“肝脾同调”中药通过菌源胆汁酸–受体轴改善代谢性疾病的研究进展

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摘要: 胆汁酸 (bile acids, BA) 已从传统的脂质消化辅助分子, 演变为调控宿主代谢的关键信号分子。近年来, 微生物来源的胆汁酸修饰酶及其介导的新型胆汁酸代谢通路, 在代谢性疾病发生发展中的作用日益凸显。这些微生物酶通过调节胆汁酸池的组成和比例, 进而影响法尼醇X受体 (FXR)、G蛋白偶联胆汁酸受体 (TGR5) 等关键受体的活性, 参与糖脂代谢、能量稳态和炎症反应的精细调控。中医药“肝脾同调”理论与该轴的稳态维持密切相关。中医学认为, “肝失疏泄”与“脾失健运”是代谢性疾病的核心病机, 现代研究则证实其与胆汁酸代谢紊乱及肠道菌群失调存在内在的生理病理联系。研究表明, “肝脾同调”中药及其活性成分能够通过靶向干预菌源胆汁酸修饰酶, 调节下游FXR、TGR5等受体信号通路, 有效纠正胆汁酸代谢异常并重塑肠道菌群结构, 最终发挥改善胰岛素抵抗、脂质堆积等代谢紊乱的作用。本文系统综述菌源胆汁酸–受体轴在代谢性疾病中的关键靶标并深入探讨“肝脾同调”中医药基于此轴的干预机制, 为中医药防治代谢性疾病提供新的科学阐释与潜在的治疗策略。

关键词: 肝脾同调; 菌源胆汁酸; 胆汁酸受体; 代谢性疾病; 中医药

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Research progress on traditional Chinese medicines for metabolic diseases *via* the microbiota-derived bile acid-receptor axis based on the "harmonizing liver-spleen" theory

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Abstract: Bile acids (BAs) have evolved from their traditional role as auxiliary molecules in lipid digestion to critical signaling molecules regulating host metabolism. In recent years, the role of microbiota-derived bile acid-modifying enzymes and their mediated novel bile acid metabolic pathways in the pathogenesis and progression of metabolic diseases has become increasingly prominent. These microbial enzymes fine-tune glucose and lipid metabolism, energy homeostasis, and inflammatory responses by modulating the composition and proportion of the bile acid pool, thereby influencing the activity of key receptors such as the farnesoid X receptor (FXR) and the G protein-coupled bile acid receptor (TGR5). The theory of "harmonizing the liver and spleen" in traditional Chinese medicine (TCM) is closely related to the maintenance of homeostasis of the liver-spleen axis. TCM posits that "liver Qi failing to ensure free flow" (liver dysfunction) and "spleen failing to transport and transform" (spleen

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dysfunction) are the core pathogenesis of metabolic diseases, while modern research has confirmed their intrinsic pathophysiological links to bile acid metabolic disorders and gut microbiota dysbiosis. Studies have shown that TCM formulations and active ingredients based on the "harmonizing the liver and spleen" principle can effectively ameliorate metabolic disorders such as insulin resistance and lipid accumulation by targeted intervention of microbiota-derived bile acid-modifying enzymes, regulating downstream receptor signaling pathways like FXR and TGR5, consequently correcting bile acid metabolic abnormalities and remodeling the gut microbiota structure. This review systematically summarizes the key targets of the microbiota-derived bile acid-receptor axis in metabolic diseases and delves into the intervention mechanisms of "harmonizing the liver and spleen" TCM strategies based on this axis, aiming to provide a new scientific explanation and potential therapeutic strategies for the prevention and treatment of metabolic diseases with TCM.

Key words: harmonizing liver and spleen; microbiota-derived bile acid; bile acid receptor; metabolic disease; traditional Chinese medicine

胆汁酸 (bile acids, BA) 代谢是连接宿主与肠道微生物的重要桥梁[1]。传统观点认为, BA 主要由肝脏合成, 在肠道菌群作用下转化为次级胆汁酸, 通过肠肝循环调节脂质消化吸收。然而, 近年研究发现, 微生物对胆汁酸的修饰远超出传统认知, 产生了许多具有独特生物学功能的新型胆汁酸[2,3]。这些菌源胆汁酸作为重要的信号分子, 经法尼醇 X 受体 (FXR)、G 蛋白偶联胆汁酸受体 (TGR5) 等特定受体介导, 广泛调控肠道稳态、免疫应答及全身能量代谢, 其信号网络的失调与肥胖、胰岛素抵抗及非酒精性脂肪性肝病等多种代谢紊乱的发生发展密切相关, 已成为代谢性疾病精准干预的潜在分子靶点[4,5]。

