屏障(胃酸、胆汁、消化酶等)、免疫屏障(肠道相关淋巴组织、免疫细胞和免疫分子)和生物屏障(肠道菌群)构成,是一个结构复杂且功能强大的选择性屏障,对保护人体免受微生物和毒素的入侵、吸收机体必要的营养物质起到重要的作用。肠道菌群是肠道屏障的重要组成部分[105-108],而LPS在肠道菌群紊乱介导肠道屏障受损推动MAFLD发生发展中发挥着关键的作用。当肠道菌群失调时,有益菌对肠道屏障的保护作用被削弱,某些致病菌(如大肠杆菌、沙门氏菌)释放的毒素或诱发的炎症反应可破坏肠道屏障同时导致LPS生成增多。肠道屏障完整性的破坏会导致LPS转移到体循环和肝脏,进入肝脏的LPS与其结合蛋白形成复合体,激活TLR4并将信号传递到下游分子,促进Kupffer细胞活化进而产生促炎细胞因子(TNF-α、IL和IFN-γ),推动MAFLD的发展[109,110]。

MAFLD常伴随肠道屏障功能下降,表现为:肠道壁组织形态发生改变,肠绒毛形态和排列异常,肠隐窝深度增加,肠黏膜受损,紧密连接蛋白ZO-1、Claudin-1和Occludin表达降低;固有层出现炎症细胞浸润,LPS和炎症因子生成增多;以及肠道菌群紊乱[24,66]。适度运动已被证明可有效增强肠道屏障功能。研究人员在HFD诱导的MAFLD大鼠模型中发现,运动可恢复肠道壁正常组织形态,改善肠绒毛和肠隐窝结构,上调紧密连接蛋白ZO-1、Claudin-1和Occludin的表达;运动还明显减少肠固有层炎症细胞浸润,下调TNF-α和IL-6等炎症因子表达,降低

LPS等促炎物质的生成[24,66]；除了增强机械屏障外，运动亦可增强肠道生物屏障，表现为运动上调乳酸菌、双歧杆菌和植物乳杆菌等有益菌的丰度，同时降低肠道中拟杆菌的相对丰度[66,111,112]。

适度运动有利于肠道屏障的恢复。相反，有研究显示高强度运动会破坏紧密连接，损害肠道屏障，增加肠道通透性[113-116]。研究人员使用雄性C57BL/6小鼠的过度训练模型证实，剧烈运动会加剧肠道炎症、破坏肠道菌群完整性，并增强肠壁通透性[117]。人群干预实验亦证实，HIIT可增强男性跑步者肠壁通透性和肠道脂肪酸结合蛋白的释放，破坏肠道屏障功能[118]。因此，在利用运动改善MAFLD肠道屏障功能时，运动强度的精准把控至关重要。

2.4 菌群移植实验为运动改善MAFLD提供佐证

上述大量研究已证实运动减轻MAFLD的同时，伴随对肠道菌群结构的优化、代谢物的调整和肠道屏障的修复，但其间的因果关系尚需进一步论证。菌群移植实验可为运动通过优化肠道生态改善MAFLD提供更为直接的证据，然而现阶段相关研究很少。Kovynev等[74]将运动小鼠的粪便和非运动对照小鼠的粪便分别植入抗生素处理的MAFLD小鼠，他们发现：与移植非运动小鼠粪便组相比，移植运动小鼠粪便可显著降低肝体重比；移植运动小鼠粪便组的MAFLD评分和肝脂质油红O染色也显示出改善趋势，但未达到运动供体小鼠水平。此外，移植运动小鼠粪便对MAFLD的改善效果出现显著个体差异。根据肝脏TG和MAFLD评分可将移植运动小鼠粪便组进一步分为响应者和非响应者，结果表明，响应者的菌群组成更接近运动供体小鼠。此项研究证实了运动改善MAFLD部分是通过优化菌群结构实现的。除上述Kovynev等的研究外，已有研究人员利用菌群移植实验证实了调整肠道菌群结构及其代谢物(SCFAs、BCAAs)在运动降低体重、改善血脂、减轻胰岛素抵抗和减少异位脂肪蓄积等MAFLD相关风险中的作用[73,119]。

