

益生菌、后生元去除内毒素的机制及应用研究进展

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摘要: 随着对微生物组学研究的深入, 革兰氏阴性细菌细胞壁成分——内毒素的健康危害日益受到关注。这类毒素在细菌死亡裂解后释放至周围环境, 可通过多种途径对人体健康造成严重威胁。为应对这一问题, 益生菌作为一种非致病性活微生物制剂, 在过去几十年中被广泛应用于内毒素相关损伤的防治领域。作为益生菌研究的延伸与拓展, 后生元凭借其无活性菌体的特性, 在稳定性与安全性方面展现出显著优势, 为内毒素相关疾病的防治提供了新的解决方案。本文主要介绍了内毒素的来源、作用途径及其症状表现, 综述了益生菌的定义、去除内毒素机制及应用发展前景, 阐述了后生元去除内毒素的机制及其在抗炎、调节肠道菌群、增强上皮屏障方面去除内毒素的应用研究进展, 以期为相关领域研究者和从业者提供有益的参考和启示。

关键词: 内毒素; 益生菌; 后生元

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Research progress in the mechanism and application of probiotics and postbiotics in removing endotoxins

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Abstract: As the research on microbiomes advances, the health hazards of endotoxins, components of the cell wall of Gram-negative bacteria, have garnered increasing attention. These toxins are released into the surrounding environment after bacterial death and lysis and pose a serious threat to human health through a variety of pathways. In response to this problem, probiotics, as non-pathogenic live microbial agents, have been widely used in the prevention and treatment of endotoxin-associated injuries in the past decades. As an extension and expansion of probiotic research, postbiotics, by virtue of their inactive organisms, have demonstrated significant advantages in terms of stability and safety, providing new solutions for the prevention and treatment of endotoxin-related diseases. This article introduces the sources, action pathways, and symptomatic manifestations of endotoxins, summarizes the definition, endotoxin-removing mechanisms, and application prospects of probiotics, and reviews the research progress in postbiotics regarding the endotoxin-removing mechanisms and the application in endotoxin removal via anti-inflammatory, intestinal flora-regulatory, and epithelial barrier-enhancing effects. It is expected to provide insights for the researchers and practitioners in the related fields.

Keywords: endotoxins; probiotics; postbiotics

近年来,随着现代生活方式的转变和膳食结构的显著改变,内源性毒素蓄积现象已成为公共卫生领域的重要议题。目前,内毒素的去除主要依赖于阴离子交换层析、两相萃取、亲和层析和超滤等技术^[1]。在应对内毒素介导的病理损伤方面,非致病性微生物制剂的应用取得了显著进展。益生菌(probiotics)作为一种生物治疗剂,已在临床和功能性食品领域获得广泛应用,但其活菌特性导致稳定性差、易受环境影响,并且存在潜在的耐药基因转移风险^[2]。

后生元(postbiotics)作为微生物组研究的新兴产物,其独特的非活菌形态赋予了产品更优越的稳定性和用药安全性^[3]。这一特性使其在替代传统益生菌制剂方面展现出巨大潜力,目

前已成为微生物疗法领域的研究焦点。胡文锋团队于1999年率先开展灭活乳酸菌的基础研究,重点探究乳杆菌对畜禽动物免疫调节、抗菌抑菌及生长性能的影响,为我国人用灭活乳杆菌的研发奠定了重要基础;自2022年起,该团队基于后生元技术,开发了针对畜禽细菌性腹泻及病毒感染的防控与替代产品,并逐步拓展至食品及个护日化等领域的应用^[4-13]。

1 内毒素定义、来源、作用途径及症状表现

1.1 内毒素定义

脂多糖(lipopolysaccharide, LPS)作为革兰氏阴性菌细胞壁的重要结构成分,在细菌发生

裂解或死亡后释放,能够激活宿主固有免疫系统的级联反应,因此被定义为典型的内毒素,从分子结构特征来看,LPS属于高分子量化合物,其分子量分布范围为10–30 kDa^[14]。化学结构解析表明,LPS由3个特征性结构域通过共价连接构成:(1)特异性O抗原多糖链,具有菌株特异性;(2)保守的核心寡糖区域;(3)具有强疏水性的脂质A结构域,其中,脂质A作为LPS的生物学活性中心,通过共价键与核心多糖紧密结合^[15]。

1.2 人体与畜禽体内内毒素来源

基于产生途径的差异性,人体与畜禽内毒素可系统地划分为内源性和外源性两大来源。大量研究证实,肠道微生态系统是内源性毒素产生的主要场所,肠道菌群作为重要的生物活性因子,在其生理周期(包括对数生长期、稳定期和衰亡期)中持续释放毒性代谢产物^[16];当免疫力下降或黏膜屏障受损时,肠道内的革兰氏阴性菌可突破局部防御,释放LPS,激活免疫细胞(如巨噬细胞)触发全身炎症反应^[17]。就外源性内毒素而言,其输入途径主要可分为环境暴露和医源性2个维度。环境暴露途径主要包括大气气溶胶中的内毒素污染、水体环境中的内毒素蓄积和土壤介质中的内毒素迁移,这些环境污染物可通过消化道摄入、呼吸道吸入和皮肤渗透等多种暴露途径进入循环系统^[18];在医源性途径方面,主要包括医疗器械的生物膜污染、注射制剂的内毒素超标和治疗性血液制品的微生物污染风险^[19]。这些暴露途径均可构成外源性内毒素侵入血液循环系统的潜在通道,最终导致外源性内毒素血症的发生。在生理稳态条件下,人体血浆内毒素浓度通常维持在0.001–0.050 ng/mL的基准水平^[20],当机体免疫功能受损或遭受病原体侵袭时,内外源性致热原将被激活,通过诱导促炎因子的级联释放,最终引发全身性发热反应。

