•综述•

肠道菌群−胆汁酸-FXR轴干预结直肠癌的研究进展及中药干预的现状分析

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摘要: 肠道菌群在结直肠癌 (colorectal cancer, CRC) 的发展中起着至关重要的作用。失衡的肠道菌群对机体产生损害并扰乱胆汁酸 (bile acids, BAs) 代谢, 增加结直肠癌易感性, 同时影响法尼醇X受体 (farnesoid X receptor, FXR) 信号传导, 进而促进结直肠癌发展。中药因其多成分、多靶点、多通路的协同调控作用在结直肠癌治疗中有独特的优势, 能够通过调节肠道菌群, 干预胆汁酸代谢及激活其受体FXR抑制结直肠癌的发生发展。基于此, 本文对肠道菌群−胆汁酸-FXR轴在结直肠癌发展中所起的主要作用进行综述, 并讨论中药干预肠道菌群−胆汁酸-FXR轴抗结直肠癌作用及机制, 以期为结直肠癌预防与治疗提供新的思路和方法。

关键词: 结直肠癌; 肠道菌群; 中药; 胆汁酸; 法尼醇X受体

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Traditional Chinese medicine regulates the gut microbiota-bile acids-FXR axis to intervene in the development of colorectal cancer

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Abstract: The gut microbiota plays a crucial role in the development of colorectal cancer (CRC). The imbalanced gut microbiota causes damage to the body and disrupts bile acids metabolism, increases susceptibility to CRC, and affects the signaling of farnesol X receptor (FXR), thereby promoting CRC progression. Traditional Chinese medicine has unique advantages in the treatment of CRC due to its synergistic regulatory effects of multiple components, targets, and pathways. It can regulate gut microbiota, intervene in bile acids metabolism, and activate its receptor FXR to inhibit the occurrence and development of CRC. Based on this, this article discusses the main role of the gut microbiota-bile acids-FXR axis in the development of CRC, and reviews the anti CRC effects and mechanisms of traditional Chinese medicine intervention on gut microbiota-bile acids-FXR axis, in

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order to provide new ideas and methods for the prevention and treatment of CRC.

Key words: colorectal cancer; intestinal microbiota; traditional Chinese medicine; bile acid; farnesoid X receptor

结直肠癌 (colorectal cancer, CRC) 是世界各国发病率和死亡率较高的恶性肿瘤之一, 位居2022年中国所有恶性肿瘤新发病例中的第二位, 占10.72%[1]。在过去的30年里, 中国结直肠癌的发病率明显上升。越来越多研究表明, 肠道菌群的失衡与结直肠癌的发生发展有着较高的相关性[2]。

肠道菌群是寄生在机体肠道内的细菌、真菌、病菌等微生物组成的群落, 是组成和保护机体肠道黏膜的一道生物屏障[3]。研究发现[4], 肠道菌群产生的代谢产物胆汁酸 (bile acids, BAs) 具有C24甾醇结构, 其羟基和羰基同向排列于甾醇核心, 而甲基反向, 这种独特的化学结构赋予了胆汁酸两亲性促进脂肪和胆固醇的消化。然而, 当肠道菌群失调, 肠道内疏水性胆汁酸浓度将异常升高。高浓度的疏水性胆汁酸具有细胞毒性, 能够通过损伤结肠上皮细胞、诱导活性氧 (reactive oxygen species, ROS) 产生及引发炎症反应等机制增加结直肠癌易感性, 加速结直肠癌的发生发展[5,6]。法尼醇X受体 (farnesoid X receptor, FXR) 作为由胆汁酸激活的核受体, 能够调节胆汁酸代谢, 将胆汁酸浓度维持在正常生理范围内, 防止胆汁酸诱导的细胞毒性[7]。肠道菌群失衡会间接引发胆汁酸合成与代谢的紊乱, 进而下调FXR的表达。研究表明[8], FXR的表达缺失不仅激活致癌信号通路, 增加结直肠癌侵袭性, 促进肿瘤发生, 还会影响肠道菌群构成, 导致促癌菌群丰度增加, 进一步加剧肠道微生态失衡, 加速结直肠癌发生发展的恶性循环。综上, 肠道菌群失调会导致胆汁酸代谢异常, 进而影响FXR的表达, 并且FXR表达的下调又促使肠道菌群向更为无序的方向进行, 肠道菌群−胆汁酸-FXR轴中的多种因素相互作用, 共同影响着结直肠癌的发展。

因此, 本文将对肠道菌群−胆汁酸-FXR轴在结直肠癌发展中起到的主要作用进行综述, 并讨论中药干预这一轴线抗结直肠癌作用, 以期为今后结直肠癌的预防与治疗提供新的思路和方法。

1 肠道菌群与胆汁酸代谢

肠道菌群作为人体的第二器官, 具有广泛的代谢谱, 能够与肝脏和肠道黏膜中哺乳动物酶互补并参与调节多种生理过程, 它们是影响饮食生化特征及宿主健康的关键因素[2]。

胆汁酸由肝脏中的胆固醇合成, 并被转运到肠道[9]。肝脏中产生的初级胆汁酸主要以氨基酸缀合物的形式被转运至肠腔[10], 在那里它们的作用是促进饮食中脂质和维生素的吸收[10]。胆汁酸通过回肠远端的主动转运和整个肠道的被动吸收的过程被重新吸收, 然后经由门静脉循环回肝脏这一过程被称为肠肝循环, 在人类中每天发生约4～12次。而未被吸收的胆汁酸则进入结肠, 由肠道菌群进行生物转化或排泄到粪便中[10]。

肠道菌群与胆汁酸之间的相互作用是一个双向的、动态的过程。一方面, 肠道菌群可以调控胆汁酸的合成、重吸收和代谢; 另一方面, 胆汁酸也可以影响肠道菌群的组成和功能。肠道菌群通过产生不同的水解酶对胆汁酸进行生物转化, 其中主要包括3-、7-和12-羟基的去偶联、氧化和差向异构化以及7-脱羟基、酯化和脱硫反应[11]。梭菌、肠球菌、双歧杆菌和乳酸杆菌等革兰阳性细菌能够产生胆汁盐水解酶 (bile salt hydrolases, BSH), 将与牛磺酸或甘氨酸结合的胆汁酸转化为非结合的游离形式[12,13]。从毛螺菌属 (*Lachnospira*) 与消化链球菌属 (*Peptostreptococcus*) 菌株中发现的*bai*基因簇能够介导胆汁酸7*α*/*β*脱羟基反应, 将未结合的初级胆汁酸转化为次级胆汁酸[11,14,15]。在肠道菌群的作用下, 小肠到大肠部分的初级胆汁酸含量逐渐降低, 而次级胆汁酸含量逐渐升高[16]。Wang等[17]发现在$Apc^{min/+}$小鼠模型中, 胆酸的膳食补充显著改变了肠道菌群结构, *Prevotella*、*Desulfovibrio*等致病菌丰度增加, *Ruminococcus*、*Lactobacillus*和*Roseburia*等有益菌的丰度降低。此外, Xu等[18]给予小鼠脱氧胆酸的实验表明, 与未接受脱氧胆酸的对照组相比, 实验组*Parabacteroides*和*Bacteroides*等菌种的丰度显著增加, 与此同时, BSH相关菌群*Lactobacillus*、*Clostridium XI*和*Clostridium XIV*丰度则显著减少。综上所述, 胆汁酸补充能够重塑肠道菌群的组成。这些数据不仅为理解胆汁酸与肠道菌群之间的相互作用提供了新的视角, 也为开发基于胆汁酸调节的肠道健康干预策略提供了科学依据。

2 胆汁酸代谢与FXR信号的互调关系

FXR是在肝脏和肠道 (主要在回肠) 中高度表达的核受体, 属于核受体超家族的转录因子, 能被部分游离和结合胆汁酸激活[19]。FXR作为调节胆汁酸稳态的关键因子, 能控制胆汁酸浓度并诱导解毒酶表达, 降低

其细胞毒性[7]。一方面, FXR通过两部分机制抑制胆汁酸的新合成。在肝脏中, FXR诱导小异源二聚体伴侣 (recombinant small heterodimer partner, SHP) 的表达, 从而抑制CYP7A1的表达[20]。在肠道中, FXR诱导人成纤维细胞生长因子19 (fibroblast growth factor 19, FGF19) 表达并释放到门静脉中, 随后FGF19在肝细胞质膜与FGF受体4结合, 最终导致CYP7A1基因的抑制, 从而抑制胆汁酸合成[21,22]。另一方面, FXR通过介导毒性胆汁酸的生物转化和诱导解毒酶表达, 降低胆汁酸毒性。小鼠肠肝系统中存在由FXR介导的醛酮还原酶1 B7 (AKR1B7)[23]。它以对映特异性的方式催化由肠道细菌产生的3-酮–胆汁酸转化为3β-羟基–胆汁酸, 并介导3α-羟基胆汁酸向3β-羟基胆汁酸的转化。在正常生理条件下, 3β-羟基胆汁酸约占人类盲肠总胆汁酸含量的30%[24], 且其细胞毒性低于3α-羟基–胆汁酸对应物。

然而, 并非所有胆汁酸种类均能以激动剂的身份激活FXR。去偶联化的牛磺胆酸和脱氧胆酸, 在生理条件下被认定为FXR的天然拮抗剂。它们不仅无法激活FXR, 反而通过与FXR结合, 占据其活性位点从而阻断或减弱了其他激动剂对FXR的正常激活作用[25,26]。

3 紊乱的肠道菌群介导胆汁酸-FXR轴促进结直肠癌发展

通过大量比较结直肠癌患者/高危人群或健康人群肠道菌群丰度研究发现, 结直肠癌肠道菌群显著失调。这种失调导致有益菌的减少和有害菌的增加, 从而影响肠道微环境的平衡[27]。一方面, 紊乱的菌群将改变胆汁酸的合成和代谢, 使胆汁酸的种类和浓度发生变化, 进而重塑肠道菌群并且影响FXR的表达。另一方面, FXR表达的改变也反过来影响胆汁酸的构成以及肠道菌群的组成和功能。这种相互作用的失衡将加速结直肠癌发生发展的恶性循环。因此, 维护肠道菌群的平衡和胆汁酸-FXR轴的稳定对于预防和治疗结直肠癌具有重要意义。未来的研究可以进一步探索通过调节肠道菌群–胆汁酸-FXR轴来治疗结直肠癌的可行性, 具体机制如图1。

3.1 肠道菌群对结直肠癌的多方面作用

与其他癌症相比, 结直肠癌的独特之处在于肠道内的共生菌群作为肿瘤微环境的重要组成部分影响着结直肠癌的发展[28]。1975年, 结直肠癌中宿主–微生物之间的相互作用首次被发现[29]。近年来, 随着新一代测序技术的出现, 研究人员对结直肠癌进展过程中微生物群落组成及丰度的研究不断深入。根据作用特征, 与结直肠癌相关的肠道菌群常被简要地划分为两

