

· 综述 ·

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双歧杆菌对慢性肝病的干预作用及其机制

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摘要: 相较于传统慢性肝病 (CLD) 治疗方法, 双歧杆菌具有干预靶点多、生物安全性高和宿主相容性好等特性, 为干预 CLD 进展提供了微生态调控新策略。多项研究表明, 双歧杆菌通过调节肠道菌群、保持抗氧化、促进能量消耗、减轻炎症、改善糖脂代谢和抗肿瘤等多个方面, 调节肝脏稳态及治疗 CLD。本文系统综述了国内外关于双歧杆菌治疗 CLD 的相关研究, 探讨其不同作用机制, 并对涉及的核转录因子红系 2 相关因子 2 和 AMP 活化的蛋白质激酶等相关信号通路与肝脏的交互作用进行阐述, 以期益生菌干预 CLD 病理提供依据, 为 CLD 的综合治疗提供新思路。

关键词: 肝疾病; 二裂菌属; 信号传导**基金项目:** 国家自然科学基金 (82160888); 广西自然科学基金 (2022GXNSFAA035573, 2023GXNSFAA026361)

Interventional effect and mechanism of *Bifidobacterium* in chronic liver disease

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Abstract: Compared with traditional therapies for chronic liver disease (CLD), *Bifidobacterium* has the characteristics of multi-target intervention, high biosafety, and good host compatibility and provides new strategies for intervention of CLD progression in terms of microecological regulation. Various studies have shown that *Bifidobacterium* regulates liver homeostasis and exerts a therapeutic effect on CLD by regulating intestinal flora, maintaining antioxidation, promoting energy consumption, alleviating inflammation, improving glycolipid metabolism, and exerting an antitumor effect. This article systematically reviews the studies on *Bifidobacterium* in the treatment of CLD in China and globally, explores their different mechanisms, and elaborates on the interaction between related signaling pathways (such as the nuclear factor erythroid 2-related factor 2 signaling pathway and the adenosine monophosphate-activated protein kinase signaling pathway) and the liver, in order to provide a basis for probiotic intervention in liver pathology, as well as new ideas for the comprehensive treatment of CLD.

Key words: Liver Diseases; Bifidobacterium; Signal Transduction**Research funding:** National Natural Science Foundation of China (82160888); Guangxi Natural Science Foundation (2022GXNSFAA035573, 2023GXNSFAA026361)

慢性肝病 (chronic liver disease, CLD) 是指肝脏在长期致病因素作用下发生的持续性损伤, 与急性期肝损伤形成鲜明对比。据统计, CLD 在全球的青、中年人群中

发病人数呈上升趋势, 且相关死亡率也维持在较高水平^[1]。CLD 的发生发展与多种高危因素密切相关, 例如长期酗酒、寄生虫、病毒感染和胆汁大量淤积等。其病

程常持续在6个月以上,若持续进展,可逐渐进展为肝纤维化、肝硬化、肝癌及肝衰竭。

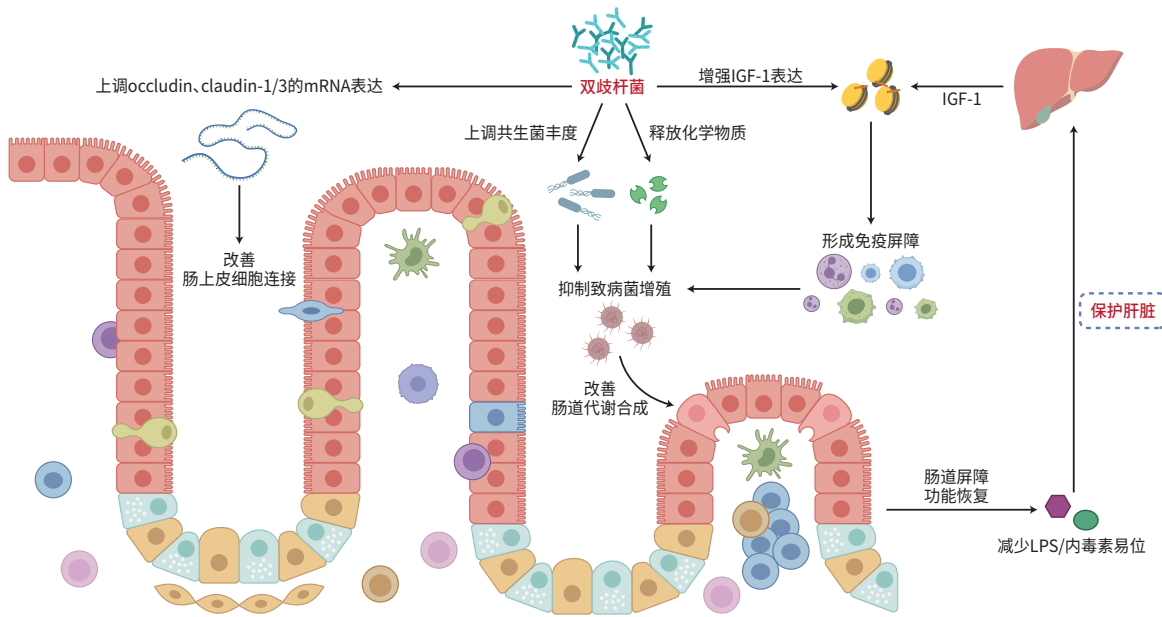
双歧杆菌(*Bifidobacterium*)是一类末端为分枝状结构的革兰阳性杆菌,具有非致病性、无毒且严格厌氧的特点,通常从母乳喂养婴幼儿的粪便中分离获得。在新生儿出生后数周内,双歧杆菌便可快速在肠道内定植,菌群丰度随宿主年龄增长呈现衰减趋势^[2]。目前,双歧杆菌属已鉴定出约80个(亚)种,广泛分布于胃肠道、口腔和血液等多个生态位定植区中,常见的有青春双歧杆菌、两歧双歧杆菌、婴儿双歧杆菌、乳双歧杆菌和长双歧杆菌。双歧杆菌属具有营养、抗菌、护肝、抗肿瘤、生物拮抗和抗衰老等作用,已在食品、保健及临床领域实现产业化应用。本文旨在根据对CLD的临床研究进展,系统综述双歧杆菌在调节肠道菌群、保持抗氧化、促进能量消耗、减轻炎症、改善糖代谢与脂质代谢以及抗肝癌等方面干预CLD及调节肝脏生理病理的作用机制,并论述其重要相关信号通路,为益生菌通过肠道及全身各脏器治疗CLD提供新思路 and 参考。

