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Review 综 述

益生菌的多重抗病毒作用及其机制

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摘　要：病毒性疾病对人类和动物健康造成了重大威胁。由于现有的免疫接种和抗病毒疗法的局限性，开发安全、广谱、廉价的新型抗病毒制剂极为迫切。益生菌是摄入后能对机体产生多种有益作用的活性微生物，其抗病毒作用及潜在机制是当前的研究热点。本文介绍了益生菌通过促进肠道细胞的紧密连接和产生有利物质来维护机体黏膜屏障；与病毒竞争结合靶点或直接捕获并抑杀病毒；刺激机体免疫系统，调节固有免疫反应和适应性免疫反应；分泌具有抗病毒作用的代谢产物来发挥抗病毒作用及其作用机制，以期为益生菌的抗病毒相关研究提供参考。

关键词：益生菌；抗病毒作用；抗病毒机制；黏膜屏障；免疫调节

Multifaceted antiviral effects and the underlying mechanisms of probiotics

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Abstract: Viral diseases pose great threats to human and animal health. In light of the limitations of vaccination and antiviral therapies available, developing safe, broad-spectrum, and inexpensive novel

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antivirals is an urgent task. Probiotics are viable microorganisms with a lot of benefits to the body. The antiviral effects and underlying mechanisms of probiotics are research hot spots at the moment. This review summarizes the multiple antiviral modes of probiotics, such as promoting the tight junction of intestinal cells and producing beneficial substances to maintain the mucosal barrier of the host, competing with viruses for targets or directly inhibiting and killing viruses, stimulating the immune system and regulating innate and adaptive immune response, or secreting antiviral metabolites to exert antiviral effects. The review is expected to provide insights into the development of probiotics-based antivirals.

Keywords: probiotics; antiviral effect; antiviral mechanism; mucosal barrier; immune regulation

益生菌主要是指能对人和动物产生有益作用的活性微生物。联合国粮农组织(Food and Agriculture Organization of the United Nations，FAO)和世界卫生组织(World Health Organization，WHO)将益生菌定义为：足量摄入后对宿主有益的活性微生物[1]。Elimetchnikov 最早发现了益生菌的有益作用并认为："由于肠道微生物对食物的依赖性，使得可以用有益的微生物来代替有害的微生物，从而对人的肠道菌群进行调节"[2]，这种替代可以抑制有害病原体对机体的损害，同时也有助于发挥益生菌的有益作用。益生菌种类繁多，目前临床上应用较多的是乳杆菌(*Lactobacillus*)和双歧杆菌(*Bifidobacterium*) 2 个属的成员，随着益生菌的相关研究越来越充分，可供选择的益生菌种类也在不断增加。益生菌对机体有很多益生功能，它可以促进机体肠道健康，对便秘、急性腹泻、抗生素相关性腹泻及过敏性腹泻具有良好的调节作用[3−4]；可以改善营养代谢类疾病症状，比如糖尿病、高胆固醇血症和高血脂等[5−7]；可以预防消化道及泌尿生殖道肿瘤的发生，改善相关临床症状，延长宿主寿命[8−9]；对于微生物感染类疾病也表现出了良好的防治效果，尤其是抵抗有害细菌及肠道病毒(enterovirus)、呼吸道病毒(respiratory viruses)和人类免疫缺陷病毒(human immunodeficiency virus，HIV)等感染[10−13]。

从十四世纪的黑死病到如今的新型冠状病毒肺炎，人和动物时常会暴发严重的病毒性疾病，所以人类健康发展史也是一部与病毒的对抗史。病毒性疾病对人类和动物健康造成了巨大危害，也严重影响了社会稳定和经济发展。为了与之抗争，需要不断提升诊断技术，开发新的疫苗和治疗性药物。在人类皮肤和黏膜上定殖着数以 10 万亿计的细菌，其比例与人体细胞数目接近[14]。大量的研究揭示，共生菌群可对人和动物的健康和疾病产生影响。皮肤和黏膜是机体抵抗病毒感染的第一道屏障，而益生菌又是皮肤和黏膜上共生菌群的重要组成部分，其益生作用尤其是抗病毒作用受到广泛关注。本文对益生菌的抗病毒作用及其相关机制进行了归纳和概述，以期为相关研究提供参考。

