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专论与综述

益生菌缓解新型冠状病毒感染症状的研究进展

刘彦芳，史璇，张和平*

内蒙古农业大学 乳品生物技术与工程教育部重点实验室 农业农村部奶制品加工重点实验室 内蒙古自治区乳品生物技术与工程重点实验室，内蒙古 呼和浩特 010018

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摘　要：由急性呼吸道综合征冠状病毒 2 (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2)引起的新型冠状病毒感染(coronavirus disease 2019, COVID-19)从 2020 年初迅速扩展至全球，成为人类历史上最严重的大流行之一。已有证据证明当 SARS-CoV-2 的刺突蛋白(S 蛋白)与细胞表面受体血管紧张素转化酶 2 (angiotensin converting enzyme 2, ACE2)结合时，可感染宿主细胞，引起肠道菌群失调，并引发不同的并发症。益生菌是活的微生物，已被证明对人体健康有益。因其在调节肠道菌群、治疗多种疾病和抗病毒方面的功效而被考虑用来改善 COVID-19。本文基于目前公开的临床前和临床试验结果，总结了益生菌在缓解 COVID-19 临床症状及胃肠道不良反应的效果，并讨论了益生菌在改善 COVID-19 后遗症方面的潜力，从而为后续管理 COVID-19 提供新的方向，进一步为呼吸系统疾病提供理论依据。

关键词：COVID-19；益生菌；抗病毒活性；肠道菌群；后遗症

Research progress of probiotics alleviating symptoms of COVID-19

LIU Yanfang, SHI Xuan, ZHANG Heping*

Key Laboratory of Dairy Biotechnology and Engineering, Ministry of Education, Key Laboratory of Dairy Products Processing, Ministry of Agriculture and Rural Affairs, Inner Mongolia Autonomous Region Key Laboratory of Dairy Biotechnology and Engineering, Inner Mongolia Agricultural University, Hohhot 010018, Inner Mongolia, China

Abstract: Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome

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*Corresponding author. E-mail: hepingdd@vip.sina.com
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coronavirus 2 (SARS-CoV-2), has rapidly spread around the globe since early 2020, becoming one of the worst pandemics in the history. The spike (S) protein of SARS-CoV-2 can bind to angiotensin-converting enzyme 2 (ACE2), a receptor on the host cell surface, to cause gut microbiota imbalance and different complications. Probiotics, proved to be capable of regulating gut microbiota to treat diseases and viral infections, have been considered to serve as an option for alleviating COVID-19. We summarize the efficacy of probiotics in alleviating clinical symptoms and gastrointestinal adverse events of COVID-19 based on the results of available preclinical and clinical trials. Furthermore, we discuss the potential of probiotics to mitigate the sequelae of COVID-19, thereby providing new directions for the subsequent management of COVID-19 and a theoretical basis for treating respiratory diseases.
Keywords: COVID-19; probiotics; antiviral activity; gut microbiota; sequelae

COVID-19 (coronavirus disease 2019)是近年来发生的一次突发且持久的公共安全事件，对人类健康造成了巨大的威胁。通常表现为头痛、流涕、打喷嚏、喉咙痛和味嗅觉丧失等。由于机体存在个体差异，因此部分人群的症状略有不同。益生菌是活的微生物，已被证明对人体健康有益。因其在调节肠道菌群、治疗多种疾病和抗病毒方面的功效而被考虑用来改善 COVID-19 症状。本文综述了目前益生菌在改善 COVID-19 症状及胃肠道不良反应的效果，讨论了益生菌在缓解 COVID-19 后遗症方面的潜力，为治疗此类疾病提供了新的见解。

1 COVID-19 症状概述

1.1 COVID-19

2019 年 12 月，一种非典型呼吸道传染病迅速席卷全球。经研究发现，这种呼吸道传染病是由一种急性呼吸道综合征冠状病毒 2 (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2)引发的感染[1]。世界卫生组织(World Health Organization, WHO)将新型冠状病毒感染命名为“2019 冠状病毒病(COVID-19)”。COVID-19 是一次突发且持久的公共安全事件，最初几年对人类健康造成严重威胁，也给其他方面带来了很大程度的影响和障碍。2023 年 3 月 11 日是 WHO 首次将 COVID-19 全球疫情暴发宣布为大流行的 3 周年，虽然确诊和死亡病例人数已呈下降趋势，但截至 3 月 26 日，全球已报告确诊病例超过 7.61 亿例，死亡病例超过 680 万例(www.who.int)。

