口服中药“肠道滞留成分”多维度调控肠–脑轴防治脑卒中的作用方式

杨思敏, 李雯雯, 刘静静, 谢 圭, 党文利, 董 菲, 葛超文, 朱 彦*, 董鹏志*

(天津中医药大学, 组分中药国家重点实验室, 天津 301617)

摘要: 脑卒中具有高发病率、高致残率、高死亡率及高复发率的特点, 目前临床治疗仍以注射性溶栓为主。口服辅助治疗药物多样, 但疗效与机制均有待评估。中医药作为多组分、多靶点的治疗体系, 在脑卒中防治中展示出潜力。近年来研究表明, 中医药可通过调节肠道菌群、维持胃肠道稳态, 并经肠–脑轴参与卒中病理调控。传统观点认为药物需吸收入血并透过血脑屏障方能发挥中枢作用, 但部分活性成分口服生物利用度较低、系统暴露水平有限, 却仍可产生神经保护效应, 提示其可能通过肠道起始的间接机制发挥作用。基于此, 我们提出“肠道滞留成分”(intestinal retention components, IRC) 概念, 指一类口服给药后因理化性质难以被肠道直接吸收, 主要滞留于肠道, 系统暴露量低, 但能通过调控肠道微环境影响脑功能并改善卒中结局的活性成分。本文旨在深入探讨肠道滞留成分经肠道菌群介导的生物转化、改善菌群失调及其代谢、修复肠道屏障、调控肠道免疫微环境等多重途径, 经肠–脑轴间接发挥抗脑卒中作用的可能机制。鉴于多种中枢神经系统疾病亦常伴肠道微环境失衡, 故以肠道微环境为切入点的肠道滞留成分研究框架或可为相关疾病口服活性成分的机制阐释与候选药物筛选提供参考。

关键词: 肠–脑轴; 脑卒中; 肠道滞留成分; 肠道菌群; 肠道屏障功能; 神经保护

中图分类号: R966 **文献标识码**: A **文章编号**: 0513-4870(2026)08-2858-09

Multidimensional regulation of the gut-brain axis by intestinal retention components of oral traditional Chinese medicine for the prevention and treatment of stroke

YANG Si-min, LI Wen-wen, LIU Jing-jing, XIE Gui, DANG Wen-li, DONG Fei, GE Chao-wen, ZHU Yan*, DONG Peng-zhi*

(*State Key Laboratory of Component-Based Chinese Medicine, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China*)

Abstract: Stroke is characterized by high incidence, high disability, high mortality, and high recurrence rates. Current clinical management relies primarily on injectable thrombolytic therapy. While a variety of oral adjuvant medications are available, their therapeutic efficacy and underlying mechanisms have not been systematically evaluated. Traditional Chinese medicine (TCM), as a multi-component and multi-target therapeutic option, has demonstrated considerable potential in the prevention and treatment of stroke. Emerging evidence indicates that TCM exerts modulatory effects on stroke-related pathological processes by regulating the gut microbiota, maintaining gastrointestinal homeostasis, and acting through the gut-brain axis. The conventional pharmacological paradigm holds that drugs must enter the systemic circulation and traverse the blood-brain barrier (BBB) to exert central effects. Despite their low oral bioavailability and limited systemic exposure, certain pharmacologically

收稿日期: 2025-12-15; 修回日期: 2026-03-16.

基金项目: 国家自然科学基金资助项目 (82474109, 81873037).

*通讯作者 Tel: 15822700439, E-mail: yanzhu.harvard@icloud.com;

Tel: 13702191524, E-mail: pengzhiryn@163.com

DOI: 10.16438/j.0513-4870.2025-1502

active constituents nonetheless exert significant neuroprotective effects, suggesting that their *in vivo* activities may be mediated by indirect gut-derived regulatory mechanisms rather than direct systemic actions. Based on these observations, we propose the concept of "intestinal retention components" (IRC), referring to a class of orally administered bioactive constituents that are poorly absorbed across the intestinal epithelium and predominantly retained within the intestinal lumen due to their physicochemical properties. Although these compounds exhibit minimal systemic exposure, they are capable of modulating the intestinal microenvironment, thereby influencing brain function and improving stroke outcomes. This review aims to systematically elucidate the potential mechanisms by which IRC indirectly exerts anti-stroke effects *via* the gut-brain axis, encompassing microbiota-mediated biotransformation, attenuation of gut microbial dysbiosis and its associated metabolic perturbations, restoration of intestinal barrier integrity, and regulation of the intestinal mucosal immune microenvironment. Given that numerous central nervous system disorders are also accompanied by intestinal microenvironmental dysregulation, the IRC-centered research framework targeting the gut microenvironment may provide a valuable reference for mechanistic elucidation and the identification of candidate drugs among orally active constituents in the context of broader neurological diseases.

Key words: gut-brain axis; stroke; intestinal retention component; gut microbiota; intestinal barrier function; neuroprotection

脑卒中作为一种因脑血管破裂或阻塞导致的急性脑血管疾病, 以其高发病率、高致残率和高死亡率构成了重大的公共卫生挑战[1,2]。现代医学主要将其划分为缺血性与出血性脑卒中, 其中缺血性脑卒中 (ischemic stroke, IS) 占主导[3]。临床治疗以在时间窗内静脉溶栓[4]、血管内取栓等恢复血流再通为主要策略[5], 然而治疗窗口狭窄、再灌注损伤及出血转化等风险限制了其应用效果[6]。目前用于防治脑卒中和助力于脑卒中后康复的辅助手段种类繁多, 大体分为抗血栓、抗炎、抗氧化应激、脑/神经保护、促血管新生等[7], 但其疗效机制尚未明确, 且均未获正式药物批准。因此, 探寻脑卒中的病理新机制, 并开发多靶点、高效且安全的防治策略, 仍处于该领域的研究前沿。

近年来, 肠–脑轴作为连接胃肠道与中枢神经系统的复杂双向通讯网络, 在神经系统疾病中的作用日益受到重视[8]。研究表明, 肠道菌群及其代谢产物在脑卒中的发生、发展及预后中扮演着关键角色[9]。脑卒中后交感神经系统过度激活、应激反应增强及肠道血流灌注不足等病理生理变化可破坏肠道微生态平衡, 导致肠道屏障功能受损、菌群失调与肠黏膜通透性增加, 有害微生物及其代谢产物移位入血, 加剧全身及神经炎症[10]。反之, 肠道可通过调节免疫稳态、神经递质水平及微生物代谢产物生成等多种途径, 对中枢神经系统功能产生持续影响[11]。这种复杂的相互作用使得靶向肠–脑轴成为治疗脑卒中具有潜力的新途径。