中医理论认为, 肝主疏泄, 调畅气机, 促进脾胃运化; 脾主运化, 统摄水谷精微, 为气血生化之源[6]。肝脾两脏在五行中属木土关系, 生理上相互资生, 病理上相互影响, 构成“肝脾同调”的理论核心[7]。中医“肝主疏泄、脾主运化”的理论为理解代谢性疾病的整体调控提供了独特视角, 肝脾同调理论与菌源胆汁酸−受体轴存在深刻的内在联系。现代研究表明, “肝失疏泄”与胆汁酸合成及肠肝循环紊乱、FXR 信号抑制密切相关, 而“脾失健运”则常与肠道菌群失调、菌源胆汁酸代谢酶功能异常相关联[8,9]。这种中西医之间的理论对接, 为深入理解代谢性疾病的发病机制及中药干预策略提供了新的思路。本文系统梳理菌源胆汁酸−受体轴的研究进展, 并将其与中医“肝脾同调”理论相结合, 探讨中药通过调控该轴防治代谢性疾病的潜在机制, 为代谢性疾病的中医药防治提供新的理论基础和研究方向。

1 中医“肝脾同调”理论的现代科学内涵

随着现代生物医学的发展, 肝脾同调理论的科学内涵逐渐得到阐释。肝脏作为人体最大的代谢器官, 参与糖、脂、蛋白质等多种物质的代谢过程, 其功能与中医“肝主疏泄”的理论高度吻合[10]。肝脏通过合成和分泌胆汁酸、调节血糖、合成脂蛋白等方式, 维持机体的代谢平衡。当肝脏功能异常时, 可导致血脂异常、血糖升高、胆汁淤积等一系列代谢紊乱, 这与中医“肝失疏泄”的理论相符[11]。

“脾主运化”的功能则与现代消化吸收、免疫调节及肠道微生态稳态密切相关[12]。从现代生物学角度看, 肠道菌群在肠黏膜保护、代谢、免疫稳态、病原抑制及消化吸收等方面发挥重要作用, 这与脾的运化功能高度一致[13,14], 可以视为“脾主运化”功能的重要组成部分。已有研究证实, 从脾虚证患者到相关模型动物均存在显著的肠道微生态失调, 继而重塑胆汁酸池引起胆汁酸代谢紊乱, 而脾虚证常用药物能有效缓解该肠道菌群紊乱[15-17]。因此, 肠道菌群失调可能是中医脾虚证重要的生物学基础[18,19] (图 1)。

基于“肝脾同调”理论视角, 本研究提出“菌源胆汁酸−受体轴”作为连接肝脾功能与代谢稳态的核心生物学桥梁。主要包含 3 个相互关联的病理生理层级: 在第一层级, 肝失疏泄 (肝郁) 直接影响肝脏胆汁酸合成与肠肝循环, 导致胆汁酸池组成谱系紊乱, 进而引起 FXR 与 TGR5 信号传导失衡[20,21]。这种受体信号失调可进一步加剧肝糖异生与脂质新生, 形成代谢紊乱的始动环节[22]。在第二层级, 脾失健运 (脾虚) 导致肠道微生态失调, 具体表现为胆汁盐水解酶 (BSH)、7α-脱羟基酶及羟基类固醇脱氢酶 (HSDH) 等关键菌源酶系的活性改变[23]。这种菌源胆汁酸修饰酶的活性变化直接导致次级胆汁酸池 (如石胆酸、脱氧胆酸等) 的重塑, 引起胆汁酸受体激活模式的选择性漂移, 从而改变下游代谢信号通路的传导效率, 进一步加重肠道菌群结构失调[24]。在第三层级, 肝郁与脾虚相互影响, 形成恶性循环: 肠道屏障完整性破坏, 内毒素易位增加, 激活 Toll 样受体 4-核因子 κB 炎症信号通路, 诱发慢性低