SARS-CoV-2 是一种具有包膜的正链单股 RNA 病毒，血管紧张素转化酶 2 (angiotensin converting enzyme 2, ACE2)是 SARS-CoV-2 进入宿主细胞的关键分子[2]，当 SARS-CoV-2 的刺突蛋白(S 蛋白)与细胞表面受体 ACE2 结合时，可感染宿主细胞[3]。尽管个体免疫反应存在差异，但大多数人的 COVID-19 症状一般是非特异性的[4]。其引起的一系列临床表现(图 1)包括发烧、干咳和疲劳等，通常累及肺部并引起肺炎，部分还会出现头痛、流涕、打喷嚏、喉咙痛和味嗅觉丧失等症状[5]。但值得注意的是，在有基础性疾病的病人(尤其是老年人)中还会表现出额外或不同的症状，如神经性疾病、脑血管疾病和皮肤疾病等[6-7]。此外，80%的患者在 COVID-19 肺炎康复后的数周到数月内会出现至少一项后遗症，包括疲劳、头痛、注意力障碍、脱发、呼吸困难、味嗅觉丧失等[8]。ACE2 在气道上皮细胞上表达，同时也存在于

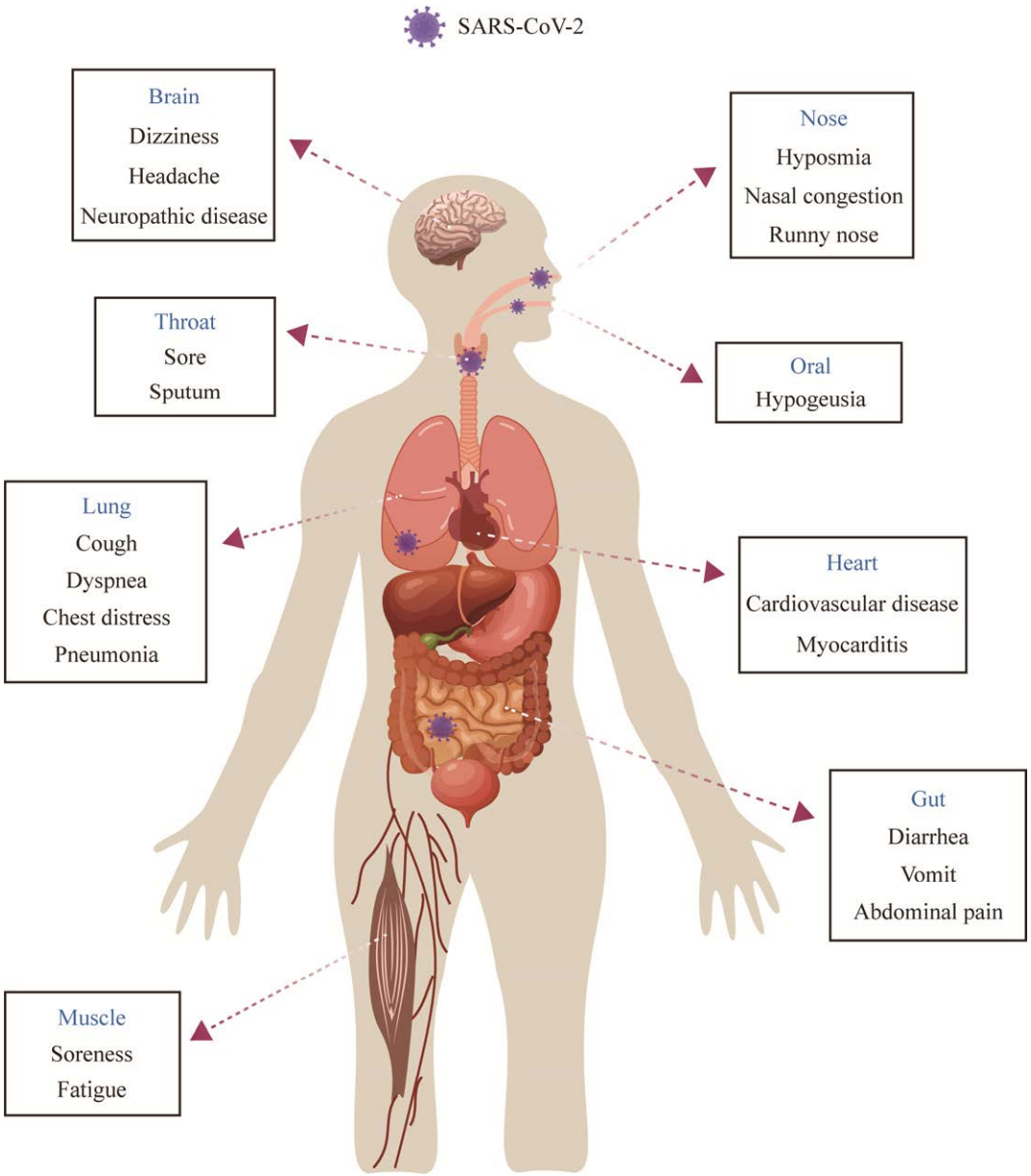

图 1　COVID-19 的临床表现

Figure 1　Clinical manifestations of COVID-19.