3 结论与展望

肠道菌群失调及其相应代谢物的改变在MAFLD发生发展中发挥重要作用。运动防治MAFLD与其对肠道菌群-代谢物和肠道屏障功能的调控密不可分。随着研究的深入，学者们发现运动不仅可调控MAFLD肠道菌群结构，还对菌群互作、肠道微生态稳定性产生积极影响。然而，现阶段相关研究仍存在一定缺陷：(1)运动对肠道菌群及其代谢物的调节和运动对MAFLD的改善作用的因果关系尚未完全明确，目前研究多停留于相关性分析，缺乏因果验证；(2)研究提示不同运动类型(有氧、抗阻、HIIT 等)和不同运动剂量(频率、强度、时长)对肠道菌群的影响不尽相同，目前尚缺乏系统性的随机对照实验来比较其效应差异，并制定合理的运动处方；(3)宿主个体因素(如遗传背景、饮食、BMI)是否与肠道菌群特征相互影响进而干扰运动疗效仍有待阐明；(4)目前多采用HFD诱导的MAFLD动物模型研究运动对MAFLD肠道菌群的影响，但不同物种间在菌群结构、代谢特点和菌群-宿主互作机制上存在差异，导致在疾病或运动干预状态下出现不同的菌群变化，例如，在MAFLD中人类以拟杆菌门变化为主，而小鼠则以厚壁菌门增加为特征。为减少临床转化风险，需谨慎解读动物模型结论，强化动物实验结果在人群研究中的验证。

参考文献

[1] Eslam M, Sanyal AJ, George J, et al. MAFLD: a consensus-driven proposed nomenclature for metabolic associated fatty liver disease. Gastroenterology, 2020, 158: 1999–2014.

[2] Eslam M, Newsome PN, Sarin SK, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol, 2020, 73: 202–9.

[3] Chan KE, Koh TJL, Tang ASP, et al. Global prevalence and clinical characteristics of metabolic-associated fatty liver disease: a meta-analysis and systematic review of 10 739 607 individuals. J Clin Endocrinol Metab, 2022, 107: 2691–700.

[4] Fan JG, Xu XY, Yang RX, et al. Guidelines for the prevention and treatment of metabolic dysfunction-associated (non-alcoholic) fatty liver disease (Version 2024). Chin J Hepatol, 2024, 32: 418–34.

[5] Wang W, Li Q, Chai WH, et al. *Lactobacillus paracasei* Jlus66 extenuate oxidative stress and inflammation via regulation of intestinal flora in rats with non alcoholic fatty liver disease. Food Sci Nutr, 2019, 7: 2636–46.

[6] Hsu CL, Schnabl B. The gut-liver axis and gut microbiota in health and liver disease. Nat Rev Microbiol, 2023, 21: 719–33.

[7] Fernandez CJ, Nagendra L, Pappachan JM. Metabolic

dysfunction-associated fatty liver disease: an urgent call for global action. touchREV Endocrinol. 2024, 20: 5–9.

[8] Volta U, Bonazzi C, Bianchi FB, et al. IgA antibodies to dietary antigens in liver cirrhosis. Ric Clin Lab, 1987, 17: 235–42.

[9] Albillos A, de Gottardi A, Rescigno M. The gut-liver axis in liver disease: pathophysiological basis for therapy. J Hepatol, 2020, 72: 558–77.

[10] Dongoran RA, Tu FC, Liu CH. Current insights into the interplay between gut microbiota-derived metabolites and metabolic-associated fatty liver disease. Tzu Chi Med J, 2023, 35: 290–9.

[11] Safari Z, Gérard P. The links between the gut microbiome and non-alcoholic fatty liver disease (NAFLD). Cell Mol Life Sci, 2019, 76: 1541–58.

[12] Tsiavos A, Antza C, Trakatelli C, et al. The microbial perspective: a systematic literature review on hypertension and gut microbiota. Nutrients, 2024, 16: 3698.

