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益生菌调控肠道衰老机制及其在年龄相关疾病中的应用

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摘要 随着全球老龄化进程加速,衰老及其相关疾病已成为重大公共卫生挑战。肠道作为重要的衰老调控器官,其衰老过程与肠道微生物群多样性丧失、肠道屏障功能受损及免疫调节障碍密切相关,并继而导致氧化应激加剧和系统性炎症状态,最终加速机体整体衰老及多种疾病的发生发展。本综述系统总结了益生菌缓解肠道衰老的作用机制与应用前景。研究表明,益生菌可通过增强肠道屏障功能、调节免疫与抗氧化活性、调控肠脑轴功能以及恢复肠道菌群多样性等多途径延缓肠道衰老进程。此外,本文进一步综述了益生菌在衰老相关疾病中的临床应用,包括通过"肠-肝轴"改善代谢性疾病(例如非酒精性脂肪性肝病, non-alcoholic fatty liver disease, NAFLD)、通过修复微生态缓解消化系统疾病、经由"肠-肌轴/骨轴"对抗运动系统功能衰退、通过免疫调节延缓年龄相关性免疫衰退、通过"肠-脑轴"改善神经退行性疾病以及通过"肠-皮肤轴"延缓皮肤老化。尽管现有研究展示了益生菌的多方面潜力,仍存在菌株特异性、个体差异及长期安全性等问题。未来需结合多组学技术、个性化干预策略及新型制剂开发,以推动益生菌在健康衰老领域的精准应用。本文旨在为益生菌干预肠道衰老及相关疾病的机制研究与临床实践提供理论参考与方向展望。

关键词 肠道衰老; 益生菌; 肠道屏障; 肠道菌群
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The Modulation of Gut Aging by Probiotics: Mechanisms and Implications for Age-related Diseases

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Abstract With the accelerating pace of global aging, senescence and its associated diseases have emerged as significant public health challenges. The gut, a crucial organ in the regulation of aging, undergoes a process characterized by a loss of gut microbiota diversity, impaired intestinal barrier function, and disrupted immune regulation. These changes subsequently lead to increased oxidative stress and a systemic inflammatory state, ultimately accelerating overall organismal aging and the onset and progression of various diseases. This review systematically summarizes the mechanisms and potential applications of probiotics in alleviating gut aging. Research indicates that probiotics can mitigate the intestinal aging process via multiple pathways, including enhancing intestinal barrier function, modulating immune and antioxidant activity, regulating gut-brain axis communication, and restoring gut microbiota diversity. Furthermore, this article reviews the clinical applications of probiotics in age-related diseases, such as improving metabolic diseases (e.g., NAFLD) *via* the "gut-liver axis", alleviating digestive disorders through microbiome restoration, counteracting musculoskeletal decline *via* the "gut-muscle/bone axis", delaying age-related immunosenescence through immune modulation, ameliorating neurodegenerative diseases *via*

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the "gut-brain axis", and slowing skin aging through the "gut-skin axis". Despite the promising potential demonstrated by existing studies, challenges remain, including strain-specific effects, individual variability, and long-term safety concerns. Future research should integrate multi-omics technologies, personalized intervention strategies, and the development of novel formulations to promote the precise application of probiotics in the field of healthy aging. This review aims to provide a theoretical reference and future perspectives for mechanistic research and clinical practice concerning probiotic interventions for gut aging and related diseases.