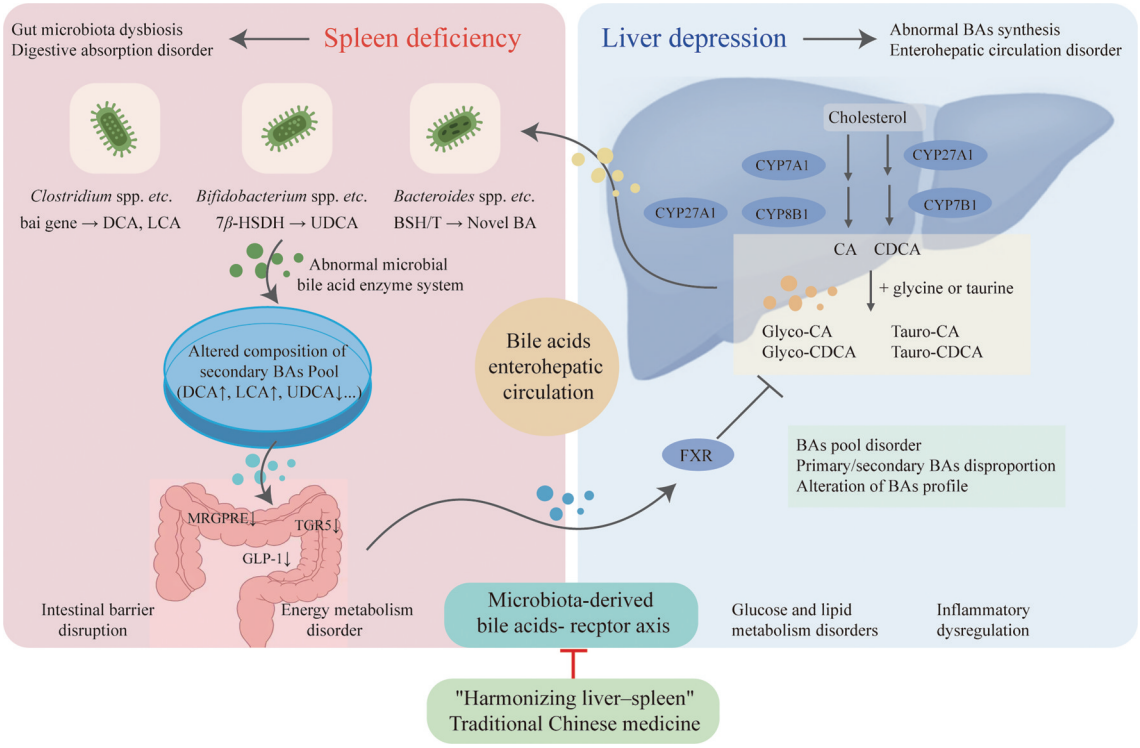


Figure 1 The mechanism of the TCM principle "harmonizing liver-spleen" and its interplay with the microbiota-derived bile acid-receptor axis. TCM: Traditional Chinese medicine; CA: Cholic acid; CDCA: Chenodeoxycholic acid; DCA: Deoxycholic acid; LCA: Lithocholic acid; UDCA: Ursodeoxycholic acid; FXR: Farnesoid X receptor; BAs: Bile acids; MRGPRE: Mas-related G protein-coupled receptor member E; TGR5: Takeda G protein-coupled receptor 5; GLP-1: Glucagon-like peptide-1; CYP7A1: Cytochrome P450 family 7 subfamily A member 1; CYP27A1: Cytochrome P450 family 27 subfamily A member 1; CYP8B1: Cytochrome P450 family 8 subfamily B member 1; CYP7B1: Cytochrome P450 family 7 subfamily B member 1

度炎症状态[25]。这种持续性炎症微环境最终导致胰岛素抵抗、非酒精性脂肪性肝病及动脉粥样硬化等代谢性疾病的发生与发展[26]。在这一框架下, 中医药干预的核心机制在于通过“疏肝”调节肝脏胆汁酸合成代谢与核受体信号网络, 通过“健脾”恢复肠道菌群稳态与菌源酶系功能平衡, 最终实现对菌源胆汁酸–受体轴的系统性重塑, 恢复机体代谢稳态[27] (图 1)。

2 菌源胆汁酸–受体轴的分子构成与调控网络

2.1 菌源胆汁酸的生物合成与修饰 肠道菌群是胆汁酸次级代谢过程中的“代谢枢纽”, 通过其基因组编码的多种酶对宿主分泌的初级胆汁酸进行结构修饰, 从而极大地丰富了胆汁酸的种类和功能[28]。菌源胆汁酸 (microbiota-derived bile acids, MDBAs) 是指由肠道菌群对肝脏合成的初级胆汁酸进行去结合、去羟基、氧化还原、异构化、氨基酸结合等代谢反应后生成的多样化胆汁酸分子 (图 2)。

人体胆汁酸池约四分之一由肠道菌群二次加工而成[29]。在经典途径中, 肝脏合成的胆酸 (CA) 与鹅脱氧胆酸 (CDCA) 随胆汁进入肠道, 菌群产生的胆盐水解酶 (BSH) 首先去结合, 释放游离型胆汁酸; 随后 *Clostridium*、*Bacteroides*、*Bifidobacterium* 等通过 bai 基因簇编码产生的 7α-脱羟基酶将 CDCA、CA 分别转化为石胆酸 (LCA) 与脱氧胆酸 (DCA)[30,31]。

除上述经典脱羟途径外, 拟杆菌门菌群还普遍表达羟基类固醇脱氢酶 (HSDH), 在胆汁酸的 C3、C7、C12 位点实施氧化–差向异构, 将疏水性的 CDCA、DCA 进一步转化为亲水性更强的熊脱氧胆酸 (UDCA) 及异构石胆酸 (iso-LCA), 一方面降低膜毒性, 另一方面选择性激动膜受体 TGR5, 从而放大棕色脂肪产热和胰高血糖素样肽-1 (GLP-1) 分泌, 调节能量代谢与免疫[32]。宏基因组学挖掘出的 NAD 依赖型 C-3 氧化还原酶 (命名 baox) 则把 CA 重新塑造成异构胆酸 (iso-CA), 该代谢物通过激活肠上皮维生素 D 受体 (VDR) 并驱动 IL-10 转录, 有效抑制 Th17 分化, 成为菌群–免疫互作的新节点。对于高疏水且潜在肝毒性的 LCA, *B. thetaiotaomicron* 等菌株利用磺基/乙酰转移酶将其硫酸化为 LCA-3S, 产物不仅水溶性骤增、可经尿液快速清除, 还能作为孕烷 X 受体 (PXR) 配体启动宿主解毒程序[33]。

最新研究揭示菌群可通过“氨基酸–胆汁酸偶联”