[13] Huang FR, Lyu B, Xie FC, et al. From gut to liver: unveiling the differences of intestinal microbiota in NAFL and NASH patients. Front Microbiol, 2024, 15: 1366744.

[14] Cai WP, Qiu T, Hu WT, et al. Changes in the intestinal microbiota of individuals with non-alcoholic fatty liver disease based on sequencing: an updated systematic review and meta-analysis. PLoS One, 2024, 19: e0299946.

[15] Carter JK, Bhattacharya D, Borgerding JN, et al. Modeling dysbiosis of human NASH in mice: loss of gut microbiome diversity and overgrowth of *Erysipelotrichales*. PLoS One, 2021, 16: e0244763.

[16] Jadhav K, Cohen TS. Can you trust your gut? Implicating a disrupted intestinal microbiome in the progression of NAFLD/NASH. Front Endocrinol (Lausanne), 2020, 11: 592157

[17] Abdollahiyan S, Nabavi-Rad A, Keshavarz Azizi Raftar S, et al. Characterization of gut microbiome composition in Iranian patients with nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. Sci Rep, 2023, 13: 20584.

[18] Lee NY, Shin MJ, Youn GS, et al. *Lactobacillus* attenuates progression of nonalcoholic fatty liver disease by lowering cholesterol and steatosis. Clin Mol Hepatol, 2021, 27: 110–24.

[19] Wang RR, Li H, Yang X, et al. Genetically obese human gut microbiota induces liver steatosis in germ-free mice fed on normal diet. Front Microbiol, 2018, 9: 1602.

[20] Aron-Wisnewsky J, Vigliotti C, Witjes J, et al. Gut microbiota and human NAFLD: disentangling microbial signatures from metabolic disorders. Nat Rev Gastroenterol Hepatol, 2020, 17: 279–97.

[21] Zhu L, Baker SS, Gill C, et al. Characterization of gut microbiomes in nonalcoholic steatohepatitis (NASH) patients: a connection between endogenous alcohol and NASH. Hepatology, 2013, 57: 601–9.

[22] Akagawa S, Kaneko K. Gut microbiota and allergic diseases in children. Allergol Int, 2022, 71: 301–9.

[23] Mouzaki M, Comelli EM, Arendt BM, et al. Intestinal microbiota in patients with non-alcoholic fatty liver disease. Hepatology, 2013, 58: 120–7.

[24] Gao LL, Ma JM, Fan YN, et al. *Lycium barbarum* polysaccharide combined with aerobic exercise ameliorated nonalcoholic fatty liver disease through restoring gut microbiota, intestinal barrier and inhibiting hepatic inflammation. Int J Biol Macromol, 2021, 183: 1379–92.

[25] Effenberger M, Grander C, Grabherr F, et al. Nonalcoholic fatty liver disease and the intestinal microbiome: an inseparable link. J Clin Transl Hepatol, 2023, 11: 1498–507.

[26] Yang WJ, Cong YZ. Gut microbiota-derived metabolites in the regulation of host immune responses and immune-related inflammatory diseases. Cell Mol Immunol, 2021, 18: 866–77.

[27] Schroeder BO, Bäckhed F. Signals from the gut microbiota to distant organs in physiology and disease. Nat Med, 2016, 22: 1079–89.

[28] Canfora EE, Jocken JW, Blaak EE. Short-chain fatty acids in control of body weight and insulin sensitivity. Nat Rev Endocrinol, 2015, 11: 577–91.

[29] Zhang BB, Zhou GC, Li C. AMPK: an emerging drug target for diabetes and the metabolic syndrome. Cell Metab, 2009, 9: 407–16.

[30] Hays KE, Pfaffinger JM, Ryznar R. The interplay between gut microbiota, short-chain fatty acids, and implications for host health and disease. Gut Microbes, 2024, 16: 2393270.

[31] Doan TNM, Maruyama D, Tian X, et al. Sequential blood collection from inferior vena cava followed by portal vein to evaluate gut microbial metabolites in mice. J Vis Exp, 2024, (208): 66673.