Key words gut aging; probiotics; gut barrier; gut microbiome

随着世界人口老年化进程加速,衰老已成为全球公共卫生和社会发展的重大挑战。衰老不仅是生命的自然组成部分,也是多种慢性疾病和代谢性障碍的根源。随着年龄增长,肠道微生物群多样性降低,损害肠道屏障并扰乱免疫功能,加速衰老及相关疾病。肠道衰老表现为肠道菌群组成和功能的显著改变,伴随肠道屏障和免疫功能的进行性衰退。在菌群层面,衰老导致微生物多样性降低,表现为产生短链脂肪酸(short chain fatty acids, SCFAs)的有益菌(例如普拉梭菌、直肠真杆菌等)减少,而潜在致病菌(例如肠杆菌)增加,引发系统性炎症[1, 2]。同时,真菌和病毒组也发生特异性变化,如百岁老人中青霉菌、曲霉菌等真菌和粗病毒目病毒增多[3, 4]。在功能层面,肠道上皮细胞(包括杯状细胞和潘氏细胞)衰老导致黏蛋白和抗菌肽分泌减少,屏障功能受损[5, 6],伴随肠道通透性增加和微生物成分易位,引发慢性低度炎症[7]。此外,免疫监视功能下降,特别是回肠生发中心 B 细胞衰老导致 IgA 产生减少,进一步改变菌群组成[8]。肠道干细胞(intestinal stem cells, ISCs)功能减退和衰老相关分泌表型(senescence-associated secretory phenotype, SASP)的积累共同促进炎症微环境形成,加速肠道功能衰退[9]。这些变化能通过微生物组分析(16S rRNA 测序、宏基因组学)、屏障功能评估(血清 LBP、乳果糖/甘露醇测试)和细胞衰老标志物检测(p16INK4A、SA-β-gal 染色)等方法进行评估,为理解肠道衰老机制和开发干预策略提供重要依据。根据国际益生菌与益生元科学协会(the International Scientific Association for Probiotics and Prebiotics, ISAPP)的共识定义[10],益生菌是指"当摄入足够数量时对宿主健康产生有益作用的活的微生物",这源于 WHO/FAO 的权威标准。目前,临床常用的益生菌主要包括 3 大类:乳杆菌属[11](经分类学修订后含 23 个新属例如乳杆菌属等),其能产生乳酸并存在于发酵食品中[12];双歧杆菌属,以其卓越的母乳低聚糖代谢能力著称[13],可通过改善肠道屏障功能[14]和调节免疫[15]发挥健康效益;以及具有双面特性的肠球菌属[16](例如粪肠球菌)。益生菌的作用具有显著的菌株特异性,例如大肠杆菌 Nissle 1917 的抗炎特性[17]与脆弱拟杆菌特定菌株产生的免疫调节多糖[18],而某些乳杆菌菌株甚至可能导致小肠细菌过度生长[19]。这些微生物主要通过产生短链脂肪酸、竞争性抑制病原体和分泌抗菌物质[20]等机制发挥作用。在 2 项针对中国长寿人群的肠道及口腔微生物组研究中,研究通过 16S rRNA 测序技术分析了不同年龄组(包括中年、老年及 90 岁以上的长寿个体)的样本,发现特定的益生菌与健康衰老和长寿显著相关。样本主要来自中国东北地区(n=142,年龄 55~102 岁)[21]和湖北长寿镇[22](n=122,年龄 43~102 岁),包括粪便和唾液样本。研究结果显示,长寿个体的肠道微生物中阿克曼菌、乳酸杆菌、双歧杆菌、另枝菌、副拟杆菌和产胆固醇真杆菌等有益菌显著富集,这些菌株与短链脂肪酸生产、胆固醇代谢、抗炎症及免疫调节功能相关。此外,口腔微生物中的唾液链球菌和双歧杆菌属在长寿人群中也表现出较高的丰度,提示口腔-肠道菌群轴可能在健康衰老中发挥作用。功能预测分析进一步表明,长寿人群的微生物组具有更强的氨基酸代谢、外源物降解及能量代谢能力。这些发现表明,富含特定益生菌的微生物组结构可能是促进健康衰老和长寿的重要因素。但是目前,关于益生菌缓解肠道衰老的综述文章较为缺乏,因此,本文将围绕益生菌在肠道衰老中的作用机制(**Fig. 1**)及其临床应用(**Table 1**)进行总结,旨在为促进健康衰老和预防衰老相关疾病提供新的视角与参考。

1 益生菌缓解肠道衰老的机制

肠道衰老是机体整体衰老的重要组成部分和驱动因素,其特征表现为肠道菌群失调、屏障功能受损、免疫炎症失衡以及肠脑轴通讯障碍。现有研究表明,益生菌可通过多靶点、多途径的协同作用干预这一过程。其核心机制主要包括:通过增强肠道屏

障完整性阻止有害物质易位;通过调节免疫应答及抗氧化防御系统缓解慢性炎症与氧化应激;通过调控肠脑轴功能改善神经退行性病变;以及通过直接调节肠道微生物群落结构,恢复其多样性与生态平衡。下文将围绕这 4 个核心机制展开详细论述。

1.1　增强肠道屏障功能

随着年龄增长,人体肠道微生物群的组成发生显著变化,老年人群的肠道微生物多样性通常降低,有益微生物(例如普拉梭菌和黏液性阿克曼氏菌)的丰度减少,而潜在致病菌(例如变形菌门)的丰度增加[23, 24]。这些变化引起肠道屏障功能受损,促使炎症介质进入血液循环,诱发全身性炎症,并加速衰老相关疾病的进程[7]。

益生菌通过多种机制增强肠道屏障功能并减少炎症反应。首先,它们显著上调了紧密连接蛋白(zonula occludens-1,ZO-1)的表达,从而强化了肠道屏障[25],同时,热灭活的副干酪乳杆菌 D3-5 通过其细胞壁中的脂磷壁酸(lipoteichoic acid, LTA)激活 Toll 样受体 2(Toll-like receptor 2, TLR-2)、p38 丝裂原活化蛋白质激酶(p38 mitogen-activated protein kinase, p38 MAPK)信号通路,促进黏液蛋白 2(mucin 2, Muc2)的表达,增加肠道黏液层厚度,减少微生物入侵和炎症,从健康婴儿肠道分离的益生菌组合通过调节肠道菌群和提高胆汁盐水解酶(bile salt hydrolase, BSH)活性,增加牛磺酸含量,进一步上调了紧密连接蛋白的表达,从而改善了肠道通透性[26]。益生菌干酪乳杆菌 HY2782 通过调控衰减加速因子-16(decay-accelerating factor-16, DAF-16)/叉头盒转录因子 O 类(forkhead box transcription factors class O, FOXO)和转录因子光头蛋白-1(skinhead-1, SKN-1)/核因子 E2 相关因子 2(nuclear factor E2-related factor 2, NRF2)信号通路增强肠道屏障功能,同时促进丁酸盐产生菌增殖并抑制致病菌,从而改善肠道通透性、减轻炎症反应和氧化应激,最终延缓肠道衰老并延长寿命[27]。

