2026, 66(7): 3139-3149
CSTR: 32112.14.j.AMS.20250916
DOI: 10.13343/j.cnki.wsxb.20250916

微生物学报
Acta Microbiologica Sinica
http://journals.im.ac.cn/actamicrocn

Review 综述

肠道菌群关键代谢物对阿尔茨海默病进程的研究进展

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ZHENG Jianxing, ZHAO Mengqing, LUO Yunchen, XIAO Tiegang, ZHAO Yueshuang, ZHAO Shuqing, XU Jun, WANG Bing. Research progress in the role of key metabolites of gut microbiota in the progression of Alzheimer's disease[J]. Acta Microbiologica Sinica, 2026, 66(7): 3139-3149.

摘　要：阿尔茨海默病(Alzheimer's disease, AD)是一种以进行性认知障碍为特征的复杂神经退行性疾病。近年来，“肠-脑轴”在AD的发病机制中发挥重要作用，而肠道菌群来源的代谢物是肠脑通信的关键媒介。本文围绕短链脂肪酸(short-chain fatty acids, SCFAs)、胆汁酸(bile acids, BAs)、吲哚类代谢物、三甲胺-*N*-氧化物(trimethylamine *N*-oxide, TMAO)和脂多糖(lipopolysaccharides, LPS)这5类关键代谢物，系统总结其在AD进程中的变化及其分子机制。这不仅为理解AD病理进程提供了新视角，也为开发基于菌群干预的诊断与治疗策略奠定了理论基础。

关键词：阿尔茨海默病；短链脂肪酸；胆汁酸；吲哚类代谢物；三甲胺-*N*-氧化物；脂多糖

资助项目：国家科技重大专项(2023ZD0509300)；国家卫生健康委员会国家中西医协同旗舰科室项目[(2024)221]；上海市“科学与创新行动计划”自然科学基金面上项目(23ZR1448400)；上海市卫生健康委员会中医药科研项目(2024BJ003)；上海市卫生健康委员会重大疑难疾病中西医协作诊疗中心项目(2-1-4)；上海市卫生健康委员会上海市中医药(临床类)重点学科建设项目(shzyyzdxk-202410)
This work was supported by the National Science and Technology Major Project (2023ZD0509300), the National Flagship Department of Integrated Chinese and Western Medicine Collaboration of the National Health Commission [(2024)221], the General Program of the Natural Science Foundation of Shanghai Under the “Science and Innovation Action Plan” (23ZR1448400), the Traditional Chinese Medicine Research Project of the Shanghai Health Commission (2024BJ003), the Integrated Chinese and Western Medicine Diagnosis and Treatment Center Program for Major and Difficult Diseases of the Shanghai Municipal Health Commission (2-1-4), and the Construction Project of Shanghai Key Discipline of Traditional Chinese Medicine (Clinical Category) of the Shanghai Health Commission (shzyyzdxk-202410).
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Received: 2025-12-08; Accepted: 2026-03-17; Published online: 2026-04-02

Research progress in the role of key metabolites of gut microbiota in the progression of Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is a complex neurodegenerative disorder characterized by progressive cognitive impairment. In recent years, the "gut-brain axis" has been recognized to play an important role in the pathogenesis of AD, with the gut microbiota-derived metabolites serving as key mediators of gut-brain communication. This review systematically summarizes the alterations and underlying molecular mechanisms of five classes of key metabolites—short-chain fatty acids, bile acids, indole derivatives, trimethylamine *N*-oxide, and lipopolysaccharides—during the progression of AD. This review not only provides new perspectives for understanding the pathological processes of AD but also lays a theoretical foundation for the development of diagnostic and therapeutic strategies based on microbiota modulation.

