微生物学报
*Acta Microbiologica Sinica*
2023, 63(12): 4467–4481
http://journals.im.ac.cn/actamicrocn
DOI: 10.13343/j.cnki.wsxb.20230280

Review 综 述

# 后生元缓解胃肠道疾病的研究进展及其潜在机制

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胡薇薇，李亚琳，全柯谕，张和平. 后生元缓解胃肠道疾病的研究进展及其潜在机制[J]. 微生物学报，2023，63(12): 4467-4481.
HU Weiwei, LI Yalin, QUAN Keyu, ZHANG Heping. Research progress and potential mechanism of postbiotics in alleviating gastrointestinal diseases[J]. Acta Microbiologica Sinica, 2023, 63(12): 4467-4481.

**摘　要：**胃肠道是全身代谢最活跃的器官之一，也是人体内最大的细菌库。人体胃肠道中含有丰富的微生物群，其与宿主健康存在着错综复杂的关系。肠道菌群处于一种动态平衡的状态，当这种平衡被打破时会引起便秘、腹泻、肠易激综合征、炎症性肠病和结直肠癌等胃肠道疾病的发生。近年来，关于后生元的研究越来越多，其对肠道屏障的保护作用与益生菌类似甚至效果更佳。本文重点介绍了当前后生元在动物实验和临床中改善胃肠道疾病的相关研究，探讨了后生元在胃肠道中的作用及其在增强上皮屏障、调节免疫系统、肠道菌群和神经系统 4 个方面的潜在作用机制。

**关键词：**后生元；胃肠道疾病；肠道菌群；动物实验；临床研究

# Research progress and potential mechanism of postbiotics in alleviating gastrointestinal diseases

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**Abstract:** The gastrointestinal tract is one of the most metabolically active organs and the largest reservoir of bacteria in the human body. The human gastrointestinal tract contains rich microbiota, which has a complex relationship with the host health. The gut microbiota is in a

资助项目：内蒙古自治区科技重大专项(2021ZD0014)
This work was supported by the Science and Technology Major Project of Inner Mongolia Autonomous Region (2021ZD0014).
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Received: 2023-04-19; Accepted: 2023-06-28; Published online: 2023-07-06

dynamic equilibrium, the disturbance of which can cause gastrointestinal diseases such as constipation, diarrhea, irritable bowel syndrome, inflammatory bowel disease, and colorectal cancer. In recent years, there have been increasing studies on postbiotics. The protective effect of postbiotics on intestinal barrier is similar or even superior to that of probiotics. We reviewed the studies of postbiotics in animal experiments and clinical studies in alleviating gastrointestinal diseases and summarized the role and mechanisms of postbiotics in enhancing the epithelial barrier and regulating the immune system, gut microbiota, and nervous system.
**Keywords:** postbiotics; gastrointestinal diseases; gut microbiota; animal experiments; clinical research

胃肠道是一个复杂的生态系统，其通过从口腔到肛门一系列器官的不同作用实现消化、吸收、分泌和免疫等功能[1]。此外，其中的肠神经系统能够独立控制肠道的大部分功能，通常被称为“第二大脑”[2]。人类和动物的胃肠道系统中含有约 $10^{12}$–$10^{14}$ 种微生物，是细菌、古菌、病毒和真核生物的集合，被称为“肠道菌群”，经过数千年的共同进化，与宿主形成了一种错综复杂的共生关系[3-4]。肠道微生物中大部分是细菌，目前为止已经确定的种类超过 1 000 种，其中拟杆菌门和厚壁菌门是健康肠道中的优势菌群，占肠道微生物中已知类别的 90%以上，它们的比例通常被认为是肠道菌群健康的相对估计值[5-6]。宿主为肠道菌群提供适当的环境和必需的营养物质，肠道菌群也参与人体各种生理功能的调节，具有为宿主提供代谢营养、参与促进生长和免疫调节、清除病原微生物和维持肠道稳态等作用[7]。

肠道菌群对肠道内外的新陈代谢、免疫耐受和营养吸收至关重要[8]，当肠道菌群生态失调时，专性厌氧菌显著减少而兼性厌氧菌相对丰度增加。例如，拟杆菌类和梭状芽胞杆菌类的严格厌氧菌减少，以及属于杆菌类(厚壁菌门)的兼性厌氧共生菌增加[9-10]。肠道菌群组成的失调通常导致肠外(感染性和过敏性)和肠道(感染性、炎症性、自身免疫性和肿瘤性)疾病的发生[11]。另外，免疫和代谢反应也是极其重要的病理因素。越来越多的证据表明，便秘、腹泻、肠易激综合征、炎症性肠病和结直肠癌等胃肠道疾病与肠道菌群失调密切相关[12-14]。

