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专论与综述

后生元抗病毒性肠胃炎实验研究进展

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摘　要：病毒性肠胃炎是由多种病毒引起的急性传染病。后生元可用于病毒性肠胃炎的预防和治疗，其具体临床可行性和治疗策略仍需进一步探究。本文详细介绍了国内外关于后生元组分抗轮状病毒、诺如病毒性肠胃炎及其作用机制的最新研究进展，分析后生元抗肠道病毒的研究现状及未来研究方向，有利于后生元在肠道病毒防治应用的研究。
关键词：后生元；病毒性肠胃炎；轮状病毒；诺如病毒

Experimental research progress in postbiotics against viral gastroenteritis

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Abstract: Viral gastroenteritis is an acute infectious disease caused by multiple different viruses. Postbiotics can be used for the prevention and treatment of viral gastroenteritis, and the

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specific clinical feasibility and treatment strategy remain to be studied. This article reviews the latest research progress in the application and mechanism of postbiotic components in treating gastroenteritis caused by rotavirus and norovirus and discusses the current status and future research directions of postbiotics in inhibiting enteroviruses. This review is conducive to the research on the application of postbiotics in the prevention and treatment of enteroviruses.
Keywords: postbiotics; viral gastroenteritis; rotavirus; norovirus

病毒性肠胃炎又称病毒性腹泻，由多种病毒引发的急性传染病，轮状病毒和诺如病毒是全球儿童病毒性胃肠炎中常见的主要病原体[1-2]。急性病毒性肠胃炎在贫困国家存在较高发病率和死亡率[3]。为控制疾病流行，需寻找经济且易代替的预防和治疗措施。病毒性肠胃炎会引发小儿腹泻、破坏肠道菌群导致免疫防御下降，所以通过调节肠道微生态、促进肠道免疫力发展及维持肠黏膜稳态可能是有效的治疗方法之一[4]。目前，人们正在研究通过调节肠道微生物群并促进健康或治疗疾病的物质，如益生菌、益生元和后生元。

益生菌属于有益活性微生物，当摄入足够量时，给予宿主健康益处[5]。益生菌广泛用于临床治疗，如调节肠道微生物和治疗腹泻[6]等。其中，鼠李糖乳杆菌(*Lactobacillus rhamnosus* GG, LGG)和布拉氏酵母菌(*Saccharomyces boulardii*)常用于治疗病毒性腹泻[7-8]。急性病毒性腹泻的儿童服用含 LGG 的口服液可缩短腹泻持续时间[9]。然而，尽管益生菌在肠道保护方面表现出益处，但对于不足月婴儿、新生婴儿、危重症成人或重症监护的婴儿以及术后、住院或免疫力低的患者，益生菌会增加感染或发病的风险[10]，并且益生菌需较高剂量才表现出疗效[11]。此外，接受酵母制剂[含酿酒酵母(*Saccharomyces cerevisiae*)/布拉氏酿酒酵母]治疗的患者部分出现真菌感染[12-13]。益生元是一类被宿主有益微生物选择性利用，从而带来健康益处的膳食成分[14]。临床研究表明，添加益生元可以降低生命早期胃肠道感染病毒风险(包括轮状病毒感染)，在病毒性腹泻中起到预防和阻断作用[15-18]。但益生元会在肠腔内出现渗透作用并在结肠中发酵，大剂量摄入时会诱发胀气和腹胀，同时可能引起肠易激综合征或胃食管反流[19]。可见益生菌和益生元给药具有局限性。

随着科学研究的深入，益生菌不再一味强调活菌，认为益生菌的衍生效应分子具有与母体益生菌相似的功能，即“后生元”。后生元研究最早可追溯到 100 年前，俄罗斯微生物学家 Elie Metchnikoff 将热灭活乳酸菌加入小鼠饮食中，使得小鼠寿命延长 8%[20]。国内后生元的研究也在逐步进行中。早在 70 年代，已有研究者成功研制乳酸菌素[21]。胡文锋团队 1999 年启动灭活乳酸菌的基础研究，以乳杆菌对畜禽动物的免疫调节、抗菌抑菌、生长性能等的影响开展动物试验，为我国人用灭活乳杆菌做出开创性工作；2022 年后以“后生元”为基石，开发了针对畜禽细菌性腹泻和病毒感染的防控及替代产品；目前该团队从食品类和个护日化类等领域应用推广后生元[22-28]。