Keywords: Alzheimer's disease; short-chain fatty acids; bile acids; indole derivatives; trimethylamine *N*-oxide; lipopolysaccharides

阿尔茨海默病(Alzheimer's disease, AD)是一种复杂的神经退行性疾病，会导致记忆丧失和认知衰退，其患病率随年龄增长而急剧上升。目前，全球约有 4 400 万 AD 患者，预计到 2030 年将达到约 8 200 万，到 2050 年将超过 1.52 亿[1]，给社会带来沉重负担。

近年研究表明，肠道菌群通过"肠-脑轴"在 AD 中发挥重要作用。其中，菌群衍生代谢物，如短链脂肪酸(short-chain fatty acids, SCFAs)、胆汁酸(bile acids, BAs)、吲哚类代谢物、三甲胺-*N*-氧化物(trimethylamine *N*-oxide, TMAO)和脂多糖(lipopolysaccharide, LPS)，不仅具备区分 AD 疾病阶段的潜力，更能通过多种分子机制直接或间接影响 AD 病理，成为影响 AD 的肠道菌群关键代谢物(图 1)。

1 SCFAs

SCFAs 是结肠微生物发酵不可消化碳水化合物(如膳食纤维)产生的代谢物，核心组分包括乙酸、丙酸和丁酸。它们不仅是肠道上皮细胞的重要能量来源(提供约 60%–70% 的能量)，还是连接肠道菌群与宿主生理功能的重要介质[2]。

多项临床研究均表明，SCFAs 代谢紊乱与 AD 进展密切相关。一项横断面观察性研究发现，SCFAs 在 AD 患者与健康人之间存在差异，并且血浆戊酸/丁酸比值和乙酸在区分非 AD 导致认知障碍与 AD 导致认知障碍中表现出高准确性[3]。另一项纳入 77 名受试者的队列研究显示，从健康对照(healthy controls, HC)、遗忘性轻度认知障碍到 AD，7 种 SCFAs (如甲酸、乙酸、丙酸等)水平呈进行性下降[4]。