中医药凭借其多靶点协同调控的特点, 在防治脑卒中方面展现出独特优势[12-15]。近年来的研究进一步发现, 中医药干预常伴随着肠道菌群结构改善、肠道屏障功能增强及全身炎症水平下降等效应[16,17], 这与其“整体观”理念高度契合[18]。研究表明, 许多明确具有抗脑卒中活性的中药成分如人参皂苷 Rg1[19]、小檗碱[20]、黄芪甲苷[21]和葸醌苷[22]等, 其口服生物利用度极低, 原型化合物在体循环及中枢神经系统中的暴露量有限, 却仍能产生显著的神经保护效应[23]。这一“低暴露–高疗效”的矛盾现象提示, 这些成分可能在肠道局部发挥作用, 并通过肠–脑轴间接影响中枢神经功能[24]。

基于此, 我们提出“肠道滞留成分” (intestinal retention components, IRC) 的概念。该类成分通常具有分子结构复杂、极性较大等理化特性, 口服后主要滞留于肠道内, 系统暴露量较低, 难以直接进入体循环抵达靶器官发挥药效, 但可通过调控肠道菌群组成、增强肠道屏障功能和调节肠道黏膜免疫反应等方式, 在肠道局部引发一系列生理生化响应, 并最终通过肠–脑轴间接影响中枢神经功能。

本文将系统综述脑卒中后肠道微生态紊乱的病理机制, 并从IRC视角梳理通过肠–脑轴发挥抗脑卒中作用的中药活性成分, 以期为阐明中药活性成分的时空差异作用机制及相关药物研发提供新的理论依据。

1 脑卒中后肠道微生态紊乱的病理机制

为阐明IRC通过肠道局部作用发挥脑保护效应的机制基础, 本节将系统概述脑卒中后肠道微生态紊乱的主要病理改变及其通过肠–脑轴影响中枢神经功能的机制, 聚焦于肠道菌群结构失调、屏障功能破坏及免疫稳态失衡三个相互关联的病理层面。

1.1 脑卒中后肠道菌群结构失调

正常生理状态下, 肠道菌群主要由厚壁菌门、拟杆

菌门、放线菌门和变形菌门组成动态平衡的微生态系统[25]。临床研究显示, 脑卒中患者的肠道菌群在门水平上普遍表现为厚壁菌门和拟杆菌门相对丰度下降, 菌群多样性降低[26,27]。在属水平上, IS患者肠道中链球菌属、肠球菌属等条件致病菌显著富集, 而粪杆菌属、普雷沃氏菌属等共生益菌显著减少[28], 且失调程度与卒中严重程度密切相关[29]。动物模型的研究结果与临床观察总体一致。在门水平上, 小鼠、大鼠、食蟹猴及猪中动脉阻塞 (middle cerebral artery occlusion, MCAO) 模型均表现为厚壁菌门/拟杆菌门比值降低, 变形菌门及放线菌门紊乱。在属水平上, 乳杆菌属、粪杆菌属等有益菌显著减少, 而假单胞菌属、梭菌属等条件致病菌明显富集[30-33]。

1.2 脑卒中后肠道屏障功能破坏与细菌移位

完整的肠道屏障是维持内环境稳态、阻止病原微生物入侵的关键枢纽[34]。脑卒中通过肠−脑轴异常激活肠道神经免疫信号通路, 诱导肠道神经胶质细胞活化, 上调核因子-κB (nuclear factor kappa B, NF-κB)、诱导型一氧化氮合酶 (induced nitric oxide synthase, iNOS) 等促炎因子, 导致上皮细胞凋亡增强、紧密连接蛋白表达抑制, 最终引起肠道通透性显著升高[35]。屏障破坏后, 肠腔共生菌及其组分可跨越屏障, 经血液或淋巴系统迁移至肺等远端器官, 形成肠源性菌移位现象[36]。临床证据显示, IS患者肺部感染中约70%的致病菌来源于肠道共生菌[37], 急性缺血性脑卒中患者在发病24 h内即可出现显著菌群失调和肠道通透性增加, 并可检测到细菌移位至肠系膜淋巴结和肺组织[38]。

1.3 脑卒中后肠道免疫稳态失衡

肠道是人体最大的免疫器官, 其免疫稳态在脑卒中后易受到显著影响。脑卒中后肠道免疫失衡主要表现为促炎性免疫细胞激活增强、调节性T细胞 (regulatory T cell, Treg) 免疫抑制功能受损以及肠道黏膜炎症反应加剧[39]。肠道免疫失衡可通过多种机制影响中枢神经系统。首先, 菌群失调可促使产白细胞介素17的$\gamma\delta$ T细胞及辅助性T细胞17 (helper T cell 17, Th17) 自肠道向脑组织异常迁移, 加重神经炎症反应[40]; 其次, 菌群代谢产物作为免疫调节信号分子参与免疫应答调控。短链脂肪酸 (short-chain fatty acids, SCFAs) 通过G蛋白偶联受体和组蛋白去乙酰化酶抑制等机制, 促进Treg分化、抑制促炎细胞因子释放, 而脑卒中后SCFAs等生成减少进一步加剧免疫失衡[41]。此外, 屏障破坏使脂多糖 (lipopolysaccharide, LPS) 等促炎产物入血, 通过激活Toll样受体4 (Toll-like receptor 4, TLR4) 信号通路诱导促炎细胞因子释放, 增强外周及中枢炎症反应[42]; 过度活化的免疫细胞反作用于肠道, 加剧肠道炎症并损伤肠上皮屏障, 形成恶性循环[43]。

综上所述, 脑卒中后肠道微生态紊乱表现为菌群失调、屏障破坏、免疫失衡三个相互促进的病理层面。这些肠道局部病理改变通过肠−脑轴的神经通路、免疫通路、代谢通路影响中枢神经系统, 最终导致预后恶化。

