

婴儿型双歧杆菌的益生功能研究现状

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摘要: 人源性双歧杆菌是肠道重要的有益菌, 其优势菌种会随着年龄变化而发生变化, 可分为婴儿型双歧杆菌和成人型双歧杆菌。近年有研究表明, 婴儿型双歧杆菌具有独特的肠道黏附及定植能力, 可特异性代谢人乳低聚糖(human milk oligosaccharides, HMOs)以及合成短链脂肪酸(short-chain fatty acids, SCFAs)、色氨酸衍生物和次级胆汁酸等生物活性物质, 在调节宿主代谢和安全性方面展现出特有的益生作用。目前研究多聚焦于功能领域, 在工业化技术研究上仍存在许多瓶颈, 严重限制其应用范围与效果。今后, 除继续对婴儿型双歧杆菌功能与机制研究外, 也应积极强化加工工艺技术研究, 以突破婴儿型双歧杆菌商业化应用的技术瓶颈, 才能使其在维护人体健康和预防疾病上发挥出更大作用。

关键词: 婴儿型双歧杆菌; 黏附及定植; 代谢产物; 生产工艺; 功能特性

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Current state of infant-type Bifidobacteria in probiotic functional research

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Abstract: Human-Residential Bifidobacteria are important beneficial bacteria in the intestinal tract. The dominant species change with age and can be classified into infant-type Bifidobacteria and Adult-type Bifidobacteria. Recent studies have shown that infant-type Bifidobacteria have unique intestinal adhesion and colonization capabilities, can specifically metabolize human milk oligosaccharides (HMOs) and synthesize bioactive substances such as short-chain fatty acids (SCFAs), tryptophan derivatives, and secondary bile acids. It demonstrates unique probiotic effects in regulating host metabolism and safety. However, current research mainly focus on the functional domain, while there are still many bottlenecks in industrial technology research, which seriously limit its application scope and efficacy. In the future, in addition to continuing to study the functions and mechanisms of infant-type Bifidobacteria, research on processing technology should also be actively developed to break through the technical bottlenecks of commercial application of infant-type Bifidobacteria, enabling it to exert a greater role in maintaining human health and preventing diseases.

Keywords: Infant-type Bifidobacteria; Adhesion and Colonization; Metabolic products; Production process; Functional characteristics

人体肠道中栖息着大量共生微生物(以细菌为优势种群), 这些微生物通过复杂的种间互作, 形成种类复杂、功能多样的生态系统, 被称之为肠道微生态。越来越多科学证据表明, 肠道微生态的平衡对人体健康至关重要。益生菌具有修复肠道黏膜, 抑制致病菌定植的能力, 被广泛用于平衡肠道微生态。根据国际益生菌和益生元科学协会(ISAPP)提出的益生菌科学定义: 益生菌是指在适当的剂量下, 能够为宿主提供健康益处的活微生物^[1]。双歧杆菌是益生菌家族的重

要一员, 尤其对婴幼儿的肠道发育起着不可或缺的作用^[2]。本文将对婴儿型双歧杆菌功能及工艺研究现状总结分析, 为突破婴儿型双歧杆菌商业化技术瓶颈提供新的思路, 使其在维护人体健康和预防疾病上发挥出更大作用。

1 婴儿型双歧杆菌

1.1 生态学分类及菌种特异性 双歧杆菌是一类有益的革兰阳性、专性厌氧、非运动性、无芽孢的杆菌, 因其菌体尖端呈分枝状(如 Y 型或 V 型)而得名。在生态学上, 双歧杆菌具有显著的宿主特异性, 整体上可按宿主来源分为人源性和非人源性双歧杆菌^[3], 目前常见的人源性双歧杆菌共有 12 种, 其中, 长双歧

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杆菌长亚种、长双歧杆菌婴儿亚种、短双歧杆菌和两歧双歧杆菌在婴儿肠道中占主导地位,称之为婴儿型双歧杆菌^[4];而角双歧杆菌、链双歧杆菌、齿双歧杆菌和青春双歧杆菌则在成人中更为普遍,称之为成人型双歧杆菌^[5]。见图 1。

