[DOI]10.12016/j.issn.2096-1456.202330447

·综述·

唾液联合乳杆菌在口腔疾病防治中的研究进展

胡玲曦，　程磊，　陈婧
口腔疾病防治全国重点实验室 国家口腔医学中心 国家口腔疾病临床医学研究中心 四川大学华西口腔医院牙体牙髓病科，四川 成都（610041）

【摘要】 口腔是人体中微生物定植最丰富的位点之一，维持其微生态的平衡能有效促进口腔健康。唾液联合乳杆菌（*Ligilactobacillus salivarius*）作为联合乳杆菌的一种，有着良好的口腔定植能力及改善口腔微生态以防治疾病的潜力。目前，唾液联合乳杆菌在口腔疾病中的应用及机制研究主要包括：通过直接抑制变异链球菌生长以及下调其致龋毒力因子葡萄糖基转移酶基因（glucosyltransferases，gtfs）表达，减少牙面黏附变异链球菌数量，防治龋病；减少牙周炎相关关键微生物，并减少伴放线菌团聚杆菌毒力因子细胞致死膨胀毒素B（cytolethal distending toxin B，CdtB）、白细胞毒素（leukotoxin，LtxA）表达，减轻牙周炎患者局部微生物刺激，同时，直接抑制巨噬细胞的丝裂原活化蛋白激酶（mitogen-activated protein kinases，MAPK）以及核因子NF-κB（nuclear factor NF-kappaB，NF-κB）通路激活进而抑制破骨作用，减轻牙周骨吸收；对于黏膜炎症，唾液联合乳杆菌可拮抗白色念珠菌，抑制致病性菌丝或胚管形成，防治念珠菌性口炎，还可减少金黄色葡萄球菌数量，并缓解其感染所致的巨噬细胞的toll样受体/磷脂酰肌醇3-激酶/蛋白激酶B/哺乳动物雷帕霉素靶蛋白（toll-like receptor/phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin，TLR/PI3K/Akt/mTOR）信号通路和toll样受体/磷脂酰肌醇3-激酶/蛋白激酶B/kappa B抑制因子/核转录因子kappaB（toll-like receptor/phosphoinositide 3-kinase/protein kinase B/inhibitors of kappa B/nuclear factor kappa B，TLR/PI3K/Akt/IκB/NF-κB）通路激活，减轻口咽部炎症反应；通过对口腔肿瘤细胞体外研究发现，唾液联合乳杆菌可下调癌细胞蛋白激酶B/细胞周期蛋白D1（protein kinase B/cyclin D1，Akt/cyclin D1）表达，诱导肿瘤细胞的直接凋亡并降低环氧合酶-2（cyclooxygenase-2，COX-2）表达水平，改善肿瘤免疫抑制微环境。然而唾液联合乳杆菌变异多，需要更深入的研究以厘清具体菌株的临床功效、安全性及其治病机制。尽管新兴微生物研究技术已出现，但在唾液联合乳杆菌的应用尚较少。如何运用这些方法来研究唾液乳杆菌对口腔疾病的作用将是未来发展方向之一。本文对唾液联合乳杆菌在口腔领域的现存研究进行综述，以期为今后的研究提供参考。

【关键词】 联合乳杆菌；　唾液联合乳杆菌；　益生菌；　菌群；　龋病；　口腔异味；　牙周疾病；　黏膜疾病；　口腔肿瘤
【中图分类号】 R78　**【文献标志码】** A　**【文章编号】** 2096-1456（2024）09-0722-08
【引用著录格式】 胡玲曦，程磊，陈婧. 唾液联合乳杆菌在口腔疾病防治中的研究进展[J]. 口腔疾病防治，2024, 32(9): 722-729. doi:10.12016/j.issn.2096-1456.202330447.

微信公众号

Research progress on *Ligilactobacillus salivarius* in the prevention and treatment of oral diseases

HU Lingxi, CHENG Lei, CHEN Jing.　State Key Laboratory of Oral Diseases & National Center for Stomatology & National Clinical Research Center for Oral Diseases & Department of Cariology and Endodontics, West China Hospital of Stomatology, Sichuan University, Chengdu 610041, China
Corresponding author: CHEN Jing, Email: 329583603@qq.com, Tel: 86-28-85503584

【Abstract】 The oral cavity harbors a diverse population of microorganisms, making it one of the most heavily colonized sites in the human body. Maintaining a balanced microecology is crucial for oral health. *Ligilactobacillus salivarius* as a species of *Ligilactobacillus*, has good oral colonization ability and potential to improve oral microecology for disease

【收稿日期】 2023-09-25；　**【修回日期】** 2023-12-23
【基金项目】 国家自然科学基金（82203008）；四川大学博士后交叉学科创新启动基金（JCXK2213）
【作者简介】 胡玲曦，硕士，Email：hulingxi_iris@foxmail.com
【通信作者】 陈婧，副研究员，博士，Email：329583603@qq.com，Tel：86-28-85503584

