从肠道菌群调控角度探讨中药汤剂中多糖组分存在的意义

沈 红[1], 伍城颖[1], 龙 芳[1], 周 静[1], 周姗姗[1], 许 军[2*], 李松林[1*]

(1. 南京中医药大学附属中西医结合医院中药质量和代谢组研究室, 江苏 南京 210028;
2. 香港浸会大学中医药学院, 香港 999077)

摘要: 汤剂为中药传统用药方式。汤剂中除小分子组分外, 亦包含多糖等大分子组分。以往中药新药研发过程中常采用“醇沉除杂”工艺, 去除多糖等口服不吸收“无效组分”, 富集小分子“有效组分”, 以改善制剂成型性。近年来, 随着人们对肠道菌群与宿主健康/疾病的密切关系及中药多糖潜在益生元作用的认识不断加深, 汤剂中多糖组分存在的价值越发值得关注。结合本课题组及文献研究进展, 本综述在简述肠道菌群与健康/疾病关系的基础上, 概述中药多糖通过调节肠道菌群干预机体代谢、肠功能、免疫、炎症、情志及肿瘤等疾病状态, 通过肠道菌群介导影响共存小分子组分吸收、代谢和转运, 以及肠道菌群调节作用的结构特异性, 以此从肠道菌群调控角度探讨多糖组分在中药汤剂中存在的重要价值, 为基于经典名方和临床验方的创新药物研发过程中重视多糖组分的存在提供启示。

关键词: 汤剂; 多糖; 肠道菌群; 中药; 新药研发

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Meanings of polysaccharides in traditional Chinese medicines decoction from the viewpoint of its gut microbiota regulation effects

SHEN Hong[1], WU Cheng-ying[1], LONG Fang[1], ZHOU Jing[1], ZHOU Shan-shan[1], XU Jun[2*], LI Song-lin[1*]

(*1. Department of Pharmaceutical Analysis and Metabolomics, Affiliated Hospital of Integrated Traditional Chinese and Western Medicine, Nanjing University of Chinese Medicine, Nanjing 210028, China; 2. School of Chinese Medicine, Hong Kong Baptist University, Hong Kong 999077, China*)

Abstract: Decoction is one of the traditional dosage forms of traditional Chinese medicines (TCMs). In addition to small molecular components, decoction also contains polysaccharides and other macromolecular components. For a long time, ethanol precipitation has been commonly used during TCMs based new drug development to remove "ineffective macromolecular components", and enrich "active small molecules components", so as to improve the subsequent formability of the preparations. With the recognition of the relationships between gut microbiota and host health/disease, and the potential prebiotic effects of natural polysaccharides, the important values of polysaccharides in TCMs decoctions have been gradually emerged. Based on the representative findings of our own research and the literatures, the potential prebiotics function of TCMs polysaccharides were reviewed regarding its related effects on host physiological and pathological processes of metabolic function, bowel function, immunity, inflammation, emotion and tumor, on the metabolism and absorption of coexisting small molecule components, as well as the structure-function features, so that the meanings of polysaccharides in TCMs decoction

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*通讯作者 Tel: 86-25-85639640, E-mail: songlinli64@126.com;
Tel: 86-852-34112423, E-mail: davidxujun@hkbu.edu.hk

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were discussed and emphasized, and hopefully to provide enlightenment for the premise of attaching importance to the existence of polysaccharide components in the process of innovative drug research and development based on classical and clinical TCMs prescriptions.