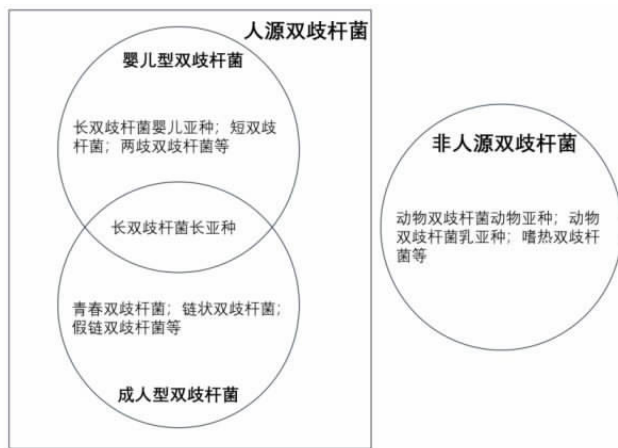


图 1 双歧杆菌根据宿主来源分类

Figure 1 Classification of Bifidobacteria according to host origin

在过去的 1 个世纪里,随着母乳喂养率的下降,婴儿肠道微生物群经历了显著变化,婴儿粪便 pH 值从 5.0 急剧上升至 6.5,粪便中的双歧杆菌减少,甚至某些婴儿型双歧杆菌面临灭绝的危险^[6],造成婴儿型双歧杆菌资源稀缺。日本学者一项研究显示人源性双歧杆菌的优势菌种会随着年龄变化而发生变化。随着研究继续深入,过敏婴儿的肠道里双歧杆菌在分类学上以成人型双歧杆菌为优势菌种,而健康婴儿的肠道里以婴儿型双歧杆菌为主,使用共培养的细胞模型证实了成人型双歧杆菌可诱导巨噬细胞高分泌促炎因子,而婴儿型双歧杆菌则诱导其高分泌抗炎因子^[7-9],进一步说明了双歧杆菌对人体健康作用有菌种特异性。见图 2。

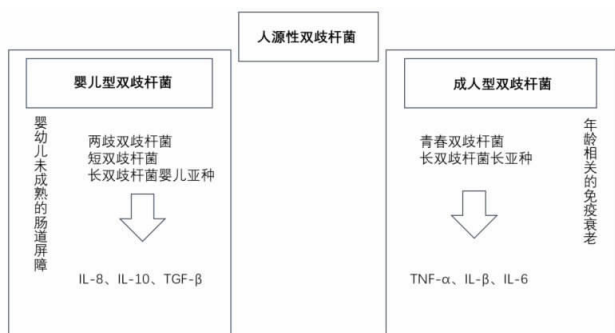


图 2 不同双歧杆菌诱导巨噬细胞产生不同细胞因子

Figure 2 Different Bifidobacteria strains induce different cytokines by macrophages

1.2 黏附及定植特性 肠黏液是宿主抵御微生物侵害的第一道防线,它能够阻止病原体和毒素进入造成肠上皮感染和炎症反应。肠黏蛋白是肠黏液的关键成分,肠道共生菌可以增加黏液产量并占据黏液上可用的结合位点来防止病原体入侵,而病原菌能增加黏液的运动性继而引起感染,因此其在预防肠道疾病方面发挥重要作用。在筛选潜在的益生菌菌株时,黏附于肠上皮/肠黏液的能力是益生菌最重要的筛选标准之一,因为黏附于肠上皮细胞被认为是定植的先决条件^[9]。有研究表明婴儿型双歧杆菌对新生儿和婴儿黏液的黏附力超过成人型双歧杆菌,黏附特性中表现出年龄/世代相关的差异^[10],基于两歧双歧杆菌对新生儿肠道黏液黏附的增强,新生儿与两歧双歧杆菌为代表的婴儿型双歧杆菌之间可能存在更深层次的共生关系还有待进一步研究证实。双歧杆菌的蛋白质组学分析研究显示,人乳低聚糖 (human milk oligosaccharides, HMOs) 可影响各种黏附因子的表达,尤其表面毛状附属物的组装是关键^[11]。近年来,在婴儿型双歧杆菌中挖掘出许多菌毛编码基因簇,最著名的是短双歧杆菌 UCC2003 中的 IVb 型紧密黏附菌毛编码基因簇^[12]和两歧双歧杆菌 PRL2010 中的分选酶依赖菌毛基因簇^[13],婴儿型双歧杆菌菌毛与宿主黏蛋白在互作关系有待进一步探究。

1.3 HMOs 特异性代谢 HMOs 是一类存在于母乳中,含量第三的以乳糖为骨架的复杂碳水化合物。HMOs 无法被宿主婴儿吸收利用,却能被婴儿型双歧杆菌特异性的代谢分解。有研究表明 HMOs 利用基因在所有长双歧杆菌婴儿亚种的菌株中都是保守的^[14],体外以 HMOs 为唯一碳源时,长双歧杆菌婴儿亚种和两歧双歧杆菌显示出大幅增长 (OD600 > 0.7)、长双歧杆菌长亚种增长适中 (OD600 > 0.5)、短双歧杆菌增长受限 (OD600 < 0.3)^[15],说明代谢 HMOs 是有菌种特异性的。两歧双歧杆菌为代表的具有细胞膜结合的乳糖-N-二糖糖苷酶,能在细胞外解聚 HMOs。长双歧杆菌婴儿亚种为代表的通过 ABC 转运体,将 HMOs 运输到胞内,由各种胞浆糖苷酶在胞内进行水解^[16]。两歧双歧杆菌和长双歧杆菌婴儿亚种可介导各自的 HMOs 降解物通过交叉喂养促进婴儿肠道内其他双歧杆菌的生长,证明了不同双歧杆菌菌种及菌株间存在功能特异性^[17-18]。婴儿型双歧杆菌与母乳高度相容更适应宿主肠道环境,对促进生命早期的肠道菌群构建有着不可或缺的作用。