2 IRC: 基于肠−脑轴调控的脑卒中治疗新策略

基于前述肠道微生态紊乱在脑卒中病理进程中的关键作用, 针对肠道的治疗干预逐渐成为脑卒中防治的潜在新方向。当前脑卒中治疗以静脉溶栓、机械取栓等血管再通策略为核心, 辅以抗血小板、抗凝与神经保护等药物治疗, 对降低早期病死率和致残率发挥了关键作用[44]。然而, 脑卒中的病理生理改变并不局限于局部脑血流中断, 而是伴随炎症反应、氧化应激、血脑屏障与肠屏障协同失衡以及全身免疫重塑等持续性阶段性病理演变[45]。现有西药治疗在针对单一、明确定义的靶点方面具有优势, 但在应对脑卒中后多因素、多阶段的病程变化方面仍显局限[46]。

中医药因其多成分、多靶点的特点, 在脑卒中治疗中展现出独特优势。如前言所述, 本文提出的IRC概念特指一类因理化性质难以直接被肠上皮细胞所吸收, 在肠道内滞留时间相对较长, 其系统及中枢效应依赖肠道转化与间接调控机制的活性成分。IRC通常具有以下共性特征: 第一, 口服生物利用度偏低。此类成分往往分子质量较大、极性较强或含有多个糖基结构, 难以在小肠中有效透膜吸收, 导致其原型成分在血液及主要靶器官中的系统暴露水平较低或无法检出。第二, 药效依赖肠道菌群及代谢酶作用。其体内效应通常需要依赖肠道微生物来源的糖苷酶、酯酶、硝基还原酶等代谢酶介导生物转化, 该过程在无菌或菌群受损状态下明显受阻。第三, 以间接调控为主的作用模式。其药理效应多通过调节肠道屏障功能、免疫反应及菌群代谢产物, 并经肠−脑轴相关神经、免疫及体液通路影响远端器官功能。

具体而言, 此类成分因分子结构特性导致口服吸收率极低, 这一吸收障碍实际上为其与肠道菌群充分相互作用提供了条件。经肠道菌群及其代谢酶的复杂转化, IRC生成的小分子代谢产物不仅生物利用度显著提升、血脑屏障通透性增强, 更重要的是在转化过程中可同时调节菌群结构、肠道屏障、免疫炎症及神经递质等多个环节, 构成其发挥脑卒中治疗作用的关键起始环节。

以下将系统阐述IRC通过菌群代谢转化驱动的多维途径调控肠−脑轴, 实现脑卒中神经功能保护与恢

复的具体机制。

3 IRC通过多维途径调控肠–脑轴治疗脑卒中

在脑卒中相关病理状态下, 肠道菌群失调、肠道屏障破损与全身免疫炎症失衡相互作用, 通过肠–脑轴加剧中枢神经损伤并影响功能恢复。IRC因其理化特性在肠道内具有高浓度富集、长时间滞留的优势, 可通过调控菌群结构、修复屏障功能、调节免疫炎症等多个环节, 系统性干预病理过程。

3.1 肠道菌群介导的生物转化: IRC发挥效应的前提

IRC多为大极性、高分子量化合物, 口服后在上消化道吸收有限, 主要在肠腔内滞留并接受肠道菌群及其代谢酶的生物转化。这一过程生成更易吸收、血脑屏障通透性更高的活性代谢物, 是构成其系统及中枢效应的关键前提。

3.1.1 皂苷类成分的脱糖基转化 皂苷类化合物因含有多个糖基而口服吸收率极低。以人参皂苷Rb1为例, 无菌大鼠灌胃后, 其血浆中几乎检测不到任何原型或代谢产物, 而在定植特定真杆菌A-44的大鼠中, Rb1可经连续脱糖基反应转化为人参皂苷CK, 转化路径为Rb1→Rd→F2→CK→原人参二醇 (protopanaxadiol, PPD), 其每一步骤均需肠道菌群分泌的糖苷水解酶参与[47]。人体研究证实, 口服人参提取物后血浆中主要检出CK而非原型Rb1, 该转化主要由双歧杆菌属、拟杆菌属等介导[48]。代谢产物CK及Rg3的脂溶性显著高于Rb1, 可更有效穿透血脑屏障[49]。黄芪甲苷同样因糖苷基团结构导致吸收受限, 其去糖基化代谢产物环黄芪醇仅在正常肠菌存在时生成, 而在抗生素处理大鼠中消失, 该代谢产物同样具有更强的血脑屏障穿透性[50]。

3.1.2 黄酮类成分的糖苷水解 天然黄酮类化合物多以糖苷形式存在, 约70%以上在小肠无法被水解吸收, 需在结肠中经菌群转化为苷元后进入体循环。黄芩苷需经肠道菌群分泌的β-葡萄糖醛酸酶转化为黄芩素方可被吸收, 该过程在无菌动物中完全阻断[51]。毛蕊异黄酮葡萄糖苷同样在肠道内水解为苷元, 后者为体循环中的主要形式[52]。柚皮苷在双歧杆菌作用下转化为柚皮素和3-羟基苯基丙酸 (3-hydroxyphenylpropionic acid, HPPA), 后者不仅吸收率提高, 还具有独特的抗炎和神经保护活性[53]。

3.1.3 生物碱与蒽醌类成分的还原与水解 小檗碱在菌群产生的硝基还原酶作用下生成二氢小檗碱, 吸收率显著提高[54]。大黄蒽醌苷类成分主要在结肠内经菌群β-葡萄糖苷酶水解释放苷元[55], 药代动力学研究显示其在肠道局部浓度高而血浆暴露低, 进一步证明其在肠腔局部滞留并经代谢转化的特征[56]。

总体而言, IRC的吸收障碍为其与肠道菌群充分相互作用提供了条件。经菌群转化后生成的小分子代谢产物不仅更易被吸收、血脑屏障通透性更高, 还可在肠道局部高浓度富集, 为后续调控肠道微生态、修复屏障功能、调节免疫炎症等多层级效应奠定基础。

3.2 调控肠道菌群结构: 逆转脑卒中后微生态失调

如前所述, 脑卒中后肠道菌群呈现变形菌门异常升高、厚壁菌门及产短链脂肪酸菌群显著下降的失调特征。IRC因在肠道内滞留时间长, 可直接作用于肠道微生物群, 从而逆转脑卒中相关菌群失调。

3.2.1 皂苷类成分的菌群调控作用 人参皂苷Rb1在大鼠MCAO模型中可提高乳酸杆菌等有益菌的相对丰度, 同时降低与炎症相关菌群比例, 其菌群变化与神经功能改善呈正相关[57]。黄芪甲苷可抑制卒中后增殖的条件致病菌如粪杆菌属、瘤胃梭菌属, 重塑肠道菌群结构[58]。三七皂苷R1在大鼠MCAO模型中下调埃希菌、志贺菌属及变形菌门的相对丰度, 并上调拟杆菌门及与SCFAs生成相关的菌群, 呈现与卒中后失衡趋势相反的调节方向[59]。

