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·综述·

益生菌防治口腔和胃肠道放化疗黏膜炎的研究进展

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【摘要】 黏膜炎是放疗、化疗最为常见的副反应，是一种发病机制不明、临床表现多样、尚无有效治疗方法的炎症性疾病，在口腔常表现为局部黏膜烧灼样刺痛，在胃肠道多表现为恶心、呕吐、腹泻等。目前发现局部菌群失调可促进放化疗黏膜炎发生发展，益生菌可作为防治黏膜炎的新兴路径。本文就益生菌防治口腔和胃肠道放化疗黏膜炎的研究进展予以综述，重点关注微生物对黏膜炎的发病机理和治疗的影响。文献复习结果显示，黏膜炎的发生发展与局部菌群组成和功能改变有关，益生菌可通过调节局部微生态及宿主免疫等机制发挥防治作用。目前用于防治黏膜炎的益生菌多为乳杆菌、双歧杆菌等，多数临床试验证实益生菌防治黏膜炎有积极作用。但由于益生菌品种繁多、肿瘤治疗方案不同，可能造成部分研究未观察到防治作用，选择有效性及安全性高的益生菌、设计最佳菌种组合及干预方案是当前领域的研究热点。

【关键词】 益生菌；　乳杆菌；　双歧杆菌；　口腔黏膜炎；　胃肠道黏膜炎；　肿瘤；　化疗；　放疗；　局部微生态；　宿主免疫

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Research progress on probiotics for the prevention and treatment of oral and gastrointestinal chemoradiotherapy mucositis

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【Abstract】 Mucositis is the most common side effect of radiotherapy and chemotherapy. It is an inflammatory disease with an unclear pathogenesis, diverse clinical manifestations and no effective treatment. It often manifests as local mucosal burning and stinging pain in the oral cavity and nausea, vomiting and diarrhea in the gastrointestinal tract. At present, it has been found that local microflora imbalance promotes the occurrence and development of chemoradiotherapy mucositis, and probiotics can be used as an emerging approach to prevent and treat mucositis. This paper reviews the research progress of probiotics in the prevention and treatment of oral and gastrointestinal chemoradiotherapy mucositis, focusing on the influence of microorganisms on the pathogenesis and treatment of gastrointestinal mucositis. Literature review results showed that the occurrence and development of mucositis may be related to changes in the composition and function of local microflora, and probiotics can play a preventive role by regulating local microecology and host immunity. At present, the main probiotics used in the prevention and treatment of mucositis are *Lactobacillus* and *Bifidobacterium*. Most clinical trials have confirmed that probiotics have a positive effect in the prevention and treatment of mucositis. However, due to the variety of probiotics and different tumor treatment regimens, prevention and treatment ef-

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fects may not be observed in some studies. Therefore, the selection of probiotics with high efficacy and safety and the design of the best combination of probiotics and intervention programs are current research hotspots.

【Key words】 probiotics; *Lactobacillus*; *Bifidobacterium*; oral mucositis; gastrointestinal mucositis; tumor; chemotherapy; radiotherapy; local microecology; host immunity

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黏膜炎发生在35%～75%接受造血干细胞移植的患者以及几乎所有接受放化疗的头颈部鳞状细胞癌的患者中，是放化疗最常见的副反应[1]。口腔黏膜炎（oral mucositis，OM）的症状在放化疗第5天到10天后开始显现，并可从红斑、开裂、发炎进展到疼痛、出血、溃疡；胃肠道黏膜炎（gastrointestinal mucositis，GM）多表现为腹泻、恶心、呕吐等症状，以腹泻最为突出和严重[2]。黏膜炎可严重影响患者的生存质量及抗肿瘤治疗效果，尚无被广泛接受的标准治疗方法[1]，是亟待解决的临床问题。随着微生物因素在黏膜炎发病机制中逐渐被关注，应用益生菌防治口腔和胃肠道放化疗黏膜炎成为研究热点。

1　放化疗黏膜炎的发病机制及微生物的作用

黏膜炎的发病机制尚未完全阐明，涉及多种促炎因子的相互作用。Sonis[3]提出的口腔黏膜炎五阶段模型指出，放化疗可直接破坏增殖活跃的黏膜上皮细胞的DNA或通过核因子κB（nuclear factor kappa-B，NF-κB）等途径激活肿瘤坏死因子α（tumor necrosis factor，TNF-α）、白细胞介素6（interleukin6，IL-6）、白细胞介素1β（interleukin1β，IL-1β）等的表达，诱导细胞凋亡和组织炎症；以上促炎因子的相互作用放大炎症反应，黏膜出现溃疡，微生物因黏膜上皮屏障完整性受损侵入黏膜下层，激活巨噬细胞并释放促炎因子，加重先前存在的黏膜病变。Alexander等[4]提出肠道菌群通过参与移位、免疫调节、药物代谢、酶促降解和多样性降低来调节化疗功效和肠黏膜毒性。