1.4 短链脂肪酸(short-chain fatty acids, SCFAs)产生

SCFAs 是由肠道微生物通过发酵不可消化碳水化合物产生的,主要包含 2~5 个碳原子的有机酸,以乙

酸、丙酸、丁酸为代表。SCFAs 在肠道及免疫发育中发挥了重要作用,可刺激肠细胞释放抗炎细胞因子或抑制促炎细胞因子产生,同时产生的醋酸盐也可提升上皮细胞防御功能^[19-20]。除了在肠道中发挥作用外,婴儿型双歧杆菌产生的 SCFAs 还可以进入循环系统,直接影响脂肪组织、肺、肝脏和脑^[21]。临床研究证明,婴儿型双歧杆菌在肠道内定植,伴随乳酸和醋酸盐的增加,可调节肠道生态和降低肠腔内 pH^[22],在免疫系统的发育和成熟中发挥了重要作用。SCFAs 还能通过调节组蛋白乙酰化来诱导表观遗传变化,并有助于维持肠道屏障的完整性^[23]。研究人员通过检测 SCFAs 形成的关键基因,揭示长双歧杆菌婴儿亚种可以高产丙酸的原因,而在成人型双歧杆菌中未找到产丙酸和丁酸的菌株^[24]。

1.5 色氨酸衍生物产生 在脑-肠轴的机制研究中,色氨酸最受关注和认可。肠道菌群代谢色氨酸产生吲哚衍生物,主要包括吲哚-3-乳酸(Indole-3-lactic acid, ILA)、吲哚-3-乙酸、吲哚-3-丙酸等,可改善肠道屏障功能^[25]和调节肠道黏膜免疫反应^[26]。ILA 作为色氨酸微生物代谢主要途径的连接器^[27-28],开始被广泛研究。ILA 的产生能力与 HMOs 同化能力有关,婴儿肠道中的婴儿型双歧杆菌能够高效生产 ILA^[29]。短双歧杆菌 Iw01 代谢产生的 ILA 可以抑制巨噬细胞在结肠炎相关肿瘤发生过程中的分化^[30]。当将 ILA 添加到 PC12(大鼠肾上腺嗜铬细胞瘤)细胞的培养物中时,ILA 以剂量依赖的方式诱导神经突生长^[31]。同时 ILA 也是一种抗炎分子,可促进未成熟肠上皮细胞的发育。有研究观察到长双歧杆菌婴儿亚种产生的 ILA 沉默辅助性 T 细胞 2 和辅助性 T 细胞 17 免疫反应,这对生命早期诱导免疫耐受和抑制肠道炎症是必需的^[32]。以上这些研究表明,ILA 可能对婴儿型双歧杆菌介导的早期免疫发育至关重要,它们能维持肠道屏障完整性,并通过激活芳香烃受体保护肠上皮细胞,还能减弱脂多糖诱导的巨噬细胞中 NF- κ B 的活化,阻断炎症因子的产生,从而减轻炎症损伤^[33]。

5-羟色胺(5-Hydroxytryptamine, 5-HT)是人类中枢神经系统的一种重要神经递质,也被称为血清素。5-HT 的合成发生在肠道和大脑中与抑郁症的进展有关^[34]。然而目前,婴儿型双歧杆菌对中枢神经系统的作用尚处于探索阶段,在小鼠实验中长双歧杆菌婴儿亚种 E41 和短双歧杆菌 M2CF22M7 联合使用,提高了 RIN14B 细胞中 Tph1 的表达和 5-羟色氨酸的分泌,显著降低了小鼠抑郁行为^[35]。长双歧杆菌婴儿亚种 CCFM687 可以显著增强 RIN14B 细胞中 5-

羟色氨酸的合成,可预防慢性应激引起的抑郁症^[36]。

1.6 次级胆汁酸产生维持胆固醇稳态 胆汁酸在肠道中可以被肠道微生物产生的胆盐水解酶(bile salt hydrolase, BSH)作用及进一步修饰,形成次级胆汁酸^[37]。次级胆汁酸可作为强效信号分子与受体结合,在调节能量稳态、葡萄糖代谢和免疫反应中发挥关键作用^[38]。使用婴儿型双歧杆菌代表性的两歧双歧杆菌 TMC3115 干预血脂异常患者三周,受试者的血浆总甘油三酯、低密度脂蛋白胆固醇显著下降,表明 TMC3115 对的血清胆固醇代谢有益^[39],类似结果在动物实验中也得到了重现^[40]。还有研究观察到血脂/血糖异常的中老年人肠道双歧杆菌与同年龄段的健康人群明显不同,使用 RT-qPCR 方法对双歧杆菌菌种进行绝对定量后发现,婴儿型双歧杆菌菌种与总甘油三酯、总胆固醇、低密度脂蛋白胆固醇呈负相关^[41]。一项为期六周的随机、双盲、安慰剂对照的临床试验显示,长双歧杆菌长亚种 CCFM1077 显著降低了高脂血症患者血清中的总胆固醇和低密度脂蛋白胆固醇水平^[42]。