1 双歧杆菌干预CLD与护肝的作用途径

1.1 重塑肠道微生态和恢复肠道屏障 人体超过70%的微生物定植于下消化道。作为人体内最大的上皮组织,胃肠道因各种生理因素而频繁与各种肠道菌群接触。健康状况下,人体菌群在相应栖息地呈保守态势^[3];但当出现严重病理变化(如肝硬化失代偿期)时,菌群会呈现迁移、数目波动及种类增减。由于肝脏与胃肠道间解剖位置相近,并通过门静脉、淋巴系统相连,肝脏疾病往往伴随肠道微生态的紊乱。肠道屏障是由肠道解剖结构及其生理功能构成的防御系统,能有效阻遏肠腔内病原微生物及其代谢产物向肝脏及体循环易位^[4]。诸多研究表明,多种双歧杆菌菌株可通过机械、生物、化学及免疫屏障等多重途径发挥微生态调节作用,有效干预CLD。对于酒精性慢性肝损伤,乳酸双歧杆菌通过增强闭合蛋白occludin与紧密连接蛋白claudin-1、claudin-3的mRNA表达,增强肠上皮细胞间的紧密连接,巩固机械屏障的功能^[5];假链双歧杆菌和链状双歧杆菌则可通过修复肠上皮细胞微绒毛结构损伤(如断裂、稀疏及形态异常),恢复肠道机械屏障,并通过保持肠道菌群定植抗力增强生物屏障功能,从而显著降低肠源性微生物向肝脏的异常易位^[6]。具体表现为抑制副萨特氏菌属等机会性病原菌的异常增殖,逆转丁酸弧菌属、粪球菌属及梭菌属XI簇菌群的短链脂肪酸(short-chain fatty acid, SCFA)功能菌群的

耗竭状态。在非酒精性脂肪性肝病(nonalcoholic fatty liver disease, NAFLD)中,青春双歧杆菌通过提高嗜齿粪杆菌属、乳杆菌属等共生菌的丰度,抑制泰兹勒氏菌属、大肠埃氏菌属-志贺氏菌属和颤杆菌属等条件致病菌增殖,促进丙酸、丁酸等有益代谢物生成,从而改善肠道环境并减轻肝脏代谢负担,发挥生物屏障作用^[7]。此外,婴儿双歧杆菌可通过增强胰岛素样生长因子1表达,进而增强免疫屏障功能^[8]。胰岛素样生长因子1作为多功能细胞调节因子,能调动免疫球蛋白、巨噬细胞、自然杀伤细胞和多种淋巴细胞,构建有效的免疫防线,从而改善肝硬化状态下的肠道屏障功能。在化学屏障方面,部分双歧杆菌还可协同其他厌氧菌,通过资源竞争和化学拮抗作用抑制致病菌生长,例如能杀灭肝硬化患者下消化道的大肠埃希菌^[9]。应当明确的是,单一的菌株干预对CLD的治疗效果有限。肠道菌群作为复杂生态系统,其中双歧杆菌的微生态调节及屏障作用常依赖于其他菌群的参与与协同。因此,现阶段应致力于开发以双歧杆菌为核心、联合其他有益菌种的多联活菌制剂,为CLD提供更好的干预策略(图1)。

1.2 抗氧化应激和保持抗氧化活性 氧化应激是体内氧化与抗氧化间的平衡失调过程,其核心机制在于过量的活性氧(reactive oxygen species, ROS)通过攻击肝细胞膜中的多不饱和脂肪酸,触发脂质过氧化链式反应。当ROS生成量突破内源性抗氧化系统的清除阈值时,相关DNA、脂质和蛋白质发生氧化,进而激活肝星状细胞,促使细胞外基质异常沉积,推动肝纤维化进程,最终可能发展为肝硬化、肝癌。研究表明,诸多双歧杆菌菌株在抗氧化应激中表现出积极作用。两歧双歧杆菌可通过上调核转录因子红系2相关因子2(nuclear factor erythroid 2 related factor 2, Nrf2)、血红素加氧酶(heme oxygenase, HO)1及NAD(P)H醌氧化还原酶1(NADPH: quinone oxidoreductase 1, NQO1)表达,增强对乙酰氨基酚(acetaminophen, APAP)诱导的急性肝损伤(acute liver injury, ALI)小鼠的肝脏抗氧化能力,延缓肝纤维化进程^[10]。在代谢功能障碍相关脂肪性肝病(metabolic dysfunction-associated steatotic liver disease, MASLD)患者中,该菌还可通过阻断固醇调节元件结合蛋白(sterol regulatory element-binding protein, SREBP)1核转位并下调CYP2E1表达,提高ROS清除效率,抑制脂质过氧化和铁死亡^[11];长双歧杆菌则可通过降低肝细胞内ROS水平,阻断肝脏向肝细胞癌(hepatocellular carcinoma, HCC)的恶性转化,其机制涉及体内的转化生长因子-β1



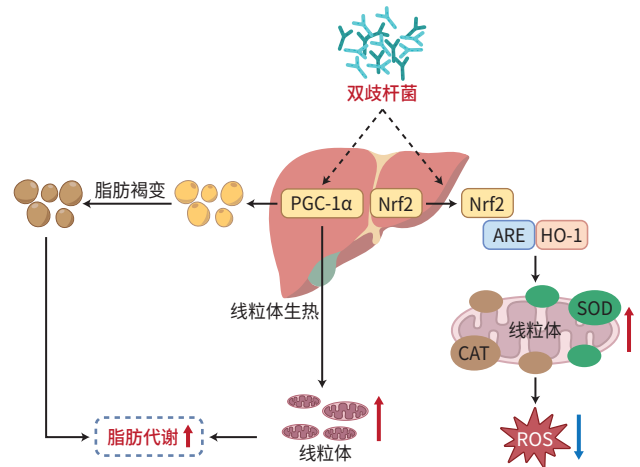
注:CLD,慢性肝病;occludin,闭合蛋白;IGF-1,胰岛素样生长因子1;LPS,脂多糖。

图1 双歧杆菌通过肠道屏障干预CLD的过程

Figure 1 The process of *Bifidobacterium* intervening CLD through the intestinal barriers

