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评 述

植物活性成分调控哺乳动物肠道健康的机制研究进展

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摘要 肠道健康是维持机体整体稳态的基石. 近年来研究证实, 肠道菌群失调、肠道屏障功能受损及免疫炎症反应异常是多种肠道相关疾病发生发展的核心病理机制. 在此背景下, 来源广泛、生物安全性高的植物活性成分, 因其具有多靶点、整体调控的独特优势, 成为肠道健康调控领域的研究热点. 本文系统综述植物多糖、多酚、萜类、生物碱、植物油脂(脂肪酸)五大类主要植物活性成分对哺乳动物肠道健康的调控作用及其潜在分子机制. 研究发现, 这些成分的调控机制既有共性, 也存在明显偏向性: 在共性层面, 它们普遍通过重塑肠道菌群结构、增强肠屏障完整性以及调节肠道炎症与免疫反应, 协同维持肠道稳态; 在偏向性层面, 植物多糖主要通过"底物发酵-短链脂肪酸生成"发挥益生元样作用, 植物多酚表现出"双生元效应-信号通路调控"的双重特征, 植物萜类则依赖脂溶性结构优势发挥膜作用及抗炎活性, 植物生物碱具有较强的靶点型免疫调控特征, 而植物油脂(脂肪酸)主要通过G蛋白偶联受体(G protein-coupled receptor, GPCR)介导的脂质信号转导参与肠道稳态调节. 本文可为深入阐明植物活性成分的生理功能提供重要理论依据, 也为功能性食品的研发及"药食同源"策略在肠道健康维护中的应用提供科学支撑, 具有重要的学术价值和实际应用前景.

关键词 植物活性成分, 肠道健康, 肠道屏障, 肠道菌群, 免疫调控

肠道作为哺乳动物体内最大的免疫器官和微生态系统, 不仅在营养物质的消化吸收中发挥着核心作用, 还通过精密调控肠道菌群平衡、维持免疫稳态及调控代谢活动, 构筑起抵御外源性病原体入侵的关键防线, 是维持机体整体健康的基石[1,2]. 近年来, 随着微生态学、分子营养学及免疫学等学科的交叉融合, 肠道健康的内在调控机制逐步被揭示. 研究表明, 肠道菌群结构紊乱、肠道屏障功能受损及免疫炎症失衡, 与多种慢性疾病的发生发展密切相关, 包括消化系统疾病、代谢综合征、神经系统疾病等[3]. 植物活性成分作为天然产物中极具研究价值的一类物质[4], 广泛存在于药食同源植物、功能性果蔬及药用植物中, 具有来源广泛、生物活性多样、毒副作用较低等优势[5~7]. 由于其多靶点、多途径调控肠道健康的独特潜力, 这

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类活性成分已受到全球研究者的高度关注[8,9]. 大量研究证实, 植物活性成分可通过调节肠道菌群组成、优化微生态结构, 或直接作用于肠道上皮细胞与免疫细胞, 影响屏障蛋白表达、炎症信号通路及代谢酶活性, 从而实现对肠道健康的全方位调控[10~12]. 目前, 关于植物活性成分与肠道健康的研究已积累了丰富数据, 但不同类型成分的作用机制分散且复杂, 缺乏系统性的梳理与整合. 基于此, 本文聚焦植物多糖、多酚、萜类、生物碱、植物油脂(脂肪酸)五大类核心植物活性成分, 系统综述其在哺乳动物肠道健康中的调控作用及潜在分子机制, 重点解析其对肠道菌群、肠道屏障及免疫功能的调控规律. 本文能为深入理解植物活性成分的生理功能提供重要依据, 也为功能性食品开发及“药食同源”策略的应用提供理论支持, 具有重要的科学和应用价值.

1 肠道健康的三层调控: 菌群、屏障与炎症免疫

肠道健康的维系依赖于多层级调控体系的协同作用, 其中, 肠腔菌群构成微生态基础, 黏液层与上皮细胞共同维持肠道屏障完整性, 而固有层内免疫细胞通过相关信号通路及炎症因子主导免疫稳态调控[13~15], 三者共同构成宿主-微生物互作网络的基础框架, 对机体代谢稳态、免疫防御及炎症反应具有决定性影响. 任一环节的失调均可通过代谢紊乱、屏障破坏或炎症级联反应, 引发炎症性肠病(inflammatory bowel disease, IBD)、肠易激综合征(irritable bowel syndrome, IBS)和结直肠癌(colorectal cancer, CRC)等肠道疾病, 甚至导致全身性功能异常[16~19].