2 婴儿型双歧杆菌生产工艺对其功能的影响

2.1 工艺研发瓶颈与研究进展 随着动物双歧乳亚种 BB12 为代表的非人源性双歧杆菌和鼠李糖乳酪杆菌 LGG 为代表的乳酸杆菌相关研究证据的不断积累,这两种益生菌菌株因其显著的生理功能特性,已成为全球微生态领域的研究焦点,并成功产业化应用于食品、保健品等领域。然而,具有宿主适配优势的婴儿型双歧杆菌进入市场,仍面临众多产业化瓶颈,严重限制其应用范围与效果。导致市场上售卖的产品多以乳酸杆菌和非人源双歧杆菌为主,且产品标注多为出厂活菌数并非到达肠道活菌数,这就为其有益功能发挥画上个问号。

婴儿型双歧杆菌工艺研发存在两个技术瓶颈,第一个是高密度培养,在高密度培养过程中,必须面对较高浓度的代谢物,会使整个发酵体系的渗透压升高,导致菌株停止生长。除了渗透压外,菌株生长所需的营养元素以及比例同样需要考虑。第二个是保护剂配方的选择,除了保护剂的材料特性,还应考虑到菌体的同化、胞内积累等不同反应效果,这些都是影响保护效果的关键因素。冷冻干燥一般来说,细胞表面积越大,在冷冻过程中由于细胞外冰晶形成而造成的膜损伤就越大。因此,在冷冻干燥过程中链球菌相较乳杆菌存活率更高^[43]。以上两个工艺问题就会对货架期内稳定性以及进入人体到达肠道的活性与定植率产生影响。关于货架期稳定性是代谢及生理差异共同作用的结果^[44],有助于提升稳定性的具体特征

还需要未来研究中得到验证。然而目前膜脂氧化是储存过程中一个公认的不利因素,但对于不饱和脂肪酸/饱和脂肪酸比值高低还未形成统一,有研究认为细胞膜不饱和脂肪酸/饱和脂肪酸比值降低,会强烈影响膜的被动通透性,对菌体造成不利影响^[45]。但也有相反观点,细胞膜不饱和脂肪酸/饱和脂肪酸比值低与高稳定性和稳健性之间呈正相关^[46]。

口服益生菌能够活着达到肠道并实现定植对其功能表征至关重要,但是胃肠道中的各种应激源、与原著微生物群竞争以及营养缺乏,这些因素严重阻碍了肠道中口服益生菌的存活和增殖。有研究利用工程益生菌输送系统来提高益生菌对胃肠道胁迫的耐受性^[47],但应用于食品上其安全性、法规上还需进一步完善。还有研究利用多酚-金属纳米结构包裹益生菌,提高其抗氧化性和定植率,最终通过减轻炎症和恢复微生物群的平衡缓解炎症性肠病症状^[48]。另一种微囊化包埋形式也有学者研究,利用改性的乳清分离蛋白构建 pH 敏感性水凝胶包埋植物乳植杆菌,使其在肠道碱性条件下进行释放^[49]。这些研究大都是体外模型测试存活率或定植率,少部分研究在小鼠模型得到证实,能够在葡聚糖硫酸钠诱导的小鼠结肠炎中通过上调抗炎细胞因子和下调促炎细胞因子来抑制炎症^[47]。

婴儿型双歧杆菌产业化环节涉及菌种活化、高密度培养、离心富集、冷冻干燥等步骤,见图 3。如溶氧、pH 调节、冷冻干燥引发的多重应激(氧化胁迫、渗透压胁迫、膜相变损伤)对菌体存活率的影响机制尚不明确,还需进一步进行科学探索。



图 3 益生菌产业化简要步骤

Figure 3 Brief steps of industrialization of probiotics

2.2 工艺对功能影响研究进展 益生菌特性除了受到菌株影响外还受到生产工艺技术的影响^[50],每一生产环节都会对产品中细胞活性和数量产生影响。有研究表明,培养基中添加低聚果糖促进菌体增殖效果取决于低聚果糖的浓度以及双歧杆菌菌株,并且糖系统还会对后续菌体细胞存活产生影响^[51]。不可发酵的糖会对菌体产生高渗透压,诱导相容溶质的积累,帮助菌体在干燥过程引起的渗透胁迫条件下稳定蛋白质和细胞膜^[52]。研究人员通过试验证实,短双歧杆菌 B2798 在不同温度下生物量、活细胞数、果糖-6-磷酸磷酸酮醇酶活性不同,但并未对具体机制进行研究^[53]。其他研究表明温度会导致细胞膜组成发生变化,影响其流动性、黏附性和疏水性^[54]。也有文献表