肠道微生物在预防胃肠道疾病和抑制病原体方面发挥着重要作用，目前常见的肠道菌群失调的治疗方式有粪菌移植(fecal microbiota transplantation, FMT)、益生菌、益生元、后生元和饮食干预等[12]。近年来，微生物疗法在预防和治疗胃肠道疾病中的应用受到研究者的广泛关注[15]。FMT 是将健康供体中的粪便菌群移植到患病个体，这种治疗方法可以有效增加有益微生物的丰度，恢复正常肠道菌群的多样性[16]。益生菌被定义为“给予足够量时对宿主健康有益的活性微生物”[17]，先前的许多研究表明益生菌可用于维持肠道稳态和治疗多种胃肠道疾病，其可通过增强肠道屏障、改善免疫系统、调节代谢过程和脑肠轴等不同的机制发挥作用[18]。但益生菌的安全性仍然存在争议，为了克服活菌细胞在临床、技术和经济方面应用相关的问题[19]，新的益生菌相关的概念被提出。2021 年 5 月，国际益生菌和益生元科学协会(International Scientific Association for Probiotics and Prebiotics, ISAPP)发表了关于后生元的共识，正式将“后生元”定义为“对宿主健康有益的无生命微生物和/或其组分的制备”[20]。

后生元活性成分主要是灭活的菌体、细菌裂解物、细胞壁成分和代谢产物等，这其中并不包括疫苗、病毒(噬菌体)、纯化后的菌株成分及代谢产物和未定义的微生物制剂等[20]。后生元可以根据其基本成分如碳水化合物、蛋白质、酶、脂质、

维生素、有机酸和某些复合物分子进行分类[21]，也可以根据其生物学功能划分为多种活性分子，主要包括细胞壁成分、胞外多糖、表面蛋白、细胞培养上清液和细菌素等，益生菌的有益代谢产物(γ-氨基丁酸、短链脂肪酸和色氨酸等)也是后生元重要组成部分。最近越来越多的证据支持后生元对胃肠道功能的保护作用与活的益生菌相似甚至更佳[22]。相比益生菌目前存在争议的安全性问题，后生元避免了毒力因子和耐药基因的传播，益生菌在肠道内的生存能力也不再是一个问题，其稳定性和安全性更利于常温下的储存和运输[23-24]。因此与益生菌相比，后生元有更明显的优势。本文结合了国内外的研究进展，旨在对后生元缓解胃肠道疾病的动物实验和临床研究中的证据进行综述，并探讨了其发挥作用的潜在机制，为后生元预防或治疗胃肠道相关疾病提供参考。

# 1 后生元缓解胃肠道疾病的动物实验证据

后生元的活性成分可通过调节肠道菌群、神经系统和促进免疫功能等维持肠道屏障完整性，从而缓解便秘、腹泻、肠易激综合征、炎症性肠病和结直肠癌等胃肠道疾病症状[25]，相关证据已在许多动物实验中得到了验证(表 1)。

## 1.1 便秘

便秘的症状主要包括排便困难、不频繁或不完全，同时可能伴有腹痛和腹胀，还会使患病个体产生焦虑抑郁等，严重影响其生活质量。年龄、饮食和压力等外界因素可能通过影响肠道菌群进而导致胃肠道功能障碍，引起便秘[26]。Zhao 等[27]发现使用 4 株菌[植物乳植杆菌(*Lactiplantibacillus plantarum*) LPL28、唾液联合乳杆菌(*Ligilactobacillus salivarius*) AP-32、长双歧杆菌婴儿亚种(*Bifidobacterium longum* subsp. *infantis*) BLI-02 和嗜酸乳杆菌(*Lactobacillus acidophilus*) TYCA06 ]复合发酵后，提取上清液并热灭活的制剂对洛哌丁胺诱导的小鼠便秘有缓解作用，可缩短小鼠第 1 次出现黑便的时间、提高粪便水含量和血清胃动素水平，促进肠道蠕动以及调节肠道菌群组成和短链脂肪酸(short-chain fatty acid, SCFA)代谢。同样，Park 等[28]给洛哌丁胺诱导的便秘模型大鼠饲喂不同剂量的热灭活植物乳植杆菌(*Lactoplantibacillus plantarum*) nF1 后发现，处理组大鼠粪便颗粒数量、重量、含水量、肠道运输长度和收缩力均有所改善。此外，还观察到肠黏膜层厚度和产生黏蛋白的隐窝上皮细胞数量增加，血清炎性细胞因子水平显著下降。在另一项研究中，伪无菌小鼠接受便秘供体粪便移植 8 周后，体内丁酸盐浓度显著降低，随后补充 2 周丁酸盐后小鼠便秘的相关症状得到了缓解[29]。

