微生物学通报
Microbiology China
http://journals.im.ac.cn/wswxtbcn

Sep. 20, 2024, 51(9): 3384−3397
DOI: 10.13344/j.microbiol.china.231019

专论与综述

肠道屏障与肠道菌群在溃疡性结肠炎中的研究进展

叶梦玲[1]，刘阳[1]，汤磊磊[2]，蒋国军[*2]

1 杭州师范大学 药学院，浙江 杭州 311121
2 杭州师范大学附属萧山医院药剂科，浙江 杭州 311200

叶梦玲, 刘阳, 汤磊磊, 蒋国军. 肠道屏障与肠道菌群在溃疡性结肠炎中的研究进展[J]. 微生物学通报, 2024, 51(9): 3384-3397.
YE Mengling, LIU Yang, TANG Leilei, JIANG Guojun. Research progress of intestinal barrier and gut microbiota in ulcerative colitis[J]. Microbiology China, 2024, 51(9): 3384-3397.

摘　要：溃疡性结肠炎(ulcerative colitis, UC)是一种发病机制不明的炎症性肠道疾病，发病率不断上升。完整的肠道屏障对维持肠道稳态和防治疾病至关重要。肠道菌群在构成肠道屏障、增强肠黏膜免疫反应和维持肠道内环境方面具有重要作用。肠道内菌群失衡会导致肠道屏障损伤，而肠道屏障损伤和肠道菌群失衡参与 UC 的发生发展。近年来，关于 UC 的研究越来越多地从肠道屏障和调节肠道菌群方面进行。本文就肠道屏障的组成及肠道菌群在 UC 中的作用进行综述，为该领域今后的研究提供理论依据。

关键词：溃疡性结肠炎；肠道屏障；肠道菌群；微生态制剂

Research progress of intestinal barrier and gut microbiota in ulcerative colitis

YE Mengling[1], LIU Yang[1], TANG Leilei[2], JIANG Guojun[*2]

1 School of Pharmacy, Hangzhou Normal University, Hangzhou 311121, Zhejiang, China
2 Department of Pharmacy, Affiliated Xiaoshan Hospital, Hangzhou Normal University, Hangzhou 311200, Zhejiang, China

Abstract: Ulcerative colitis (UC) is an inflammatory bowel disease with unknown pathogenesis and increasing incidence. An intact intestinal barrier is essential for maintaining intestinal homeostasis and preventing diseases. The gut microbiota plays a crucial role in constituting the intestinal barrier, enhancing the immune response of the intestinal mucosa, and maintaining the intestinal environment. The gut microbiota imbalance can lead to intestinal barrier damage, and

资助项目：杭州生物医药和健康产业发展扶持科技专项(2022WJC139)
This work was supported by the Hangzhou Biomedical and Health Industry Development Support Technology Special Project (2022WJC139).
*Corresponding author. E-mail: jguojun999@hznu.edu.cn
Received: 2023-12-02; Accepted: 2024-03-18; Published online: 2024-04-22

both intestinal barrier damage and gut microbiota imbalance are involved in the development of UC. In recent years, increasing studies of UC focused on the intestinal barrier and regulation of gut microbiota have been carried out. This article reviews the components of the intestinal barrier and the role of gut microbiota in UC, aiming to provide a theoretical basis for the future research in this field.

Keywords: ulcerative colitis; intestinal barrier; gut microbiota; microecological preparation

溃疡性结肠炎(ulcerative colitis, UC)实质是一种由免疫介导并伴有复发和缓解性的炎症性肠病(inflammatory bowel disease, IBD)，始于远端，向近端延伸，蔓延整个结肠，其常见症状包括带血性腹泻、腹痛、疲劳及大便失禁[1-2]。尽管 UC 的确切发病机制不明，但遗传易感性、环境因素、免疫异常、肠道菌群和肠道屏障均被认为是其致病因素[2-3]。流行病学显示，一些具有代表性的亚洲国家(韩国、中国和日本)中 UC 的发病率和患病率在过去 40 年里增加了 1.5−20.0 倍[4]。相较于健康人群，UC 患者死于胃肠道疾病、呼吸系统疾病、非酒精性肝病和肺栓塞的风险较高，增加了结直肠癌的易感性[4-5]。目前尚无彻底治愈 UC 的药物，临床治疗主要采用 5-氨基水杨酸、糖皮质激素、生物制剂、免疫抑制剂，以及通过调节肠道菌群发挥治疗作用的微生态制剂和粪菌移植等[1,6]。

肠道是人体内部与外部环境接触面最大的器官，完整的肠道屏障对于维持肠道稳态和防治疾病是必要的[7]。由物理屏障、化学屏障、免疫屏障和生物屏障组成完整的胃肠道屏障系统，维持机体内外环境的稳态[8]。在功能上，肠道屏障具有双重作用，一方面吸收消化机体的水和营养物质，另一方面抵挡病原体、外来抗原及毒素的攻击[9]。然而，肠道屏障可能受到遗传性易感性、饮食、抗生素、酒精和心理应激等因素的影响，研究发现肠道屏障损伤已经成为 UC 的恶化标志[8-10]。

每个人的肠道内存在数万亿的微生物，种类达到 1 000 多种，主要包含细菌、古细菌、病毒、真菌和其他生命形式，这些统称为肠道菌群[11]。肠道菌群蕴含的基因总数是人类基因组的 100 倍，如果不能正确调节如此数量的肠道菌群，可能会引起肠道炎症[10]，体现为肠道屏障损伤和肠道菌群失衡，导致自身免疫性疾病和肠道疾病的形成，如 1 型糖尿病、系统性红斑狼疮、克罗恩病、UC 及乳糜泻[9-10]。尽管肠道菌群与人类健康和疾病的关系错综复杂，但肠道菌群作为靶点是 UC 的治疗策略[7,10]。本文以肠道屏障与肠道菌群为切入点，对 UC 中存在的肠道屏障损伤、肠道菌群失衡及肠道菌群作为治疗措施进行综述，有望为 UC 的临床治疗提供更多的思路。

1 肠道屏障与 UC

1.1 物理屏障与 UC

物理屏障由完整的杯状细胞、潘氏细胞和吸收细胞组成的肠上皮细胞与相邻肠上皮细胞之间的紧密连接构成，是肠道黏膜的防御层[12]。研究发现，肠道黏膜中的物理屏障一旦损伤，将刺激位于隐窝底部的残存干细胞进行自我分化，变成成熟的上皮细胞，修复损伤黏膜；因此，调节肠道干细胞可能是治疗 UC 的新方向[13]。肠道中相邻上皮细胞间的连接构成了连接复合物，依次为紧密连接(tight junction, TJ)、缝隙连接、黏附连接及桥粒[14]。作为物理屏障的关键部分，紧密连接主要由闭合蛋白(claudin)、咬合蛋白(occludin)、连接黏附分子(junctional adhesion

molecule, JAM)和闭锁小带蛋白-1 (zonula occludens-1, ZO-1)构成，维持着上皮细胞之间结构的稳定，并且有选择渗透性作用，允许水和溶质转运，限制毒素和某些病原体移位[14-15]。同时，黏附连接和桥粒协调上皮细胞的形状、定位及组织生长分化，作为连接点充当细胞间的通信枢纽，整合化学和机械通路，满足肠道屏障和免疫调节等需要[16]。临床研究发现，相较于正常对照组，UC 患者中能够观察到 occludin 和 ZO-1 等相关蛋白表达的下调[17]。动物研究发现，葡聚糖硫酸钠(dextran sodium sulfate, DSS)诱导小鼠造成肠道炎症组织和屏障损伤，引发有害物入侵肠道上皮层和固有层；黄芩素激活 3 型天然淋巴样细胞(group 3 innate lymphoid cell, ILC3)内的 AhR/IL-22 途径，改善肠道屏障结构和功能，促进 ZO-1 和 occludin 表达，保护肠上皮细胞，逆转病理损害[18]。最近的研究采用UC小鼠模型验证得到相似结论，丁酸盐促进 claudin-1 和 occludin 的表达，改善肠道屏障完整性[19]。因此，保护肠道上皮细胞，上调连接蛋白表达，保护物理屏障可以达到改善 UC 的效果[13,18-19]。