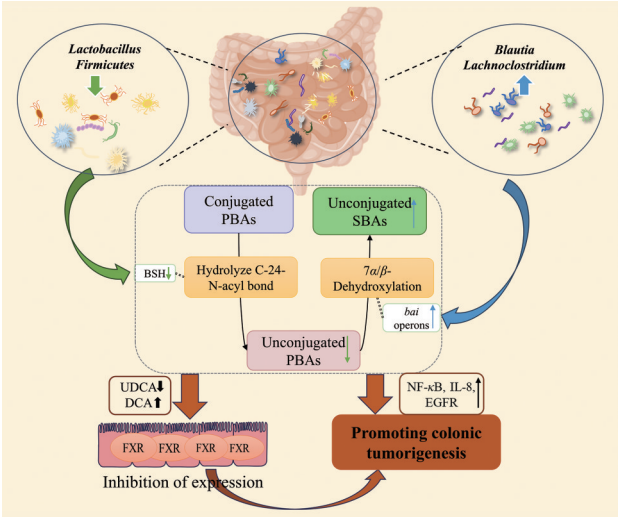

Figure 1 Gut microbiota-bile acids-FXR axis on colorectal cancer. PBAs: Primary bile acid; SBAs: Secondary bile acids; BSH: Bile salt hydrolases; DCA: Deoxycholic acid; UDCA: Ursodeoxycholic acid; FXR: Farnesoid X receptor; NF-κB: Nuclear factor kappa-B; IL-8: Interleukin-8; EGFR: Epidermal growth factor receptor

大类: 致病菌和益生菌。致病菌能够通过促进炎症、破坏肠道屏障等方式加剧结直肠癌发展, 而益生菌则可能通过调节肠道微生态平衡、产生有益代谢物等方式对结直肠癌产生抑制作用[28]。因此, 对这两类菌群深入研究有助于更好地理解结直肠癌的发生发展, 并为结直肠癌的预防和治疗提供新思路。

3.1.1 致病菌

小鼠模型、体外实验及流行病学研究发现, 几种特定细菌在结直肠癌发病机制中发挥着驱动作用。促进结直肠癌发展的三大主要致病菌分别为: 具核梭杆菌 (*Fusobacterium nucleatum*, *F.n*)、产肠毒素的脆弱拟杆菌 (Enterotoxigenic *Bacteroides fragilis*, ETBF) 和*pks*+大肠杆菌 (*pks*$^+$ *Escherichia.coli*, *pks*$^+$ *E. coli*)。这些微生物通过多样化的过程促进结直肠癌发展, 包括降低基因组完整性、激活致癌信号、促进细胞迁移、诱发炎症状态和表观遗传学变化等[30]。

3.1.1.1 *F.n* *F.n*是一种侵袭性厌氧菌, 曾被认为与癌症无直接关联。然而, 随后的研究发现[31,32], 与正常标本相比, 结直肠癌患者的粪便和肿瘤组织中*F.n*序列显著过度表达, 提示*F.n*可能是结直肠癌的一个危险因素。后续的研究揭示了*F.n*参与结直肠癌致癌的多种机制。一方面, *F.n*通过YAP/FOXD3/METTL3/KIF26B轴减少N6-甲基腺苷修饰, 增加结直肠癌攻击性[33]。另一方面, *F.n*还能通过激活Toll样受体4 (Toll like receptor 4, TLR4) 上调miRNA-21的表达, 进而激活核

因子 κB (nuclear factor kappa-B, NF-κB), 增加结直肠癌细胞增殖[34]。另外, *F.n* 的表面黏附素 FadA 会与肠上皮细胞的 E-钙黏蛋白结合 (E-cadherin, E-cad) 并激活 β-连接蛋白 (β-catenin, β-cat) 信号传导, 导致细胞周期蛋白 D1、膜联蛋白 A1 和 Chk2 的表达增加和肿瘤的发生[35]。同时, 异常比例的 *F.n* 还能通过特定的信号通路降低抗肿瘤免疫应答能力, 促进结直肠癌的发展。Gur 等[36]发现, *F.n* 的 Fap2 蛋白可与 TIGIT 直接相互作用, 抑制自然杀伤细胞的细胞毒性, 导致肿瘤细胞免疫逃避。更有研究表明[37], 喂食小鼠 *F.n* 后, 其体内的肿瘤相关巨噬细胞数量增加约 7.8 倍, $CD4^+$ T 细胞被抑制。

近期的研究进一步揭示了 *F.n* 在结直肠癌微环境中的独特作用。*F.n* 可以选择性地募集肿瘤浸润的髓系细胞, 形成利于肿瘤进展的促炎微环境[38]。并且, *F.n* 还能利用氨基酸和多肽作为肿瘤微环境中的营养来源, 并产生甲酰基−甲氧基−亮氨酸−苯丙氨酸和短链脂肪酸等氨基酸代谢产物。这些产物被认为是髓细胞化学引诱剂, 将肿瘤代谢、细菌代谢和肿瘤微环境中的免疫细胞功能联系起来[38]。

尽管大量研究一致认为, 结直肠癌患者的微生物组中 *F.n* 富集, 且其丰度随着结直肠癌的恶化而增加, 但 *F.n* 是结直肠癌的病因还是后果尚不明确。

3.1.1.2 ETBF 脆弱双歧杆菌 (*Bacteroides fragilis*, *B. fragilis*) 被认为是常见的结肠共生菌, 约占结肠细菌的 0.1%～0.5%[39]。尽管脆弱双歧杆菌被认为是共生生物, 但其子集 ETBF 会产生脆弱双歧杆菌毒素 (bacteroides fragilis toxin, BFT) 增加肠道致癌风险。

BFT 是热不稳定锌依赖性金属蛋白酶毒素, 也是唯一公认的 ETBF 特异性毒力因子, 与急性腹泻病、炎症性肠病和结直肠癌密切相关[40,41]。人体研究发现[42], 与健康对照组相比, ETBF 患者的结直肠癌患病率增加。体外研究表明[43,44], BFT 能够通过激活 Wnt/β-catenin 信号传导, 诱导原癌基因 c-Myc 的转录和翻译, 介导肠道疾病产生。BFT 还激活 NF-κB 信号传导和组织损伤提高肠道通透性、引发慢性肠道炎症, 最终导致结直肠癌[41]。Goodwin 等[45]发现, 纯化的 BFT 可上调 HT29/c1 和 T84 结肠上皮细胞中的精胺氧化酶, 导致 ROS 增加和 DNA 损伤, 进而促进癌症生长。精胺氧化酶能够产生与肿瘤发生直接相关的 ROS, 有潜力成为化学预防结直肠癌的独特靶点。此外, ETBF 可通过激活 TLR4-NFAT5 依赖性通路诱导转录因子 SOX2 和 Nanog 的上调, 介导 ETBF 诱导的结直肠癌癌症干细胞, 从而促进结直肠癌的发生[46]。Cao 等[47]认为 ETBF 将下调癌细胞外泌体中的 miR-149-3p 并进一步促进 PHF5A 介导 KAT2A 的 RNA 可变剪切, 最终诱导结直肠癌的发生。此外, 在临床样本验证中发现外泌体包裹的 miR-149-3p 的含量在结直肠癌和活动性肠炎病患者中均显著性降低。miR-149-3p 有希望成为预测肠道炎癌转化以及肠炎活动进展的生物标志物。靶向 ETBF/miR-149-3p 通路可作为一种潜在的医疗手段来治疗肠道内富含 ETBF 的肠炎和结直肠癌患者。

3.1.1.3 *pks*$^+$ *E. coli* *pks*$^+$ *E. coli* 是一类特定的致病性大肠杆菌菌株, 这些菌株的基因组中携带有编码聚酮合酶 (polyketide synthases, PKS) 和非核糖体肽合酶 (non-ribosomal peptide synthetases, NRPS) 的 *pks* 基因组岛[48]。与正常组织相比, 结直肠癌组织中内化的致病性大肠杆菌明显增加[49], 暗示了它们可能与结直肠癌的发生和发展有关。通过将 *pks*$^+$ *E. coli* 注射到类器官 (上皮细胞的自组织、三维体外培养系统) 的实验证明了这种结直肠癌相关微生物与肠道干细胞突变之间的直接因果关系[50]。进一步的研究表明[51,52], *pks* 岛基因负责大肠杆菌素的合成, 大肠杆菌素是一种异质性酮化合物, 可诱导双链断裂、非整倍体和不当的细胞分裂, 促进结直肠癌的发展。P53 通路中的基因突变被认为是结直肠癌的早期生物学事件[53]。P53 C 端泛素化将促进肿瘤生长, 同时使肿瘤抑制基因 miR-34 失活[54]。Iftekhar 等[55]研究发现, *pks*$^+$ *E. coli* 通过产生大肠杆菌素介导 c-Myc 转录因子诱导 miR-20a-5p 的表达, 最终诱导并催化 P53 C 端类泛素化, 进一步导致结直肠癌的恶性发展。

尽管关于 *pks*$^+$ *E. coli* 在结直肠癌中影响的研究日益深入, 但是, 在该领域中仍存在诸多未解的难题和挑战。如在约 20% 的健康个体中发现了 *pks*$^+$ *E. coli*[56], 其在不同个体间的致癌风险存在显著差异。同样, 含有 *pks* 岛的大肠杆菌菌株 *Nissle 1917* 却在临床上被认为是“益生菌”, 常用于治疗胃肠功能障碍性疾病[57]。这表明, 即使细菌携带相同的 *pks* 基因, 不同环境或菌株下的生物活性也可能截然不同。*pks* 基因在不同条件下的调节机制, 以及这些机制如何影响 *pks*$^+$ *E. coli* 的致病性仍需进一步探索。

3.1.1.4 其他致病菌 多种与结直肠癌相关的细菌已被高通量微生物组测序技术鉴定, 这些细菌亦被广泛视作结直肠癌的潜在病因, 并受到深入研究。Deng 等[58]通过粪便 DNA 测序发现牛链球菌 (*Streptococcus bovis*, *S. bovis*) 在结直肠癌发展过程中丰度增加。同时, 研究表明, *S. bovis* 通过募集 $CD11b^+TLR4^+$细胞参与结直肠肿瘤的发生。Tsoi 等[59]发现消化链球菌属的厌氧消化链球菌在结直肠癌患者粪便和肠黏膜微生物

群中显著富集。这种细菌表面的蛋白与结直肠癌细胞上表达的整合素$\alpha2/\beta1$受体相互作用, 触发黏着斑激酶的磷酸化, 激活下游的PI3K-AKT信号通路, 最终导致细胞增殖和NF-κB的激活[60]。