正常情况下，常驻微生物与机体保持动态平衡，构成的生物屏障能通过竞争生态位等防御机制，防止外来病原体的定植以维护机体健康。抗肿瘤治疗中唾液腺功能受损、免疫抑制及化疗药物本身的抗菌活性可影响正常微生物，促进病原体生长及黏膜损伤。Hong等[5]纵向对照研究显示，化疗引发OM并破坏口腔微生物组，OM的严重程度与口腔微生物群失调的程度相关；在三维多层口腔黏膜模型中，随OM加重而富集的潜在致病菌具核梭杆菌表现出促炎和促凋亡的能力，在OM期间减少的潜在共生菌唾液链球菌则几乎没有促炎和促凋亡能力。同时，放疗期间口腔微生物组成发生改变，革兰阴性菌特别是牙周病病原菌的相对丰度增加被证明会加剧鼻咽癌患者OM的严重程度[6-8]。这些革兰阴性菌可通过内毒素、菌毛等细菌成分激活宿主模式识别受体促进黏膜炎症的加剧和促炎因子的产生，导致OM恶化[9]。在OM愈合阶段，体外共培养实验发现伤口愈合能力与微生物组成相关[10]。此外，辐射还可通过诱导生物膜形成、提高致病菌毒力等方式改变常驻口腔微生物的功能行为，成为OM发生发展的危险因素[11]。

在胃肠道，5-氟尿嘧啶（5-fluorouracil，5-FU）可使小鼠肠道菌群发生显著变化，并伴有黏膜屏障破坏和炎症信号通路激活，健康小鼠的粪便移植可减轻结肠黏膜炎，而5-FU处理小鼠的粪便移植则可诱导明显的结肠黏膜炎症状，表明肠道菌群变化参与5-FU诱导的肠黏膜炎的病理过程[12]。Gerassy-Vainberg等[13]证明辐射可改变小鼠肠道微生物组成，受辐射小鼠的粪便微生物群与结肠上皮细胞共培养6～7 h后，上皮细胞TNF-α、IL-1β表达增加；接种受辐射小鼠粪便微生物群的Swiss Webster无菌小鼠放疗后结肠IL-1β水平升高，并表现出更严重的放射损伤病理特征。

基于以上论述，可推测放化疗诱发了早期黏膜炎症反应与微生物群改变，微生物群与机体间的动态平衡被打破，向病理性演变，逐渐对黏膜上皮造成“毒力负荷”，进一步放大了放化疗本身对炎症反应状态的诱导，促进黏膜炎的发展。

2　益生菌防治口腔和胃肠道放化疗黏膜炎的原理

益生菌是指通过摄取适当的量，对食用者的

身体健康能发挥有效作用的经严格选择的活菌[14]。益生菌可通过产生抗菌物质、与病原体竞争上皮黏附和营养、参与宿主的免疫调节、抑制细菌毒素的产生发挥有益作用[14]。口腔内已被发现存在多种益生菌，如乳杆菌属、双歧杆菌属等可通过共聚集作用形成屏障、黏附上皮细胞并竞争营养物质抑制致病菌定植及生长、产生过氧化氢和抑菌素等抗菌物质、调节免疫反应等方式参与口腔健康维护，并在防治龋病、牙周病等口腔疾病中发挥重要作用[15]。

鉴于益生菌在肠道菌群调节中的有益作用，可作为减少放化疗诱导的肠黏膜炎的有效治疗选择。其机制包括：①恢复肠道菌群；②保持紧密连接完整性以保护上皮屏障；③诱导黏蛋白和IgA产生；④抑制病原体的定植和生长；⑤产生具有抗炎特性的短链脂肪酸等代谢产物；⑥通过代谢产物如γ-氨基丁酸与肠-脑轴相互作用；⑦调节宿主的固有和(或)特异性免疫反应；⑧诱导自噬减轻氧化应激诱导的肠损伤等[16]。