1.3 内毒素的作用途径

作为革兰氏阴性细菌,内毒素在生理条件

下可通过门脉循环以低浓度、间歇性的方式进入肝脏,并经由肝实质细胞和Kupffer细胞的协同作用被有效清除^[21]。当肠道屏障功能障碍或网状内皮系统清除能力显著降低时,外源性LPS可通过呼吸道和消化道途径大量蓄积,这种病理性累积不仅会加剧肠道上皮损伤,还可诱发腹泻综合征和系统性炎症反应^[22]。当肠道微生态失衡发生时,条件致病菌的相对丰度显著升高,导致肠道黏膜屏障的结构完整性受损,主要体现为紧密连接蛋白的表达下调,包括claudin-1、occludin、JAM-1及闭锁小带-1(zonula occludens-1, ZO-1)等关键蛋白的表达异常^[23],这种分子水平的改变显著增加了肠道通透性,最终导致LPS的异位转运现象^[24]。

内毒素经由血液循环抵达肝脏,与肝细胞表面的Toll样受体4(Toll-like receptor 4, TLR4)结合,激活LPS/TLR4信号通路^[25]。该过程通过髓样分化因子88(myeloid differentiation factor 88, MyD88)介导的信号转导机制,进一步激活核因子- κ B(nuclear factor- κ B, NF- κ B)和激活蛋白-1(activating protein-1, AP-1)信号通路,促进炎症细胞因子如肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、白细胞介素-1 β (interleukin-1 β , IL-1 β)、IL-6、IL-12的分泌,激活Toll样受体信号通路,触发级联免疫反应,导致肝细胞损伤并释放更多促炎因子,形成恶性循环,最终引发肝脏疾病^[26-27]。内毒素入侵机制见图1。

1.4 内毒素引发的症状表现

内毒素通过“肠-器官轴”参与多系统疾病,核心机制涉及TLR4通路的激活与炎症级联反应^[28],提示调控肠道屏障功能或阻断LPS信号可能成为治疗新靶点。

1.4.1 肺动脉高压(pulmonary arterial hypertension, PAH)