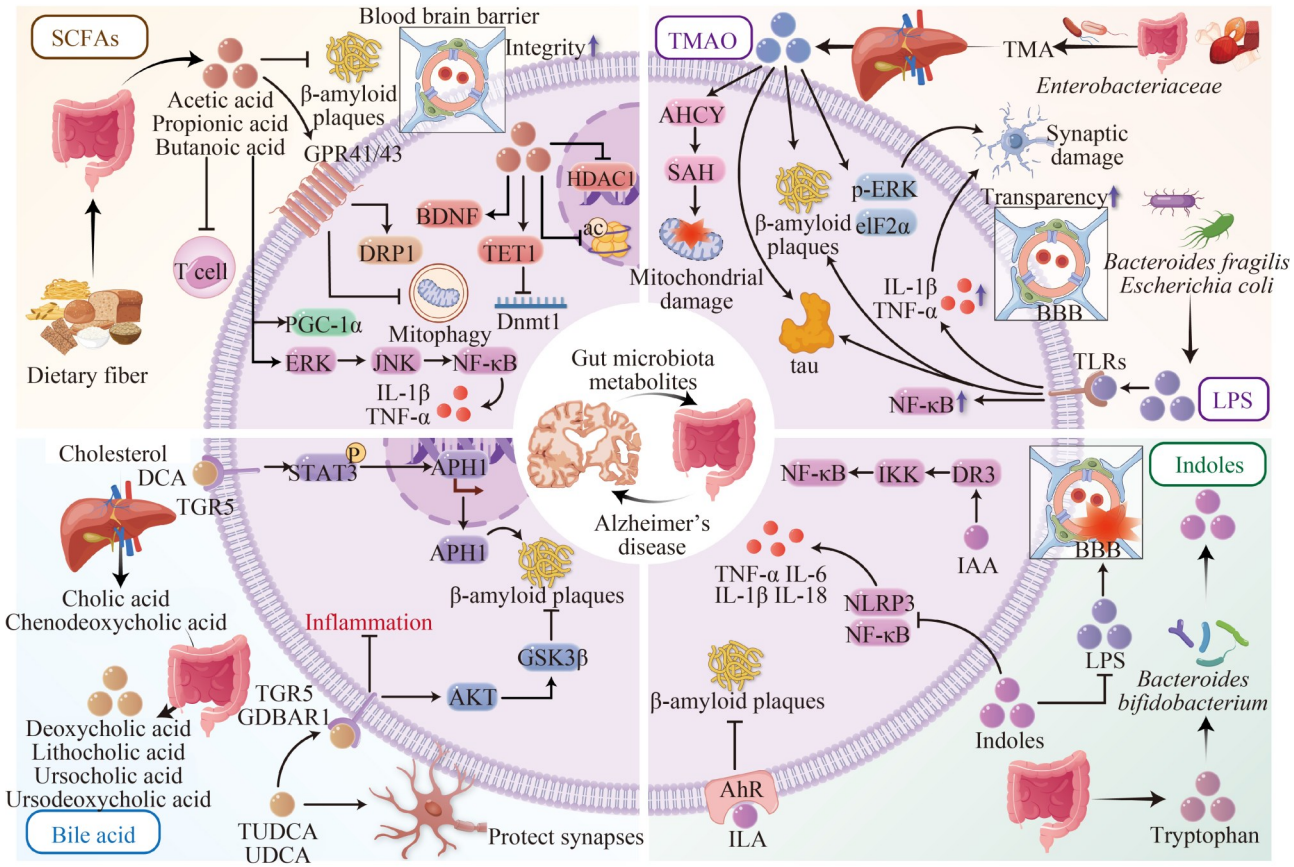

图1 肠道菌群关键代谢物调控阿尔茨海默病的机制示意图

Figure 1 Schematic diagram of the mechanisms underlying the regulation of Alzheimer's disease by key metabolites of gut microbiota (by Adobe illustrator).

1.1 对 β-淀粉样蛋白(amyloid β-protein, Aβ)斑块沉积的影响

SCFAs 对 Aβ 沉积的影响具有双重性。丁酸可以显著降低 5xFAD 小鼠脑内 Aβ 异常沉积水平，并改善认知功能[5]。戊酸可呈剂量依赖性直接抑制 Aβ1-40 与 Aβ1-42 二聚体、三聚体的形成；同时，戊酸还可有效阻碍单体 Aβ1-40 和 Aβ1-42 向 Aβ 纤维的转化过程[6]。无菌 APP/PS1 小鼠与 SPF APP/PS1 小鼠补充混合 SCFAs 后可加重 Aβ 沉积，且 SCFAs 并非直接影响 Aβ 的产生，而是通过重编程小胶质细胞表型(增强其向 Aβ 斑块的募集能力但降低 Aβ 吞噬功能)，上调小胶质细胞来源的载脂蛋白 E (apolipoprotein E, ApoE)及 ApoE-髓系细胞触发受体 2 (triggering receptor expressed on myeloid cells 2, TREM2)信号轴，进而调控 Aβ 沉积与清除[7]。同样，乙酸也可诱导小胶质细胞促炎表型，上调促炎因子表达，以及通过代谢重编程重塑小胶质细胞状态进而抑制小胶质细胞对 Aβ 的吞噬作用[8]。总之，SCFAs 既可以是神经保护剂，直接干扰 Aβ 聚集与纤维化，延缓 AD 进程。然而，在特定实验条件和疾病背景下，它们也可能促进 Aβ 沉积，主要通过重塑小胶质细胞的功能状态来实现。因此，开发 SCFAs 需要充分考虑实验模型、疾病阶段、SCFAs 类型与浓度、个体菌群构成等一系列变量。

1.2 表观遗传调控

SCFAs 可激活 AD 小鼠脑内组蛋白去乙酰

化酶 1 (histone deacetylase 1, HDAC1)，抑制组蛋白去乙酰化酶 3 (histone deacetylase 3, HDAC3)的过度表达，降低海马区异常乙酰化水平，对脑内表观遗传修饰进行调控[9]。丁酸通过抑制组蛋白去乙酰化酶(histone deacetylase, HDAC)增强组蛋白 H3 第 18 位赖氨酸(histone H3 lysine 18, H3K18)乙酰化，并激活 10-11 易位甲基胞嘧啶双加氧酶 1 (ten-eleven translocation methylcytosine dioxygenase 1, TET1)介导的 DNA 去甲基化，协同上调脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)表达，增强神经发生与突触可塑性，从而改善认知功能[10-11]。

1.3 神经炎症调控

乙酸可通过激活 G 蛋白偶联受体 41 (G-protein-coupled receptor 41, GPR41)，抑制细胞外调节蛋白激酶(extracellular signal-regulated kinase, ERK)/c-Jun 氨基末端激酶(c-Jun N-terminal kinase, JNK)/核因子 κB (nuclear factor kappa-light-chain-enhancer of activated B cells, NF-κB)信号通路，减少小胶质细胞激活及促炎因子释放[12]。丙酸则能减弱 Aβ 驱动的炎症反应，下调促炎基因表达，并调节外周 T 细胞分化，间接抑制神经炎症[13-14]。此外，SCFAs 能调节 T 细胞，改变抗原呈递细胞表型，诱导具有抗炎作用的 IL-10+调节性 T 细胞的形成，进一步抑制神经炎症[15]。这些发现揭示了 SCFAs 在调控神经免疫稳态中的核心作用。