作为重要的上游调节因子, 肠道菌群在哺乳动物肠道内形成结构相对稳定的微生态系统, 主要包括厚壁菌门(Firmicutes)、拟杆菌门(Bacteroidetes)、放线菌门(Actinobacteria)、变形菌门(Proteobacteria)等重要功能性菌群[20~22]. 其中的有益菌(如阿克曼菌(*Akkermansia*)、罗斯氏菌(*Roseburia*)等)可通过膳食发酵产生短链脂肪酸(short chain fatty acids (SCFAs), 如乙酸、丙酸、丁酸), 同时参与维生素合成、胆汁酸代谢, 为肠道上皮和免疫细胞提供代谢支持与能量来源[23,24]. 同时, 肠道菌群也可通过竞争性抑制病原体及分泌抗菌物质等方式, 形成生物防御屏障, 限制有害微生物定植[25,26]. 反之, 当菌群多样性降低或结构失衡, 尤其是变形菌门的异常增殖, 常伴随肠道通透性增加和低度慢性炎症, 进而促进肥胖、代谢综合征及炎症性肠病的发生[14,25,27~29]. 肠道屏障作为宿主抵御外源有害物质的结构基础, 其功能依赖于物理、化学和生物屏障的协同作用[13,30]. 物理屏障由单层肠上皮细胞及其间的紧密连接(tight junction, TJ)构成, 主要包括闭合小带蛋白(zonula occludens; ZO-1, ZO-2, ZO-3)、密封蛋白(occludin)、闭合蛋白家族(claudins), 这些结构直接决定肠道通透性, 在保障营养吸收的同时限制有害物质跨上皮转运[31~33]; 化学屏障主要由杯状细胞(goblet cells, GCs)分泌的黏蛋白(mucin, MUC)黏液层, 以及肠上皮细胞产生的抗菌肽(antimicrobial peptides, AMPs)和消化酶组成, 通过调控黏膜表面微环境抑制细菌黏附与侵袭[34~36]; 生物屏障则以共生菌群及其代谢产物为核心, 其中丁酸可促进肠上皮细胞能量代谢与紧密连接蛋白合成, 显著增强屏障稳定性[37~39]. 肠道健康的维持还依赖于免疫与炎症反应的精细调控, 而炎症因子及其相关信号通路在此过程中发挥核心整合作用[40]. 具体而言, 在免疫调控层面, 肠道相关淋巴组织(gut-associated lymphoid tissue, GALT)是机体最大的黏膜相关淋巴组织, 它通过持续产生免疫效应细胞来维持体内平衡, 这些免疫效应细胞会扩散至整个肠道, 维持免疫耐受与免疫防御之间的动态平衡[41~43]. 其中, 调节性T细胞(regulatory T cells, Treg)与辅助性T细胞17(T helper 17, Th17)之间的平衡被认为是决定炎症反应走向的关键因素: Treg细胞通过分泌白细胞介素-10(interleukin-10, IL-10)和转化生长因子-β(transforming growth factor-β, TGF-β)等抗炎因子, 抑制过度免疫反应并维持黏膜耐受; 而Th17细胞的异常激活则可促进肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)、IL-6和IL-17等促炎因子的持续释放, 驱动炎症信号放大并加重组织损伤[44~48]. 此类炎症因子的失衡通常伴随核因子κB(nuclear factor κB, NF-κB)、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)、Janus激酶(Janus kinase, JAK)/信号转导及转录激活因子(signal transducer and activator of transcription, STAT)等经典炎症信号通路的异常激活, 从分子层面推动肠道疾病的发生与发展[49~52].