1 益生菌可以维护机体黏膜屏障

病毒作为专性细胞内寄生的病原体，可通过皮肤和黏膜表面进入宿主体内，进而入侵宿主细胞，利用宿主细胞遗传机制来进行自我复制并产生致病作用[15]。由于病毒在细胞内增殖，干扰和破坏了宿主细胞的正常代谢，可导致感染细胞的损伤和死亡[16]。病毒感染宿主细胞后，细胞表面可产生新的病毒抗原，诱发宿主产生免疫应答和炎症反应，从而造成病理损伤[17−18]。

益生菌可通过维护机体黏膜屏障，与病毒直接作用，抑制或杀灭病毒，也可通过刺激宿主免疫系统，调节病毒感染导致的过度炎症反应和免疫紊乱。另外，益生菌还可以分泌一系列具有抗病毒作用的代谢产物来发挥抗病毒作用(图 1)。

黏膜是包括病毒在内许多病原体入侵机体的门户，益生菌可以增强肠道上皮细胞(intestinal epithelial cells，IECs)间紧密连接蛋白(tight junction proteins，TJ 蛋白)的功能。TJ 蛋白是维持紧密连接结构和功能的重要组成蛋白，由咬合蛋白及闭合蛋白等跨膜蛋白和闭合小环蛋白等胞浆蛋白组成。紧密连接是聚集在侧膜顶端区域的特殊连接性复合体，是肠道黏膜屏障功能的主要组成部分[19]，当肠道黏膜上皮细胞间紧密连接受损时，会改变肠道屏障的通透性，致使病毒等病原体更容易进入机体细胞[20]。LABs 可以通过调节干扰素调节因子 3 (IRF3)和 NF-κB 通路来维护 TJ 蛋白，进而增强肠道细胞屏障功能[21]。例如，鼠李糖乳酪杆菌(*Lacticaseibacillus rhamnosus*)可