[32] Reshetova M, Markin P, Appolonova S, et al. Tryptophan metabolites in the progression of liver diseases. Biomolecules, 2024, 14: 1449.

[33] Zhang MY, Xiao BY, Chen XQ, et al. Physical exercise plays a role in rebalancing the bile acids of

enterohepatic axis in non-alcoholic fatty liver disease. Acta Physiol (Oxf), 2024, 240: e14065.

[34] Wang BB, Han D, Hu XY, et al. Exploring the role of a novel postbiotic bile acid: interplay with gut microbiota, modulation of the farnesoid X receptor, and prospects for clinical translation. Microbiol Res, 2024, 287: 127865.

[35] Wang JH, Zang JZ, Yu Y, et al. Lingguizhugan oral solution alleviates MASLD by regulating bile acids metabolism and the gut microbiota through activating FXR/TGR5 signaling pathways. Front Pharmacol, 2024, 15: 1426049.

[36] Teunis C, Nieuwdorp M, Hanssen N. Interactions between tryptophan metabolism, the gut microbiome and the immune system as potential drivers of non-alcoholic fatty liver disease (NAFLD) and metabolic diseases. Metabolites, 2022, 12: 514.

[37] Sui GY, Jia LQ, Quan DM, et al. Activation of the gut microbiota-kynurenine-liver axis contributes to the development of nonalcoholic hepatic steatosis in nondiabetic adults. Aging (Albany NY), 2021, 13: 21309–24.

[38] Wegermann K, Howe C, Henao R, et al. Serum bile acid, vitamin E, and serotonin metabolites are associated with future liver-related events in nonalcoholic fatty liver disease. Hepatol Commun, 2021, 5: 608–17.

[39] Hoyles L, Fernández-Real JM, Federici M, et al. Molecular phenomics and metagenomics of hepatic steatosis in non-diabetic obese women. Nat Med, 2018, 24: 1070–80.

[40] Iida A, Kuranuki S, Yamamoto R, et al. Analysis of amino acid profiles of blood over time and biomarkers associated with non-alcoholic steatohepatitis in STAM mice. Exp Anim, 2019, 68: 417–28.

[41] de Mello VD, Sehgal R, Männistö V, et al. Serum aromatic and branched-chain amino acids associated with NASH demonstrate divergent associations with serum lipids. Liver Int, 2021, 41: 754–63.

[42] Mansoori S, Ho MYM, Ng KKW, et al. Branched-chain amino acid metabolism: pathophysiological mechanism and therapeutic intervention in metabolic diseases. Obes Rev, 2025, 26: e13856.

[43] Henao-Mejia J, Elinav E, Jin C, et al. Inflammasome-mediated dysbiosis regulates progression of NAFLD and obesity. Nature, 2012, 482: 179–85.

[44] Le Roy T, Llopis M, Lepage P, et al. Intestinal microbiota determines development of non-alcoholic fatty liver disease in mice. Gut, 2013, 62: 1787–94.

[45] Chiu CC, Ching YH, Li YP, et al. Nonalcoholic fatty liver disease is exacerbated in high-fat diet-fed gnotobiotic mice by colonization with the gut microbiota from patients with nonalcoholic steatohepatitis. Nutrients, 2017, 9: 1220.

[46] Hu WB, Gao WY, Liu ZM, et al. Specific strains of *Faecalibacterium prausnitzii* ameliorate nonalcoholic fatty liver disease in mice in association with gut microbiota regulation. Nutrients, 2022, 14: 2945.

[47] Nian FL, Wu LY, Xia QY, et al. *Akkermansia muciniphila* and *Bifidobacterium bifidum* prevent NAFLD by regulating FXR expression and gut microbiota. J Clin Transl Hepatol, 2023, 11: 763–76.

[48] Han YQ, Ling QL, Wu L, et al. *Akkermansia muciniphila* inhibits nonalcoholic steatohepatitis by orchestrating TLR2-activated γδT17 cell and macrophage polarization. Gut Microbes, 2023, 15: 2221485.