1.4 维持脑能量代谢与线粒体功能

AD 患者脑内葡萄糖代谢下降与糖酵解及三羧酸循环(tricarboxylic acid cycle, TCA cycle)关键酶的氧化损伤相关。SCFAs 通过抑制氧化应激保护这些酶活性，恢复腺苷三磷酸(adenosine triphosphate, ATP)生成，并减少 Aβ 诱导的线粒体膜电位损伤[16]。丁酸可通过上调过氧化物酶体增殖物激活受体 γ 共激活因子 1α (peroxisome proliferator-activated receptor gamma coactivator 1 alpha, PGC-1α)的表达，提升 ATP 水平，恢复线粒体膜电位，显著改善 Aβ 诱导的星形胶质细胞线粒体功能障碍[17]。丙酸通过 GPR41 下调线粒体裂变蛋白(mitochondrial fission protein, DRP1)，同时通过 G 蛋白偶联受体 43 (G-protein coupled receptor 43, GPR43)增强 PTEN 诱导的假定激酶 1 (PTEN-induced kinase 1, PINK1)/帕金蛋白(parkin protein, Parkin)介导的线粒体自噬，维持线粒体功能[18]。鉴于线粒体功能障碍是 AD 早期病理事件之一，SCFAs 对线粒体的保护作用可能具有疾病修饰潜力。

1.5 血脑屏障保护

SCFAs 可上调并重组血脑屏障(blood brain barrier, BBB)中的紧密连接蛋白，促进脑血管内皮细胞分化来维持 BBB 正常通透性，同时能促进脑内小胶质细胞成熟及抗炎功能，间接减少小胶质细胞过度激活对 BBB 的损伤[19]。其中，丙酸的保护作用最为明确，能通过游离脂肪酸受体 2 依赖机制，上调脑内皮细胞紧密连接蛋白表达，减少 BBB 通透性，从而阻止外周有害物质进入中枢神经系统[20]。

2 BAs

BAs 可分为初级胆汁酸和次级胆汁酸。初级胆汁酸由胆固醇在肝脏中合成，主要包括胆酸(cholic acid, CA)和鹅去氧胆酸(chenodeoxycholic acid, CDCA)，它们随胆汁进入肠道，在肠道菌群分泌的胆汁酸水解酶和 7α-脱羟基酶的作用下形成游离型胆汁酸，并发生脱羟基反应形成次级胆汁酸，包括脱氧胆酸(deoxycholic acid, DCA)、石胆酸(lithocholic acid, LCA)、熊胆酸(ursocholic acid, UCA)和熊去氧胆酸(ursodeoxycholic acid, UDCA)等[21]。

胆汁酸谱改变与 AD 认知障碍密切相关。一项纳入 1 464 名参与者(包括认知正常的老年人、早期轻度认知障碍者、晚期轻度认知障碍者和 AD 患者)的多中心研究表明，AD 进程中存在 CA 降低、DCA 及其结合形式升高的特征性改

变，且 DCA:CA 比率可作为认知下降的潜在标志物[22]。另外一项研究发现，5 种 BAs 及相关比值与脑脊液中 tau 蛋白和磷酸化 tau 蛋白(phosphorylated tau protein, p-tau)相关，3 种 BAs 与脑脊液 Aβ1-42 相关，提示 BAs 代谢紊乱可能参与 AD 核心病理进程[23]。