未来不同菌株制备的后生元制剂可能用于改善肠道菌群紊乱引起的多种生理疾病。2021 年国际益生菌和益生元科学协会发布了后生元定义，指对宿主有益的无生命微生物或其成分[29]。相较于活菌，后生元可以更好地黏附在肠道黏液上[30]，对治疗免疫功能低下或极度不适的儿童急性肠胃炎患者，后生元可能是一种更安全的替代品。益生菌、益生元和后生元差异见表 1。

表 1 益生菌、益生元、后生元差异

Table 1 A comparison of the differences between probiotics, prebiotics and postbiotics

Item	Probiotics	Prebiotics	Postbiotics
功能[31] Function[31]	可在肠道中定殖,增强其微生物平衡；大部分后生元前身 Can colonize the gut, enhancing its microbial balance; They can produce postbiotics	为有益细菌提供食物，促进其生长和活动[32] Provide food for beneficial bacteria, promoting their growth and activity[32]	间接影响宿主微生物群的组成，从而产生有益影响 May not directly affect microbiota composition but exert beneficial effects on host health
稳定性[31] Stability[31]	对温度和胃酸等条件敏感 Sensitive to environmental conditions like temperature and stomach acid	一般稳定，不受温度或胃酸的影响 Generally stable and not affected by temperature or stomach acid	稳定；对温度、胃酸或消化酶不敏感 Stable; Not sensitive to temperature, stomach acid, or digestive enzymes
安全性[31] Safety[31]	可引起免疫功能低下的个体感染 Can cause infections in immunocompromised individuals	过量食用会导致肠胃不适 Overconsumption can lead to gastrointestinal discomfort	通常是安全的,但大量摄入的影响尚不明确 Generally safe, but the effects of large amounts are not well-known
注意点[33] Note[33]	有效剂量的活性益生菌必须在保质期内 An efficacious dose of viable probiotics must be preserved within the shelf life	并非所有纤维都是益生元 Not all fibers are prebiotics	纯化的代谢物不能定义为后生元 Purified metabolites do not qualify as postbiotics

后生元可直接或间接影响机体微生物群组，并有高生物活性和安全性，在治疗病毒性肠胃炎方面具备更好优势。本文总结了近年来后生元治疗诺如病毒和轮状病毒引起的病毒胃肠道疾病的研究进展及作用机制，并展望了其应用前景。

1 后生元的分类

后生元是多种活性物质组成的复杂混合物，包括灭活微生物、菌体成分、微生物裂解物和微生物代谢产物[29]，见图 1。灭活微生物是指经特定方式(热或非热处理)杀死菌株的细胞，绝大部分是灭活益生菌[29]。微生物裂解物是指已灭活微生物再通过物理或化学等处理释放的细胞内生理活性物质[34-35]。此外，依据微生物群代谢产物，后生元的活性物质包括短链脂肪酸、胞内多糖、酶、蛋白质、有机酸和其他代谢物[36]；根据灭活菌体成分可分为磷壁酸、碳水化合物(如富含半乳糖的多糖)、细胞壁蛋白(p40、p75 分子)和其他复杂分子(脂磷壁酸、肽聚糖衍生的多肽)[37-40]。

2 后生元抗病毒的潜在作用机制

后生元是多种活性物质组成的混合物，可能通过不同途径影响目标宿主的健康。后生元抗病毒作用机制可能通过调节免疫系统、增强肠上皮屏障功能和调节肠道微生物菌群来实现。

2.1 调节免疫系统

后生元刺激先天性和适应性免疫系统发出抗炎信号和产生抗病毒物质,发挥抗病毒入侵作用。热灭活微生物或灭活发酵乳可以增强免疫蛋白产生，抑制促炎因子从而调节免疫[41-44]。在临床随机对照试验中，后生元可减少免疫细胞炎症，促进分泌型免疫球蛋白 A (secretory immunoglobulin A, SigA)、人中性粒细胞防御素(alpha-defensins, HNP1-3)、人 β-防御素 2 (human β-defensins 2, HBD-2)和抗菌肽 LL-37 产生，从而预防病原体的侵害[42,45-46]。部分革兰氏阴性