3.2.2 生物碱与多酚类成分的菌群调节 小檗碱、白藜芦醇等可降低毛螺菌科、丹毒丝菌科等炎症相关菌群丰度, 并提高拟杆菌科、乳酸杆菌属等有益菌比例, 改善脑卒中相关肠道微生态环境[60,61]。

3.2.3 多糖类成分的益生元作用 多糖类成分因其独特的分子结构, 在肠道内可作为益生元促进有益菌生长。葛根抗性淀粉可选择性富集阿克曼菌属、双歧杆菌属等益生菌[62]; 枸杞多糖通过促进双歧杆菌科、乳酸杆菌属等有益菌生长, 并抑制肠杆菌科等条件致病菌扩增, 对脑卒中后菌群失衡状态产生调节作用[63]。这些研究表明, IRC可逆转脑卒中后菌群失调的典型特征, 促进有益菌富集、抑制条件致病菌增殖、恢复菌群多样性, 为后续屏障修复、免疫调节及神经保护效应奠定了微生态基础。

3.3 修复肠道屏障功能: 阻断肠–脑轴有害信号传递

在脑卒中相关病理状态下, 肠道屏障结构受损与通透性增加是菌群来源有害信号异常进入循环系统并影响中枢的重要前提。IRC可通过修复肠道屏障结构, 降低肠道通透性, 阻断LPS等促炎产物的异常入血。

3.3.1 直接增强紧密连接蛋白表达 三七皂苷R1可上调闭锁小带蛋白-1 (zonula occludens-1, ZO-1) 和闭锁蛋白 (occludin) 表达, 改善肠上皮细胞间连接结构, 从而修复受损的肠黏膜屏障并减少菌群衍生毒素向循环系统的移位[59]。小檗碱通过激活腺苷酸活化蛋白激

酶 (AMP-activated protein kinase, AMPK) 并抑制肌球蛋白轻链激酶 (myosin light chain kinase, MLCK) 活性, 稳定紧密连接蛋白结构、减少其降解和内化, 从而增强肠上皮屏障功能[64]。黄芪甲苷通过改善杯状细胞功能和黏液层结构, 降低肠道通透性, 减少LPS等毒素向血液中的转移[58]。七叶皂苷同样可通过上调肠道紧密连接蛋白表达, 对肠上皮屏障结构的完整性产生保护作用[65]。

3.3.2 通过菌群代谢途径间接改善屏障功能 灯盏花素通过促进吲哚类代谢产物生成, 激活孕烷X受体 (pregnane X receptor, PXR), 从而增强肠道屏障功能[66]。葛根抗性淀粉经肠道菌群缓慢发酵后促进褪黑素生成, 与肠道屏障功能增强呈相关性[62]。丹参酮IIA可通过提高肠道SCFAs水平、减轻局部炎症反应并改善紧密连接蛋白表达, 从而对肠道屏障完整性产生保护作用, 其肠道效应与脑卒中后脑损伤恢复表现呈正相关[67]。

总体而言, IRC通过直接增强紧密连接蛋白表达和间接调节菌群代谢途径, 系统性修复肠道屏障功能, 阻断肠−脑轴病理性信号的传递, 为减轻全身及中枢炎症反应、改善神经功能恢复创造了条件。

3.4 调控免疫炎症反应: 重建肠−脑轴免疫平衡

在菌群结构重塑与屏障功能修复的基础上, IRC及其代谢产物可进一步通过调节免疫炎症反应, 参与卒中后肠−脑轴病理进程的多层次调控。

3.4.1 抑制关键促炎信号通路 人参皂苷类代谢产物化合物K和Rg3可抑制NF-κB/丝裂原活化蛋白激酶 (mitogen-activated protein kinase, MAPK) 信号通路活化, 降低小胶质细胞活化程度并减少促炎因子释放[57]。三七皂苷R1可抑制TLR4/髓样分化因子88 (myeloid differentiation factor 88, MyD88)/NF-κB通路的激活, 减轻卒中相关神经炎症反应[68]。小檗碱活性代谢物可下调NOD样受体蛋白3 (NOD-like receptor protein 3, NLRP3) 表达, 抑制小胶质细胞和星形胶质细胞的过度活化, 降低白细胞介素-1β (interleukin-1β, IL-1β)、白细胞介素-6 (interleukin-6, IL-6) 和肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α) 等促炎因子的释放[60]。

3.4.2 调节肠道免疫微环境 白藜芦醇通过调节肠道菌群组成, 促进小肠固有层中Treg/Th17平衡向Treg方向偏移, 从而减轻全身及神经炎症反应[69]。山茱萸苷通过菌群相关途径抑制白细胞介素-17F (interleukin-17F, IL-17F)/肿瘤坏死因子受体相关因子6 (tumor necrosis factor receptor-associated factor 6, TRAF6)/NF-κB信号通路, 对肠道及神经炎症产生调节作用[70]。七叶皂苷可抑制下丘脑−垂体−肾上腺轴 (hypothalamic-pituitary-adrenal, HPA) 的过度激活, 并通过调控糖皮质激素受体 (glucocorticoid receptor, GR)/p38 MAPK/NF-κB及LPS/TLR4/NF-κB等通路减轻炎症反应[65]。

3.4.3 促进神经递质稳态恢复 大黄蒽醌苷通过重塑肠道菌群功能, 降低脑组织和结肠中兴奋性氨基酸谷氨酸和天冬氨酸水平, 同时提高γ-氨基丁酸和5-羟色胺含量, 其递质变化与卒中后神经功能改善呈相关性[71]。

本章系统梳理了IRC对肠−脑轴的多层级调控作用。IRC成分可通过调节脑卒中后失衡的肠道菌群结构、修复受损的肠道屏障功能, 并在此基础上参与免疫炎症反应及神经递质稳态的调控, 从而在外周与中枢层面共同影响脑卒中相关病理过程。这一作用呈现出由肠道微生态重塑到屏障功能改善, 再到免疫与神经功能调节的特征, 体现了IRC通过肠−脑轴发挥脑卒中治疗作用的系统性调控机制。现将代表性IRC在肠道菌群重塑、肠屏障修复、免疫炎症调控及神经递质稳态维持等方面的作用机制总结于表1[47-51,53-58,60-71]所示。