综上所述, 肠道健康的调控可归纳为肠道菌群组成、肠道屏障功能以及炎症因子及其相关信号通路三

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大相互关联的核心层面. 肠道菌群作为重要的上游调节单元, 塑造肠道代谢与免疫微环境; 肠道屏障完整性为肠道稳态提供结构基础; 而炎症因子及信号通路的动态平衡则在分子层面整合多种调控信号, 决定炎症反应的走向与强度. 三者之间并非独立存在, 而是通过"菌群代谢-屏障调控-免疫响应"的级联与反馈调控网络形成动态稳态. 基于此, "菌群-屏障-免疫"的三层框架为系统解析植物活性成分的作用机制提供了统一的理论基础: 不同类型的植物活性成分可根据其理化性质与生物利用度差异, 分别作用于菌群结构重塑、屏障功能修复和炎症信号调控等不同层级, 并通过多层级联动实现整体调节效应. 因此, 从该整合框架出发, 对植物多糖、多酚、萜类、生物碱及植物油脂(脂肪酸)进行分类阐述, 有助于揭示其作用机制的共性规律与特异性差异.

2 植物活性成分对肠道健康的调控机制

植物活性成分是植物应对病原菌侵袭、紫外线辐射等胁迫时产生的次级代谢产物, 广泛分布于植物各组织中[53]. 这类天然功能因子具有来源广泛、化学结构多样及生物相容性良好的特点. 与人工合成药物相比, 它们不仅能避免潜在的毒副作用, 还能通过与肠道微生态系统形成有益互作, 在肠道健康调控领域展现出重要的研究价值[54,55]. 基于核心化学骨架与生物活性特征, 植物活性成分可归纳为多糖、多酚、萜类、生物碱及植物油脂(脂肪酸)五大类. 下文将系统阐述各类植物活性成分及其代表性化合物对肠道健康的具体调控作用与分子机制.

2.1 植物多糖

植物多糖是一类由多个单糖残基通过糖苷键连接形成的复杂碳水化合物, 作为来源广泛的植物源性天然活性成分, 广泛存在于黄芩、黄芪、人参、板蓝根等药用植物及生姜、荔枝、山楂等食源性植物中. 其兼具生物安全性高、结构多样的特性, 可被肠道菌群高效发酵利用, 通过增强肠道屏障功能、抑制炎症反应等多重途径, 全面维护肠道健康[56~58].

在菌群层面, 植物多糖含有的糖苷键作为肠道微生物直接利用的重要碳源, 通过"底物选择性-微生物酶解"机制对特定功能菌群(碳水化合物降解及SCFAs生成相关菌群)产生定向调控作用, 从而表现出益生元样作用[59~62]: 肠道微生物通过其表面糖类识别与转运系统(如拟杆菌门的SusC/SusD复合体、厚壁菌门的胞外多糖感应受体EPSRs)对多糖结构进行识别, 从而诱导碳水化合物活性酶(carbohydrate-active enzymes, CAZymes)的表达, 将多糖逐步降解为寡糖和单糖, 进一步通过微生物发酵代谢途径生成SCFAs关键功能性代谢产物. SCFAs可降低肠腔pH, 抑制变形菌门等条件致病菌的异常扩增[63~66], 进一步选择性促进有益菌群的生长, 从而优化肠道菌群组成, 促进肠道健康. 研究表明, 植物多糖干预可促进厚壁菌门下的乳杆菌属(*Lactobacillus*)、罗斯氏菌属、颤螺菌属(*Oscillospira*)、粪球菌属(*Coprococcus*)、丁酸球菌属(*Butyricicoccus*)等核心有益菌富集, 以及疣微菌门(Verrucomicrobiota)下阿克曼菌属、放线菌门下双歧杆菌属(*Bifidobacterium*)等功能菌群的相对丰度, 从而促进肠道代谢环境的改善、强化肠黏膜屏障完整性、调节肠道免疫平衡[65,67~69]; 与此同时, 可有效抑制变形菌门这一肠道炎症标志性菌门的异常增殖, 降低其下属大肠杆菌-志贺氏菌属(*Escherichia-Shigella*)、脱硫弧菌属(*Desulfovibrio*)等条件致病菌相对丰度, 并抑制厚壁菌门中葡萄球菌属(*Staphylococcus*)等有害菌的过度生长[70,71]. 例如, 在小鼠结肠炎模型中, 黄芩多糖可显著提高双歧杆菌属、乳杆菌属及罗斯氏菌属丰度, 同时抑制拟杆菌属(*Bacteroides*)和葡萄球菌属的异常增殖[68]; 山楂多糖通过提高厚壁菌门及乳杆菌属、候选糖单胞菌属(Candidatus *Saccharimonas*)丰度, 降低变形菌门水平缓解肠道炎症[72]. 在肠道屏障层面, 植物多糖可通过多靶点机制维护屏障完整性. 一方面, 植物多糖本身能直接参与黏液层保护: 可激活杯状细胞内的蛋白激酶C(protein kinase C, PKC)信号通路, 上调囊泡运输蛋白表达, 促进黏蛋白的快速胞吐释放, 或刺激肠道干细胞增殖并诱导其分化为杯状细胞, 从源头增加黏液分泌细胞数量, 并与杯状细胞分泌物MUC2发生氢键、静电等物理相互作用, 形成稳定的多糖-黏蛋白复合网络, 增强黏液的黏弹性和屏障强度[73]. 例如, 三叶青多糖、莱阳梨渣多糖可显著增加杯状细胞数量及MUC2表达[74,75]. 另一方面, 植物多糖以及发酵物SCFAs也能发挥相似作用: SCFAs(如丁酸)是结肠上皮细胞的主要能量来源, 可维持细胞能量稳态; 还通过激活G蛋白偶联受体(如GPR41, GPR43, GPR109A)及抑制组蛋白去