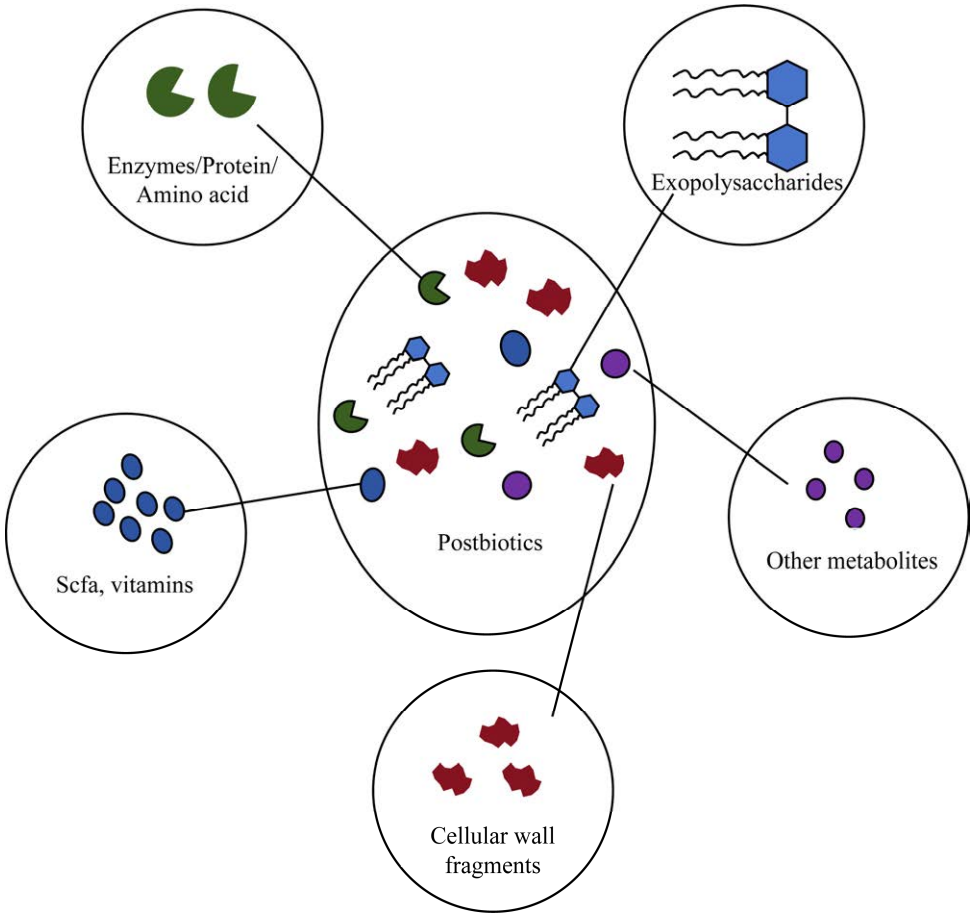

图 1　后生元活性成分分类

Figure 1　Classification of the active ingredients of postbiotics.

杆菌属后生元可诱导抗病毒细胞因子与特定的细胞表面受体结合进而触发病原体驱动的免疫应答[47-48]。此外，部分后生元作为病毒黏附宿主特定的可溶性受体类似物，与病原体相互作用，将黏附的病原体从肠道中移出或干扰病毒进入细胞，降低了病原体的传染性并增强宿主免疫系统的作用[49-50]。

2.2　增强肠上皮屏障功能

肠屏障功能完整是维持肠道健康并预防潜在病原体入侵的重要防御机制[51]。保护上皮屏障功能的一个重要机制是肠上皮细胞间紧密连接蛋白(tight junction, TJ)的形成[52]。在细胞系研究中发现，后生元可以增强 TJ 蛋白、闭锁小带蛋白-1 (zonula occludens 1, ZO-1)和下调促炎细胞因子的表达来增强肠道屏障强度[53-54]。部分研究表明，后生元可刺激上皮细胞和杯状细胞产生与分泌黏蛋白和防御素，形成免疫屏障，抵御病原体入侵[42,54-55]。同时，后生元还可通过微生物代谢物和酶通路调节上皮屏障完整性[55-56]。如灭活发酵乳可调节细胞外信号调节激酶(extracellular signal-regulated kinases, ERK)/c-Jun 氨基末端激酶(c-Jun N-terminal kinases, JNK)通路，起到减少肠道屏障损伤的作用[53-54]。植物乳杆菌(*Lactiplantibacillus plantarum*) LRCC5310 的胞外多糖(exopolysaccharides, EPS)通过诱导肿瘤坏死因子 α (tumor necrosis factor, TNF-α)的分泌，