1.2 化学屏障与 UC

化学屏障由黏液、黏蛋白、水、消化酶、抗菌肽和其他物质组成，也称黏液层[8,15]。结肠的黏液分为内部致密黏液层和外部松散黏液层(共生细菌栖息)，黏液层保护上皮细胞免于接触肠腔[20]。杯状细胞分泌的黏蛋白(mucin 2, Muc 2)是内部黏液层的主要成分，黏蛋白组成的凝胶是支撑黏液层的骨架结构[21]。一项单中心临床病例研究收集 36 例处于活动期 UC 患者、28 例缓解期患者和 47 例阴性对照患者的结肠活检样本，结果显示黏液中主要成分 Muc2 降低可导致屏障完整性弱化，并且被认为是 UC 发病机制的早期事件[22]。敲除黏蛋白 Muc2 的基因缺陷型小鼠在后续的成长中自发出现UC和肠道屏障损伤[23]。患者结肠杯状细胞的分化缺陷导致黏液分泌减少，黏液层损伤[24]。因此，结肠中的黏液异常可能是造成肠道屏障损伤和 UC 的机制之一[22-24]。同时，黏液溶菌酶的活性增加也是黏液层降解和细菌入侵肠上皮的原因，Zhang 等[25]研究发现降低黏液溶菌酶活性和丰度可改善因 UC 造成的肠道病理损伤。肠上皮细胞和潘氏细胞分泌的抗菌肽(antimicrobial peptide, AMP)耐受肠道菌群，具有维持肠道稳态的作用，可能作为临床的肠道炎症生物标志物；主要类型为防御素(α-防御素和 β-防御素)、cathelicidins、再生(Reg)蛋白家族的凝集素和金属螯合肽等[26]。AMP 表达与小鼠的肠道炎症有关，补充人 β-防御素 2 可以恢复结肠炎症状态和隐窝丢失，效果优于抗肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)[27]。

1.3 免疫屏障与 UC

免疫屏障通常由肠道相关淋巴组织(gut-associated lymphoid tissue, GALT)和分泌型免疫球蛋白 A (secretory immunoglobulin A, sIgA)构成[28]。肠系膜淋巴结(mesenteric lymph node, MLN)和 GALT 是肠道免疫的诱导位点，GALT 包括派尔斑(peyer's patches, pp)及孤立的淋巴滤泡(isolated lymphoid follicle, ILF)，而肠道黏膜固有层和上皮效应细胞作为免疫效应位点[29-30]。派尔斑被认为是人和小鼠肠道免疫反应的关键位点，在 UC 的免疫进程中不可忽视，一项单中心研究显示，UC 复发者的窄带成像发现 pp 形态学的改变，观察 pp 可以辅助临床诊断[29-31]。结构方面，GALT 和免疫系统的淋巴结类似，从黏膜表面识别抗原以激活浆细胞分泌 sIgA，发挥免疫功能[32]。特定条件饲养的无菌小鼠表现出 GALT 缺陷，肠道免疫反应不足，MLN 普遍较小，ILF 生长受损，而 UC 中可见基底淋巴

聚集[33]。肠道固有层中的免疫细胞如巨噬细胞、肥大细胞、杯状细胞及中性粒细胞等构成了肠道黏膜免疫系统，直接或间接发挥免疫排斥或免疫中和特性，抑制或清除病原体和抗原入侵[34]。此外，UC 更是一种受细胞因子影响的复杂疾病，患者个体差异和疾病状态影响其表达水平，如 TNF-α、白介素-1β (interleukin-1β, IL-β)、IL-6、IL-8 和 γ 干扰素(interferon-γ, IFN-γ)等均可参与炎症或免疫反应[35]。越来越多的证据支持将细胞因子作为治疗靶标，IL-12 和 IL-23 主要来源于肠道的巨噬细胞，两种细胞因子诱导辅助性 T 细胞 1 (helper T cell 1, Th1)分化的同时维持 Th17 细胞的促炎作用，引起肠道炎症；乌司奴(ustekinuma, UST)单克隆抗体通过抑制效应 T 细胞分化，靶向阻断 2 种细胞因子的共享亚基，抑制肠道屏障损伤和 UC 产生[36]。另外，sIgA 是肠黏膜中最丰富的免疫球蛋白亚型之一，也是肠道免疫防御的第一道防线[30]。Li 等[37]研究发现，促进肠道中 sIgA 分泌可调节肠黏膜免疫屏障的功能，增加病原体抵抗力并促进肠道稳态恢复。

1.4 生物屏障与 UC

人类出生时肠道菌群就开始建立，随着宿主不断进化、演变，这种共生关系形成一个稳定的微生态屏障系统，即生物屏障[38]。肠道菌群作为机体的“虚拟器官”参与新陈代谢、促进免疫系统成熟和保护神经功能，可以直接或间接调节机体的生理病理过程[10,39]。在门水平上，肠道菌群主要包含厚壁菌门(*Firmicutes*)、变形菌门(*Proteobacteria*)、放线菌门(*Actinobacteria*)和拟杆菌门(*Bacteroidetes*)等[10,40]。Chen 等[19]采用 16S rRNA 基因测序 UC 小鼠的粪便样本得到相似的结论，这些菌门的丰度发生了显著变化。肠道菌群与肠道屏障在正常状态下和谐相处，维持肠道稳态[10,38]。相反，这种状态一旦被打破，肠道的致病菌可能引起炎症，加速 UC 发展；在无菌小鼠中表现出免疫缺陷，这证实肠道中缺乏正常菌群也可能影响免疫功能[33]。

肠道菌群分为益生菌、致病菌和机会病原体。益生菌如乳杆菌(*Lactobacillus* sp.)，是肠道的优势菌群；致病菌如破伤风梭菌(*Clostridium tetani*)，入侵机体可能导致肠道菌群失衡，引起疾病；机会病原体如肠球菌(*Enterococcus* sp.)，正常情况下无害，某些条件下可能致病[41]。研究发现，丁酸梭菌(*Clostridium butyricum*)预处理逆转 DSS 诱导造成小鼠肠道菌群失衡，增强肠道上皮细胞紧密连接，修复肠黏膜的完整性进而缓解 UC，其代谢物产生类似作用；丁酸梭菌(*C. butyricum*)衍生的肠道外囊泡给药调节氨基酸产生，直接作用于结肠部位调节炎症反应，参与黏蛋白分泌以及 occludin、claudin 和 ZO-1 的表达，降低促炎基因表达，保护肠道屏障[42]。此外，肠道菌群衍生的特定代谢物短链脂肪酸(short chain fatty acid, SCFA)可以为肠道菌群和上皮细胞提供能量来源，最具代表性的是丁酸盐；丁酸盐可以激活巨噬细胞/WNT/ERK 通路，恢复结肠黏膜损伤后杯状细胞的数量和功能，促进黏液分泌，菌群、上皮细胞及外黏液层协同作用维持肠道屏障的完整性[43]。另外，肠道菌群的多样性可以调节肠道稳态[10,44]。16S rRNA 基因和鸟枪法宏基因组学显示，相较于正常对照组，儿童 UC 患者肠道内的菌群 α 多样性低且 β 多样性多变，存在菌群失衡，进一步印证 UC 的疾病状态影响肠道菌群[44]。在 UC 中，基于肠道菌群的免疫疗法可以通过免疫刺激，特异性激活免疫反应，也可以利用共生菌群在肠内定殖，抑制抗原活化 T 细胞和 B 细胞引发的促炎免疫应答，改善肠道屏障[45-46]。靶向肠道菌群恢复健康的微生物群落，重塑生物屏障不失为 UC 的一种治疗措施[7,10,42]。