表达和Smad3磷酸化的相关信号通路调控^[12]。在酒精联合高脂饮食(high-fat diet, HFD)^[13]或⁶⁰Co γ 射线诱导的相关模型^[14]中,两歧双歧杆菌干预可显著提升肝脏超氧化物歧化酶(superoxide dismutase, SOD)与过氧化氢酶活性,同时降低丙二醛(malondialdehyde, MDA)含量。此外,两歧双歧杆菌与乳酸双歧杆菌均可提升谷胱甘肽过氧化物酶、谷胱甘肽等多种抗氧化酶的水平^[15]。但二者的抗氧化作用机制存在差异:两歧双歧杆菌主要通过清除ROS实现效应,而乳酸双歧杆菌则通过生成叶酸、谷胱甘肽、丁酸盐等代谢产物协同调节实现效应。肝线粒体作为ROS产生和作用的关键场所,其功能障碍会进一步加剧氧化应激。肝硬化失代偿期的患者常因感染引发脓毒症,某些双歧杆菌通过产生大量苯乳酸和对羟基苯乳酸衍生物等代谢产物,修复肝脏线粒体功能,降低脓毒症引发的免疫过度和ROS生成^[16]。上述研究显示,两歧双歧杆菌的抗氧化机制相较其他菌株更为丰富,既可通过激活Nrf2/HO-1这一“主开关”来增强抗氧化能力,又可从源头上减少ROS生成。相较之下,乳酸双歧杆菌更依赖于生成代谢产物以提供营养支持。尽管现有研究成果显著,但仍有诸多机制尚不明确,例如乳酸双歧杆菌及其代谢产物具体通过哪些信号通路影响MDA、SOD和过氧化氢酶等氧化应激指标,仍需进一步探索(图2)。

1.3 加快能量释放和促进产热 肝脏能量代谢失衡是



注:CLD,慢性肝病;PGC-1 α ,过氧化物酶增殖激活受体- γ 共激活因子-1 α ;Nrf2,核转录因子红系2相关因子2;ARE,抗氧化响应元件;HO-1,血红素加氧酶1;CAT,过氧化氢酶;SOD,超氧化物歧化酶;ROS,活性氧。

图2 双歧杆菌通过抗氧化和消耗能量干预慢性肝病的过程
Figure 2 The process of *Bifidobacterium* intervening CLD through antioxidation and energy consumption

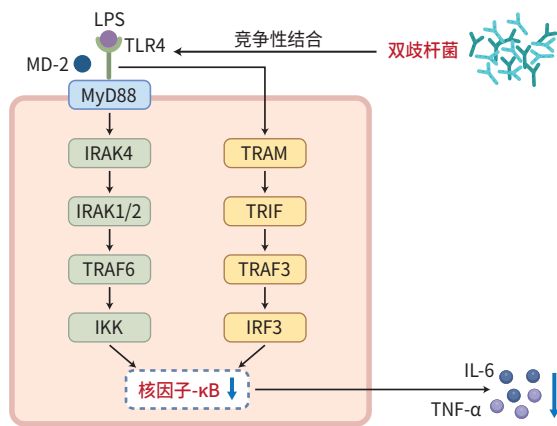
MASLD等主要CLD发生的病理基础,同时也是肥胖及2型糖尿病(type 2 diabetes, T2DM)等代谢综合征的重要诱因。研究表明,婴儿双歧杆菌、两歧双歧杆菌和长双歧杆菌在调节MASLD相关能量代谢方面具有显著作用。MASLD患者常因肝脏能量储存远大于消耗而出现胰岛素抵抗,进而诱发氧化应激和肝脏炎症相互加剧的

恶性循环。棕色脂肪(brown adipose tissue, BAT)作为专能性产热器官,在能量代谢调控中发挥重要作用,可改善血脂异常并预防肥胖相关的胰岛素抵抗。白色脂肪(white adipose tissue, WAT)作为机体重要的能量储存器官,具有强大可塑性。WAT米色化褐变可激活非颤抖性产热,显著提升全身能量代谢水平。多项研究表明,婴儿双歧杆菌可通过诱导过氧化物酶体增殖激活受体 γ 驱动WAT米色化褐变及BAT功能活化,并通过诱导早期B-细胞因子2和成纤维细胞生长因子21表达,增强米色脂肪细胞的产热能力,从而改善肥胖状态,该产热过程可能涉及AMP活化的蛋白质激酶(AMP-activated protein kinase, AMPK)和蛋白激酶A/p38丝裂原激活的蛋白激酶信号通路^[17-20]。另一方面,线粒体作为细胞能量代谢的调控器,在产热中发挥重要作用。两歧双歧杆菌与长双歧杆菌可通过诱导过氧化物酶增殖激活受体 γ 共激活因子-1 α 促进线粒体生物发生和氧化磷酸化,提升线粒体生物合成效率及氧化电子传递链活性,进而增强产热效应,该产热过程可能涉及C3H10T1/2间充质干细胞中蛋白激酶A/p38丝裂原激活的蛋白激酶信号通路^[20-22]。另有研究报道,某些双歧杆菌可通过调控生长激素促泌剂受体1a信号传导,抑制生长素释放肽,从而减少食物摄入、加快能量消耗以及促进新陈代谢,最终抑制MASLD小鼠的体重增长^[23]。尽管上述双歧杆菌菌株在实验中展现良好的调节能量代谢能力,但其临床转化仍面临挑战。值得注意的是,BAT主要聚集于老鼠等幼小哺乳动物体内,而在人类等成熟哺乳动物体内分布较少,此等种间差异可能导致实验结论与临床应用存在差距。因此,应加大相关菌株在临床上的产热机制研究,精准筛选人体受用的菌株(图2)。

1.4 介导炎症传导和抑制炎症反应 肝脏炎症是肝脏对损伤或刺激作出的防御性反应,涉及诸多炎症介质、促炎及抗炎因子的调控。持续存在的炎症可促使肝纤维化及肝硬化的发生。研究表明,相关双歧杆菌菌株有着良好的抗炎潜力。肠道菌群失调与肝脏炎症密切相关,假链双歧杆菌通过重塑肠道菌群结构从而抑制肝脏炎症,具体表现为提高具有抗炎特性的拟杆菌丰度,降低具有促炎特性的伯克霍尔德菌丰度,从而延缓ALI向CLD进展^[24]。该菌株还可恢复调节性T细胞(Treg细胞)与B淋巴细胞间的免疫平衡,降低白细胞介素(interleukin, IL)-17A、肿瘤坏死因子(tumor necrosis factor, TNF)- α 等炎症标志物及内毒素水平,促进肝脏Treg细胞增殖,并调控干扰素 γ 与IL-1 β 的表达^[25]。动物双歧杆菌