prevention and control. Currently, the application and mechanism of *Ligilactobacillus salivarius* in oral diseases include several aspects. First, by directly inhibiting the growth of *Streptococcus mutans* and downregulating the expression of its cariogenic virulence factor, gtfs, the aim is to reduce the number of adherent *Streptococcus mutans* on the tooth surface, thereby preventing dental caries. Second, reducing the number of keystone taxa in periodontitis, and the virulence factors of *Aggregatibacter actinomycetemcomitans*, including CdtB and LtxA, can alleviate local stimulation in patients with periodontitis. Additionally, directly inhibiting macrophage MAPK and NF-κB pathway activation suppresses osteoclastogenesis and reduces periodontal bone absorption. In mucosal inflammation, *Ligilactobacillus salivarius* competes with *Candida albicans*, inhibits the formation of pathogenic hyphae or germ tubes, and prevents monilial stomatitis. *Ligilactobacillus salivarius* can also reduce the amount of *Staphylococcus aureus* and mitigate the activation of the macrophage TLR/PI3K/Akt/mTOR and TLR/PI3K/Akt/IκB/NF-κB pathways induced by *S. aureus* infections, thus alleviating inflammation in the oral and pharyngeal regions. *In vitro* studies on oral tumors have revealed that *Ligilactobacillus salivarius* can downregulate the expression of cancer cell Akt/Cyclin D1, induce direct apoptosis of tumor cells, reduce COX-2 expression, and improve the tumor immune-suppressive microenvironment. Previous studies have revealed considerable variability in *Ligilactobacillus salivarius*, necessitating more detailed research to clarify its clinical effects, safety, and mechanisms. Despite the emergence of novel microbiological research techniques, their application to *Ligilactobacillus salivarius* remains relatively limited. One crucial direction for future research is to better utilize these methods to investigate the effects of *Ligilactobacillus salivarius* on oral diseases. Considering these factors, this study provides a comprehensive review of existing research studies on *Ligilactobacillus salivarius* in the fields of oral medicine and dentistry, with the aim to serve as a reference and guide for future studies.

【Key words】 *Ligilactobacillus*; *Ligilactobacillus salivarius*; probiotics; microbiota; dental caries; halitosis; periodontal diseases; mucositis; oral neoplasms

J Prev Treat Stomatol Dis, 2024, 32(9): 722-729.

【Competing interests】 The authors declare no competing interests.

This study was supported by the grants from National Natural Science Foundation of China (No. 82203008) and Sichuan University Postdoctoral Interdisciplinary Innovation Fund (No. JCXK2213).

世界卫生组织和联合国粮食及农业组织定义益生菌为能在适当条件下给宿主带来健康益处的活微生物[1]。来自人和动物的口腔、胃肠道及粪便中的益生菌及其产物已在包括细菌炎症、胃肠道疾病、口腔疾病、免疫疾病在内的多种疾病治疗中广泛使用，有较好的应用前景。联合乳杆菌是食品行业及临床应用中最常见的益生菌之一，具有良好的安全性以及宿主微生态调节作用[2-8]。

人的口腔环境由软、硬组织以及唾液共同组成，在口腔环境中存活并发挥作用的益生菌大多满足：①能耐受唾液中的酶、②能代谢口腔中的碳水化合物、③可黏附在软硬组织表面等。联合乳杆菌属中的唾液联合乳杆菌是人类以及仓鼠口腔和胃肠道的固有微生物组成，它们中的一部分菌株天然满足口腔定植的条件，具有良好的口内应用前景[9]。目前，多项针对唾液联合乳杆菌的临床前研究和临床试验获得了其在口腔疾病防治的相关研究结果，本文将就这些研究进行阐述及总结。

1　唾液联合乳杆菌

唾液联合乳杆菌是一种革兰氏阳性菌，获得了欧洲食品安全局安全资格认证[10]。2020年，乳酸菌分类进行了调整，唾液乳杆菌（*Lactobacillus salivarius*）改名为唾液联合乳杆菌，从属于联合乳杆菌属（由16种细菌组成）[11]。唾液联合乳杆菌具有丰富的来源，最常见的来源包括人、猪、禽类的口腔、胃肠道、阴道以及乳汁[12-13, 10]。早在十年前，唾液联合乳杆菌就已被用于临床研究。早期研究发现其在消化道有高存活率，并具有抗菌及调节免疫的特性，具有临床转化的潜力[14]。此后，唾液联合乳杆菌的应用场景被逐渐扩展到口腔疾病、代谢疾病等领域。一部分唾液联合乳杆菌，特别是消化道来源的唾液联合乳杆菌，如唾液联合乳杆菌AR809已被证明能耐受酸、溶菌酶、过氧化氢，具有良好的口腔环境适应性[15]。

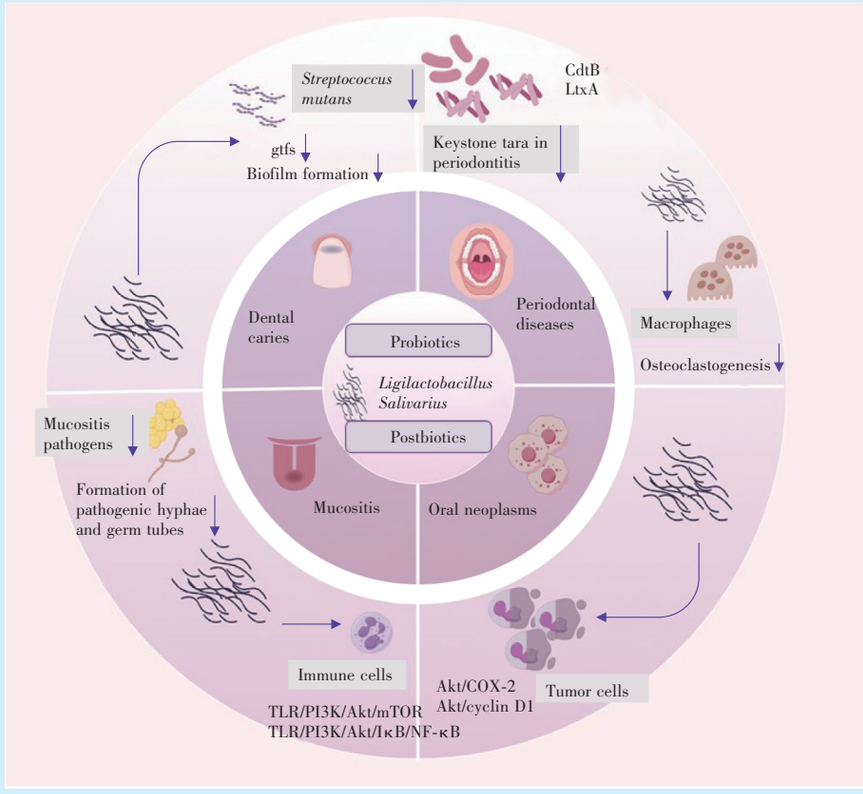
唾液联合乳杆菌的益生机制涉及多个方面[9, 16]。①产生抗菌肽及细菌素：唾液联合乳杆菌CRL