Key words: decoction; polysaccharide; gut microbiota; traditional Chinese medicine; drug development

汤剂是中药主要传统剂型之一,具有起效快、疗效好等特点。中药汤剂中不但含有黄酮、皂苷等小分子组分,更含有多糖等大分子组分。以往基于中药汤剂的创新药研发主要关注小分子组分,包括活性评价、量值转移、含量测定及稳定性评价等,而对于多糖大分子组分因其口服不吸收,通常被认为是“无效组分”,故在制剂工艺研究过程中采用“醇沉除杂”方法将其作为“杂质”去除,从而富集小分子活性组分,以改善提取物黏稠、易吸潮和后续制剂不易成型等缺点[1]。

近年来,生命科学领域的重大研究进展之一就是发现肠道菌群与宿主健康/疾病存在密切关联。正常生理状态下,肠道菌群中有益菌 (又称益生菌, probiotics)、有害菌和条件致病菌维持着动态平衡[2,3],而菌群失调则伴随着生理机能的改变及肿瘤、糖尿病、抑郁等疾病的发生[4-6]。同时研究证实,果胶、菊粉等天然多糖组分具有益生元 (prebiotics) 作用,即可扶植有益菌的生长,发挥抗炎、免疫调节等作用[7]。越来越多的研究也发现,某些中药的多糖组分同样具有肠道菌群调节功能,从而影响机体代谢、炎症等[8]。因此,肠道菌群可能是中药多糖组分贡献药效的潜在靶标。由此可见,中药汤剂中多糖组分存在的价值有必要重新认识。

基于经典名方和临床验方的创新药物研发是当前中医药传承创新的重要策略和举措。而汤剂又是经典名方和临床验方的主要剂型,从肠道菌群调控角度深入探讨中药汤剂中多糖组分存在的价值对基于经典名方和临床验方的创新药物研发无疑具有重要启发。本综述在简要阐述肠道菌群与人体健康/疾病关系的基础上,重点概述天然多糖特别是中药多糖组分通过调节肠道菌群干预健康/疾病状态,影响共存活性小分子组分的代谢、吸收和转运,以及肠道菌群调节作用的结构特异性,以此探讨多糖组分在中药汤剂中存在的药效价值,为基于经典名方和临床验方的创新药物研发提供启示。

1 肠道菌群是疾病预防和治疗的重要靶标

肠道菌群被视为人体的重要“器官”,在维持机体健康与疾病产生中扮演了重要角色。肠道菌群参与宿主能量代谢、免疫及消化系统构建等,对情绪、行为甚至更高的认知功能也起着重要作用[9-12]。肠道菌群可为宿主提供必需的营养物质,抵御条件致病菌的定植,对肠道生理屏障的构建发挥重要作用[13]。此外,哺乳动物免疫系统的发育及功能成熟亦取决于肠道共生菌,菌群促发信号刺激免疫细胞成熟并维持正常的免疫功能[14]。健康成年个体的肠道菌群组成及功能处于动态平衡状态[15],饮食、机体内外环境的改变会打破其平衡状态,引发机体生理功能障碍,如代谢紊乱、炎症、免疫亢进、精神情志疾病,甚至引发肿瘤[16-19]。鉴于肠道菌群与宿主生理功能的维持及疾病的发生、发展密切相关,肠道菌群成为疾病预防与治疗的重要潜在靶标,可通过干预肠道菌群多样性,扶植有益菌,营造健康的肠道微生态,减缓疾病的发生与发展。