## 1.2 腹泻

腹泻指每天排出 3 次以上稀便或液体粪便，超出个体正常排便次数的情况，其可能原因是病毒或细菌感染、食源性疾病、过敏和饮食等造成的肠道炎症和功能性障碍，并伴有腹痛、恶心和呕吐等现象。后生元疗法已被证明对腹泻有预防或治疗的效果[30]。产肠毒素大肠杆菌是引起新生断奶仔猪腹泻的主要因素，此外还会引起肠道菌群失调以及小肠中的免疫反应和氧化应激，从而降低生长性能甚至死亡[31]。养殖场常用抗生素和氧化锌治疗，但存在抗生素耐药性和重金属污染等问题。Ho 等[32]在仔猪日粮中添加后生元和 10 种益生菌的混合物，持续干预 6 周后发现处理组的饲料转化率更高，粪便气味更少，同时改善仔猪的腹泻症状，表明后生元和益生菌复合物可以作为解决仔猪断奶腹泻问题的替代方案。轮状病毒是呼肠孤病毒科的一种无包膜病毒，可引起儿童和幼畜(包括小牛和仔猪)腹泻、呕吐和发热。Morales-Ferré 等[33]发现后生元[短双歧杆菌(*Bifidobacterium breve*)和嗜热链球菌(*Streptococcus*

*thermophilus*)发酵灭活产物]和益生元混合物可预防轮状病毒诱导的大鼠腹泻，其机制可能是后生元增强了 Toll 样受体(Toll-like receptors, TLR)的表达，从而降低腹泻的发生率和严重程度。

### 1.3 肠易激综合征

肠易激综合征(irritable bowel syndrome, IBS)是一种没有器质性病理的慢性功能性肠病，其特征是反复腹痛和排便紊乱[34]。IBS 的病理生理学尚未明确，但涉及多种因素，例如胃肠道动力改变、内脏超敏反应、低度黏膜炎症、环境因素和肠道菌群失调等[35]。Seong 等[36]为了研究后生元在大鼠疾病模型中对 IBS 症状改善的作用，给予大鼠热灭活干酪乳酪杆菌(*Lacticaseibacillus casei*) DKGF7 干预 4 周，结果表明与对照组相比，治疗组在结肠组织中的炎症细胞因子 IL-1β、IL-12p70 和 TNF-α 与血清皮质酮水平较低，且后生元可显著改善 IBS 大鼠模型的相关症状。另一项研究中，Wang 等[37]给小鼠灌胃不同浓度的鼠李糖乳酪杆菌(*Lacticaseibacillus rhamnosus*) GG 上清液，发现其通过上调人结肠癌细胞 HT-29 和人结直肠腺癌细胞 Caco-20 中 5-羟色胺转运蛋白的表达，进而降低 5-羟色胺(5-hydroxytryptamine, 5-HT)水平，最终缓解以腹泻为主的 IBS。

### 1.4 炎症性肠病

炎症性肠病(inflammatory bowel disease, IBD)是一种涉及结肠和小肠的慢性炎症性疾病，其临床表现包括克罗恩病(crohndisease, CD)和溃疡性结肠炎(ulcerative colitis, UC)两种类型。IBD 的病因与免疫、微生物、遗传和环境因素之间的多方面相互作用有关，肠道菌群失调已被证明是其中一个原因[38]。为了探究后生元对 IBD 的作用，Feng 等[39]用热灭活的两歧双歧杆菌(*Bifidobacterium bifidum*) B1628 处理葡聚糖硫酸钠(dextran sodium sulfate, DSS)诱导的 IBD 小鼠，发现与 DSS 组相比，HB1628 组的疾病活动指数(disease activity index, DAI)、组织学评分和血清中促炎细胞因子(IL-1β 和 TNF-α)水平更低，并改善了 IBD 小鼠的肠道菌群失调。另一项研究中，Zhang 等[24]对比了青春双歧杆菌(*Bifidobacterium adolescentis*) B8598 和其代谢产物对 DSS 诱导的 IBD 小鼠的作用效果，发现益生菌和后生元均可改善结肠炎的症状，两组的组织学评分均显著降低，但后生元在调节肠道菌群结构和组成方面比益生菌表现出更好的效果。此外，Chandhni 等[40]从 3 株益生菌中提取的表面蛋白均显著缓解了结肠炎小鼠的组织病理学损伤，降低了过氧化物酶活性和 TNF-α 的表达，且 3 个益生菌组的 IL-10 水平均有所提高，表明益生菌的表面蛋白能改善结肠炎小鼠的病理和生理学表现。

### 1.5 结直肠癌

结直肠癌(coloretal cancer, CRC)是一种肠上皮异质性疾病，它的特点是免疫反应失调、干细胞突变积累、肠道屏障破坏和菌群失调。多项研究认为其与肠道菌群组成和功能的改变有关[41]。迄今为止，只有少数动物研究评估了后生元在体内 CRC 预防和治疗的有效性。Ma 等[42]为了确定植物乳植杆菌(*Lactiplantibacillus plantarum*)-12 的胞外多糖(exopolysaccharide, EPS)对小鼠结肠癌的缓解作用，通过饲喂小鼠 EPS 85 d 后发现小鼠结肠紧密连接蛋白表达增强，结肠长度缩短和肿瘤负荷也有所改善，显著降低了小鼠血清中的促炎因子 TNF-α、IL-8 和 IL-1β 水平，并逆转了结肠炎小鼠肠道菌群的改变。另一项研究中，Sharma 等[43]使用鼠李糖乳酪杆菌(*Lacticaseibacillus rhamnosus*) MD 14 的代谢提取物饲喂大鼠，发现其中的 SCFAs 和其他活性化合物通过减少粪便致癌酶来改变促癌基因的表达，下调原癌基因(K-ras、β-连环蛋白、Cox-2 和 NF-κB)并上调肿瘤抑制基因 p53，可以改善结肠细胞形态，从而预防早期结肠癌的发生。