1.2　调节免疫及抗氧化活性

在衰老过程中,慢性低度炎症成为影响健康的关键因素。例如,老年人肠道中拟杆菌比例增加,而厚壁菌减少所引发的肠道菌群失衡,可激活核因子-κB(nuclear factor -κB,NF-κB)信号通路,促进促炎因子的释放,成为炎症状态的重要诱因之一[28, 29]。研究表明,不同益生菌菌株通过多种调节免疫及抗氧化机制在缓解肠道衰老过程中发挥重要作用。例如,2 种乳酸菌混合 2 种双歧杆菌的益生菌组合显著降低了 Toll 样受体 4(Toll-like receptor 4,TLR4/NF-κB 炎症信号通路中 TLR4、髓系分化的原发性反应 88(myeloid differentiation primary response 88, MyD88)和磷酸化 p65(phosphorylated-p65, p-p65)的表达,进而抑制肠道炎症的发生[25],而长双歧杆菌 2C、动物双歧杆菌 Bb-12 通过调节肠道菌群组成,下调促炎细胞因子肿瘤坏死因子-α(tumor necrosis factor alpha, TNF-α)并上调抗炎细胞因子(transforming growth factor-β1, TGF-β1)的水平,从而改善肠道健康并延缓衰老[30]。益生菌还通过增加抗炎菌群(例如普拉梭菌、黏液性阿克曼氏菌)和减少潜在致病菌(例如变形菌),增强肠道屏障功能,调节宿主免疫系统(例如促进调节性 T 细胞生成和短链脂肪酸丁酸的产生),有效缓解慢性低度炎症及肠道衰老。此外,特定菌株如加氏乳杆菌 KS-13、两岐双岐杆菌 G9-1、长双歧杆菌 MM-2 通过维持 $CD4^+$ 淋巴细胞比例并上调抗炎因子 IL-10 水平,进一步降低炎症反应[31]。动物双歧杆菌、乳酸菌 BPL1™ 通过胰岛素样生长激素-1(insulin-like growth factor-1, IGF-1)依赖机制改善氧化应激、肠道通透性和感染保护,延缓秀丽隐杆线虫寿命[32]。其他菌株例如乳球菌亚属和加氏乳杆菌 SBT2055,其通过活化核因子 E2 相关因子 2(nuclear factor E2-related factor 2, Nrf2)信号通路和上调血红素加氧酶 1(heme oxygenase-1, HO-1)的表达,增强抗氧化能力并减少晚期糖基化终末产物(advanced glycation end-products, AGEs)的积累[33],而魏斯氏菌和乳酸菌通过调节 DAF-16、叉头盒 FoxO 和 AMPK 信号通路增强抗氧化防御[34]。长双歧杆菌通过激活糖精去乙酰化酶-2.1(sirtuin deacetylase, SIR-2.1)和部分依赖转录因子光头蛋白-1(skinhead-1, SKN-1)的 DAF-16/FoxO 通路,上调抗氧化基因表达,减少脂褐素积累,显著延长寿命并延缓衰老[35]。

1.3　调节肠脑轴功能

衰老过程中,肠道屏障受损导致微生物代谢产物进入血液循环,进而诱导神经炎症,并加剧阿尔茨海默病(Alzheimer's disease, AD)等神经退行性疾病的发展[7, 36]。益生菌通过脑肠轴改善衰老相关神经系统疾病的机制是多方面的,首先,酪丁酸梭菌、希他梭状芽孢杆菌等益生菌能够强化肠道屏障的完整性,减少肠道微生物及其代谢产物的迁移,从而降低全身性炎症反应,减轻中枢神经系统的炎症负担[37, 38]。鼠李糖乳杆菌 GG、长双歧杆菌、粘液阿克曼氏菌、丁酸梭菌通过发酵膳食纤维产生 SCFAs,

例如乙酸、丙酸、丁酸等代谢产物通过激活 G 蛋白偶联受体（G-protein-coupled receptor 43/41，GPR43/41）和抑制组蛋白去乙酰化酶（histone deacetylases，HDACs），调节免疫反应及基因表达，以减轻神经炎症[39, 40]。此外，乳酸菌能够调节肠道中的神经递质水平，例如血清素和 γ-氨基丁酸（γ-gamma-aminobutyric acid，γ-GABA），并通过脑肠轴调节中枢神经系统功能[41, 42]，还可以调控肠道免疫系统，促进调节性 T 细胞（Treg）的生成，并抑制促炎细胞因子的分泌，减轻全身性炎症，进而减少炎症因子对中枢神经系统的损伤[43, 44]，并且鼠李糖乳杆菌 GG、长双歧杆菌通过竞争性抑制有害菌的增殖，从而恢复肠道菌群平衡，降低有害代谢产物的生成，从而改善脑肠轴的功能[45, 46]. 最后，嗜黏液阿克曼菌通过调节肠道激素（例如胰高血糖素样肽-1（glucagon-like peptide 1，GLP-1）的分泌，改善胰岛素敏感性和能量代谢，进而对中枢神经系统产生保护作用[47, 48]。这些结果表明，益生菌在调控脑肠轴及改善衰老相关神经系统疾病方面具有重要的应用潜力。