PAH是一种以肺动脉平均压病理性升高(≥ 20 mmHg)为特征的临床综合征,具有显著的病理异质性,其典型临床表现包括进行性呼吸

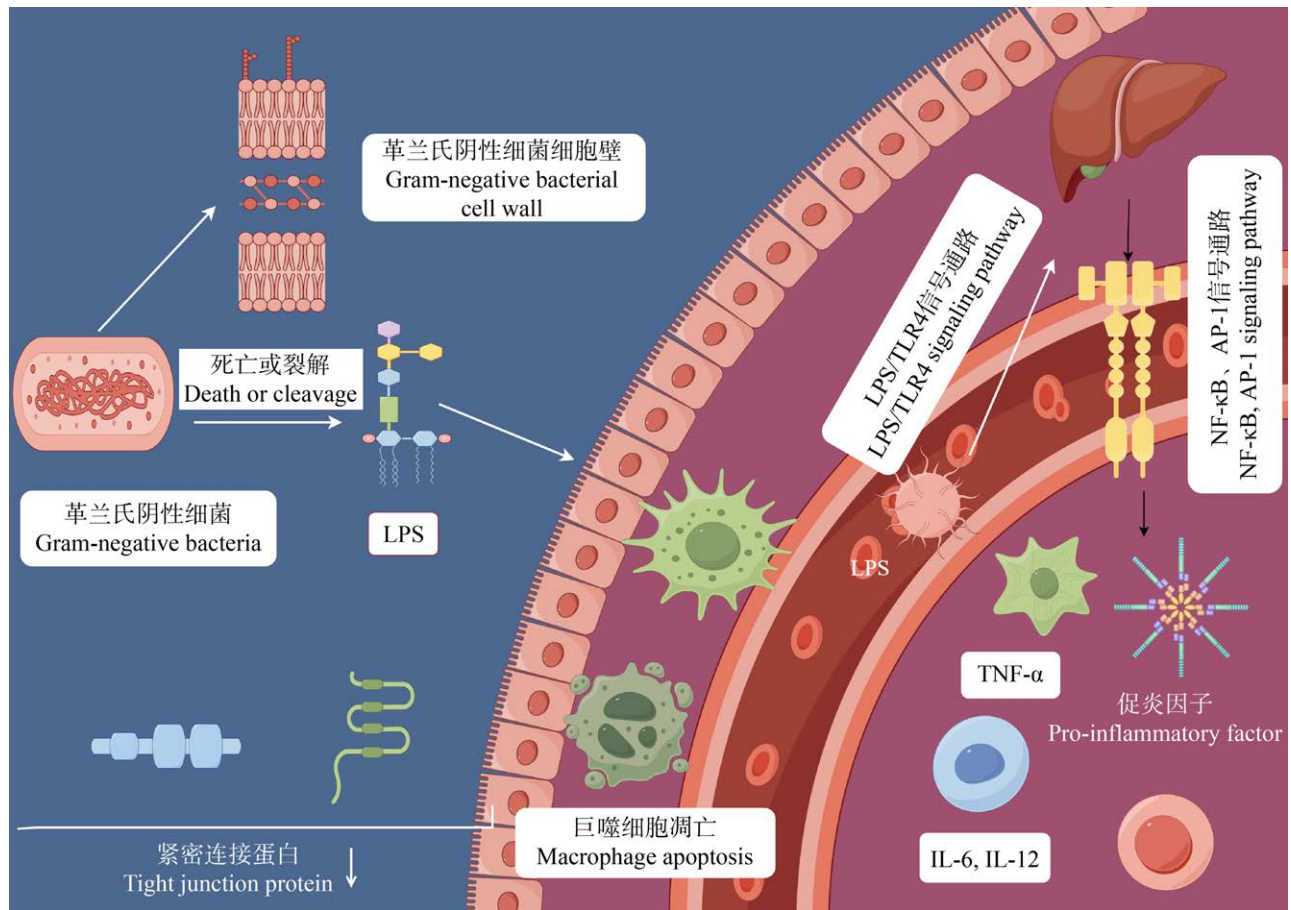


图 1 内毒素入侵机制

Figure 1 Mechanism of endotoxin invasion.

困难、运动耐量降低、右心功能不全，严重者可发展为右心衰竭甚至死亡^[29]。研究发现，肠道菌群失调通过多重机制影响 PAH 的病理进程，肠道菌群失衡可导致肠道上皮屏障完整性受损，促使 LPS 易位进入体循环，循环中的 LPS 通过与 TLR4 结合，激活 NF- κ B 信号通路，诱发系统性炎症反应；这一病理过程可促进肺血管周围炎症细胞浸润，加速肺血管重构，包括肺动脉中膜增厚和血管新生，最终推动 PAH 的病理进展^[30]。

1.4.2 代谢相关脂肪性肝病 (metabolic-associated fatty liver disease, MAFLD)

MAFLD 也被称为非酒精性脂肪性肝病，其病理特征主要表现为肝细胞内脂质异常蓄积^[31]。作为人体最大的代谢器官，肝脏在解毒代谢和

内环境稳态维持中发挥着核心作用，同时也是内毒素作用的主要靶器官之一^[32]。研究表明，内毒素诱导肝损伤主要通过以下 2 种机制：(1) 内毒素通过与肝细胞表面 TLR4 复合物结合，激活 NF- κ B 信号通路，促进炎症细胞因子的合成与释放，这一过程可激活 Kupffer 细胞，引发级联放大效应，导致活性氧大量产生，最终造成肝细胞氧化应激损伤^[33]；(2) 内毒素可通过诱导巨噬细胞活化，促进肝脏脂肪变性的进展^[34]，TNF- α 可导致肝细胞线粒体功能障碍，促进细胞色素 C 释放，同时增加脂质过氧化水平，从而加重肝细胞损伤^[35]。

1.4.3 急性心力衰竭 (acute heart failure, AHF)

AHF 是心血管疾病中常见的临床类型，其

发病的重要诱因之一是感染性内毒素血症。该病症与革兰氏阴性菌感染密切相关，其细胞壁外膜的关键致病成分为脂多糖。LPS 可引发心肌组织损伤，进而导致心力衰竭的发生^[36]。

鉴于内毒素可通过 TLR4/NF- κ B 信号通路诱发系统性炎症反应，并导致肠道屏障损伤、脓毒症等严重后果，探索安全有效的 LPS 清除策略至关重要。传统方法(如抗生素和血液净化)虽有一定效果，但存在耐药性、高成本等局限。因此，近年来，生物干预手段尤其是益生菌的应用备受关注。益生菌作为一类具有明确健康效益的活性微生物，可通过多种机制拮抗内毒素，为 LPS 相关疾病的防治提供了新思路。

2 益生菌的定义、去除内毒素机理以及发展前景

2.1 益生菌的定义

益生菌是指摄入后能够对宿主健康产生积极影响、定植于胃肠道黏膜并具有多种临床应用及免疫调节功能的活性微生物^[37]。

2.2 益生菌去除内毒素的机理

内毒素主要由革兰氏阴性菌(即腐败菌或过路菌)产生,通过补充原籍益生菌(即长期定植

于肠道的固有菌群),特别是具有免疫调节功能的益生菌株,可产生多生物生物学效应:(1) 通过营养竞争和生态位点占据抑制腐败菌的过度增殖;(2) 维持肠道微生态平衡;(3) 增强肠道相关淋巴组织的免疫功能,激活相关细胞内信号通路,从而抑制多种炎症因子的合成与释放,进一步降低内毒素水平^[38-39]。

2.3 益生菌通过增强肠道屏障及调节肠道菌群去除内毒素

益生菌通过调节肠道菌群、增强肠道屏障功能、抗炎及增强免疫反应等机制,有效缓解因内毒素水平升高引发的多种健康问题。目前广泛应用于内毒素清除的益生菌主要包括乳酸菌(*Lactobacillus*)、链球菌(*Streptococcus*)、双歧杆菌(*Bifidobacterium*)、酵母菌(*Saccharomyces*)及芽孢杆菌(*Bacillus*)等传统菌种,如表 1 所示。

2.3.1 益生菌通过增强肠道屏障功能及调节免疫系统降低内毒素水平

益生菌通过降低炎症反应、增强肠紧密连接蛋白表达以修复肠道损伤,并强化肠道屏障功能,从而降低内毒素水平。益生菌可通过不同机制的作用对内毒素实现抑制,Gu 等^[58]研究发现,从鼠李糖乳杆菌(*Lactobacillus rhamnosus*)