肠道的四大屏障并不是独立的部分，而是相辅相成的整体，作为高度动态的半透性屏障，支持机体营养物质转运、识别抗原信号、激活免疫应答、维持肠道内环境稳态。肠道内菌群失衡可导致肠道黏液层变薄、细胞间的紧密连接结构和功能无法维持、上皮细胞的通透性增加、有益菌减少，以及致病菌的过度繁殖造成细菌和毒素通过屏障移位入血，产生的炎症引发级联反应，由此形成了一个恶性循环，加重UC损害。长期以来，UC常规治疗方法往往伴随副作用和复发性，而肠道菌群对人体具有广泛的作用，目前已经成为众多研究者重视的领域，改善肠道屏障、调节肠道菌群，可能是未来UC治疗的主要方向。

2 肠道菌群与UC

基于肠道菌群在UC发病进程中的意义，目前与肠道菌群相关的治疗措施包括微生态制剂(益生元、益生菌、合生元、后生元)、粪菌移植、抗生素和中药[1,6,47-48]。

2.1 微生态制剂

2.1.1 益生元

益生元是一类对宿主产生有益作用且不被消化的食物成分，通过肠道菌群的代谢和利用达到刺激有益菌生长活性的目的[6,49]。常规的益生元类型包括低聚半乳糖、果聚糖、乳果糖和其他低聚糖类等[49]。临床研究发现，摄入9周的菊粉型果聚糖增加双歧杆菌科(*Bifidobacteriaceae*)和毛螺菌科(*Lachnospiraceae*)的丰度，促进丁酸盐产生，可用作轻中度UC患者的辅助治疗[50]。动物研究发现，α-低聚半乳糖(α-galacto-oligosaccharide, α-GOS)抑制NOD样受体蛋白3 (NOD-like receptor protein-3, NLRP3)炎症小体的激活，降低促炎因子TNF-α、IL-1β和IL-6的表达，改善肠道菌群多样性及其功能，提高ZO-1和claudin-1表达，保护肠道屏障完整性，可作为UC的预防和辅助治疗[51]。日常服用富含膳食纤维的谷物(燕麦麸)，观察到患者粪便内丁酸盐水平上升，后期疾病状态得到改善，复发率明显降低[52]。因此，益生元作为一种膳食成分可以调节或恢复肠道内菌群丰度及功能，产生的SCFA在UC治疗中具有重要意义[50,52]。

2.1.2 益生菌

益生菌是具有生物活性，摄入对宿主健康有益的一类活菌制剂，功能表现为调节肠道菌群微环境、改善肠道屏障及诱导保护性免疫应答[53]。Ma等[42]研究发现丁酸梭菌(*C. butyricum*)及其代谢物降低埃希氏菌属(*Escherichia*)和志贺氏菌属(*Shigella*)的丰度，增加产丁酸盐的狭义梭菌属-1 (*Clostridium sensu stricto*-1)和丁酸球菌属(*Butyricicoccus*)的丰度，可以维持小鼠肠道稳态。此外，口服植物乳杆菌(*Lactobacillus plantarum*)可诱导小鼠产生抗炎细胞因子如转化生长因子(transforming growth factor, TGF-β)和IL-10，降低促炎细胞因子TNF-α、IL-17A、IL-17F和IL-6，调节肠道常驻菌稳态和免疫反应[54]。研究发现富硒长双歧杆菌(selenium-enriched *Bifidobacterium longum*) DD98改善肠道菌群多样性，促进有益菌丰度，通过抑制toll样受体4 (toll-like receptor 4, TLR4)通路激活，降低促炎细胞因子表达，缓解DSS诱导的炎症反应；此外，富硒长双歧杆菌DD98还促进TJ蛋白的表达如ZO-1和occludin，改善了小鼠肠道屏障完整性[55]。Kaur等[56]分析了纳入的14项UC相关的标准研究(865名受试者)，相较于安慰剂，益生菌治疗后患者临床缓解危险比为1.73，临床疾病评分得到改善，相较于5-氨基水杨酸(5-aminosalicylates, 5-ASA)，益生菌制剂不良事件更少、更安全。

2.1.3 合生元

合生元是由一种或多种益生元和益生菌组成的合剂，作为 UC 的补充和替代疗法[57]。合生元被国际益生菌和益生元科学协会(international scientific association for probiotics and prebiotics, ISAPP)定义为：宿主微生物(宿主或定殖宿主)选择性利用的活微生物和底物组成的混合物，可赋予宿主健康益处，包括协同和互补模式[58]。合生元的成分组合可以提供更大的健康益处，例如增强细胞壁成分促进益生菌更好地定殖在肠道[59]。研究表明凝结芽孢杆菌(*Bacillus coagulans*)与壳寡糖组成的合生元增加菌群多样性，并且增加产 SCFA 的阿克曼氏菌属(*Akkermansia*)和瘤胃菌科(*Ruminococcaceae*)的丰度，相较于对照组，合生元组明显改善免疫调节功能，UC 小鼠整体的细胞因子水平已恢复正常(IL-4、IL-10、IL-6、IL-8)，并增强 TJ 和 Muc2 蛋白以恢复屏障完整性，疗效优于单用[60]。Kamarlı Altun 等[61]发现，UC 患者服用合生元可见血清 C 反应蛋白降低，临床和内窥镜活性缓解，合生元疗法可有效改善炎症，预防 UC。总之，合生元集益生菌和益生元于一体，促进益生菌在肠道定殖的同时诱导益生菌、益生元自生，具有发展前景。

2.1.4 后生元

后生元是不再具有生命、已经死亡或灭活之后衍生的物质，可以是灭活的细胞、细菌代谢物、化合物或结构片段[47,62]。益生菌类制剂需要在有效期内保持一定水平的活菌存活，而无生命的后生元在制备和储存方面具有一定的稳定性，并且失去了复制能力，安全性提高[47,62]。研究发现，后生元相关作用机制和益生菌类似：(1) 调节肠道菌群，产生 SCFA[19,43,50]；(2) 调节免疫反应，*Alistipes* 3BBH6 和内脏臭气杆菌(*Odoribacter splanchnicus*)加速色氨酸代谢为吲哚乳酸，作为芳香烃受体(aryl hydrocarbon receptor, AhR) 和 3 型羟基羧酸受体(hydroxycarboxylic acid receptor 3, HCAR3)信号激活肠道先天免疫反应[63]；(3) 保护肠道屏障功能，研究发现丁酸盐上调 TJ 蛋白的表达，改善肠道屏障的完整性[19]；(4) 调节机体代谢，处理后的嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*)通过调节尿酸代谢和炎症，改善小鼠高尿酸血症[64]；(5) 作用于中枢神经系统，灭活后的植物乳杆菌(*L. plantarum*)改善沙门氏菌属(*Salmonella*)导致的脑损伤和神经炎症，预处理调节神经活性分子如 5-羟色胺和 γ-氨基丁酸水平，其代谢物改善肠脑轴[65]。因此，后生元成为基于传统的益生菌类制剂治疗 UC 之外的新一代疗法，因其无活性的特性更容易被胃肠道应激系统所接受[66]。后生元 SCFA 在 UC 中研究较多，调节肠道菌群丰度，促进 Muc2 和 TJ 蛋白表达，保护肠道屏障和增强免疫功能，尚需更多的临床研究来证实 SCFA 在 UC 中的疗效[19,43,50]。