[49] Yang C, Wu JL, Yang LG, et al. Altered gut microbial profile accompanied by abnormal short chain fatty acid metabolism exacerbates nonalcoholic fatty liver disease progression. Sci Rep, 2024, 14: 22385.

[50] Hu S, Kuwabara R, de Haan BJ, et al. Acetate and butyrate improve β-cell metabolism and mitochondrial respiration under oxidative stress. Int J Mol Sci, 2020, 21: 1542.

[51] Li DG, Bai XY, Jiang Y, et al. Butyrate alleviates PTZ-induced mitochondrial dysfunction, oxidative stress and neuron apoptosis in mice via Keap1/Nrf2/HO-1 pathway. Brain Res Bull, 2021, 168: 25–35.

[52] Chen J, Vitetta L. Gut microbiota metabolites in NAFLD pathogenesis and therapeutic implications. Int J Mol Sci, 2020, 21: 5214.

[53] Liang LP, Liu L, Zhou WY, et al. Gut microbiota-derived butyrate regulates gut mucus barrier repair by activating the macrophage/WNT/ERK signaling pathway. Clin Sci (Lond), 2022, 136: 291–307.

[54] Jiao N, Baker SS, Chapa-Rodriguez A, et al. Suppressed hepatic bile acid signalling despite elevated production of primary and secondary bile acids in NAFLD. Gut, 2018, 67: 1881–91.

[55] Cipriani S, Mencarelli A, Palladino G, et al. FXR activation reverses insulin resistance and lipid abnormalities and protects against liver steatosis in zucker (fa/fa) obese rats. J Lipid Res, 2010, 51: 771–84.

[56] Liu Y, Xing HY, Zhou T, et al. Kynurenine 3-hydroxylase inhibitor RO 61-8048 alleviates nonalcoholic fatty liver disease in high-fat diet-induced obese mice. J Biochem Mol Toxicol, 2025, 39: e70511.

[57] Celinski K, Konturek PC, Slomka M, et al. Effects of

treatment with melatonin and tryptophan on liver enzymes, parameters of fat metabolism and plasma levels of cytokines in patients with non-alcoholic fatty liver disease–14 months follow up. J Physiol Pharmacol, 2014, 65: 75–82.

[58] Sewerynek E, Melchiorri D, Reiter RJ, et al. Lipopolysaccharide-induced hepatotoxicity is inhibited by the antioxidant melatonin. Eur J Pharmacol, 1995, 293: 327–34.

[59] Knudsen C, Neyrinck AM, Leyrolle Q, et al. Hepatoprotective effects of indole, a gut microbial metabolite, in leptin-deficient obese mice. J Nutr, 2021, 151: 1507–16.

[60] Beaumont M, Neyrinck AM, Olivares M, et al. The gut microbiota metabolite indole alleviates liver inflammation in mice. FASEB J, 2018, 32: 201800544.

[61] Zhang FY, Zhao SH, Yan WJ, et al. Branched chain amino acids cause liver injury in obese/diabetic mice by promoting adipocyte lipolysis and inhibiting hepatic autophagy. EBioMedicine, 2016, 13: 157–67.

[62] Takegoshi K, Honda M, Okada H, et al. Branched-chain amino acids prevent hepatic fibrosis and development of hepatocellular carcinoma in a non-alcoholic steatohepatitis mouse model. Oncotarget, 2017, 8: 18191–205.

[63] Harrison SA, Baum SJ, Gunn NT, et al. Safety, tolerability, and biologic activity of AXA1125 and AXA1957 in subjects with nonalcoholic fatty liver disease. Am J Gastroenterol, 2021, 116: 2399–409.

[64] Iwao M, Gotoh K, Arakawa M, et al. Supplementation of branched-chain amino acids decreases fat accumulation in the liver through intestinal microbiota-mediated production of acetic acid. Sci Rep, 2020, 10: 18768.

[65] Zhang R, Mu H, Li Z, et al. Oral administration of branched-chain amino acids ameliorates high-fat diet-induced metabolic-associated fatty liver disease via gut microbiota-associated mechanisms. Front Microbiol, 2022, 13: 920277.