表 1 益生菌去除内毒素的应用

Table 1 Application of probiotics for endotoxin removal

研究对象/作用器官 Subjects of study/Organs of action	研究模型 Research model	菌属 Genus	功能 Functionality	参考文献 Reference
断奶仔猪 Weaned piglet	LPS 诱导的断奶仔猪 LPS-induced weaning of piglets	植物乳杆菌、德氏乳杆菌、地衣芽孢杆菌 <i>Lactobacillus plantarum</i> , <i>Lactobacillus delbrueckii</i> <i>Bacillus licheniformis</i>	调节肠道菌群;降低 LPS 水平;增强肠上皮屏障功能;改善仔猪的生长性能 Regulate intestinal flora; reduce LPS level; enhance intestinal epithelial barrier function; improve piglet growth performance	[40-42]
小鼠 Mice	高脂饮食喂养的小鼠 Mice fed a high-fat diet	嗜酸乳杆菌 LA5、清酒乳杆菌 OK67 <i>Lactobacillus acidophilus</i> LA5, <i>Lactobacillus sakei</i> OK67	产生抗炎分子;减轻内毒素血症;调节肠道菌群,改善肥胖 Produces anti-inflammatory molecules; reduces endotoxemia; regulates intestinal flora, improves obesity	[43-44]

(待续)

(续表 1)

研究对象/作用器官 Subjects of study/Organs of action	研究模型 Research model	菌属 Genus	功能 Functionality	参考文献 Reference
肠 Colorectal	LPS 诱导的炎症小鼠、肠损伤大鼠 LPS-induced inflammation in mice, intestinal injury in rats	动物双歧杆菌乳亚种、鼠李糖乳酪杆菌、罗伊氏乳杆菌、双歧杆菌 <i>Bifidobacterium animalis</i> subsp. <i>lactis</i> , <i>Lactocaseibacillus rhamnosus</i> , <i>Lactobacillus reuteri</i> , <i>Bifidobacterium</i>	改善肠道菌群失衡, 释放抗炎细胞因子, 增强肠屏障功能 Improve intestinal flora imbalance, release anti-inflammatory cytokines, enhance intestinal barrier function	[45-46]
肾 Liver	伏马毒素 B1 诱导的肝损伤肉鸡、手术诱导的肾病小鼠 Fumonisin B1-induced hepatic injury in broiler chickens and surgically induced nephropathy in mice	植物乳杆菌 MYS6、鼠李糖乳杆菌 GG <i>Lactobacillus plantarum</i> MYS6, <i>Lactobacillus rhamnosus</i> GG	调节肠道微生物群, 增加有益微生物丰度; 降低血清内毒素和促炎细胞因子水平, 改善肾功能 Regulates intestinal microbiota and increases the abundance of beneficial microorganisms; reduces serum endotoxin and pro-inflammatory cytokine levels and improves renal function	[47-48]
肝 Pancreas	长期饮酒的肝脏损伤小鼠 Chronic alcohol consumption in liver-injured mice	短双歧杆菌 ATCC 15700、瑞士乳杆菌 CICC 6064、复合益生菌(植物乳杆菌 DSR J266、短乳杆菌 DSR J301) <i>Bifidobacterium shortum</i> ATCC 15700, <i>Lactobacillus helveticus</i> CICC 6064, probiotic complex (<i>Lactobacillus plantarum</i> DSR J266, <i>Lactobacillus shortum</i> DSR J301)	调节肠道微生物; 增加抗炎因子含量; 降低内毒素血症; 促进肠屏障功能, 减轻酒精性肝损伤 Regulates intestinal microorganisms; increases levels of anti-inflammatory factors; reduces endotoxemia; promotes intestinal barrier function and attenuates alcoholic liver injury	[49-50]
	高脂饮食诱导的非酒精性脂肪肝小鼠、大鼠 High-fat diet-induced nonalcoholic fatty liver disease in mice and rats	副干酪乳杆菌 Jlus66、鼠李糖乳杆菌 hsryfm 1301、干酪乳杆菌 YRL577 <i>Lactobacillus paracasei</i> Jlus66, <i>Lactobacillus rhamnosus</i> hsryfm 1301, <i>Lactobacillus casei</i> YRL577	促进抗炎因子产生, 减轻炎症反应; 调节肠道菌群, 降低内毒素浓度; 减轻非酒精性肝损伤 Promote the production of anti-inflammatory factors to reduce the inflammatory response; regulate intestinal flora and reduce endotoxin concentration; reduce non-alcoholic liver injury	[51-53]
	LPS 诱导的肝损伤小鼠 LPS-induced liver injury in mice	副干酪乳杆菌 CCFM 1223、布氏乳杆菌 TCP016 <i>Lactobacillus paracasei</i> CCFM 1223, <i>Lactobacillus buchneri</i> TCP016	调节肠道菌群, 降低 LPS 诱导的炎性细胞因子, 保护肝脏 Regulates intestinal flora, reduces LPS-induced inflammatory cytokines and protects the liver	[54-55]
肺 Lungs	LPS 诱导的急性肺损伤小鼠 LPS-induced acute lung injury in mice	丁酸梭菌、罗伊氏乳杆菌 <i>Clostridium butyricum</i> , <i>Lactobacillus reuteri</i>	减少促炎细胞因子的释放; 促进抗炎因子表达; 调节肠道微生物菌群, 促进肠道屏障功能, 减轻肺损伤 Reduces the release of pro-inflammatory cytokines; promotes the expression	[56-57]