则通过竞争性结合Toll样受体4(Toll like receptor 4, TLR4),抑制髓分化因子88相关促炎通路,减少IL-1受体相关激酶4、IL-1受体相关激酶1/2、E3泛素连接酶和kappa B抑制因子激酶等关键因子的连续活化,降低肝脏核因子 κ B(nuclear factor kappa-B, NF- κ B)活化水平,进而缓解HFD诱导的NAFLD大鼠的炎症反应^[26]。在脂肪性肝炎的模型中,长双歧杆菌通过启动易位关联膜蛋白1衔接蛋白,激活血清 β 干扰素TIR结构域衔接蛋白相关抗炎途径,其中涉及肿瘤坏死因子受体相关因子3、干扰素调节因子3等抗炎因子,下调TLR4表达及NF- κ B⁺CD11c⁺细胞数量,降低脂多糖(lipopolysaccharide, LPS)诱导的血液和肝脏中TNF- α 、IL-6水平,同时减少甘油三酯和总胆固醇含量,从而缓解炎症损伤^[27]。该菌株还可通过调节特定菌属(如埃希氏菌-志贺氏菌、毛螺菌科NK4A136组及梭菌UCG-014)丰度,显著促进SCFA(如乙酸与丁酸)的生物合成,其代谢产物通过调控TLR4/NF- κ B信号通路,改善肝组织炎症损伤^[28]。短双歧杆菌通过调节巨噬细胞极化的方式减轻肝细胞炎症,具体表现为下调M1型促炎标志物Cd86的表达,上调M2型抗炎标志物Arg1 mRNA的转录水平^[29]。此外,某些双歧杆菌通过调控TLR2/4信号通路,改善IL-33介导的Treg/Th17细胞免疫失衡,缓解自身免疫性肝炎^[30]。尽管诸多双歧杆菌菌株可从微生态、免疫调节和脂质代谢等层面缓解肝脏炎症,但其作用机制的多样性也为临床菌株的选择带来挑战。因此,进一步研究各菌株在相同肝病中的抗炎共性机制,挑选最合适的菌株显得尤为重要(图3)。

1.5 减轻胰岛素抵抗和糖代谢紊乱 流行病学研究显示,全球约65%的T2DM患者合并患有MASLD^[31]。MASLD的肝纤维化进程及HCC发生风险与糖尿病病程呈显著正相关。MASLD通过诱导脂肪因子分泌,进一步损害胰岛素受体信号转导,形成糖代谢紊乱与胰岛素抵抗相互加剧的恶性循环。在CLD的糖代谢与胰岛素干预策略方面,青春双歧杆菌、动物双歧杆菌和两歧双歧杆菌有着巨大潜力。T2DM的进程常伴随慢性低度炎症状态,青春双歧杆菌可通过提高乙酸、丁酸等SCFA的浓度,降低TNF- α 、IL-6等促炎因子和干扰素 γ 等免疫因子表达,从而恢复胰岛素信号传导、减轻胰岛素抵抗,延缓MASLD进展^[32]。动物双歧杆菌则可通过激活胰岛素受体底物/磷脂酰肌醇3激酶(phosphoinositide 3-kinase, PI3K)/Akt信号通路,诱导Akt抑制叉头框蛋白O1,下调肝细胞中磷酸烯醇式丙酮酸羧化激酶和葡萄糖-6-磷酸酶的基因表达,抑制肝糖异生^[33]。该菌株还可通过降低



注:CLD,慢性肝病;LPS,脂多糖;MD-2,髓样分化蛋白2;TLR4,Toll样受体4;MyD88,髓分化因子88;IRAK,白细胞介素-1受体相关激酶;TRAM,易位关联膜蛋白1;TRIF,血清 β 干扰素TIR结构域衔接蛋白;TRAF,肿瘤坏死因子受体相关因子;IKK,kappa B抑制因子激酶;IRF3,干扰素调节因子3;IL-6,白细胞介素-6;TNF- α ,肿瘤坏死因子- α 。

图3 双歧杆菌通过相关炎症机制干预慢性肝病的过程

Figure 3 The process of *Bifidobacterium* intervening CLD through the related inflammatory mechanisms

NF- κ B蛋白表达及血清和肝脏中TNF- α 水平改善炎症状态,同时通过降低MDA水平、增加SOD和谷胱甘肽过氧化物酶活性改善氧化应激,最终促进MASLD状态下葡萄糖稳态的恢复^[34]。此外,两歧双歧杆菌能够重塑糖尿病肠道菌群结构,强化肠道黏膜屏障功能,改善机体新陈代谢及外周组织胰岛素敏感性,从而抑制自身免疫性糖尿病及相关MASLD进程^[35]。上述证据表明,CLD与糖尿病存在密切的共病关系,利用双歧杆菌进行T2DM干预时,应把握其剂量、干预时长,以优化疗效。

1.6 减少脂肪沉积和促进脂质代谢 HFD可诱发肠道菌群紊乱及肠黏膜通透性增加,导致内毒素和胆汁酸经门静脉系统迁移至肝脏,引发过度的肝脏炎症和脂质异常蓄积。脂质代谢失衡不仅是MASLD的进展诱因,也是心血管疾病和T2DM等慢性疾病的驱动因素。相关研究显示,诸多双歧杆菌菌株可有效调节脂质代谢,延缓MASLD进展。脂质代谢紊乱在肠道中表现为有益菌群减少和致病菌群增多,长双歧杆菌通过干预特定菌群及其代谢产物组成与数量,改善HFD引起的脂质代谢紊乱,并部分逆转慢性肝损伤^[36];假链双歧杆菌则通过增强次级胆汁酸生物合成,促进脂类排泄,从而减轻MASLD相关的肝脏脂肪变性及损伤^[37]。一般来说,脂肪生成酶在全身的脂质代谢中发挥重要作用。对于脂质紊乱现象,两歧双歧杆菌可通过下调乙酰辅酶A羧化酶(acetyl-CoA

carboxylase, ACC)、脂肪酸合成酶(fatty acid synthase, FAS)及苹果酸酶等脂肪生成酶的表达,并抑制SREBP-1的核转位活性,降低肝脏脂质合成速率。该菌株还可通过抑制载脂蛋白B100介导的脂质运输,减少脂质异位沉积^[38]。另一方面,该菌通过激活AMPK α 1与过氧化物酶体增殖物激活受体 α -1,增强脂质的 β -氧化,从而协调脂质代谢、降低胆固醇和血脂水平,发挥肝保护作用。胆汁酸代谢紊乱是脂质失衡的重要诱因,动物双歧杆菌通过激活法尼酯X受体/成纤维细胞生长因子15/胆固醇7 α -羟化酶通路,降低甘氨酸共轭的胆汁酸和差异代谢物石胆酸诱导的肠道法尼酯X受体的水平,实现对胆汁酸代谢的调节^[39]。婴儿双歧杆菌可通过下调肝脏胆固醇7 α -羟化酶减少胆汁酸合成,并通过增加回肠胆汁酸膜受体TGR5信号传导的活性,改善非酒精性脂肪性肝炎^[40]。