[66] Carbajo-Pescador S, Porras D, García-Mediavilla MV, et al. Beneficial effects of exercise on gut microbiota functionality and barrier integrity, and gut-liver crosstalk in an in vivo model of early obesity and non-alcoholic fatty liver disease. Dis Model Mech, 2019, 12: 039206.

[67] Cheng R, Wang L, Le S, et al. A randomized controlled trial for response of microbiome network to exercise and diet intervention in patients with nonalcoholic fatty liver disease. Nat Commun, 2022, 13: 2555.

[68] Csader S, Chen X, Leung H, et al. Gut ecological networks reveal associations between bacteria, exercise, and clinical profile in non-alcoholic fatty liver disease patients. mSystems, 2023, 8: e0022423.

[69] Imdad S, So B, Jang J, et al. Temporal variations in the gut microbial diversity in response to high-fat diet and exercise. Sci Rep, 2024, 14: 3282.

[70] Munukka E, Ahtiainen JP, Puigbó P, et al. Six-week endurance exercise alters gut metagenome that is not reflected in systemic metabolism in over-weight women. Front Microbiol, 2018, 9: 2323.

[71] Larabi AB, Masson HLP, Bäumler AJ. Bile acids as modulators of gut microbiota composition and function. Gut Microbes, 2023, 15: 2172671.

[72] Ye XC, Sun P, Lao SW, et al. FGF21-*Dubosiella* axis mediates the protective effects of exercise against NAFLD development. Life Sci, 2023, 334: 122231.

[73] Liu Y, Wang Y, Ni YQ, et al. Gut microbiome fermentation determines the efficacy of exercise for diabetes prevention. Cell Metab, 2020, 31: 77–91.

[74] Kovynev A, Ying Z, Zhang S, et al. Timing matters: late, but not early, exercise training ameliorates MASLD in part by modulating the gut-liver axis in mice. J Pineal Res, 2024, 76: e70003.

[75] Kovynev A, Charchuta MM, Begtašević A, et al. Combination of dietary fiber and exercise training improves fat loss in mice but does not ameliorate MASLD more than exercise alone. Am J Physiol Gastrointest Liver Physiol, 2025, 328: 399–410.

[76] Zhang XJ, Cheng YB, Wei QY, et al. Exercise and berberine intervention ameliorate high-fat diet-induced MAFLD by regulating gut microbiota and hepatic fatty acid beta-oxidation. J Inflamm Res, 2025, 18: 2837–54.

[77] Han YX, Quan HJ, Ji W, et al. Moderate-intensity continuous training and high-intensity interval training alleviate glycolipid metabolism through modulation of gut microbiota and their metabolite SCFAs in diabetic rats. Biochem Biophys Res Commun, 2024, 735: 150831.

[78] Koh A, Vadder FD, Kovatcheva-Datchary P, et al. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell, 2016, 165: 1332–45.

[79] Yu CX, Liu SJ, Chen LQ, et al. Effect of exercise and butyrate supplementation on microbiota composition and lipid metabolism. J Endocrinol, 2019, 243: 125–35.

[80] Allen JM, Mailing LJ, Niemiro GM, et al. Exercise alters gut microbiota composition and function in lean and obese humans. Med Sci Sports Exerc, 2018, 50: 747–57.

[81] Xu L, Zhang Y, Ni Z. Exercise, gut microbial metabolite: short chain fatty acid and regulation of skeletal muscle metabolism. Chin J Biochem Mol Biol, 2022, 1: 1–7.

[82] Jiang Y, Zhao LL, Ma J, et al. Preventive mechanisms of Chinese Tibetan medicine triphala against nonalcoholic fatty liver disease. Phytomedicine, 2024, 123: 155229.

[83] Wetzel P, Hasse A, Papadopoulos S, et al. Extracellular carbonic anhydrase activity facilitates lactic acid transport in rat skeletal muscle fibres. J Physiol, 2001, 531: 743–56.

[84] Mukhopadhya I, Louis P. Gut microbiota-derived short-chain fatty acids and their role in human health and disease. Nat Rev Microbiol, 2025, 23: 635–51.