Table 1 Gut-brain axis mechanisms of representative intestinal retention components (IRC) in stroke models. BBB: Blood-brain barrier; MCAO: Middle cerebral artery occlusion; CNS: Central nervous system; SCFAs: Short-chain fatty acids; ZO-1: Zonula occludens-1; TLR4: Toll-like receptor 4; LPS: Lipopolysaccharide; HPA: Hypothalamic-pituitary-adrenal; GABA: Gamma-aminobutyric acid; 5-HT: 5-Hydroxytryptamine; PPD: Protopanaxadiol; HPPA: 3-Hydroxyphenylpropionic acid; AMPK: AMP-activated protein kinase; MLCK: Myosin light chain kinase; IL-17F: Interleukin-17F

Chemical class	Representative component	Comprehensive mechanisms of action and evidence	Reference
Saponin	Ginsenoside Rb1	Gut microbiota transformation: Converted to compound K and PPD by β-glucosidase from *Eubacterium A-44*, *Bifidobacterium*, and *Bacteroides*, significantly enhancing BBB permeability Gut microbiota modulation: Upregulated *Lactobacillus* and downregulated inflammation-associated bacteria in rat MCAO models, with increased microbial diversity Immune regulation: Metabolites compound K and Rg3 inhibited NF-κB/MAPK pathways in the CNS, reduced microglial activation, and decreased IL-1β, TNF-α, and IL-6 levels, exerting neuroprotective effects	[47-49,57]

Continued

Chemical class	Representative component	Comprehensive mechanisms of action and evidence	Reference
	Astragaloside IV	Gut microbiota transformation: Converted to cycloastragenol by glycosidases from commensal gut microbiota, enhancing BBB permeability and anti-inflammatory activity Gut microbiota modulation: Upregulated Bacteroidetes and downregulated *Faecalibacterium* and *Ruminococcus* in rat stroke models, restoring microbial balance Barrier repair: Improved goblet cell function, enhanced mucus layer structure, reduced intestinal permeability and LPS translocation, ameliorating neurological function	[50,58]
	Escin	Immune regulation: Inhibited GR/p38 MAPK/NF-κB and LPS/TLR4/NF-κB pathways, reduced HPA axis activation and inflammatory cytokine levels, improving neurological function	[65]
	Notoginsenoside R1	Gut microbiota modulation: Upregulated Bacteroidetes and Bacteroidaceae, downregulated *Escherichia*, *Shigella*, and Proteobacteria in rat stroke models, with increased microbial diversity Barrier repair: Upregulated ZO-1 and occludin expression, enhanced tight junction integrity, reduced intestinal permeability and LPS translocation into bloodstream Immune regulation: Inhibited TLR4/MyD88/NF-κB pathway, reduced inflammatory cell infiltration and pro-inflammatory cytokines, attenuated neuroinflammation, exerting anti-inflammatory and neuroprotective effects	[68]
Flavonoid	Baicalin	Gut microbiota transformation: Converted to baicalein by β-glucosidase from gut microbiota, enhancing absorption and antioxidant activity Gut microbiota modulation and barrier repair: Improved gut microbial structure and enhanced intestinal barrier function Immune regulation: Exerted antioxidant stress effects	[51]
	Naringin	Gut microbiota transformation: Converted to naringenin and HPPA by glycosidases from specific *Bifidobacterium*, enhancing anti-inflammatory activity and exerting neuroprotective effects	[53]
	Breviscapine	Gut microbiota modulation: Upregulated Bifidobacteriaceae and *Lactobacillus*, downregulated Enterobacteriaceae in stroke models, improving microbial diversity Barrier repair: Promoted indole metabolite production and activated PXR, upregulated barrier function-related genes, enhancing intestinal barrier function	[66]
Alkaloid	Berberine	Gut microbiota transformation: Converted to dihydroberberine by nitroreductase from gut microbiota, significantly enhancing absorption Gut microbiota modulation: Upregulated Bacteroidaceae and *Lactobacillus*, downregulated Lachnospiraceae and Erysipelotrichaceae in stroke models, improving microbial diversity Barrier repair: Activated AMPK and inhibited MLCK, enhanced tight junction protein stability, improving intestinal epithelial barrier function Immune regulation: Metabolites inhibited NLRP3 inflammasome, reduced microglial and astrocyte activation, decreased IL-1β, IL-6, and TNF-α levels, attenuating brain injury	[54,60,64]
Anthraquinone	Rhubarb anthraquinone glycosides	Gut microbiota transformation: Converted to aglycones by β-glucosidase from colonic microbiota, achieving high local intestinal concentrations Gut microbiota modulation: Regulated gut microbial composition Immune regulation: Promoted neurotransmitter balance through microbiota modulation, reduced glutamate and aspartate, increased GABA and 5-HT, improving neurological function	[55,56,71]
Polyphenol	Resveratrol	Gut microbiota modulation: Upregulated Bacteroidaceae and *Lactobacillus*, downregulated Lachnospiraceae and Erysipelotrichaceae in stroke models, improving microbial diversity Immune regulation: Promoted Treg/Th17 balance through microbiota modulation, reduced systemic and neuroinflammation, exerting immunomodulatory effects	[61,69]
Polysaccharide	Pueraria resistant starch	Gut microbiota transformation: Fermented by gut microbiota to produce melatonin and SCFAs Gut microbiota modulation: Upregulated *Akkermansia* and *Bifidobacterium*, downregulated opportunistic pathogens in prebiotic models, with increased microbial diversity Barrier repair: Upregulated barrier-related proteins *via* melatonin pathway, enhanced barrier function, exerting metabolic regulatory and barrier protective effects	[62]
	Lycium barbarum polysaccharides	Gut microbiota modulation: Upregulated Bifidobacteriaceae and *Lactobacillus*, downregulated Enterobacteriaceae in prebiotic models, with increased microbial diversity Barrier repair: Improved mucus layer function through prebiotic effects Immune regulation: Exerted intestinal immunomodulatory effects	[63]
Terpenoid	Tanshinone IIA	Gut microbiota modulation: Regulated gut microbial metabolic functions Barrier repair: Elevated SCFAs levels, improved tight junctions, upregulated ZO-1 and occludin expression, enhanced barrier integrity Immune regulation: Reduced intestinal and neuroinflammation	[67]
Iridoid glycoside	Morroniside	Immune regulation: Inhibited IL-17F/TRAF6/NF-κB pathway, modulated inflammatory cells, reduced IL-17F levels, ameliorated intestinal and neuroinflammation	[70]