1.4 调节肠道菌群多样性

益生菌能够通过调节肠道菌群组成，恢复微生物多样性并改善宿主健康。Fang 等人发现，发酵乳杆菌 SX-0718、长双歧杆菌 SX-1326、干酪乳杆菌 SX-1107 及动物双歧杆菌 SX-0582 的益生菌组合在衰老小鼠（senescence-accelerated mouse prone 8，SAMP8）中增加了肠道菌群的丰富度和多样性。具体而言，该组合降低了潜在致病菌 Alistipes 和 Prevotella 的相对丰度，同时提升了异普雷沃菌属、产乙酸菌属和梭菌 XIVa 群的丰度，从而改善了肠道微环境[25]。此外，黏液性阿克曼氏菌通过增加自身丰度并减少乳酸菌科的相对丰度，进一步增强肠道屏障功能并降低炎症反应，显著缓解了肠道衰老[49]。Kim 等人进一步研究发现，副棘白芽孢杆菌 PS23 通过增加乳酸菌丰度、减少有害菌的丰度来调节肠道微环境，降低肠道通透性及促炎因子的表达，从而改善老年小鼠的肠道功能[50]，与此类似，发酵乳杆菌 DR9、副干酪乳杆菌 OFS 0291 和瑞士乳杆菌 OFS 1515 通过提升厚壁菌门/拟杆菌门的比例，减少有害菌（如变形菌），增加有益菌（例如乳杆菌属和布

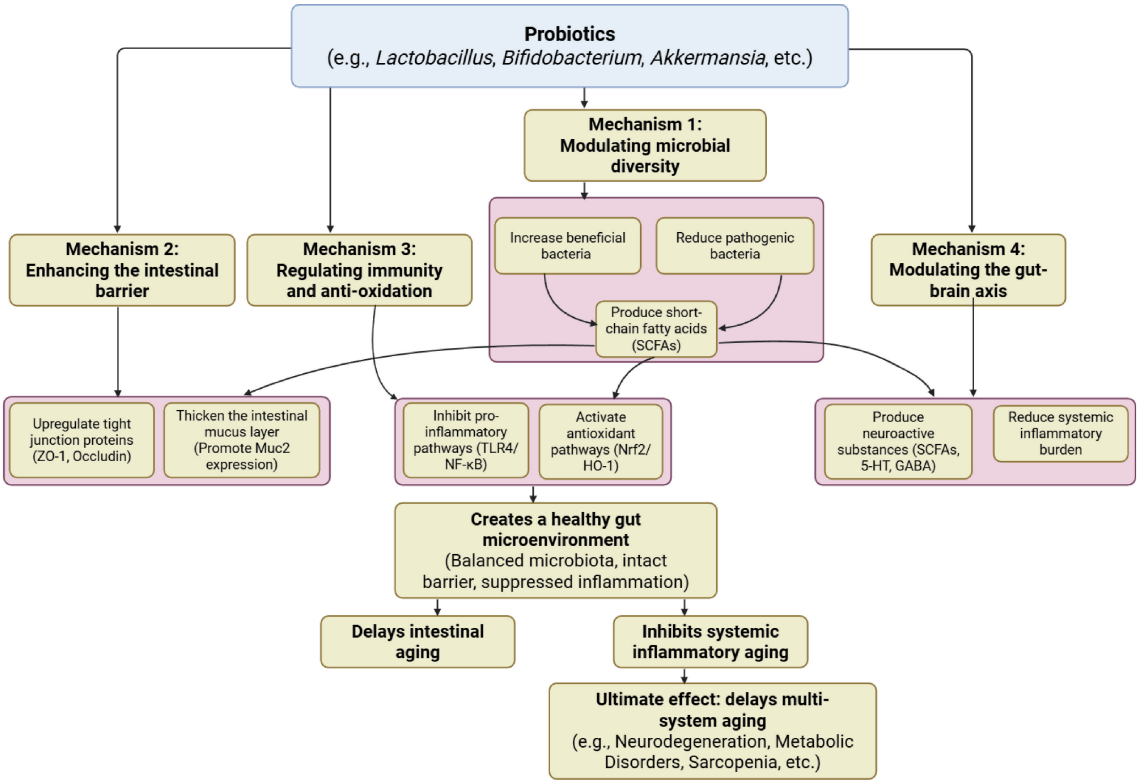

Fig. 1 The mechanism of probiotics in intestinal aging Probiotics delay multi-system aging through gut-centric mechanisms. Specific probiotics (e.g., *Lactobacillus*, *Bifidobacterium*) counteract aging by: 1) modulating gut microbiota diversity and producing SCFAs; 2) enhancing the intestinal barrier; 3) regulating immunity and anti-oxidation; and 4) modulating the gut-brain axis. These integrated actions create a healthy gut microenvironment, which inhibits local and systemic inflammatory aging, ultimately delaying decline in organs such as the brain and metabolism

劳特菌属),从而增强肠道屏障功能,缓解氧化应激和炎症反应[51],其他菌株例如加氏乳杆菌 KS-13、两岐双岐杆菌 G9-1 和长双歧杆菌 MM-2 则通过增加粪便中双歧杆菌、抗炎菌群(如普拉梭菌、粪杆菌)和乳酸菌的丰度,降低大肠杆菌的丰度,改善菌群组成、调节免疫活性和降低炎症水平[31]。