2.2 FMT

FMT 是将健康供体粪便中的功能菌群提取移植到患者肠道，达到重建或者恢复功能正常的肠道菌群稳态的目的，以治疗疾病[53,67]。张发明[68]在 2012 年编译、推动 FMT，引发国内 FMT 治疗疾病的开端。目前，FMT 治疗 UC 的安全性和有效性研究得到许多关注，在 122 例 UC 患者的单中心前瞻性队列研究中证实，患者接受 FMT (菌液)或糖皮质激素(泼尼松)治疗达到同等缓解，FMT 降低血清中 TNF-α 和 IL-6 表达且不良事件少于糖皮质激素给药[69]。FMT 调节肠道菌群实现 UC 患者的临床缓解，制备的菌液样品经内镜肠道植管术(transendoscopic enteral tubing, TET)给药 4 周后，增加普氏栖粪杆菌(*Faecalibacterium prausnitzii*)水平(P<0.05)[67]。

结肠 TET 是一种肠内治疗，在内窥镜引导下通过肛门将细软管插入深结肠并固定在特定位置进行药物递送，可以实现全结肠覆盖；此外，结肠 TET 是粪菌移植(fecal microbiota transplantation, FMT)、结肠引流和减压，以及宿主-微生物群之间研究的新途径[70]。相较于其他方法，结肠 TET 给药的患者满意度高，安全有效[67,69-70]。Wen 等[71]研究发现，FMT 可以恢复化学诱导小鼠的肠道菌群失衡，上调乳酸菌丰度，降低苏黎世杆菌属(*Turicibacter*)丰度，并调节与肠道菌群相关的基因表达来抑制结肠中 T 淋巴细胞的活化，维持肠道稳态并改善结肠炎。因此，接受 FMT 治疗可以缓解患者的临床症状，特别是结肠 TET 给药，但 FMT 后续是否产生严重不良事件，目前尚无统计学意义，这仍是一个值得讨论的问题[67,69]。

2.3 抗生素

抗生素是治疗 UC 的方法之一，抗生素在调节肠道菌群组成、管腔黏膜的菌负荷、细菌酶活性及抗感染方面起作用[6,72]。一项包含 104 名 UC 的前瞻性研究显示，抗生素联合应用(阿莫西林、磷霉素和甲硝唑)显示出良好的疗效和安全性，可能与恢复肠道菌群失衡有关，适合长期治疗[73]。抗生素和 FMT 的联合促进了供体菌株在肠道内定殖，缓解肠道菌群失衡，促进拟杆菌门(*Bacteroidetes*)定殖[74]。此外，口服四联抗生素(阿莫西林、甲硝唑、环丙沙星和多西环素)可作为儿童中重度难治性 UC 的治疗选项，小儿 UC 活动指数(pediatric ulcerative colitis activity index, PUCAI)评分显示，25/63 (39.7%)患者可以实现临床缓解(PUCAI<10 分)，并挽救生物制剂(抗 TNF-α)治疗的失败[75]。另外，抗生素的效用与治疗的阶段、药物类型、维持时间、抗性基因出现、有益菌和致病菌减少等因素有关，因此，有针对性地进行个体化用药是治疗的关键[76]。

2.4 中药

中药在我国的应用具有数千年的历史，来源广泛，药理活性强，在抗炎、抗氧化、调节肠道菌群及肠黏膜免疫等方面具有重要作用[48,77]。红参和薏苡仁调节肠道菌群结构，促进肠道有益菌如动物乳酸杆菌(*Bifidobacterium animalis*)和鼠李糖乳杆菌(*Lactobacillus rhamnosus*)的生长繁殖，并抑制金黄色葡萄球菌(*Staphylococcus aureus*)等病原体菌株的数量[78]。黄芩汤上调肠道菌群丰度恢复肠道稳态，促进氨基酸代谢进而激活 mTOR 信号通路，增加 TJ 蛋白表达，保护肠道屏障完整性[79]。类似地，中药还通过调节肠道菌群及其相关代谢物水平起效，丹皮酚来源于牡丹花树皮，可以间接激活胆汁酸合成的信号通路，包括肝脏途径 FXR-SHP/LRH-1 和回肠途径 FXR-FGF15，恢复小鼠粪便中石胆酸和鹅去氧胆酸水平，并使乳杆菌属(*Lactobacillus*)丰度提高[80]。白头翁汤出自张仲景的《伤寒杂病论》，是治疗 UC 的经典方剂，由白头翁、秦皮、黄连、黄柏四味中药材组成，有清热解毒、凉血止痢的功效[81]。现代研究发现白头翁汤防治 UC 效果显著，具体表现为调节小鼠肠道免疫反应，促进肠免疫平衡恢复；抑制致病菌生长、增加益生菌丰度，调节肠道内菌群失衡；抑制促炎因子释放，增加 TJ 蛋白表达，维持肠黏膜紧密连接结构的完整性，从而保护肠道屏障功能[81-82]。此外，在一项为期 6 周的临床实验中，虎地胶囊改善轻中度 UC 的疗效达到 91.09%，而(美沙拉嗪)对照组为 84.62%，该实验证明中药虎地胶囊(虎杖、白及、朱砂七、甘草、二色补血草、白花蛇舌草、北败酱、地榆炭)是安全和有效的[83]。有关肠道屏障或肠道菌群改善 UC 的机制信息、患者或 UC 动物模型详见表 1。

表 1　肠道屏障或肠道菌群改善溃疡性结肠炎

Table 1　Intestinal barrier or gut microbiota ameliorate ulcerative colitis

治疗 Treatment	患者/动物模型 Patient/Animal model	机制 Mechanism	参考文献 Reference
黄芩素 Baicalein	DSS (小鼠) DSS (mice)	激活 ILC3s 中的 AhR/IL-22 通路，改善肠道屏障的结构和功能 Activates the AhR/IL-22 pathway in ILC3s and improves the structure and function of the intestinal barrier	[18]
丁酸钠 Sodium butyrate	DSS (小鼠) DSS (mice)	促进 claudin-1 和 occludin 表达，改善肠道屏障完整性 Promotes the expression of claudin-1 and occludin and improves intestinal barrier integrity	[19]
人 β-防御素 2 Human β-defensin 2	DSS (小鼠) DSS (mice)	构成肠道屏障，作为免疫调节剂 Constitutes the intestinal barrier and acts as an immune-modulator	[27]
苦参酮 Kurarinone	DSS (小鼠) DSS (mice)	促进 sIgA 的分泌，调节肠道免疫屏障 Promotes the secretion of sIgA and regulates the intestinal immune barrier	[37]
丁酸盐 Butyrate	DSS (小鼠) DSS (mice)	激活巨噬细胞/WNT/ERK 通路，促进杯状细胞增殖和黏液产生 Activates macrophage/WNT/ERK pathway to promote goblet cell proliferation and mucus production	[43]
益生元(菊粉型果聚糖) Prebiotics (inulin-type fructans)	轻度/中度活动性 UC 患者 Patients with a mild/moderately active UC	促进结肠丁酸盐的产生，调节肠道菌群组成 Promotes colonic butyrate production and regulates the composition of gut microbiota	[50]
益生元(α-低聚半乳糖) Prebiotics (α-galacto-oligosaccharide)	DSS (小鼠) DSS (mice)	抑制 NLRP3 炎症小体的激活，降低促炎因子表达，改善肠道菌群多样性，保护肠道屏障完整性 Inhibits the activation of NLRP3 inflammasome, reduces the expression of pro-inflammatory factors, improves the diversity of gut microbiota, and protects barrier integrity	[51]
益生元(燕麦麸) Prebiotics (oat bran)	缓解期 UC 患者 Patients with UC in remission	促进丁酸盐产生 Promotes butyrate production	[52]
益生菌(植物乳杆菌) Probiotics (*Lactobacillus plantarum*)	DSS (小鼠) DSS (mice)	改善肠道菌群失衡，调节免疫反应 Improves gut microbiota imbalance and regulates immune response	[54]
益生菌(富硒长双歧杆菌 DD98) Probiotics (selenium-enriched *Bifidobacterium longum* DD98)	DSS (小鼠) DSS (mice)	改善肠道菌群多样性，抑制 TLR4 通路，促进 ZO-1 和 occludin 表达，改善肠道屏障完整性 Improves the diversity of gut microbiota, inhibits the TLR 4 pathway, promotes the expression of ZO-1 and occludin, and improves the intestinal barrier integrity	[55]
合生元(凝结芽孢杆菌和壳寡糖) Synbiotic (*Bacillus coagulans* and chitooligosaccharides)	DSS (小鼠) DSS (mice)	富集益生菌，调节肠道菌群组成和免疫反应，促进 SCFA 产生，恢复肠道屏障 Enriches probiotics regulate the composition of gut microbiota and immune response, promotes the production of SCFAs, and restores the intestinal barrier	[60]