1328、DPC6005、UCC118被证实能产生细菌素，进而抑制芽孢杆菌、李斯特菌、肠球菌和葡萄球菌等多种条件致病菌[17]。②调节宿主免疫：小鼠炎症模型中，唾液联合乳杆菌LI01能提升血清中抑炎因子白细胞介素-10（interleukin -10，IL-10）的含量，降低促炎因子水平，进而缓解疾病进展[18-19]；而在肿瘤模型中，唾液联合乳杆菌Ren能降低COX-2及Cyclin D1的表达量，改善免疫抑制微环境。③其他：唾液联合乳杆菌能通过代谢循环、与其他病原体竞争等多种机制减少病原体在菌群中的比例。

2　唾液联合乳杆菌在口腔疾病防治中的应用

微生物之间及微生物与宿主之间的相互作用是影响口腔健康的重要因素[20-21]。一些唾液联合乳杆菌可在口腔位点定植，并通过多种机制防治龋病、牙周疾病、黏膜疾病及癌症，具体作用机制见图1。

2.1　龋病



Ligilactobacillus salivarius and its postbiotics inhibit caries mainly by reducing the number of *Streptococcus mutans* and the expression of its virulence factor gtfs, which affects biofilm formation. Periodontal disease was inhibited by reducing the number of keystone taxa and the expression of virulence factors CdtB and LtxA, and inhibiting the osteoclastogenesis of macrophages. Mucositis was inhibited by inhibiting the growth of mucosal disease pathogens, the formation of pathogenic hyphae and germ tubes of *Candida albicans*, and the overactivation of immune cells by *Staphylococcus aureus*. By inhibiting the Akt/COX - 2 and Akt/cyclin D1 pathways in tumor cells, immunosuppression of the microenvironment can be improved to prevent the occurrence and development of oral cancer. gtfs: glucosyltransferases; CdtB: cytolethal distending toxin B; LtxA: leukotoxin; TLR/PI3K/Akt/mTOR: toll-like receptor/phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin; TLR/PI3K/Akt/IκB/NF-κB: toll-like receptor/phosphoinositide 3-kinase/protein kinase B/inhibitors of kappaB/nuclear factor kappa B; Akt/COX-2: protein kinase B/cyclooxygenase-2; Akt/cyclin D1: protein kinase B/cyclin D1

Figure 1　Mechanisms of oral disease prevention and treatment by *Ligilactobacillus salivarius*

图1　唾液联合乳杆菌在口腔疾病防治中的作用机制

部分乳杆菌在产酸的同时被发现能抑制多种龋病病原体，其用于龋病防治由来已久。多项研究发现，鼠李糖乳酪杆菌、副干酪乳酪杆菌等可以减少龋病致病菌数量，阻滞龋病进展[22-25]。变异链球菌是龋病的主要病原体之一，它能黏附于牙面并表达葡萄糖基转移酶，代谢外部多糖产酸，诱导龋坏形成。而唾液联合乳杆菌抑制变异链球菌致龋的机制包括显著降低变异链球菌对表面的附着，进而减缓或阻止生物膜的形成；降低葡萄糖基转移酶基因的表达，进而阻滞pH降低等[26]。Nishihara等[27]评价了唾液联合乳杆菌WB21对变异链球菌的影响。该研究中，参与者服用含有唾

液联合乳杆菌WB21（2.0×10^9 CFU/day）的片剂2周后，唾液变异链球菌水平显著下降。唾液联合乳杆菌MG4265的培养液也具有抑制变异链球菌的效果[28]。Staszczyk等[29]直接评价了唾液联合乳杆菌的临床防龋功能，通过使140位儿童每天服用含有热灭活唾液联合乳杆菌HM6 Paradens的咀嚼片2周，一年后观察发现，处理组龋失补牙数增量明显小于对照组。

有研究者通过分析微生物群落变化及比较大鼠龋病模型建立的时长，发现唾液联合乳杆菌具有潜在的致龋作用[30]。但需要注意的是，在这些实验中，建立大鼠龋病模型采用了含44%~56%蔗糖饮水的致龋饮食，这些实验室分析对临床环境的模拟程度有限。