2.1 益生菌防治放化疗口腔黏膜炎

Gerhard等[17]通过动物实验发现5-FU化疗前30 d补充枯草芽孢杆菌、两歧双歧杆菌、粪肠球菌、嗜酸乳杆菌益生菌组合可减轻OM严重程度，且促进了口腔黏膜的恢复。Gupta等[18]利用动物实验证明提前1周口服罗伊氏乳杆菌DSM 17938和ATCC PTA 5289可减轻黏膜氧化应激和炎症反应，益生菌可通过核因子E2相关因子2(nuclear factor E2-related factor-2，Nrf-2)信号通路激活细胞抗氧化防御系统和抑制NF-κB介导的炎症反应，保护口腔黏膜免受5-FU诱导的损伤，且未导致系统性的细菌移位，有良好的安全性。

Sharma等[19]纳入200名受试者进行随机双盲安慰剂对照研究，在为期7周的放疗同时顺铂化疗期间及完成后1周内，每日接受含短乳杆菌CD2(*Lactobacillus brevis* CD2，LB CD2)含片可降低受试者3、4级OM发病率，且与较低的OM总体发生率以及较高的抗癌治疗完成率相关。Sharma等[20]将LB CD2含片应用于高剂量化疗后行造血干细胞移植的患者，也发现了类似的积极效果，可能机制为LB CD2产生精氨酸脱氨酶减少口腔中可利用的精氨酸含量，抑制精氨酸依赖的炎症相关微生物的生长；精氨酸含量降低导致精氨酸酶的作用减弱，使促炎因子一氧化氮产生减少而起到缓解OM的作用。而De Sanctis等[21]进行的多中心随机研究则未能证明LB CD2的功效，与使用碳酸氢钠漱口水相比，益生菌不能改善接受调强放疗和(或)化疗患者OM的严重性，原因可能是：①调强放疗提高了患者的口腔黏膜耐受性，减少了LB CD2潜在的有益影响；②纳入的受试者少，仅有75名；③对照组使用碳酸氢钠漱口水而非安慰剂。Limaye等[22]开展的随机安慰剂对照试验显示，含重组乳酸乳球菌的漱口液AG013可通过释放黏膜保护因子，降低5-FU诱导的2级以上OM发病率，并显示出良好的安全性和耐受性。Jiang等[23]开展的随机双盲安慰剂对照试验发现，调强放疗同时顺铂化疗期间食用长双歧杆菌、乳杆菌和粪肠球菌益生菌组合制剂的鼻咽癌患者OM发病率和严重程度降低，机体$CD3^+$T细胞、$CD4^+$T细胞、血红蛋白、淋巴细胞比例得到恢复，免疫力的增强有利于抗肿瘤治疗和黏膜炎防治；补充益生菌组合制剂还可促进恢复受试者肠道微生物多样性，从而提高放化疗的疗效并降低其黏膜毒性。

2.2 益生菌防治放化疗胃肠道黏膜炎

Oh等[24]证明嗜酸乳杆菌A4通过刺激黏蛋白基因的表达，降低髓过氧化物酶活性并抑制促炎因子(如IL-1β)的表达，降低5-FU引起的GM的严重程度。小鼠每日食用两歧双歧杆菌G9-1可减轻5-FU诱导升高的肠道髓过氧化物酶活性及TNF-α和IL-1β的表达，调节肠道菌群组成，缓解GM[25]。干酪乳杆菌鼠李糖亚种可抑制化疗诱导的肠黏膜细胞凋亡，调节化疗诱导的肠道菌群组成并可降低化疗后肠道促炎因子(TNF-α、IL-6)的表达，减轻大肠癌小鼠化疗诱导的肠黏膜炎[26]。在重症联合免疫缺陷/非肥胖糖尿病小鼠化疗诱导的GM模型中，干酪乳杆菌鼠李糖亚种或两歧双歧杆菌口服给药可降低血清TNF-α、IL-1β等促炎因子水平，且不导致菌血症[27]。婴儿双歧杆菌不仅可降低结直肠癌大鼠化疗诱导的血清IL-6，IL-1β和TNF-α水平，还可通过调节T细胞免疫反应减轻GM严重程度[28]。然而，并非所有的研究都表明益生菌对缓解GM有效。Maioli等[29]指出酿酒酵母不能改善5-FU引起的黏膜炎，这提示益生菌的效果会因动物模型、菌株、剂量和治疗计划而有差异。

益生菌组合也在动物实验中显示出减少由5-FU诱导的GM的有效性。胃内给服益生菌混合物(短双歧杆菌DM8310，嗜酸乳杆菌DM8302，干酪乳杆菌DM8121和热链球菌DM8309)可降低5-FU化疗大鼠的肠道促炎因子(TNF-α，IL-4，IL-6)水平