2　肠道益生菌缓解衰老相关疾病的应用

随着衰老进程,机体多个系统功能逐渐衰退,易引发一系列与年龄相关的慢性疾病。近年来,研究表明肠道菌群失调是加速衰老及推动相关疾病发生发展的关键因素之一。基于对“肠-X 轴”(如肠-肝轴、肠-脑轴、肠-肌轴等)相互作用机制的深入理解,益生菌的应用已从单一的消化道健康维护,拓展至对多种系统性衰老相关疾病的干预。其在调节免疫、抑制炎症、改善代谢和保护神经等方面的多效性作用,显示出广阔的应用前景。本节将系统综述益生菌在代谢性疾病、消化系统疾病、运动系统疾病、免疫系统功能衰退、神经系统退行性病变以及皮肤衰老等领域的基础研究与临床证据,阐述其具体应用机制与潜在价值。

2.1　代谢性疾病

基于现有文献研究,肠道益生菌在缓解衰老相关的 NAFLD 中展现出显著潜力,其作用机制主要围绕“肠-肝轴”展开。衰老伴随的肠道菌群失调,表现为有益菌减少和致病菌增加,导致肠道屏障完整性受损和氧化应激加剧[52, 53]。这种失调通过多种途径促进 NAFLD 发展,包括内毒素(例如脂多糖)易位激活肝内 TLR4 通路引发炎症反应、短链脂肪酸(SCFAs)生成减少削弱抗炎和代谢调节功能,以及胆汁酸代谢紊乱[54-57]。益生菌(例如乳杆菌和双歧杆菌属)可通过恢复微生物平衡、增强紧密连接蛋白的表达及调节代谢产物,从而多靶点干预 NAFLD 进程[58]。

在动物模型中,益生菌对 NAFLD 的改善作用已得到广泛验证。研究多采用高脂饮食(high-fat diet, HFD)或蛋氨酸-胆碱缺乏(methionine and choline-deficient, MCD)饮食诱导的衰老或 NAFLD 小鼠/大鼠模型,干预周期为 8~21 周,常用菌株包括鼠李糖乳杆菌 GG、长双歧杆菌及复合益生菌制剂 VSL#3[53]。其作用机制涵盖多个方面:抑制炎症通路(例如 IKK-β/NF-κB)降低 TNF-α 和 IL-6 水平、增强抗氧化酶(超氧化物歧化酶,superoxide dismutase, SOD)和谷胱甘肽过氧化物酶(glutathione peroxide, GSH-Px)活性缓解氧化损伤、调节脂代谢关键基因(例如下调固醇调节元件结合蛋白-1c(sterol regulatory element-binding protein-1c, SREBP-1c)和上调过氧化物酶体增殖物激活受体-α(peroxisome proliferator-activated receptor-alpha, PPAR-α))减少肝脂肪蓄积,通过增加黏蛋白分泌和紧密连接蛋白表达以修复肠道屏障功能[59-62]。下一代益生菌如嗜黏蛋白阿克曼菌,其通过改善黏蛋白层厚度和胆汁酸代谢进一步减轻肝脂肪变性[63, 64]。

临床试验进一步证实,益生菌对人类老年 NAFLD 患者的益处。多项随机对照试验(RCTs)显示,补充益生菌(例如副干酪乳杆菌 HII01、短双歧杆菌、长双歧杆菌或复合制剂 VSL#3)8 周至 12 个月可显著改善代谢指标[53, 65]。具体效果包括:肠道屏障功能增强(乳果糖/甘露醇比率降低 48%及血清 LPS 下降)、血脂谱改善(HDL-C 升高,LDL-C 和甘油三酯降低)、系统性炎症抑制(TNF-α、IL-6 和 hsCRP 水平下降)以及肝内酶(丙氨酸氨基转移酶(alanine aminotransferase, ALT)、天冬氨酸氨基转移酶(aspartate aminotransferase, AST)和 γ-谷氨酰转肽酶(gamma-glutamyl transpeptidase, GGT))正常化。此外,益生菌还能调节神经代谢途径,例如降低喹啉酸(QA)影响色氨酸代谢和脑-肠轴通信。这些效益主要归因于 SCFAs(如丁酸和丙酸)产量增加、IgA 分泌增强及胆汁酸代谢调节。综上所述,益生菌通过多机制协同缓解衰老相关 NAFLD,但其临床转化仍需优化菌株组合、剂量方案并评估长期疗效。

2.2　消化系统疾病

目前的研究充分证实,肠道益生菌通过多靶点协同作用机制有效改善衰老相关的消化系统疾病。在多种实验模型中,益生菌及其后生元展现出三大核心作用机制:首先是通过重构肠道菌群生态,显著增加毛螺菌科和产丁酸菌(如粪杆菌属)的丰度,使结肠丁酸浓度提升至 93.4 mmol/L;其次是修复肠道屏障功能,上调紧密连接蛋白(Claudin-1 ↑ 1.72 倍)和改善膜流动性;最后是抑制炎症反应,例如后生元 P-HF08 中的 TLR4 抑制剂(金雀异黄素)可降低 NF-κB 表达量达 64%[66]。多菌株联合干预通过调节胆汁酸代谢轴产生更全面的保护效应[67],而间歇性禁食与益生菌联用可使结肠隐窝深度显著增加 37%[68]。