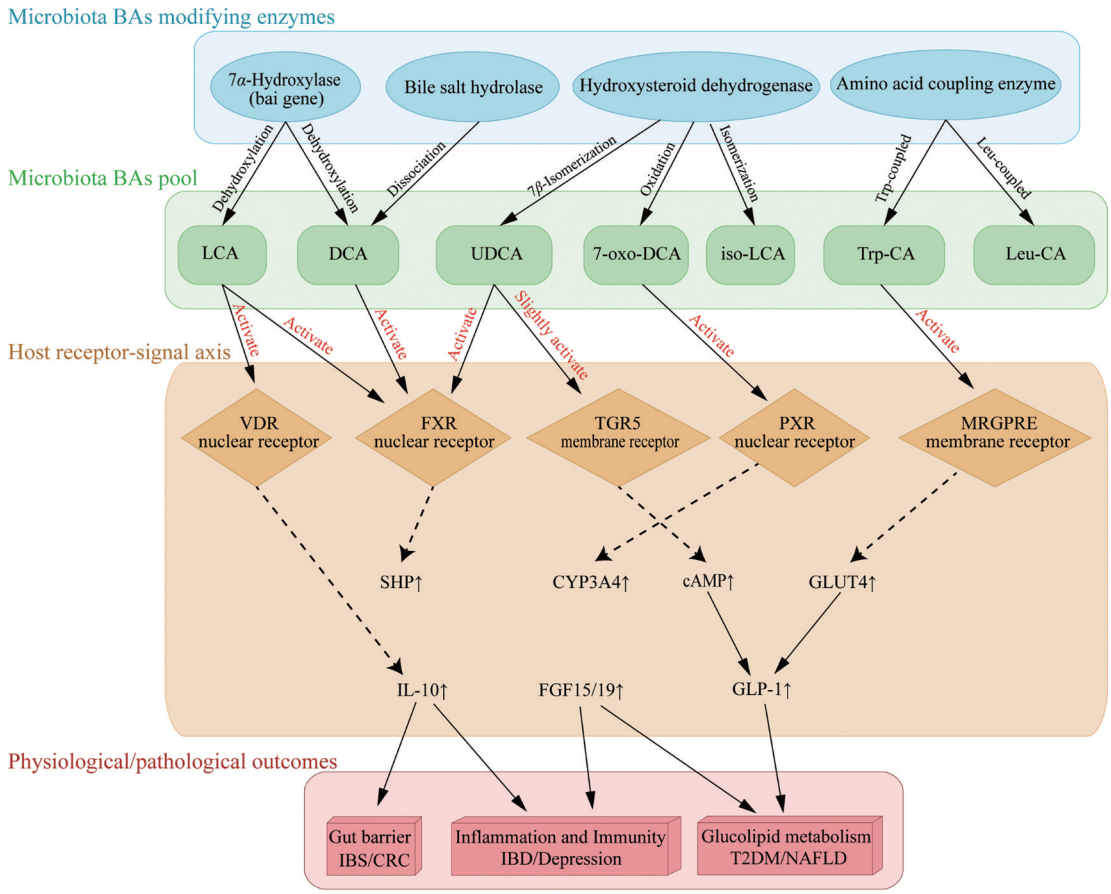


Figure 2 Key metabolites and target pathways in the microbiota-derived bile acid-receptor axis. VDR: Vitamin D receptor; PXR: Pregnane X receptor; SHP: Small heterodimer partner; CYP3A4: Cytochrome P450 family 3 subfamily A member 4; cAMP: Cyclic adenosine monophosphate; GLUT4: Glucose transporter type 4; IL-10: Interleukin-10; FGF15/19: Fibroblast growth factor 15/19; IBS: Irritable bowel syndrome; IBD: Inflammatory bowel disease; CRC: Colorectal cancer; T2DM: Type 2 diabetes mellitus; NAFLD: Non-alcoholic fatty liver disease

生成全新骨架的微生物胆汁酸，如色氨酸−胆酸(Trp-CA)[34]。新近发现的3-酰基化修饰及其关键酶3-suc-CA合成酶(BAS-suc)的鉴定，揭示了其在MASH防治中的潜在价值[35]。此外，5α/β-还原酶(5AR/5BR)是另一类重要的菌源胆汁酸修饰酶。5AR能催化3-oxo-Δ4-LCA生成isoalloLCA，该代谢物在百岁老人肠道富集，能通过核受体亚家族4组A成员1(NR4A1)调控Treg细胞活性，并对耐药菌(如艰难梭菌)具有强杀菌作用[36]。这些发现极大地拓展了研究人员对菌源胆汁酸功能多样性的认知。

通过这些层次分明的菌源胆汁酸修饰酶的作用，肠道菌群将传统意义上仅参与脂质乳化的胆汁酸转化为兼具代谢、免疫及神经调控功能的多效内源性分子；后者通过FXR、TGR5等受体以组织特异性方式调控肝糖异生、棕色脂肪产热、肠屏障完整性及中枢摄食信号，从而把局部微生物代谢事件整合为系统性能量稳态网络，实现菌群由代谢辅助角色向全身内分泌调控节点的功能性跃迁。