缩短病毒性腹泻时间和病毒脱落持续时间，从而保护肠上皮细胞完整性[57]。此外，鼠李糖乳杆菌培养上清液还可通过减少细胞氯化物分泌和氧化应激[58-60]，预防病毒感染。

2.3 调节肠道微生物菌群

肠道微生物菌群保持动态平衡决定机体健康状态，肠道病毒感染可能会改变肠道微生物组成。在感染轮状病毒和诺如病毒的患者中观察到肠道微生物群紊乱，微生物丰富度和多样性较低，而后生元可直接或间接作用于病原体，使其丧失活性，从而调节肠道菌群的稳态[4,61]。如乳酸菌代谢产生乳酸，能够降低肠腔 pH 值，从而使病毒衣壳蛋白变性[61]，并且促进肠道益生菌[如双歧杆菌(*Bifidobacterium*)]的丰度，影响肠道微生物的代谢[41,62]。副干酪乳杆菌(*Lacticaseibacillus paracasei*) CBAL74 发酵乳作为膳食补充剂还可调节肠道微生物群的组成并刺激丁酸盐的产生[62]。此外，后生元物质与病原体竞争肠附着位，防止病原体定殖，从而降低病原体活性来调节肠道菌群[61,63]。

3 后生元组分对病毒性肠胃炎的治疗作用

3.1 后生元对轮状病毒肠炎的治疗作用

轮状病毒肠炎是由轮状病毒(rotavirus, RV)引起的急性肠道传染病[64]。RV 感染和复制主要发生在小肠绒毛尖端附近的非分裂成熟肠细胞中，最终导致腹泻、呕吐和发热等[65]。

轮状病毒是全世界婴幼儿严重腹泻率和死亡率的主要原因之一。根据后生元预防和治疗 RV 的相关研究，来自特定细菌菌株分泌的代谢物和发酵过程中产生的生物活性物质在病毒和宿主细胞的相互作用中起到重要作用。目前，不同后生元对 RV 引起的腹泻预防和治疗效果见表 2。

3.1.1 乳杆菌属后生元组分增强肠道屏障预防 RV 感染

乳杆菌后生元通过降低病原体的黏附及刺激对病原体的免疫反应，来维持肠道屏障，预防 RV 感染。两项体外研究发现[53-54]，副干酪乳杆菌 CBA L74 (*Lactobacillus paracasei* CBA L74, FM-CBAL74)发酵牛奶制备的后生元(FM-CBA L74)能够促进黏蛋白表达，增加 HBD-2 和抗菌肽 LL-37 先天免疫肽产生，同时还能激活 ERK/JNK 激酶通路，阻止 RV 诱导的活性氧产生、促炎细胞因子白细胞介素(interleukin, IL)-8、IL-6 和 TNF-α 释放，来保护肠道屏障完整性。RV 感染细胞产生的肠毒素非结构蛋白 4 (nonstructural protein 4, NSP4)与肠上皮细胞结合，最终导致氯离子分泌到肠腔引起分泌性腹泻[74-75]。两项研究发现，鼠李糖乳杆菌培养上清液能够降低肠上皮细胞氧化应激，减少病毒诱导的氯离子分泌，保护肠上皮细胞，从而阻碍了病毒病理作用[58,60]。Kim 等[57]在细胞系进行免疫研究中发现，植物乳杆菌 LRCC5310 的胞外多糖可以通过促 TNF-α 的分泌来保护肠黏膜免受 RV 的侵入；此外，他们在小鼠模型中还进一步证实，口服植物乳杆菌 LRCC5310 的胞外多糖可缩短 RV 诱导的腹泻时间和病毒脱落的持续时间，防止病毒感染对小鼠肠上皮细胞完整性的破坏。

临床试验中也证明了乳杆菌属后生元可有效预防 RV 相关腹泻及其症状。两项随机对照试验中观察到，摄入 FM-CBA L74 使 HNP1-3、HBD-2 和 LL-37 显著增加，同时 SigA 的产生也明显增多，进而预防 RV 感染[42-43]。Roggero 等[41]在针对新生儿的随机临床试验中，比较了两种不同饮食方案(标准配方和 FM-CBA L74 配方)与母乳喂养婴儿参考组在免疫防御机制(抗菌肽、SigA)、微生物群及其代谢组方面的活性差异；试验发现，含后生元配方奶会诱导 SigA