人类肠道上皮细胞中[9]。在肠道中，ACE2 通过维持氨基酸稳态、抗菌肽表达和影响肠道菌群来调节肠道免疫[10]。但 SARS-CoV-2 会使 ACE2 活性改变，进而导致肠道菌群失调，引发胃肠道炎症，进一步加重 COVID-19 的严重程度[11]。因此，通常在 COVID-19 初期阶段会观察到厌食、腹泻、恶心、呕吐或腹痛/不适等一些肠道并发症[2]。

1.2　肠道菌群与 COVID-19

肠道是人体最大的消化器官，也是宿主与外界环境“互动交流”最频繁的部位，在人体免疫方面发挥着重要作用[12]。人体胃肠道中的微生物数量超过 10^{14} 个，其中定殖的细菌、古菌和真菌的集合被称为“肠道菌群”，与宿主共同

进化了数千年，形成了一种错综复杂且互助互利的关系[13-14]。肠道菌群被认为是维持人体健康的最重要微生物群，从能量代谢到增强免疫力等方面都发挥着重要作用。正常的肠道菌群一般由 6 个门组成，其中厚壁菌门(*Firmicutes*)和拟杆菌门(*Bacteroidetes*)是主要类型[15]。事实上，越来越多的证据表明，肠道菌群可以在细菌和病毒感染过程中调节免疫反应，成为某些疾病管理的潜在目标[16]。例如，在肺炎链球菌感染的小鼠模型中，小鼠肠道菌群的减少导致了细菌传播、炎症、器官损伤和死亡率增加，这表明肠道菌群在宿主感染期间发挥重要作用[17]。COVID-19 通过攻击呼吸道的方式给人们的身体健康带来巨大威胁，更好地了解 COVID-19 的病理学是当务之急。在很多 COVID-19 病例(甚至是轻度病例)的报告中均发现，患者会伴随胃肠道症状[18-19]。最近的研究报告称，COVID-19 患者在住院期间的肠道微生物发生改变，而且在 COVID-19 长期并发症的患者肠道中发现了持续的菌群改变[20]。

一项单中心横断面研究证实 COVID-19 患者的肠道菌群结构和组成都发生了显著变化[21]。此外，在具有胃肠道症状的患者肠道菌群中发现了条件致病菌富集、有益共生菌减少，并且在住院期间肠道菌群特征持续发生变化。Zuo 等[22]对 SARS-CoV-2 感染住院的 COVID-19 患者的肠道菌群变化进行了研究，发现粪便中一种抗炎细菌普拉梭菌(*Faecalibacterium prausnitzii*)的丰度与疾病严重程度呈负相关关系，同时条件致病菌，如哈氏梭菌(*Clostridium hathewayi*)、粘性放线菌(*Actinomyces viscosus*)和北拟杆菌(*Bacteroides nordii*)的数量增加。类似地，另一项研究也显示 COVID-19 患者中出现了肠道菌群失调：与轻症患者相比，中重症患者肠道中产生丁酸盐的细菌，如 *F. prausnitzii*、丁酸梭菌(*Clostridium butyricum*)、柔嫩梭菌(*Clostridium leptum*)和直肠真杆菌(*Eubacterium rectale*)的丰度显著降低；而常见的机会致病菌肠杆菌和肠球菌的丰度明显高于对照组[23]。这表明肠道菌群与 COVID-19 密切相关。复杂的肠道生态系统可以防止潜在致病菌的入侵，相反地，当肠道菌群多样性或结构受到损害时会增加致病菌感染的风险。重症 COVID-19 病例通常会使用抗生素和抗病毒处方进行治疗，而这可能大大影响免疫力低下患者的肠道菌群稳态，进一步导致耐药性感染和感染性休克的发生率。对于有基础疾病的患者，用广谱抗性药物如利巴韦林、氯喹、利托那韦和肝素等治疗时带来的副作用更为明显[24]。抗生素对于肠道菌群的破坏是深远的，即使 COVID-19 患者在康复后依旧可能发生肠道菌群失调相关疾病。

以上结果表明，COVID-19 患者中可观察到不同于健康人的肠道菌群结构差异，且在住院期间接受抗生素治疗的患者中更为明显。虽然疾病症状与肠道菌群之间的因果关系尚不清楚，但这提示了调节肠道菌群可能是缓解 COVID-19 的一个潜在靶点。

2 益生菌概述

2.1 益生菌的发展情况

国际益生菌和益生元科学协会将益生菌定义为“活的微生物，当以足够的量使用时会给宿主带来健康益处”[25]。在日常生活中，常见的益生菌有乳杆菌属(*Lactobacillus*)和双歧杆菌属(*Bifidobacterium*)，此外还有乳球菌属(*Lactococcus*)、链球菌属(*Streptococcus*)、芽孢杆菌属(*Bacillus*)、肠球菌属(*Enterococcus*)和酵母菌属(*Saccharomyces*)等[26]。这些具有长期安全使用历史的微生物被称为传统益生菌；而通过下一代测序技术和生物信息学分析方法筛选