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乙酰化酶(histone deacetylase, HDAC), 促进ZO-1, occludin和claudin等紧密连接蛋白的表达, 降低黏膜通透性; 亦可通过稳定缺氧诱导因子-1α(hypoxia-inducible factor-1α, HIF-1α)上调紧密连接蛋白表达以及诱导肠上皮细胞产生抗菌肽(如β-防御素), 增强肠道物理化学屏障[62,65,66,75~79]. 例如, 在小鼠结肠炎模型中, 黄芩多糖、茯苓多糖、山楂多糖、莱阳梨渣多糖均可显著提高ZO-1, occludin及不同claudin亚型(claudin-5或claudin-1)的蛋白水平[65,68,72,75]; 丁酸上调紧密连接相关蛋白的表达水平来保护肠道屏障功能并降低肠黏膜通透性[80]. 在免疫调控层面, 植物多糖通过多靶点协同调控免疫与氧化应激: 通过抑制上游Toll样受体(Toll like receptors, TLR, 如TLR4)及髓样分化因子88 (myeloid differentiation factor 88, MyD88)轴、降低核因子κB抑制蛋白α(inhibitor of nuclear factor kappa-B kinase subunit alpha, IκBα)磷酸化水平并抑制核因子κB p65亚基(nuclear factor kappa-B p65 subunit, p65)核转位, 进而阻断NF-κB通路与NOD样受体蛋白3(NOD-like receptor protein 3, NLRP3)炎症小体活化[81~85]; 通过降低JAK2和STAT3的磷酸化水平, 抑制p-STAT3及RORγt表达, 从而调控JAK/STAT信号通路[74,86]; 通过激活核因子E2相关因子2(nuclear factor erythroid 2-related factor 2, Nrf2)/血红素氧合酶-1(heme oxygenase-1, HO-1)信号通路, 降低丙二醛(malondialdehyde, MDA)和一氧化氮(nitric oxide, NO), 升高超氧化物歧化酶(superoxide dismutase, SOD)、过氧化氢酶(catalase, CAT)、谷胱甘肽过氧化物酶(glutathione peroxidase, GSH-Px)等抗氧化酶活性, 减轻中性粒细胞浸润和氧化损伤[75,87~90]. 通过调控以上通路, 多糖可降低促炎因子(如TNF-α, IL-1β, IL-6, IL-17A, IL-18)和增加抗炎因子(如IL-10和TGF-β), 抑制炎症信号的异常放大[71,91], 这些炎症因子的变化, 可促进Treg细胞分化并抑制Th17细胞活性, 从而恢复Th17/Treg平衡[65,66,74]. 例如, 在小鼠结肠炎模型中, 黄芪多糖、茯苓多糖、蒲公英多糖、莱阳梨渣多糖及杏仁多糖均可降低IκBα磷酸化水平并抑制p65核转位, 从而阻断NF-κB激活, 减少TNF-α, IL-1β, IL-6等促炎因子编码基因的转录[61,65,66,75,90,92,93]; 鱼腥草多糖同样抑制p-STAT3及RORγt表达, 从而减少IL-6, IL-17A等促炎介质, 并促进上皮再生[71]; 莱阳梨渣多糖显著降低MDA和NO, 升高SOD, CAT, GSH-Px[75,90]; 三叶青多糖和茯苓多糖通过上调叉头框蛋白P3(Foxp3)和IL-10, 下调RORγt及IL-17A, 促进Treg分化并抑制Th17活性, 从而恢复Th17/Treg平衡[65,66,74].