Cheng等[27]认为并不是某种特定的微生物导致了结直肠癌的发展, 而是大量细菌的有害作用超过了其有益部分, 共同促进了结直肠癌的形成。许多在肠道中持续定殖的共生细菌, 在正常肠道条件下, 不会展现出致病的特性。一旦肠道菌群失调或宿主自身免疫力低下等情况发生, 这些共生菌极有可能转化为结直肠癌风险因素。

粪肠球菌 (*Enterococcus faecalis*, *E. faecalis*) 作为人类粪便中常见的共生肠球菌之一, 它们在结直肠癌患者的粪便样本中富集[61]。*E. faecalis*的致癌活性主要基于两个核心机制: 其产生的超氧化物损伤宿主DNA, 导致染色体不稳定; 其次, 该细菌上调COX-2等关键因子的表达, 进一步推动肿瘤的发展[62]。这些发现在后来的研究中得到重现。研究表明[63], *E. faecalis*在结直肠癌细胞系HCT 116、RKO和YAMC中导致整倍体、四倍体和γH2AX灶的产生, 并诱导G2期细胞周期停滞。流行病学证据表明, *E. faecalis*的定殖与患者不同的基因组和转录组特征有关。这些关联的主要特征是癌前病变中解毒酶的增加或*E. faecalis*定殖结直肠癌病例中炎症信号通路的增加[64]。

3.1.2 有益菌

健康的肠道微生物组保持相对稳定的平衡状态, 其中有益微生物物种占据了生态位的主导地位。这些有益物种可降解难消化膳食纤维中的复杂多糖, 进而产生乳酸和其他促进肠道稳态的代谢产物[65]。它们与致病菌富集的互惠网络呈负相关[66], 被广泛称为益生菌, 这些益生菌能够对结直肠癌产生抑制作用, 有被开发为结直肠癌预防和治疗的生物制剂的潜力。

3.1.2.1 丁酸梭菌 丁酸盐能够为上皮细胞提供能量底物、产生抗炎反应、保护结肠细胞免受ROS诱导的DNA损伤, 并作为组蛋白脱乙酰酶抑制剂调节氧化应激[67]。这种代谢产物对结直肠癌的发展具有积极的调节作用。然而, 与健康人相比, 结直肠癌患者的丁酸产生菌丰度往往更低[68]。丁酸梭菌 (*Clostridium butyricum*, *C. butyricum*) 作为人类消化系统中的共生体, 通过在肠道中发酵纤维状食物产生丁酸盐和乙酸盐等短链脂肪酸 (short chain fatty acids, SCFAs)[69]维护肠道健康。

此外, *C. butyricum*能够与Wnt/β-catenin信号通路相互拮抗, 抑制结直肠癌细胞的增殖, 并诱导结直肠癌细胞凋亡。同时, 它还能调节肠道微生物群的组成, 降低继发性胆汁酸的分泌, 增强短链脂肪酸的分泌, 并激活抑制肿瘤生长的G蛋白偶联受体, 进而抑制肿瘤生长[70]。在肠上皮存在促炎信号的情况下, *C. butyricum*可通过介导致耐受APC促进Treg反应, 发挥免疫调节作用[71]。

3.1.2.2 鸡乳杆菌 鸡乳杆菌 (*Lactobacillus gallinarum*, *L. gallinarum*) 已被确认为结直肠癌患者粪便中最缺乏的益生菌之一[72]。Sugimura等[73]发现, *L. gallinarum*不仅能够显著降低小鼠肠道肿瘤的数量和大小, 更能促进结直肠癌类器官和C细胞的凋亡, 同时对正常肠上皮细胞没有影响。体内外研究表明[73,74], 由*L. gallinarum*产生的代谢产物吲哚-3-乳酸具有抗炎特性, 能够抑制上皮自噬缓解小鼠结肠炎, 并抑制肠道肿瘤的生长以及结直肠癌细胞的活力。除此之外, 另一种由*L. gallinarum*衍生的代谢产物吲哚-3-羧酸具有调节免疫功能作用。吲哚-3-羧酸通过抑制$CD4^+$ Treg分化和调节IDO1/Kyn/AHR轴增强$CD8^+$ T细胞功能, 进而提高结直肠癌的抗PD-1疗效[75]。这些发现为*L. gallinarum*及其代谢产物在结直肠癌预防和治疗中的应用提供了有力的支持。

3.1.2.3 嗜热链球菌 嗜热链球菌 (*Streptococcus thermophilus*, *S. thermophilus*) 一种革兰阳性发酵厌氧细菌, 可从酸奶等发酵乳制品中分离得到。Li等[76]通过对$Apc^{min/+}$和偶氮甲烷 (azoxymethane, AOM) 注射的小鼠灌胃*S. thermophilus*发现, 结直肠癌肿瘤形成显著减小。进一步研究揭示, *S. thermophilu*分泌的β-半乳糖苷酶能够抑制细胞增殖, 降低集落形成, 诱导细胞周期停滞, 促进培养的结直肠癌细胞凋亡, 延缓结直肠癌异种移植物的生长。此外, *S. thermophilu*通过β-半乳糖苷酶增加了双歧杆菌和乳杆菌等益生菌的肠道丰度。该结果展示了*S. thermophilu*作为一种潜在的益生菌, 在预防和治疗结直肠癌方面的潜力。

3.1.2.4 其他有益菌 不同阶段结直肠癌患者的粪便菌群变化非常明显, 而菌群的变化将导致其相关的代谢物发生改变[77]。与健康肠道相比, 结直肠癌患者肠道有益菌群及有益代谢物丰度明显降低。Sheng等[78]通过16S rRNA检测也发现, 与正常组相比, 有益菌乳酸杆菌、埃希氏–志贺氏菌属和双歧杆菌数量减少, 它们的变化程度与肿瘤的大小、大肠癌恶化的级别显著相关。De Preter等[79]通过几项研究证明, 双歧杆菌属和乳酸杆菌属细菌能够减弱初级胆汁酸的脱羟基作用和降低粪便脱氧胆酸浓度, 限制有毒代谢物的形成进而保护肠道, 抑制结直肠癌的发生发展。

3.2 肠道菌群失调介导胆汁酸稳态失衡促进结直肠癌发展

研究表明, 浓度高于正常生理范围的次级胆汁酸

会对机体产生不良作用, 包括DNA氧化损伤、炎症、激活NF-κB通路和促进细胞增殖等[80]。因此, 异常浓度次级胆汁酸被认为是结直肠癌发展的促进因子。同时, 研究表明[81], 次级胆汁酸合成相关基因的丰度与人类结直肠癌显著相关。有学者[82]通过对7个不同国家进行8项结直肠癌无偏倚荟萃研究发现, 结直肠癌患者的粪便基因组和转录组中*bai*基因高度富集以及次级胆汁酸的产生增加。Ocvirk等[83]也发现, 结直肠癌发病率最高的阿拉斯加人粪便中菌群*Blautia*和*Lachnoclostridium*丰度增加。这两种菌属都属于毛螺菌科, 涵盖了由7α-脱羟基细菌组成或与之相连的物种。并且, *Blautia*也被证明在结直肠癌患者的粪便微生物群中富集[84]。更有研究表明[15], 厚壁菌门中的BSH基因的丰度与结直肠癌呈负相关。BSH基因的下降会导致初级结合胆汁酸的增加, 而*bai*基因的上升也意味着次级胆汁酸转化的增加。最近的一项前瞻性临床试验表明, 几种初级结合和次级胆汁酸的血浆水平与结直肠癌风险呈正相关[85]。这些研究进一步证明了失调微生物介导胆汁酸代谢转化的转变与结直肠癌风险之间的联系。

在紊乱的肠道菌影响下, 次级胆汁酸的产生增加。然而, 次级胆汁酸又被称为“受损的胆汁酸”[86]。大量的实验研究证明了胆汁酸的致瘤活性, 特别是脱氧胆酸和石胆酸。已有研究表明[87,88], 结直肠癌患者的粪便中脱氧胆酸和石胆酸的水平升高。

石胆酸通过产生ROS, 减少细胞凋亡、增强细胞增殖、造成氧化性DNA损伤、介导炎症反应和激活NF-κB信号通路这些途径促使肠上皮细胞结构被破坏[89]。Nguyen等[90]使用石胆酸处理结直肠癌HCT116细胞, 石胆酸能够激活Erk1/2, 进而抑制STAT3磷酸化, 从而诱导HCT116细胞中白细胞介素-8的表达并刺激内皮细胞增殖和管状形成。在结直肠癌中, 检测到白细胞介素-8的过度表达, 会导致预后不良。

1940年, 脱氧胆酸首次被证明是一种致癌物, 可诱导小鼠结直肠癌的发展[9]。它被认为是最危险的胆汁酸。脱氧胆酸的疏水性和清净性通过激活蛋白激酶C和NADPH氧化酶的机制扰乱细胞膜、促进ROS和活性氮的积累、引起氧化应激、破坏DNA、破坏碱基切除修复途径, 并诱导NF-κB活化[91,92], 进一步促进结直肠癌发展。脱氧胆酸还能够激活表皮生长因子受体(EGFR)从而促进结肠直肠黏膜过度增殖[93]。丁酸可诱导结肠腺瘤(AA/C1)凋亡, 对结直肠癌产生保护作用, 然而, 结肠中的脱氧胆酸显著抑制丁酸保护作用, 诱导AA/C1细胞凋亡[94]。此外, 脱氧胆酸可通过靶向质膜Ca^{2+}-ATP酶抑制活化T细胞的Ca^{2+}-核因子信号传导介导$CD8^+$ T细胞的抑制, 促进结直肠癌肿瘤生长[95]。

Di Ciaula等[91]提出虽然部分胆汁酸能够推动结直肠癌的产生, 但是胆汁酸在没有致癌物、诱变剂或基因突变的情况下并不能诱导肿瘤形成, 因此胆汁酸在结直肠癌的发生发展中承担肿瘤启动子的角色, 而不是诱变剂。尽管胆汁酸失衡在结直肠癌的发展中具有重要作用, 但仍需研究肿瘤发生中涉及的特定胆汁酸代谢通路, 以避免在治疗过程中干扰正常的生理性肠肝胆汁酸循环。

3.3 调控胆汁酸代谢过程的FXR异常变化与结直肠癌

大量研究证明[26,96], FXR在结直肠癌中扮演着至关重要的角色, 它能够直接调控参与结直肠癌肿瘤抑制因子的表达。Yu等[97]研究发现, FXR能够通过拮抗Wnt/β-catenin信号传导发挥结直肠癌抑制作用。Fu等[26]发现肠道FXR的选择性激活不仅限制了Lgr5干细胞的异常增殖, 还促进肠道健康, 包括强化肠道屏障功能和恢复胆汁酸稳态。此外, Inagaki等[98]观察到FXR缺乏小鼠体内回肠细菌水平增加, 上皮屏障受损, 研究表明FXR诱导参与肠道保护的基因表达, 抑制回肠细菌过度生长和黏膜损伤。