培养物中分离出的 LGG 衍生的外泌体样纳米颗粒(LGG-derived ELNP)可增加肠上皮细胞中紧密连接蛋白的表达,并保护巨噬细胞免受脂多糖诱导的炎症反应,LDNP 通过激活肠道白介素-22-Reg3 和核因子红细胞 2 相关因子 2 (nuclear factor erythroid 2-related factor 2, Nrf2)紧密连接信号通路,抑制酒精性肝病(alcohol-associated liver disease, ALD)小鼠的细菌易位和内毒素释放。Wang 等^[59]研究表明,鼠李糖乳杆菌通过抑制 TLR4 和 TLR5 介导的内毒素激活,减少 TNF- α 的产生,从而缓解酒精诱导的肝脏炎症。Wu 等^[60]发现罗伊氏乳杆菌(*Lactobacillus reuteri*)可激活 Wnt/ β -catenin 通路,刺激肠上皮细胞的增殖,修复肠道上皮损伤,保护肠道黏膜屏障免受肠道炎症的影响,减少了肠道内毒素泄漏,抑制了血液内毒素增高。这一作用机制最终减少了炎症因子向肝脏的转移,有效改善了非酒精性脂肪性肝病的症状。

2.3.2 益生菌通过调节肠道菌群降低内毒素水平

益生菌的作用地点是肠道,通过调节肠道菌群丰度,可有效降低内毒素水平。Kang 等^[61]研究表明,嗜酸乳杆菌(*Lactobacillus acidophilus*)能够有效逆转高脂饮食诱导的肠道菌群失调,具体表现为降低厚壁菌门(*Firmicutes*)与拟杆菌门(*Bacteroides*)的比例,减少革兰氏阴性菌及其内毒素水平,维持肠道屏障的完整性,减轻代谢性内毒素血症,并通过抑制 TLR4/NF- κ B 信号通路改善肥胖及相关疾病,如高脂血症、非酒精性脂肪肝及胰岛素抵抗。Xue 等^[62]研究证实,益生菌可通过调节肠道菌群微生态平衡,上调 occludin 表达,抑制 LPS/TLR4 信号通路介导的内毒素及炎性细胞因子释放,进而缓解非酒精性脂肪肝病中的肝脏及全身炎症反应。

2.4 益生菌去除内毒素的发展前景

近年来,益生菌在内毒素清除领域的研究取得了突破性进展。临床研究证实,特定益生菌菌株如丁酸梭菌(*Clostridium butyricum*)、乳杆菌

属(*Lactobacillus*)及双歧杆菌属(*Bifidobacterium*)等在改善肝病者内毒素血症方面展现出显著疗效^[63-65],其作用机制主要包括:(1)通过竞争性抑制作用,有效抑制肠道内腐败菌及尿素酶产生菌的过度增殖;(2)显著降低门静脉系统内毒素浓度;(3)改善外周血液循环中内毒素水平。进一步研究表明,益生菌可通过多重机制维护肠道屏障功能:(1)促进肠上皮细胞紧密连接蛋白的表达,维持肠黏膜屏障完整性^[66];(2)减少肠源性内毒素的产生;(3)抑制细菌易位^[67]。这些作用在急慢性肝炎、肝硬化、肝功能衰竭及其并发症的辅助治疗中具有重要意义。在代谢性疾病防治方面,益生菌通过调节肠道菌群平衡抑制条件致病菌的增殖,增强肠道屏障功能,促进内毒素排泄,从而发挥肠道保护作用^[68];特别在抗肥胖领域,益生菌可通过调控肠道菌群结构,减少膳食脂肪吸收,改善内毒素血症^[69],为代谢性疾病的防治提供了新的思路。

尽管益生菌具有诸多优势,但其在生产过程中面临确保活菌数量达到最低有效值并保持稳定性的技术挑战,抗生素耐药性风险及其作用机制的非特异性,限制了益生菌在食品和制药领域的广泛应用潜力。大量动物实验与临床研究表明,益生菌可能存在微生物移位及抗生素耐药性风险,研究还发现,益生菌活菌的使用可能引发真菌感染、胃肠胀气及抗生素耐药性增强等不良反应^[70]。相较于益生菌,后生元在提升动物生长性能及增强免疫功能方面展现出更为显著的优势。

3 后生元及其去除内毒素的应用

3.1 后生元定义

2021年5月,国际益生菌和益生元科学协会发布了关于后生元的共识声明,清晰地界定了后生元的概念及范畴:后生元是指对宿主健康具有积极作用的非活性微生物或其成分的制剂,但不包括单纯的微生物代谢物及疫苗产品^[71]。其涵

盖范围包括微生物代谢产物, 如短链脂肪酸、胞外多糖、有机酸及蛋白质等, 以及经灭活处理的菌体及其成分, 如肽聚糖、磷壁酸、细胞壁多糖和细胞表层蛋白等^[72]。

3.2 后生元去除内毒素的机制

后生元通过抗炎作用及诱导调节性 T 细胞活性实现内毒素去除(图 2)。研究表明, 后生元在调节和减轻炎症反应方面具有显著效果, 其抗炎机制主要通过抑制促炎细胞因子(如 IL-12、TNF- α 、IL-6 和 IFN- γ)实现^[73]。Yang 等^[74]发现, 急性慢性肝衰竭对 E2F1 介导的内生性凋亡通路的作用, 其主要机制为内毒素水平升高, 导致 TNF- α 和 IL-6 等炎症因子水平上升, 最终诱导细胞凋亡。在研究中发现, 后生元可通过下