和分离未得到广泛应用的益生菌称为下一代益生菌(next generation probiotics, NGP)，主要包括普氏栖粪杆菌(*Faecalibacterium prausnitzii*)、脆弱拟杆菌(*Bacteroides fragilis*)、嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*)、粪便普雷沃氏菌(*Prevotella copri*)、多形拟杆菌(*Bacteroides thetaiotaomicron*)和古氏副拟杆菌(*Parabacteroides goldsteinii*)等[27]。

益生菌可以增强肠道屏障的完整性，调节肠道免疫力，改变肠上皮和免疫细胞对肠腔中微生物的反应从而对肠道产生益处[28]。例如，植物乳植杆菌 P-9 能通过改变慢性便秘患者肠道菌群从而改善临床症状和患者生活质量[29]。急性腹泻患者服用屎肠球菌 SF68 后能得到有效治疗并预防抗生素相关性腹泻[30]。此外，复合益生菌辅助治疗溃疡性结肠炎(ulcerative colitis, UC) 12 周后，患者疾病活动指数、菌群多样性和丰富度下降，从而缓解 UC 症状[31]。结直肠癌患者术后服用复合益生菌 6 个月，促炎细胞因子水平明显降低[32]。益生菌除了可以改善肠道症状外，在改善脂质谱、胰岛素抵抗和葡萄糖耐量以及调节 ACE 抑制肽方面也具有一定潜力[33]。高脂血症患者在接受 3 个月 Probio-X®后，可以调节宿主的肠道菌群平衡、脂质代谢和生活方式，从而缓解其症状[34]。肥胖人群使用益生菌胶囊 GP2 后，腰围、总脂肪面积等肥胖相关指标显著降低[35]。冠心病患者食用 Probio-M8 联合常规疗法可以提高治疗效果，从而改善微生物代谢潜力和血清代谢谱[36]。一方面，益生菌可以通过抑制病原微生物的生长来平衡局部微生物群；另一方面，益生菌影响肠道内容物中微生物群的组成和活性，从而增强局部和全身免疫反应[37]。因此，益生菌可能作为治疗肺部和呼吸道疾病的一种策略。急性呼吸道感染儿童使用动物双歧杆菌乳亚种 Probio-M8 可以减少鼻咽部和流感样症状持续时间，同时减少了抗生素使用和住院时间[38]。哮喘患者摄入 Probio-M8 还可显著改善哮喘症状，并改善肠道菌群的组成及活性代谢产物，调节血清代谢组[39]。由此可以看出，益生菌可能会改善 COVID-19 引起的某些肠道并发症，减轻基础性疾病患者的危害，并改善 COVID-19 患者的肺部和呼吸道症状。

2.2 益生菌的抗病毒活性

随着病毒变异、疫情变化、疫苗接种普及和防控经验积累，我国新冠疫情防控进入了新阶段。在当前开放政策环境下，被 COVID-19 病毒感染几乎无法避免，因此还需积极寻找预防、治疗和缓解 COVID-19 的方案。提高机体的免疫力是防止病毒入侵的方式之一，而肠道黏膜是人体免疫的重要防线。已有证据表明，益生菌可以抑制致病菌在肠道内的定殖，防止病毒吸附到黏膜上皮表面，有助于建立健康的肠道黏膜保护层，从而增强宿主免疫系统[40-41]。某些特定的乳杆菌，如植物乳植杆菌和鼠李糖乳酪杆菌通常具有抗病毒活性和增强免疫的能力，因此常被用于临床前研究。Miettinen 等[42]发现活菌状态的鼠李糖乳酪杆菌 GG 和 LC705 在巨噬细胞中诱导了不同的基因表达谱，虽然鼠李糖乳酪杆菌 GG 和 LC705 在宿主防御反应中的功能有所不同，但都激活了巨噬细胞抗甲型流感病毒的潜力。动物实验中，Tomosada 等[43]使用 2 种不同的鼠李糖乳酪杆菌分别对小鼠进行鼻腔给药，发现鼠李糖乳酪杆菌 CRL1505 和 CRL1506 可分别调节 Toll 样受体 3/视黄酸诱导基因 I (TLR3/RIG-I)触发的抗病毒呼吸免疫反应，且 2 种菌株都能增加幼鼠对呼吸道合胞病毒感染的抵抗力。此外，双歧杆菌、嗜热链球菌、片球菌属也有一定的免疫增强作用和抗病毒活性。双歧杆菌被认为是最有益的益生菌之