明不同的不同培养条件及干燥方法会对其理化性质及品质结构产生影响^[55]。在不受 pH 控制的发酵过程中,菌体细胞比受 pH 控制的更能抵抗热应激,这些发现表明,酸休克或适应酸休克可能产生表现出不同生理状态的细胞,对其他应激具有不同的耐受性^[56]。在高渗透压培养条件下,在培养基中添加脯氨酸显著提高了长双歧杆菌长亚种 CCFM 1029 的抗冻性,可能是脯氨酸促进了蛋白质间优先水合,被迫采用了一种更紧凑蛋白质构象,以减少其暴露的表面,有助于在冻干过程中维持膜完整性和酶活性^[57]。在相同的干燥或储存条件下,不同双歧杆菌甚至同一双歧杆菌不同菌株的生存能力是不同的^[52],这就造成不同工艺的菌株功能特异性。此方面双歧杆菌的研究甚少,只有部分乳酸杆菌有所研究。研究人员将四种含有鼠李糖乳酪杆菌 Lcr35[®] 的不同商业产品进行对比,结果表明不同产品对肠细胞的黏附及抑制病原菌效果有差异,制造工艺会对特性产生影响^[58]。还有研究者做了类似研究,对从不同国家含鼠李糖乳酪杆菌 GG 的不同产品中,分离出 13 株鼠李糖乳酪杆菌 GG,对其进行黏附实验首次发现,不同来源的鼠李糖乳酪杆菌 GG 在益生菌特性上存在差异,表明了益生菌的体外特性可能因其不同生产条件而发生变化^[59]。

通过对婴儿型双歧杆菌的工艺挑战相关研究进行总结分析,表明婴儿型双歧杆菌益生功能发挥了菌株本身因素外还与其下游加工技术紧密相关,各个工艺技术都会影响其益生功能,见图 4。



图 4 益生菌功能性的影响因素

Figure 4 Factors influencing probiotic functionality

3 总结与展望

相较于传统益生菌(如乳酸杆菌和非人源性双歧杆菌),婴儿型双歧杆菌凭借可特异性的黏附在肠上皮细胞上并且利用 HMOs 产生多种代谢物,如 SCFAs、色氨酸衍生物、次级胆汁酸等,在调节宿主代谢和安全性方面倍受关注。婴儿型双歧杆菌通过外源性补充实现结肠定植是其发挥代谢调节与免疫调节功能的关键递送路径。然而,在外源补充时,能否

活着到达肠道至关重要。从口服到定植肠道,经历了胃肠道中的各种应激源(如胃液,胆汁酸,溶菌酶等),这严重阻碍了婴儿型双歧的存活和定植,继而影响其益生功能。当前产业化应用面临三重壁垒:其一,菌株资源失衡,我国《可用于婴幼儿食品的菌种名单》尚未收录本土来源婴儿型双歧杆菌菌株,全球原料供应链呈现跨国企业技术垄断格局;其二,工业化生产中存在包括活性氧累积导致的菌体活性下降,以及货架期内膜脂氧化造成的活性衰减;其三,服用后菌体在人体胃肠转运过程中菌体活性及数量的损失还无法实现无损的精准测定。

今后在婴儿型双歧杆菌的研究中,除了益生功能机制的研究外,还要关注婴儿型双歧杆菌的工艺技术,生产工艺技术会对其益生功能产生影响。首先增强婴儿型双歧杆菌对温度和氧气的抗性,从而提高其货架期的稳定性。其次研究新型包埋材料与技术,帮助婴儿型双歧克服常见的胃肠道应激源(如胃液,胆汁,溶菌酶等),以提高生存率或定植率。最后婴儿型双歧杆菌的人类临床试验至关重要,当前基于粪便菌群测序和肠镜下黏膜刮取物培养的传统检测方法,通过定量分析婴儿型双歧杆菌生物量以间接评估其肠道定植率的策略存在显著局限。亟待开发新型无创检测技术以实现直接对定植效果的动态监测,评估其临床安全性与有效性。