**表 1　后生元缓解胃肠道疾病动物实验**

Table 1　Animal experiment of postbiotics alleviating gastrointestinal diseases

| Study | Study object | Main symptom | Postbiotics type | Dose | Group | Intervention cycle | Results |
|---|---|---|---|---|---|---|---|
| Zhao et al. 2022[27] | Male mouse | Constipation | After fermentation, the supernatant of *L. plantarum* LPL28, *L. salivarius* AP-32, *B. longum* subsp. *infantis* BLI-02, and *Lactobacillus acidophilus* TYCA06 was extracted and heat-killed | 0.5 mg/d, 2.5 mg/d | 8 treatment groups, each group (*n*=8) | 8 days | Increase the content of feces, promote intestinal movement, and increase the level of serum gastricin, change the composition of gut microbiota and SCFAs metabolism |
| Park et al. 2021[28] | Male rat | Constipation | Heat-killed *Lactoplantibacillus plantarum* nF1 | $3.2\times10^{10}$ CFU/mL, $8\times10^{10}$ CFU/mL, $1.6\times10^{11}$ CFU/mL | 8 treatment groups, each group (*n*=12) | 5 weeks | The number, weight, and moisture content of rats have improved, and the level of inflammatory cytokines decreased |
| Ge et al. 2017[29] | Pseudo-sterile mice | Constipation | Butyrate | 1.1% | Health group (*n*=40), constipation group (*n*=40) | 8 weeks | Symptoms related to constipation are relieved |
| Ho et al. 2020[32] | Weaned piglet | Diarrhea | Four kinds of heat-killed probiotics and 10 kinds of mixed probiotics | $>1\times10^{7}$ CFU/g | 6 treatment groups, each group (*n*=24) | 6 weeks | The feed conversion rate of the treatment group is higher and the smell of feces is less |
| Morales-Ferré et al. 2022[33] | Newborn rat | Diarrhea | The fermentation inactivated product of *Bifidobacterium breve* and *Streptococcus thermophilus* | 0.92 g/100 g | 5 treatment groups, each group (*n*=2) | 16 days | Reduce the incidence and severity of diarrhea |
| Seong et al. 2021[36] | Male rat | IBS | Heat-killed *Lacticaseibacillus casei* DKGF7 | $1\times10^{11}$ CFU/d | Treatment group (*n*=7), control group (*n*=7) | 4 weeks | The level of inflammatory cytokine and serum cortexylone in colon tissue is low, which significantly improves the symptoms of the rats IBS model |
| Wang et al. 2015[37] | Male mouse | IBS | Cell-free supernatant of *Lacticaseibacillus rhamnosus* GG | 1.0 mL/d | Undiluted group (*n*=12), double dilution group (*n*=12), triple dilution group (*n*=12), control group (*n*=12) | 4 weeks | The expression of 5-hydroxylin transport proteins in HT-29 cells and CACO-2 cells is reduced, reducing the level of 5-HT |

(待续)

(续表 1)

| Study | Study object | Main symptom | Postbiotics type | Dose | Group | Intervention cycle | Results |
|---|---|---|---|---|---|---|---|
| Feng et al. 2022 | Male mouse | IBD | Heat-killed *Bifidobacterium bifidum* B1628 | $2\times10^9$ CFU/0.2 mL normal saline | Control group (*n*=8), DSS group (*n*=8), HB1628 group (*n*=8) | 10 days | DAIS, tissue scores and serum inflammatory cytokine levels are low |
| Zhang et al. 2022[24] | Male mouse | IBD | Heat-killed *Bifidobacterium adolescentis* B8598 | $2\times10^9$ CFU/d | Control group (*n*=7), DSS group (*n*=7), postbiotics group (*n*=7), probiotics group (*n*=7) | 7 days | Improve the symptoms of colitis, the significant scores of the tissue scores, regulate the composition of fecal flora, β diversity, and macroscopic group |
| Chandhni et al. 2021[40] | Male mouse | IBD | The surface proteins of *Lactoplantibacillus plantarum* MTCC 5690, *Limosilactobacillus fermentum* MTCC 5689, and *Lactobacillus acidophilus* NCFM | 12 mg/kg weight | IBD group (*n*=7), control group (*n*=7), MTCC 5690 group (*n*=7), MTCC 5689 group (*n*=7), NCFM group (*n*=7) | 72 days | The IL-10 level has increased the level of IL-10 to alleviate tissue pathological damage, reduce the activity of peroxidase activity and TNF-α |
| Sharma et al. 2020[43] | Male rat | CRC | The metabiotics extracted from *Lacticaseibacillus rhamnosus* MD 14 | 1 mL/kg, 2 mL/kg, 4 mL/kg | Control group (*n*=6), DMH group (*n*=6), ME group (*n*=6), LDME group (*n*=6), MDME group (*n*=6), HDME group (*n*=6) | 6 weeks | Downant the genetic cancer gene, increase the tumor inhibitory gene P53, and improve the shape of colon cells |
| Ma et al. 2021[42] | Male mouse | CRC | The exopolysaccharide of *Lactiplantibacillus plantarum*-12 | 200 mg/kg | N_Con group (*n*=15), M_Con group (*n*=15), M_5ASA group (*n*=15), M_EPS group (*n*=15) | 85 days | Mouse colon is tightly connected to the expression of protein, which improves the length of the colon and the tumor load, and significantly reduces the level of inflammatory factor in the serum of mice |