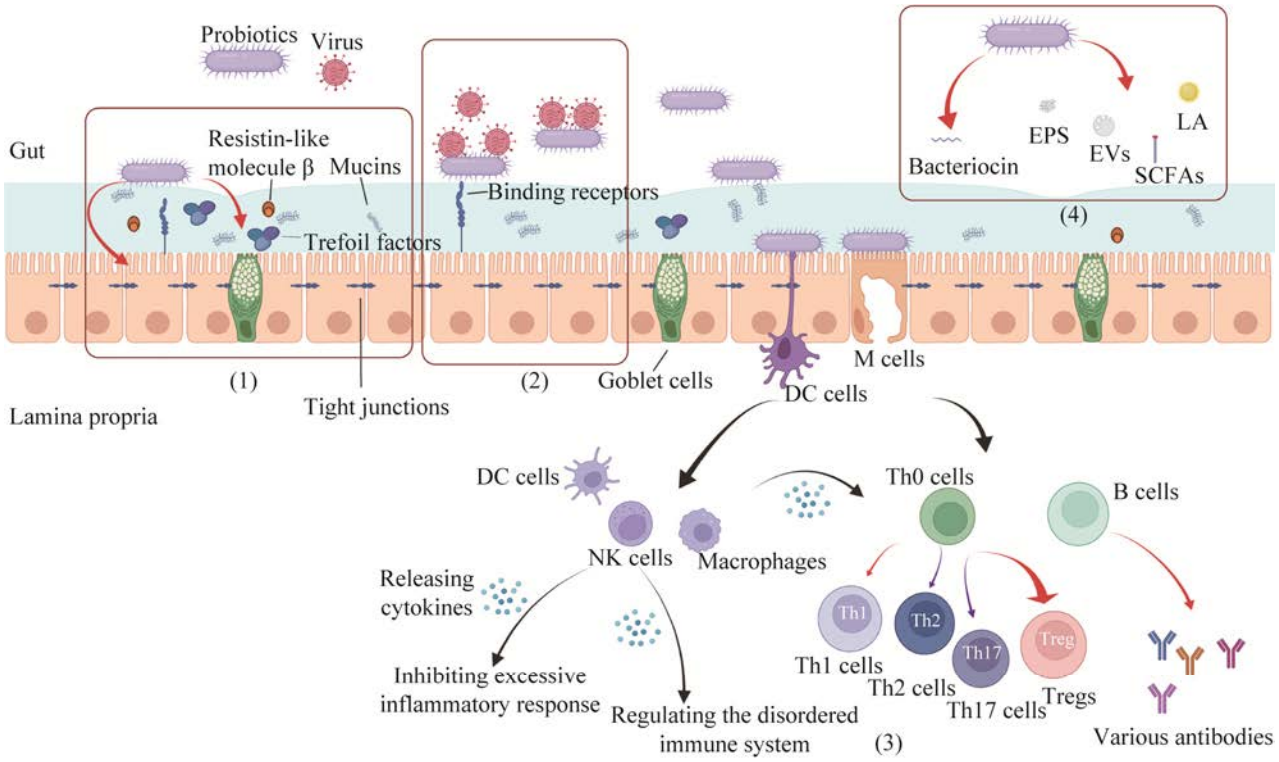

图 1　益生菌的抗病毒作用及其机制

Figure 1　Antiviral effects and the underlying mechanisms of probiotics. (1): probiotics promote tight junctions of intestinal cells and stimulate the host to produce substances that are beneficial to intestinal barrier function (such as mucins, trefoil factors, resistin-like molecules β, etc.) to maintain mucosal barrier; (2): probiotics can directly inhibit and kill viruses by competing with viruses for binding sites and capturing viruses; (3): probiotics regulate excessive inflammatory response and disordered immune system caused by viral infection by releasing related cytokines from innate immune cells, and promote Th0 cells to differentiate towards Th1 cells through related cytokines, regulate the balance between Th17/Tregs, and promote the release of antibodies by B lymphocytes; (4): probiotics can secrete metabolites with antiviral effects such as bacteriocins, EPS, EVs, LA, and SCFAs. The red arrows represent promoting effects, the purple arrows represent inhibiting effects.

以改善由轮状病毒(rotavirus, RV)感染引起的猪只空肠绒毛和隐窝深度比以及空肠绒毛下降的情况，提升肠道中分泌型 IgA (secretory IgA, sIgA)和 IL-4 的表达水平，通过维护空肠黏膜屏障功能来缓解 RV 感染引起的腹泻[22]。其机制可能是通过活化蛋白激酶 B 从而抑制 TNF-α 诱导的 IECs 凋亡[23]，且其代谢的色氨酸可以通过刺激孕烷 X 受体(pregnane X receptor，PXR)/NF-κB 信号通路，激活 PXR 和芳烃受体[24]，PXR 可抑制 c-Jun 氨基端激酶(c-Jun N-terminal kinase，JNK)的磷酸化，促进 IECs 紧密连接成分的表达[25]。从健康婴儿肠道分离的 5 株乳杆菌和 5 株肠球菌(*Enterococcus*)组合的人源性益生菌混合物也具有相似的作用，可减少 TNF-α 的表达，增强 IECs 的紧密连接[26]。益生菌除了可以增强 IECs 的紧密连接外，还可以刺激或抑制机体产生一些对肠道屏障功能有影响的物质来维护黏膜屏障。益生菌可以通过抑制 TNF-α 的表达来抑制 IECs 凋亡[23,26]，还可以刺激机体产生一些有利于肠道屏障功能的物质，如黏蛋白、三叶因子(trefoil factors，TFFs)和抵抗素样分子 β (resistin-like molecule β，RELMβ)等来维护黏膜屏障[27]。胃肠道黏膜表面有一到两层黏液层，黏液中除了水外，其结构很大程度上是由黏蛋白(mucins)构成的，黏蛋白能提供益生菌的黏附位点并阻止病毒直接接触 IECs[20,28]。TFFs 在黏膜保护和修复过程中发挥关键作用，可以促进黏膜修复，同时调节细胞连接、细胞凋亡、血管生成和黏膜分化等过程[29–30]。RELMβ 是一种杀菌蛋白，能够限制病原体与 IECs 的接触[31]。此外，益生菌代谢产生的丁酸也可通过促进黏蛋白和 TFFs 的合成来保护肠道黏膜屏障[32]。