利益冲突声明 本研究不存在任何利益冲突

参考文献

- [1] Hill C, Guarner F, Reid G, et al. The international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic [J]. *Nature Reviews Gastroenterology & Hepatology*, 2014, 11(8): 506–514.
- [2] Stuijvenberg GA, Burton JP, Bron PA, et al. Why are bifidobacteria important for infants?[J]. *Microorganisms*, 2022, 10(2): 278.
- [3] Liu S, Fang Z, Wang H, et al. Gene–Phenotype associations involving Human–Residential bifidobacteria (HRB) reveal significant species–and Strain–Specificity in carbohydrate catabolism [J]. *Microorganisms*, 2021, 9(5): 883.
- [4] Khonsari S, Suganthy M, Burczynska B, et al. A comparative study of bifidobacteria in human babies and adults[J]. *Biosci Microbiota Food Health*, 2016, 35(2): 97–103.
- [5] Wong CB, Odamaki T, Xiao JZ. Insights into the reason of Human–Residential Bifidobacteria (HRB) being the natural inhabitants of the human gut and their potential health–promoting benefits [J]. *FEMS Microbiology Review*, 2020, 44(3): 369–385.
- [6] Henrick BM, Hutton AA, Palumbo MC, et al. Elevated fecal pH indicates a profound change in the breastfed infant gut microbiome due to reduction of bifidobacterium over the past century [J]. *mSphere*, 2018, 3(2): e00041–18.
- [7] Morita H, He F, Fuse T, et al. Adhesion of lactic acid bacteria to caco–2 cells and their effect on cytokine secretion [J]. *Microbiology and Immunology*, 2002, 46(4): 293–297.
- [8] He F, Morita H, Hashimoto H, et al. Intestinal bifidobacterium species induce varying cytokine production[J]. *The Journal of Allergy and Clinical Immunology*, 2002, 109(6): 1035–1036.
- [9] Ennis D, Shmorak S, Jantscher–Krenn E, et al. Longitudinal quantification of *Bifidobacterium longum* subsp. *Infantis* reveals late colonization in the infant gut Independent of maternal milk HMO composition[J]. *Nature Communications*, 2024, 15(1): 894.
- [10] Harata G, Yoda K, Wang RP, et al. Species– and age/Generation– Dependent adherence of *bifidobacterium bifidum* to human intestinal mucus in vitro[J]. *Microorganisms*, 2021, 9(3): 542.
- [11] Walsh C, Owens RA, Bottacini F, et al. HMO–primed bifidobacteria exhibit enhanced ability to adhere to intestinal epithelial cells[J]. *Frontiers in Microbiology*, 2023, 14(1): 26.
- [12] Püngel D, Treveil A, Dalby MJ, et al. *Bifidobacterium breve* UCC2003 Exopolysaccharide Modulates the Early Life Microbiota by Acting as a Potential Dietary Substrate [J]. *Nutrients*, 2020, 12(4): 948.
- [13] Alessandri G, Ossiprandi MC, MacSharry J, et al. Bifidobacterial dialogue with its human host and consequent modulation of the immune system[J]. *Frontiers in Immunology*, 2019, 10: 2348.
- [14] Thomson P, Medina DA, Garrido D. Human milk oligosaccharides and infant gut bifidobacteria: Molecular strategies for their utilization [J]. *Food Microbiology*, 2018, 75: 37–46.
- [15] Ojima MN, Jiang L, Arzamasov AA, et al. Priority effects shape the structure of infant–type *Bifidobacterium* communities on human milk oligosaccharides[J]. *ISME Journal*, 2022, 16(9): 2265–2279.
- [16] Sakanaka M, Hansen ME, Gotoh A, et al. Evolutionary adaptation in fucosyllactose uptake systems supports bifidobacteria–infant symbiosis[J]. *Sci Adv*, 2019, 5(8): eaaw7696.
- [17] Lyons KE, Ryan CA, Dempsey EM, et al. Breast milk, a source of beneficial microbes and associated benefits for infant health [J]. *Nutrients*, 2020, 12(4): 1039.
- [18] Nishiyama K, Nagai A, Uribayashi K, et al. Two extracellular sialidases from *Bifidobacterium bifidum* promote the degradation of sialyl–oligosaccharides and support the growth of *Bifidobacterium breve*[J]. *Anaerobe*, 2018, 52: 22–28.
- [19] Deleu S, Arnauts K, Deprez L, et al. High acetate concentration protects intestinal barrier and exerts anti–inflammatory effects in organoid–derived epithelial monolayer cultures from patients with ulcerative colitis[J]. *Int J Mol Sci*, 2023, 24(1): 768.
- [20] Fukuda S, Toh H, Hase K, et al. Bifidobacteria can protect from enteropathogenic infection through production of acetate [J]. *Nature*, 2011, 469(7331): 543–547.
- [21] Koh A, De Vadder F, Kovatcheva–Datchary P, et al. From dietary fiber to host physiology: Short–Chain fatty acids as key bacterial metabolites[J]. *Cell*, 2016, 165(6): 1332–1345.
- [22] Mills D, German J, Lebrilla C, et al. Translating neonatal microbiome science into commercial innovation: metabolism of human milk oligosaccharides as a basis for probiotic efficacy in breast–fed infants [J]. *Gut Microbes*, 2023, 15(1): 2192458.
- [23] Van der hee B, Wells JM. Microbial regulation of host physiology by short–chain fatty acids [J]. *Trends in Microbiology*, 2021, 29(8):