2 天然多糖的益生元功能

多糖是由10个以上单糖组成的聚合高分子碳水化合物,广泛存在于自然界中,依据其组成单糖种类及糖苷键连接方式,可分为淀粉、纤维、杂多糖等多种结构类型。多种天然多糖被证明具有益生元作用,如菊粉可增加肠道中双歧杆菌 (*Bifidobacterium*) 和厌氧杆菌 (*Anaerostipes*) 丰度,降低嗜胆菌属 (*Bilophila*) 丰度,且该菌属的变化与改善轻度便秘有关[20];瓜尔胶部分水解物可促进瘤胃球菌 (*Ruminococcus*)、镰刀菌 (*Fusicatenibacter*)、粪杆菌 (*Faecalibacterium*) 和拟杆菌 (*Bacteroides*) 在肠道中大量繁殖,同时抑制罗氏菌属 (*Roseburia*)、毛螺菌属 (*Lachnospiracea*) 和布劳特氏菌属 (*Blautia*) 的增殖[21];果胶可促进拟杆菌属 (*Bacteroides*)、梭菌属 (*Clostridium*)、粪杆菌属 (*Faecalibacterium*) 和真杆菌属 (*Eubacterium*) 增殖,具有益生元作用,发挥免疫调节和抗炎等功能[22]。人类缺乏合成多糖代谢酶的基因,而其肠道菌群可编码上千种糖苷酶,包括糖苷水解酶、多糖裂解酶、碳水化合物酯解酶及糖基转移酶等,多糖代谢产物糖原作为肠道微生物的能量来源,可促进肠菌增殖[23,24];糖原进一步酵解产物短链脂肪酸 (short-chain fatty acids, SCFAs),降低肠道pH值,可促进有益菌的繁殖,抑制潜在病原菌的繁殖,营造健康的肠道微生态[25]。SCFAs利用单羧酸转运蛋白和钠碘转运体蛋白8等载体进行转运[26],激活G蛋白偶联受体、抑制组蛋白去乙酰化酶信号通路发挥其免疫调节、抗炎等生物学效应[27-29]。此外,SCFAs可作为结肠细胞的能量来源改善肠道通透性环境[30]、调节能量平衡和代谢[31,32],刺激迷走神经,加强血脑屏

障, 促进小胶质细胞成熟及降低食欲等[33], 是多糖调节肠道菌群发挥其生物活性最重要的信号分子之一。

3 基于肠道菌群调节的中药多糖功能活性研究

中药多糖也具有益生元功能。研究发现人参 (*Panax ginseng*) 多糖可促进大鼠肠道中乳酸杆菌 (*Lactobacillus*) 和拟杆菌 (*Bacteroides*) 增殖, 具有益生元功能[34]; 天麻 (*Gastrodia elata*) 两种均质多糖能显著促进高脂饮食 (high fat diet, HFD) 小鼠肠道有益菌阿克曼菌 (*Akkermansia Muciniphila*) 的增殖[35]; 玉屏风汤剂总多糖能通过调节肠道菌群平衡及肠道内环境的健康[36]。中药多糖口服不吸收, 却表现出免疫调节、降糖、抗炎等作用, 与其肠道菌群调节功能有关。

3.1 对代谢性疾病的调节 中药多糖可通过调节肠道菌群多样性、干预特异肠菌的增殖, 影响宿主代谢。灵芝 (*Ganoderma lucidum*) 菌丝体水提取物 (WEGL) 可通过逆转肠道菌群失调, 回调厚壁菌门与拟杆菌门比例, 减轻 HFD 诱导的肥胖小鼠体重, 并缓解炎症和胰岛素抵抗, 维持肠道屏障完整性; 从 WEGL 分离所得高分子质量多糖 (> 300 kDa), 亦可通过调节肠道菌群发挥类似抗肥胖作用, 证明该多糖组分是灵芝水提物抗肥胖作用的物质基础[37]。冬虫夏草 (*Cordyceps sinensis*) 菌丝体多糖 H1 (> 300 kDa) 显著降低 HFD 小鼠体重, 改善代谢紊乱, 增强肠道完整性, 降低炎症水平, 改善胰岛素敏感性, 调节肠道菌群结构, 其中金氏副杆菌 (*Parabacteroides goldsteinii*) 的增殖是 H1 减轻肥胖症状, 增强脂肪组织产热及胰岛素抵抗水平, 保护肠道完整性, 最终发挥减肥及代谢调节功能的关键肠菌[38]。茯苓 (*Poria cocos*) 多糖可有效改善酒精性脂肪肝的炎症损伤和脂肪堆积, 与其激活过氧化物酶体增殖物激活受体-γ (peroxisome proliferator-activated receptor-γ, PPAR-γ) 信号传导, 减少结肠上皮细胞炎症, 维持肠道缺氧状态, 抑制真菌和变形杆菌的过度生长有关[39]。麦冬 (*Ophiopogon japonicus*) 水溶性*β*-*D*-果聚糖可通过降低肥胖小鼠厚壁菌门/拟杆菌门比例, 改变其代谢特征, 增加乳酸菌酵解产物牛磺酸、SCFAs 等水平, 促进能量代谢, 发挥降糖降脂作用[40]; 该多糖还可促进肠道阿克曼菌的增殖, 改变肠道微生物群多样性, 调节脂质代谢途径, 从而抑制肥胖和非酒精性脂肪肝的疾病状态[41]。