尽管bsh、bai、hsdh、3-suc-CA-synthase及5α/β-reductase等基因已被鉴定，但其菌株−地域分布高度可变，且不断有新基因簇被报道。为避免给读者造成静态或片面的菌群归类印象，本文未提供相关总结性图表，关于胆汁酸修饰基因−菌株数据可参考持续更新的公共数据库以及新近研究。

2.2 受体信号网络 胆汁酸作为重要的内源性信号分子，通过激活一系列特定的受体，广泛调控着宿主的代谢、免疫与能量稳态。该网络主要由FXR、TGR5以及多种核受体[PXR、VDR、组成型雄甾烷受体(CAR)]构成，共同维持胆汁酸的代谢平衡并介导其多样化的生理功能[37]。其中，FXR主要表达于肝、肠，负反馈调节胆汁酸合成并促进其外排；PXR/CAR在肝高表达，诱导CYP3A4及SULT2A1生成，加速LCA硫酸化解毒；TGR5分布于胆管上皮及棕色脂肪，调控胆汁流动与能量消耗；VDR在肝−肠轴拮抗FXR，抑制

炎症[38-40]。

FXR-FGF15/19轴是胆汁酸合成的核心负反馈调节器。FXR作为胆汁酸代谢最重要的核受体, 对初级胆汁酸CDCA及次级胆汁酸DCA表现出高亲和力, 激活后诱导小分子异二聚体伴侣 (SHP) 和成纤维细胞生长因子15/19 (FGF15/19) 转录, 通过负反馈抑制胆固醇7α-羟化酶 (CYP7A1), 减少肝内胆汁酸合成; 同时FXR可阻断NF-κB核转位, 降低炎症因子表达, 改善胰岛素敏感性[41,42]。

TGR5-cAMP轴是机体能量代谢与糖稳态的核心膜受体信号通路。TGR5是膜定位G蛋白偶联受体, LCA、UDCA及猪胆酸 (HCA) 等均可激活该受体, 升高细胞内cAMP水平, 促进GLP-1分泌、棕色脂肪组织产热及巨噬细胞M2型极化, 从而增强能量消耗并抑制慢性炎症[43,44]。PXR/VDR/CAR是外源物代谢与肠道炎症的解毒–抗炎重要受体。孕烷X受体 (PXR)、维生素D受体 (VDR) 和组成型雄甾烷受体 (CAR) 被报道可部分识别胆汁酸代谢产物, 参与药物代谢、解毒及肠道屏障功能的调节[45]。

此外, 新近研究鉴定出Trp-CA为孤儿受体MRGPRE的内源性配体, 受体激活后通过Gs-cAMP和β-arrestin-1-ALDOA双信号通路促进GLP-1和胰岛素的分泌, 为2型糖尿病 (T2DM) 的治疗提供了新靶点[34], 也预示着针对特定菌源胆汁酸–受体轴进行精准干预的可能。

3 菌源胆汁酸–受体轴与代谢性疾病

菌源胆汁酸–受体轴的失调是肥胖、T2DM、非酒精性脂肪性肝病 (NAFLD)/非酒精性脂肪性肝炎 (NASH)、炎症性肠病 (IBD) 乃至肝细胞癌 (HCC)/结直肠癌 (CRC) 等一系列代谢性疾病发生发展的重要环节[46,47]。在肥胖状态下, 菌群BSH活性下降引致的游离胆汁酸减少, 会过度激活肠道FXR信号, 进而促进肝脏脂肪生成[48]; 而在T2DM中, 菌群7α-脱羟基化作用增强则使DCA生成过多, 诱发肝脏胰岛素抵抗[49]。有研究发现, 肥胖与T2DM患者普遍存在厚壁菌门/拟杆菌门比值升高、BSH活性菌减少, 导致胆汁酸去结合能力下降, 回肠FXR过度激活, 抑制肝脏胆汁酸合成, 加重脂质堆积和胰岛素抵抗[50]。

此外, 过量DCA还能通过激活TGR5受体, 驱动肝星状细胞促纤维化反应, 加速非酒精性脂肪性肝病 (NAFLD/NASH) 的疾病进程[51]。研究显示, 在NAFLD/NASH患者中, 肝郁脾虚证患者粪便中7α-脱羟基菌 (如 *Clostridium scindens*) 富集, 次级胆汁酸DCA升高, 通过激活肝星状细胞TGR5-IL-6-STAT3通路促进纤维化[52]。此外, 代谢相关脂肪性肝病 (MAFLD) 中, “土壅木郁”证患者肠道阿克曼菌 (*Akkermansia*) 丰度降低, 胆汁酸谱中UDCA、TUDCA等抗炎胆汁酸减少, FXR信号抑制不足, 加速疾病进展[53]。而在肠道局部, 抗炎胆汁酸 (如iso-LCA、UDCA) 的减少会削弱VDR信号, 造成Th17/Treg免疫失衡, 从而加剧IBD[54]。更值得注意的是, DCA还能通过激活β-catenin、EGFR-Src等促癌信号通路直接驱动HCC与CRC的发生, 且菌群7α-脱羟酶 (baiE) 基因丰度与结直肠癌术后复发风险呈正相关[55]。

