从 COVID-19 与肠道菌群关系探讨中医药治疗的潜在作用机制*

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摘　要:新型冠状病毒肺炎(COVID-19)仍肆虐全球,尚未研发出针对 COVID-19 的特效药。疫情伊始,我国对 COVID-19 患者积极采用中医药疗法,效果显著。大量临床证据表明,COVID-19 患者普遍存在肠道菌群失调症,且与不良预后相关,而对肠道菌群进行有效干预可以一定程度上改善其临床症状。中医药(如金花清感颗粒、连花清瘟颗粒(胶囊)、血必净注射液、清肺排毒汤、麻杏石甘汤)治疗 COVID-19 已被临床实践证明是安全有效的,而组方中共有的中药如甘草、金银花、黄芩、黄芪等对肠道菌群、免疫系统和血管紧张素转化酶 2 均有一定的调节作用。更重要的是,清肺排毒汤、麻杏石甘汤和血必净注射液已被证实可以调节肠道菌群。据此,我们提出肠道菌群可能是中医药防治 COVID-19 及其并发症的重要“靶点”。

关键词:COVID-19;SARS-CoV-2;中医药;肠道菌群;血管紧张素转化酶 2
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Potential Mechanism of Chinese Medicine Treatment from Relationship Between COVID-19 and Intestinal flora

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Abstract: COVID-19 is still rampant around the world, and no specific drug has been developed for it. At the beginning of the epidemic, China actively adopted Chinese medicine treatment for COVID-19 patients, with remarkable results. A large amount of clinical evidence shows that COVID-19 patients generally have intestinal flora disorder, which is related to poor prognosis, and effective intervention of intestinal flora can improve their clinical symptoms to a certain extent. Traditional Chinese medicine (such as Jinhua Qinggan Granule, Lianhua Qingwen Granule (capsule), Xuebijing Injection, Qingfei Detox Decoction, Maxing Shigan Decoction) has been proved to be safe and effective in the treatment of COVID-19 by clinical practice, while the traditional Chinese medicine commonly used in the formula, such as Licorice, Honeysuckle, Scutellaria baicalensis, and Astragalus membranaceus, have certain regulatory effects on intestinal flora, immune system and angiotensin converting enzyme 2. More importantly, Qingfei Jiedu Decoction, Maxing Shigan Decoction and Xuebijing Injection have been proved to regulate intestinal flora. It is suggested that intestinal flora may be an important “target” for the prevention and treatment of COVID-19 and its complications by traditional Chinese medicine.

Key words: COVID-19; SARS-CoV-2; Traditional Chinese medicine; Intestinal flora; Angiotensin converting enzyme 2

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新型冠状病毒肺炎(coronavirus disease 2019,COVID-19)是由新型冠状病毒(SARS-CoV-2)引起的严重呼吸道疾病,于 2019 年 12 月爆发并迅速蔓延全球。由于所有人对 COVID-19 易感,且 SARS-CoV-2 在人群中隐匿传播,人类的生命健康受到严重威胁[1]。据统计,全球累计确诊 COVID-19 人数超 5.30 亿,死亡超 630 万例[2]。除疫苗外,尚未发现 COVID-19 的特效药物,而已报道有一定临床疗效的药物主要包括抗病毒类药物(瑞德西韦、洛匹那韦/利托那韦、法匹拉韦)、康复期患者血浆、血管紧张素转换酶 2(ACE2)阻断剂等,但效果不尽如人意,甚至存在争议[3]。中国政府高度重视此次疫情,在防治 COVID-19 的过程中,强调中医与西医并重,中西医结合治疗 COVID-19 取得了较显著的临床总体疗效[4-9]。然而,中医药防治 COVID-19 的基础研究严重滞后于临床实践,潜在作用机制亟待阐明。

肠道中共生的菌群是宿主生态系统的有机组成部分,在维持宿主的稳态和健康方面起着重要作用[10]。大量研究证实,肠道症状是 COVID-19 的主要肺外症状之一,且粪口途径是 SARS-CoV-2 感染的潜在途径。近半数 COVID-19 确诊患者的粪便样本中检测出病毒核酸[11]。同时,COVID-19 患者的肠道菌群紊乱程度与病情严重程度之间呈现高度的相关性[12-13]。然而,目前尚无确切研究报道肠道菌群参与中医药防治 COVID-19 的效应过程。因此,我们在综述有关 COVID-19、肠道菌群、中医药治疗 COVID-19 的文献基础上,提出肠道菌群可能是中医药防治 COVID-19 及其并发症的重要“靶点”。