2 益生菌可以直接抑杀病毒

益生菌除了可以通过维护黏膜屏障功能来抑制病毒感染宿主细胞外，还可以通过与病毒直接作用来抑制病毒感染宿主细胞，这种作用主要依靠其与病毒竞争细胞结合位点和对病毒的捕获能力。嗜热双歧杆菌(*B. thermophilum*)可以降低 RV 在体外对肠道细胞的黏附，攻毒前喂饲 *B. thermophilum* RBL67 可以抑制 RV 在肠道细胞上的复制，缩短腹泻时间。其作用机制可能是通过与 RV 竞争宿主细胞结合靶点和加强肠上皮细胞之间的紧密连接[33]。粪肠球菌(*E. faecium*) NCIMB 10415 株可以直接捕获猪流感病毒(swine influenza virus，SIV)，与对照组相比，益生菌处理组的病毒滴度下降了约 100 倍，且细菌沉淀物中可检测到大量的病毒粒子，证明了 *E. faecium* 对 SIV 的直接捕获作用[34]。双歧杆菌和乳杆菌的某些菌株可以捕获水泡性口炎病毒(vesicular stomatitis virus，VSV)[35]。但值得注意的是，益生菌与病毒之间的直接作用存在特异性。例如，格氏乳杆菌(*Lactobacillus gasseri*) CMUL57 株可以捕获有囊膜的单纯疱疹病毒 2 型(herpes simplex virus type 2，HSV-2)，但对无囊膜的柯萨奇病毒(coxsackie virus，CV)的入侵没有保护作用[36]，而罗伊氏粘液乳杆菌(*Limosilactobacillus reuteri*)可以通过与 CV 直接作用来阻碍其进入宿主细胞[37]。益生菌和病毒特异性识别和作用的机制目前尚不清楚，但这种抗病毒差异性提示，在应用益生菌进行抗病毒研究时需要筛选合适的菌株。

益生菌与病毒的直接作用离不开其黏附性。作为最常用的益生菌，乳杆菌和双歧杆菌都是革兰氏阳性菌，其表面分子如脂磷壁酸、表层相关蛋白和黏蛋白结合蛋白，可以和机体肠道的黏液成分相互作用起到黏附效果[38]。益生菌对肠黏膜表面的黏附最初是通过疏水作用非特异性的物理结合[39]，随后通过特定的细胞

壁成分如黏附素等进行黏附[40]。菌毛和黏液结合蛋白可以促进益生菌的黏附作用，LGG 的高黏附性就与其表达的黏液结合蛋白 SpaC 有关[41]。此外，一些表面蛋白(如纤维连接蛋白结合蛋白和表面层蛋白)也在益生菌与肠道的黏附中发挥重要作用[42–43]。益生菌对肠道的黏附可以阻止病原体入侵肠道细胞，且益生菌的黏附作用不仅在于与宿主细胞的黏附，还可以对其他有害病原体进行黏附[44]。多项研究表明，益生菌可通过与病原菌结合成共同聚集体，抑制有害病原菌感染中经常涉及的生物膜过程，从而发挥保护作用[45–46]。

3 益生菌通过调节免疫反应发挥抗病毒作用

当病毒等病原体突破机体的皮肤及黏膜屏障侵入宿主细胞后，机体主要通过局部和全身免疫系统启动固有免疫反应和适应性免疫反应来清除入侵的病原体。益生菌可以刺激机体免疫系统[47]，通过固有免疫反应和适应性免疫反应来调节病毒感染引起的过度炎症反应和免疫紊乱现象，从而发挥抗病毒效应[48]。

3.1 益生菌调节固有免疫反应

益生菌可以调节机体的固有免疫反应，通过作用于固有免疫细胞的模式识别受体(pattern recognition receptors，PRRs)，促进相关细胞因子的产生从而发挥抗病毒作用(表 1)。这种作用不仅局限于黏膜免疫系统，也对非黏膜部位的免疫器官起作用。在无菌小鼠非黏膜淋巴器官中的自然杀伤细胞不能启动有效的抗病毒免疫，巨噬细胞和树突状细胞对病毒感染不能产生 I 型 IFN，其机制可能是由于共生菌群影响单核巨噬细胞上 PRRs 与转录相应细胞因子的启动子结合[49]。