4 总结与展望

综合现有研究可见, 脑卒中后的病理进程并不局限于中枢神经系统本身, 而是伴随显著的肠道微生态失衡、肠屏障功能受损及肠道免疫紊乱。这在一定程度上解释了单一中枢靶向神经保护策略临床疗效受限的原因, 也为从外周切入的干预策略提供了理论依据。

在此背景下, IRC 因其药动学特征展现出与传统中枢靶向药物本质不同的作用模式。传统神经保护药物需穿透血脑屏障直接作用于脑组织, 而 IRC 则通过肠道局部富集、菌群与屏障及免疫系统性调控、削弱外周炎症向中枢输入的间接路径发挥中枢保护效应。然而, 目前 IRC 在脑卒中的研究仍以动物实验和关联性证据为主, 其关键作用菌群、核心代谢物及因果性信号通路尚未得到系统验证, 且不同研究在模型与评价指标方面存在一定差异性。

基于上述机制阐述与现有研究局限, 未来可重点推进以下三个方向。其一, IRC 的制剂策略优化。针对 IRC 以肠道为主要作用靶部位的特性, 可开发结肠定位给药系统或肠道缓释制剂, 延长 IRC 在肠道的滞留时间与浓度, 增强其对肠道菌群结构、屏障功能及免疫微环境的调控效率, 进一步提升治疗效果。其二, IRC 与现有脑卒中治疗手段的联合探索。IRC 通过外周肠道途径发挥间接中枢保护效应, 与直接作用于中枢的溶栓药物、神经保护剂在机制上具有互补性。系统评估二者联合应用的协同效应, 为不同病程阶段脑卒中治疗提供方案。其三, 推进基于个体菌群特征的精准干预。IRC 的体内效应依赖菌群的代谢转化能力, 而个体间菌群差异显著, 结合菌群基因组学与代谢组学手段, 解析菌群构成对 IRC 生物转化效率的影响, 可为不同菌群背景患者制定个性化 IRC 干预方案奠定基础。

值得进一步强调的是, IRC 所提出的肠−脑轴介导的间接中枢调控并非仅限于脑卒中。鉴于多种中枢神经系统疾病同样存在肠道微生态紊乱、屏障受损与免疫代谢异常, 并可通过肠−脑轴影响中枢炎症与神经功能, IRC 概念有望拓展用于神经退行性疾病及精神障碍等相关疾病中口服活性成分的机制阐释与候选药物筛选。未来研究应在明确 IRC 作用机制的同时, 积极推进临床转化, 探索其在脑卒中及其他中枢神经系统疾病中的应用价值, 最终实现从概念创新到临床实践的跨越。

作者贡献: 杨思敏负责综述撰写和插图绘制; 李雯雯负责插图绘制; 刘静静、谢圭、党文利、董菲、葛超文协助文章修改; 董鹏志负责文章修改、校对和审核; 朱彦负责文章立意构思、修改与审核。

利益冲突: 作者声明本文不存在任何利益冲突。

References

[1] Feske SK. Ischemic stroke [J]. Am J Med, 2021, 134: 1457-1464.

[2] Feigin VL, Brainin M, Norrving B, et al. World Stroke Organization: Global stroke fact sheet 2025 [J]. Int J Stroke, 2025, 20: 132-144.

[3] Hu ZL, Zhao MY, Shen HY, et al. Organelle symphony: Nuclear factor erythroid 2-related factor 2 and nuclear factor-kappa B in stroke pathobiology [J]. Neural Regen Res, 2026, 21: 1483-1496.

[4] Gottlieb M, Carlson JN, Westrick J, et al. Endovascular thrombectomy with *versus* without intravenous thrombolysis for acute ischaemic stroke [J]. Cochrane Database Syst Rev, 2025, 4: CD015721.

[5] Kim BJ, Singh N, Menon BK. Hemodynamics of leptomeningeal collaterals after large vessel occlusion and blood pressure management with endovascular treatment [J]. J Stroke, 2021, 23: 343-357.

[6] Xu AN, Zhang HH, Zhang YH, et al. Ischemic stroke and intervention strategies based on the timeline of stroke progression: Review and prospects [J]. Acta Pharm Sin B, 2025, 15: 4543-4581.

[7] Qin C, Yang S, Chu YH, et al. Signaling pathways involved in ischemic stroke: Molecular mechanisms and therapeutic interventions [J]. Signal Transduct Target Ther, 2022, 7: 215.

[8] Sittipo P, Choi J, Lee S, et al. The function of gut microbiota in immune-related neurological disorders: A review [J]. J Neuroinflammation, 2022, 19: 154.

[9] Zhang SX, Jin MQ, Ren JH, et al. New insight into gut microbiota and their metabolites in ischemic stroke: A promising therapeutic target [J]. Biomed Pharmacother, 2023, 162: 114559.

[10] Chidambaram SB, Rathipriya AG, Mahalakshmi AM, et al. The influence of gut dysbiosis in the pathogenesis and management of ischemic stroke [J]. Cells, 2022, 11: 1239.

[11] Peh A, O'Donnell JA, Broughton BRS, et al. Gut microbiota and their metabolites in stroke: A double-edged sword [J]. Stroke, 2022, 53: 1788-1801.

[12] Yin XY, Li ST, Wang JW, et al. Research progress of active compounds from traditional Chinese medicine in the treatment of stroke [J]. Eur J Med Chem, 2025, 291: 117599.

[13] Zhu T, Wang L, Feng Y, et al. Classical active ingredients and extracts of Chinese herbal medicines: Pharmacokinetics, pharmacodynamics, and molecular mechanisms for ischemic stroke [J]. Oxid Med Cell Longev, 2021, 2021: 8868941.

[14] Zhu T, Wang L, Wang LP, et al. Therapeutic targets of neuroprotection and neurorestoration in ischemic stroke: Applications for natural compounds from medicinal herbs [J]. Biomed Pharmacother, 2022, 148: 112719.

[15] Desikan RS. Local point: Traditional Chinese medicine for ischaemic stroke [J]. Lancet Neurol, 2018, 17: 745.