SCFAs: Short-chain fatty acid; IBS: Irritable bowel syndrome; IBD: Inflammatory bowel disease; CRC: Coloretal cancer; HT-29: Human colon cancer cell; Caco-2: Human colorectal adenocarcinoma cells; DAI: Disease activity index; TNF-α: Tumor necrosis factor-α; IL-10: Interleukin 10.

## 2 后生元缓解胃肠道疾病的临床研究证据

后生元可通过改善肠道微生态平衡进而促进人体健康，对胃肠道疾病产生直接或间接的影响，但目前大多数关于后生元的体内试验还仅应用于模式动物中，相关临床研究(表 2)仍十分有限。一项针对成年人便秘或腹泻的随机、双盲、安慰剂对照试验发现，摄入热灭活格氏乳杆菌(*Lactobacillus gasseri*) CP2305 7 周后，粪便中 SCFAs 的浓度增加，并对调节肠道功能有积极作用；热灭活 *Lactobacillus gasseri* CP2305 可显著改善粪便特性(包括排便量、粪便颜色和气味强度)、肠道环境和排便后的感觉，在有便秘倾向的受试者中尤其明显[44]。此外，后生元在临床上对于缓解急性和慢性腹泻也有效果。一项研究中，71 名急性水样腹泻儿童(3 个月–4 岁)被随机分配接受热灭活的乳杆菌(*Lactobacillus*)或安慰剂对照。结果发现，与对照组相比，治疗组的腹泻持续时间显著缩短[45]。另一项研究中，Xiao 等[46]将 137 名慢性腹泻患者随机分配接受热灭活的嗜酸乳杆菌(*Lactobacillus acidophilus*) LB 或活菌治疗 4 周，发现灭活菌株可通过减少排便频率、腹痛和腹胀和改善粪便一致性来缓解腹泻症状，并且在治疗慢性腹泻方面比活菌更有效。

IBS 是影响患者生活质量最常见的肠道功能性疾病之一。两歧双歧杆菌(*Bifidobacterium bifidum*) HI-MIMBb75 先前已被证明对缓解 IBS 症状有效，但灭活菌株是否也发挥相同作用仍有待研究。Andresen 等[47]研究显示，每天服用含灭活 *Bifidobacterium bifidum* HI-MIMBb75 胶囊，持续 8 周，能够显著缓解 IBS 患者的临床症状，并且后生元比活菌治疗对患者的腹痛、腹胀、排便相关疼痛和排便频率等症状有更大的改善。类似的，另一项研究发现使用热灭活 *Lactobacillus* LB 治疗腹泻为主的 IBS 患者，服用后生元 1 个月后患者疼痛评分、腹胀和生活质量得到改善[48]。

## 3 后生元缓解肠道疾病的相关作用机制

### 3.1 增强上皮屏障功能

肠屏障功能的完整性有助于保护肠黏膜免受病原体、毒素和过敏原的侵害，维持肠道菌群的平衡并预防胃肠道疾病的发生，是保持肠道健康的关键因素[49]。研究表明，后生元可能以益生菌相同的特性发挥肠道保护作用，一些双歧杆菌属被证明可以定植于肠黏液层，促进杯状细胞产生黏液，同样来自某些特定双歧杆菌属的胞外多糖也可以刺激黏液产生以增强肠道屏障功能[50-51]。研究发现，在鼠李糖乳酪杆菌(*Lacticaseibacillus rhamnosus*)细胞培养液中的一种新型后生元活性分子，即分泌蛋白 HM5093，能够预防 DSS 诱导的小鼠结肠炎及肠道屏障功能障碍[22]。Izuddin 等[49]将植物乳植杆菌(*Lactiplantibacillus plantarum*) RG14 的上清液饲喂断奶后的羔羊 60 d 后，发现摄入的后生元通过上调 *TJP-1*、*CLDN-1* 和 *CLDN-4* 基因的表达来提高肠道屏障的完整性，减少肠道中病原体的数量，进而改善肠黏膜的状态。此外，肠道微生物合成产生的维生素也具有保护上皮屏障或监测肠道免疫等功能[52]。人体必需的氨基酸色氨酸也是后生元重要组成部分，其被宿主和肠道微生物分解产生的代谢物(吲哚衍生物、血清素、色胺和犬尿氨酸等)通过上调芳烃受体，可刺激抗菌肽的表达、上皮细胞增殖、紧密连接蛋白表达和黏蛋白的产生，同时抑制 LPS 诱导的炎症，从而实现调节肠道屏障功能作用[53-54]。