乳酸杆菌和双歧杆菌等革兰氏阳性菌主要作用于 Toll 样受体 2 (TLR2)，双歧杆菌属的 *B. animalis* ssp. *lactis* BB-12 是一种常用的益生菌，可通过 TLR2 途径诱导人外周骨髓细胞以及猪单核细胞和肠系膜淋巴结细胞产生 IL-10[50–51]。IL-10 是公认的炎性抑制因子，可以抑制病毒引起的过度炎症反应，同时 IL-10 还可以促进 B 细胞的生长和分化。此外，乳杆菌的脂磷壁酸通过 TLR2 诱导巨噬细胞产生 TNF-α，诱发炎症，阻止肿瘤的发生和病毒复制[52]。但值得注意的是，不同乳杆菌菌株诱导促炎性细胞因子产生的能力差异较大，罗伊氏乳杆菌诱导机体产生 TNF-α 和 IL-1β 的能力远大于干酪乳酪杆菌(*Lacticaseibacillus casei*)[53]。脆弱拟杆菌的荚膜多糖 A 可以通过 TLR4-TRIF 途径诱导结肠树突细胞分泌 IFN-β 来维持机体免疫平衡，增强对病毒感染的抵抗力[54]。乳杆菌的一些成员可以通过抑制 TLR4 相关途径来抑制机体的相关炎症反应[55–56]。LGG 和植物乳植杆菌(*Lactiplantibacillus plantarum*)中的一些菌株可以减轻 TLR3 介导的肠道组织损伤，增加 IFN-β 和 IL-10 的产生，降低 IL-15、IL-6 的产生和减少肠道组织损伤，从而发挥抗病毒作用[21,57]。此外，益生菌还可以通过上调 TLR7 信号通路激活炎性小体来调节呼吸道黏膜免疫，通过提高 IFN-γ、IL-17 的水平和降低 IL-4、IL-10 的水平来发挥抗病毒作用[58]。某些益生菌也可以作用于 TLR9，从而介导机体的抗炎作用，且无活力的益生菌也被发现具有同样的效果[59]。除了 Toll 样受体外，益生菌也能作用于 NOD 样受体(NLR)，通过抑制 TNF-α、IL-1β、IL-6 和 IFN-γ 等细胞因子的产生来抑制炎症反应[60–62]。

表 1　益生菌作用于模式识别受体

Table 1　Probiotics interacting with pattern recognition receptors

PRRs	Probiotics	Outcome	References
TLR2	*B. lactis BB12*	IL-10↑	[50–51]
	Lc. casei YIT 9029, *Lc. rhamnosus* YIT 0232, *Lm. fermentum* YIT 0159, *Lm. reuteri* YIT 0197, *Lp. plantarum* YIT 0102, *L. acidophilus* YIT 0070	TNF-α↑	[52–53]
TLR3	*Lp. plantarum* CRL1506, *Lc. rhamnosus* CRL1505	IL-10↑, IFN-β↑	[57]
	Lp. plantarum DU1, *Weissella cibaria* DU1, *Latilactobacillus sakei* DU2	IL-15↓, TNF-α↓	[21]
		IL-10↑, IFN-β↑	
		IFN-α↑, TNF-α↓	
TLR4	*Bacteroides fragilis*	IFN-β↑	[54]
	Golden bifid	TNF-α↓, IL-1β↓	[55]
	Probiotic-4	TNF-α↓, IL-6↓	[56]
TLR7	Bifico	IFN-γ↑, IL-17↑	[58]
		IL-4↓, IL-10↓	
TLR9	VSL#3	IL-6↑	[59]
		IL-12↑	
NOD1	LGG, *B. longum* ssp. *infantis* S12	IL-8↓, hBD-2↑	[60]
NOD2	LGG, *B. longum* ATCC15697	IL-1β↓	[61]
	BLS-mix	IL-22↑, IL-8↑	[62]

Probiotics: Golden bifid: *B. longum*, *L. bulgaricus*, *S. thermophilus*; Bifico: *B. longum*, *L. acidophilus*, *E. faecalis*; VSL#3: 4 *Lactobacillus* strains (*Lc. casei*, *Lp. plantarum*, *L. acidophilus*, *L. delbrueckii* subsp. *bulgaricus*), 3 *Bifidobacterium* strains (*B. longum*, *B. breve*, *B. infantis*), 1 *Streptococcus* strains (*S. salivarius* subsp. *thermophilus*); BLS-mix: *Bacillus licheniformis*, *Bacillus subtilis*. Outcome: ↑indicates the expression increased significantly; ↓indicates the expression reduced significantly.