在临床转化方面,益生菌干预策略展现出显著的应用潜力,但也面临重要挑战。活菌与后生元各具优势:活菌 HF08 在肠道屏障完整时调节

菌群效果更佳,而后生元 P-HF08 在屏障受损时安全性更高(FITC-葡聚糖泄漏减少 62.3%)[66]。临床研究证实,特定菌株如嗜黏蛋白阿克曼菌通过增强黏蛋白层厚度改善肠道屏障[27],而复合制剂 VSL#3 能显著提升次级胆汁酸水平($P < 0.01$)[69]。然而,现有研究存在明显局限性:个体化治疗方案缺乏标准化评估方法,菌株协同潜力探索不足,且大多数研究的随访期较短(8~12 周),长期安全性数据仍待完善。

未来研究应当着重解决 3 个关键问题:首先需要加强机制研究的时空分辨率,采用单细胞测序等技术解析益生菌对肠道不同区段上皮细胞的特异性影响;其次应开发动态监测技术,实现肠道屏障状态的实时评估;最后必须推动多中心、长周期的临床研究。山楂-益生菌后生元研究展示的"多组分-多靶点"策略可能代表未来发展方向[70]。只有通过这种多学科交叉的深入研究,才能真正实现益生菌疗法在老年消化系统疾病中的精准应用,为老龄化社会提供有效的健康干预方案。

2.3 运动性疾病

肠道益生菌在缓解衰老相关运动系统疾病(例如肌肉减少症和骨质疏松症)中的应用已得到多项研究的支持。在动物实验中,例如使用老年小鼠模型的研究表明,特定益生菌株例如乳酸杆菌(LC122)和双歧杆菌(BL986)能够改善肌肉质量和功能。其机制涉及调节肠道微生物群组成,增加有益代谢物短链脂肪酸的产量,从而抑制肌肉萎缩相关基因(例如肌肉萎缩 F 盒蛋白, Atrogin-1 和肌肉环指蛋白 1(muscle ring finger 1, MuRF1))的表达,并促进线粒体功能。此外,益生菌还通过减少炎症因子(如 TNF-α 和 IL-6)和增强肠道屏障功能,间接改善肌肉健康[71]。另一项研究显示,厌氧钙化杆菌 CML199 通过产生丁酸盐,促进骨形成和抑制骨吸收,从而缓解年龄相关性骨丢失[72]。此外,长双歧杆菌补充能够加速骨折愈合,促进骨痂形成和力学性能的恢复,这主要归因于其对肠道屏障的保护、系统性炎症的抑制以及肠道微生物群的稳定,从而减轻骨折引起的全身病理反应[73]。这些发现表明,益生菌通过调节"肠-肌肉轴"和"肠-骨轴"发挥多效性作用。

在人体试验中,研究涉及老年肌肉减少症患者。例如,一项临床试验使用乳双歧杆菌 Probio-M8,结果显示补充该益生菌能够改善身体性能(例如 5 次坐立测试时间减少 16%),并增加血清肌酸水平,这可能通过抑制有害微生物代谢物(例如 n-十二酰基高丝氨酸内酯)来实现[74]。机制上,益生菌可能通过增强 SCFAs(如丁酸盐)的产生,改善能量代谢和减少炎症,从而延缓肌肉和骨丢失[72]。然而,人体试验结果存在不一致性,例如某些研究未观察到肌肉质量的显著增加,突显了个体差异和剂量依赖效应的挑战[71, 74]。

总体而言,益生菌通过调节肠道微生物组及其代谢物,在缓解衰老相关运动系统疾病中展现出潜力,但需进一步大规模临床试验验证其有效性和安全性。未来研究应聚焦于个性化益生菌干预,结合多组学技术,以优化治疗策略。

2.4 免疫系统疾病

在动物实验层面,多项研究揭示了特定益生菌株通过免疫调节机制缓解衰老相关疾病的作用。罗伊氏乳杆菌 KBL346(分离自婴儿粪便)在环磷酰胺诱导的免疫抑制小鼠模型中,通过激活巨噬细胞吞噬功能、促进一氧化氮(nitric oxide, NO)/前列腺素 E_2(prostaglandin E_2, PGE2)分泌及 TNF-α/IL-6/IL-1β 等细胞因子释放,增强 TLR-MAPK/NF-κB 信号通路,改善脾的结构、NK 细胞活性及 T/B 淋巴细胞增殖,并提升 CD4+/CD8+ T 细胞数量和血清免疫球蛋白水平[75]。与此类似,干酪乳杆菌 CRL431 在衰老和肥胖小鼠模型中,通过恢复胸腺皮质-髓质比、增加 CD4+ T 细胞数量和 IL-7/IL-3 分泌,调控肠道菌群(例如增加乳杆菌属),降低促炎因子(IL-6、TNF-α)并提升抗炎因子 IL-10,从而改善年龄相关的免疫衰退[76]。乳酸乳球菌乳脂亚种 C60 在 IL-18 缺陷衰老小鼠中,通过增强树突状细胞抗原提呈能力、促进 IFN-γ+ CD4+ T 细胞(Th1)分化,修复小肠固有层 T 细胞群缺失,其热灭活形式(postbiotic)同样有效[77]。此外,乳酸乳球菌 HF08 及其后生元(P-HF08)在 D-半乳糖诱导的衰老及结肠炎模型中,通过抑制 TLR4/NF-κB 通路(降低 p-IκBα/p-NF-κB p65)、上调紧密连接蛋白表达、增加短链脂肪酸产生及调节菌群(例如增加阿克曼菌属),减轻肠道屏障损伤和炎症;后生元因含潜在 TLR4 抑制剂(例如环氧孕酮、木二糖)而更具安全性[66]。