综上所述, 菌源胆汁酸–受体轴在不同代谢性疾病中通过调控代谢、炎症与纤维化等关键病理过程扮演着关键角色 (图2), 这不仅为“肝脾同调”理论铺垫了分子证据, 也为从“肝脾同调”整体观出发, 运用中医药调控该轴为防治代谢性疾病提供了坚实的现代科学依据及精准靶点。

4 中医药通过“肝脾同调”调控菌源胆汁酸–受体轴的机制

中医“肝脾同调”理论是指导代谢性疾病辨证论治的核心思想之一, 其认为肝主疏泄、脾主运化, 肝脾功能失调是代谢病发生发展的关键病机。近年来, 随着“肠–肝”轴和“菌–胆–病”轴研究的深入, 越来越多的证据表明, 中医“肝脾同调”理论的生物学基础可能与菌源胆汁酸–菌群轴的稳态密切相关 (图3)。

4.1 疏肝健脾类方剂调节BSH与胆汁酸去结合

逍遥散是“肝脾同调”的代表方剂, 由柴胡、白芍、白术、茯苓等组成。研究发现, 逍遥散可改善肝郁脾虚型T2DM大鼠的抑郁表型和血糖异常, 同时增加其肠道乳酸杆菌、双歧杆菌等BSH高表达菌的丰度, 提升粪便去结合胆汁酸比例, 降低回肠FXR活性, 增加肝脏CYP7A1表达, 促进胆汁酸合成和排泄, 改善糖脂代谢[56]。并且, 体外实验也发现逍遥散的含药血清可上调NCM460细胞TGR5和GLP-1表达, 其作用与增加UDCA和iso-LCA, 以及调节肝郁脾虚型T2DM糖代谢失调相关[56]。

四逆散作为疏肝解郁、调和肝脾的鼻祖方剂, 其现代药理机制得以深化。研究表明, 四逆散能有效缓解肝损伤和纤维化, 并通过调节肠道菌群结构而提高肠道微生物BSH的活性, 改变胆汁酸池组成, 进而激活FXR受体, 最终改善肝纤维化[57]。这为四逆散“疏肝解郁”靶向“菌群-BA-FXR”轴改善糖脂代谢提供了直接证据。

四逆泻心合方 (半夏泻心汤合四逆散) 是治疗MAFLD的常用方。临床随机对照试验表明, 该方干预肝郁脾虚型MAFLD患者4周后, 有效逆转了患者血清肝酶学 (ALT、AST) 异常水平及胁肋疼痛、胸脘痞满等肝郁脾虚表型, 粪便BSH活性菌 (如 *Lactobacillus johnsonii*) 丰度上升, 血清TCA、TCDCA水平下降,