3.2 对肠功能的调节 多糖肠道菌群酵解产物可为肠黏膜细胞提供充足的能量, 改变肠道生态环境, 促进特定肠道菌的增殖, 对胃肠功能性疾病具有调节作用。人参多糖可显著改变抗生素诱发腹泻小鼠肠道乳酸杆菌、乳球菌 (*Lactococcus*) 和链球菌 (*Streptococcus*) 的相对丰度, 降低拟杆菌的相对丰度, 调节宿主碳水化合物、氨基酸和能量代谢, 使其逆转为正常水平, 促进黏膜结构的恢复, 发挥其腹泻治疗作用[42]。肉苁蓉 (*Cistanche deserticola*) 多糖可促进有益菌的增殖, 同时减少条件致病菌的丰度, 形成"行为-肠道菌-代谢物"网络, 调节老年大鼠便秘引起的行为、微生物多样性及代谢物谱的异常, 发挥老年便秘治疗作用[43]。

3.3 对免疫、炎症功能的调节 中药多糖多具有免疫调节及抗炎作用。由于多糖结构的复杂性及口服不吸收等特性, 经典的入血成分研究方法始终未能揭示其作用机制。随着肠道菌群与宿主免疫、炎症关系研究的发展, 以肠道菌群为靶标的中药多糖免疫调节及抗炎作用机制研究成为关注点。肠道菌群在中药多糖缓解消化道炎症、原位及系统免疫调节作用中扮演关键角色。例如, 传统补益类中药黄芪 (*Astragalus membranaceus*) 和党参 (*Codonopsis pilosula*) 具有免疫调节作用, 其多糖联合给药可重建结肠炎小鼠免疫平衡, 减轻结肠黏膜损伤, 与其恢复肠道菌群结构, 激活芳烃受体, 上调异戊酸和丁酸水平有关[44]; 山楂 (*Crataegus pinnatifida*) 多糖与五味子 (*Schisandra chinensis*) 水溶性多糖均可调节肠道菌群结构, 上调 SCFAs 水平, 缓解肠道炎性细胞浸润, 改善炎症状态[45,46]; 茯苓及其水溶性多糖可减轻顺铂引起的回肠及结肠炎性损伤, 与其回调肠道菌群结构及改变宿主代谢谱等有关[47]; 柴胡 (*Bupleurum smithii* var. *parvifolium*) 多糖可增加肠道菌群多样性, 改善肠道屏障功能, 降低链脲佐菌素诱导糖尿病肾病小鼠的血糖、血肌酐和尿白蛋白水平, 缓解肾脏和结肠炎症[48]。

3.4 对精神、情志性疾病的调节 利用"脑-肠轴"干预大脑神经递质水平, 是治疗各种情志性疾病 (如抑郁症) 的潜在策略。银杏叶 (*Ginkgo biloba*) 水溶性多糖可显著降低小鼠焦虑样行为, 上调其海马、大脑皮层和嗅球部位血清素和多巴胺水平, 减轻压力性抑郁症状, 药效与帕罗西汀类似, 同时逆转了抑郁伴随的肠道菌群失调, 且抗抑郁活性与其逆转肠道菌群失调并增加乳酸杆菌丰度呈现高度相关性[49]。随着年龄增长, "脑-肠轴"的改变可能会导致认知障碍。肉苁蓉多糖可恢复认知衰退小鼠肠道菌群稳态及肌酐、缬氨酸、*L*-蛋氨酸、邻甲苯胺、*n*-乙基苯胺、尿酸和脯氨酸代谢水平, 从而减轻氧化应激和外周炎症, 改善小鼠认知功能, 可能与干预"脑-肠轴"功能有关[50]。