综上，不可否认唾液联合乳杆菌用于龋病防治存在两面性。乳酸菌能产酸，其过度增殖可使环境pH下降从而增加患龋的可能。但同时，唾液联合乳杆菌能抑制变异链球菌等致龋菌，通过调节微生态发挥防龋作用。由于Nishihara等[27]、Staszczyk等[29]在正常人口内施用唾液联合乳杆菌的研究更贴近实际临床应用环境，其结果相较于体外研究及大鼠龋病模型获得的结论更令人信服。然而，尚需更多的临床研究验证唾液联合乳杆菌用于龋病防治的应用效果。此外，一种新兴方向是使用热灭活细菌或过滤细菌得到无增殖活性的后生元[31, 29]。后生元无法代谢产酸，避免了微环境pH降低的情况，更有利于龋病防治。

2.2　牙周疾病

唾液联合乳杆菌在一些研究中被证实对牙周病病原体有抑制作用，能改善牙周疾病的主要症状及伴随症状[32]。

Suzuki等[33]使用双盲随机对照实验研究了使用唾液联合乳杆菌WB21片剂两周之后患者牙周细菌、探诊深度以及口腔异味的改变。实验结果显示，相较于安慰剂组，实验组甲硫醇评分和平均牙周探诊深度均显著降低（$P<0.05$）。进一步推测牙周炎症的改善和挥发性硫化物的减少可能与实验组具核梭杆菌的减少（$P<0.05$）有关。除了使用片剂进行治疗，为了避免木糖醇对于实验结果的影响，Suzuki等[34]采用含有4.0×10^8 CFU唾液联合乳杆菌WB21的大豆油（大豆油中不含其他对牙周疾病有益成分）在口内使用。两周后发现，与溶剂组相比，添加了唾液联合乳杆菌WB21的组别探诊出血指数明显降低，这可能与实验组细菌总数及产生挥发性硫化物的细菌数量减少有关。Mayanagi等[35]、Shimauchi等[36]、Kijima等[37]围绕牙周炎患者、吸烟的无牙周炎人群、老年人群展开了临床试验，其结果显示不论试验对象是否患有牙周炎，其牙周病相关致病菌丰度较试验开始时都明显降低。而最近几项针对唾液联合乳杆菌SGL03的研究显示，其对于牙周病“红色复合体”有抑制作用，并能减少牙周探诊深度[38-39]。此外，唾液联合乳杆菌也显示出了联合疗法的潜力。唾液联合乳杆菌WB21和表没食子儿茶素没食子酸酯（epigallocatechin gallate，EGCG）合用可抑制牙龈卟啉单胞菌的生长，并具有协同作用[40]。

Nissen等[41]发现唾液联合乳杆菌OMZ520抑制伴放线菌团聚杆菌的毒力因子表达是改善牙周炎的机制之一，即虽然伴放线菌团聚杆菌生长未受明显影响，但CdtB和LtxA的表达显著降低。

此外，针对唾液联合乳杆菌MG4265的研究提示，唾液联合乳杆菌能抑制巨噬细胞内核因子κB受体活化因子配体（receptor activator of nuclear factor-kappaB ligand，RANKL）诱导的MAPK通路以及NF-κB通路激活，促进血红素氧合酶1（heme oxygenase-1，HO-1）表达上调，进而抑制转录因子（c-fos及活化T细胞核因子1）和破骨相关因子（抗酒石酸酸性磷酸酶，组织蛋白酶K以及基质金属蛋白酶-9）表达，最终抑制破骨作用，但体内效果还需要进一步验证[28]。

以上研究均显示唾液联合乳杆菌可抑制牙周炎症，减轻口腔异味；作用机制包括降低伴放线菌团聚杆菌的毒力因子表达、抑制破骨作用[42]。然而，在不同牙周疾病类别及不同人群中，唾液联合乳杆菌与其他乳酸菌的比较研究尚不充分[43-44]。

2.3　口腔黏膜疾病

白色念珠菌（*Candida albicans*）是口腔黏膜病的机会致病菌之一，在人体中的携带率高，能在免疫低下的人群中引起念珠菌病[45]。在唾液联合乳杆菌的研究中，Kang等[46]研究了利用唾液联合乳杆菌MG242对白色念珠菌进行生物防治的潜力。斑点杂交实验（spot overlay assay）结果显示，唾液联合乳杆菌MG242在共培养模型中抑制了99.99%±0.01%的白色念珠菌生长。在变异链球菌和念珠菌双菌种模型中，加入唾液联合乳杆菌HM6 Paradens后，白色念珠菌没有形成具有致病潜力的菌丝或胚管，且变异链球菌和白色念珠菌生物膜的形成被抑制[47]。这提示唾液联合乳杆菌可

减少白色念珠菌的数量及致病性，削弱其致病潜能。

除了白色念珠菌之外，金黄色葡萄球菌也是口腔黏膜疾病的主要致病菌之一。含有唾液联合乳杆菌IDCC3551的组合细菌在一项研究中被证实能抑制金黄色葡萄球菌[48]。Jia等[49]发现，唾液联合乳杆菌AR809可以抑制金黄色葡萄球菌的生长并进一步抑制金黄色葡萄球菌导致的免疫细胞过度激活。进一步研究发现，AR809可能通过调控巨噬细胞TLR/PI3K/Akt/mTOR信号通路和TLR/PI3K/Akt/IκB/NF-κB通路来抑制金黄色葡萄球菌诱导的口咽部炎症反应。