### 3.2 调节免疫系统

后生元发挥作用的机制不仅表现在调节肠道菌群方面，也表现在通过刺激先天免疫系统来调节宿主的健康[55]。宿主和关键微生物成分之间

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**表 2　后生元缓解胃肠道疾病临床研究**

Table 2　Clinical study of postbiotics alleviating gastrointestinal diseases

| Study | Study type | Research object | Main symptom | Postbiotics type | Dose | Group | Time | Result |
|---|---|---|---|---|---|---|---|---|
| Sawada et al. 2016[44] | A randomized, double-blind, placebo-controlled trial | Volunteers with constipation or diarrhea (male: 15; female: 24) | Constipation and diarrhea | Heat-killed *Lactobacillus gasseri* CP2305 | 190 g/d | Placebo group (*n*=20) and CP2305 group (*n*=19) | 3 weeks | The concentration of SCFAs in feces metabolites increases and significantly improves the characteristics of feces, intestinal environment, and after defecation |
| Salazar-Lindo et al. 2007[45] | A phase III multicenter, randomized, double-blind study | Children aged 3–42 months | Acute diarrhea | Heat-killed *Lactobacillus bacteria* | $2\times10^{10}$ CFU killed cell | LB group (*n*=36) and placebo group (*n*=35) | 4 months | The duration of diarrhea in the treatment group was significantly shortened |
| Xiao et al. 2003[46] | A multicenter, randomized, controlled trial | Patients over 16 years of age with chronic diarrhea | Chronic diarrhea | Heat-killed *Lactobacillus acidophilus* LB | 5 tablets/ times, 3 times/d | LB group (*n*=64) and live *lactobacilli* group (*n*=69) | 4 weeks | Reduce defecation, abdominal pain and bloating, and improve the consistency of feces |
| Andresen et al. 2020[47] | A double-blind, placebo-controlled trial | Patients over 18 years old with IBS | IBS | Killed *Bifidobacterium bifidum* HI-MIMBb75 | $1\times10^{9}$ CFU killed cell | Placebo group (*n*=187), HI-MIMBb75 group (*n*=190) | 8 weeks | Relieve symptoms such as abdominal pain, abdominal distension, stool-related pain, and frequency of defecation |
| Tarrerias et al. 2011[48] | A cohort study | Diarrhea-dominated IBS patients | IBS | Heat-killed *Lactobacillus* LB | 2 capsules/d | All were given postbiotics (*n*=297) | 1 month | Patients have improved pain scores, bloating and quality of life after treatment |

IBS: Irritable bowel syndrome; SCFAs: Short-chain fatty acid.

的相互作用通过模式识别受体(pattern recognition receptors, PRR)介导，它可以识别病原体中常见的分子或受损细胞释放的分子[56]，研究发现可识别后生元分子的 PRR 包括核苷酸寡聚化结构域样受体(nucleotide oligomerization domain-like receptors, NLR)、TLR、C 型凝集素样受体(C-type lectin receptor, CTLR)和 G 蛋白偶联受体(G protein-coupled receptors, GPCRs)等[57]，其中 NLR 和 TLR 在控制宿主的先天免疫反应中起主要作用，二者之间通过识别不同的细菌配体和肠道细胞传递信号来协同作用[56]。