和中性粒细胞浸润，改善肠通透性，这些有益作用与肠道微生物稳态重建和Toll样受体2信号通路改变有关[30]。另一项使用益生菌混合物（嗜酸乳杆菌，副干酪乳杆菌，鼠李糖乳杆菌和乳酸双歧杆菌）的研究表明，口服益生菌组合能增加小肠绒毛/隐窝比率，并降低丙二醛、髓过氧化物酶、TNF-α和IL-6在所有小肠段中的水平，对GM防治起到有益作用[31]。Gerhard等[17]证明5-FU诱导黏膜炎前30 d，小鼠口服枯草芽孢杆菌、两歧双歧杆菌、粪肠球菌、嗜酸乳酸杆菌的益生菌组合可促进GM恢复并保护肠绒毛结构。

在最新的跨国癌症支持治疗协会和国际口腔肿瘤学协会指南中，已建议使用含有乳杆菌属的益生菌预防接受放化疗的盆腔恶性肿瘤患者的腹泻[32]。在150例接受5-FU化疗的大肠癌患者的随机研究中，与瓜尔胶相比，口服胶囊补充鼠李糖乳杆菌GG可以减少严重腹泻和腹部不适的发作，减少化疗剂量需要，并显示出良好的安全性[33]。其机制包括促进肠黏膜上皮细胞的增殖，增加保护性黏蛋白的分泌，使致病菌与肠壁的黏附减少，抑制细菌向组织内的转移以及刺激对病原体的局部和全身免疫反应。Motoori等[34]发现食管癌患者在新辅助化疗期间服用含短双歧杆菌、干酪乳杆菌的合生元后，严重腹泻发生率较对照组有所改善，但大多数临床参数在两组间无差异。荟萃分析仅证明了益生菌对单独放疗引起的腹泻防治有功效，但对化疗或靶向治疗引起的腹泻则无益处[35]。未来的研究应集中在将胃肠道毒性与某些微生物表型配对，以实现针对性控制肠道微生物群组，更好地设计个性化的益生菌策略。

3　总结与展望

益生菌由于对菌群平衡和宿主炎症反应的有益特性受到越来越多的关注。但需注意的是，益生菌施用于癌症治疗、造血干细胞移植等免疫受损的患者可能涉及安全问题。当前，造血干细胞移植患者服用乳杆菌已展现出较好的安全性[36]。但由于当下证据有限，仍有必要开展更多研究以评估益生菌在临床应用的安全性。此外，口腔与胃肠道的pH及局部微环境的差异使选用益生菌的种类及给药方式存在不同。鉴于现有研究之间因抗肿瘤治疗方案、细菌种类和施用方法等不同而存在的较大异质性，需要更高质量的动物实验和临床试验以证实益生菌防治黏膜炎的作用和机制，并探索最佳治疗方案。

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参考文献

[1] Mccullough RW. US oncology-wide incidence, duration, costs and deaths from chemoradiation mucositis and antimucositis therapy benefits[J]. Future Oncol, 2017, 13(30): 2823-2852. doi: 10.2217/fon-2017-0418.

[2] Thomsen M, Vitetta L. Adjunctive treatments for the prevention of chemotherapy- and Radiotherapy-Induced mucositis[J]. Integr Cancer Ther, 2018, 17(4): 1027 - 1047. doi: 10.1177/1534735418794885.

[3] Sonis ST. Oral mucositis[J]. Anticancer Drugs, 2011, 22(7): 607-612. doi: 10.1097/CAD.0b013e3283462086.

[4] Alexander JL, Wilson ID, Teare J, et al. Gut microbiota modulation of chemotherapy efficacy and toxicity[J]. Nat Rev Gastroenterol Hepatol, 2017, 14(6): 356-365. doi: 10.1038/nrgastro.2017.20.

[5] Hong BY, Sobue T, Choquette L, et al. Chemotherapy-induced oral mucositis is associated with detrimental bacterial dysbiosis[J]. Microbiome, 2019, 7(1): 66. doi: 10.1186/s40168-019-0679-5.

[6] Hou J, Zheng H, Li P, et al. Distinct shifts in the oral microbiota are associated with the progression and aggravation of mucositis during radiotherapy[J]. Radiother Oncol, 2018, 129(1): 44-51. doi: 10.1016/j.radonc.2018.04.023.