(待续)

(续表 1)

治疗 Treatment	患者/动物模型 Patient/Animal model	机制 Mechanism	参考文献 Reference
粪菌移植 Fecal microbiota transplantation (FMT)	轻度/中度活动性 UC 患者 Patients with a mild/moderately active UC	调节肠道菌群，增加普氏栖粪杆菌水平 Regulates the gut microbiota and increases *F. prausnitzii* levels	[67]
粪菌移植 FMT	DSS (小鼠) DSS (mice)	调节肠道菌群，抑制 T 细胞活化 Regulates the gut microbiota and inhibits T cell activation	[71]
抗生素粪菌移植联合疗法 Combination therapy of FMT and antibiotics	UC 患者 UC patients	缓解肠道菌群失衡，促进拟杆菌门定殖 Alleviates the imbalance of gut microbiota and promotes colonization of *Bacteroidetes*	[74]
黄芩汤 Huangqin decoction	DSS (小鼠) DSS (mice)	调节肠道菌群，促进氨基酸代谢，激活 mTOR 通路，保护肠道屏障的完整性 Regulates the gut microbiota, promotes amino acid metabolism, activates the mTOR pathway, and protects intestinal barrier integrity	[79]
丹皮酚 Paeonol	DSS (小鼠) DSS (mice)	调节肠道菌群和代谢物 Regulates the gut microbiota and metabolites	[80]
白头翁汤 Baitouweng decoction	DSS (小鼠) DSS (mice)	调节肠道菌群，增加 TJ 蛋白表达，保护肠道屏障功能 Regulates the gut microbiota, increases TJ protein expression, and protects intestinal barrier function	[82]

DSS：葡聚糖硫酸钠；UC：溃疡性结肠炎

DSS: Dextran sodium sulfate; UC: Ulcerative colitis.

3 结论与展望

肠道屏障损伤和肠道菌群失衡与各种肠道和肠外疾病关系密切，UC 的发展进程中也伴随着这两种情况。近年来的研究认为微生态制剂、FMT、抗生素和中药能够应用于 UC 治疗，与肠道菌群相关，且取得了一定效果。微生态制剂促进有益菌生长、抑制致病菌水平、调节肠道菌群组成、保护肠道屏障和免疫系统活性。FMT 抑制 T 细胞活化和促炎因子表达、促进有益菌的定殖并恢复肠道菌群多样性，结肠 TET 给药治疗 UC 具有发展前景。此外，抗生素在调节肠道菌群和中重度难治性 UC 方面显示出疗效。中药在治疗 UC 方面是一个独特的资源，通过调节肠道菌群结构、丰度及代谢物水平来恢复肠道微生态平衡，抑制促炎因子释放，调节肠道免疫平衡，保护肠道屏障功能。可以说，现有的证据都表明改善肠道屏障、调节肠道菌群失衡可以预防或改善 UC 的病理状态，但明确 UC、肠道屏障与肠道菌群三者之间的因果关系和作用机制还需大规模的临床研究进行论证，未来以肠道菌群为中心的治疗措施仍值得期待。

REFERENCES

[1] ADAMS SM, CLOSE ED, SHREENATH AP. Ulcerative colitis: rapid evidence review[J]. American Family Physician, 2022, 105(4): 406-411.

[2] DU L, HA C. Epidemiology and pathogenesis of ulcerative colitis[J]. Gastroenterology Clinics of North America, 2020, 49(4): 643-654.

[3] COUFAL S, GALANOVA N, BAJER L, GAJDAROVA Z, SCHIEROVA D, ZAKOSTELSKA ZJ, KOSTOVCIKOVA

K, JACKOVA Z, STEHLIKOVA Z, DRASTICH P, TLASKALOVA-HOGENOVA H, KVERKA M. Inflammatory bowel disease types differ in markers of inflammation, gut barrier and in specific anti-bacterial response[J]. Cells, 2019, 8(7): 719.

[4] WEI SC, SOLLANO J, HUI YT, YU W, SANTOS ESTRELLA PV, LLAMADO LJQ, KORAM N. Epidemiology, burden of disease, and unmet needs in the treatment of ulcerative colitis in Asia[J]. Expert Review of Gastroenterology & Hepatology, 2021, 15(3): 275-289.

[5] JESS T, GAMBORG M, MUNKHOLM P, SØRENSEN TIA. Overall and cause-specific mortality in ulcerative colitis: meta-analysis of population-based inception cohort studies[J]. The American Journal of Gastroenterology, 2007, 102(3): 609-617.

[6] POPOV J, CAPUTI V, NANDEESHA N, RODRIGUEZ DA, PAI N. Microbiota-immune interactions in ulcerative colitis and colitis associated cancer and emerging microbiota-based therapies[J]. International Journal of Molecular Sciences, 2021, 22(21): 11365.

[7] FARHADI A, BANAN A, FIELDS J, KESHAVARZIAN A. Intestinal barrier: an interface between health and disease[J]. Journal of Gastroenterology and Hepatology, 2003, 18(5): 479-497.

[8] AN J, LIU YQ, WANG YQ, FAN R, HU XR, ZHANG F, YANG JH, CHEN JW. The role of intestinal mucosal barrier in autoimmune disease: a potential target[J]. Frontiers in Immunology, 2022, 13: 871713.

[9] MARTEL J, CHANG SH, KO YF, HWANG TL, YOUNG JD, OJCIUS DM. Gut barrier disruption and chronic disease[J]. Trends in Endocrinology and Metabolism: TEM, 2022, 33(4): 247-265.

[10] KOBOZIEV I, WEBB CR, FURR KL, GRISHAM MB. Role of the enteric microbiota in intestinal homeostasis and inflammation[J]. Free Radical Biology & Medicine, 2014, 68: 122-133.

[11] BRODY H. The gut microbiome[J]. Nature, 2020, 577(7792): S5.

[12] CHEN SS, ZHANG C, HE BH, HE RN, XU L, ZHANG S. The role of lncRNAs in regulating the intestinal mucosal mechanical barrier[J]. BioMed Research International, 2021, 2021: 2294942.

[13] ZHENG L, DUAN SL. Molecular regulation mechanism of intestinal stem cells in mucosal injury and repair in ulcerative colitis[J]. World Journal of Gastroenterology, 2023, 29(16): 2380-2396.