NLR 在细胞内表达，并且已被证明对细胞壁成分、毒素和宿主来源的配体有反应[58]。NLR 是后生元重要的传感器，可以感知细菌肽聚糖(peptidoglycan, PGN)[59]，优先激活 NOD1 和 NOD2 受体，经过一系列结合反应进一步激活 I 型干扰素、MAPK 和 NF-κB 信号通路[60]。也有研究认为，某些细胞因子(如干扰素)可能通过激活 T 细胞和 B 细胞来帮助 NLR 对后生元做出反应，并且 IL-4、IL-6 和 IL-10 的产生也可能会因后生元的摄入而增加[61]。另外，TLR 在抵御病原体入侵的先天防御机制中也起着至关重要的作用，其可被后生元中存在的活性因子激活[56]。例如，与 MD2 复合物的 TLR4 负责识别细菌脂多糖(lipopolysaccharide, LPS)，并将炎症信号传递到细胞膜上[62-63]，来自革兰氏阳性菌的 PGN 和脂磷壁酸(lipteichoic acid, LTA)以 TLR2 依赖性方式激活细胞[64]。在一项研究中发现，鼠李糖乳酪杆菌(*Lacticaseibacillus rhamnosus*) GG 及其表层蛋白和 EPS 通过调节 TLR 表达抑制 MAPK 和 NF-κB 信号传导，缓解猪肠上皮细胞 LPS 诱导的炎性细胞因子[65]，同时 EPS 也可通过 TLR2/4 介导的 NF-κB 和 MAPK 途径激活巨噬细胞[66]。另一项研究表明，SCFAs 可增强 TLR 配体诱导的 NF-κB 活化，刺激肠上皮细胞中促炎细胞因子(如 IL-6、IL-1β、IL-8 和 TNF-α)的产生，启动炎症反应并消除致病菌[67]。

### 3.3 调控肠道菌群

目前关于后生元对胃肠道的作用机制尚未完全明确，但体外试验和体内研究表明，后生元大多数以益生菌类似的作用方式调控肠道菌群。后生元在抗菌方面表现出比抗生素更大的优势：其通过竞争肠道附着位点来干扰病原菌的产生，从而抑制致病菌的活性来调节肠道菌群。益生菌代谢产物，如乳酸、有机酸、细菌素、过氧化物和胞外多糖等具有抗菌特性，可以直接在肠道内发挥抗菌作用，竞争性地与病原体所需的受体结合，从而改变宿主基因表达或调节肠道菌群局部环境[68-69]。此外，代谢产物 SCFAs 被认为是益生菌产生的典型后生元，在肠道中参与多个能量代谢通路的调节，其中丁酸盐是结肠上皮的主要能量来源，SCFAs 的吸收也有助于维持肠道内酸碱平衡并促进 $Na^+$的吸收[70]。给结肠炎小鼠补充丁酸盐可增加变形杆菌和乳杆菌科的丰度，并通过增强免疫调节和组织修复机制的表达改善细胞损伤，增加肠炎小鼠中产生丁酸盐细菌的丰度[71]。肠道菌群相关的代谢物共同调节 NLRP6 炎症小体信号传导、IL-18 分泌和下游抗菌肽来恢复正常的微生物群并改善结肠炎，微生物和宿主相互作用通过代谢物介导的免疫系统共同维持肠道菌群稳定[72]。另外，肠道菌群中梭状芽孢杆菌和乳杆菌释放胆汁酸水解酶等，这些酶促进胆汁酸脱氢和双羟基化，使肠道菌群和胆汁酸之间相互作用并通过法尼醇 X 受体和 GPCRs 调节脂质和脂蛋白代谢[73-74]。

### 3.4 调节神经递质和激素水平

肠道菌群与肠道之间的双向通信途径及其与中枢神经系统的相互作用被称为脑-肠-微生物轴，后生元也可以通过大脑自主神经系统来调

节肠道功能和肠道菌群的结构[75]。后生元如 γ-氨基丁酸(γ-aminobutyric acid, GABA)和 SCFAs 可穿过血脑屏障调节大脑功能和神经递质水平。研究发现在植物乳植杆菌(*Lactiplantibacillus plantarum*)后生元处理的小鼠大脑和血清中发现了高浓度的关键性神经递质 5-HT，且热灭活益生菌和肠道菌群代谢物也有促进结肠中 5-HT 合成的作用[76]。此外，SCFAs 可以刺激肠嗜铬细胞(enterochromaffin cells, ECs)释放 5-HT，从而改变结肠运动，也可直接抑制组蛋白脱乙酰酶，并作为能量底物影响生理过程的各个方面[29]。例如，调节血脑屏障(blood-brain barrier，BBB)完整性、与 GPCRs 相互作用、促进突触标记和捕获、调节免疫系统和迷走神经活性等[77]，是胃肠道疾病的潜在治疗靶点。GABA 是中枢神经系统的主要抑制性神经递质，在大脑中的抑制性神经元和肠内神经系统的神经元以及黏膜内分泌细胞中合成，并通过 BBB 被消除到循环血液中，GABA 也可以刺激 ECs 释放 5-HT[78]，通过激活 $GABA_A$ 和 $GABA_B$ 受体来刺激或抑制肠内神经元，其受体存在于大脑和胃肠道的不同区域，对于缓解焦虑和抑郁样行为也至关重要[76-79]。

## 4 结论与展望

本文综述了后生元对胃肠道疾病方面的积极影响及其在肠道内作用的潜在机制，从上皮屏障功能、肠道菌群、免疫系统及神经系统四个方面对促进肠道健康产生有益作用(图 1)。体外试