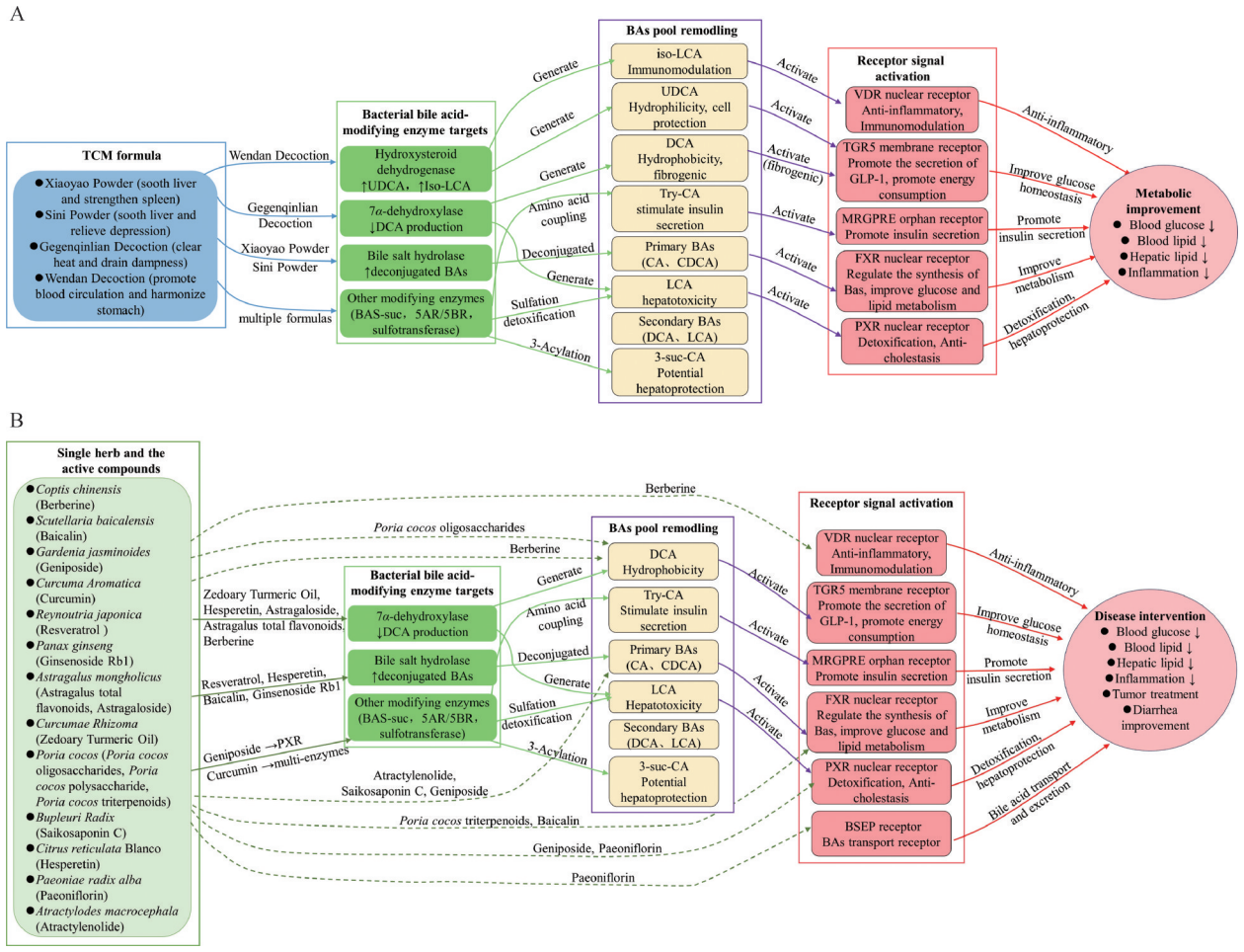


Figure 3 Potential targets and mechanism pathways of TCM prescription (A) and single herb with their active ingredients (B) in regulating the microbiota-derived bile acid-receptor axis. 3-suc-CA: 3-Succinylcholic acid; BSEP: Bile salt export pump

FGF19减少, 肝脂肪变性和炎症评分显著改善[58]。机制上, 该方可能通过抑制回肠FXR/FGF15轴, 促进肝脏CYP7A1介导的胆汁酸合成, 加速胆固醇转化。

4.2 健脾化湿类方剂调控7α/β-脱羟基与次级胆汁酸代谢 健脾化湿方 (含黄芪、白术、薏苡仁等) 在*Apc*$^{Min/+}$小鼠模型中显示抗肠道肿瘤作用。该方可以减少肠道腺瘤数量, 抑制肠道肿瘤发生, 保护肠道完整性和抑制炎症反应, 并显著增加阿克曼菌 (*Akkermansia*)、厌氧弧菌 (*Anaerovorax*) 等有益菌, 降低*Alistipes*、*Helicobacter*等有害菌, 并上调β-UDCA和TUDCA水平。相关性分析显示, TUDCA与阿克曼菌丰度正相关, 与*Alistipes*负相关, 表明其通过重塑菌群−胆汁酸互作抑制肿瘤[59]。

芩连红曲汤 (含黄芩、黄连、红曲) 改善高脂血症大鼠模型的血脂异常, 减轻肝脂质和脂滴的沉积, 其机制与降低厚壁菌门/拟杆菌门比值、增加拟杆菌门丰度、促进胆汁酸排泄相关。靶向代谢组学显示, 该方降低结肠内容物初级胆汁酸 (TCA、TCDCA), 提升次级胆汁酸 (DCA、LCA) 比例, 激活TGR5-GLP-1通路[60]。

葛根芩连汤作为清热利湿的代表方, 其调控机制更为精细。研究发现, 它可减缓肠黏液屏障受损, 减轻肠道炎症和病理损伤, 并通过抑制微生物baiE基因的表达, 减少次级胆汁酸DCA的生成; 同时, 它能提高另一种菌源胆汁酸iso-LCA的水平, 从而激活VDR受体, 促进抗炎因子IL-10的产生; 此外, 它还能恢复肠道紧密连接蛋白ZO-1的表达[61]。这三重机制共同作用, 有效维护肠道屏障与免疫稳态。

温胆汤针对痰证, 其化痰和胃、疏肝利胆的功效在代谢综合征模型中得到诠释。该方能有效降低体脂和血脂, 改善胰岛素抵抗及脂多糖蓄积, 并降低肠道菌群中厚壁菌门/拟杆菌门的比值, 提升具有肝保护作用的UDCA水平, 并抑制肠道FXR-FGF15信号通路, 解除肝脏CYP7A1的抑制, 促进胆汁酸合成与胆固醇清除, 从而减少肝脏脂肪堆积[62]。

4.3 补肾活血类方剂影响HSDH与次级胆汁酸生成 补肾活血方在T2DM视网膜病变 (DR) *db*/*db*小鼠

中, 减轻了小鼠的血糖异常, 以及视网膜慢性炎症及视网膜微血管病变相关指标, 并通过增加毛螺菌科(Lachnospiraceae) 丰度, 降低血清胆酸和石胆酸, 提升UDCA水平, 抑制视网膜NF-κB炎症通路, 减轻微血管病变[63]。