以上实验证明唾液联合乳杆菌在防治黏膜疾病上具有一定潜力。然而，尚无相关临床试验证实唾液联合乳杆菌的临床效果。

2.4　口腔肿瘤

目前，已有不少发现益生菌抗肿瘤潜力的研究[50-52]。一项研究显示，在雄性大鼠模型中，唾液联合乳杆菌Ren可以抑制4-硝基喹啉1-氧化物（4-nitroquinoline 1-oxide，4-NQO）的致口腔癌作用。此外，Dong等[53]研究提示，唾液联合乳杆菌Ren可通过Akt通路抑制二甲基肼对结直肠癌的诱导，它通过抑制Akt的激活抑制下游蛋白COX-2以及Cyclin D1表达，进而抑制癌变进程。以上研究均发现，经过唾液联合乳杆菌Ren处理的细胞，其COX-2的表达量降低。而COX-2介导前列腺素E2（prostaglandin E2，PGE-2）等的合成，它们在癌症中表达上调，促进了免疫抑制微环境的形成。唾液联合乳杆菌Ren可能通过抑制Akt通路，抑制下游COX-2以及Cyclin D1表达，进而改善了免疫抑制微环境。这可能一定程度上解释了唾液联合乳杆菌降低4-NQO所诱导癌症发生率的原因[10]。

目前，含有唾液联合乳杆菌的多种益生菌制剂正被用于乳腺癌患者的临床研究（NCT03358511），这项研究针对Ⅰ-Ⅲ期乳腺癌患者，试验组将在手术前接受2～4周的益生菌制剂Primal Defense Ultra®的治疗。然而在口腔癌领域，唾液联合乳杆菌的作用仍然需要更多的临床试验来探究。

3　唾液联合乳杆菌的安全性

有至少3项已注册的临床试验检测了不同唾液联合乳杆菌在人体运用的安全性。1项临床试验（NCT00724204）在80例儿童中评估了唾液联合乳杆菌CECT5713连续6个月每天处理的安全性，目前已公开的阶段试验结果未观察到不良事件的发生。另一项（NCT01124448）评估唾液联合乳杆菌PS2在患或不患乳腺炎女性中的安全性临床试验，未观察到不良事件的发生。Chen等[54]（NCT04140604）评估了唾液联合乳杆菌AP-32在76例7 d至2个月大婴幼儿群体中的安全性，也未观察到不良事件的发生。

总之，尽管目前鲜有服用唾液联合乳杆菌导致全身副作用的报道，但不同的唾液联合乳杆菌的安全性及长期稳定性尚不明确，还需要进一步优化工艺流程及进行菌株安全性相关的评估工作[55-56]。

4　后生元

与益生菌相对应，后生元是有益于宿主的无生命微生物或微生物代谢物[57, 22]。后生元有可能规避益生菌的一些副作用，研究表明它们比益生菌更稳定和安全[58, 25]。已有多项临床研究聚焦唾液联合乳杆菌后生元在口腔领域的应用[59-60, 22]。然而，有研究认为活菌可能具有一些后生元所不具备的能力[61]。目前，关于唾液联合乳杆菌来源的后生元在口腔疾病防治方面的研究报道仍较少见，还需更多的研究以进一步明确唾液联合乳杆菌来源的后生元在维护口腔健康方面的使用价值。

5　总结与展望

口腔是唾液联合乳杆菌的重要来源，部分唾液联合乳杆菌天然具有更良好的口腔环境适应性。唾液联合乳杆菌能通过与其他细菌及与宿主之间的相互作用，改变微生态的组成、调节宿主免疫，从而达到防治疾病的效果，具有较高的临床应用价值。此外，随着乳酸菌基因工程技术的快速发展，通过基因编辑手段深入解析唾液联合乳杆菌防治口腔疾病的具体作用机制，有助于未来开发基于唾液联合乳杆菌的口腔疾病精准防治策略。此外，在探究唾液联合乳杆菌以益生菌形式发挥口腔保健作用的同时，发掘唾液联合乳杆菌相关后生元在口腔疾病防治的潜力也是未来的一种新选择。

【Author contributions】 Hu LX conceptualized and wrote the article. Cheng L, Chen J conceptualized and reviewed the article. All authors read and approved the final manuscript as submitted.

参考文献

[1] Amiri Khosroshahi R, Zeraattalab-Motlagh S, Sarsangi P, et al. Effect of probiotic supplementation on chemotherapy - and radiotherapy-related diarrhoea in patients with cancer: an umbrella review of systematic reviews and meta-analyses [J]. Br J Nutr, 2023, 130(10): 1754-1765. doi: 10.1017/S0007114523000910.

[2] Field D, Fernandez de Ullivarri M, Ross RP, et al. After a century of nisin research - where are we now? [J]. FEMS Microbiol Rev, 2023, 47(3): fuad023. doi: 10.1093/femsre/fuad023.

[3] Zou H, Wang H, Zhang Z, et al. Immune regulation by fermented milk products: the role of the proteolytic system of lactic acid bacteria in the release of immunomodulatory peptides [J]. Crit Rev Food Sci Nutr, 2023: 1-19. doi: 10.1080/10408398.2023.2225200.

[4] Aprea G, Del Matto I, Tucci P, et al. *In vivo* functional properties of dairy bacteria [J]. Microorganisms, 2023, 11(7): 1787. doi: 10.3390/microorganisms11071787.

[5] Krüger W, Vielreicher S, Kapitan M, et al. Fungal-bacterial interactions in health and disease [J]. Pathogens, 2019, 8(2): 70. doi: 10.3390/pathogens8020070.