脱氧胆酸被认为是天然肠道FXR拮抗剂, 其异常积累能够驱动肿瘤干细胞的增殖并诱导DNA损伤, 加剧肿瘤的恶性发展。进一步研究揭示, 浓度异常升高的脱氧胆酸将特异性抑制肠干细胞中FXR信号的传导, 削弱FXR在维持肠道稳态中的关键作用导致结直肠癌恶化[26]。此外, Bai等[99]发现熊去氧胆酸能够上调FXR, 抑制TLR4的蛋白表达, 并阻断p65的过度磷酸化。然而, 多数结直肠癌患者的肠道菌群处于显著失衡状态, 这种失衡状态干扰胆汁酸的合成与代谢, 导致胆汁酸池中脱氧胆酸异常积累以及熊去氧胆酸含量降低, 最终影响FXR的表达与功能的发挥。后续研究进一步证明[100], FXR的下调会导致ETBF丰度和黏附性增加。而激活结肠炎动物模型中的FXR, 将增加I-BABP和SHP的结肠表达, 减少相关炎症因子IL-1β、IL-2、IL-6、TNF-α和IFN-γ mRNA的表达, 最终减轻疾病严重程度[101]。以上研究表明, 激活FXR能够改变肠道微生物群, 减少炎症因子表达, 拮抗致癌信号级联。因此, 从治疗的角度来看, 重新激活结直肠癌中FXR表达的策略可能有助于治疗结直肠癌。

4 中药调节肠道菌群−胆汁酸-FXR轴干预结直肠癌发生发展

临床研究和动物实验都证明, 结直肠癌的发展与机体肠道菌群及代谢物改变有着密切的联系。因此, 调节肠道菌群−胆汁酸-FXR轴, 可在结直肠癌肿瘤治

疗中有所裨益。在肿瘤治疗过程中, 中药以其多成分、多靶点、多通路的协同调控作用脱颖而出, 其中活性单体成分众多, 作用机制复杂多样。近年来, 中医药以其突出的优势受到国内外的重视, 被广泛应用于结直肠癌的治疗中, 具体机制如图2。

4.1 中药复方

补益剂的代表汤剂四君子汤能够维持肠道微生态平衡, 使肠道中紊乱的双歧杆菌、肠杆菌和肠球菌恢复至正常水平、调节免疫球蛋白和T淋巴细胞亚群从而提高机体免疫力, 抑制结肠癌模型小鼠体内肿瘤生长[102]。Wan等[103]研究发现益气散结方通过增加肠道有益细菌的相对含量以治疗结直肠癌。Liu等[104]发现传统化痰方二陈汤能够改善高脂饮食结直肠癌肠道菌群结构, 使厚壁菌门/拟杆菌门比值下降趋向于普通饮食小鼠的结构, 并且他们认为上调FXR表达及增加下游的限速酶CYP7A1也可能是二陈汤起作用的机制。采取莪黄汤保留灌肠并联合足三针治疗后, 结直肠癌手术患者肠道菌群数量发生变化, 菌群结构改变, 乳酸杆菌、双歧杆菌、粪肠球菌数量均下降, 大肠杆菌数量上升, 并趋于稳定[105]。片仔癀, 一种公认的传统药物, 对炎症和癌症有有益的作用。在小鼠模型和人类结直肠癌患者癌细胞来源的类器官模型中证实[106], 传统中药片仔癀可改善肠道菌群及其代谢产物, 改善肠道屏障功能, 抑制致癌和促炎通路, 从而抑制结直肠癌的发生。白头翁汤可有效改善溃疡性结肠炎发生引起的肠道菌群紊乱, 调控胆汁酸的合成与代谢, 从而激活FXR/TGR5相关受体信号通路, 最终发挥抑制肠炎发生的生物功能[107]。香连丸 (XLP) 是一种由黄连、木香制成的中成药, 在控制肠道菌群失调和炎症方面具有独特的优势。Ye等[108]发现XLP通过减少促炎细胞因子IL-6和TNF-α的表达, 减少促炎巨噬细胞的浸润来保护肠屏障的完整性, 抑制结直肠癌的发生。

血清代谢组学研究表明[109], 复方肠泰能够增加结直肠癌荷瘤小鼠$CD4^+$和$CD8^+$ T淋巴细胞的水平, 同时纠正微生态紊乱以发挥作用抗肿瘤作用。服用薏苡附子败酱散 (YYFZBJS) 志愿者的粪便移植给小鼠实验证明[110], YYFZBJS介导了Treg细胞的改变, 进而抑制了结直肠癌癌细胞的生长, 调节了动物的天然肠道菌群同时降低了β-连环蛋白的磷酸化, 从而阻断了$Apc^{Min/+}$小鼠的肿瘤发生和发展。葛根芩连汤具有强大的抗病原微生物作用, 抗内、外毒素作用, 抗细菌耐药作用, 以及对绝大多数肠道致病菌的抑杀作用, 能够有力地控制肠道感染源。用其治疗结直肠癌, 能够调节肠道菌群, 调控肠道菌群的多样性, 抑制Wnt/β-catenin通路的活化和调节下游蛋白的表达作用, 有效抑制结肠炎症的诱发与结肠癌的发生、发展[111]。仙连解毒方 (XLJDD) 在临床上广泛用于治疗结直肠癌, Duan团队[112]发现XLJDD能够通过降低有害菌的丰度, 增加益生菌丰度, 以及丁酸和异戊酸的含量, 缓解肠道微生物菌群失衡和代谢紊乱, 进而抑制结肠内壁肿瘤的发生。中医用于治疗结肠炎和结直肠癌的古老方剂安肠愈疡汤 (AYD) 已被证实能够显著减少AOM/DSS诱导的大鼠结肠腺瘤数量、ACF和肿瘤相关蛋白 (如p53、PCNA) 的表达, 调节肠道菌群结构, 增强SCFA产生从而阻止结肠炎相关癌变的进展[113]。目前, 通过调控肠道菌群−胆汁酸-FXR轴抑制结直肠癌的中药复方如表

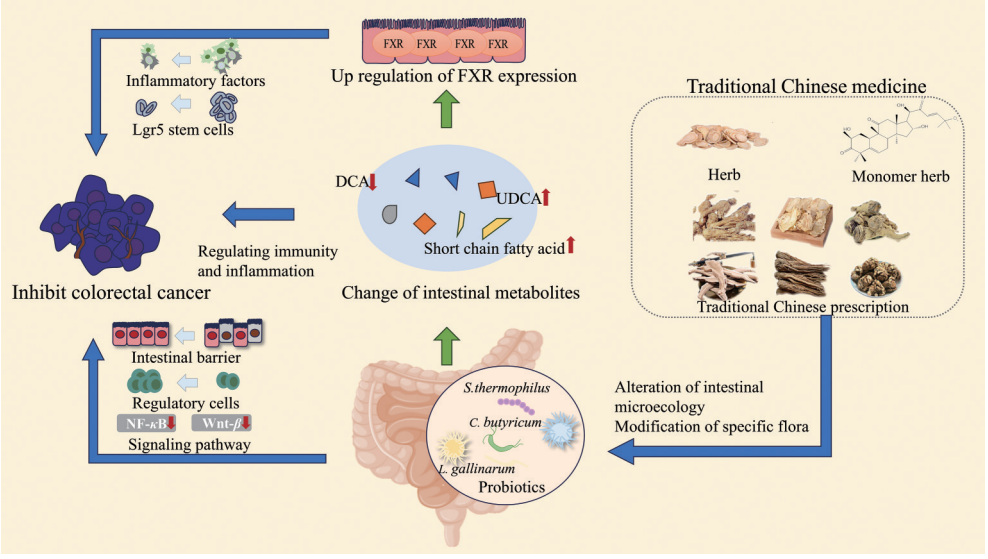

Figure 2 Traditional Chinese medicine regulate gut microbiota-bile acids-FXR axis intervention in the development of colorectal cancer. *S. thermophilus*: *Streptococcus thermophilus*; *L. gallinarum*: *Lactobacillus gallinarum*; *C. butyricum*: *Clostridium butyricum*

1[102-113]总结所示。

4.2 单味中药

中医认为, 结直肠癌患者的病因病机以湿浊、热毒、瘀阻等为主, 其治法以清热解毒为主[114], 常用的清热解毒药物, 如黄连、黄芩、黄柏在长期给予临床等效剂量情况下可增加部分有益菌水平, 进而调节胆汁酸代谢[115]; 在临床上也常使用党参、白术、茯苓[116]等健脾药, 增加益生菌乳杆菌、双歧杆菌的数量, 能够很好地对肠道菌群进行调节。Peng等[117]研究发现, 乳香 (醋炙) 可通过抑制CYP7A1来调控初级胆汁酸的合成, 回调机体初级胆汁酸水平。Guo等[118]认为红参和薏仁通过改善肠道微生物群的结构, 缓解结肠炎。两者皆能够促进体外培养的益生菌双歧杆菌和乳酸杆菌的生长, 红参还抑制了大肠杆菌等致病菌株的生长。马齿苋作为一种常见的抗氧化、抗癌药用植物, 其提取物能够剂量依赖性地降低AOM/DSS处理的小鼠体内大肠杆菌、沙门氏菌等有害菌丰度, 增加双歧杆菌、拟杆菌、乳酸菌等有益菌丰度[119]。矿物原料药芒硝用于治疗胃肠道疾病已有数千年的历史。最新研究证明[120], 芒硝可以通过特异性富集乳酸菌的丰度调控肠道微生物, 从而改善胆汁酸代谢, 进一步激活结直肠癌小鼠的FXR, 抑制结直肠癌发展。目前, 通过调控肠道菌群−胆汁酸-FXR轴抑制结直肠癌的单味中药如表2[115-120]总结所示。

Table 1 Mechanism of traditional Chinese prescription inhibiting colorectal cancer by regulating gut microbiota-bile acids-FXR axis. AOM: Azoxymethane; DSS: Dextran sulphate sodium; HFD: High fat diet; CYP7A1: Sterol 7*α*-hydroxylase; Hs-CRP: Hypersensitive C-reactive protein; TNF-*α*: Tumor necrosis factor *α*; HDCA: Hyodeoxycholic acid; *α*-MCA: *α*-Muricholic acid; *β*-MCA: *β*-Muricholic acid; CA: Cholic acid; GLCA: Glycolithocholic acid; CRC: Colorectal cancer; IL-6: Interleukin-6; IL-10: Interleukin-10; LPCs: Lysophosphatidylcholines; PCs: Phosphatidylcholine; LPS: Lipopolysaccharide; TGR5: Takeda G protein receptor 5; SCFAs: Short chain fatty acids