3.2　益生菌调节适应性免疫反应

益生菌对适应性免疫的调节主要是通过相关细胞因子对 T、B 细胞的分化、生长以及增殖的促进作用和促进抗体的产生来实现的。益生菌可以调节 T 细胞的功能，增加 IFN-γ 的表达以及通过巨噬细胞分泌 IL-12 来促进 Th1 细胞的发育[63–64]，同时抑制外周血单核细胞(peripheral blood mononuclear cells，PBMC)分泌 Th2 细胞因子[65]。所以益生菌可以通过刺激单核细胞、巨噬细胞或树突状细胞释放相关细胞因子，间接调节 Th1 与 Th2 平衡，使其趋向 Th1[66]。有研究表明，副干酪乳酪杆菌(*Lacticaseibacillus paracasei*) NCC2461 株可以促进调节性 T 细胞(regulatory T cells，Tregs)表达 TGF-β，抑制 $CD4^+$ T 细胞的增殖活性，显著降低 Th1 和 Th2 效应细胞因子的表达(IFN-γ、IL-4 和 IL-5)，维持 IL-10 的水平，从而降低过度的炎症反应[67]。此外，益生菌可以改善肺炎患者的发烧持续时间和相关临床症状，并使炎症标志物水平正常化，早期感染和炎症恢复可能是由于益生菌通过促进 Tregs 亚群和抑制 Th17 与 Tregs 比率而发挥免疫调节作用[68]。但 *B. bifidum* BI-504、*B. bifidum* BI-98 和嗜酸乳杆菌(*L. acidophilus*) NCFM 株可以通过修饰抗原递呈细胞导致 Tregs 活性降低，这种对 Tregs 功能的抑制作用可以限制抗炎活性[69]。总之，益生菌双向调节机体免疫平衡，纠正紊乱的免疫系统。对于体液免疫，有研究表明，每天摄入益生菌的哺乳期母亲相较不摄入益生菌的母亲，母乳中的 IL-6 水平更高，且母乳中 IL-6 水平升高与 IgA、IgG 呈正相关[70]。此外，饲喂益生菌也可以增加小鼠血清中 IgE、IgM 和 IFN-γ 的表达[71]。益生菌还可以增加育肥鸡群的日增重和饲料转化率，提高鸡传染性法氏囊疫苗免疫后的抗体效价，但对新城疫疫苗的抗体效价无显著影响[72]。

益生菌对适应性免疫的调节不仅在于增强细胞免疫、控制炎症反应，还可以促进抗体应答。基于益生菌的这种特性，其作为疫苗载体应用于黏膜疫苗的开发最近几年受到广泛关注。黏膜免疫比传统的肠外免疫具有潜在的优势，可以在黏膜和全身组织中诱导免疫防御，从而保护黏膜表面免受病原体入侵[73]。本团队研究显示，表达猪瘟病毒 E2 蛋白的重组植物乳杆菌 NC8-pSIP409-E2 可以显著提高免疫组小鼠外周血中 $CD4^+$和 $CD8^+$ T 细胞水平，可有效刺激淋巴细胞的增殖[74]。所以益生菌的抗病毒应用方向是多样化的，其应用潜力值得发掘。

4 益生菌可以分泌具有抗病毒作用的代谢产物

益生菌除了本身可以直接抑杀病毒和刺激机体免疫系统外，其分泌的很多代谢产物也被证明具有多样的抗病毒效果，我们大致可将其分为蛋白类抗病毒代谢产物和非蛋白类抗病毒代谢产物。