综上所述, 植物多糖对肠道健康的调控呈现“菌群-屏障-免疫”三位一体的多层级机制(图1). 在菌群层面, 植物多糖作为益生元, 选择性富集产SCFAs的有益菌(如乳杆菌属、双歧杆菌属、阿克曼菌属、罗斯氏菌属等), 同时抑制变形菌门等条件致病菌, 优化肠道微生态. 在屏障层面, 植物多糖通过上调紧密连接蛋白(ZO-1, occludin, claudins)修复物理屏障, 通过促进杯状细胞分化与MUC2分泌增厚黏液层、增强抗菌肽表达强化化学屏障, 菌群代谢产生的SCFAs则进一步反馈增强屏障功能. 在免疫层面, 植物多糖多靶点抑制NF-κB及JAK/STAT炎症通路, 调节Treg/Th17平衡, 增强黏膜免疫(sIgA, T/B细胞), 并发挥抗氧化作用减轻氧化应激损伤. 上述三层面机制相互协同, 共同构成植物多糖系统维护肠道健康的分子基础(表1).

2.2 植物多酚

植物多酚是含有苯环并连接两个或多个羟基(-OH)的一类化合物[96,97], 广泛分布于日常饮食中, 如水果、蔬菜、茶叶、坚果等, 典型化合物包括茶叶中富含的表没食子儿茶素没食子酸酯(epigallocatechin gallate, EGCG)、果蔬及药用植物中普遍存在的槲皮素, 以及桑葚和仙人掌等植物中的花青素类成分等[98]. 在肠道内, 多酚可以被肠道菌群代谢, 该过程不仅影响了其自身生物活性, 还可生成新的活性代谢产物, 进而调节肠道菌群平衡、增强肠道屏障功能、抑制炎症反应、调控免疫等[99~101], 在哺乳动物的肠道健康中发挥着重要调控作用[102].

在菌群层面, 植物多酚表现出独特的“双生元”效应, 即抗菌与益生元机制并存[103]. 一方面, 多酚可通过多种途径抑制条件致病菌: 可与多种致病菌表面的A型分选酶(sortase A)结合, 阻断其将表面蛋白锚定到细胞壁的过程, 从而抑制细菌对宿主细胞的黏附[104,105]; 可凭借疏水与亲水特性, 插入细菌细胞膜的脂双层, 改变膜的流动性和完整性, 导致膜通透性增加和胞内物质泄漏, 最终引起细菌死亡[106~109]; 可进入细菌胞内, 抑制细菌DNA促旋酶(DNA gyrase)和拓扑异构酶Ⅳ(DNA topoisomerase IV)的活性, 使细菌增殖停滞[110~113]; 可结合并抑制细菌F1F0-ATP合酶, 阻断ATP