一，其预防和治疗特定病理条件的作用已被广泛研究。H1N1 流感病毒感染的小鼠连续 17 d 服用长双歧杆菌长亚种 MM-2 可改善临床症状，降低死亡率，抑制下呼吸道炎症，并降低病毒滴度、细胞死亡和促炎因子水平[44]。婴儿口服长双歧杆菌长亚种 BORI 及嗜酸乳杆菌 AD031 可以缩短因轮状病毒感染引起的腹泻持续时间[45]。此外，益生菌的代谢物或衍生物如胞外多糖(extracellular polysaccharides, EPS)也能够调节全身和黏膜免疫反应，从而对宿主产生健康益处。例如，嗜热链球菌 ST538 产生的 EPS 具有调节猪肠上皮细胞中 Toll 样受体 3 (TLR3)激活引发的先天抗病毒免疫反应的能力，并且能够显著改善 IFN-β、IL-6 和 CXCL-10 对 TLR3 刺激的表达[46]。由此可以看出益生菌对多种病毒有良好的抗病毒效果，因此补充益生菌可能会对 SARS-CoV-2 有抑制作用，从而使人群免受其入侵。

基于益生菌对调节肠道菌群、影响代谢和呼吸系统以及抗病毒的作用，我们推测益生菌可能对 SARS-CoV-2 引起的一系列症状有一定的改善作用，尤其是胃肠道症状。目前，益生菌已被用于 COVID-19 的临床前和临床研究。

3 益生菌与 COVID-19

3.1 益生菌缓解 COVID-19 的临床前研究

SARS-CoV-2 在人与人之间存在较高传播性，会对身体造成不同程度的损害，但目前尚缺乏有效的管理和预防措施来降低病毒的传播[47]。因为益生菌对胃肠道和呼吸系统疾病具有良好的治疗效果且有一定的抗病毒作用，所以被用于 COVID-19 的临床前研究来探究是否对此疾病具有改善或调节作用。一项动物试验发现，小鼠喂养鼠李糖乳酪杆菌 EH8 和真菌菌丝后，肺内 SARS-CoV-2 膜糖蛋白诱导的 IL-6 分泌和磷酸二酯酶 4 表达显著降低[48]。此外，小鼠模型证实植物乳植杆菌 GUANKE 与疫苗共同给药会增强 SARS-CoV-2 特异性 T 淋巴细胞和 B 淋巴细胞反应，通过系统地动员其诱导的免疫反应并穿过黏膜肠道屏障，从而影响肠-脾和肠-肺免疫调节轴，这表明植物乳植杆菌 GUANKE 与 SARS-CoV-2 疫苗结合使用可提高 SARS-CoV-2 疫苗接种的疗效[49]。Islam 等[50]利用体外细胞培养评估了植物乳植杆菌在人肺腺癌细胞(Calu-3)中的免疫调节作用，结果表明，特定的植物乳植杆菌菌株对 Calu-3 早期干预可以显著增加细胞因子 IFN-β 和 IL-6 的产生，同时降低趋化因子 CCL-5、CXCL-8 和 CXCL-10 的浓度；此外，植物乳植杆菌 MPL16 比菌株 CRL1506 更有效地增加 Calu-3 对 SARS-CoV-2 接种试验的抗性。细菌素是某些细菌在代谢过程中由核糖体 RNA 合成的多功能蛋白质化合物，在一定浓度下具有抗菌潜力[51]。体外试验证实，植物乳植杆菌的细菌素(植物乳杆菌素 W、D 和 JLA-9)可以通过阻断 ACE2 受体和病毒转录(靶向 S 蛋白和阻断 RNA 聚合酶)来抑制 SARS-CoV-2 的侵入[52]。另有研究表明，来自乳酸乳球菌的糖素 F 和来自植物乳植杆菌的乳杆菌素 G 是与 SARS-CoV-2 S、N 蛋白和 3CL 蛋白酶具有高亲和力的常见肽，这 2 种生物肽被优化后可以转化为适合 SARS-CoV-2 蛋白抑制的治疗因子，可能是控制 COVID-19 的潜在药物[53]。以上体外试验表明益生菌及其代谢产物对 SARS-CoV-2 有良好的抑制作用，但需要进一步在人群中进行临床研究，以确定用于辅助治疗 COVID-19 的益生菌特定菌株。