1.7 干涉肝癌进展和诱导肝肿瘤凋亡 近年来,原发性肝癌位列全球恶性肿瘤发病率第6位,死亡率高居第3位^[41]。其中,HCC占据原发性肝癌总病例数的80%以上,其次为肝内胆管癌(cholangiocarcinoma, CCA)。研究表明,假链双歧杆菌、长双歧杆菌对HCC与CCA均有干涉作用。在HCC方面,假链双歧杆菌分泌的乙酸可与肝细胞表面的G蛋白偶联受体43受体结合,通过抑制IL-6/Janus激酶/信号转导及转录活化因子3信号通路阻断肿瘤进展^[42];长双歧杆菌则通过调节转化生长因子- β 1/Smad信号通路,减轻肝纤维化、凋亡及氧化损伤,从而抑制HCC的发展^[12]。对于CCA,胆管癌细胞会持续保持表皮生长因子受体激活状态,且环氧合酶2参与疼痛与炎症加剧过程^[43]。相关双歧杆菌通过下调表皮生长因子受体与环氧合酶2的表达,发挥癌症预防作用^[44]。在联合治疗方面,双歧杆菌脂壁酸与5-氟尿嘧啶联用可激活叉头框蛋白p3/T细胞免疫球蛋白黏蛋白3信号通路,协同抑制Treg CD4⁺CD25⁺的免疫抑制活性,表现为促凋亡蛋白Bax表达上调,抗凋亡蛋白Bcl-2及凋亡执行因子Caspase-3活性水平下降,从而抑制肝肿瘤生长^[45]。在不进行坏死性凋亡和自噬的前提下,双歧杆菌重组胸苷激酶联合更昔洛韦的基因治疗能诱导肝肿瘤凋亡,仅需两次瘤内注射即可取得83%的肝癌小鼠存活效果^[46]。该联合方案还可通过抑制TNF- α 的表达,缓解肿瘤微环境中的炎症反应。此外,长双歧杆菌可充当内皮抑素等抗肿瘤基因的基因递送载体,抑制肝实体瘤的生长^[47]。尽管上述联合疗法表现出显著抗肝肿瘤效果,但仍需警惕免疫调节引发的炎症风险,尤其是免疫系统严重紊乱的晚期肝癌患者,需权衡治疗获益与潜在风险。

1.8 其他机制 长双歧杆菌可通过下调 α -平滑肌肌动蛋白和胶原蛋白的表达,减轻脂肪性肝炎中的肝纤维化程度^[27]。此外,便秘是肝性脑病的重要诱因,长双歧杆菌、婴儿双歧杆菌可通过增加共生菌的丰度和减少致病菌的丰度来缓解便秘症状^[48]。双歧杆菌调节CLD的机制繁多且复杂,该菌属通过多种生化机制对肝脏产生一种或多种干涉,为CLD治疗提供更多的潜在策略。

2 双歧杆菌干预CLD的信号通路

2.1 Nrf2信号通路及相关肝病 Nrf2是肝细胞中发挥抗氧化作用的细胞保护性转录因子,在正常状态下与抑制蛋白Keap1结合,保持低活性。当肝细胞受到氧化应激或炎症攻击时,该结合体松动,Nrf2释放后与抗氧化响应元件结合,启动NQO1、HO-1等抗氧化酶的转录和表达(图2)。研究表明,长双歧杆菌在Nrf2信号通路中表现活跃,可通过调节多种抗氧化酶干预CLD。长双歧杆菌通过调控肠道关键代谢物sedenolide的表达水平,上调Nrf2、NQO1、HO-1的表达,激活Nrf2通路,显著减轻APAP造成的肝细胞长期损伤^[49]。此外,长双歧杆菌还可促进萝卜硫素在Nrf2信号通路中的生物转化。萝卜硫素可通过诱导Nrf2蛋白表达,上调HO-1、NQO1和谷胱甘肽S-转移酶 μ 3等抗氧化酶的水平,减少肝细胞内的脂质蓄积和过氧化反应,抑制乙醛诱导的肝纤维化^[50]。另有研究发现,萝卜硫素通过上调HO-1表达,激活PI3K/Nrf2信号通路,修复肝线粒体功能障碍,抑制丙型肝炎病毒的复制^[51]。值得注意的是,在ALI中,快速激活Nrf2信号通路并清除ROS是治疗的关键,而在CLD中,则需适度上调该通路及其抗氧化酶的活性,避免长期过度激活带来的潜在风险。

2.2 AMPK信号通路及相关肝病 AMPK是细胞能量代谢的关键蛋白激酶。当肝细胞能量减少时,AMPK被迅速激活并启动一系列下游信号,以恢复能量。在肝脏脂质代谢方面,AMPK通过抑制ACC、SREBP-1c等脂肪合成关键酶,减少脂肪酸和甘油三酯的合成;或通过抑制ACC,促进脂肪酸进入肝线粒体进而分解供能。研究发现,长双歧杆菌通过激活AMPK信号通路降低附睾脂肪垫重量以及血液中甘油三酯、总胆固醇和LPS水平,显著改善HFD导致的肥胖及肝脏脂肪变性程度^[52]。乳酸双歧杆菌通过激活AMPK信号通路而抑制SREBP-1/FAS信号传导,从而改善NAFLD的病理进程^[24]。短双歧杆菌可能通过Akt和AMPK途径,促进腓肠肌中氧化性肌纤维的组成和改变代谢功能,发挥协同抗肥胖效

应,有效阻遏肝脏脂肪堆积^[53]。两歧双歧杆菌通过AMPK/Nrf2、LPS/TLR4/NF- κ B、AMPK α /过氧化物酶增殖激活受体 γ 共激活因子-1 α 及SREBP-1/FAS/ACC等多通路精准调节相关脂质合成基因及蛋白磷酸化修饰,抑制NAFLD进展中的肝脏脂质蓄积及氧化应激反应^[54]。在其他机制方面,AMPK信号通路可干涉炎症和氧化应激。乳酸双歧杆菌通过重塑肠道微生态,经抑制TLR4/NF- κ B炎症通路并激活PI3K-Akt/AMPK信号通路,发挥肠道定植优势及显著抗炎、抗氧化活性,实现对NAFLD的显著干预^[55]。此外,肝性脑病的发病机制在于血脑屏障功能障碍引发的神经毒性物质在中枢蓄积,而假链双歧杆菌可通过激活AMPK/沉默信息调节因子1信号通路维持血脑屏障通透性屏障功能,阻遏血氨及炎症因子等神经毒素对脑实质的浸润^[56]。AMPK作为能量代谢的关键调控酶,在脂质代谢方面的研究已日渐深入,但其在糖代谢等其他代谢途径中的研究有待进一步探索。

另外还有诸多信号通路对CLD发挥调控作用。以双歧杆菌属为代表的革兰阳性益生菌通过靶向调控Hippo-YAP信号通路,以减少支链氨基酸寡肽生成,进而拮抗APAP介导的肝毒性作用和肝实质细胞坏死^[57]。当前研究领域仍存在大量未被阐明的调控肝脏稳态与病理进程的信号通路,这些分子机制亟待肝病科研究者深入解析,为CLD治疗提供新的治疗靶点与干预策略。