[6] Sionek B, Szydłowska A, Zielińska D, et al. Beneficial bacteria isolated from food in relation to the next generation of probiotics [J]. Microorganisms, 2023, 11(7): 1714. doi: 10.3390/microorganisms11071714.

[7] Abdul Hakim BN, Xuan NJ, Oslan SNH. A comprehensive review of bioactive compounds from lactic acid bacteria: potential functions as functional food in dietetics and the food industry [J]. Foods, 2023, 12(15): 2850. doi: 10.3390/foods12152850.

[8] Icer MA, Özbay S, Ağagündüz D, et al. The impacts of acidophilic lactic acid bacteria on food and human health: a review of the current knowledge [J]. Foods, 2023, 12(15): 2965. doi: 10.3390/foods12152965.

[9] Yang Y, Song X, Xiong Z, et al. Complete genome sequence of *Lactobacillus salivarius* AR809, a probiotic strain with oropharyngeal tract resistance and adhesion to the oral epithelial cells [J]. Curr Microbiol, 2022, 79(9): 280. doi: 10.1007/s00284-022-02963-w.

[10] Guerrero Sanchez M, Passot S, Campoy S, et al. *Ligilactobacillus salivarius* functionalities, applications, and manufacturing challenges [J]. Appl Microbiol Biotechnol, 2022, 106(1): 57-80. doi: 10.1007/s00253-021-11694-0.

[11] Zheng J, Wittouck S, Salvetti E, et al. A taxonomic note on the genus *Lactobacillus*: Description of 23 novel Genera, emended description of the genus *Lactobacillus* Beijerinck 1901, and union of Lactobacillaceae and Leuconostocaceae [J]. Int J Syst Evol Microbiol, 2020, 70(4): 2782-2858. doi: 10.1099/ijsem.0.004107.

[12] Jastaniah SDS, Hafsan H, Tseng CJ, et al. Effects of dietary pectin and *Lactobacillus salivarius* ATCC 11741 on growth performance, immunocompetence, gut microbiota, antioxidant capacity, and disease resistance in narrow-clawed crayfish, postantacus leptodactylus[J]. Aquac Nutr. 2022, 2022: 1861761. doi: 10.1155/2022/1861761.

[13] Pino A, Bartolo E, Caggia C, et al. Detection of vaginal lactobacilli as probiotic candidates [J]. Sci Rep, 2019, 9(1): 3355. doi: 10.1038/s41598-019-40304-3.

[14] Fernández L, Castro I, Arroyo R, et al. Application of *Ligilactobacillus salivarius* CECT5713 to achieve term pregnancies in women with repetitive abortion or infertility of unknown origin by microbiological and immunological modulation of the vaginal ecosystem [J]. Nutrients, 2021, 13(1): 162. doi: 10.3390/nu13010162.

[15] Jia GC, Che N, Xia YJ, et al. Adhesion to pharyngeal epithelium and modulation of immune response: *Lactobacillus salivarius* AR809, a potential probiotic strain isolated from the human oral cavity [J]. J Dairy Sci, 2019, 102(8): 6738-6749. doi: 10.3168/jds.2018-16117.

[16] Canut-Delgado N, Giovannoni ML, Chimenos-Küstner E. Are probiotics a possible treatment of periodontitis? Probiotics against periodontal disease: a systematic review [J]. Br Dent J, 2021. doi: 10.1038/s41415-021-3624-5.

[17] Darbandi A, Asadi A, Mahdizade Ari M, et al. Bacteriocins: properties and potential use as antimicrobials [J]. J Clin Lab Anal, 2022, 36(1): e24093. doi: 10.1002/jcla.24093.

[18] Yao M, Lu Y, Zhang T, et al. Improved functionality of *Ligilactobacillus salivarius* Li01 in alleviating colonic inflammation by layer-by-layer microencapsulation [J]. NPJ Biofilms Microbiomes, 2021, 7(1): 58. doi: 10.1038/s41522-021-00228-1.

[19] Fei Y, Zhang S, Han S, et al. The role of dihydroresveratrol in enhancing the synergistic effect of *Ligilactobacillus salivarius* Li01 and resveratrol in ameliorating colitis in mice [J]. Research (Wash D C), 2022, 2022: 9863845. doi: 10.34133/2022/9863845.

[20] Saïz P, Taveira N, Alves R. Probiotics in oral health and disease: a systematic review[J]. Applied Sciences, 2021, 11(17): 8070. doi: 10.3390/app11178070.

[21] Willis JR, Gabaldón T. The human oral microbiome in health and disease: from sequences to ecosystems [J]. Microorganisms, 2020, 8(2): 308. doi: 10.3390/microorganisms8020308.

[22] Homayouni Rad A, Pourjafar H, Mirzakhani E. A comprehensive review of the application of probiotics and postbiotics in oral health [J]. Front Cell Infect Microbiol, 2023, 13: 1120995. doi: 10.3389/fcimb.2023.1120995.

[23] Guo M, Wu J, Hung W, et al. *Lactobacillus paracasei* ET-22 suppresses dental caries by regulating microbiota of dental plaques and inhibiting biofilm formation [J]. Nutrients, 2023, 15(15): 3316. doi: 10.3390/nu15153316.

[24] Abikshyeet P, Mishra P, Bhuyan L, et al. Probiotics: dawn of a new era in dental caries management [J]. J Pharm Bioallied Sci, 2022, 14(suppl 1): S34-S38. doi: 10.4103/jpbs.jpbs_801_21.