3.5 抗肿瘤作用 肠道菌群结构及功能状态与多种肿瘤的发生、发展有关, 同时影响肿瘤治疗效果, 是肿瘤治疗潜在靶标[51,52]。本课题组研究发现, 联合抗生素清除荷瘤小鼠肠道内的拟杆菌等优势菌后, 普罗威登斯菌 (*Providencia*)、变形杆菌 (*Proteus*)、双歧杆菌等

丰度上调, MC38结肠肿瘤的生长被抑制; 口服人参多糖可上调肠杆菌 (*unclassified_f_Enterobacteriaceae*) 和肠球菌 (*Enterococcus*) 丰度, 抑制普罗威登斯菌及变形杆菌丰度, 干预荷瘤小鼠脂质代谢、初级胆汁酸代谢等, 影响肿瘤Toll样受体2/4/9 (Toll-like receptor 2/4/9, TLR2/4/9) 表达, 抑制肿瘤核因子-*κ*B 亚基 p65 (nuclear factor kappa-B p65, NF-*κ*B p65) 信号通路, 表现出抗MC38结肠肿瘤作用[53]。另有研究发现, 人参多糖与程序性死亡受体1单克隆抗体 (alpha programmed cell death protein-1 monoclonal antibody, *α* PD-1 mAb) 联用可增加戊酸水平, 降低*L*-犬尿氨酸及犬尿氨酸/色氨酸比值, 增强机体对PD-1抑制剂的免疫反应, 有助于抑制调节性T细胞 (regulatory T cells, Tregs) 分化, 促进效应T细胞的表达, 与多糖富集狄氏副拟杆菌 (*Parabacteroides distasonis*) 和普通拟杆菌 (*Bacteroides vulgatus*), 将肠道微生物群从无应答重塑为应答模式有关[54]。

4 中药多糖影响汤剂中共存小分子组分的肠菌代谢及吸收、转运

皂苷、黄酮苷等糖苷类成分是中药汤剂中重要的小分子活性组分, 口服后存在肠道菌代谢过程, 经肠菌糖苷酶脱糖、水解代谢为各种次生苷、苷元及其衍生物[55]。中药多糖组分具有肠道菌群调节功能, 继而可能会影响小分子苷类组分的肠菌代谢过程及生物活性。本课题组研究发现[56], 人参多糖能改善人参皂苷Re和Rc的肠道菌群代谢水平; 其次生皂苷20(*S*)-人参皂苷Rd和20(*S*)-人参皂苷Rg3的药时曲线下面积 (AUC) 或达峰浓度C_{max}增加, 与增加*Lactobacillus* spp.和*Bacteroides* spp.的丰度有关[34]; 人参多糖还可回调*β*-葡萄糖苷酶活性, 加快Rb1代谢转化, 使其P_{app}值从10^{-7}增加到10^{-6} cm·s^{-1}, 显著上调肠上皮对Rb1的吸收, 增强Rb1的系统暴露水平[56]。可见人参多糖通过调节肠道菌群多样性可影响小分子人参皂苷体内行为, 协同发挥药效。另外, 党参多糖、肉苁蓉多糖等也可通过促进特异肠道菌的增殖, 增加与其共存的皂苷或苯乙醇苷类成分的吸收, 亦存在协同增效关系[57,58]。