芍药甘草汤治疗脾气虚证多囊卵巢综合征(PCOS) 的研究发现, 该方能有效减轻PCOS大鼠体重及卵巢重量, 恢复动情周期规律, 调节性激素及血脂水平; 此外, 该方还可上调肠道阿克曼氏菌属、拟杆菌属、布劳特氏菌属、粪球菌属、颤螺菌属和瘤胃球菌属, 促进UDCA和TUDCA生成, 提高初级BAs/次级BAs比例, 激活胆汁酸-FXR轴, 改善卵巢胰岛素抵抗和激素紊乱[64]。

4.4 中药活性成分对菌源胆汁酸–受体轴的干预作用 中药活性成分凭借其确定的化学结构, 为在分子层面破译“成分–菌源胆汁酸–受体”间的因果联系提供了可能, 从而极大地推动了相关药理机制的精准解析。因此, 本综述总结了调和肝脾类中药 (黄芪、莪术、茯苓、柴胡、陈皮、白芍、白术等) 中已报道的部分重要中药活性成分, 调控胆汁酸及其受体信号轴缓解肝郁脾虚证候疾病的研究现状[65-72] (图3)。

小檗碱主要来源于黄连等中药, 具有降血脂、降血糖、抗菌、抗病毒、抗炎、抗阿尔茨海默病和抗肿瘤等多种药理活性。其被证实是微生物胆汁酸代谢的强力调节剂, 能直接抑制肠道细菌的baiE, 减少毒性次级胆汁酸DCA的生成; 同时, 它又能激活TGR5受体, 通过cAMP-PKA信号通路增加GLP-1的分泌, 双重机制协同发挥降糖作用[46]。

黄芩苷是黄芩等中药的重要活性成分, 被发现能够缓解药物导致的早期腹泻, 减轻结肠损伤, 维持肠道屏障及肠道菌群稳态, 且其作用靶点指向肠道FXR。具体而言, 它通过抑制肠道FXR的活性, 解除其对肝脏CYP7A1的转录抑制, 促进胆汁酸合成。此外, 它还能提高BSH活性, 增加游离型胆汁酸的比例, 优化胆汁酸池[73]。

栀子中含有的京尼平苷则展示了通过调控胆汁酸代谢解毒途径发挥保肝作用的机制。它对肝损伤有明显的抑制作用, 可有效改善大鼠肝功能, 降低血清中总胆红素 (TBIL) 和直接胆红素 (DBIL) 等胆汁淤积标志物水平, 还能够抑制CYP7A1和激活FXR, 加速胆汁酸排泄, 从而减轻胆汁淤积性肝损伤[74]。

姜黄素是姜黄的主要活性成分, 具有抗炎、抗氧化等药理作用, 被发现在调节胆汁酸合成与能量代谢方面具有较强活性。它不仅可改善高脂饮食诱导的大鼠肠道炎症, 减轻肝脂肪变性, 还能调节肠道菌群增加DCA和LCA的含量, 进一步的TGR5敲除实验证实, 姜黄素通过激活TGR5-UCP1信号轴促进白色脂肪组织褐变与能量消耗的起效机制, 为其抗肥胖作用提供了新解释[75]。

白藜芦醇为一种著名的植物多酚, 具有降脂、降血糖、抗氧化和抗炎等药理作用, 其益处与肠道微生态重塑紧密相连。它能够特异性上调阿克曼菌的丰度, 降低厚壁菌门/拟杆菌门比值, 重塑肠道菌群平衡, 并增强BSH活性, 通过介导回肠胆汁酸受体FXR影响胆汁酸组成, 保护肠道以抵御有害微生物的侵害而改善高脂血症[76]。

人参皂苷Rb1被证实可通过重塑宿主–微生物代谢稳态延缓动脉粥样硬化的发生。它可增加肠道乳酸杆菌丰度, 增强BSH活性, 促进肠道共轭胆汁酸水解和排泄, 进而抑制肠肝FXR-FGF15信号, 从而增加CYP7A1转录表达, 促进胆固醇代谢消除改善动脉粥样硬化[77]。

5 总结与展望

近年来, 科学研究逐渐揭示了中医证候与胆汁酸–菌群轴之间的内在联系。肝郁证、脾虚证及湿热证等常见证型均表现出特征性的胆汁酸谱与肠道菌群结构改变。这些发现为中医证候的客观化诊断提供了潜在生物标志物, 也为阐释“肝失疏泄”与“脾失健运”等病机的现代科学内涵提供了新的视角。然而, 该领域研究仍存在一定局限性。现有证据多来源于横断面研究, 样本量有限, 且缺乏标准化的证候评判与检测流程, 导致结果可比性不足。此外, 现有分析多基于单一指标, 尚需建立能够整合多维度数据的判别模型以提升证候识别的准确性与可靠性。

未来研究应着力于推动研究方法的标准化和多组学数据的整合。建立统一的检测方案与标准操作程序, 涵盖核心胆汁酸定量、菌群宏基因组功能分析及宿主遗传背景评估。并在此基础上, 构建“证候–胆汁酸谱–菌群功能”的研究框架, 通过多组学技术与机器学习方法, 系统解析证候的生物学基础、发掘可靠的生物标志物、阐明中药的干预机制, 并推动其在辅助诊断与精准治疗中的转化应用, 从而为中医药防治代谢性疾病提供更具说服力的科学依据。

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