[14] ZHAO XJ, ZENG HL, LEI L, TONG XL, YANG L, YANG Y, LI S, ZHOU Y, LUO LP, HUANG JH, XIAO R, CHEN J, ZENG QH. Tight junctions and their regulation by non-coding RNAs[J]. International Journal of Biological Sciences, 2021, 17(3): 712-727.

[15] SALVO-ROMERO E, ALONSO-COTONER C, PARDO-CAMACHO C, CASADO-BEDMAR M, VICARIO M. The intestinal barrier function and its involvement in digestive disease[J]. Revista Espanola De Enfermedades Digestivas, 2015, 107(11): 686-696.

[16] RÜBSAM M, BROUSSARD JA, WICKSTRÖM SA, NEKRASOVA O, GREEN KJ, NIESSEN CM. Adherens junctions and desmosomes coordinate mechanics and signaling to orchestrate tissue morphogenesis and function: an evolutionary perspective[J]. Cold Spring Harbor Perspectives in Biology, 2018, 10(11): a029207.

[17] TAN Y, GUAN YD, SUN Y, ZHENG CQ. Correlation of intestinal mucosal healing and tight junction protein expression in ulcerative colitis patients[J]. The American Journal of the Medical Sciences, 2019, 357(3): 195-204.

[18] LI YY, WANG XJ, SU YL, WANG Q, HUANG SW, PAN ZF, CHEN YP, LIANG JJ, ZHANG ML, XIE XQ, WU ZY, CHEN JY, ZHOU L, LUO X. Baicalein ameliorates ulcerative colitis by improving intestinal epithelial barrier via AhR/IL-22 pathway in ILC3s[J]. Acta Pharmacologica Sinica, 2022, 43: 1495-1507.

[19] CHEN HP, QIAN YF, JIANG CS, TANG LL, YU JW, ZHANG LD, DAI YY, JIANG GJ. Butyrate ameliorated ferroptosis in ulcerative colitis through modulating Nrf2/GPX4 signal pathway and improving intestinal barrier[J]. Biochimica et Biophysica Acta Molecular Basis of Disease, 2024, 1870(2): 166984.

[20] PELASEYED T, BERGSTRÖM JH, GUSTAFSSON JK, ERMUND A, BIRCHENOUGH GMH, SCHÜTTE A, van der POST S, SVENSSON F, RODRÍGUEZ-PIÑEIRO AM, NYSTRÖM EEL, WISING C, JOHANSSON MEV, HANSSON GC. The mucus and mucins of the goblet cells and enterocytes provide the first defense line of the gastrointestinal tract and interact with the immune system[J]. Immunological Reviews, 2014, 260(1): 8-20.

[21] PAONE P, CANI PD. Mucus barrier, mucins and gut microbiota: the expected slimy partners?[J]. Gut, 2020, 69(12): 2232-2243.

[22] van der POST S, JABBAR KS, BIRCHENOUGH G, ARIKE L, AKHTAR N, SJOVALL H, JOHANSSON MEV, HANSSON GC. Structural weakening of the

colonic mucus barrier is an early event in ulcerative colitis pathogenesis[J]. Gut, 2019, 68(12): 2142-2151.

[23] van der SLUIS M, de KONING BAE, de BRUIJN ACJM, VELCICH A, MEIJERINK JPP, van GOUDOEVER JB, BÜLLER HA, DEKKER J, van SEUNINGEN I, RENES IB, EINERHAND AWC. Muc2-deficient mice spontaneously develop colitis, indicating that MUC_2 is critical for colonic protection[J]. Gastroenterology, 2006, 131(1): 117-129.

[24] SÜNDERHAUF A, HICKEN M, SCHLICHTING H, SKIBBE K, RAGAB M, RASCHDORF A, HIROSE M, SCHÄFFLER H, BOKEMEYER A, BETTENWORTH D, SAVITT AG, PERNER S, IBRAHIM S, PEERSCHKE EI, GHEBREHIWET B, DERER S, SINA C. Loss of mucosal p32/gC1qR/HABP1 triggers energy deficiency and impairs goblet cell differentiation in ulcerative colitis[J]. Cellular and Molecular Gastroenterology and Hepatology, 2021, 12(1): 229-250.

[25] ZHANG BW, ZHAO CY, ZHANG XJ, LI X, ZHANG YH, LIU XX, YIN J, LI XY, WANG J, WANG S. An elemental diet enriched in amino acids alters the gut microbial community and prevents colonic mucus degradation in mice with colitis[J]. mSystems, 2022, 7(6): e0088322.

[26] GUBATAN J, HOLMAN DR, PUNTASECCA CJ, POLEVOI D, RUBIN SJ, ROGALLA S. Antimicrobial peptides and the gut microbiome in inflammatory bowel disease[J]. World Journal of Gastroenterology, 2021, 27(43): 7402-7422.

[27] KOENINGER L, ARMBRUSTER NS, BRINCH KS, KJAERULF S, ANDERSEN B, LANGNAU C, AUTENRIETH SE, SCHNEIDAWIND D, STANGE EF, MALEK NP, NORDKILD P, JENSEN BAH, WEHKAMP J. Human β-defensin 2 mediated immune modulation as treatment for experimental colitis[J]. Frontiers in Immunology, 2020, 11: 93.

[28] QUIROZ-OLGUÍN G, GUTIÉRREZ-SALMEÁN G, POSADAS-CALLEJA JG, PADILLA-RUBIO MF, SERRALDE-ZÚÑIGA AE. The effect of enteral stimulation on the immune response of the intestinal mucosa and its application in nutritional support[J]. European Journal of Clinical Nutrition, 2021, 75: 1533-1539.

[29] MÖRBE UM, JØRGENSEN PB, FENTON TM, von BURG N, RIIS LB, SPENCER J, AGACE WW. Human gut-associated lymphoid tissues (GALT); diversity, structure, and function[J]. Mucosal Immunology, 2021, 14: 793-802.

[30] LI Y, JIN L, CHEN TX. The effects of secretory IgA in the mucosal immune system[J]. BioMed Research International, 2020, 2020: 2032057.

[31] HIYAMA S, IIJIMA H, KAWAI S, MUKAI A, SHIRAISHI E, IWATANI S, YAMAGUCHI T, ARAKI M, HAYASHI Y, SHINZAKI S, MIZUSHIMA T, TSUJII M, TAKEHARA T. Narrow-band imaging with magnifying endoscopy for Peyer's patches is useful in predicting the recurrence of remissive patients with ulcerative colitis[J]. Intestinal Research, 2016, 14(4): 314-321.

[32] OHNO H. Intestinal M cells[J]. The Journal of Biochemistry, 2016, 159(2): 151-160.

[33] ROUND JL, MAZMANIAN SK. The gut microbiota shapes intestinal immune responses during health and disease[J]. Nature Reviews Immunology, 2009, 9: 313-323.

[34] SCHOULTZ I, KEITA ÅV. Cellular and molecular therapeutic targets in inflammatory bowel disease-focusing on intestinal barrier function[J]. Cells, 2019, 8(2): 193.

[35] NAKASE H, SATO N, MIZUNO N, IKAWA Y. The influence of cytokines on the complex pathology of ulcerative colitis[J]. Autoimmunity Reviews, 2022, 21(3): 103017.

[36] PUGLIESE D, PRIVITERA G, FIORANI M, PARISIO L, CALVEZ V, PAPA A, GASBARRINI A, ARMUZZI A. Targeting IL12/23 in ulcerative colitis: update on the role of ustekinumab[J]. Therapeutic Advances in Gastroenterology, 2022, 15: 17562848221102283.