1 COVID-19 与肠道菌群的关系

肠道菌群由细菌、真菌、病毒和古生菌等组成[10],参与宿主代谢、调节全身免疫、维持胃肠道稳态,与宿主的健康和疾病有关[14]。在病毒感染过程中,病毒与细菌会相互影响[15]。例如,呼吸道流感病毒感染会改变肺和肠道微生物的组成[16-17]。一系列临床研究表明,COVID-19 患者的肠道菌群组成发生显著变化,肠道菌群多样性降低,占主导地位的是病原菌和条件致病菌(包括哈氏梭菌、*Bacteroides nordii* 和粘放线菌),而产生抗炎物质的普拉梭菌(*Faecalibacterium prausnitzii*)丰度与疾病严重程度呈负相关。在 SARS-CoV-2 清除和呼吸道症状缓解后,肠道菌群失调情况仍然持续存在[12]。对不同 COVID-19 患者的粪便样本进一步区分可以发现,具有高 SARS-CoV-2 传染性特征的样本含有更多的条件致病菌,如产气柯林斯菌(*Collinsella aerofaciens*)、*Collinsella tanakaei*、婴儿链球菌(*Streptococcus infantis*)和摩氏摩根菌(*Morganella morganii*),且核苷酸和氨基酸的生物合成以及碳水化合物代谢的功能增强,而在低 SARS-CoV-2 传染性特征的样品中,短链脂肪酸生成菌的丰度较高,如屎拟杆菌(*Parabacteroides merdae*)、粪便拟杆菌(*Bacteroides stercoris*)、*Alistipes onderdonkii* 和 *Lachnospiraceae bacterium* 1_1_57*FAA*[18]。此外,直肠拭子的高通量测序结果表明,与正常人相比,重症监护室中 COVID-19 患者肠道菌群丰度和螺旋体(*Spirochetes*)数量均下降[19]。Yeoh 等[20]研究发现,肠道菌群可能通过调节宿主免疫反应影响 COVID-19 患者的严重程度,即炎症因子(白细胞介素-10,肿瘤坏死因子-α)、趋化因子(C-X-C 基元配体 10)、组织损伤血液标志物(天冬氨酸转氨酶)随着患者粪便中拟杆菌门的增加而增加。李兰娟院士团队利用 8 种口腔菌群和 7 种粪便菌群对不同区域的人群中感染 COVID-19 的诊断效能高达 87.24%,并且成功将 IgG 阳性的疑似患者诊断为确诊患者,诊断效能达 92.11%[21]。该团队重点研究 COVID-19 患者的 10 种主要肠道优势菌的丰度变化,证实这些肠道微生物的变化与疾病严重程度和血液学指标有关。譬如产丁酸的细菌,如普拉梭菌、酪酸梭菌(*Clostridium butyricum*)、柔嫩梭菌(*Clostridium leptum*)和直肠真杆菌(*Eubacterium rectale*)的丰度显著降低,可用于区分危重型与普通型和重型患者。而常见的条件致病菌如肠球菌(*Enterococcus*,Ec)和肠杆菌科细菌(*Enterobacteriaceae*,E)的丰度在患者粪便中增加,尤其对于预后较差的危重型患者,提示 Ec/E 值可用于预测危重型患者预后情况[22]。此外,该团队对 30 名 COVID-19 患者的肠道菌群丰富度进行纵向分析(即急性期、恢复期、出院后半年),发现患者在该 3 个节点的肠道菌群丰富度(Chao 1 指数)均显著低于健康对照组,且随着病情好转及痊愈,肠道菌群丰度逐渐呈现非

显著的增加,而痊愈后较低的肠道菌群丰度与急性期的 C-反应蛋白水平升高、重症监护室治疗、高流量经鼻导管氧疗及恢复期的肺功能降低等密切相关[23]。类似的报道,如:香港中文大学科研团队发现,与健康对照组相比,COVID-19 患者肠道菌群显著改变,导致产短链脂肪酸和 L-异亮氨酸合成能力受损且持续至痊愈后,而痊愈后粪便中短链脂肪酸和 L-异亮氨酸的降低程度与疾病严重程度和机体炎症因子水平负相关[24]。同样,儿童在 SARS-CoV-2 感染后的 2 个月内肠道菌群持续失衡且极具波动,在康复出院后的 2 ~ 3 w 依然存在[25]。因此,肠道菌群在 SARS-CoV-2 感染期间的纵向动力学研究将会有助于开发基于肠道菌群的治疗方法,减轻胃肠后遗症,更便于预测患者的预后。