表 2　后生元对轮状病毒引起的腹泻预防和治疗效果

Table 2　Therapeutic and preventive effects of postbiotic elements on rotavirus-induced diarrhea

后生元来源 Source of postbiotic	后生元类型 Type of postbiotic	试验模型 Experimental model	功能 Function	参考文献 Reference
副干酪乳杆菌 CBA L74 *Lacticaseibacillus paracasei* CBA L74	热灭活发酵乳 Heat-inactivated fermented milk	临床 Clinical	促进 SigA 的分泌，增强免疫 Promote the secretion of SigA and enhance immunity	[41-43]
		体外 *In vitro*	促进黏蛋白表达，增加免疫肽产生 Promote the expression of mucins and improve innate immunity peptide synthesis	[53]
		体外 *In vitro*	激活酶通路，促进黏蛋白表达，保护肠上皮细胞屏障 Activate the enzyme pathway, promote the expression of mucins and protect intestinal barrier integrity	[54]
益生 EcN 菌和共生大肠杆菌 EcoR12 probiotic EcN and commensal intestinal *Escherichia coli*	胞外囊泡 EVs	小鼠 Mice	激活免疫细胞，改善肠道屏障 Activate immune cells and improve intestinal barrier	[55]
植物乳杆菌 LRCC5310 *Lactobacillus plantarum* LRCC5310	胞外多糖 Extracellular polysaccharide	体外/小鼠 *In vitro*/Mice	促进 TNF-α 的分泌，缩短腹泻持续时间，改善了肠道屏障 Promote TNF-α secretion, shorter duration of diarrhea and improve intestinal barrier	[57]
鼠李糖乳酪杆菌 *Lacticaseibacillus rhamnosus* GG	无细胞上清液 Cell-free supernatant	体外 *In vitro*	抑制氯离子分泌保护肠上皮细胞屏障 Inhibit chloride ion secretion and protect intestinal barrier integrity	[58]
嗜酸乳杆菌 LB *Lactobacillus acidophilus* LB	热灭活 Heat-inactivated	临床 Clinical	缩短腹泻持续时间 Shorter duration of diarrhea	[66-67]
双歧杆菌 *Bifidobacterium*	细胞提取物 Cell lysates	体外 *In vitro*	后生元与细胞表面受体竞争 Postbiotic compete with cell surface receptors	[68]
双歧杆菌 CEC77210 *Bifidobacterium* CEC77210	无细胞上清液 Cell-free supernatant	体外 *In vitro*	后生元直接抑制 RV 复制 Postbiotic directly inhibit RV replication	[69]
双歧杆菌属 *Bifidobacterium*	无细胞上清液 Cell-free supernatant	体外 *In vitro*	调节细胞肠毒素；抑制病毒复制 Regulate cellular enterotoxins; Inhibit viral replication	[70]
短双歧杆菌 C50 嗜热链球菌 065 *Bifidobacterium breve* C50 *Streptococcus thermophilus* 065	热灭活 Heat-inactivated	临床 Clinical	促进 SigA 的分泌，增强免疫 Promote the secretion of SigA and enhance immunity	[71]
	热灭活 Heat-inactivated	小鼠 Mice	与 RV 相互作用并移除，增强免疫 Interact with and remove RV to enhance immunity	[72]
	热灭活 Heat-inactivated	小鼠 Mice	降低粪便 pH 值，促进黏蛋白，改善肠道屏障功能 Decrease fecal pH, increase expression of mucins and improve intestinal barrier function	[73]

增加,但不引起抗菌肽、微生物群的多样性增加,有利于婴儿免疫系统、微生物群和代谢组的成熟。此外,FM-CBA L74 作为膳食补充剂还具有诱导肠道微生物群组成并刺激丁酸盐产生的作用[62]。热灭活细菌也在急性腹泻儿童中进行了测试。在急性腹泻儿童中将冻干、热灭活的嗜酸乳杆菌(*Lactobacillus acidophilus*) LB 与安慰剂作为口服补充剂,治疗 24 h 后,发现热灭活嗜酸乳杆菌 LB 组中 RV 阳性患儿明显降低水样粪便数量,与安慰组相比,腹泻的平均持续时间大幅度缩短[66],与 Szajewska 等[67]的研究一致。