调 IL-17A、TNF- α 、IL-6、IL-1 β 和 IFN- γ 水平, 同时上调 IL-10 及肠黏膜功能蛋白(如 ZO-1 和 MUC-2)的表达, 改善葡聚糖硫酸钠(dextran sulfate sodium salt, DSS)诱导的溃疡性结肠炎症状^[75]。Zhang 等^[76]通过剂量依赖性实验发现, 鼠李糖乳杆菌 1.0320 后生元干预可显著减轻 DSS 诱导的结肠炎大鼠症状及炎症反应, 具体表现为脾脏指数改善、结肠组织损伤减轻及血清细胞因子(如 TNF- α 和 IL-1 β)水平降低。证实了后生元可以通过反馈调节炎症细胞因子的表达进而减轻炎症反应。

第 2 种机制可能涉及后生元诱导的调节性 T 细胞(Tregs)及细胞因子的生成^[77]。研究表明, 热灭活的加氏乳杆菌(*Lactobacillus gasseri*)

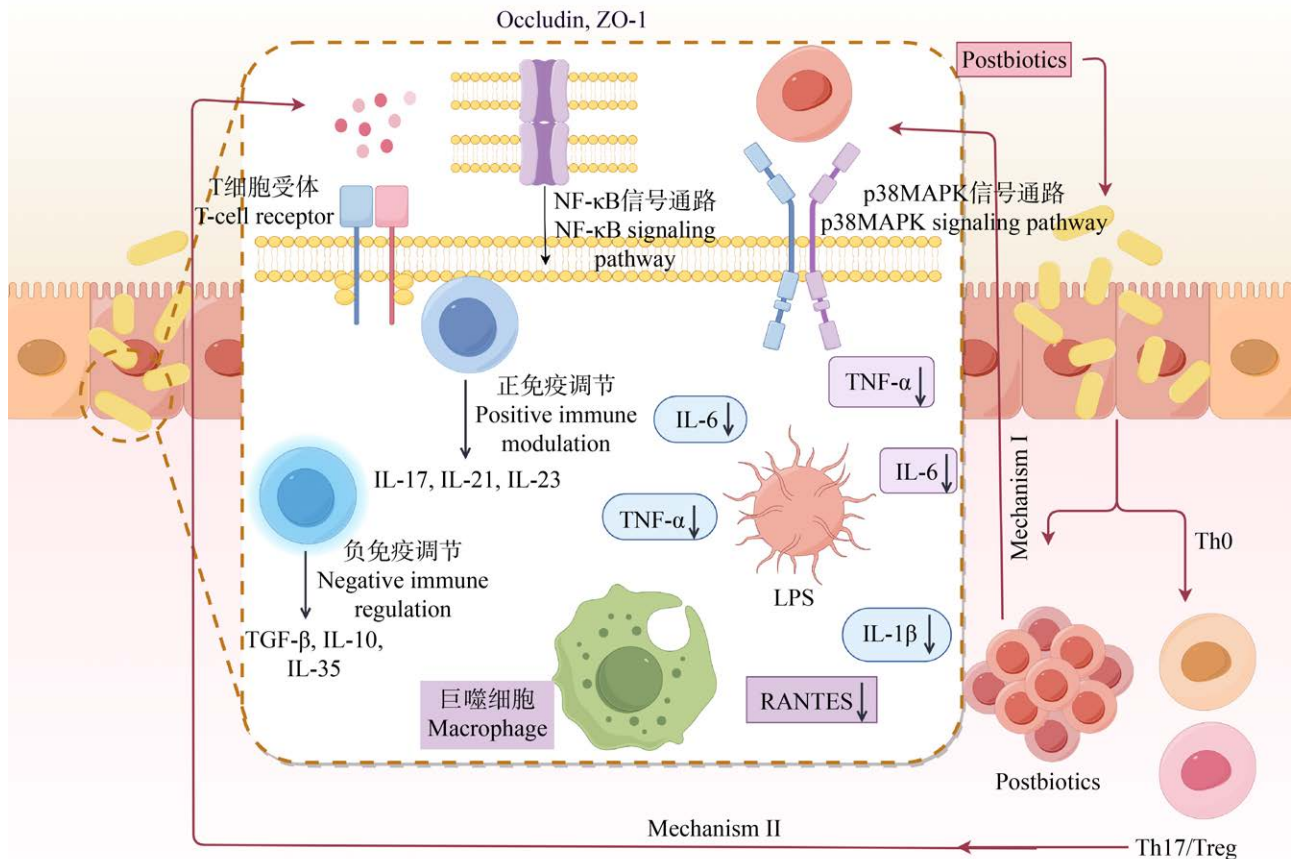


图 2 后生元作用机制

Figure 2 Mechanism of action of postbiotics.

TMC0356 可通过 T 细胞介导的免疫激活及细胞因子生成增强免疫反应^[78]。Xin 等^[79]研究发现, 瑞士乳杆菌(*Lactobacillus helveticus*) KLDS 1.8701 后生元具有平衡 T 辅助细胞 17 (Th17) 与调节性 T 细胞的能力, 可通过调节血清 IL-17 及转化生长因子- β (transforming growth factor- β , TGF- β) 水平影响免疫反应。

3.3 后生元去除内毒素的应用

后生元在去除内毒素方面具有显著优势, 其通过抗炎作用、调节肠道微生态平衡、增强肠道屏障功能及直接结合或降解内毒素, 能够

安全有效地降低体内内毒素水平, 从而改善健康状况(表 2)。相较于抗生素等传统方法, 后生元具有副作用少、生物利用度高的特点。

3.3.1 后生元通过抗炎作用降低内毒素水平

后生元中的可溶性因子能够促进细胞免疫和体液免疫, 调节免疫反应, 并调控抗炎因子与促炎因子的表达^[85], 起到抑制内毒素的目的。Layús 等^[86]通过皮下注射脂多糖诱导葡萄膜炎小鼠模型, 评估了植物乳杆菌 CRL759 无细胞上清液(POF-759)在 Sorensen 改良磷酸盐缓冲液中的抗炎活性, 结果表明 POF-759 显著抑制