4.1 益生菌产生的蛋白类抗病毒代谢产物

益生菌产生的具有抗病毒效应的蛋白类代谢物主要是各种细菌素。细菌素是许多细菌在初级生长阶段以核糖体方式合成的具有抗微生物、抗癌和抗生物膜作用的抗菌肽[75]。关于细菌素抗有害菌感染的报道很多，而有关其抗病毒与抗肿瘤作用最近几年也开始被关注。1999 年，Wachsman 发现 *E. faecium* CRL35 分泌的肠球菌素(enterocin) CRL35 具有抗 HSV 的活性[76]，这可能是第一例关于细菌素抗病毒的报道。后续相关研究表明，enterocin CRL 抑制 HSV 传播主要是由于阻止晚期糖蛋白合成所致[77]。此外，一些肠球菌分泌的肠球菌素还被证明具有抗脊髓灰质炎病毒和抗流感病毒的作用[78–79]。

乳酸菌产生的细菌素其抗病毒作用是目前相关研究的重点，除了肠球菌素外，其他类乳酸菌产生的细菌素发挥的抗病毒作用也有报道。从德氏乳杆菌(*L. delbrueckii*)中分离并提纯的分子质量约为 5.0 kDa 的细菌素对 H7N7 和 H7N1 亚型流感毒株具有高度特异性的抑制作用，作者猜测这种抑制作用机制可能与病毒复制中的某些细胞内特定步骤被抑制有关[80]。本团队从大兴安岭地区健康野猪肠道分离出 5 株对胆盐和低 pH 良好耐受性的乳酸菌，并且各乳酸菌均具有自凝集和共凝聚能力。其中，唾液联合乳杆菌(*Ligilactobacillus salivarius*) M2-71 株的黏附能力和 24 h 的自凝集率最高，并表现出最强的抑菌能力；黏膜黏液乳杆菌(*Limosilactobacillus mucosa*) M4-7 株和 *Lg. salivarius* M2-71 株具备杀灭非洲猪瘟病毒和伪狂犬病病毒的活性。初步证实，这些菌株发挥抗病毒作用的成分可能是大于 10 kDa 的蛋白(数据待发表)。新型冠状病毒肺炎是近年来最严重、危害最大的病毒性传染病。冠状病毒主要通过刺突糖蛋白(spike glycoprotein, S 蛋白)与宿主细胞血管紧张素转换酶 2 (angiotensin-converting enzyme 2，ACE2)受体蛋白结合进入宿主细胞，S 蛋白结构域的细胞受体结合区(receptor binding domain，RBD)直接参与了宿主细胞受体的识别，该区域的氨基酸突变会导致病毒的种属嗜性和感染特性发生变化[81]。通过计算机模拟，植物乳杆菌素(plantaricin) BN、plantaricin JLA-9、plantaricin W、plantaricin D 可通过阻断 S 蛋白上的 RBD 或 S 蛋白与 ACE2 受体蛋白相互作用来对抗新冠肺炎感染[82]。与之相似，通过计算机模拟分析，片球菌素(pediocin) PA-1 与新冠病毒野生型和 β 变异体(谱系 B.1.351)的 S 蛋白上的 RBD 也有较强的结合能

力[83]。这些数据暗示了益生菌及其产生的细菌素在预防和治疗新冠肺炎上的潜力。此外，*Lp. plantarum* NIBR97 分泌的细菌素 plantaricin 3 (Pln3)和 plantaricin 5 (Pln5)具有抗慢病毒和甲型 H3N2 病毒的能力。通过扫描电镜分析，发现 Pln3 可以通过包膜塌陷导致慢病毒裂解，而 Pln5 则没有这种作用，这提示 Pln3 和 Pln5 可能通过不同的机制发挥抗病毒作用[84]。

虽然目前已经有针对某些病毒(例如丙型肝炎病毒和 HIV)的有效抗病毒治疗策略，但对大多数病毒而言，现在依然缺乏相应的抗病毒药物或疫苗[85]。最近几年，大量新的具有抗病毒效应的细菌素的发现提示其在抗病毒感染中的应用潜力，而且相较其他抗病毒药物，益生菌产生的细菌素具有“绿色”、安全、易于获得的优势。