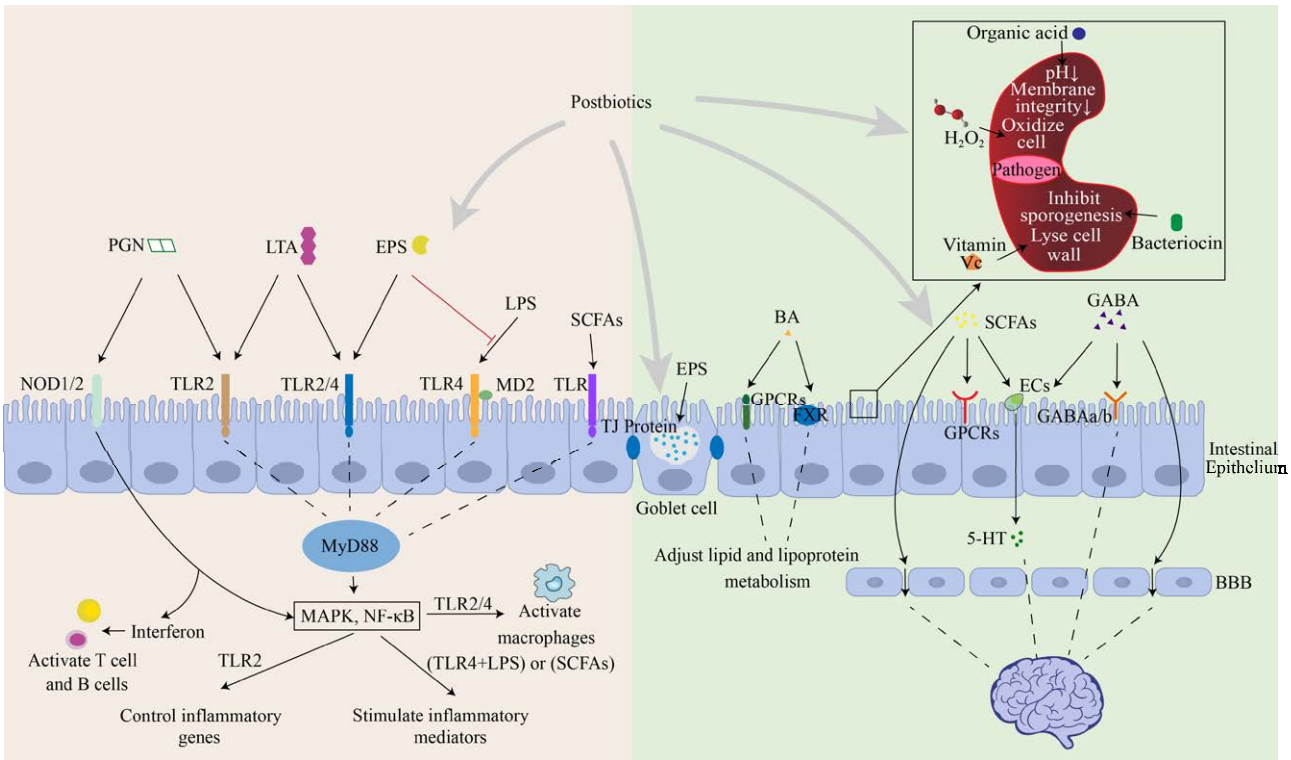


**图 1　后生元缓解胃肠道疾病作用机制图**

Figure 1　Mechanism of probiotics in alleviating gastrointestinal diseases. PGN: Peptidoglycan; LTA: Lipoteichoic acid; EPS: Extracellular polysaccharide; LPS: Lipopolysaccharide; SCFAs: Short-chain fatty acids; BA: Bile acid; GABA: Gamma-aminobutyric acid; ECs: Intestinal chromaffin cells; GPCRs: G protein-coupled receptors; 5-HT: 5-hydroxytryptamine; BBB: Blood-brain barrier; NOD: Nucleotide oligomerization domain; TLR: Toll-like receptor; FXR: Farnesoid X receptor.

验和体内研究也证明后生元中的活性成分可缓解胃肠道疾病，为宿主健康带来益处。目前，已经开发出多种后生元产品，并应用于动物(IBD)、人群(护肤品)和临床(便秘腹泻、龋齿)方面的研究，为保健食品、特殊医用配方食品、婴幼儿食品等领域的开发奠定基础。另外，后生元是一种稳定且安全改善健康的疗法，与活菌相比，其在储存和运输方面的挑战较小，因此在预防和改善疾病及开发功能性食品方面具有良好的发展前景。后生元的应用在国际市场已成为趋势，其中日本、北美、欧洲等发达地区的后生元产业链初具规模，其相关产品已陆续进入市场。虽然对益生菌及其代谢物的研究已经进行了多年，但后生元在被正式定义后仍处于萌芽阶段，其对宿主健康影响的机制还并不完全清楚，未来后生元的发展方向应侧重于机制研究，因此还需要更多大规模和高质量的临床试验、动物模型和体外研究去精准化其菌株特异性、剂量等方面的影响，也需要更多的证据来支持后生元作为健康补充剂的主张。

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