3.1.2 双歧杆菌属(*Bifidobacterium*)后生元组分阻断病毒侵入

双歧杆菌属中部分菌种的提取和代谢物质,在病毒和宿主细胞之间发挥着重要抗病毒作用。Salas-Cárdenas 等[68]报道,双歧杆菌属富含蛋白质的提取物可通过结合 β3-整合素和热激蛋白 70 来干扰 RV 在细胞系上的黏附。双歧杆菌 CECT7210 无细胞上清液的蛋白质内含一种由 11 个氨基酸组成的小肽,可直接抑制轮状病毒复制[69]。RV 病毒肠毒素对肠道神经系统的刺激会使得 NSP4 介导的细胞内钙浓度增加,从而诱导肠内分泌 5-羟色胺,激活小肠的肠神经,增加肠蠕动,导致腹泻[55,76]。青春双歧杆菌(*Bifidobacetrium adolensentis*)分泌蛋白可通过调节细胞内 NSP4 蛋白量和影响钙离子(Ca^{2+})释放[70]。此外,后生元直接与病毒颗粒结合,从而阻断轮状病毒侵入细胞[77-78]。许多研究发现,基于蛋白质的化合物表现出抗 RV 活性。但在一项研究中发现,长双歧杆菌(*Bifidobacterium longum*)菌株的细胞提取物中的低分子量、非蛋白质成分在抑制 RV 感染起到重要作用,但该抗病毒活性物质仍然需要进一步研究和鉴定[79]。

灭活发酵乳的生物活性物质对小鼠肠道和人体肠道微生物群组成和代谢有益[72,80-81],也是改善早期轮状病毒诱导的腹泻预防和治疗的良好策略之一[71-72]。Rigo-Adrover 等[72]小鼠模型研究表明,热灭活处理的发酵乳中的生物活性物质可作为病毒黏附宿主特定的可溶性受体的类似物,与病原体相互作用,并将黏附的病原体从肠道中移出,从而改善因 RV 感染的乳鼠腹泻发生率、持续时间和严重程度,并增强宿主免疫系统的作用。Morales-Ferré 等[73]发现摄入发酵乳可降低粪便 pH 值,促进黏蛋白 MUC2 和 Toll 样受体(Toll-like receptors, TLR)的表达,保护肠道屏障功能,增加肠道双歧杆菌并影响微生物菌群代谢,对生命早期胃肠道的免疫防疫产生有益影响;此外,后生元增强 Toll 的表达,从而降低腹泻发生率和严重程度。Thibault 等[71]通过临床试验证明,摄入热灭活处理短双歧杆菌(*Bifidobacterium breve*) C50 和嗜热链球菌(*Streptococcus thermophilus*) 065 的发酵乳可使机体增强特异性抗 RV 的 sigA 的产生,从而降低 RV 感染导致腹泻的严重程度。

3.1.3 其他细菌属后生元组分减轻 RV 腹泻

后生元可在多个水平上调节肠上皮屏障完整性,并激活免疫细胞反应,从而保护肠上皮细胞免受病原体感染[82]。Martínez-Ruiz 等[55]临床前研究发现,益生菌 EcN 和共生大肠杆菌 *EcoR*12 产生的胞外囊泡(extracellular vesicles, EVs)均能够增强血清免疫球蛋白和脾自然杀伤细胞、细胞毒性 T 细胞和阳性 T 细胞受体 γδ 细胞对病毒感染的免疫力,还能下调肠道血清素受体-3 的表达,从而减轻 RV 腹泻。此外,两种菌株的 EVs 还表现出特异性,共生菌 *EcoR*12 EVs 可激活肠道分化簇 68 表达和 TLR2 信号传导,增加促炎性 IL-12 的产生。EcN EVs 可改善肠道成熟度(类 Fc 受体 1 表达)、屏障特性(杯状细胞数量和黏蛋白 2 表达)和吸收功能[55]。

3.2 后生元对诺如病毒肠炎的治疗作用

诺如病毒(norovirus, NV)属于杯状病毒科，正链 RNA 基因组的无包膜病毒。NV 胃肠炎呈自限性病程，健康个体中临床症状通常持续 2–4 d。然而，该病已经被证明持续时间更长或更严重，特别是对于幼儿、老年人、免疫功能低下个体和有基础病(如慢性心脏病或肾脏疾病)的患者会出现危及生命的情况[83-84]。目前尚无有效的抗病毒药物和疫苗。