中药汤剂是包含多糖大分子颗粒物的复杂混悬体系, 多糖颗粒对肠道菌群及肠道生态系统具有调节功能, 可通过多种机制促进汤剂中共存成分的吸收, 影响其体内行为, 发挥协同增效作用。对黄连 (*Coptis chinensis*) 汤剂中混悬颗粒进行研究发现, 该类粒子主要由黄连多糖组成, 具有百纳米级大小及负电荷的特征, 这些带负电荷的多糖颗粒可通过调节肠上皮细胞之间的紧密连接蛋白复合物, 促进黄连汤中小檗碱的主动转运和胞内吞噬, 使其肠道吸收表现出电荷依赖性, 提高小檗碱的体内吸收[59]。同时, 黄连多糖颗粒还可调节肠道菌群结构、小肠PPs (Peyer's patches) 和肠上皮免疫反应, 改善肠道微环境[60], 是黄连汤不可或缺的效应组分。

5 中药多糖对肠道菌群调节的结构特异性

本课题组研究发现[61], 生晒参 (WEWG) 和红参 (WERG) 水提物均有减肥活性, 但与WERG相比, WEWG能更好改善HFD肥胖小鼠脂肪积累, 其机制可能与WEWG中性多糖/酸性多糖比例、低聚糖DP2-3/DP4-7比例、蔗糖与蜜二糖比例、麦芽糖与海藻糖比例及人参皂苷初生苷与次生苷比例更高, 从而扶植与肥胖关联的益生菌丰度更高, 进而调控内源性胆酸代谢和肝脏系统性炎症水平更强有关[61]。对白魔芋 (*Amorphophallus albus*) 葡甘露聚糖 (AGM) 及其酶降解产物降血糖作用研究发现[62], 不同分子质量的AGM及其酶降解产物的降血糖活性相当, 对肠道菌群多样性及其代谢物SCFAs和机体内源性代谢物的调节能力也相似, 表明AGM的降血糖活性与其单糖的聚合度无关, 而是由AGM特定的葡萄糖-甘露糖的糖苷键组成特征决定。

6 总结与展望

肠道菌群与多种疾病的发生发展密切相关, 是疾病预防和治疗的潜在靶标。中药多糖组分可通过调节肠道菌群结构和功能发挥抗炎、免疫、代谢调节等作用; 多糖还可影响汤剂中共存小分子组分的代谢和吸收, 发挥潜在协同作用, 可见多糖组分是中药汤剂潜在的效应组分 (图1)。长期以来, 由于研究手段和科学认知的局限性, 人们低估了中药汤剂中多糖类组分的效应贡献, 使“醇沉除杂”去除多糖等大分子组分成了中药创新药研发的普适工艺, 不仅造成了资源的浪费, 更可能影响基于传统汤剂创新药的安全和有效。

经典名方和临床验方是中医长期临床实践的智慧结晶, 既有中医理论指导基础, 也有临床安全有效实据。基于经典名方和临床验方的创新药研发是中医药传承创新的有效抓手之一, 而传承是有效创新的基础。经典名方和临床验方汤剂中多糖组分药效贡献的阐释则是其正确传承和有效创新的要义之一, 是阐明药效物质和进行精准质控的必经路径。

如何阐释中药汤剂中多糖组分的药效贡献还面临诸多挑战, 例如多糖组分结构的精确解析。经典名方和临床验方多为复方制剂, 多糖组分更为复杂, 建立有效的方法对复杂多糖组分进行结构表征是必须解决的瓶颈问题; 复方制剂中多糖组分基于肠道菌靶标的起效机制是必须解决的另一重要问题。多糖组分是调控单一肠道菌起效还是调控肠道微生态起效, 是某均一多糖起效还是多个多糖协同起效, 以及如何协同起效