[37] LI ZC, LIN ML, LI YD, SHAO J, HUANG RT, QIU YY, LIU Y, CHEN L. Total flavonoids of *Sophora flavescens* and kurarinone ameliorated ulcerative colitis by regulating Th17/Treg cell homeostasis[J]. Journal of Ethnopharmacology, 2022, 297: 115500.

[38] GOMAA EZ. Human gut microbiota/microbiome in health and diseases: a review[J]. Antonie Van Leeuwenhoek, 2020, 113(12): 2019-2040.

[39] ADAK A, KHAN MR. An insight into gut microbiota and its functionalities[J]. Cellular and Molecular Life Sciences, 2019, 76(3): 473-493.

[40] ALMEIDA A, NAYFACH S, BOLAND M, STROZZI F, BERACOCHEA M, SHI ZJ, POLLARD KS, SAKHAROVA E, PARKS DH, HUGENHOLTZ P, SEGATA N, KYRPIDES NC, FINN RD. A unified catalog of 204, 938 reference genomes from the human gut microbiome[J]. Nature Biotechnology, 2021, 39(1): 105-114.

[41] HORNEF M. Pathogens, commensal symbionts, and pathobionts: discovery and functional effects on the host[J]. ILAR Journal, 2015, 56(2): 159-162.

[42] MA LY, SHEN QC, LYU WT, LV L, WANG W, YU MJ, YANG H, TAO SY, XIAO YP. *Clostridium butyricum* and its derived extracellular vesicles modulate gut homeostasis and ameliorate acute experimental colitis[J]. Microbiology Spectrum, 2022, 10(4): e0136822.

[43] LIANG LP, LIU L, ZHOU WY, YANG CH, MAI GH, LI HL, CHEN Y. Gut microbiota-derived butyrate regulates gut mucus barrier repair by activating the macrophage/WNT/ERK signaling pathway[J]. Clinical Science, 2022, 136(4): 291-307.

[44] ZUO WX, WANG BB, BAI X, LUAN YH, FAN YY, MICHAIL S, SUN FZ. 16S rRNA and metagenomic shotgun sequencing data revealed consistent patterns of gut microbiome signature in pediatric ulcerative colitis[J]. Scientific Reports, 2022, 12: 6421.

[45] SHAM HP, BAZETT M, BOSILJCIC M, YANG H, LUK B, LAW HT, MORAMPUDI V, YU HB, PANKOVICH J, SUTCLIFFE S, BRESSLER B, MARSHALL JK, FEDORAK RN, CHEN J, JONES M, GUNN H, KALYAN S, VALLANCE BA. Immune stimulation using a gut microbe-based immunotherapy reduces disease pathology and improves barrier function in ulcerative colitis[J]. Frontiers in Immunology, 2018, 9: 2211.

[46] YOO JY, GROER M, DUTRA SVO, SARKAR A, McSKIMMING DI. Gut microbiota and immune system interactions[J]. Microorganisms, 2020, 8(10): 1587.

[47] VINDEROLA G, SANDERS ME, SALMINEN S. The concept of postbiotics[J]. Foods, 2022, 11(8): 1077.

[48] YANG YF, WANG Y, ZHAO L, WANG F, LI MX, WANG Q, LUO HM, ZHAO QY, ZENG JP, ZHAO YS, DU FK, CHEN Y, SHEN J, WEI SL, XIAO ZG, WU X. Chinese herbal medicines for treating ulcerative colitis via regulating gut microbiota-intestinal immunity axis[J]. Chinese Herbal Medicines, 2023, 15(2): 181-200.

[49] GUARINO MPL, ALTOMARE A, EMERENZIANI S, Di ROSA C, RIBOLSI M, BALESTRIERI P, IOVINO P, ROCCHI G, CICALA M. Mechanisms of action of prebiotics and their effects on gastro-intestinal disorders in adults[J]. Nutrients, 2020, 12(4): 1037.

[50] VALCHEVA R, KOLEVA P, MARTÍNEZ I, WALTER J, GÄNZLE MG, DIELEMAN LA. Inulin-type fructans improve active ulcerative colitis associated with microbiota changes and increased short-chain fatty acids levels[J]. Gut Microbes, 2019, 10(3): 334-357.

[51] HE NN, WANG YY, ZHOU ZH, LIU N, JUNG S, LEE MS, LI SY. Preventive and prebiotic effect of α-galacto-oligosaccharide against dextran sodium sulfate-induced colitis and gut microbiota dysbiosis in mice[J]. Journal of Agricultural and Food Chemistry, 2021, 69(33): 9597-9607.

[52] NYMAN M, NGUYEN TD, WIKMAN O, HJORTSWANG H, HALLERT C. Oat bran increased fecal butyrate and prevented gastrointestinal symptoms in patients with quiescent ulcerative colitis: randomized controlled trial[J]. Crohn's & Colitis 360, 2020, 2(1): otaa005.

[53] SHEN ZH, ZHU CX, QUAN YS, YANG ZY, WU S, LUO WW, TAN B, WANG XY. Relationship between intestinal microbiota and ulcerative colitis: mechanisms and clinical application of probiotics and fecal microbiota transplantation[J]. World Journal of Gastroenterology, 2018, 24(1): 5-14.

[54] KHAN I, WEI JS, LI AP, LIU ZR, YANG PR, JING YP, CHEN XJ, ZHAO T, BAI YR, ZHA LJ, LI CH, ULLAH N, CHE TJ, ZHANG CJ. *Lactobacillus plantarum* strains attenuated DSS-induced colitis in mice by modulating the gut microbiota and immune response[J]. International Microbiology, 2022, 25(3): 587-603.

[55] HU YJ, JIN XL, GAO F, LIN T, ZHU H, HOU X, YIN Y, KAN SD, CHEN DJ. Selenium-enriched *Bifidobacterium longum* DD98 effectively ameliorates dextran sulfate sodium-induced ulcerative colitis in mice[J]. Frontiers in Microbiology, 2022, 13: 955112.

[56] KAUR L, GORDON M, BAINES PA, IHEOZOR-EJIOFOR Z, SINOPOULOU V, AKOBENG AK. Probiotics for induction of remission in ulcerative colitis[J]. The Cochrane Database of Systematic Reviews, 2020, 3(3): CD005573.

[57] RUFINO MN, Da COSTA AL, JORGE EN, PAIANO VF, CAMPAROTO ML, KELLER R, BREMER-NETO H. Synbiotics improve clinical indicators of ulcerative colitis: systematic review with meta-analysis[J]. Nutrition Reviews, 2022, 80(2): 157-164.

[58] SWANSON KS, GIBSON GR, HUTKINS R, REIMER RA, REID G, VERBEKE K, SCOTT KP, HOLSCHER HD, AZAD MB, DELZENNE NM, SANDERS ME. The international scientific association for probiotics and prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics[J]. Nature Reviews