Traditional Chinese medicine	Model	Anti-cancer mechanism	Ref.
Sijunzi Decoction	AOM/DSS induced mice	Maintain intestinal microecological balance, regulate immunoglobulin and T lymphocyte subsets to improve body immunity	[102]
Yiqi Sanjie Recipe	AOM/DSS induced mice	Increase the abundance of beneficial bacteria *Ruminococcus_1* and *Prevotellaceae_UCG_001*, repair DNA damage and improve iron free anemia	[103]
Erchen soup	HFD + AOM/DSS induced mice	It decreases the ratio of Firmicutes/Bacteroidetes, up-regulates the expression of FXR and increases the downstream rate limiting enzyme CYP7A1	[104]
Ehuang Decoction + Zusanzhen	Manikin	Reduce the number of *Lactobacillus*, *Bifidobacterium* and *Enterococcus faecalis*, increase the number of *Escherichia coli*, and reduce the levels of Hs-CRP and TNF-*α*	[105]
Pianzihuang	AOM/DSS induced $Apc^{min/+}$ mice	Increase the abundance of probiotics *Pseudobutyrivibrio xylanivorans* and *Eubacterium limosum*, deplete pathogenic bacteria *Aeromonas veronii*, *Campylobacter jejuni*, *Collinsella aerofaciens* and *Peptiphilus harei*, increase the contents of taurine, bile acids and unsaturated fatty acids, and inhibit carcinogenic and pro-inflammatory pathways	[106]
Pulsatilla Decoction	3.5% DSS induced mice	Increase the concentrations of UDCA, HDCA, *α*-MCA, *β*-MCA, CA and GLCA increase the relative abundance of Firmicutes, Proteobacteria, Actinobacteria, Tenericutes and TM7, decrease the abundance of *Bacteroides*, and increase the expression of FXR and TGR5 in liver	[107]
Xianglian pill	AOM/DSS induced CRC model of mice exposed to HFD	Increase the proportion of probiotics (particularly *Akkermansia muciniphila*) and significantly reduce fecal DCA, a microbiota-derived metabolite of bile acids closely related to Muribaculaceae	[108]
Compound Changtai	CT 26-LUC induced mice	Increase the abundance of Firmicutes, decrease the abundance of Bacteroidetes, and increase the abundance of *Turicibacter* and *Roseburia*	[109]
Coix monkshood Patrinia powder	$Apc^{min/+}$ mice	Reduce the expression levels of Foxp3, IL-6 and IL-10 in conventional T cells in adenomas, and increase the abundance of *Dubosiella*, *Lactobacillus*, *Bacteroides fragilis* and Lachnospiraceae	[110]
Gegen Qinlian Decoction	Mice were induced by subcutaneous injection of dimethylhydrazine and drinking 2% DSS	Reduce LPS and inflammatory reaction, reduce the number of *Escherichia coli*, *Enterococcus*, *Lactobacillus*, *Bifidobacterium* and intestinal flora, and increase the level of Wnt/*β*-catenin pathway protein	[111]
Xianlian Jiedu Recipe	AOM/DSS induced mice	Reduce the abundance of *Turicibacter*, *Clostridium_sensus_stricto_1* and the levels of sphingosine, LPCs and PC, increase the abundance of probiotics *Enterorhabdus* and *Alistipes*, and the content of butyric acid and isovaleric acid	[112]
Anchang Yuyang Decoction	AOM/DSS induced mice	Increase the relative abundance of *Romboutsia*, *Monoglobus*, *norank_f_Oscillospiraceae*, and *norank_f_Ruminococcaceae*, enhance SCFA production, particularly butyric acid, propionic, and valeric acids	[113]

Table 2 Mechanism of Chinese herbal inhibiting colorectal cancer by regulating gut microbiota-bile acids-FXR axis. CYP8B1: Sterol 12 α-hydroxylase; BACS: Bile acid-CoA synthetase; BAAT: Bile acid-CoA: amino acid N-acetyltransferase

Traditional Chinese medicine	Model	Anti-cancer mechanism	Ref.
Rhizoma Coptidis, Radix Scutellariae, Cortex Phellodendri	Normal mice	Decrease the abundance of Firmicutes and increase the abundance of Bacteroidetes to regulate bile acids metabolism	[115]
Codonopsis pilosula, Atractylodes macrocephala and Poria cocos	Normal mice	High dose Codonopsis pilosula can significantly increase the level of intestinal *Lactobacillus* and reduce the level of *Escherichia coli*; high dose of Poria cocos can significantly improve the level of intestinal *Bifidobacterium*	[116]
Mangxiao	*APC*$^{Min/+}$ male mice	Mangxiao exerts therapeutic effects by changing the abundance of *Lactobacillus* and upregulating BSH to increase the expressional levels of unconjugated BAs in *APC*$^{Min/+}$ mice	[117]
Frankincense (roasted with vinegar)	2,4,6-Trinitrobenzene sulfonic acids (TNBS)-induced mice	Inhibition of CYP7A1, up regulation of CYP8B1, and callback of primary bile acids level in pathological state, up regulation of binding primary bile acids synthase BACS and BAAT	[118]
Red Ginseng and Semen Coicis	TNBS induced mice	Red Ginseng and Semen Coicis can promote the growth of probiotics *Bifidobacterium* and *Lactobacillus*, and Red Ginseng can also inhibit the growth of pathogenic bacteria such as *Escherichia coli*	[119]
Purslane	AOM/DSS induced mice	The abundance of harmful bacteria such as *Escherichia coli* and *Salmonella* in mice treated with purslane extract decreased, while the abundance of beneficial bacteria such as *Bifidobacterium*, *Bacteroides* and lactic acid bacteria increased significantly, and played a role in a significant dose-dependent manner	[120]

4.3 中药单体

在FDA批准的有效抗癌分子中, 有63%来自中草药, 这表明中药作为抗肿瘤药物的潜力很大[121]。中药中常见的抗肿瘤活性成分有生物碱、萜类、黄酮类、多糖、多酚等[122]。研究表明[123], 山柰酚能够增加CYP27A1和CYP8B1的表达, 上调FXR的表达, 调节胆汁酸的信号传导和肠道微生物群的稳态, 有效减轻*Apc*$^{Min/+}$小鼠自发性结直肠癌模型的负担。从白芍和赤芍中提取的单萜类糖苷芍药苷主要在肠道中发挥药效, 能够逆转小鼠肠道菌群失调并选择性促进益生菌乳酸杆菌的生长, 还能够促进初级胆汁酸转化为次级胆汁酸, 从而调控胆汁酸代谢紊乱起到修复小鼠肠屏障功能损伤的作用[124]。绞股蓝中分离得到的三萜皂苷产物能通过增加有益细菌丰度、减少硫酸还原细菌丰度和缓解肠道炎症修复肠道环境来逆转雄性*Apc*$^{Min/+}$小鼠的炎症表型, 以发挥结直肠癌预防作用[125]。小檗碱可通过下调Hedgehog信号通路活性和调节肠道微生物群, 通过抑制COX-2/PGE2-JAK2/STAT3轴阻止结直肠癌细胞的增殖、迁移、侵袭和集落形成, 发挥治疗结直肠癌的作用[126]。McFadden等[127]的实验证明了从姜黄根茎中提取出来的活性成分姜黄素增加了乳酸杆菌的相对丰度, 并降低了科氏菌的数量, 减少或消除了结肠肿瘤负担。金钱草是一种传统中药, 因其抗炎和抗肿瘤特性而被广泛使用。药理研究表明, 金钱草皂苷是主要的生物活性成分。同时, Li等[128]发现金钱草皂苷可以改变肠道微生物群和血浆代谢物的水平来发挥抗结直肠癌作用。人参皂苷Rh4是一种从人参中分离出来的活性化合物, Bai等[99]发现其能剂量依赖性地调节肠道微生物介导的胆汁酸代谢, 抑制结直肠癌。

植物精油主要由叶、花瓣、茎、树皮、种子等部位的特殊分泌细胞产生, 天然来源的植物精油因其广泛的药理活性和良好的安全性, 在针对结直肠癌的药物研发中备受关注[129]。广藿香精油及其衍生物广藿香醇和广藿香酮通过降低小鼠肠道致病菌*Desulfovibrio*、*Mycoplasma Genitalium*, 改善*Apc*$^{min/+}$小鼠的肠道微环境而发挥有效的抗癌作用[130]。Luo等[131]发现薄荷醇通过调节β-catenin、Ki67等生物标志物和IL-6、TNF-α等细胞因子表达, 改善肠道菌群结构, 有效改善AOM/DSS诱导的肿瘤发展。目前, 通过调控肠道菌群−胆汁酸-FXR轴抑制结直肠癌的中药单体如表3[99,123-128,130,131]总结所示。

5 结语与展望

综上所述, 肠道菌群−胆汁酸-FXR轴在结直肠癌发展中起着关键的作用。在当前的人类组学研究中, 多数聚焦于元基因组学, 或者专注于与胆汁酸相关的代谢组学。然而, 这些研究尚未充分阐明肠道微生物群落丰度与功能变动与胆汁酸浓度之间的确切关联, 该领域研究尚处于起步阶段, 对肠道微生物群落调节干预结直肠癌中胆汁酸-FXR轴的研究仍不够深入、系统。这不仅包括识别更多能够影响胆汁酸产生、代谢的肠道菌群, 还需深入探究这些菌群与FXR受体之间的相互作用, 以及这些互作如何影响结直肠癌的发生发展。同时, 临床数据的缺乏也限制了微生物预防和治疗的应用。因此, 建议从以下几个方面进行研究。

Table 3 Mechanism of monomer herb inhibiting colorectal cancer by regulating gut microbiota-bile acids-FXR axis. CYP27A1: Sterol 27 hydroxylase; PPAR-γ: Peroxisome proliferator activated receptor-γ; PYY: Peptide yy; GPR41: G protein coupled receptor 41; GPR43: G protein coupled receptor 43; GPR109A: G protein coupled receptor 109 A