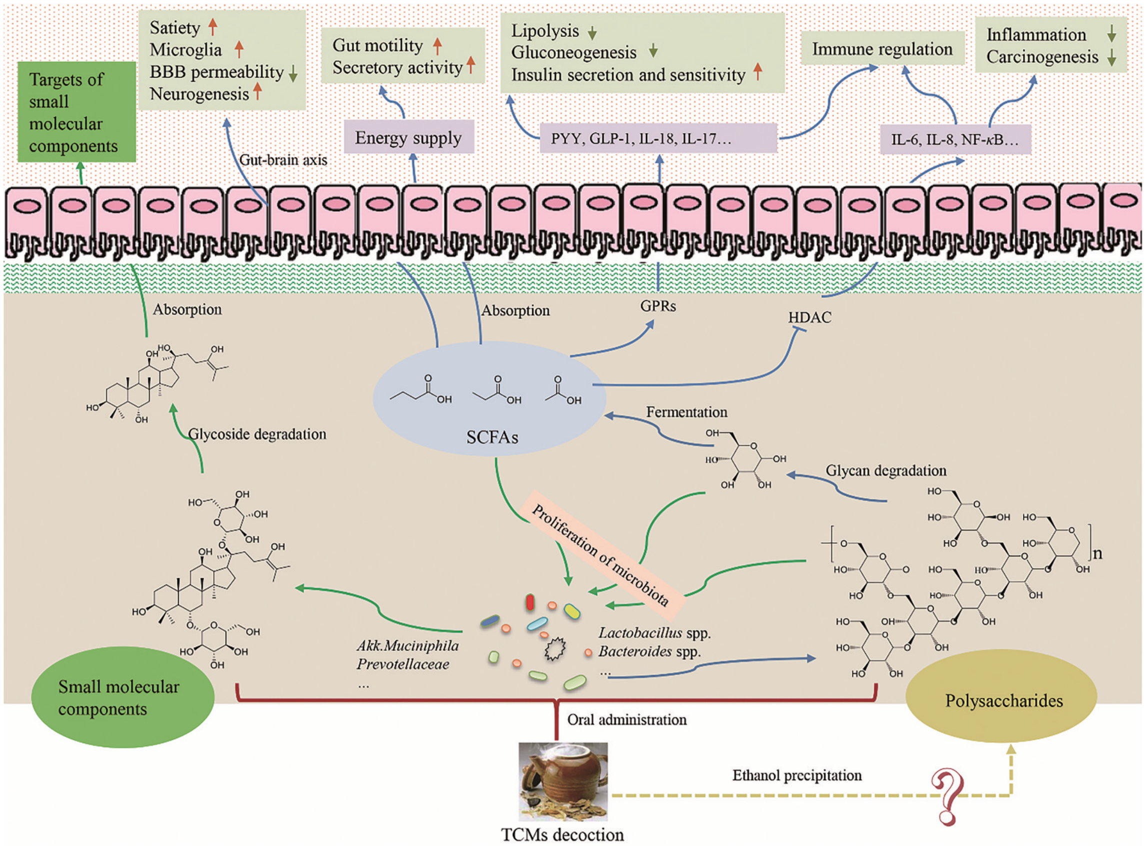

Figure 1 Effect mechanisms of polysaccharides in traditional Chinese medicines (TCMs) decoction mediated by its gut microbiota regulation function. BBB: Blood-brain barrier; PYY: Peptide tyrosine-tyrosine; GLP-1: Glucagon-like peptide-1; IL: Interleukin; NF-κB: Nuclear factor kappa B; GPRs: G protein-coupled receptors; HDAC: Histone deacetylase; SCFAs: Short-chain fatty acids

等都是值得深入探讨的问题; 另外, 中药汤剂中多糖组分如何与共存的小分子组分特别是苷类小分子组分发挥协同作用也是值得关注的问题。无论是多糖组分还是苷类小分子都会与肠道菌互作, 因此它们有可能通过肠道菌介导发挥协同作用。相信随着糖化学技术的不断进步, 肠道菌群与健康和疾病关系研究的不断深入, 中药汤剂中多糖组分的药效贡献会得到更加深入系统的阐明, 必将为基于经典名方和临床验方的创新药研发过程中重视多糖组分的价值提供启示, 为中医药的传承创新研究提供新的思路。

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