3.2 益生菌缓解 COVID-19 的临床研究

COVID-19 患者常伴随着肠道菌群失调甚至胃肠道疾病的发生，而益生菌可以通过调节肠道菌群缓解胃肠道症状，因此有望成为改善

COVID-19 相关症状的一项策略。COVID-19 患者口服复合益生菌制剂后，腹泻和其他症状得到缓解[54]，且降低了呼吸衰竭的风险[55]。还有研究发现，益生菌治疗 COVID-19 患者后，患者在急性感染和恢复期肠道菌群中的耐药基因(antibiotic resistance genes, ARGs)显著减少[56]。此外，益生菌干预后的患者肠道菌群得到恢复，如大肠杆菌(*Escherichia coli*)和肺炎克雷伯菌(*Klebsiella pneumoniae*)的 RNA 表达降低，而 *F. prausnitzii* 和人罗斯拜瑞氏菌(*Roseburia hominis*)的 RNA 表达升高，从而与健康对照组更为相似[57]。复合益生菌还可以影响 COVID-19 患者的葡萄糖利用率和能量通路中的关键代谢物，并降低身体和精神疲劳程度来防止慢性疲劳的发展，从而改善患者的生活质量[58-59]。益生菌除了对患者的腹泻等肠道症状、肠道菌群、能量代谢有良好的效果外，也可能影响患者的核酸检测转阴时间。COVID-19 患者接受益生菌治疗后体内病毒清除，发热持续时间和住院时间减少，临床预后相关症状也得到了改善[60-64]。以上临床研究表明益生菌对 COVID-19 患者症状有良好的缓解作用(表 1)。此外还有许多临床试验也探究了益生菌在预防和治疗 COVID-19 方面的有效性(ClinicalTrials.gov，表 2)。然而并不是所有的益生菌都能缓解 COVID-19 引起的不适。双歧杆菌乳杆菌三联活菌片辅助治疗 COVID-19 患者 7 d 后并不能改善患者免疫状态[65]。有些 COVID-19 患者使用鼠李糖乳酪杆菌和双歧杆菌辅助抗病毒药物治疗后对死亡率和大多数生物标志物无显著影

表 1　益生菌缓解 COVID-19 症状的临床研究

Table 1　Clinical study on probiotics relieving symptoms of COVID-19

Strain (dose)	Object	Intervention cycle (d)	Number of subjects	Experimental design	Effect	References
Streptococcus thermophilus DSM 32345 *Lactobacillus acidophilus* DSM 32241 *Lactobacillus helveticus* DSM 32242 *Bifidobacterium animalis* subsp. *lactis* DSM 32246 etc. (2.4×10^{12} CFU/d)	Adult	7	Probiotics group (*n*=28) Control group (*n*=42)	Controlled trial	Diarrhea and other symptoms were relieved An eight-fold reduction in the risk of respiratory failure	[55]
Bifidobacterium (2×10^{20} CFU/d)	Adult	28	SIM01 group (*n*=22) Control group (*n*=10) Virus scavenging group (*n*=20)	Open label pilot study	Antimicrobial resistance genes in gut microbiota↓	[56]
Bifidobacterium animalis subsp. *lactis* HNO19 *Lacticaseibacillus casei* subsp. Lc-11 *Lactiplantibacillus plantarum* subsp. Lp-15 *Bifidobacterium animalis* subsp. *lactis* B420 etc. (2×10^{11} CFU/d)	Adult	14	Probiotics group (*n*=13) Control group (*n*=15) Non-covid-19 control group (*n*=15)	Controlled trial	Restoration of gut microbiota	[57]

(待续)

(续表 1)

Strain (dose)	Object	Intervention cycle (d)	Number of subjects	Experimental design	Effect	References
Streptococcus thermophilus DSM 32245 *Bifidobacterium animalis* subsp. *lactis* DSM 32246 *Lactobacillus helveticus* DSM 32242 *Lacticaseibacillus paracasei* DSM 32243 etc. (2.4×10^{12} CFU/d)	Adult	19–38	Probiotics group (*n*=24) Control group (*n*=34)	Controlled trial	Fatigue ratio of probiotic group was significantly lower than control group Serum arginine, asparagine and lactic acid↑ 3-hydroxyisobutyric acid↓	[58]
Bacillus coagulans LBSC (DSM 17654) *Bacillus subtilis* PLSSC (ATCCSD 7280) *Bacillus clausii* 088AE (MCC 0538) (2×10^{10} CFU/d)	Adult	14	Probiotics group (*n*=100) Placebo group (*n*=100)	Randomized, double-blind, placebo-controlled trial	Physical and mental fatigue↓ Functional status and quality of life↑	[59]
Bifidobacterium *Lactobacillus* *Enterococcus* (6×10^{7} CFU/d)	Adult	14–28	Probiotics group (*n*=150) Control group (*n*=150)	Controlled trial	Clinical improvement time, fever duration, virus excretion time, length of hospital stay↓	[60]
Bifidobacterium longum subsp. *longum* ($\geq0.5\times10^{7}$ CFU/d) *Lactobacillus bulgaricus* *Streptococcus thermophilus* ($\geq0.5\times10^{6}$ CFU/d)	>14 years	7	Probiotics group (*n*=23) Control group (*n*=35)	Controlled trial	Diarrhea, time to turn negative↓ Procalcitonin, C-reactive protein and other inflammatory indicators↓	[61]
Bifidobacterium (1×10^{11} CFU/d)	Adult	28	SIM01group (*n*=25) Control group (*n*=30)	Open label pilot study	SARS-CoV-2 IgG, bacterial species abundance↑ IL-6, MCP-1, M-CSF, TNF-α, IL-1RA↓	[62]
Lactiplantibacillus plantarum KABP022, KABP023, KAPB033 *Pediococcus acidilactici* KABP021 (2×10^{9} CFU/d)	Adult	30	Probiotics group (*n*=150) Placebo group (*n*=150)	Single-center, four-blind, randomized trial	Nasopharyngeal viral load, pulmonary infiltration, and duration of digestive and non-digestive symptoms↓ SARS-CoV2-specific IgM and IgG↑	[63]
Lacticaseibacillus rhamnosus GG (age<5 years, 1 capsule/d; >5 years, 2 capsule/d)	≥1 year	28	Probiotics group (*n*=91) Placebo group (*n*=91)	Randomized, double-blind, placebo-controlled trial	Associated symptoms↓ Gut microbiome structure changes	[64]