- 700–712.
- [24] Bunesova V, Lacroix C, Schwab C. Fucosyllactose and L-fucose utilization of infant *Bifidobacterium longum* and *Bifidobacterium kashiwanohense*[J]. *BMC Microbiology*, 2016, 16(1): 248.
- [25] Ye XW, Li HY, Anjum K, et al. Dual role of indoles derived from intestinal microbiota on human health [J]. *Frontiers in Immunology*, 2022, 13: 903526.
- [26] Huang WY, Cho KY, Meng D, et al. The impact of indole-3-lactic acid on immature intestinal innate immunity and development: a transcriptomic analysis[J]. *Scientific Reports*, 2021, 11(1): 8088.
- [27] Benech N, Rolhion N, Sokol H. Gut microbiota reprogramming of tryptophan metabolism during pregnancy shapes host insulin resistance[J]. *Gastroenterology*, 2022, 162(6): 1587–1589.
- [28] Li BH, Ye LX, Chen YF, et al. Genomic insights into probiotic metabolism of dietary carbohydrates, proteins, and fats [J]. *Current Opinion in Food Science*, 2025, 61: 101241.
- [29] Laursen MF, Sakanaka M, von Burg N, et al. *Bifidobacterium* species associated with breastfeeding produce aromatic lactic acids in the infant gut[J]. *Nat Microbiol*, 2021, 6(11): 1367–1382.
- [30] Li YK, Li QX, Yuan RS, et al. *Bifidobacterium breve*-derived indole-3-lactic acid ameliorates colitis-associated tumorigenesis by directing the differentiation of immature colonic macrophages [J]. *Theranostics*, 2024, 14(7): 2719–2735.
- [31] Wong CB, Tanaka A, Kuhara T, et al. Potential effects of indole-3-lactic acid, a metabolite of human bifidobacteria, on NGF-induced neurite outgrowth in PC12 cells [J]. *Microorganisms*, 2020, 8(3): 398.
- [32] Henrick BM, Rodriguez L, Lakshmikanth T, et al. *Bifidobacteria*-mediated immune system imprinting early in life[J]. *Cell*, 2021, 184(15): 3884–3898.
- [33] Meng D, Sommella E, Salviati E, et al. Indole-3-lactic acid, a metabolite of tryptophan, secreted by *Bifidobacterium longum* subspecies *infantis* is anti-inflammatory in the immature intestine[J]. *Pediatric Research*, 2020, 88(2): 209–217.
- [34] Pan Y, Huang Q, Liang Y, et al. *Bifidobacterium breve* BB05 alleviates depressive symptoms in mice via the AKT/mTOR pathway [J]. *Front Nutr*, 2025, 12: 1529566.
- [35] Tian PJ, Wang G, Zhao JX, et al. *Bifidobacterium* with the role of 5-hydroxytryptophan synthesis regulation alleviates the symptom of depression and related microbiota dysbiosis[J]. *Journal of Nutritional Biochemistry*, 2019, 66: 43–51.
- [36] Tian PJ, Zou RY, Song LH, et al. Ingestion of *bifidobacterium longum* subspecies *infantis* strain CCFM687 regulated emotional behavior and the central BDNF pathway in chronic stress-induced depressive mice through reshaping the gut microbiota [J]. *Food & Function*, 2019, 10(11): 7588–7598.
- [37] Collins SL, Stine JG, Bisanz JE, et al. Bile acids and the gut microbiota: metabolic interactions and impacts on disease [J]. *Nature Reviews Microbiology*, 2023, 21(4): 236–247.
- [38] Lee MH, Nuccio SP, Mohanty I, et al. How bile acids and the microbiota interact to shape host immunity [J]. *Nature Reviews Immunology*, 2024, 24(11): 798–809.
- [39] Wang K, Yu XH, Li Y, et al. *Bifidobacterium bifidum* TMC3115 Can Characteristically Influence Glucose and Lipid Profile and Intestinal Microbiota in the Middle-Aged and Elderly [J]. *Probiotics and Antimicrobial Proteins*, 2019, 11(4): 1182–1194.
- [40] Zhou WX, Luo YT, Miao ZH, et al. Effects of cephalosporin ceftriaxone used in early life on glucose and lipid metabolism in mice and the improvement effect of *Bifidobacterium bifidum* TMC3115[J]. *Chinese Journal of Antibiotics*, 2020, 45(9): 947–952.
- [41] Wang K, Cui J, Lu Q, et al. Relationship between blood glucose and lipid levels and intestinal bifidobacterium in middle-aged and older adults in Chengdu [J]. *Journal of Sichuan University (Medical Sciences)*, 2022, 53(2): 297–302.
- [42] Chu CQ, Jiang JC, Yu LL, et al. *Bifidobacterium longum* CCFM1077 Attenuates Hyperlipidemia by Modulating the Gut Microbiota Composition and Fecal Metabolites: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial [J]. *Engineering*, 2023, 28: 193–205.
- [43] Fonseca F, Béal C, Corrieu G. Method of quantifying the loss of acidification activity of lactic acid starters during freezing and frozen storage[J]. *Journal of Dairy Research*, 2000, 67(1): 83–90.
- [44] Schöpping M, Goel A, Jensen K, et al. Novel insights into the molecular mechanisms underlying robustness and stability in probiotic bifidobacteria [J]. *Applied and Environment Microbiology*, 2023, 89(3): e0008223.
- [45] Zuo MN, Wei L, Qi Q, et al. The effect of protectants on the freeze-drying survival rate of *Lactobacillus fermentum* BLHN3[J]. *Journal of Chinese Institute of Food Science and Technology*, 2024, 24(8): 178–186.
- [46] Mohedano MT, Konzock O, Chen Y. Strategies to increase tolerance and robustness of industrial microorganisms [J]. *Synth Syst Biotechnol*, 2022, 7(1): 533–540.
- [47] Pan C, Jiang XX, Wei JC, et al. Ameba-inspired strategy enhances probiotic efficacy via prebound nutrient supply [J]. *Nature Communications*, 2025, 16(1): 1827.
- [48] Zhu Y, Fang ZQ, Bai J, et al. Orally administered functional Polyphenol-Nanozyme-Armored probiotics for enhanced amelioration of intestinal inflammation and microbiota dysbiosis[J]. *ADVANCED SCIENCE*, 2025, 12(17): e2411939.
- [49] Zhang AQ, He JL, Wang Y, et al. Whey protein isolate modified with Sodium tripolyphosphate gel: A novel pH-sensitive system for controlled release of *Lactobacillus plantarum*[J]. *Food Hydrocolloids*, 2021, 120: 106924.
- [50] Haindl R, Neumayr A, Frey A, et al. Impact of cultivation strategy, freeze-drying process, and storage conditions on survival, membrane integrity, and inactivation kinetics of *Bifidobacterium longum* [J]. *Folia Microbiologica*, 2020, 65(6): 1039–1050.
- [51] Parhi P, Song KP, Choo WS. Growth and survival of *Bifidobacterium breve* and *Bifidobacterium longum* in various sugar systems with fructooligosaccharide supplementation [J]. *Journal of Food Science and Technology*, 2022, 59(10): 3775–3786.
- [52] Fu N, Hao F, Zhang SY, et al. The survival and stability of *Lactobacillus rhamnosus* GG as affected by particle formation during spray drying and spray-freeze drying [J]. *Journal of Food Engineering*, 2024, 383(12): 112252.
- [53] Liu K, Liu Y, Yang Z, et al. Regulation of cultivation temperature on biomass and activity of *bifidobacterium breve* B2798 [J].