据报道，后生元组分可激活免疫系统，诱导免疫分子作用于病原体，从而直接或间接用于预防和减轻诺如病毒的感染，发挥抗病毒作用(表 3)。

3.2.1 乳酸菌属后生元组分抑制病毒感染

乳杆菌后生元组分可能通过激活细胞免疫的途径发挥抗病毒作用。曹颖雯等[85]研究发现，乳酸杆菌的菌体裂解液可通过刺激宿主细胞 IFN-β 的表达，保护肠上皮细胞，间接抑制鼠诺如病毒(murine norovirus, MNV)感染。Li 等[87]发现，源于百岁老人肠源性发酵莫利乳杆菌(*Limosilactobacillus fermentum*) PV22 的基因组中含独特基因 *gadB*，使该菌株产生抗病毒活性的γ-氨基丁酸(gamma-aminobutyric acid, GABA)，GABA 通过“GABA 分流”通路传递信号，从而调节缺氧诱导分子 1α 和 IL-1β 的产生来预防肠道 MNV 感染。此外，在临床上，GABA 可预防肠道病毒感染，缓解冠状病毒感染症状并降低死亡率[89]。早期研究发现，乳酸菌及其代谢物具有抗氧化、抗肿瘤和抗菌等作用。Seo 等[86]测试了 142 种不同的乳酸菌(*Lactic acid bacteria*, LAB)菌株及其后生元，发现戊糖片球菌(*Pediococcus pentosaceus*) (CAU170229-2 和 CAU170230-3)、类肠膜魏斯氏菌(*Weissella cibaria*) (CAU170231-1 和 CAU170231-3)、清酒乳杆菌(*Lactobacillus sakei*) (CAU170208-2 和 CAU170210-4)和弯曲乳杆菌(*Lactobacillus curvatus*) (CAU170210-2 和 CAU170235-3)可使 MNV-1 水平显著降低，此外，以上菌株的无细胞上清液对 MNV-1 同样具有抗病毒作用，但与活菌相比，其抗病毒水平效果更弱。

3.2.2 其他细菌属后生元组分限制病毒复制

后生元可诱导抗病毒细胞因子与特定的细胞表面受体结合进而触发病原体驱动的免疫应答[47-48]。Bhar 等[56]研究中，用 3 种革兰氏阴性菌产生的外膜囊泡(outer membrane vesicles, OMVs)处理感染 MNV 的细胞系，结果发现 MNV 可以附着在外膜囊泡上，这种附着促进病毒和囊泡的共同接种进入靶细胞，使促炎细胞因子的产生。此外，OMVs 处理还可诱导干扰素(interferon, IFN)反应，激活先天免疫，从而达到抗病毒作用[56]。在小鼠回肠的离体培养物[50]中，通过多次口服 γ-PGA 激活小鼠的 TRIF 依赖性途径来诱导 I 型 IFN 的产生，增加了血清 IFN-β 水平从而限制细胞系中的 MNV 复制，此外，γ-PGA 通过干扰病毒进入细胞，并抑制炎性细胞因子(IL-1α/β、IL-6 和 TNF-α)的产生，使回肠产生针对诺如病毒的强大抗病毒先天免疫力。胃肠道的黏膜免疫系统具有高度区域化。有研究发现，微生物代谢物对 MNV 感染的抑制作用在肠道不同区域存在相反作用[88]。肠道共生细菌产生的胆汁酸通过共生细菌酶在肠腔中发生生物转化，进而诱导III型 IFN 信号传导的产生，从而抑制近端肠道 MNV-1 的感染而增强了远端肠道 MNV-1 的感染[88]。

3.3 后生元抑制其他病毒的作用

益生菌的生物活性分子已被用于预防和减轻轮状病毒和诺如病毒感染引起的腹泻。除了上述治疗外，一些后生元也被证明能有效防治其他病毒。Sunmola 等[63]研究中发现，植物乳杆菌、淀粉乳杆菌和平肠肠球菌的肉汤培养、

表 3 不同后生元对诺如病毒引起的腹泻预防和治疗作用

Table 3 Preventive and therapeutic effects of different postbiotic elements on diarrhea caused by norovirus