[85] Danese E, Salvagno GL, Tarperi C, et al. Middle-distance running acutely influences the concentration and composition of serum bile acids: potential implications for cancer risk? Oncotarget, 2017, 8: 52775–82

[86] Schranner D, Kastenmüller G, Schönfelder M, et al. Metabolite concentration changes in humans after a bout of exercise: a systematic review of exercise metabolomics studies. Sports Med Open, 2020, 6: 11.

[87] Morville T, Sahl RE, Trammell SA, et al. Divergent effects of resistance and endurance exercise on plasma bile acids, FGF19, and FGF21 in humans. JCI Insight, 2018, 3: e122737.

[88] Mouzaki M, Wang AY, Bandsma R, et al. Bile acids and dysbiosis in non-alcoholic fatty liver disease. PLoS One, 2016, 11: e0151829.

[89] Wang JJ, Cai XB, Lu LG. Association between bile acids and nonalcoholic fatty liver disease. J Clin Hepatol, 2023, 39: 1166–71.

[90] Shi JS, Cui JC, Zheng TL, et al. Comparative effects of aerobic and resistance exercise on bile acid profiles and liver function in patients with non-alcoholic fatty liver disease. BMC Gastroenterol, 2025, 25: 239.

[91] Babu AF, Csader S, Männistö V, et al. Effects of exercise on NAFLD using non-targeted metabolomics in adipose tissue, plasma, urine, and stool. Sci Rep, 2022, 12: 6485.

[92] Zheng XJ, Huang FJ, Zhao AH, et al. Bile acid is a significant host factor shaping the gut microbiome of diet-induced obese mice. BMC Biol, 2017, 15: 120.

[93] Meissner M, Lombardo E, Havinga R, et al. Voluntary wheel running increases bile acid as well as cholesterol excretion and decreases atherosclerosis in hypercholesterolemic mice. Atherosclerosis, 2011, 218: 323–9.

[94] Pinto PR, Rocco DDFM, Okuda LS, et al. Aerobic exercise training enhances the *in vivo* cholesterol trafficking from macrophages to the liver independently of changes in the expression of genes involved in lipid flux in macrophages and aorta. Lipids Health Dis, 2015, 14: 109.

[95] Mercer KE, Maurer A, Pack LM, et al. Exercise training and diet-induced weight loss increase markers of hepatic bile acid (BA) synthesis and reduce serum total BA concentrations in obese women. Am J Physiol Endocrinol Metab, 2021, 320: e864–73.

[96] Farahnak Z, Magri Tomaz L, Bergeron R, et al. The effect of exercise training on upregulation of molecular markers of bile acid metabolism in the liver of ovariectomized rats fed a cholesterol-rich diet. ARYA Atheroscler, 2017, 13: 184–92.

[97] Gupta B, Liu Y, Chopyk DM, et al. Western diet-induced increase in colonic bile acids compromises epithelial barrier in nonalcoholic steatohepatitis. FASEB J, 2020, 34: 7089–102.

[98] Ortega-Santos CP, Al-Nakkash L, Whisner CM. Exercise and/or genistein treatment impact gut microbiota and inflammation after 12 weeks on a high-fat, high-sugar diet in C57BL/6 mice. Nutrients, 2020, 12: 3410.

[99] Ngo Sock ET, Farahnak Z, Lavoie JM. Exercise training decreases gene expression of endo- and xeno-sensors in rat small intestine. Appl Physiol Nutr Metab, 2014, 39: 1098–103.

[100] Hajighasem A, Farzanegi P, Mazaheri Z, et al. Effects of resveratrol, exercises and their combination on farnesoid X receptor, liver X receptor and sirtuin 1 gene expression and apoptosis in the liver of elderly rats with nonalcoholic fatty liver. PeerJ, 2018, 6: e5522.

[101] Mohammadpour-Asl S, Roshan-Milani B, Roshan-Milani S, et al. Endoplasmic reticulum stress PERK-ATF4-CHOP pathway is involved in non-alcoholic fatty liver disease in type 1 diabetic rats: the rescue effect of treatment exercise and insulin-like growth factor I. Heliyon, 2024, 10: e27225.