3 总结与展望

双歧杆菌作为在肠道定植的核心益生菌,在干预CLD进程中展现出独特优势。相较于传统CLD治疗,双歧杆菌具有干预靶点多、生物安全性高和宿主相容性好等特性,为CLD治疗提供了全新的微生态调控策略。然而,现有研究仍存在局限,例如菌株个体效果差异显著、临床证据不足(多数局限于动物实验)、信号通路研究不深入和个体化治疗方案稀少等。未来可从多个角度对双歧杆菌进行探索:(1)深入研究双歧杆菌与各种信号通路的交互作用,系统阐明其在各种CLD中的治疗靶点;(2)深入研究不同种类双歧杆菌的药理性质,以便制定不同菌株的个体化治疗策略;(3)深入推进多中心、大样本的临床研究,为肝病提供更安全的治疗方案;(4)开展相关中药、西药的活性成分与双歧杆菌的联合研究,为CLD综合治疗提供新路径。

总之,双歧杆菌干预CLD的机制复杂,仍需要在技术与思路上实现重大突破与创新,从而为CLD患者提供更优质的诊治体验,减轻患者的疾病负担。

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参考文献:

- [1] PAIK JM, KABBARA K, EBERLY KE, et al. Global burden of NAFLD and chronic liver disease among adolescents and young adults[J]. *Hepatology*, 2022, 75(5): 1204-1217. DOI: 10.1002/hep.32228.
- [2] TURRONI F, DURANTI S, MILANI C, et al. Bifidobacterium bifidum: A key member of the early human gut microbiota[J]. *Microorganisms*, 2019, 7(11): 544. DOI: 10.3390/microorganisms7110544.
- [3] LI K, BIHAN M, METHÉ BA. Analyses of the stability and core taxonomic memberships of the human microbiome[J]. *PLoS One*, 2013, 8(5): e63139. DOI: 10.1371/journal.pone.0063139.
- [4] XU Z, LIAO YS, FENG XL. The role of exercise in the prevention and treatment of liver diseases by regulating intestinal flora[J]. *J Clin Hepatol*, 2025, 41(8): 1693-1699. DOI: 10.12449/JCH250834. 徐珍, 廖粤生, 冯晓露. 运动调控肠道菌群在肝脏疾病防治中的作用[J]. *临床肝胆病杂志*, 2025, 41(8): 1693-1699. DOI: 10.12449/JCH250834.
- [5] SHU X, WANG J, ZHAO L, et al. Bifidobacterium lactis TY-S01 protects against alcoholic liver injury in mice by regulating intestinal barrier function and gut microbiota[J]. *Heliyon*, 2023, 9(7): e17878. DOI: 10.1016/j.heliyon.2023.e17878.
- [6] FANG DQ, SHI D, LV LX, et al. Bifidobacterium pseudocatenulatum LI09 and Bifidobacterium catenulatum LI10 attenuate D-galactosamine-induced liver injury by modifying the gut microbiota[J]. *Sci Rep*, 2017, 7(1): 8770. DOI: 10.1038/s41598-017-09395-8.
- [7] WANG LL, JIAO T, YU QQ, et al. Bifidobacterium bifidum shows more diversified ways of relieving non-alcoholic fatty liver compared with Bifidobacterium adolescentis[J]. *Biomedicines*, 2021, 10(1): 84. DOI: 10.3390/biomedicines10010084.
- [8] WANG W, SUN M, ZHENG YL, et al. Effects of Bifidobacterium infantis on cytokine-induced neutrophil chemoattractant and insulin-like growth factor-1 in the ileum of rats with endotoxin injury[J]. *World J Gastroenterol*, 2019, 25(23): 2924-2934. DOI: 10.3748/wjg.v25.i23.2924.
- [9] YIN JY, SHAN HY. Effect of probiotics combined with compound Glycyrrhizin glycoside for hepatitis B cirrhosis and its influences on gut microbiota and serum inflammatory factors[J]. *Chin J Microecol*, 2024, 36(7): 803-807, 812. DOI: 10.13381/j.cnki.cjm.202407009. 殷景远, 单红艳. 微生态制剂联合复方甘草酸苷治疗肝炎肝硬化的效果及对肠道菌群和血清炎症因子水平的影响[J]. *中国微生态学杂志*, 2024, 36(7): 803-807, 812. DOI: 10.13381/j.cnki.cjm.202407009.
- [10] YIN J, CHEN L, LIN YY, et al. Bifidobacterium bifidum reduces oxidative stress and alters gut flora to mitigate acute liver injury caused by N-acetyl-p-aminophenol[J]. *BMC Microbiol*, 2025, 25(1): 87. DOI: 10.1186/s12866-025-03775-1.
- [11] BU GK, CHEN G, LI J, et al. Bifidobacterium bifidum BGN4 fractions ameliorate palmitic acid-induced hepatocyte ferroptosis by inhibiting SREBP1-CYP2E1 pathway[J]. *J Investig Med*, 2024, 72(1): 67-79. DOI: 10.1177/10815589231204058.
- [12] LI B, CHI XC, HUANG Y, et al. Bifidobacterium longum-derived extracellular vesicles prevent hepatocellular carcinoma by modulating the TGF- β 1/smad signaling in mice[J]. *Front Biosci*, 2024, 29(7): 241. DOI: 10.31083/j.fbi2907241.
- [13] YI HW, ZHU XX, HUANG XL, et al. Selenium-enriched Bifidobacterium longum protected alcohol and high fat diet induced hepatic injury in mice[J]. *Chin J Nat Med*, 2020, 18(3): 169-177. DOI: 10.1016/S1875-5364(20)30018-2.