后生元来源 Source of postbiotics	后生元类型 Type of postbiotics	实验模型 Experimental model	功能 Function	参考文献 Reference
芽孢杆菌 *Bacillus sphaericus*	聚 γ-谷氨酸 Poly-γ-glutamic acid	小鼠 Mice	诱导 IFN-β 表达抑制 MNV 复制，并且干扰病毒进入细胞 Inhibit MNV replication by inducing IFN-β expression and interfere with viral entry into cells	[50]
革兰氏阴性菌 Gram negative bacteria	外膜囊泡 Extracellular membrane vesicles	体外 *In vitro*	诱导 IFN 反应，降低细胞毒性和抑制病毒复制 Induce IFN responses, reduce cytotoxicity and inhibit viral replication	[56]
乳酸乳球菌 LM0230 *Lactococcus lactis* subsp. *lactis* LM0230	细菌细胞悬液 Cell suspension	体外 *In vitro*	降低猫杯状病毒滴度 Reducing virus titers	[61]
乳酸菌属 *Lactobacillus*	无菌上清液 菌体裂解液 Cell-free supernatant Cell lysates	体外 *In vitro*	刺激宿主细胞 IFN-β 的表达 Stimulate host cell IFN-β expression	[85]
乳酸菌属 *Lactobacillus*	无细胞上清液 Cell-free supernatant	体外 *In vitro*	降低 MNV-1 病毒滴度 Reducing MNV-1 virus titers	[86]
发酵莫利乳杆菌 PV22 *Limosilactobacillus fermentum* PV22	γ-氨基丁酸 GBBA	体外 *In vitro*	通过“GBBA 分流”通路传递信号，调节缺氧诱导分子 1α 和白细胞介素-1β Transmit signals via the “GABA shunt” pathway and modulating hypoxia-inducible factor 1α and interleukin-1β production	[87]
肠道共生菌 Commensal bacteria	胆汁酸 Bile acid	小鼠 Mice	诱导III型 IFN 抑制近端肠道 MNV-1 感染 Induce type III IFN inhibit MVN-1 infection in the proximal intestinal tract	[88]

无细胞上清液和细胞沉淀物均可抑制埃可病毒 7 和 13，其机制可能是菌株可产生有机酸、过氧化氢等代谢物作用于病原体，从而降低病毒的感染。微生物代谢产生的细菌素具有抑制病毒的活性。Cavicchioli 等[90]研究发现，杜兰肠球菌(*Enterococcus durans*) GEn14 产生的细菌素在病毒以剂量依赖性方式吸附 HSV-1 之前表现出高于 50%的抑制效果。SARS-CoV-2 与轮状病毒腹泻发病机制相似。Poeta 等[60]研究再次证明，LGG 的无细胞上清液可通过防止 ROS 的产生和减少氯离子分泌，从而减缓腹泻。Paparo 等[91]发现 FM-CBA L74 可通过阻断病毒受体结合域，降低血管紧张素转化酶 2 的表达，阻止 SARS-CoV-2 进入人肠上皮细胞。一项双盲试验中发现，2 种乳酸杆菌菌株(LGG 和副干酪乳杆菌 CRL431)发酵酸化的乳制品能刺激抗脊髓灰质炎病毒特异性中和抗体的产生[92]。在动物实验中，使用热灭活的粪肠球菌(*Enterococcus faecalis*)，可以显著增强小鼠体内的抗病毒反应，降低小鼠感染肠道病毒 71 型后血清中 IL-1 和单核细胞趋化蛋白-1 的水平，减弱病毒感染造成的临床症状[93]。

4 结论与展望

从体外研究积累的证据表明，后生元可通过调节免疫、改善肠道屏障、调节肠道菌群结构，发挥抗肠道病毒作用并缩短腹泻时间。因此，后生元可能是一种安全的替代品，可用于预防肠道病毒性疾病。

目前，有研究已经致力于确定起关键作用的后生元特定组分，未来后生元研究开发重点可能在于“精准后生元”。大部分研究中并未明确探讨出抗诺如病毒或轮状病毒作用的具体物质剂量。后续仍需深入细化和研究后生元具体起作用的组分和剂量，以达到最佳的治疗效果，同时为后生元抑制其他病毒研究提供思路和理论基础。此外，大部分后生元作用机制都是体外进行的，仅针对某个靶向病原体或宿主的机制。因此，还需要大量针对后生元对宿主-病原体相互作用的临床相关研究来验证这些生物活性分子的有效性和安全性。

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