Traditional Chinese medicine	Model	Anti-cancer mechanism	Ref.
Kaempferol	*Apc*$^{Min/+}$mice	Restore the damaged intestinal barrier, down regulate the expression of Ki67, Lgr5 and pro-inflammatory cytokines, increase the expression of CYP27A1 and CYP8B1, up regulate the expression of CDCA and 12α-hydroxylated BAs, up regulate the expression of FXR, and increase the abundance of *A. muciniphila* and *P. goldsteini*	[123]
Paeoniflorin	Mice induced by 3% DSS	Inhibit the levels of TNF-α, IL-1β and IL-6, promoting the release of IL-10, increasing the relative abundance of *Lactobacillus*, reduce the relative abundance of *Bacteroides*, and reversing the metabolic disorder of BAs	[124]
Triterpene saponin	*Apc*$^{Min/+}$mice	Up regulation of *Bifidobacterium*, *Clostridium cochleae*, *Lactobacillus intestines*, *Parabacteroides distasonis*, *Streptococcus thermophilus* abundance, down regulation of sulfate reducing bacteria abundance	[125]
Berberine	Mice induced by AOM/DSS	Reduce the activity of Hedgehog signaling pathway, reduce the β-diversity of intestinal microbiota in mice, inhibit the COX-2/PGE2-JAK2/STAT3 axis, increase the abundance of probiotics in mice, such as *Lactobacillus*, *Allobaculum* and *Muribaculum*, and disable pathogenic *Shigella*, *Dubosiella*, *Akkermansia* and *Alloprevotellalla* in mice	[126]
Curcumin	AOM induced mice	Inhibit the age-related decrease of α-diversity, increase the relative abundance of *Lactobacillus*, and reduce the number of *Klebsiella*	[127]
Lysimachia capillipes Hemsl	SW620 induced mice	Microbial community (α-diversity index) as well as the number of OTUs in the mice's intestines both improved after the administration of LCS. Regulates the relative abundance of *Firmicutes* and *Bacteroidetes*	[128]
Ginsenoside Rh4	Mice induced by AOM/DSS	Enrich the probiotic *Akkermansia muciniphila*, and alleviate gut microbiota dysbiosis caused by CRC, promote the production of UDCA by enhancing the activity of 7α-hydroxysteroid dehydrogenase. UDCA further activates FXR, modulates the TLR4-NF-κB signaling pathway	[99]
Patchouli essential oil and its derivatives patchouli alcohol and pogostone	*Apc*$^{min/+}$ mice	The drugs stimulate the SCFA-producers and the key SCFA-sensing receptors (GPR41, GPR43, and GPR109A). The activation of SCFAs/GPSs also triggers the alterations of PPAR-γ, PYY, and HSDCs signaling mediators in the treated mice	[130]
Menthol	AOM/DSS induced mice	Compared with the control group, α diversity is higher, the abundance of butyric acid producing bacteria (*Allobaculum*, *Roseburia* and *Intestinimonas*) increase, and the fecal butyric acid concentration increase	[131]

首先, 肠道菌群作为一个复杂的生态系统, 可使用高通量测序及生物信息学分析等方法找出结直肠癌的肠道靶菌, 并通过临床试验和动物实验等, 探讨肠道细菌与宿主间的关系。其次, 目前已经发现十几种由肠道菌群代谢产生的胆汁酸, 但这些新发现的胆汁酸是否干预结直肠癌仍需进一步探索。

中医药在结直肠癌治疗中具有多成分、多靶点、多通路的协同调控作用, 可以维持肠道微生态平衡, 调节失衡的肠道菌群, 预防结直肠癌的发生和发展。针对肠道菌群−胆汁酸-FXR 轴起干预作用的中药 (单味中药或其提取物、中药复方) 有望为结直肠癌预防与治疗开辟新方向。目前, 中药在这一过程中的具体作用机制尚不明确, 且中药对肠道菌群−胆汁酸-FXR 轴的研究大部分局限于通过调节该轴来治疗肝胆疾病。因此, 需要更多的研究来多方面揭示中药通过调节肠道菌群−胆汁酸-FXR 轴在结直肠癌预防和治疗中的潜在价值。

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References

[1] Zheng RS, Chen R, Han BF, et al. Cancer incidence and mortality in China, 2022 [J]. Chin J Oncol (中华肿瘤杂志), 2024, 46: 221-231.

[2] Rowland I, Gibson G, Heinken A, et al. Gut microbiota functions: metabolism of nutrients and other food components [J]. Eur J Nutr, 2018, 57: 1-24.

[3] Iacob S, Iacob DG, Luminos LM. Intestinal microbiota as a host defense mechanism to infectious threats [J]. Front Microbiol, 2018, 9: 3328.

[4] Salic K, Kleemann R, Wilkins-Port C, et al. Apical sodium-dependent bile acid transporter inhibition with volixibat improves metabolic aspects and components of non-alcoholic steatohepatitis in Ldlr$^{-/-}$. Leiden mice [J]. PLoS One, 2019, 14: e0218459.

[5] Nguyen TT, Ung TT, Kim NH, et al. Role of bile acids in colon carcinogenesis [J]. World J Clin Cases, 2018, 6: 577-588.

[6] Taranto MP, Perez-Martinez G, Valdez GF. Effect of bile acid on the cell membrane functionality of lactic acid bacteria for oral administration [J]. Res Microbiol, 2006, 157: 720-725.

[7] Degirolamo C, Modica S, Palasciano G, et al. Bile acids and colon cancer: solving the puzzle with nuclear receptors [J]. Trends Mol Med, 2011, 17: 564-572.

[8] Maran RR, Thomas A, Roth M, et al. Farnesoid X receptor deficiency in mice leads to increased intestinal epithelial cell proliferation and tumor development [J]. J Pharmacol Exp Ther, 2009, 328: 469-477.

[9] Caliceti C, Punzo A, Silla A, et al. New insights into bile acids related signaling pathways in the onset of colorectal cancer [J]. Nutrients, 2022, 14: 2964.

[10] Gonzalez FJ. Nuclear receptor control of enterohepatic circulation [J]. Compr Physiol, 2012, 2: 2811-2828.

[11] Ridlon JM, Harris SC, Bhowmik S, et al. Consequences of bile salt biotransformations by intestinal bacteria [J]. Gut Microbes, 2016, 7: 22-39.

[12] Jones BV, Begley M, Hill C, et al. Functional and comparative metagenomic analysis of bile salt hydrolase activity in the human gut microbiome [J]. Proc Natl Acad Sci U S A, 2008, 105: 13580-13585.

[13] Patel AK, Singhania RR, Pandey A, et al. Probiotic bile salt hydrolase: current developments and perspectives [J]. Appl Biochem Biotechnol, 2010, 162: 166-180.

[14] Funabashi M, Grove TL, Wang M, et al. A metabolic pathway for bile acid dehydroxylation by the gut microbiome [J]. Nature, 2020, 5821: 566-570.

[15] Jin WB, Li TT, Huo D, et al. Genetic manipulation of gut microbes enables single-gene interrogation in a complex microbiome [J]. Cell, 2022, 185: 547-562.e22.

[16] Zhang CC, Wu JF, Wang YL. Gender difference in intestinal bile acid profiles in C57BL/6 mice [J]. Chin J Magn Reson (波谱学杂志), 2018, 35: 328-337.

[17] Wang S, Dong W, Liu L, et al. Interplay between bile acids and the gut microbiota promotes intestinal carcinogenesis [J]. Mol Carcinog, 2019, 58: 1155-1167.

[18] Xu M, Cen M, Shen Y, et al. Deoxycholic acid-induced gut dysbiosis disrupts bile acid enterohepatic circulation and promotes intestinal inflammation [J]. Dig Dis Sci, 2021, 66: 568-576.

[19] Mangelsdorf DJ, Thummel C, Beato M, et al. The nuclear receptor superfamily: the second decade [J]. Cell, 1995, 83: 835-839.

[20] Gadaleta RM, Garcia-Irigoyen O, Moschetta A. Bile acids and colon cancer: is FXR the solution of the conundrum? [J]. Mol Aspects Med, 2017, 56: 66-74.

[21] Shin DJ, Wang L. Bile acid-activated receptors: a review on FXR and other nuclear receptors [J]. Handb Exp Pharmacol, 2019, 256: 51-72.

[22] Wang LX, Frey MR, Kohli R. The role of FGF19 and MALRD1 in enterohepatic bile acid signaling [J]. Front Endocrinol (Lausanne), 2021, 12: 799648.

[23] Schmidt DR, Schmidt S, Holmstrom SR, et al. AKR1B7 is induced by the farnesoid X receptor and metabolizes bile acids [J]. J Biol Chem, 2011, 286: 2425-2432.

[24] Hamilton JP, Xie G, Raufman JP, et al. Human cecal bile acids: concentration and spectrum [J]. Am J Physiol Gastrointest Liver Physiol, 2007, 293: G256-G263.

[25] Sayin SI, Wahlström A, Felin J, et al. Gut microbiota regulates bile acid metabolism by reducing the levels of tauro-beta-muricholic acid, a naturally occurring FXR antagonist [J]. Cell Metab, 2013, 17: 225-235.

[26] Fu T, Coulter S, Yoshihara E, et al. FXR regulates intestinal cancer stem cell proliferation [J]. Cell, 2019, 176: 1098-1112.e18.

[27] Cheng Y, Ling Z, Li L. The intestinal microbiota and colorectal cancer [J]. Front Immunol, 2020, 11: 615056.

[28] Wong CC, Yu J. Gut microbiota in colorectal cancer development and therapy [J]. Nat Rev Clin Oncol, 2023, 20: 429-452.

[29] Reddy BS, Weisburger JH, Narisawa T, et al. Colon carcinogenesis in germ-free rats with 1,2-dimethylhydrazine and *N*-methyl-n'-nitro-*N*-nitrosoguanidine [J]. Cancer Res, 1974, 34: 2368-2372.

[30] Dougherty MW, Jobin C. Intestinal bacteria and colorectal cancer: etiology and treatment [J]. Gut Microbes, 2023, 15: 2185028.

[31] Castellarin M, Warren RL, Freeman JD, et al. *Fusobacterium nucleatum* infection is prevalent in human colorectal carcinoma [J]. Genome Res, 2012, 22: 299-306.

[32] Aitchison A, Pearson JF, Purcell RV, et al. Detection of *Fusobacterium nucleatum* DNA in primary care patient stool samples does not predict progression of colorectal neoplasia [J]. PLoS One, 2022, 17: e0269541.

[33] Chen S, Zhang L, Li M, et al. *Fusobacterium nucleatum* reduces METTL3-mediated m^6A modification and contributes to colorectal cancer metastasis [J]. Nat Commun, 2022, 13: 1248.

[34] Yang Y, Weng W, Peng J, et al. *Fusobacterium nucleatum* increases proliferation of colorectal cancer cells and tumor development in mice by activating Toll-like receptor 4 signaling to nuclear factor-κB, and up-regulating expression of microRNA-21 [J]. Gastroenterology, 2017, 152: 851-866.e24.

[35] Rubinstein MR, Baik JE, Lagana SM, et al. *Fusobacterium nucleatum* promotes colorectal cancer by inducing Wnt/β-catenin modulator Annexin A1 [J]. EMBO Rep, 2019, 20: e47638.

[36] Gur C, Ibrahim Y, Isaacson B, et al. Binding of the Fap2 protein of *Fusobacterium nucleatum* to human inhibitory receptor TIGIT protects tumors from immune cell attack [J]. Immunity, 2015, 42: 344-355.

[37] Chen T, Li Q, Zhang X, et al. TOX expression decreases with progression of colorectal cancers and is associated with CD4 T-cell density and *Fusobacterium nucleatum* infection [J]. Hum Pathol, 2018, 79: 93-101.

[38] Kostic AD, Chun E, Robertson L, et al. *Fusobacterium nucleatum* potentiates intestinal tumorigenesis and modulates the tumor-immune microenvironment [J]. Cell Host Microbe, 2013, 14: 207-215.