尽管人体试验目前的证据有限,但动物实验的机制研究为临床应用提供了理论基础。例如,罗伊氏乳杆菌 KBL346 的安全评估(无溶血性、抗生素敏感)支持其潜在益生菌用途[75],而干酪乳杆菌 CRL431 对胸腺功能的调控提示其对年龄相关免疫

Table 1　The role of probiotics in age-related diseases

Disease category	Probiotic strain(s)	Mechanism	References
Metabolic diseases (e.g., NAFLD)	*Lactobacillus rhamnosus* GG, *Bifidobacterium longum*, VSL#3 (multi-strain)	Inhibits the IKK-β/NF-κB pathway to reduce hepatic TNF-α and IL-6 levels; enhances intestinal barrier function by upregulating mucin and tight junction protein expression.	[53], [59-62]
	Akkermansia muciniphila	Improves mucin layer thickness and regulates bile acid metabolism, thereby reducing liver steatosis and inflammation.	[63, 64]
Digestive system diseases	*Akkermansia muciniphila*	Enhances the thickness of the intestinal mucin layer, strengthening the gut barrier and improving its function.	[27]
	VSL#3 (Multi-strain)	Modulates bile acid metabolism, significantly increasing levels of secondary bile acids to promote gut health.	[69]
Motor system diseases (Sarcopenia/Osteoporosis)	*Lactobacillus casei* LC122, *Bifidobacterium longum* BL986	Increases SCFA production to inhibit expression of muscle atrophy genes (Atrogin-1, MuRF1) and reduce inflammatory cytokines (TNF-α, IL-6).	[71]
	Anaerostipes caccae CML199	Produces butyrate to promote bone formation and inhibit bone resorption, alleviating age-related bone loss.	[72]
	Bifidobacterium longum	Protects the intestinal barrier, inhibits systemic inflammation, and stabilizes gut microbiota to accelerate fracture healing.	[73]
Immune system diseases (Immunosenescence)	*Limosilactobacillus reuteri* KBL346	Activates the TLR-MAPK/NF-κB signaling pathway in macrophages to enhance phagocytosis and promote secretion of NO, PGE2, and cytokines (TNF-α, IL-6, IL-1β).	[75]
	Lactobacillus casei CRL431	Modulates gut microbiota (e.g., increases *Lactobacillus*), reduces pro-inflammatory cytokines (IL-6, TNF-α), and increases anti-inflammatory IL-10 to restore thymic function and T-cell populations.	[76]
Nervous system diseases (e.g., AD, PD)	*Bifidobacterium longum* NK46	Reduces LPS production from gut microbiota, inhibits NF-κB activation, and increases tight junction protein expression to alleviate neuroinflammation and cognitive decline.	[78]
	Bifidobacterium breve CCFM1067, *Clostridium butyricum*	Increases SCFA (acetate, butyrate) levels, inhibits microglial activation, and restores dopaminergic neuron function in a PD model.	[79, 80]
	Engineered Lactococcus lactis MG1363-pMG36e-GLP-1	Secretes GLP-1 to activate the Keap1/Nrf2/GPX4 pathway, inhibiting ferroptosis and astrocyte senescence.	[81, 82]
Skin aging	*Bifidobacterium breve* B-3	Inhibits UVB-induced skin water loss (TEWL), epidermal thickening, and production of the inflammatory cytokine IL-1β.	[84]
	Lactobacillus plantarum HY7714	Its exopolysaccharide (EPS) regulates intestinal tight junction proteins (ZO-1, Occludin-1), indirectly inhibiting skin MMP activity and promoting hyaluronic acid synthesis for improved skin hydration and anti-photoaging.	[85]

衰退的干预价值[76]。后生元(如热灭活 C60 或 HF08)在肠道屏障受损状态下(如结肠炎)可能比活菌更安全,避免菌群移位风险[66, 77]。未来需推进人群研究(尤其是老年人)验证这些菌株在免疫衰老、炎症性肠病中的应用,并探索个体化菌株配伍及后生元制剂开发,以平衡功效与安全性。

2.5　神经系统疾病

近年来,肠道益生菌在神经系统衰老相关疾病中的应用受到广泛关注,其作用机制涉及微生物-肠-脑轴的调节。多项动物实验表明,特定益生菌株例如长双歧杆菌 NK46、短双歧杆菌 CCFM1067、乳酸乳球菌 MG1363-pMG36e-GLP-1、丁酸梭菌以及其