Mendelian randomization analysis [J]. *BMJ Open Diabetes Res Care*, 2020, 8(1): e001217.

- [18] Kernan WN, Inzucchi SE, Viscoli CM, et al. Insulin resistance and risk for stroke[J]. *Neurology*, 2002, 59(6): 809–815.
- [19] Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American heart

association/American stroke association [J]. *Stroke*, 2021, 52 (7): e364–e467.

- [20] Kernan WN, Inzucchi SE, Viscoli CM, et al. Impaired insulin sensitivity among nondiabetic patients with a recent TIA or ischemic stroke[J]. *Neurology*, 2003, 60(9): 1447–1451.

收稿日期:2025-04-18

(上接第 2859 页)

- [17] 郝春芬, 张晓媛, 刘伟, 等. 2016–2023 年北京市海淀区沙门菌血清型、耐药性及耐药基因分析[J]. *现代预防医学*, 2025, 52 (4): 736–741.

Hao CF, Zhang XY, Liu W, et al. Serovars and antimicrobial resistance and antimicrobial resistance genes of *Salmonella* in Haidian District, Beijing, 2016–2023 [J]. *Modern Preventive Medicine*, 2025, 52(4): 736–741.(In Chinese)

- [18] 聂丽, 邓颖, 罗万军, 等. 2017–2022 年武汉地区儿童食源性疾病监测中沙门菌感染情况和耐药性分析[J]. *中国人兽共患病学报*, 2024, 40(8): 750–757.

Nie L, Deng Y, Luo WJ, et al. *Salmonella* infection and drug resistance in foodborne disease surveillance among children in Wuhan from 2017 to 2022[J]. *Chinese Journal of Zoonoses*, 2024, 40 (8): 750–757.(In Chinese)

- [19] Anonym. WHO bacterial priority pathogens list, 2024: arterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance [EB/OL]. [2025-05-30]. <https://www.who.int/publications/i/item/9789240093461>.

- [20] 赵月, 王湘如, 彭忠, 等. 沙门菌和大肠埃希氏菌耐药基因 qnrS 研究进展[J]. *动物医学进展*, 2021, 42(3): 74–77.

Zhao Y, Wang XR, Peng Z, et al. Progress on drug resistance gene qnrS in *Salmonella* and *escherichia coli* [J]. *Progress in Veterinary Medicine*, 2021, 42(3): 74–77.(In Chinese)

- [21] Qiu YF, Nambiar RB, Xu XB, et al. Global genomic characterization of *Salmonella enterica* serovar telelkebir [J]. *Frontiers in Microbiology*, 2021, 12: 704152.

收稿日期:2025-03-26

(上接第 2871 页)

Fermentation, 2024, 10(11): 553.

- [54] Barros CP, Pimentel TC, Silva R, et al. A comprehensive review of the use of traditional and emerging technologies for attenuation of probiotics strains[J]. *Food Control*, 2024, 165: 110667.

- [55] Gundogan BN, Saricoban C, Unal K. The effect of different drying methods on some physico-chemical, functional and protein structure properties of liquid egg white fermented by *Lactobacillus rhamnosus* GG [J]. *Journal of Food Science and Technology*, 2023, 60 (9): 2433–2443.

- [56] Abee T, Wouters JA. Microbial stress response in minimal processing [J]. *International Journal of Food Microbiology*, 1999, 50 (1/2): 65–91.

- [57] Cui S, Zhou W, Tang X. The effect of proline on the Freeze-Drying survival rate of *bifidobacterium longum* CCFM 1029 and its inherent mechanism[J]. *International Journal of Molecular Sciences*, 2022, 23 (21): 13500.

- [58] Nivoliez A, Camares O, Paquet-Gachinat M, et al. Influence of manufacturing processes on in vitro properties of the probiotic strain *Lactobacillus rhamnosus* Ler35?[J]. *Journal of Biotechnology*, 2012, 160(3/4): 236–241.

- [59] Grześkowiak L, Isolauri E, Salminen S, et al. Manufacturing process influences properties of probiotic bacteria [J]. *British Journal of Nutrition*, 2011, 105(6): 887–894.

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