BAs 通过多种机制参与 AD 病理调节，其作用因种类和浓度而异。在 Aβ 病理方面，AD 早期脑内 DCA 升高诱导 G 蛋白偶联受体 5 (takeda G protein-coupled receptor 5, TGR5)上调，可激活磷酸化信号转导与转录激活因子 3 (phospho-STAT3, p-STAT3)，促进其向细胞核转移并结合 APH1 的启动子，上调 γ-分泌酶复合物关键亚基的表达，进而增强 γ-分泌酶活性以促进淀粉样蛋白前体蛋白(β-amyloid precursor protein, APP)加工生成 Aβ[24]。牛磺熊去氧胆酸(tauroursodeoxycholic acid, TUDCA)是 UDCA 的一种牛磺酸结合衍生物。补充 TUDCA 可以减少 AD 模型鼠海马体和前额叶皮层的淀粉样蛋白沉积，其机制可能与改善外周内质网应激与代谢异常有关[25-26]。在神经炎症方面，TUDCA 可以激活 AKT/糖原合成酶激酶 3β (glycogen synthase kinase 3β, GSK3β)信号通路，进而减轻神经炎症反应[27]。TUDCA 还可与小胶质细胞中的 G 蛋白偶联胆汁酸受体 1 (G protein-coupled bile acid receptor 1, GPBAR1)/TGR5 结合，诱导小胶质细胞产生抗炎表型，减轻炎症反应[28]。在突触功能与认知能力方面，结合型初级胆汁酸(conjugated primary bile acids, CPBAs)和氨共同诱导了突触损失[29]，提示 BAs 代谢失调可能间接导致突触功能障碍。TUDCA 具有保护突触作用，体内外实验证明了其可以提升突触后标记物 PSD-95 水平，增加树突棘密度，恢复 Aβ 导致的突触后电流频率降低，维持突触结构与功能[30]。TUDCA 可以改善 AD 多种病理，但 BAs 总体失衡才是 AD 进展的重要驱动因素，提示应聚焦于恢复胆汁酸谱平衡而非单纯调节总量。

3 吲哚类代谢物

吲哚类代谢物是肠道菌群代谢色氨酸产生的一类重要衍生物。拟杆菌属、副拟杆菌属、双歧杆菌属等肠道菌群能够将色氨酸直接转化为多种吲哚衍生物，包括吲哚-3-丙酮酸(indole-3-pyruvic acid, IPYA)、吲哚-3-乳酸(indole-3-lactic acid, ILA)、吲哚-3-丙酸(indole-3-propionic acid, IPA)和吲哚乙酸(indole-3-acetic acid, IAA)等[31]。

AD 患者体内吲哚类代谢模式发生显著改变。首先在 AD 患者肠道中产生吲哚的细菌的丰度有所下降[32]。从轻度认知障碍(mild cognitive impairment, MCI)到 AD，IPYA 呈现逐渐富集的趋势，显示出作为鉴别诊断生物标志物的潜力[4]。在 AD 进程中具有神经保护潜力的代谢物(如 IPA 和 ILA)被下调或消耗[33-34]。

吲哚类代谢物通过多途径发挥神经保护效应。在清除 Aβ 方面，ILA 通过激活芳香烃受体(aryl hydrocarbon receptor, AhR)信号通路促进小胶质细胞和星形胶质细胞的 Aβ 清除作用，进而降低脑内 Aβ 水平[35]。吲哚类代谢物还能够抵消 LPS 的有害作用，增强 BBB 的完整性[36]，可能间接起到保护作用。在调节神经炎症方面，吲哚类代谢物能抑制 NF-κB 与死亡受体 3 (death receptor 3, DR3)/IκB 激酶(IκB kinase, IKK)/NF-κB 信号通路，以及 NOD 样受体热蛋白结构域相关蛋白 3 (NOD-like receptor family pyrin domain containing 3, NLRP3)炎症小体的形成，进而减少肿瘤坏死因子-α (tumor necrosis factor alpha, TNF-α)、白细胞介素-6 (interleukin-6, IL-6)、白细胞介素-1β (interleukin-1 beta, IL-1β)等促炎因子的释放[37-38]。补充 IPA 可以增强突触可塑性并改善学习记忆表现[39]。吲哚-酚类衍生物能显著提高人神经母细胞瘤细胞损伤模型中的线粒体代谢活性，从而增加细胞活力[40]，表明吲哚类可通过保护线粒体功能对抗氧化应激和 Aβ 诱导的细胞毒性。