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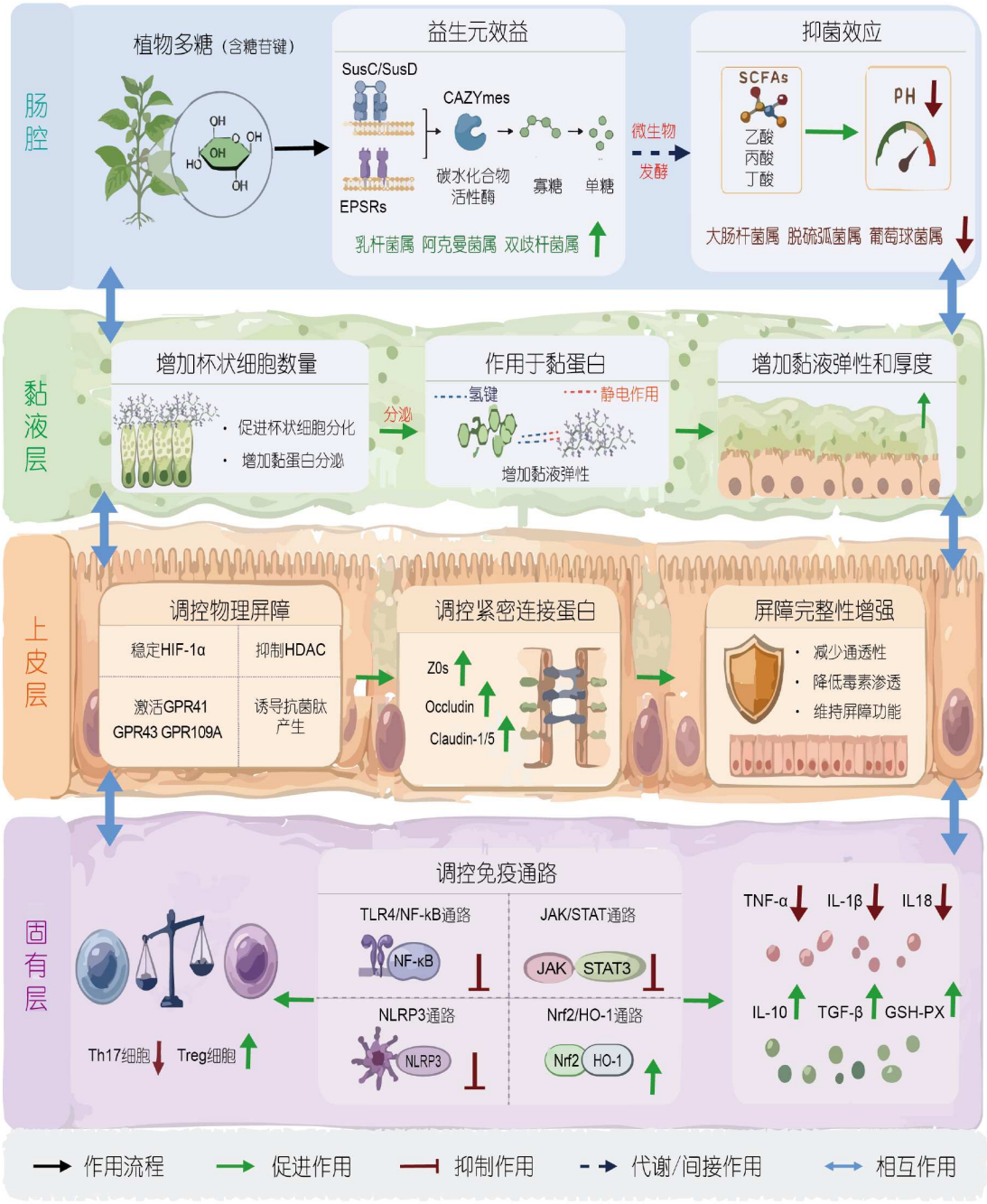


图 1 植物多糖对哺乳动物肠道健康的调控
Figure 1 Regulation of mammalian intestinal health by plant polysaccharides

合成, 使细菌能量代谢枯竭[114~116]; 可干扰细菌的群体感应系统, 从而降低毒力因子的表达, 并抑制生物膜的形成, 使病原菌更易被宿主免疫系统清除[117~119]. 另一方面, 多酚可被特定有益菌代谢利用发挥益生元效应: 肠道中真杆菌属(*Eubacterium*)、双歧杆菌属、乳杆菌属等编码的β-葡萄糖苷酶、鞣酸酶等多酚代谢相关酶(polyphenol-metabolizing enzymes, PAZymes)可将多酚转化为小分子酚酸, 这些小分子化合物可作为信号分子进一步调节宿主免疫和屏障功能[120~122]. 在多酚干预后, 变形菌门这一肠道炎症状态的标志性菌门, 常