除肠道中的细菌外,COVID-19 患者入院时粪便中的真菌也发生显著变化,主要表现为白色念珠菌的富集,且在住院期间,患者肠道中条件致病真菌如白色念珠菌、耳念珠菌及黄曲霉菌的比例显著升高[13]。与此同时,COVID-19 重症患者的真菌感染率明显高于轻症患者,主要特征是曲霉属和青霉菌属等真菌的丰度减少[26]。基础研究发现,未接种疫苗的小鼠感染 SARS-CoV-2 后,肠道内同时发生病毒变化和细菌紊乱,且肠上皮中免疫/感染相关基因表达也发生变化[27]。香港中文大学黄秀娟团队发现,与非感染者相比,COVID-19 患者粪便中 RNA、DNA 病毒丰度较低,与疾病严重程度呈负相关,且在治愈 30 d 后持续存在该现象。值得一提的是,COVID-19 患者的病毒组具有更强的应激、炎症和毒力相关基因编码能力,且病毒丰度与血液中促炎蛋白、白细胞和中性粒细胞水平呈负相关,提示肠道病毒组在 COVID-19 治疗中的重要性[28]。

综上所述,COVID-19 患者的肠道菌群组成发生了显著变化,主要特征是肠道菌群多样性降低、有益菌减少、条件致病菌富集和病毒丰度降低,同时肠道菌群的代谢物发生相应变化,进而影响体内代谢与免疫调节。因此,调节肠道菌群组成和功能并抑制肠道中 SARS-CoV-2 活性可能是治疗 COVID-19 的有效策略。

2 ACE2 与肠道菌群的关系

ACE2 广泛分布于肺、胃、肠、心脏和肾脏组织,是肾素-血管紧张素系统的重要组成部分[29-31]。SARS-CoV-2 可与肺泡和小肠的上皮细胞上的 ACE2 结合,改变肠道菌群,增强全身炎症反应,引起患者肺部感染[17,32-33]。有研究表明,阻断 ACE2 可间接减少抗菌肽的分泌,从而改变肠道菌群组成[34]。近期研究发现,肠道菌群可以下调小鼠肠道 ACE2 的表达,如 *Bacteroides dorei*、多形拟杆菌(*Bacteroides thetaiotaomicron*)、*Bacteroides massiliensis* 和卵形拟杆菌(*Bacteroides ovatus*)[12]。Peng 等[35]研究证明,拟杆菌产生的鞘脂可以抑制 SARS-CoV-2 刺突蛋白与 ACE2 的结合,减少病毒进入宿主细胞。同时,消化链球菌属(*Peptostreptococcus*)、梭杆菌属(*Fusobacterium*)和柠檬酸杆菌属(*Citrobacter*)可减少 SARS-CoV-2 诱导的肠道炎症因子白介素-18 的产生[36]。无菌大鼠实验进一步证明,肠道菌群可以调节结肠 ACE2 表达从而影响 SARS-CoV-2 的传染性[32]。因此,在 SARS-CoV-2 致病过程中,肠道 ACE2 与菌群互相作用,进而影响 COVID-19 患者的免疫系统和炎症水平。

3 干预肠道菌群是 COVID-19 的有效治疗手段

临床研究证实,肠道菌群紊乱的 COVID-19 患者往往具有侵袭性临床病程,包括急性呼吸窘迫综合征,肝损伤,高烧和休克[37]。在疫情爆发之初,肠道微生态调节剂已作为治疗方案被国家卫生健康委与国家中医药管理局联合发布的《新型冠状病毒肺炎诊疗方案(试行第六版)》推荐,即维持肠道微生态平衡,预防继发细菌感染[38]。

除常规西药治疗外,一种特殊的细菌制剂(嗜热链球菌 DSM32345、嗜酸乳杆菌 DSM32241、瑞士乳杆菌 DSM32242、副干酪乳杆菌 DSM32243、植物乳杆菌 DSM32244、短乳杆菌 DSM27961、乳双歧杆菌 DSM32246 和 DSM32247)可以显著改善 COVID-19 患者的临床症状,提示肠-肺轴在控制 SARS-CoV-2 中的重要性[39]。此外,一项随机对照非盲试验证实 COVID-19 患者补充益生菌(联用鼠李糖乳杆菌 PDV1705、两歧双歧杆菌 PDV0903、长双歧杆菌婴儿亚种 PDV1911 和长双歧杆菌长亚种 PDV2301)可显著降低医院内获得性腹泻的风险[40],且粪菌移植术治疗 COVID-19 的临床试验正在进行中[41]。值得一提的是,罗格斯大学的赵立平教授团队开发了一种专注于管理肠道微生物

治疗方法 NBT-NM108，已获得美国食品药品监督管理局的新药临床试验申请批准，正在开展Ⅱa 期临床试验，主要招募 SARS-CoV-2 检测呈阳性或在 7 d 内出现了 COVID-19 样症状的糖尿病前期或糖尿病患者[42]。因此，肠道菌群干预有望成为缓解 COVID-19 患者的临床症状甚至治疗 COVID-19 的有效策略之一。