4 TMAO 与 LPS

TMAO 前体三甲胺(trimethylamine, TMA)是由假单胞菌门、芽孢杆菌门、放线菌门等肠道菌群降解饮食中的肉碱、胆碱和卵磷脂产生[41]。随后在肝脏内被黄素依赖型单加氧酶 1 (flavin-containing monooxygenase 1, FMO2)和黄素依赖型单加氧酶 3 (flavin-containing monooxygenase 3, FMO3)氧化成 TMAO[42]。LPS 是革兰氏阴性细菌外膜的主要成分，具有高度的免疫刺激性和毒性，其中脆弱拟杆菌(*Bacteroides fragilis*)和大肠埃希氏菌(*Escherichia coli*)等革兰氏阴性杆菌是 LPS 的主要来源[43]。

大量临床研究提示 TMAO 和 LPS 参与 AD 进程。一项针对 410 名参与者(包括 AD、MCI 及 HC)的研究发现，MCI 和 AD 痴呆患者的脑脊液中的 TMAO 水平高于认知正常者，且 TMAO 水平与 AD 病理生物标志物(p-tau、p-tau/Aβ42)及神经元变性标志物(总 tau、神经丝轻链蛋白)呈正相关[44]。AD 和 MCI 患者血液及脑脊液中的 LPS 水平显著高于认知健康个体，并且其水平与脑脊液 Aβ42 和 tau 浓度呈正相关[45]。这些结果表明，TMAO 和 LPS 不仅是 AD 的一个潜在生物标志物，还可能在其病理进程中发挥重要作用。

TMAO 是一种小分子，可以通过“分子拥挤”效应促进蛋白质折叠并稳定形成的构象，促进 Aβ 和 tau 的聚集[46]。TMAO 水平与 Aβ1-42 和 β-分泌酶活性增加密切相关，进一步加剧了 Aβ 斑块的形成[47]。TMAO 能激活内质网应激信号通路[如蛋白激酶 R 样内质网激酶(protein kinase R-like endoplasmic reticulum kinase, PERK)/真核细胞起始因子 2 (eukaryotic translation initiator factor 2α, eIF2α)途径]，导致突触可塑性受损和神经元功能紊乱[48]。TMAO 激活纹状体和海马的小胶质细胞与星形胶质细胞，抑制 sirtuin 3-超氧化物歧化酶 2-线粒体活性氧 (sirtuin 3-superoxide dismutase 2-mitochondrial reactive oxygen species signaling, SIRT3-SOD2-mtROS)信号通路促进 NLRP3 炎症小体活化与促炎因子(如 IL-1β、TNF-α)的释放，引发神经炎症[49-50]。生理相关浓度的 TMAO 通过膜联蛋白 A1 (annexin A1, ANXA1)及甲酰肽受体 2 (formyl peptide receptor 2, FPR2)增强 BBB 完整性，TMA 则会破坏 BBB 功能，导致 BBB 通透性增加[51]。除此之外，TMAO 还可抑制 *S*-腺苷同型半胱氨酸水解酶(*S*-adenosylhomocysteine hydrolase, AHCY)活性，导致 *S*-腺苷同型半胱氨酸(*S*-adenosyl-L-homocysteine, SAH)积累，从而干扰 DNA 和组蛋白甲基化修饰，最终引起线粒体功能异常[52]，也可能介导 AD 的发病机制。

LPS 主要作为一种强烈的致病因子推动 AD 病理。LPS 通过 Toll 样受体(Toll-like receptor, TLR)触发炎症反应，还会促进 Aβ 的沉积，神经纤维缠结和神经元损伤[43,53]。在分子层面，LPS 可以介导 NF-κB-小 RNA (microRNA, miRNA)-神经丝轻链(neurofilament light chain, NF-L)病理信号通路，导致神经元萎缩，轴突结构破坏，突触可塑性丧失[54]。LPS 可以在神经元核周区域聚集，并抑制 DNA 转录产物的输出，干扰神经元的正常功能[55]。

5 调节关键代谢物抗 AD 的干预策略与药物进展

5.1 益生菌、益生元、合生元

益生菌、益生元及合生元通过干预调节肠道菌群关键代谢物，对改善 AD 进程具有潜力。长双歧杆菌(*Bifidobacterium longum*)、丁酸梭菌(*Clostridium butyricum*)及复合制剂 SLAB51 可提高 SCFAs 水平，降低炎症标志物[56]。菊粉等益生元可富集有益菌，提升 SCFAs 和 IPA 水平[57]；特定合生元组合[如生孢梭菌(*Clostridium sporogenes*) + 木聚糖，绥棱乳酪杆菌(*Lacticaseibacillus suilingensis*)+菊粉]则可通过调