- [14] PU R, ZHANG DC, QIU J, et al. Studies on radioprotective effect of Bifidobacterium on C57BL mice[J]. *Chin J Microecol*, 2007, 19(4): 330-332. DOI: 10.13381/j.cnki.cjm.2007.04.008. 蒲荣, 张德纯, 邱建, 等. 双歧杆菌 C57BL 小鼠抗辐射能力的研究[J]. *中国微生态学杂志*, 2007, 19(4): 330-332. DOI: 10.13381/j.cnki.cjm.2007.04.008.
- [15] LEE JY, KANG CH. Probiotics alleviate oxidative stress in H2O2-exposed hepatocytes and t-BHP-induced C57BL/6 mice[J]. *Microorganisms*, 2022, 10(2): 234. DOI: 10.3390/microorganisms10020234.
- [16] BELOBORODOVA N, BAIRAMOV I, OLENIN A, et al. Effect of phenolic acids of microbial origin on production of reactive oxygen species in mitochondria and neutrophils[J]. *J Biomed Sci*, 2012, 19(1): 89. DOI: 10.1186/1423-0127-19-89.
- [17] HOSSAIN M, PARK DS, RAHMAN MS, et al. Bifidobacterium longum DS0956 and Lactobacillus rhamnosus DS0508 culture-supernatant ameliorate obesity by inducing thermogenesis in obese-mice[J]. *Benef Microbes*, 2020, 11(4): 361-374. DOI: 10.3920/bm2019.0179.
- [18] HU JM, KYROU I, TAN BK, et al. Short-chain fatty acid acetate stimulates adipogenesis and mitochondrial biogenesis via GPR43 in brown adipocytes[J]. *Endocrinology*, 2016, 157(5): 1881-1894. DOI: 10.1210/en.2015-1944.
- [19] RAHMAN MS, KANG I, LEE Y, et al. Bifidobacterium longum subsp. infantis YB0411 Inhibits Adipogenesis in 3T3-L1 Pre-adipocytes and Reduces High-Fat-Diet-Induced Obesity in Mice[J]. *J Agric Food Chem*, 2021, 69(21): 6032-6042. DOI: 10.1021/acs.jafc.1c01440.
- [20] RAHMAN MS, LEE Y, PARK DS, et al. Bifidobacterium bifidum DS0908 and Bifidobacterium longum DS0950 culture-supernatants ameliorate obesity-related characteristics in mice with high-fat diet-induced obesity[J]. *J Microbiol Biotechnol*, 2023, 33(1): 96-105. DOI: 10.4014/jmb.2210.10046.
- [21] VENTURA-CLAPIER R, GARNIER A, VEKSLER V. Transcriptional control of mitochondrial biogenesis: the central role of PGC-1 α [J]. *Cardiovasc Res*, 2008, 79(2): 208-217. DOI: 10.1093/cvr/cvn098.
- [22] CHENG CF, KU HC, LIN H. PGC-1 α as a pivotal factor in lipid and metabolic regulation[J]. *Int J Mol Sci*, 2018, 19(11): 3447. DOI: 10.3390/ijms19113447.
- [23] TORRES-FUENTES C, GOLUBEVA AV, ZHDANOV AV, et al. Short-chain fatty acids and microbiota metabolites attenuate ghrelin receptor signaling[J]. *FASEB J*, 2019, 33(12): 13546-13559. DOI: 10.1096/fj.201901433R.
- [24] GUO WL, CUI SM, TANG X, et al. Intestinal microbiomics and hepatic metabolomics insights into the potential mechanisms of probiotic Bifidobacterium pseudolongum CCFM1253 preventing acute liver injury in mice[J]. *J Sci Food Agric*, 2023, 103(12): 5958-5969. DOI: 10.1002/jsfa.12665.
- [25] MOYA-PÉREZ A, NEEF A, SANZ Y. Bifidobacterium pseudocatenulatum CECT 7765 reduces obesity-associated inflammation by restoring the lymphocyte-macrophage balance and gut microbiota structure in high-fat diet-fed mice[J]. *PLoS One*, 2015, 10(7): e0126976. DOI: 10.1371/journal.pone.0126976.
- [26] YAN Y, LIU CY, ZHAO SM, et al. Probiotic Bifidobacterium lactis V9 attenuates hepatic steatosis and inflammation in rats with non-alcoholic fatty liver disease[J]. *AMB Express*, 2020, 10(1): 101. DOI: 10.1186/s13568-020-01038-y.
- [27] LEE DY, SHIN JW, SHIN YJ, et al. Lactobacillus plantarum and Bifidobacterium longum alleviate liver injury and fibrosis in mice by regulating NF- κ B and AMPK signaling[J]. *J Microbiol Biotechnol*, 2024, 34(1): 149-156. DOI: 10.4014/jmb.2310.10006.
- [28] DONG JH, PING LJ, MENG YY, et al. Bifidobacterium longum BL-10 with antioxidant capacity ameliorates lipopolysaccharide-induced acute liver injury in mice by the nuclear factor- κ B pathway[J]. *J Agric Food Chem*, 2022, 70(28): 8680-8692. DOI: 10.1021/acs.jafc.2c02950.
- [29] FONTANA L, PLAZA-DÍAZ J, ROBLES-BOLÍVAR P, et al. Bifidobacterium breve CNCM I-4035, Lactobacillus paracasei CNCM I-4034 and Lactobacillus rhamnosus CNCM I-4036 modulate macrophage gene expression and ameliorate damage markers in the liver of Zucker-Leprfa/