[25] Sabahi S, Homayouni Rad A, Aghebati-Maleki L, et al. Postbiotics as the new frontier in food and pharmaceutical research [J]. Crit Rev Food Sci Nutr, 2023, 63(26): 8375-8402. doi: 10.1080/10408398.2022.2056727.

[26] Colautti A, Orecchia E, Comi G, et al. Lactobacilli, a weapon to counteract pathogens through the inhibition of their virulence factors [J]. J Bacteriol, 2022, 204(11): e0027222. doi: 10.1128/jb.00272-22.

[27] Nishihara T, Suzuki N, Yoneda M, et al. Effects of *Lactobacillus salivarius*-containing tablets on caries risk factors: a randomized open-label clinical trial [J]. BMC Oral Health, 2014, 14: 110. doi: 10.1186/1472-6831-14-110.

[28] Jung JI, Baek SM, Nguyen TH, et al. Effects of probiotic culture supernatant on cariogenic biofilm formation and RANKL-induced osteoclastogenesis in RAW 264.7 macrophages [J]. Molecules, 2021, 26(3): 733. doi: 10.3390/molecules26030733.

[29] Staszczyk M, Jamka-Kasprzyk M, Kościelniak D, et al. Effect of a short-term intervention with *Lactobacillus salivarius* probiotic on early childhood caries-an open label randomized controlled trial [J]. Int J Environ Res Public Health. 2022 , 19(19): 12447. doi: 10.3390/ijerph191912447.

[30] Chaves BD, Brashears MM, Nightingale KK. Applications and safety considerations of *Lactobacillus salivarius* as a probiotic in animal and human health [J]. J Appl Microbiol, 2017, 123(1): 18-28. doi: 10.1111/jam.13438.

[31] Lin CW, Chen YT, Ho HH, et al. Impact of the food grade heat-killed probiotic and postbiotic oral lozenges in oral hygiene [J]. Aging (Albany NY), 2022, 14(5): 2221-2238. doi: 10.18632/aging.203923.

[32] Kumbargere Nagraj S, Eachempati P, Uma E, et al. Interventions for managing halitosis [J]. Cochrane Database Syst Rev, 2019, 12 (12): CD012213. doi: 10.1002/14651858.CD012213.

[33] Suzuki N, Yoneda M, Tanabe K, et al. *Lactobacillus salivarius* WB21-containing tablets for the treatment of oral malodor: a double-blind, randomized, placebo-controlled crossover trial [J]. Oral Surg Oral Med Oral Pathol Oral Radiol, 2014, 117(4): 462-470. doi: 10.1016/j.oooo.2013.12.400.

[34] Suzuki N, Tanabe K, Takeshita T, et al. Effects of oil drops containing *Lactobacillus salivarius* WB21 on periodontal health and oral microbiota producing volatile sulfur compounds [J]. J Breath Res, 2012, 6(1): 017106. doi: 10.1088/1752-7155/6/1/017106.

[35] Mayanagi G, Kimura M, Nakaya S, et al. Probiotic effects of orally administered *Lactobacillus salivarius* WB21-containing tablets on periodontopathic bacteria: a double-blinded, placebo-controlled, randomized clinical trial [J]. J Clin Periodontol, 2009, 36(6): 506-513. doi: 10.1111/j.1600-051x.2009.01392.x.

[36] Shimauchi H, Mayanagi G, Nakaya S, et al. Improvement of periodontal condition by probiotics with *Lactobacillus salivarius* WB21: a randomized, double-blind, placebo-controlled study [J]. J Clin Periodontol, 2008, 35(10): 897-905. doi: 10.1111/j.1600-051X.2008.01306.x.

[37] Kijima S, Suzuki N, Hanioka T, et al. Application of Lactobaillus salivarius WB21 to the oral care of healthy older adults: a randomized, double-blind, placebo-controlled crossover comparative study [J]. Life (Basel), 2022, 12(9): 1422. doi: 10.3390/life12091422.

[38] Kucia M, Wietrak E, Szymczak M, et al. Effect of *Ligilactobacillus salivarius* and other natural components against anaerobic periodontal bacteria [J]. Molecules, 2020, 25(19): 4519. doi: 10.3390/molecules25194519.

[39] NĘdzi-GÓra M, WrÓblewska M, GÓrska R. The effect of *Lactobacillus salivarius* SGL03 on clinical and microbiological parameters in periodontal patients [J]. Pol J Microbiol, 2020, 69(4): 441-451. doi: 10.33073/pjm-2020-047.

[40] Higuchi T, Suzuki N, Nakaya S, et al. Effects of *Lactobacillus salivarius* WB21 combined with green tea catechins on dental caries, periodontitis, and oral malodor [J]. Arch Oral Biol, 2019, 98: 243-247. doi: 10.1016/j.archoralbio.2018.11.027.

[41] Nissen L, Sgorbati B, Biavati B, et al. *Lactobacillus salivarius* and L. gasseri down-regulate *Aggregatibacter actinomycetemcomitans* exotoxins expression [J]. Ann Microbiol, 2014, 64(2): 611-617. doi: 10.1007/s13213-013-0694-x.

[42] Ishikawa KH, Bueno MR, Kawamoto D, et al. Lactobacilli postbiotics reduce biofilm formation and alter transcription of virulence genes of *Aggregatibacter actinomycetemcomitans* [J]. Mol Oral Microbiol, 2021, 36(1): 92-102. doi: 10.1111/omi.12330.