4 肠道菌群在中医药治疗 COVID-19 中的潜在关系分析

中医基础理论中讲“肺与大肠相表里”，与现代医学的“肠-肺轴”不谋而合。大数据分析发现，抗 COVID-19 的中医药如清肺排毒汤等都具有“健脾祛湿”的作用。在中医理论中，“脾”是消化系统（如脾、胃、肠）的抽象总称，而 COVID-19 的发病机制与脾、胃、肠等多器官的消化系统功能异常相关，进一步凸显了在中医药治疗 COVID-19 的过程中调节肠道功能和保持肠道菌群稳态的重要性[43]。

临床研究发现，肥胖、高血压和糖尿病等基础疾病会加重 COVID-19 患者的临床症状，甚至增加患者的死亡风险[44-47]。同时，SARS-CoV-2 会引起心血管疾病在内的多种并发症[48]，且心血管代谢疾病患者对 SARS-CoV-2 有不同易感性，其背后的潜在机制可能是肠道菌群的组成和功能不同。现有报道证实中医药可以通过调节肠道菌群治疗心血管代谢性疾病[10]，还可以靶向作用于 ACE2，抑制 SARS-CoV-2 活性，调节免疫功能，从而间接影响肠道菌群。譬如，清肺排毒汤主要通过预防细胞因子风暴和靶向 ACE2 受体对抗 COVID-19[49-51]；蒲地蓝消炎口服液、疏风解毒胶囊、透解祛瘟颗粒、清津降火汤和热炎宁合剂在体内对 SARS-CoV-2 均有抑制作用[52-56]；连花清瘟胶囊的活性组分（即大黄酸、连翘苷 A、连翘苷 I、新绿原酸及其异构体）对 ACE2 具有较高的抑制作用[57]，而双黄连口服液中的连翘苷、黄芩苷和黄芩素具有抑制 SARS-CoV-2 活性[58]。

最新基础研究发现，清肺排毒汤的短期干预可以显著影响正常大鼠的肠道菌群组成，即上调 *Romboutsia*、*Turicibacter* 和 *Clostridium_sensu_stricto_1* 的丰度，而下调 *norank_f_Lachnospiraceae* 的丰度[59]。同样，麻杏石甘汤的短期干预也可显著改变正常小鼠的肠道菌群组成，如 *Lachnospiracea-NK4A136-group* 和 *Alistipes* 丰度明显增加，*Prevotellaceae_UCG_001* 的丰度显著降低[60]。血必净注射液可改变中暑模型大鼠的肠道菌群，主要增加拟杆菌门而降低放线菌门丰度[61]，也能升高急性坏死性胰腺炎模型大鼠肠道菌群的丰度和多样性，促进有益菌的增殖，减少内毒素和促炎因子释放，改善肠黏膜屏障功能[62]。此外，麻杏石甘汤可显著改善邪热壅肺证模型小鼠高热、喘促等症状，主要是通过提高肠道菌群多样性，增加副拟杆菌和产短链脂肪酸菌属数量，降低梭菌属、乳酸菌属数量，恢复肠道菌群稳态[63]。该研究提示了肠道菌群在麻杏石甘汤治疗 COVID-19 邪热壅肺证患者中的潜在作用。尤为重要的是，大量临床证据表明，连花清瘟胶囊、疏风解毒胶囊、麻杏石甘汤、宣肺排毒汤能够有效缓解 COVID-19 患者腹泻的症状[64]，预示了中医药在治疗 COVID-19 的过程中对肠道菌群的潜在调节作用。综上，肠道菌群可能是中医药防治 COVID-19 及其并发症的重要“靶点”。

5 结语与展望

COVID-19 仍肆虐全球，虽然接种疫苗已证明可以降低感染率和疾病的严重程度，但疫苗反应的强度和持续时间仍不确定。对于出现症状或需要住院治疗的 COVID-19 患者，仍然迫切需要药物治疗。研究发现，SARS-CoV-2 感染可诱发患者肠道菌群紊乱，显著影响疾病的进程。肠道 ACE2 异常表达也会导致肠道菌群紊乱（如益生菌减少，条件致病菌增多），进而影响 COVID-19 患者的免疫系统。大量研究证实，中医药具有调节肠道菌群的功能。在中医药治疗 COVID-19 患者过程中，肠道菌群可能是除 ACE2 和 SARS-CoV-2 外的重要“靶点”。然而，从 COVID-19 与肠道菌群关系探讨中医药治疗的潜在作用机制存在一些关键的科学问题。首先，动物实验对于中医药作用机制研究是必要的，但目前还没有建立起能够准确模拟人类 SARS-CoV-2 感染的动物模型。其次，中医药对肠道菌群的调节作用与其抗 COVID-19 的效应是否具有因果关系链亟待构建。最后，该假说仍需开展更多基于证据的临床试验来证实，这将对阐明中医药治疗 COVID-19 的安全性和有效性具有

重要意义,也将加快推动中医药现代化、国际化,为全球的 COVID-19 治疗提供可行的方案。

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