Gastroenterology & Hepatology, 2020, 17: 687-701.
[59] NGUYEN TT, NGUYEN PT, PHAM MN, RAZAFINDRALAMBO H, HOANG QK, NGUYEN HT. Synbiotics: a new route of self-production and applications to human and animal health[J]. Probiotics and Antimicrobial Proteins, 2022, 14(5): 980-993.
[60] LIU ZZ, JIANG ZY, ZHANG ZT, LIU T, FAN YR, LIU T, PENG N. *Bacillus coagulans* in combination with chitooligosaccharides regulates gut microbiota and ameliorates the DSS-induced colitis in mice[J]. Microbiology Spectrum, 2022, 10(4): e0064122.
[61] KAMARLı ALTUN H, AKAL YıLDıZ E, AKıN M. Effects of synbiotic therapy in mild-to-moderately active ulcerative colitis: a randomized placebo-controlled study[J]. The Turkish Journal of Gastroenterology, 2019, 30(4): 313-320.
[62] SALMINEN S, COLLADO MC, ENDO A, HILL C, LEBEER S, QUIGLEY EMM, SANDERS ME, SHAMIR R, SWANN JR, SZAJEWSKA H, VINDEROLA G. The International Scientific Association of Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of postbiotics[J]. Nature Reviews Gastroenterology & Hepatology, 2021, 18: 649-667.
[63] CHEN QY, FAN YY, ZHANG BZ, YAN CS, ZHANG Q, KE YH, CHEN ZR, WANG L, SHI HX, HU YQ, HUANG QW, SU JL, XIE CX, ZHANG X, ZHOU LX, REN JL, XU HZ. Capsulized fecal microbiota transplantation induces remission in patients with ulcerative colitis by gut microbial colonization and metabolite regulation[J]. Microbiology Spectrum, 2023, 11(3): e0415222.
[64] ZHANG LH, LIU JX, JIN T, QIN NB, REN XM, XIA XD. Live and pasteurized *Akkermansia muciniphila* attenuate hyperuricemia in mice through modulating uric acid metabolism, inflammation, and gut microbiota[J]. Food & Function, 2022, 13(23): 12412-12425.
[65] WU YP, WANG Y, HU AX, SHU X, HUANG WX, LIU JS, WANG BK, ZHANG RQ, YUE M, YANG CM. *Lactobacillus plantarum*-derived postbiotics prevent *Salmonella*-induced neurological dysfunctions by modulating gut-brain axis in mice[J]. Frontiers in Nutrition, 2022, 9: 946096.
[66] ŠTOFILOVÁ J, KVAKOVÁ M, KAMLÁROVÁ A, HIJOVÁ E, BERTKOVÁ I, GUĽAŠOVÁ Z. Probiotic-based intervention in the treatment of ulcerative colitis: conventional and new approaches[J]. Biomedicines, 2022, 10(9): 2236.
[67] CHEN HT, HUANG HL, XU HM, LUO QL, HE J, LI YQ, ZHOU YL, NIE YQ, ZHOU YJ. Fecal microbiota transplantation ameliorates active ulcerative colitis[J]. Experimental and Therapeutic Medicine, 2020, 19(4): 2650-2660.
[68] 张发明. 粪菌移植: 1700年的医学史及其临床应用[J]. 湖北民族学院学报(医学版), 2012, 29(3): 1-4.
ZHANG FM. Fecal bacteria transplantation: 1700 years of medical history and its clinical application[J]. Journal of Hubei University Minzu University (Medical Edition), 2012, 29(3): 1-4 (in Chinese).
[69] HUANG CL, HUANG ZH, DING L, FU Y, FAN JJ, MEI QX, LOU LH, WANG JJ, YIN NM, LU YY, GUO SW, ZENG Y. Fecal microbiota transplantation versus glucocorticoids for the induction of remission in mild to moderate ulcerative colitis[J]. Journal of Translational Medicine, 2022, 20(1): 354.
[70] WANG WH, LU GC, WU X, WEN Q, ZHANG FM. Colonic transendoscopic enteral tubing is a new pathway to microbial therapy, colonic drainage, and host-microbiota interaction research[J]. Journal of Clinical Medicine, 2023, 12(3): 780.
[71] WEN X, WANG HG, ZHANG MN, ZHANG MH, WANG H, YANG XZ. Fecal microbiota transplantation ameliorates experimental colitis *via* gut microbiota and T-cell modulation[J]. World Journal of Gastroenterology, 2021, 27(21): 2834-2849.
[72] LEDDER O. Antibiotics in inflammatory bowel diseases: do we know what we're doing?[J]. Translational Pediatrics, 2019, 8(1): 42-55.
[73] NISHIKAWA Y, SATO N, TSUKINAGA S, UCHIYAMA K, KOIDO S, ISHIKAWA D, OHKUSA T. Long-term outcomes of antibiotic combination therapy for ulcerative colitis[J]. Therapeutic Advances in Chronic Disease, 2021, 12: 20406223211028790.
[74] ISHIKAWA D, SASAKI T, TAKAHASHI M, KUWAHARA-ARAI K, HAGA K, ITO S, OKAHARA K, NAKAJIMA A, SHIBUYA T, OSADA T, HIRAMATSU K, WATANABE S, NAGAHARA A. The microbial composition of *Bacteroidetes* species in ulcerative colitis is effectively improved by combination therapy with fecal microbiota transplantation and antibiotics[J]. Inflammatory Bowel Diseases, 2018, 24(12): 2590-2598.
[75] BRETON J, KASTL A, HOFFMANN N, ROGERS R, GROSSMAN AB, MAMULA P, KELSEN JR, BALDASSANO RN, ALBENBERG L. Efficacy of

combination antibiotic therapy for refractory pediatric inflammatory bowel disease[J]. Inflammatory Bowel Diseases, 2019, 25(9): 1586-1593.

[76] KUMARI R, YADAV Y, MISRA R, DAS U, DAS ADHIKARI U, MALAKAR P, DUBEY GP. Emerging frontiers of antibiotics use and their impacts on the human gut microbiome[J]. Microbiological Research, 2022, 263: 127127.

[77] LIU Y, LI BG, SU YH, ZHAO RX, SONG P, LI H, CUI XH, GAO HM, ZHAI RX, FU XJ, REN X. Potential activity of Traditional Chinese Medicine against Ulcerative colitis: a review[J]. Journal of Ethnopharmacology, 2022, 289: 115084.

[78] GUO MZ, DING S, ZHAO CH, GU XX, HE XY, HUANG KL, LUO YB, LIANG ZH, TIAN HT, XU WT. *Red Ginseng* and *Semen Coicis* can improve the structure of gut microbiota and relieve the symptoms of ulcerative colitis[J]. Journal of Ethnopharmacology, 2015, 162: 7-13.

[79] LI MX, LI MY, LEI JX, WU YZ, LI ZH, CHEN LM, ZHOU CL, SU JY, HUANG GX, HUANG XQ, ZHENG XB. Huangqin decoction ameliorates DSS-induced ulcerative colitis: role of gut microbiota and amino acid metabolism, mTOR pathway and intestinal epithelial barrire[J]. Phytomedicine: International Journal of Phytotherapy and Phytopharmacology, 2022, 100: 154052.

[80] ZHENG JH, LI H, ZHANG P, YUE SJ, ZHAI BT, ZOU JB, CHENG JX, ZHAO CB, GUO DY, WANG J. Paeonol ameliorates ulcerative colitis in mice by modulating the gut microbiota and metabolites[J]. Metabolites, 2022, 12(10): 956.

[81] 李云从, 刘星星. 白头翁汤治疗溃疡性结肠炎的作用机制研究进展[J]. 华中科技大学学报(医学版), 2022, 51(2): 267-271.
LI YC, LIU XX. Research progress on the mechanism of *Pulsatilla* decoction in the treatment of ulcerative colitis[J]. Acta Medicinae Universitatis Scientiae et Technologiae Huazhong, 2022, 51(2): 267-271 (in Chinese).

[82] MIAO ZW, CHEN LP, FENG H, GU MJ, YAN J, XU Y, YE B. Baitouweng decoction ameliorates ulcerative colitis in mice partially attributed to regulating Th17/Treg balance and restoring intestinal epithelial barrier[J]. Frontiers in Pharmacology, 2021, 11: 531117.

[83] KOU FS, SHI L, LI JX, WANG ZB, SHI R, MAO TY, KE X, ZHANG BP, YANG XJ, WEN XL, ZHENG WY, HAN X, DING PH, DONG J. Clinical evaluation of traditional Chinese medicine on mild active ulcerative colitis: a multi-center, randomized, double-blind, controlled trial[J]. Medicine, 2020, 99(35): e21903.