[43] Ausenda F, Barbera E, Cotti E, et al. Clinical, microbiological and immunological short, medium and long-term effects of different strains of probiotics as an adjunct to non-surgical periodontal therapy in patients with periodontitis. Systematic review with meta-analysis [J]. Jpn Dent Sci Rev, 2023, 59: 62-103. doi: 10.1016/j.jdsr.2023.02.001.

[44] Özener HÖ, Kuru L, Kadir T, et al. *Bifidobacterium animalis* subsp. lactis as adjunct to non-surgical periodontal treatment in periodontitis: a randomized controlled clinical trial [J]. Clin Oral Investig, 2023, 27(5): 1965-1972. doi: 10.1007/s00784-023-04870-1.

[45] Patel M. Oral cavity and *Candida albicans*: colonisation to the development of infection [J]. Pathogens, 2022, 11(3): 335. doi: 10.3390/pathogens11030335.

[46] Kang CH, Han SH, Kim Y, et al. *In vitro* probiotic properties of *Lactobacillus salivarius* MG242 isolated from human vagina [J]. Probiotics Antimicrob Proteins, 2018, 10(2): 343-349. doi: 10.1007/s12602-017-9323-5.

[47] Krzyściak W, Kościelniak D, Papież M, et al. Effect of a *Lactobacillus salivarius* probiotic on a double-species *Streptococcus mutans* and *Candida albicans* caries biofilm [J]. Nutrients, 2017, 9 (11): 1242. doi: 10.3390/nu9111242.

[48] Lee YR, Bang WY, Baek KR, et al. Safety evaluation by phenotypic and genomic characterization of four Lactobacilli strains with probiotic properties [J]. Microorganisms, 2022, 10(11): 2218. doi: 10.3390/microorganisms10112218.

[49] Jia G, Liu X, Che N, et al. Human-origin *Lactobacillus salivarius* AR809 protects against immunosuppression in S. aureus-induced pharyngitis via Akt-mediated NF-κB and autophagy signaling pathways [J]. Food Funct, 2020, 11(1): 270-284. doi: 10.1039/c9fo02476j.

[50] Wan Mohd Kamaluddin WNF, Rismayuddin NAR, Ismail AF, et al. Probiotic inhibits oral carcinogenesis: a systematic review and meta-analysis [J]. Arch Oral Biol, 2020, 118: 104855. doi: 10.1016/j.archoralbio.2020.104855.

[51] Lu K, Dong S, Wu X, et al. Probiotics in cancer [J]. Front Oncol,

2021, 11: 638148. doi: 10.3389/fonc.2021.638148.

[52] Shang F, Jiang X, Wang H, et al. The inhibitory effects of probiotics on colon cancer cells: *in vitro* and *in vivo* studies [J]. J Gastrointest Oncol, 2020, 11(6): 1224-1232. doi: 10.21037/jgo-20-573.

[53] Dong Y, Zhu J, Zhang M, et al. Probiotic *Lactobacillus salivarius* Ren prevent dimethylhydrazine-induced colorectal cancer through protein kinase B inhibition [J]. Appl Microbiol Biotechnol, 2020, 104(17): 7377-7389. doi: 10.1007/s00253-020-10775-w.

[54] Chen JF, Ou-Yang MC, Hsia KC, et al. A three-arm, randomized, double-blind, placebo-controlled study to evaluate the safety of *Lactobacillus salivarius* AP-32 and *Bifidobacterium animalis* CP-9 used individually in healthy infants [J]. Nutrients, 2023, 15(15): 3426. doi: 10.3390/nu15153426.

[55] Fenster K, Freeburg B, Hollard C, et al. The production and delivery of probiotics: a review of a practical approach [J]. Microorganisms, 2019, 7(3): 83. doi: 10.3390/microorganisms7030083.

[56] Cunningham M, Vinderola G, Charalampopoulos D, et al. Applying probiotics and prebiotics in new delivery formats-is the clinical evidence transferable? [J]. Trends Food Sci Technol, 2021, 112: 495-506. doi: 10.1016/j.tifs.2021.04.009.

[57] Salminen S, Collado MC, Endo A, et al. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics [J]. Nat Rev Gastroenterol Hepatol, 2021, 18(9): 649-667. doi: 10.1038/s41575-021-00440-6.

[58] Thorakkattu P, Khanashyam AC, Shah K, et al. Postbiotics: current trends in food and pharmaceutical industry [J]. Foods, 2022, 11(19): 3094. doi: 10.3390/foods11193094.

[59] Butera A, Pascadopoli M, Pellegrini M, et al. Domiciliary use of chlorhexidine vs. postbiotic gels in patients with peri-implant mucositis: a split-mouth randomized clinical trial[J]. Applied Sciences, 2022, 12(6): 2800. doi:10.3390/app12062800.

[60] Butera A, Gallo S, Pascadopoli M, et al. Home oral care of periodontal patients using antimicrobial gel with postbiotics, lactoferrin, and *Aloe* barbadensis leaf juice powder *vs*. conventional chlorhexidine gel: a split-mouth randomized clinical trial [J]. Antibiotics (Basel), 2022, 11(1): 118. doi: 10.3390/antibiotics11010118.

[61] Chen YT, Hsieh PS, Ho HH, et al. Antibacterial activity of viable and heat-killed probiotic strains against oral pathogens [J]. Lett Appl Microbiol, 2020, 70(4): 310-317. doi: 10.1111/lam.13275.

（编辑　罗燕鸿）

官网