表 2 后生元去除内毒素应用

Table 2 Application of postbiotic elements for endotoxin removal

研究模型	菌属来源	实验结果
Research model	Sources of postbiotic	Experimental result
LPS 诱导的 Caco-2 细胞 ^[80]	热灭活的副干酪乳杆菌 HK-LP	调节了 LPS 诱导的 Caco-2 细胞单层中炎性细胞因子的产生并上调 TJ 蛋白的表达, 通过 NF- κ B/MLC 信号通路改善 LPS 诱导的肠道屏障功能障碍
LPS-induced Caco-2 cells ^[80]	Heat-inactivated <i>Lactobacillus paracasei</i> HK-LP	Modulates LPS-induced inflammatory cytokine production and upregulates TJ protein expression in Caco-2 cell monolayers to ameliorate LPS-induced intestinal barrier dysfunction via the NF- κ B/MLC signaling pathway
LPS 诱导的 Caco-2 细胞 ^[81]	副干酪乳杆菌 SNB 衍生的后生元成分	调节肠道菌群, 降低细胞单层上清液中 IL-8 的含量, 上调 ZO-1、occludin 的表达水平, 改善肠道健康
LPS-induced Caco-2 cells ^[81]	<i>Lactobacillus paracasei</i> SNB-derived postbiotic ingredients	Regulates intestinal flora, reduces IL-8 in cell monolayer supernatant, upregulates ZO-1 and occludin expression levels, and improves intestinal health
LPS 诱导的 Caco-2 细胞 ^[82]	植物乳杆菌 1.0386 表面蛋白	有效改善 Caco-2 细胞跨上皮电阻降低、细胞通透性增加、炎症因子释放和紧密连接蛋白的破坏, 修复肠上皮紧密连接损伤
LPS-induced Caco-2 cells ^[82]	Heat-inactivated <i>Lactobacillus plantarum</i> 1.0386	Effectively ameliorate the decreased trans-epithelial resistance, increased cell permeability, inflammatory factor release and disruption of tight junction proteins in Caco-2 cells, and repair intestinal epithelial tight junction damage
LPS 诱导的小鼠巨噬细胞 RAW264.7 ^[83]	植物乳杆菌 L-14 胞外多糖	通过抑制促炎介质, 如环氧合酶 2、IL-6、TNF- α 和 IL-1 β , 并下调一氧化氮合酶的表达, 阻断 LPS 与 TLR4 的相互作用, 具有抗炎作用
LPS-induced mouse macrophage RAW264.7 ^[83]	<i>Lactobacillus plantarum</i> L-14 extracellular polysaccharide	Extracellular polysaccharide of <i>Lactobacillus plantarum</i> L-14 has anti-inflammatory effects by inhibiting pro-inflammatory mediators, such as cyclooxygenase 2, IL-6, TNF- α , and IL-1 β , and down-regulating the expression of nitric oxide synthase and blocking the interaction between LPS and TLR4
高脂饮食诱导的糖尿病大鼠 ^[84]	热灭活酿脓链球菌	增加了 IL-10, 同时降低了 LPS、IL-6 和 TNF- α 的水平, 增强肠上皮屏障和肠黏膜的免疫力, 降低炎症水平
High-fat diet-induced diabetic rats ^[84]	Heat-inactivated <i>Streptococcus pyogenes</i>	Heat-inactivated <i>Streptococcus pyogenes</i> increased IL-10 while decreasing levels of LPS, IL-6 and TNF- α , enhancing the intestinal epithelial barrier and intestinal mucosal immunity, and decreasing inflammation levels

LPS 刺激的 RAW264.7 细胞产生 IL-6、TNF- α 及 NO, 并且在室温、4 °C 和 -20 °C 条件下储存 30 d 后仍能保持其抗炎活性, 证实其对 LPS 诱导的内毒素炎症具有持续抑制作用。Liu 等^[87] 利用 D-gal/DSS 诱导衰老结肠炎小鼠模型, 发现乳酸乳球菌(*Lactococcus lactis*) 衍生的后生元 (*Lactococcus lactis* HF08 derived postbiotic) 的抗炎作用机制与 LPS-TLR4/NF- κ B 通路中关键蛋白的下调相关, 通过分子对接分析, 研究人员从其代谢物中鉴定出 4 种潜在的 TLR4 抑制剂, 包括依普利酮、染料木黄酮、吲哚丙烯酸和松油糖, 这些代谢物可能通过直接阻断 LPS-TLR4 相互作用来缓解内毒素驱动的肠道炎症。

Sokol 等^[88] 通过对比研究评估了普氏栖粪杆菌 (*Faecalibacterium prausnitzii*) 及其后生元制剂在体外和体内的抗炎效果, 研究表明普氏栖粪杆菌在 Caco-2 细胞及三硝基苯磺酸 (2,4,6-trinitrobenzenesulfonic acid sol, TNBS) 诱导的结肠炎模型中均表现出显著的抗炎活性, 进一步分析发现, 普氏栖粪杆菌无细胞上清培养液中富含代谢产物丁酸, 其通过阻断 NF- κ B 信号通路激活并抑制 IL-8 生成, 从而有效缓解炎症反应。热灭活的罗伊氏乳杆菌可差异调节肠道细胞对 TNF 和 IL-8 的反应, 抑制 IL-6、IL-8 及 TNF 等炎症因子的产生, 从而有效阻止革兰氏阴性病原菌引发的肠道炎症^[89]。