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表 1 植物多糖对哺乳动物肠道健康的调控

Table 1 Regulation of mammalian intestinal health by plant polysaccharides

植物多糖	动物模型	调控机制
杏仁多糖(almond polysaccharide, AP-1)	DSS诱导的UC小鼠模型[93]	屏障: MPO↓, NO↓ 免疫: 抑制NF-κB信号通路/iNOS/COX-2(p65↓, p-IκBα↓); TNF-α↓, IL-1β↓, IL-6↓, T-SOD↑, GSH-Px↑, IL-10↑
黄芪多糖(*Astragalus* polysaccharide, APS)	断奶仔猪、小鼠等[61,94]	菌群: *Lactobacillus*↑, *Bifidobacterium*↑, *Allobaculum*↑, *Bacteroides S24-7*↑, *Anaerostipes*↑, *L. amylovorus*↑, *Lactobacillus gasseri*↑, Firmicutes↑, Negativicutes↑, *Escherichia coli*↓, Clostridiales↓, Firmicutes/Bacteroidetes↓, SCFAs↑ 屏障: ZO-1↑, occludin↑, claudin-1↑ 免疫: 抑制NF-κB及NLRP3炎症小体(TNF-α↓, IL-1β↓, IL-6↓, IL-17↓, IL-18↓); IgA↑, IgM↑
蒲公英多糖(dandelion polysaccharide, DP)	DSS诱导的UC小鼠模型[90]	屏障: MPO↓, F4/80$^+$巨噬细胞浸润↓ 免疫: 抑制NF-κB信号通路(p-IκBα↓, p65核转位↓); 抑制NLRP3炎症小体; TNF-α↓, IL-1β↓, IL-6↓, MDA↓, NO↓, Nrf2/HO-1↑
茯苓多糖(*Poria cocos* polysaccharide, PCP)	DSS诱导的UC小鼠模型[65,66]	菌群: *Lactobacillus*↑, *Akkermansia*↑, *Oscillospira*↑, *Prevotella*↑, *Ruminococcus*↑, *Pseudomonas*↓, Erysipelotrichaceae↓ 屏障: ZO-1↑, occludin↑, claudin-1↑ 免疫: 抑制NF-κB信号通路(IκBα↓, p-IκBα↓, NF-κB p6↓); IL-1β↓, IL-6↓, TNF-α↓, IL-10↑
三叶青多糖(*Tetrastigma hemsleyanum* polysaccharide, THP)	DSS诱导的UC小鼠模型[74]	菌群: *Lactobacillus*↑, *Lachnospiraceae NK4A136_group*↑, *Lachnospiraceae UCG-006*↑, *Alistipes*↑, *Bacteroides*↓, *Streptococcus*↓, *Escherichia-Shigella*↓, Firmicutes/Bacteroidetes↑ 屏障: claudin-1↑, MUC2↑, sIgA↑, β-防御素↑, Ki67↑, 胶原沉积↓, 上皮细胞凋亡↓, D-乳酸↓, DAO↓ 免疫: 抑制JAK2/STAT3通路(p-JAK2↓, p-STAT3↓); IL-6↓, TNF-α↓, IL-17A↓, MCP-1↓, IFN-γ↓, Foxp3↑; 恢复Th17/Treg平衡
地黄多糖(*Rehmannia glutinosa* polysaccharides, RGP)	正常小鼠[62]	菌群: *Lactobacillus*↑, *Akkermansia*↑, Lachnospiraceae↑, Ruminococcaceae↑, Bacteroidaceae↑, Rikenellaceae↑ 屏障: ZO-1↑, occludin↑, SCFAs↑ 免疫: CD3$^+$ T细胞↑, CD19$^+$ B细胞↑, CD4$^+$/CD8$^+$比值↑, sIgA↑, IgA$^+$细胞↑, IL-2↑, IL-6↑, TGF-β↑, APRIL↑
鱼腥草多糖(*Houttuynia cordata* polysaccharides, HCPs)	DSS诱导的UC小鼠模型[71]	菌群: Firmicutes↑, Bacteroidetes↑, Lachnospiraceae↑; Proteobacteria↓, Enterobacteriaceae↓ 屏障: ZO-1↑, MUC2↑, 杯状细胞↑; 肠上皮细胞凋亡↓ 免疫: 抑制TLR4/NF-κB通路(TLR4↓, p65↓); 抑制巨噬细胞浸润及M1极化(F4/80$^+$↓, iNOS↓, NO↓, TNF-α↓, IL-1β↓, IL-6↓); 调节Th17/Treg平衡(p-STAT3↓, RORγt↓, IL-17A↓, IL-22↓, Foxp3↑, IL-10↑)
芦荟多糖(aloe polysaccharide)	TNBS诱导的UC大鼠模型[86]	免疫: 抑制JAK2/STAT3通路(JAK2↓, p-JAK2↓, STAT3↓, p-STAT3↓); IL-6↓、结肠上皮细胞凋亡↓
莱阳梨渣多糖(Laiyang pear residue polysaccharides, LPP)	DSS诱导的UC小鼠模型[75]	菌群: Firmicutes/Bacteroidetes↓, *Lactobacillus*↑, Verrucomicrobiota↓, *Turicibacter*↓, *Romboutsia*↓, α多样性↑ 屏障: ZO-1↑, occludin↑, claudin-1↑, 杯状细胞↑ 免疫: 抑制NF-κB通路(p-NFκB/NFκB↓, iNOS↓, COX-2↓); IL-1β↓, IL-6↓, TNF-α↓, MDA↓, SOD↑, CAT↑, GSH-Px↑
黄连多糖(*Coptis chinensis* Franch. polysaccharides, CCP)	正常大鼠模型[95]	菌群: Firmicutes↓, Proteobacteria↑, Bacteroidetes↑, Actinobacteria↑, *Lactobacillus*↓, *Romboutsia*↑, *Turicibacter*↑, *Streptococcus*↑ 免疫: IFN-γ↑, IL-4↑, IL-17↑, TGF-β↑; 平衡Th1/Th2及Th17/Treg