[7] Zhu XX, Yang XJ, Chao YL, et al. The potential effect of oral microbiota in the prediction of mucositis during radiotherapy for nasopharyngeal carcinoma[J]. EBioMedicine, 2017, 18(18): 23-31. doi: 10.1016/j.ebiom.2017.02.002.

[8] Vesty A, Gear K, Biswas K, et al. Oral microbial influences on oral mucositis during radiotherapy treatment of head and neck cancer[J]. Support Care Cancer, 2020, 28(6): 2683 - 2691. doi: 10.1007/s00520-019-05084-6.

[9] Vasconcelos RM, Sanfilippo N, Paster BJ, et al. Host-Microbiome cross-talk in oral mucositis[J]. J Dent Res, 2016, 95(7): 725-733. doi: 10.1177/0022034516641890.

[10] Vanlancker E, Vanhoecke B, Sieprath T, et al. Oral microbiota reduce wound healing capacity of epithelial monolayers, irrespective of the presence of 5-fluorouracil[J]. Exp Biol Med (Maywood), 2018, 243(4): 350-360. doi: 10.1177/1535370217753842.

[11] Vanhoecke BW, De Ryck TR, De BK, et al. Low-dose irradiation affects the functional behavior of oral microbiota in the context of mucositis[J]. Exp Biol Med (Maywood), 2016, 241(1): 60-70. doi: 10.1177/1535370215595467.

[12] Li HL, Lu L, Wang XS, et al. Alteration of gut microbiota and inflammatory cytokine/chemokine profiles in 5-fluorouracil induced intestinal mucositis[J]. Front Cell Infect Microbiol, 2017, 7: 455. doi: 10.3389/fcimb.2017.00455.

[13] Gerassy-Vainberg S, Blatt A, Danin-Poleg Y, et al. Radiation induces proinflammatory dysbiosis: transmission of inflammatory susceptibility by host cytokine induction[J]. Gut, 2018, 67(1): 97-

107. doi: 10.1136/gutjnl-2017-313789.

[14] Markowiak P, Śliżewska K. Effects of probiotics, prebiotics, and synbiotics on human health[J]. Nutrients, 2017, 9(9): 1021. doi: 10.3390/nu9091021.

[15] Seminario-Amez M, López-López J, Estrugo-Devesa A, et al. Probiotics and oral health: a systematic review[J]. Med Oral Patol Oral Cir Bucal, 2017, 22(3): e282-e288. doi: 10.4317/medoral.21494.

[16] Batista VL, da Silva TF, de Jesus LCL, et al. Probiotics, prebiotics, synbiotics, and paraprobiotics as a therapeutic alternative for intestinal mucositis[J]. Front Microbiol, 2020, 11: 544490. doi: 10.3389/fmicb.2020.544490.

[17] Gerhard D, Sousa F, Andraus RAC, et al. Probiotic therapy reduces inflammation and improves intestinal morphology in rats with induced oral mucositis[J]. Braz Oral Res, 2017, 31: e71. doi: 10.1590/1807-3107BOR-2017.vol31.0071.

[18] Gupta N, Ferreira J, Hong CHL, et al. Lactobacillus reuteri DSM 17938 and ATCC PTA 5289 ameliorates chemotherapy-induced oral mucositis[J]. Sci Rep, 2020, 10(1): 16189. doi: 10.1038/s41598-020-73292-w.

[19] Sharma A, Rath GK, Chaudhary SP, et al. Lactobacillus brevis CD2 lozenges reduce radiation- and chemotherapy-induced mucositis in patients with head and neck cancer: a randomized double-blind placebo-controlled study[J]. Eur J Cancer, 2012, 48(6): 875-881. doi: 10.1016/j.ejca.2011.06.010.

[20] Sharma A, Tilak T, Bakhshi S, et al. Lactobacillus brevis CD2 lozenges prevent oral mucositis in patients undergoing high dose chemotherapy followed by haematopoietic stem cell transplantation[J]. ESMO Open, 2016, 1(6): e000138. doi: 10.1136/esmoopen-2016-000138.

[21] De Sanctis V, Belgioia L, Cante D, et al. Lactobacillus brevis CD2 for prevention of oral mucositis in patients with head and neck tumors: a multicentric randomized study[J]. Anticancer Res, 2019, 39(4): 1935-1942. doi: 10.21873/anticanres.13303.