[39] Valguarnera E, Wardenburg JB. Good gone bad: one toxin away from disease for *Bacteroides fragilis* [J]. J Mol Biol, 2020, 432: 765-785.

[40] Li RX, Li Q, Ji Q. Study on the effects of intestinal flora on tumor immunity and intervention of traditional Chinese medicine [J]. China J Tradit Chin Med Pharm (中华中医药杂志), 2020, 35: 2999-3002.

[41] Sears CL. Enterotoxigenic *Bacteroides fragilis*: a rogue among symbiotes [J]. Clin Microbiol Rev, 2009, 22: 349-369.

[42] Boleij A, Hechenbleikner EM, Goodwin AC, et al. The *Bacteroides fragilis* toxin gene is prevalent in the colon mucosa of colorectal cancer patients [J]. Clin Infect Dis, 2015, 60: 208-215.

[43] Wu S, Lim KC, Huang J, et al. *Bacteroides fragilis* enterotoxin cleaves the zonula adherens protein, E-cadherin [J]. Proc Natl Acad Sci U S A, 1998, 95: 14979-14984.

[44] Wu S, Morin PJ, Maouyo D, et al. *Bacteroides fragilis* enterotoxin induces c-Myc expression and cellular proliferation [J]. Gastroenterology, 2003, 124: 392-400.

[45] Goodwin AC, Destefano Shields CE, Wu S, et al. Polyamine catabolism contributes to enterotoxigenic *Bacteroides fragilis*-induced colon tumorigenesis [J]. Proc Natl Acad Sci U S A, 2011, 108: 15354-15359.

[46] Liu QQ, Li CM, Fu LN, et al. Enterotoxigenic *Bacteroides fragilis* induces the stemness in colorectal cancer *via* upregulating histone demethylase JMJD2B [J]. Gut Microbes, 2020, 12: 1788900.

[47] Cao Y, Wang Z, Yan Y, et al. Enterotoxigenic *Bacteroides fragilis* promotes intestinal inflammation and malignancy by inhibiting exosome-packaged miR-149-3p [J]. Gastroenterology, 2021, 161: 1552-1566.e12.

[48] Nougayrède JP, Homburg S, Taieb F, et al. *Escherichia coli* induces DNA double-strand breaks in eukaryotic cells [J]. Science, 2006, 313: 848-851.

[49] Bonnet M, Buc E, Sauvanet P, et al. Colonization of the human gut by *E. coli* and colorectal cancer risk [J]. Clin Cancer Res, 2014, 20: 859-867.

[50] Pleguezuelos-Manzano C, Puschhof J, Rosendahl Huber A, et al. Mutational signature in colorectal cancer caused by genotoxic *pks*$^{+}$ *E. coli* [J]. Nature, 2020, 580: 269-273.

[51] Faïs T, Delmas J, Barnich N, et al. Colibactin: more than a new bacterial toxin [J]. Toxins (Basel), 2018, 10: 151.

[52] Cuevas-Ramos G, Petit CR, Marcq I, et al. *Escherichia coli* induces DNA damage *in vivo* and triggers genomic instability in mammalian cells [J]. Proc Natl Acad Sci U S A, 2010, 107: 11537-11542.

[53] Calibasi-Kocal G, Mashinchian O, Basbinar Y, et al. Nutritional control of intestinal stem cells in homeostasis and tumorigenesis [J]. Trends Endocrinol Metab, 2021, 32: 20-35.

[54] Liebl MC, Hofmann TG. The role of p53 signaling in colorectal cancer [J]. Cancers (Basel), 2021, 13: 2125.

[55] Iftekhar A, Berger H, Bouznad N, et al. Genomic aberrations after short-term exposure to colibactin-producing *E. coli* transform primary colon epithelial cells [J]. Nat Commun, 2021, 12: 1003.

[56] Buc E, Dubois D, Sauvanet P, et al. High prevalence of mucosa-associated *E. coli* producing cyclomodulin and genotoxin in colon cancer [J]. PLoS One, 2013, 8: e56964.

[57] Lynch JP, Goers L, Lesser CF. Emerging strategies for engineering *Escherichia coli* Nissle 1917-based therapeutics [J]. Trends Pharmacol Sci, 2022, 43: 772-786.

[58] Deng Q, Wang C, Yu K, et al. *Streptococcus bovis* contributes to the development of colorectal cancer *via* recruiting CD11b^{+}TLR-4^{+} cells [J]. Med Sci Monit, 2020, 26: e921886.

[59] Tsoi H, Chu ESH, Zhang X, et al. *Peptostreptococcus anaerobius* induces intracellular cholesterol biosynthesis in colon cells to induce proliferation and causes dysplasia in mice [J]. Gastroenterology, 2017, 152: 1419-1433.e5.

[60] Long X, Wong CC, Tong L, et al. *Peptostreptococcus anaerobius* promotes colorectal carcinogenesis and modulates tumour immunity [J]. Nat Microbiol, 2019, 4: 2319-2330.

[61] Balamurugan R, Rajendiran E, George S, et al. Real-time polymerase chain reaction quantification of specific butyrate-producing bacteria, *Desulfovibrio* and *Enterococcus faecalis* in the feces of patients with colorectal cancer [J]. J Gastroenterol Hepatol, 2008, 23: 1298-1303.

[62] Wang X, Huycke MM. Extracellular superoxide production by *Enterococcus faecalis* promotes chromosomal instability in mammalian cells [J]. Gastroenterology, 2007, 132: 551-561.

[63] Wang X, Allen TD, May RJ, et al. *Enterococcus faecalis* induces aneuploidy and tetraploidy in colonic epithelial cells through a bystander effect [J]. Cancer Res, 2008, 68: 9909-9917.

[64] Lennard KS, Goosen RW, Blackburn JM. Bacterially-associated transcriptional remodelling in a distinct genomic subtype of colorectal cancer provides a plausible molecular basis for disease development [J]. PLoS One, 2016, 11: e0166282.

[65] Pessione E. Lactic acid bacteria contribution to gut microbiota complexity: lights and shadows [J]. Front Cell Infect Microbiol, 2012, 2: 86.

[66] Jian X, Zhu Y, Ouyang J, et al. Alterations of gut microbiome accelerate multiple myeloma progression by increasing the relative abundances of nitrogen-recycling bacteria [J]. Microbiome, 2020, 8: 74.

[67] Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer [J]. Cell, 2010, 140: 883-899.

[68] Chen HM, Yu YN, Wang JL, et al. Decreased dietary fiber intake and structural alteration of gut microbiota in patients with advanced colorectal adenoma [J]. Am J Clin Nutr, 2013, 97: 1044-1052.

[69] Koh A, De Vadder F, Kovatcheva-Datchary P, et al. From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites [J]. Cell, 2016, 165: 1332-1345.

[70] Chen D, Jin D, Huang S, et al. *Clostridium butyricum*, a butyrate-producing probiotic, inhibits intestinal tumor development through modulating Wnt signaling and gut microbiota [J]. Cancer Lett, 2020, 469: 456-467.

[71] Stoeva MK, Garcia-So J, Justice N, et al. Butyrate-producing human gut symbiont, *Clostridium butyricum*, and its role in health and disease [J]. Gut Microbes, 2021, 13: 1-28.

[72] Dai Z, Coker OO, Nakatsu G, et al. Multi-cohort analysis of colorectal cancer metagenome identified altered bacteria across populations and universal bacterial markers [J]. Microbiome, 2018, 6: 70.

[73] Sugimura N, Li Q, Chu ESH, et al. *Lactobacillus gallinarum* modulates the gut microbiota and produces anti-cancer metabolites to protect against colorectal tumourigenesis [J]. Gut, 2021, 71: 2011-2021.

[74] Meng D, Sommella E, Salviati E, et al. Indole-3-lactic acid, a metabolite of tryptophan, secreted by *Bifidobacterium longum* subspecies infantis is anti-inflammatory in the immature intestine [J]. Pediatr Res, 2020, 88: 209-217.

[75] Fong W, Li Q, Ji F, et al. *Lactobacillus gallinarum*-derived metabolites boost anti-PD1 efficacy in colorectal cancer by inhibiting regulatory T cells through modulating IDO1/Kyn/AHR axis [J]. Gut, 2023, 72: 2272-2285.

[76] Li Q, Hu W, Liu WX, et al. *Streptococcus thermophilus* inhibits colorectal tumorigenesis through secreting β-galactosidase [J]. Gastroenterology, 2021, 160: 1179-1193.e14.

[77] Yachida S, Mizutani S, Shiroma H, et al. Metagenomic and metabolomic analyses reveal distinct stage-specific phenotypes of the gut microbiota in colorectal cancer [J]. Nat Med, 2019, 25: 968-976.

[78] Sheng Q, Du H, Cheng X, et al. Characteristics of fecal gut microbiota in patients with colorectal cancer at different stages and different sites [J]. Oncol Lett, 2019, 18: 4834-4844.

[79] De Preter V, Hamer HM, Windey K, et al. The impact of pre- and/or probiotics on human colonic metabolism: does it affect human health? [J]. Mol Nutr Food Res, 2011, 55: 46-57.

[80] Pearson JR, Gill CI, Rowland IR. Diet, fecal water, and colon cancer--development of a biomarker [J]. Nutr Rev, 2009, 67: 509-526.

[81] Cai J, Sun L, Gonzalez FJ. Gut microbiota-derived bile acids in intestinal immunity, inflammation, and tumorigenesis [J]. Cell Host Microbe, 2022, 30: 289-300.

[82] Wirbel J, Pyl PT, Kartal E, et al. Meta-analysis of fecal metagenomes reveals global microbial signatures that are specific for colorectal cancer [J]. Nat Med, 2019, 25: 679-689.

[83] Ocvirk S, Wilson AS, Posma JM, et al. A prospective cohort analysis of gut microbial co-metabolism in Alaska native and rural African people at high and low risk of colorectal cancer [J]. Am J Clin Nutr, 2020, 111: 406-419.

[84] Baxter NT, Zackular JP, Chen GY, et al. Structure of the gut microbiome following colonization with human feces determines colonic tumor burden [J]. Microbiome, 2014, 2: 20.

[85] Kühn T, Stepien M, López-Nogueroles M, et al. Prediagnostic plasma bile acid levels and colon cancer risk: a prospective study [J]. J Natl Cancer Inst, 2020, 112: 516-524.

[86] Perez MJ, Briz O. Bile-acid-induced cell injury and protection [J]. World J Gastroenterol, 2009, 15: 1677-1689.

[87] Bajor A, Gillberg PG, Abrahamsson H. Bile acids: short and long term effects in the intestine [J]. Scand J Gastroenterol, 2010, 45: 645-664.

[88] Mcgarr SE, Ridlon JM, Hylemon PB. Diet, anaerobic bacterial metabolism, and colon cancer: a review of the literature [J]. J Clin Gastroenterol, 2005, 39: 98-109.