[16] Dong X, Zhang T, Zhang C, et al. Traditional Chinese herbal medicines for the treatment of ischemic stroke in China [J]. Ageing Res Rev, 2025, 110: 102803.

[17] Fan G, Liu M, Liu J, et al. Traditional Chinese medicines treat ischemic stroke and their main bioactive constituents and mechanisms [J]. Phytother Res, 2024, 38: 411-453.

[18] Gao L, Xia XW, Shuai YQ, et al. Gut microbiota, a hidden protagonist of traditional Chinese medicine for acute ischemic stroke [J]. Front Pharmacol, 2023, 14: 1164150.

[19] Long J, Sun Y, Liu S, et al. Ginsenoside Rg1 treats ischemic stroke by regulating CKLF1/CCR5 axis-induced neuronal cell pyroptosis [J]. Phytomedicine, 2024, 123: 155238.

[20] Duan HJ, Hu JY, Deng Y, et al. Berberine mediates the production of butyrate to ameliorate cerebral ischemia *via* the gut microbiota in mice [J]. Nutrients, 2024, 16: 9.

[21] Li Y, Zhang YN, Zhang PL, et al. Inhibition of citrate transport reduces HIF-1alpha/GABA-T-mediated succinate accumulation in macrophages: The role of astragaloside IV in ischemic stroke [J]. Phytomedicine, 2025, 139: 156449.

[22] Li RR, Liu XF, Feng SX, et al. Pharmacodynamics of five anthraquinones (aloe-emodin, emodin, rhein, chrysophanol, and physcion) and reciprocal pharmacokinetic interaction in rats with cerebral ischemia [J]. Molecules, 2019, 24: 1898.

[23] Chen F, Wen Q, Jiang J, et al. Could the gut microbiota reconcile the oral bioavailability conundrum of traditional herbs? [J]. J Ethnopharmacol, 2016, 179: 253-264.

[24] Gong X, Li X, Bo A, et al. The interactions between gut microbiota and bioactive ingredients of traditional Chinese medicines: A review [J]. Pharmacol Res, 2020, 157: 104824.

[25] Pluta R, Januszewski S, Czuczwar SJ. The role of gut microbiota in an ischemic stroke [J]. Int J Mol Sci, 2021, 22: 915.

[26] Yin J, Liao SX, He Y, et al. Dysbiosis of gut microbiota with reduced trimethylamine-*N*-oxide level in patients with large-artery atherosclerotic stroke or transient ischemic attack [J]. J Am Heart Assoc, 2015, 4: e002699.

[27] Zeng XL, Gao XX, Peng Y, et al. Higher risk of stroke is correlated with increased opportunistic pathogen load and reduced levels of butyrate-producing bacteria in the gut [J]. Front Cell Infect Microbiol, 2019, 9: 4.

[28] Xia GH, You C, Gao XX, et al. Stroke dysbiosis index (SDI) in gut microbiome are associated with brain injury and prognosis of stroke [J]. Front Neurol, 2019, 10: 397.

[29] Li N, Wang X, Sun C, et al. Change of intestinal microbiota in cerebral ischemic stroke patients [J]. BMC Microbiol, 2019, 19: 191.

[30] Singh V, Roth S, Llovera G, et al. Microbiota dysbiosis controls the neuroinflammatory response after stroke [J]. J Neurosci, 2016, 36: 7428-7440.

[31] Liu L, Chen X, Wang Y, et al. Modulation of gut microbiota alleviates cerebral ischemia/reperfusion injury in rats by inhibiting M1 polarization of microglia [J]. Front Pharmacol, 2023, 14: 1123387.

[32] Chen YH, Liang JH, Ouyang FB, et al. Persistence of gut microbiota dysbiosis and chronic systemic inflammation after cerebral infarction in cynomolgus monkeys [J]. Front Neurol, 2019, 10: 661.

[33] Jeon J, Lourenco J, Kaiser EE, et al. Dynamic changes in the gut microbiome at the acute stage of ischemic stroke in a pig model [J]. Front Neurosci, 2020, 14: 587986.

[34] Camilleri M, Madsen K, Spiller R, et al. Intestinal barrier function in health and gastrointestinal disease [J]. Neurogastroenterol Motil, 2012, 24: 503-512.

[35] Ye D, Hu Y, Zhu N, et al. Exploratory investigation of intestinal structure and function after stroke in mice [J]. Mediators Inflamm, 2021, 2021: 1315797.

[36] Houlden A, Goldrick M, Brough D, et al. Brain injury induces specific changes in the caecal microbiota of mice *via* altered autonomic activity and mucoprotein production [J]. Brain Behav Immun, 2016, 57: 10-20.

[37] Xie X, Wang L, Dong S, et al. Immune regulation of the gut-brain axis and lung-brain axis involved in ischemic stroke [J]. Neural Regen Res, 2024, 19: 519-528.

[38] Błaż M, Natorska J, Bembenek JP, et al. Elevated lipopolysaccharide level is largely driven by time since symptom onset in acute ischemic stroke: The impact on clinical outcomes [J]. J Thromb Haemost, 2024, 22: 3161-3171.

[39] Yan J, Greer JM, Etherington K, et al. Immune activation in the peripheral blood of patients with acute ischemic stroke [J]. J Neuroimmunol, 2009, 206: 112-117.

[40] Benakis C, Brea D, Caballero S, et al. Commensal microbiota affects ischemic stroke outcome by regulating intestinal gammadelta T cells [J]. Nat Med, 2016, 22: 516-523.

[41] Fock E, Parnova R. Mechanisms of blood-brain barrier protection by microbiota-derived short-chain fatty acids [J]. Cells, 2023, 12: 657.

[42] Catorce MN, Gevorkian G. Evaluation of anti-inflammatory nutraceuticals in LPS-induced mouse neuroinflammation model: An update [J]. Curr Neuropharmacol, 2020, 18: 636-654.

[43] Tuz AA, Hasenberg A, Hermann DM, et al. Ischemic stroke and concomitant gastrointestinal complications-a fatal combination for patient recovery [J]. Front Immunol, 2022, 13: 1037330.

[44] Ghosh D, Sehgal K, Sodnar B, et al. Drug repurposing for stroke intervention [J]. Drug Discov Today, 2022, 27: 1743-1760.

[45] Iadecola C, Anrather J. The immunology of stroke: From mechanisms to translation [J]. Nat Med, 2011, 17: 796-808.