3.3.2 后生元通过调节肠道菌群降低内毒素水平

后生元主要作用于肠道^[90], 宿主健康与肠道菌群之间存在密切的相互作用关系, 后生元通过改善肠道菌群生态平衡, 能够显著促进宿主健康。

研究表明, 发酵黏液乳杆菌 (*Limosilactobacillus fermentum*) HF06 衍生的副益生菌 (HF06-based paraprobiotic, 6-PA) 和后生元 (HF06-based postbiotic, 6-PS) 通过调节有益微生物 [如双歧杆菌、粪杆菌 (*Faecalibacterium*)、毛霉科 (*Mucorales*) 和乳酸菌] 及有害细菌 [如棒

状杆菌 (*Corynebacterium*)、埃希氏菌 (*Escherichia*) 和梭状芽孢杆菌 (*Clostridium*)] 的含量, 同时调控短链脂肪酸水平, 从而改善肠道菌群失调^[91]。两歧双歧杆菌 (*Bifidobacterium bifidum*) HB1628 处理的 DSS 结肠炎小鼠粪便微生物群中, 乳酸菌数量显著增加^[92]。Peng 等^[93] 发现由酵母和乳酸菌混合物组成的复合后生元能够降低血清内毒素水平、恢复肠道屏障完整性、增加肠道有益微生物、促进胆汁酸代谢、减轻肝脏炎症, 证实其对 ALD 小鼠肠道菌群重塑具有积极作用。此外, 副干酪乳杆菌 (*Lactobacillus paracasei*) CCFM1224 的后生元处理高脂饮食小鼠后, 肠道菌群中阿克曼氏菌属 (*Akkermansia*) 相对丰度增加, 而毛螺菌科 (*Lachnospiraceae*) NK4A136 组、瘤胃球菌属 (*Ruminococcus*) 及嗜胆菌属 (*Bilophila*) 相对丰度降低, 通过调节肠道菌群和肝脏代谢发挥其功效^[94], 表明后生元可能通过调节肠道菌群降低内毒素水平。

3.3.3 后生元通过增强肠上皮屏障 (intestinal epithelial barrier, IEB) 功能及免疫反应降低内毒素水平

IEB 作为机体与外界环境的关键界面结构, 在维持肠道稳态中发挥着不可或缺的生理作用。研究表明, 肠道上皮细胞通过与固有层免疫细胞 (如树突状细胞、巨噬细胞等) 建立复杂的细胞间通讯网络, 形成独特的免疫-上皮协同防御机制。这种多层次的屏障系统能够精确识别并选择性阻止病原微生物及其代谢产物的跨膜转运, 同时确保营养物质的有效吸收, 从而维持机体内环境的稳定^[95]。后生元通过增加蛋白表达增强肠道屏障功能及特殊免疫机制降低内毒素水平, Liu 等^[91] 研究发现, 6-PA 和 6-PS 给药可缓解葡聚糖硫酸钠诱导的溃疡性结肠炎小鼠的体重减轻及结肠缩短现象, 并显著降低肠道粪便水分含量、促炎细胞因子水平及氧化应激水平; 此外, 6-PA 和 6-PS 通过显著上调 ZO-1 和 occludin 蛋白的表达, 增强了肠黏膜屏障功能。Zeng 等^[96] 研究发现, 一款热灭活酸奶中含有保

加利亚乳杆菌(*Lactobacillus bulgaricus*)、嗜热链球菌(*Streptococcus thermophilus*)及嗜酸乳杆菌等多种后生元成分,可有效预防由不同抗原引起的肠道屏障损伤,其作用机制为激活促炎细胞因子生成并促进 NO 合成,从而保护肠道屏障完整性。Algieri 等^[97]通过体外和体内试验证实,副干酪乳杆菌 CNCMI-5220 衍生的后生元(*Lactobacillus paracasei* CNCMI-5220-derived postbiotic)在维持肠道屏障完整性方面具有显著作用,增强肠道屏障功能使肠道免受内毒素入侵。

后生元在去除内毒素领域的研究显示出显著潜力。其通过抗炎作用缓解肠道炎症,调节肠道菌群平衡以减少有害菌内毒素生成,并增强肠道上皮屏障功能以阻止内毒素侵入。目前研究已取得初步成果,未来有望开发更高效、精准的后生元制品,为内毒素相关疾病的预防与治疗提供新的解决方案。

4 展望

综上所述,益生菌与后生元在肠道健康维护中发挥重要作用。其作用机制主要体现在益生菌与后生元可通过分子结合作用直接中和肠道内毒素,有效降低内毒素向循环系统的渗透;通过调节肠道菌群微生态平衡,抑制条件致病菌的过度增殖,从而从源头上减少内毒素的产生。更为重要的是,这类物质能够增强肠道上皮细胞间的紧密连接,提高肠道屏障功能,阻断内毒素的肠-肝循环途径。基于上述多重作用机制,益生菌与后生元在预防肠道相关疾病方面展现出显著的应用价值。

现有研究证实,复合益生菌、后生元可通过多菌株协同作用可产生优于单一菌株的效果。这为未来后生元产品的开发提供了重要方向:研发科学配伍的复合后生元配方;探索不同后生元组分的最佳配比;建立基于特定功效的复配标准。通过系统优化复合后生元的组分组合,有望开发出更具针对性和高效性的新型

功能产品。

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