工程化菌株丁酸梭菌-pMTL007-GLP-1 和复合益生菌制剂(P2 和 P3 混合物),能够通过调节肠道菌群组成、抑制炎症反应、减轻氧化应激和神经元凋亡,改善认知功能障碍和神经病理变化。例如,在 5XFAD 转基因小鼠和老年小鼠中,长双歧杆菌 NK46 通过降低肠道菌群脂多糖产量、抑制 NF-κB 活化并增加紧密连接蛋白表达,减轻结肠炎症和海马体神经炎症,从而缓解认知衰退[78]。在 1-甲基-4-苯基-1,2,3,6-四氢吡啶(1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, MPTP)诱导的帕金森病(Parkinson's disease, PD)小鼠模型中,短双歧杆菌 CCFM1067 和丁酸梭菌通过增加短链脂肪酸例如乙酸和丁酸的水平,抑制小胶质细胞活化,恢复多巴胺能神经元功能,并改善运动缺陷[79, 80]。工程菌株如乳酸菌 MG1363-pMG36e-GLP-1 和丁酸梭菌-pMTL007-GLP-1 则通过持续分泌 GLP-1,激活 Keap1/Nrf2/GPX4 和 p53/p21 通路,抑制铁死亡和星形胶质细胞衰老,进一步发挥神经保护作用[81, 82]。此外,多菌株益生菌[83](例如 P3 混合物)在 SAMP8 小鼠中通过调节 AKT/GSK-3β 信号通路,减少 Aβ 沉积和 Tau 蛋白过度磷酸化,并降低神经炎症标志物如 TNF-α 水平。

在人体试验方面,目前直接证据相对有限,但部分临床研究已显示,益生菌对神经系统疾病的潜在益处。例如,益生菌(如乳酸杆菌和双歧杆菌属混合物)可改善 PD 患者的胃肠症状和运动功能障碍,并降低炎症因子水平[79, 80]。然而,大多数人体研究仍处于初步阶段,需更多大规模、随机对照试验验证其疗效和机制。

目前认为,益生菌通过微生物-肠-脑轴的多途径作用(例如调节 SCFAs、抑制炎症和氧化应激、增强肠道屏障功能)为神经系统衰老相关疾病提供了新型治疗策略。然而,当前研究主要集中在动物模型,人体试验的证据仍不充分,且益生菌的菌株特异性、剂量和长期安全性需进一步优化。未来研究应深入探索益生菌的作用机制,并结合多组学技术推动临床转化。

2.6 皮肤衰老

肠道益生菌通过皮肤-肠道轴在缓解皮肤衰老及相关疾病中展现出多途径作用机制和临床应用潜力。

动物实验表明,短双歧杆菌 B-3 口服补充显著抑制了紫外线诱导的小鼠皮肤水分流失、表皮增厚和炎症因子 IL-1β 的产生,并改善了紧密连接结构[84]。与此类似,植物乳杆菌 HY7714 通过其胞外多糖(extracellular polymeric substances, EPS)调控肠道紧密连接蛋白的表达,间接抑制皮肤中基质金属蛋白酶(matrix metalloproteinase, MMP-1、MMP-13)的活性,减少胶原降解,并促进透明质酸(hyaluronic acid, HA)合成酶(HAS)的表达,从而增强皮肤保湿和抗光老化能力。这些效应与益生菌调节肠道免疫稳态、减少全身性氧化应激和炎症密切相关[85]。在人体临床研究中,一项随机双盲试验显示,口服植物乳杆菌 HY7714(6×10^9 CFU/d,12 周)显著改善了中老年女性(41~59 岁)的皮肤弹性、皱纹深度和水分含量[85]。研究使用含约氏乳杆菌的乳霜局部涂抹,减少了特应性皮炎患者皮肤的金黄色葡萄球菌定植并改善了屏障功能[86]。此外,嗜热链球菌通过增加皮肤角质层神经酰胺水平,增强皮肤屏障,缓解湿疹症状[87]。

目前证据表明,益生菌通过直接抑制皮肤 MMPs 活性、促进胶原合成、调节肠道免疫和屏障功能以及通过代谢产物(如 SCFAs)影响皮肤免疫微环境等多途径协同作用,但其菌株特异性效应显著,未来需更大规模人群试验明确菌株-剂量-效应关系。

3 问题与展望

尽管益生菌在延缓肠道衰老及相关疾病防治中展现出巨大潜力,但其临床转化仍面临多重挑战,亟需在机制探索和技术应用层面实现突破。目前研究主要存在以下核心问题:首先,益生菌干预与抗衰老效应间缺乏明确的因果证据,其作用究竟源于菌体本身、代谢产物(如短链脂肪酸)还是对宿主固有菌群的次级调控尚不明确;其次,益生菌作用存在显著的菌株特异性及个体差异性,不同菌株组合的协同效应难以预测,且宿主年龄、遗传背景及基线微生态结构显著影响干预效果;此外,益生菌制剂的长期安全性,特别是对老年群体肠道菌群生态稳定性的潜在影响仍需大规模长期研究评估。

为解决上述瓶颈,未来研究应致力于以下方向:一方面需借助多组学整合分析、类器官共培养模型等前沿技术,在分子层面精准解析益生菌与肠道屏障、免疫细胞及神经内分泌网络的相互作用机制;另一方面应积极开发下一代益生菌疗法,包括利用合成生物学工具构建功能增强型工程菌(例如靶向递送特定抗衰老分子的工程化菌株),以及推进难培养但功能明确的新菌种(例如嗜黏蛋白阿克曼菌)

及其后生元制剂的临床转化研究。

综上所述,通过跨学科合作将微生物学、免疫学与临床医学深度融合,有望克服现有研究瓶颈。未来需重点开展以客观衰老生物标志物为终点的大规模长期临床试验,建立基于宿主多维数据的个性化干预模型,最终将益生菌从宏观概念转化为能精准对抗肠道衰老及衰老相关疾病的有效治疗策略。

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