[46] Schneider AM, Regenhardt RW, Dmytriw AA, et al. Cerebroprotection in the endovascular era: An update [J]. J Neurol Neurosurg Psychiatry, 2023, 94: 267-271.

[47] Akao T, Kida H, Kanaoka M, et al. Intestinal bacterial hydrolysis is required for the appearance of compound K in rat plasma after oral administration of ginsenoside Rb1 from *Panax ginseng* [J]. J Pharm Pharmacol, 1998, 50: 1155-1160.

[48] Lee J, Lee E, Kim DH, et al. Studies on absorption, distribution and metabolism of ginseng in humans after oral administration [J]. J Ethnopharmacol, 2009, 122: 143-148.

[49] Kim DH. Gut microbiota-mediated pharmacokinetics of ginseng saponins [J]. J Ginseng Res, 2018, 42: 255-263.

[50] Jin Y, Guo XJ, Yuan B, et al. Disposition of astragaloside IV *via* enterohepatic circulation is affected by the activity of the intestinal microbiome [J]. J Agric Food Chem, 2015, 63: 6084-6093.

[51] Yan YC, Amur SA, Liu H, et al. Endogenous crude *Scutellaria baicalensis* polysaccharide robustly enhances one-pot extraction and deglycosylation of baicalin [J]. Int J Biol Macromol, 2024, 263: 130349.

[52] Ruan JQ, Li S, Li YP, et al. The presystemic interplay between gut microbiota and orally administered calycosin-7-*O*- *β* -*D*-glucoside [J]. Drug Metab Dispos, 2015, 43: 1601-1611.

[53] Chen T, Wu H, He Y, et al. Simultaneously quantitative analysis of naringin and its major human gut microbial metabolites naringenin and 3- (4-hydroxyphenyl)propanoic acid *via* stable isotope deuterium-labeling coupled with RRLC-MS/MS method [J]. Molecules, 2019, 24: 4287.

[54] Feng R, Shou JW, Zhao ZX, et al. Transforming berberine into its intestine-absorbable form by the gut microbiota [J]. Sci Rep, 2015, 5: 12155.

[55] Li QY, Guo Y, Yu XH, et al. Protective mechanism of rhubarb anthraquinone glycosides in rats with cerebral ischaemia-reperfusion injury: Interactions between medicine and intestinal flora [J]. Chin Med, 2020, 15: 60.

[56] Zhang J, Zou J, Zhang P, et al. Pharmacokinetics, tissue distribution, and excretion of anthraquinones and their glucuronide metabolites from raw and steamed pieces of Rhei Radix et Rhizoma extract in constipation rats [J]. Sci Tradit Chin Med, 2025, 3: 259-269.

[57] Chen HM, Shen JJ, Li HF, et al. Ginsenoside Rb1 exerts neuroprotective effects through regulation of *Lactobacillus helveticus* abundance and $GABA_A$ receptor expression [J]. J Ginseng Res, 2020, 44: 86-95.

[58] Li ZL, Hu E, Zheng F, et al. The effects of astragaloside IV on gut microbiota and serum metabolism in a mice model of intracerebral hemorrhage [J]. Phytomedicine, 2023, 121: 155086.

[59] Li HF, Xiao JC, Li XN, et al. Low cerebral exposure cannot hinder the neuroprotective effects of Panax notoginsenosides [J]. Drug Metab Dispos, 2017, 45: 1238-1246.

[60] Wang XY, Zhang JM, Wang SS, et al. Berberine modulates gut microbiota to attenuate cerebral ferroptosis induced by ischemia-reperfusion in mice [J]. Eur J Pharmacol, 2023, 953: 175782.

[61] Chen XX, Zhang J, Yin N, et al. Resveratrol in disease prevention and health promotion: A role of the gut microbiome [J]. Crit Rev Food Sci Nutr, 2024, 64: 5878-5895.

[62] Lian Z, Xu Y, Wang C, et al. Gut microbiota-derived melatonin from Puerariae Lobatae Radix-resistant starch supplementation attenuates ischemic stroke injury *via* a positive microbial co-occurrence pattern [J]. Pharmacol Res, 2023, 190: 106714.

[63] Wang Y, Sun MY, Jin HY, et al. Effects of *Lycium barbrum* polysaccharides on immunity and the gut microbiota in cyclophosphamide-induced immunosuppressed mice [J]. Front Microbiol, 2021, 12: 701566.

[64] Wang H, Zhang H, Gao Z, et al. The mechanism of berberine alleviating metabolic disorder based on gut microbiome [J]. Front Cell Infect Microbiol, 2022, 12: 854885.

[65] Li M, Wang SG, Zhang C, et al. Escin alleviates stress-induced intestinal dysfunction to protect brain injury by regulating the gut-brain axis in ischemic stroke rats [J]. Int Immunopharmacol, 2023, 115: 109659.

[66] Chen HD, Jiang MZ, Zhao YY, et al. Effects of breviscapine on cerebral ischemia-reperfusion injury and intestinal flora imbalance by regulating the TLR4/MyD88/NF- *κ*B signaling pathway in rats [J]. J Ethnopharmacol, 2023, 300: 115691.

[67] Jeon JH, Kaiser EE, Waters ES, et al. Tanshinone IIA-loaded nanoparticles and neural stem cell combination therapy improves gut homeostasis and recovery in a pig ischemic stroke model [J]. Sci Rep, 2023, 13: 2520.

[68] Zhang SX, Chen QY, Jin MQ, et al. Notoginsenoside R1 alleviates cerebral ischemia/reperfusion injury by inhibiting the TLR4/MyD88/NF-*κ*B signaling pathway through microbiota-gut-brain axis [J]. Phytomedicine, 2024, 128: 155530.

[69] Dou ZC, Rong XF, Zhao EX, et al. Neuroprotection of resveratrol against focal cerebral ischemia/reperfusion injury in mice through a mechanism targeting gut-brain axis [J]. Cell Mol Neurobiol, 2019, 39: 601-616.

[70] Yan C, Liu ZH, Xie WE, et al. Cornuside protects against ischemic stroke in rats by suppressing the IL-17F/TRAF6/NF*κ*B pathway *via* the brain-gut axis [J]. Exp Neurol, 2024, 373: 114672.

[71] Guo Y, Li QY, Yu XH, et al. Rhubarb anthraquinone glycosides protect against cerebral ischemia-reperfusion injury in rats by regulating brain-gut neurotransmitters [J]. Biomed Chromatogr, 2021, 35: e5058.