[22] Limaye SA, Haddad RI, Cilli F, et al. Phase 1b, multicenter, single blinded, placebo-controlled, sequential dose escalation study to assess the safety and tolerability of topically applied AG013 in subjects with locally advanced head and neck cancer receiving induction chemotherapy[J]. Cancer, 2013, 119(24): 4268-4276. doi: 10.1002/cncr.28365.

[23] Jiang C, Wang H, Xia C, et al. A randomized, double-blind, placebo-controlled trial of probiotics to reduce the severity of oral mucositis induced by chemoradiotherapy for patients with nasopharyngeal carcinoma[J]. Cancer, 2019, 125(7): 1081-1090. doi: 10.1002/cncr.31907.

[24] Oh NS, Jy L, Lee JM, et al. Mulberry leaf extract fermented with Lactobacillus acidophilus A4 ameliorates 5-fluorouracil-induced intestinal mucositis in rats[J]. Lett Appl Microbiol, 2017, 64(6): 459-468. doi: 10.1111/lam.12741.

[25] Kato S, Hamouda N, Kano Y, et al. Probiotic bifidobacterium bifidum G9-1 attenuates 5-fluorouracil-induced intestinal mucositis in mice via suppression of dysbiosis-related secondary inflammatory responses[J]. Clin Exp Pharmacol Physiol, 2017, 44(10): 1017-1025. doi: 10.1111/1440-1681.12792.

[26] Chang CW, Liu CY, Lee HC, et al. Lactobacillus casei variety rhamnosus probiotic preventively attenuates 5-fluorouracil/oxaliplatin-induced intestinal injury in a syngeneic colorectal cancer model[J]. Front Microbiol, 2018, 9: 983. doi: 10.3389/fmicb.2018.00983.

[27] Huang L, Chiang CJ, Cheng ML, et al. SCID/NOD mice model for 5-FU induced intestinal mucositis: Safety and effects of probiotics as therapy[J]. Pediatr Neonatol, 2019, 60(3): 252-260. doi: 10.1016/j.pedneo.2018.07.007.

[28] Mi H, Dong Y, Zhang B, et al. Bifidobacterium infantis ameliorates chemotherapy-induced intestinal mucositis via regulating T cell immunity in colorectal cancer rats[J]. Cell Physiol Biochem, 2017, 42(6): 2330-2341. doi: 10.1159/000480005.

[29] Maioli TU, de Melo Silva B, Dias MN, et al. Pretreatment with *Saccharomyces boulardii* does not prevent the experimental mucositis in Swiss mice[J]. J Negat Results Biomed, 2014, 13(1): 6. doi: 10.1186/1477-5751-13-6.

[30] Tang Y, Wu Y, Huang Z, et al. Administration of probiotic mixture DM#1 ameliorated 5-fluorouracil-induced intestinal mucositis and dysbiosis in rats[J]. Nutrition, 2017, 33: 96-104. doi: 10.1016/j.nut.2016.05.003.

[31] Quaresma M, Damasceno S, Monteiro C, et al. Probiotic mixture containing *Lactobacillus spp*. and *Bifidobacterium spp*. attenuates 5-fluorouracil-induced intestinal mucositis in mice[J]. Nutr Cancer, 2020, 72(8): 1355-1365. doi: 10.1080/01635581.2019.1675719.

[32] Lalla RV, Bowen J, Barasch A, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy[J]. Cancer, 2014, 120(10): 1453-1461. doi: 10.1002/cncr.28592.

[33] Osterlund P, Ruotsalainen T, Korpela R, et al. Lactobacillus supplementation for diarrhoea related to chemotherapy of colorectal cancer: a randomised study[J]. Br J Cancer, 2007, 97(8): 1028-1034. doi: 10.1038/sj.bjc.6603990.

[34] Motoori M, Yano M, Miyata H, et al. Randomized study of the effect of synbiotics during neoadjuvant chemotherapy on adverse events in esophageal cancer patients[J]. Clin Nutr, 2017, 36(1): 93-99. doi: 10.1016/j.clnu.2015.11.008.

[35] Wardill HR, Van Sebille YZA, Ciorba MA, et al. Prophylactic probiotics for cancer therapy-induced diarrhoea: a meta-analysis[J]. Curr Opin Support Palliat Care, 2018, 12(2): 187-197. doi: 10.1097/SPC.0000000000000338.

[36] Ladas EJ, Bhatia M, Chen L, et al. The safety and feasibility of probiotics in children and adolescents undergoing hematopoietic cell transplantation[J]. Bone Marrow Transplant, 2016, 51(2): 262-266. doi: 10.1038/bmt.2015.275.

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