- rats[J]. *Nutrients*, 2021, 13(1): 202. DOI: 10.3390/nu13010202.
- [30] SONG JG, DAI J, CHEN XP, et al. *Bifidobacterium* mitigates autoimmune hepatitis by regulating IL-33-induced Treg/Th17 imbalance via the TLR2/4 signaling pathway[J]. *Histol Histopathol*, 2024, 39(5): 623-632. DOI: 10.14670/HH-18-669.
- [31] EN LI CHO E, ANG CZ, QUEK J, et al. Global prevalence of non-alcoholic fatty liver disease in type 2 diabetes mellitus: An updated systematic review and meta-analysis[J]. *Gut*, 2023, 72(11): 2138-2148. DOI: 10.1136/gutjnl-2023-330110.
- [32] QIAN X, SI Q, LIN GP, et al. *Bifidobacterium adolescentis* is effective in relieving type 2 diabetes and may be related to its dominant core genome and gut microbiota modulation capacity[J]. *Nutrients*, 2022, 14(12): 2479. DOI: 10.3390/nu14122479.
- [33] ZHANG JL, WANG SB, ZENG Z, et al. Anti-diabetic effects of *Bifidobacterium animalis* 01 through improving hepatic insulin sensitivity in type 2 diabetic rat model[J]. *J Funct Foods*, 2020, 67: 103843. DOI: 10.1016/j.jff.2020.103843.
- [34] HANCHANG W, DISSOOK S, WONGMANEE N, et al. Antidiabetic effect of *Bifidobacterium animalis* TISTR 2591 in a rat model of type 2 diabetes[J]. *Probiotics Antimicrob Proteins*, 2025, 17(6): 4298-4313. DOI: 10.1007/s12602-024-10377-2.
- [35] MA QT, LI YQ, LI PF, et al. Research progress in the relationship between type 2 diabetes mellitus and intestinal flora[J]. *Biomed Pharmacother*, 2019, 117: 109138. DOI: 10.1016/j.biopha.2019.109138.
- [36] JIANG T, LI Y, LI LY, et al. *Bifidobacterium longum* 070103 fermented milk improve glucose and lipid metabolism disorders by regulating gut microbiota in mice[J]. *Nutrients*, 2022, 14(19): 4050. DOI: 10.3390/nu14194050.
- [37] ZHA AD, QI M, DENG YK, et al. Gut *Bifidobacterium pseudocatenulatum* protects against fat deposition by enhancing secondary bile acid biosynthesis[J]. *Imeta*, 2024, 3(6): e261. DOI: 10.1002/imt.2261.
- [38] DEV K, BEGUM J, BISWAS A, et al. Hepatic transcriptome analysis reveals altered lipid metabolism and consequent health indices in chicken supplemented with dietary *Bifidobacterium bifidum* and mannan-oligosaccharides[J]. *Sci Rep*, 2021, 11(1): 17895. DOI: 10.1038/s41598-021-97467-1.
- [39] LIANG X, ZHENG XM, WANG P, et al. *Bifidobacterium animalis* subsp. *lactis* F1-7 alleviates lipid accumulation in atherosclerotic mice via modulating bile acid metabolites to downregulate intestinal FXR[J]. *J Agric Food Chem*, 2024, 72(5): 2585-2597. DOI: 10.1021/acs.jafc.3c05709.
- [40] JENA PK, SHENG LL, NAGAR N, et al. Synbiotics *Bifidobacterium infantis* and milk oligosaccharides are effective in reversing cancer-prone nonalcoholic steatohepatitis using western diet-fed FXR knockout mouse models[J]. *J Nutr Biochem*, 2018, 57: 246-254. DOI: 10.1016/j.jnutbio.2018.04.007.
- [41] BRAY F, LAVERSANNE M, SUNG H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. *CA Cancer J Clin*, 2024, 74(3): 229-263. DOI: 10.3322/caac.21834.
- [42] SONG Q, ZHANG X, LIU WX, et al. *Bifidobacterium pseudolongum*-generated acetate suppresses non-alcoholic fatty liver disease-associated hepatocellular carcinoma[J]. *J Hepatol*, 2023, 79(6): 1352-1365. DOI: 10.1016/j.jhep.2023.07.005.
- [43] YOON JH, GWAK GY, LEE HS, et al. Enhanced epidermal growth factor receptor activation in human cholangiocarcinoma cells[J]. *J Hepatol*, 2004, 41(5): 808-814. DOI: 10.1016/j.jhep.2004.07.016.
- [44] ZHANG NN, ZHU WW, ZHANG SW, et al. A novel *Bifidobacterium/Klebsiella* ratio in characterization analysis of the gut and bile microbiota of CCA patients[J]. *Microb Ecol*, 2023, 87(1): 5. DOI: 10.1007/s00248-023-02318-3.
- [45] GUO B, XIE N, WANG Y. Cooperative effect of *Bifidobacteria lipoteichoic acid* combined with 5-fluorouracil on hepatoma-22 cells growth and apoptosis[J]. *Bull Cancer*, 2015, 102(3): 204-212. DOI: 10.1016/j.bulcan.2014.09.003.
- [46] WANG CD, MA YP, HU QW, et al. *Bifidobacterial* recombinant thymidine kinase-ganciclovir gene therapy system induces FasL and TNFR2 mediated antitumor apoptosis in solid tumors[J]. *BMC Cancer*, 2016, 16: 545. DOI: 10.1186/s12885-016-2608-3.
- [47] FU GF, LI X, HOU YY, et al. *Bifidobacterium longum* as an oral delivery system of endostatin for gene therapy on solid liver cancer[J]. *Cancer Gene Ther*, 2005, 12(2): 133-140. DOI: 10.1038/sj.cgt.7700758.
- [48] WANG LL, HU LJ, XU Q, et al. *Bifidobacteria* exert species-specific effects on constipation in BALB/c mice[J]. *Food Funct*, 2017, 8(10): 3587-3600. DOI: 10.1039/c6fo01641c.
- [49] LI SJ, ZHUGE AX, XIA JF, et al. *Bifidobacterium longum* R0175 protects mice against APAP-induced liver injury by modulating the Nrf2 pathway[J]. *Free Radic Biol Med*, 2023, 203: 11-23. DOI: 10.1016/j.freeradbiomed.2023.03.026.
- [50] ISHIDA K, KAJI K, SATO S, et al. Sulforaphane ameliorates ethanol plus carbon tetrachloride-induced liver fibrosis in mice through the Nrf2-mediated antioxidant response and acetaldehyde metabolism with inhibition of the LPS/TLR4 signaling pathway[J]. *J Nutr Biochem*, 2021, 89: 108573. DOI: 10.1016/j.jnutbio.2020.108573.
- [51] YU JS, CHEN WC, TSENG CK, et al. Sulforaphane suppresses hepatitis C virus replication by up-regulating heme oxygenase-1 expression through PI3K/Nrf2 pathway[J]. *PLoS One*, 2016, 11(3): e0152236. DOI: 10.1371/journal.pone.0152236.
- [52] YUN SW, SHIN YJ, MA XY, et al. *Lactobacillus plantarum* and *Bifidobacterium longum* alleviate high-fat diet-induced obesity and depression/cognitive impairment-like behavior in mice by upregulating AMPK activation and downregulating adipogenesis and gut dysbiosis[J]. *Nutrients*, 2024, 16(22): 3810. DOI: 10.3390/nu16223810.
- [53] TODA K, YAMAUCHI Y, TANAKA A, et al. Heat-killed *Bifidobacterium breve* B-3 enhances muscle functions: Possible involvement of increases in muscle mass and mitochondrial biogenesis[J]. *Nutrients*, 2020, 12(1): 219. DOI: 10.3390/nu12010219.
- [54] LU J, SHATAER D, YAN HZ, et al. Probiotics and non-alcoholic fatty liver disease: Unveiling the mechanisms of *Lactobacillus plantarum* and *Bifidobacterium bifidum* in modulating lipid metabolism, inflammation, and intestinal barrier integrity[J]. *Foods*, 2024, 13(18): 2992. DOI: 10.3390/foods13182992.
- [55] LV HH, TAO FY, PENG LL, et al. In vitro probiotic properties of *Bifidobacterium animalis* subsp. *lactis* SF and its alleviating effect on non-alcoholic fatty liver disease[J]. *Nutrients*, 2023, 15(6): 1355. DOI: 10.3390/nu15061355.
- [56] ZENG QW, QI ZH, HE X, et al. *Bifidobacterium pseudocatenulatum* NCU-08 ameliorated senescence via modulation of the AMPK/Sirt1 signaling pathway and gut microbiota in mice[J]. *Food Funct*, 2024, 15(8): 4095-4108. DOI: 10.1039/d3fo04575g.
- [57] GAO WK, WANG G, YUAN H, et al. Gram-positive probiotics improves acetaminophen-induced hepatotoxicity by inhibiting leucine and Hippo-YAP pathway[J]. *Cell Biosci*, 2025, 15(1): 32. DOI: 10.1186/s13578-025-01370-5.

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