4.2 益生菌产生的非蛋白类抗病毒代谢产物

除了细菌素外，益生菌还可以分泌一系列具有抗病毒作用的非蛋白类代谢产物，比如胞外多糖(exopolysaccharides，EPS)、胞外囊泡(extracellular vesicles，EVs)、乳酸(lactic acid，LA)和短链脂肪酸(short-chain fatty acids，SCFAs)等。乳酸菌分泌的 EPS 是乳酸菌在生长代谢过程中分泌的具有不同化学组成和性质的单糖或寡糖的重复单元[86]。由地衣芽孢杆菌(*Bacillus licheniformis*)产生的 EPS 可以诱导 IL-12、IFN-γ、IFN-α、TNF-α 和 IL-18 等细胞因子的产生，但对 Th2 细胞产生的 IL-4 的表达没有影响，所以其可能通过增强 Th1 细胞作用来抑制 HSV-2 在人类 PBMC 中的复制[87]。由 *Lp. plantarum* 分泌的 EPS 可减轻猪流行性腹泻病毒导致的炎症反应，降低 IL-1β、IL-6、IL-8 和 MCP-1 等促炎性细胞因子的水平，但 TNF-α 的表达水平被提高了。除此之外，*Lp. plantarum* 分泌的 EPS 可以黏附在 PEDV 上防止其吸附宿主细胞，同时诱导损伤细胞早期凋亡[88]。人阴道的共生乳酸菌分泌的 EVs 在体外可以保护组织和细胞免受 HIV 的感染，经质谱分析，这种 EVs 主要含有有机酸、氨基酸、糖和氮碱类物质，其保护作用是减少病毒对靶细胞的附着[89]。此外，有大量证据表明乳酸菌分泌的 LA 对 HIV 感染具有抑制作用，其抑制机制包括提供足够的酸性环境，正常女性宫颈阴道液样本 pH 值范围在 2.8–4.2，用盐酸将培养基酸化到这个 pH 值足以消除 HIV-1 的复制；此外，LA 在体外被证明对 HIV-1 具有抑制作用，特别是它的 L-异构体，不依赖于低 pH 值即可产生抑制作用；LA 还可以诱导人宫颈和阴道上皮细胞的抗炎反应，抑制 HIV 感染导致的炎性细胞因子的增加[90–92]。益生菌通过分解代谢纤维可以产生 SCFAs，SCFAs 具有抗呼吸道合胞体病毒感染的作用，其主要是通过介导 IFN-β 的产生来抑制病毒对机体的侵害[93]。

这些证据说明，不同的益生菌代谢产物(如 EPS、EVs、LA 和 SCFAs 以及细菌素等)可以通过不同的机制来发挥抗病毒作用。这些代谢产物称之为“后生元”，由于肠道菌群的复杂性，益生菌在体内的应用效果可能和体外实验有较大的差异，且人们对部分益生菌的安全性和有效性还存在质疑，利用其代谢产物来提高机体健康度，或许可以规避这些不足。

5 总结及展望

益生菌是一种绿色、安全且可对机体产生多种有益作用的微生物，通过维护宿主肠道黏膜屏障和直接抑杀病毒来降低病毒的入侵概率和数量；益生菌可以刺激宿主的免疫系统，促进免疫细胞分泌细胞因子调节机体免疫反应，增强细胞免疫和体液免疫，抑制过度的炎症反应来对抗病毒感染；还能分泌多种具有抗病毒

活性的代谢产物，比如 EPS、EVs、LA 和 SCFAs 以及细菌素等。总之，益生菌在很大程度上符合我们对抗病毒新产品的期待，随着新的病毒性疾病不断出现和外来病毒性疾病的传入，人们对益生菌的重视程度不断增加，关于其抗病毒方面的作用和应用也越来越被认可。

随着人们对益生菌和肠道菌群的认识不断深入，其在抗病毒领域的应用也不断地被开发，比如对于目前在我国肆虐的非洲猪瘟，养殖场可以通过饲喂益生菌制剂提高猪群的肠道健康和免疫力进而提高猪只对非洲猪瘟病毒的耐受力。益生菌作为一种“绿色”生态制剂，其作为口服疫苗的载体也受到高度重视，其本身具有佐剂作用，口服给药的方式可以减轻免疫的工作量和疫苗接种所产生的应激。益生菌的抗病毒作用及其应用场景是多方面的，但仍有许多实际问题需要解决，比如对耐酸、耐胆盐同时具有高效抗病毒效应菌株的筛选、克服肠道共生菌群差异对益生菌体内效果的影响、作为疫苗载体提高目的抗原体内表达量等都需要深入探讨。

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