IgG：免疫球蛋白 G；IL-6：白细胞介素-6；MCP-1：单核细胞趋化蛋白-1；M-CSF：巨噬细胞集落刺激因子；TNF-α：抗肿瘤坏死因子-α；IL-1RA：白细胞介素-1 受体拮抗剂；IgM：免疫球蛋白 M

IgG: Immunoglobulin G; IL-6: Interleukin-6; MCP-1: Monocyte chemoattractant protein-1; M-CSF: Macrophagecolony stimulating factor; TNF-α: Tumor necrosis factor-α; IL-1RA: Interleukin-1 receptor antagonist; IgM: Immunoglobulin M.

表 2 临床试验注册中心(ClinicalTrials.gov)注册的已完成研究

Table 2 Completed studies registered with ClinicalTrials.gov

Trial No.	Title	Strain (dose)	Object	Intervention cycle	Number of subjects	Experimental design
NCT05080244	WHO COVID-19-evaluation of the Efficacy of probiotics to reduce the occurrence of long COVID (PROVID-LD)	2 strains (1–10 d: 2×10^{10} CFU/d) (11–25 d: 1×10^{10} CFU/d)	Adult	25 d	*n*=618	Randomized, controlled trial
NCT04621071	Efficacy of probiotics in reducing duration and symptoms of COVID-19 (PROVID-19)	2 strains (1–10 d: 2×10^{10} CFU/d) (11–25 d: 1×10^{10} CFU/d)	Adult	25 d	*n*=17	Randomized, double-blind, placebo-controlled trial
NCT05474144	Monitoring the efficacy of a probiotic dietary supplement SmartProbio C in patients with severe COVID-19 infection	*Lactobacillus acidophilus* NCFM *Bifidobacterium longum* subsp. *infantis* Bi-07 *Lacticaseibacillus rhamnosus* LR22 etc. (5×10^{10} CFU/d)	Adult	2 weeks	*n*=83	Randomized, double-blind, placebo-controlled trial
NCT04390477	Study to evaluate the effect of a probiotic in COVID-19	(1×10^{9} CFU/d)	Adult	30 d	*n*=41	Prospective controlled pilot study
NCT04458519	Efficacy of intranasal probiotic treatment to reduce severity of symptoms in COVID19 infection	*Lactococcus lactis* W136 (4.8×10^{9} CFU/d)	Adult	14 d	*n*=23	Controlled trial
NCT04907877	Bifido- and Lactobacilli in symptomatic adult COVID-19 outpatients (ProCOVID)	*Bifidobacterium* *Lactobacillus* (5×10^{9} CFU/d)	Adult	28 d	*n*=70	Randomized, controlled trial
NCT04937556	Evaluation of a probiotic supplementation in the immune response of participants with COVID-19 (coronavirus disease) (PROVID)	*Ligilactobacillus salivarius* (1×10^{9} CFU/d)	Adult	28 d	*n*=41	Randomized, double-blind, placebo-controlled trial
NCT04734886	The effect of probiotic supplementation on SARS-CoV-2 antibody response after COVID-19	*Limosilactobacillus reuteri* DSM 17938 (2×10^{8} CFU/d)	Adult	6 months	*n*=161	Controlled trial
NCT05043376	Study to investigate the treatment benefits of probiotic *Streptococcus* Salivarius K12 for hospitalised patients (Non-ICU) with COVID-19	*Streptococcus salivarius* K12 (2 tablets/day)	Adult	14 d	*n*=50	Controlled trial
NCT05175833	Oral probiotics and secondary bacterial pneumonia in severe COVID-19	*Streptococcus salivarius* K12 (6×10^{9} CFU) *Lactobacillus brevis* CD2 (1.2×10^{10} CFU)	Adult	7 d	*n*=70	Controlled trial

(待续)

(续表 2)