[89] Sinha SR, Haileselassie Y, Nguyen LP, et al. Dysbiosis-induced secondary bile acid deficiency promotes intestinal inflammation [J]. Cell Host Microbe, 2020, 27: 659-670.e5.

[90] Nguyen TT, Lian S, Ung TT, et al. Lithocholic acid stimulates IL-8 expression in human colorectal cancer cells *via* activation of Erk1/2 MAPK and suppression of STAT3 activity [J]. J Cell Biochem, 2017, 118: 2958-2967.

[91] Di Ciaula A, Wang DQ, Molina-Molina E, et al. Bile acids and cancer: direct and environmental-dependent effects [J]. Ann Hepatol, 2017, 16: s87-s105.

[92] Ridlon JM, Bajaj JS. The human gut sterolbiome: bile acid-microbiome endocrine aspects and therapeutics [J]. Acta Pharm Sin B, 2015, 5: 99-105.

[93] Dong W, Liu L, Dou Y, et al. Deoxycholic acid activates epidermal growth factor receptor and promotes intestinal carcinogenesis by ADAM17-dependent ligand release [J]. J Cell Mol Med, 2018, 22: 4263-4273.

[94] Mcmillan L, Butcher S, Wallis Y, et al. Bile acids reduce the apoptosis-inducing effects of sodium butyrate on human colon adenoma (AA/C1) cells: implications for colon carcinogenesis [J]. Biochem Biophys Res Commun, 2000, 273: 45-49.

[95] Cong J, Liu P, Han Z, et al. Bile acids modified by the intestinal microbiota promote colorectal cancer growth by suppressing $CD8^+$ T cell effector functions [J]. Immunity, 2024, 57: 876-889.e11.

[96] Modica S, Cariello M, Morgano A, et al. Transcriptional regulation of the intestinal nuclear bile acid farnesoid X receptor (FXR) by the caudal-related homeobox 2 (CDX2) [J]. J Biol Chem, 2014, 289: 28421-28432.

[97] Yu J, Li S, Guo J, et al. Farnesoid X receptor antagonizes Wnt/β-catenin signaling in colorectal tumorigenesis [J]. Cell Death Dis, 2020, 11: 640.

[98] Inagaki T, Moschetta A, Lee YK, et al. Regulation of antibacterial defense in the small intestine by the nuclear bile acid receptor [J]. Proc Natl Acad Sci U S A, 2006, 103: 3920-3925.

[99] Bai X, Duan Z, Deng J, et al. Ginsenoside Rh4 inhibits colorectal cancer *via* the modulation of gut microbiota-mediated bile acid metabolism [J]. J Adv Res, 2024. DOI: 10.1016/j.jare.2024.06.028.

[100] Guo S, Peng Y, Lou Y, et al. Downregulation of the farnesoid X receptor promotes colorectal tumorigenesis by facilitating enterotoxigenic *Bacteroides fragilis* colonization [J]. Pharmacol Res, 2022, 177: 106101.

[101] Vavassori P, Mencarelli A, Renga B, et al. The bile acid receptor FXR is a modulator of intestinal innate immunity [J]. J Immunol, 2009, 183: 6251-6261.

[102] Ouyang QW, Fei Y, Wei YJ, et al. Regulatory effect of Sijunzi Decoction on intestinal flora and immune function in mice with colon cancer [J]. Chin J Gerontol (中国老年学杂志), 2021, 41: 4819-4823.

[103] Wan X, Tou F, Zeng J, et al. Integrative analysis and identification of key elements and pathways regulated by traditional Chinese medicine (Yiqi Sanjie formula) in colorectal cancer [J]. Front Pharmacol, 2022, 13: 1090599.

[104] Liu RF. Effect of Phlegm Syndrome on the Incidence Rate of Colorectal Cancer in Mice Based on the Abnormal Cholesterol-bile Acid Metabolism (从胆固醇−胆汁酸代谢异常探讨痰对小鼠结直肠癌发病率的影响研究) [D]. Fuzhou: Fujian University of Traditional Chinese Medicine, 2021.

[105] Qin YQ, Zhao J, Dong SB, et al. Effect of Ehuang Decoction retention enema combined with 3-leg point on intestinal microecology, function and rehabilitation quality of patients with colorectal cancer after operation [J]. J Sichuan Tradit Chin Med (四川中医), 2020, 38: 112-115.

[106] Gou H, Su H, Liu D, et al. Traditional medicine Pien Tze Huang suppresses colorectal tumorigenesis through restoring gut microbiota and metabolites [J]. Gastroenterology, 2023, 165: 1404-1419.

[107] Hua YL, Jia YQ, Zhang XS, et al. Baitouweng Tang ameliorates DSS-induced ulcerative colitis through the regulation of the gut microbiota and bile acids *via* pathways involving FXR and TGR5 [J]. Biomed Pharmacother, 2021, 137: 111320.

[108] Ye C, Wu C, Li Y, et al. Traditional medicine Xianglian pill suppresses high-fat diet-related colorectal cancer *via* inactivating TLR4/MyD88 by remodeling gut microbiota composition and bile acid metabolism [J]. J Ethnopharmacol, 2024, 333: 118411.

[109] Cai M, Xiao Y, Lin Z, et al. Disordered gut microbiota in colorectal tumor-bearing mice altered serum metabolome related to Fufangchangtai [J]. Front Pharmacol, 2022, 13: 889181.

[110] Sui H, Zhang L, Gu K, et al. YYFZBJS ameliorates colorectal cancer progression in $Apc^{Min/+}$ mice by remodeling gut microbiota and inhibiting regulatory T-cell generation [J]. Cell Commun Signal, 2020, 18: 113.

[111] Wang N, Fang XG, Liao S, et al. Mechanism of Gegen Qinlian Decoction on intestinal flora of colon cancer model rats based on Wnt/β-catenin signaling pathway [J]. J Liaoning Univ Tradit Chin Med (辽宁中医药大学学报), 2023, 25: 49-53.

[112] Cai K, Cao XY, Chen F, et al. Xianlian Jiedu Decoction alleviates colorectal cancer by regulating metabolic profiles, intestinal microbiota and metabolites [J]. Phytomedicine, 2024, 128: 155385.

[113] Wei X, Liang J, Liu J, et al. Anchang Yuyang Decoction inhibits experimental colitis-related carcinogenesis by regulating PPAR signaling pathway and affecting metabolic homeostasis of host and microbiota [J]. J Ethnopharmacol, 2024, 326: 117995.

[114] Wang XN, Huo JG. Discussion on the ideas and methods of treating colorectal cancer with traditional Chinese medicine [J]. J Basic Chin Med (中国中医基础医学杂志), 2007, 13: 681-682.

[115] Li XR, Sheng XJ, Yang Y, et al. Effects of four commonly used Chinese medicines with clearing heat and drying dampness on intestinal flora mediated bile acids and short chain fatty acids metabolism [J]. J Nanjing Univ Tradit Chin Med (南京中医药大学学报), 2023, 39: 442-451.

[116] Song KY, Jiang ZY, Yan QU, et al. Experimental study on the effect of *Radix codonopsis* and Poria on intestinal flora in mice [J]. Chin J Clin Pharmacol (中国临床药理学杂志), 2011, 27: 142-145.

[117] Peng ST, Liu ZL, Wang C, et al. Study on efficiency enhancing mechanism of vinegar processed Olibanum on ulcerative colitis *via* primary bile acids synthesis [J]. Chin Tradit Herb Drugs (中草药), 2022, 53: 107-116.

[118] Guo M, Ding S, Zhao C, et al. Red Ginseng and Semen Coicis can improve the structure of gut microbiota and relieve the symptoms of ulcerative colitis [J]. J Ethnopharmacol, 2015, 162: 7-13.

[119] Wu PD. Study on the Mechanism of Portulaca oleracea Extract Inhibiting the Progression of Colon Cancer (马齿苋提取物抑制结肠癌进展及其机制研究) [D]. Nanjing: Southeast University, 2022.

[120] Zhou X, Sun H, Ren J, et al. Mineral crude drug mirabilite (Mangxiao) inhibits the occurrence of colorectal cancer by regulating the *Lactobacillus*-bile acid-intestinal farnesoid X receptor axis based on multiomics integration analysis [J]. MedComm (2020), 2024, 5: e556.

[121] Zou Y, Wang S, Zhang H, et al. The triangular relationship between traditional Chinese medicines, intestinal flora, and colorectal cancer [J]. Med Res Rev, 2024, 44: 539-567.

[122] Zhang R, Wang Y, Song X, et al. Eco-friendly mechanobiological assisted extraction of phenolic acids and flavonoids from *Chrysanthemum* [J]. J Pharm Biomed Anal, 2020, 186: 113327.

[123] Li X, Khan I, Huang G, et al. Kaempferol acts on bile acid signaling and gut microbiota to attenuate the tumor burden in $Apc^{Min/+}$ mice [J]. Eur J Pharmacol, 2022, 918: 174773.

[124] Wang X, Zhu M, Dong SJ, et al. Paeoniflorin regulates gut microbiota and bile acids metabolism in colitis mice [J]. Acta

Pharm Sin (药学学报), 2021, 56: 1811-1819.

[125] Chen L, Brar MS, Leung FC, et al. Triterpenoid herbal saponins enhance beneficial bacteria, decrease sulfate-reducing bacteria, modulate inflammatory intestinal microenvironment and exert cancer preventive effects in *Apc*$^{Min/+}$ mice [J]. Oncotarget, 2016, 7: 31226-31242.

[126] Sun Q, Yang H, Liu M, et al. Berberine suppresses colorectal cancer by regulation of Hedgehog signaling pathway activity and gut microbiota [J]. Phytomedicine, 2022, 103: 154227.

[127] McFadden RM, Larmonier CB, Shehab KW, et al. The role of curcumin in modulating colonic microbiota during colitis and colon cancer prevention [J]. Inflamm Bowel Dis, 2015, 21: 2483-2494.

[128] Li W, Guan S, Hu X, et al. *Lysimachia capillipes* Hemsl. saponins ameliorate colorectal cancer in mice *via* regulating gut microbiota and restoring metabolic profiles [J]. Fitoterapia, 2024, 175: 105959.

[129] Liu H, Li J, Lin JZ, et al. Research progress on mechanism of plant essential oils and their active components against colorectal cancer [J]. Chin Tradit Herb Drugs (中草药), 2023, 54: 956-965.

[130] Leong W, Huang G, Liao W, et al. Traditional Patchouli essential oil modulates the host's immune responses and gut microbiota and exhibits potent anti-cancer effects in *Apc*$^{Min/+}$ mice [J]. Pharmacol Res, 2022, 176: 106082.

[131] Luo L, Yan J, Chen BY, et al. The effect of menthol supplement diet on colitis-induced colon tumorigenesis and intestinal microbiota [J]. Am J Transl Res, 2021, 13: 38-56.