[102] Sasaki T, Kuboyama A, Mita M, et al. The exercise-inducible bile acid receptor Tgr5 improves skeletal muscle function in mice. J Biol Chem, 2018, 293: 10322–32.

[103] Shi XL, Yin HY, Li J, et al. Circulating branch chain amino acids and improvement in liver fat content in response to exercise interventions in NAFLD. Sci Rep, 2021, 11: 13415.

[104] Vanweert F, Boone SC, Brouwers B, et al. The effect of physical activity level and exercise training on the association between plasma branched-chain amino acids and intrahepatic lipid content in participants with obesity. Int J Obes (Lond), 2021, 45: 1510–20.

[105] Gou HZ, Zhang YL, Ren LF, et al. How do intestinal probiotics restore the intestinal barrier? Front Microbiol, 2022, 13: 929346

[106] Wang J, Ji H, Wang S, et al. Probiotic *Lactobacillus plantarum* promotes intestinal barrier function by strengthening the epithelium and modulating gut microbiota. Front Microbiol, 2018, 9: 1953.

[107] Tilg H, Zmora N, Adolph TE, et al. The intestinal microbiota fuelling metabolic inflammation. Nat Rev Immunol, 2020, 20: 40–54.

[108] Usuda H, Okamoto T, Wada K. Leaky gut: effect of dietary fiber and fats on microbiome and intestinal barrier. Int J Mol Sci, 2021, 22: 7613.

[109] Mostafavi Abdolmaleky H, Zhou JR. Gut microbiota dysbiosis, oxidative stress, inflammation, and epigenetic alterations in metabolic diseases. Antioxidants (Basel), 2024, 13: 985.

[110] Pan X, Niu X, Li Y, et al. Preventive mechanism of lycopene on intestinal toxicity caused by cyclophosphamide chemotherapy in mice by regulating TLR4-MyD88/TRIF-TRAF6 signaling pathway and gut-liver axis. Nutrients, 2022, 14: 4467.

[111] Wang Y, Wu Y, Wang Y, et al. Antioxidant properties of probiotic bacteria. Nutrients, 2017, 9: 521.

[112] Sicard JF, Le Bihan G, Vogeleer P, et al. Interactions of intestinal bacteria with components of the intestinal mucus. Front Cell Infect Microbiol, 2017, 7: 387.

[113] Takami M, Aoi W, Matsumoto K, et al. High-intensity exercise impairs intestinal barrier function by generating oxidative stress. J Clin Biochem Nutr, 2024, 74: 136–40.

[114] Hou P, Wang D, Lang H, et al. Dihydromyricetin attenuates high-intensity exercise-induced intestinal barrier dysfunction associated with the modulation of the phenotype of intestinal intraepithelial lymphocytes. Int J Mol Sci, 2022, 24: 221.

[115] Dmytriv TR, Storey KB, Lushchak VI. Intestinal barrier permeability: the influence of gut microbiota, nutrition, and exercise. Front Physiol, 2024, 15: 1380713.

[116] Roca Rubio MF, Folkesson M, Kremp C, et al. Associations between various markers of intestinal barrier and immune function after a high-intensity exercise challenge. Physiol Rep, 2024, 12: e16087.

[117] Hou P, Zhou X, Yu L, et al. Exhaustive exercise induces gastrointestinal syndrome through reduced ILC3 and IL-22 in mouse model. Med Sci Sports Exerc, 2020, 52: 1710–8.

[118] Pugh JN, Impey SG, Doran DA, et al. Acute high-intensity interval running increases markers of gastrointestinal damage and permeability but not gastrointestinal symptoms. Appl Physiol Nutr Metab, 2017, 42: 941–7.

[119] Men J, Li H, Cui C, et al. Fecal bacteria transplantation replicates aerobic exercise to reshape the gut microbiota in mice to inhibit high-fat diet-induced atherosclerosis. PLoS One, 2025, 20: e0314698.