Trial No.	Title	Strain (dose)	Object	Intervention cycle	Number of subjects	Experimental design
NCT05781945	COVID-19 pneumonia and gut inflammation	*Bifidobacterium animalis* subsp. lactis LA 304 *Ligilactobacillus salivarius* LA 302 *Lactobacillus acidophilus* LA 201	Adult	10 d	*n*=80	Randomized, controlled trial
NCT04847349	Live microbials to boost anti-severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) immunity clinical trial	Undisclosed	Adult	21 d	*n*=54	Controlled trial
NCT04517422	Efficacy of *L. Plantarum* and *P. acidilactici* in adults with SARS-CoV-2 and COVID-19	*Lactiplantibacillus plantarum* CECT30292 *Pediococcus acidilactici* CECT 7483 etc.	Adult	30 d	*n*=300	Randomized, controlled trial

响[66]。还有研究报道了两例在重症加强护理病房(intensive care unit, ICU)住院的 COVID-19 重症患者在补充酿酒酵母菌后发生了酵母菌血流感染[67]。

这些研究表明，部分益生菌在临床辅助治疗 COVID-19 时能改善患者的肠道症状并减轻临床症状，可能是未来改善 COVID-19 症状的潜在策略。然而这些研究的主要结果因益生菌菌株特异性、剂量、干预周期及个体健康水平不同而存在较大差异，未来还需要更多的理论和试验数据来进一步探讨。

3.3 益生菌与 COVID-19 后遗症

随着人们对 COVID-19 认识的提高以及 COVID-19 疫苗的广泛接种，疫情已得到控制。然而纵向流行病学调查和随访发现，许多轻度至中度 COVID-19 患者可能成为“长期受害者”。一项纳入 151 项研究的系统回顾和荟萃分析表明，50.1%的 COVID-19 幸存者在感染后长达 12 个月出现至少一种后遗症症状，包括肺 CT 异常和肺功能检查异常，其次是全身症状，如疲劳、精神症状和神经症状等[68]。此外，多项研究报道 COVID-19 可造成长期肠道菌群失调及胃肠道后遗症。Su 等[69]对 155 名 COVID-19 患者进行平均超过 1 年的随访后发现，肠道细菌多样性及丰富度仍显著低于健康对照，β 多样性也存在显著差异，并且肠道潜在致病菌增加有益菌减少。此外，117 名 COVID-19 患者出院后 90 d 随访发现 44%患者出现食欲减退、恶心、胃酸反流和腹泻等胃肠道后遗症[70]。一项前瞻性研究发现 COVID-19 患者在随访 3 个月和 6 个月时，与健康对照组相比，COVID-19 导致新发功能性胃肠道疾病/肠脑相互作用障碍的患者数量显著增加[71]。因此，COVID-19 后遗症的治疗应该是后疫情时代的重点。虽然使用益生菌来缓解 COVID-19 后遗症的研究十分有限，但由于益生菌是公认在调节胃肠道症状方面具有有益作用的微生态制剂，在其他疾病中也显示出一定的疗效，而且改善了 COVID-19 患者相关临床症状，因此有望成为缓解 COVID-19 后遗症的一项策略。

4 局限性和未来方向

目前益生菌对不同人群 COVID-19 症状缓解的效果不一致，推测可能是机体存在个体差异；同时，由于菌株间存在菌株特异性，因此使用的菌株、剂量、干预周期不同也会对宿主产生差异效果，后续应对效果显著的菌株展开深入研究，确定其最佳剂量和干预周期。此外，现有研究结果大多局限于临床结局方面，对机体的具体作用机制尚不清晰，未来应加大体外试验和动物试验并结合多组学技术鉴定出有效的微生物种类及功能，阐明益生菌对缓解 COVID-19 症状的作用机制。值得注意的是，一些体质较差和年长的群体在感染后会出现长期后遗症症状，但目前对后遗症的研究有限，可能是由于试验缺乏随访期或随访时间不足导致，下一步应加大试验周期，明确益生菌对 COVID-19 后遗症的作用效果。

5 总结与展望

在当前开放政策环境下，SARS-CoV-2 病毒也不断适应性突变和进化，被感染一次后可能再次感染相同或不同的变异株。不同的环境因素，如年龄、基础疾病和药物使用等会使患者在发病时会表现出不一样的症状，而最常见的并发症则是胃肠道症状。益生菌将许多世纪以来建立的传统医学知识的元素与强大的微生态制剂结合起来，并由复杂的现代微生物学和生物技术进行识别和评估，其益生功效已经在各种疾病尤其在胃肠道疾病中得到证实。然而由于机体存在个体差异，此外益生菌对 COVID-19 症状方面改善的效果似乎也有菌株特异性，同时益生菌对 COVID-19 的作用机制和后遗症影响尚不清晰，未来应进一步研究特定菌株的作用效果，并明确益生菌在缓解 COVID-19 症状中的具体机制和对后遗症的作用效果，根据不同人群制定相应的治疗策略或将成为辅助治疗呼吸系统疾病的有效方案。

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