节 IPA/ILA 代谢，激活 AhR 通路改善认知功能[33,58]。

5.2 粪菌移植

来自野生型小鼠或甲硫氨酸限制饮食小鼠的粪菌移植(fecal microbiota transplantation, FMT)可提高受体 SCFAs 水平，改善认知功能[59-60]。FMT 还可降低 LPS 水平，减轻神经炎症[61]。虽然前期研究显示 FMT 在缓解 AD 病理方面具有显著潜力，但其在安全性与标准化问题上仍面临挑战。

5.3 中药的多靶点调控潜力

中药具有“多靶点，多通路”的协同效应，这一特点与 AD 进程中多种肠道菌群代谢物失调高度契合，对干预 AD 进程具有天然优势。甘麦大枣汤可直接逆转 AD 大鼠粪便中异常升高的初级胆汁酸代谢物水平[62]。当归芍药散可以降低 LPS，促进 IPA 的释放，发挥神经保护作用[63]。开心散与七福饮均可提升丁酸水平[64-65]。人参-五味子药对可以提升 AD 大鼠中吲哚类代谢物的水平，人参首乌方可以明显提高 AD 小鼠脑内 IPA，以及血清中的 IPA、IAA、ILA 水平[66-67]。利胆化痰活血方可以改善肥胖引起的认知受损与 BAs 代谢紊乱(降低粪便 LCA，升高 CA 水平)，对改善 AD 肠道菌群代谢物失衡具有潜力[68-69]。

6 总结与展望

本文系统梳理了 5 种肠道菌群关键代谢物(SCFAs、BAs、吲哚类代谢物、TMAO 及 LPS)在 AD 进程中的作用。现有研究表明，这 5 种肠道菌群关键代谢物在 AD 患者体内发生了显著且具有阶段特征性的改变，并且通过多途径直接或间接地调控 AD 的病理进程，促进或抑制 Aβ 的生成与聚集，影响 tau 蛋白磷酸化，调节神经炎症，通过表观遗传机制影响神经可塑性，干扰脑能量代谢与线粒体功能，以及改变 BBB 的通透性。这些发现确立了肠道菌群代谢物作为“肠-脑轴”核心媒介在 AD 进程中的重要地位。

尽管已证明肠道菌群关键代谢物在 AD 进程中具有重要作用，但仍面临诸多挑战。(1) 部分代谢物对 AD 的影响具有双重性或浓度依赖性，其具体作用机制尚未完全明确，未来需利用多组学、基因编辑动物模型等技术进一步阐明。(2) 目前多数证据仍停留于相关性，难以明确肠道菌群代谢物与 AD 进程的因果关联，亟需通过临床干预研究结合前沿的体内外模型实验，为二者的因果关系提供更充足的证据。(3) 肠道菌群组成具有高度的个体化特征，年龄、遗传背景、饮食结构、基础共病等混杂因素均会影响肠道菌群代谢特征，后续研究需充分考量上述因素的干扰以实现精准干预。在临床转化方面，基于肠道菌群关键代谢物开发新型生物标志物，用于 AD 的早期筛查、疾病分期与预后评估已展现出重要的应用潜力。中药具有多成分协同作用，可作用于多种肠道菌群代谢物，对 AD 的干预展现出独特的优势。未来，随着多组学技术与人工智能的深度融合发展，更多肠道菌群关键代谢物将被挖掘，这不仅能进一步揭示“肠-脑轴”调控 AD 病理的复杂网络机制，也将为 AD 开发出更精准、高效的靶向治疗策略。

作者贡献声明

郑建星：全文撰写，机制图设计与绘制；赵梦晴：参与机制图辅助绘制，文献筛选分类；骆云晨：承担综述内容修改，语言润色；肖铁刚：协助完成机制图的图形优化与排版；赵月双：负责中英文文献检索与获取工作；赵淑晴：承担引用格式校对与补充检索工作；徐俊：负责选题构思，框架搭建，全程指导论文写作思路；王兵：负责设计与整体方向把控，指导论文逻辑体系构建与内容优化。

作者利益冲突公开声明

作者声明不存在任何可能会影响本文所报告工作的已知经济利益或个人关系。

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