表现出显著下降, 其下属的大肠杆菌-志贺氏菌群、脱硫弧菌属和幽门螺杆菌属(*Helicobacter*)等条件致病菌亦受到有效抑制, 还能抑制厚壁菌门中葡萄球菌属、图利杆菌属(*Turicibacter*)、梭杆菌属(*Fusobacterium*)和肠球菌属(*Enterococcus*)等潜在有害菌的过度增殖[123~129], 此外可特异性促进疣微菌门下阿克曼菌属、厚壁菌门下乳杆菌属、放线菌门下双歧杆菌属等具有多酚代谢能力的核心有益菌增殖, 同时促进拟杆菌门相关功能菌群, 如拟杆菌属、普雷沃氏菌属(*Prevotella*)和鼠杆菌科(Muribaculaceae)的扩增, 并增加多种与SCFAs产生密切相关的厚壁菌门成员, 包括梭菌纲(Clostridia)、杜博西菌属(*Dubosiella*)、别样杆菌属

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(*Alistipes*)和理研菌属(*Rikenella*)等, 从而在部分多酚干预条件下促进肠道SCFAs生成并改善整体代谢环境[130~133]. 在肠道屏障层面, 多酚可显著上调紧密连接蛋白的表达并促进其在细胞膜上的正确组装[110]: 通过调控上游信号通路及氧化还原状态, 间接影响特异性蛋白1(specificity protein 1, SP1)、激活蛋白-1(activator protein-1, AP-1)及GATA结合转录因子(GATA-binding transcription factor, GATA)对claudin-4基因启动子的结合与染色质开放修饰, 从而上调claudin-4的表达[134,135]; 通过增强occludin在苏氨酸和丝氨酸位点的磷酸化, 从而促进ZO-2, occludin及claudin-1向紧密连接结构的组装, 维持其结构的形成与稳定[136,137]; 促炎因子(如TNF-α, IL-6)可通过激活外调节蛋白激酶1/2 (extracellular signal-regulated kinase 1/2, ERK1/2)及磷脂酰肌醇3-激酶(phosphoinositide 3-kinase, PI3K)通路上调成孔蛋白claudin-2, 增加肠道通透性, 而多酚则通过抑制细胞ERK1/2活化下调claudin-2表达, 从而逆转紧密连接通透性增加[138,139]; 通过直接作用于肠上皮细胞, 促进杯状细胞分化和黏蛋白分泌, 其菌群代谢物(如尿石素A)还可通过激活芳香烃受体(aryl hydrocarbon receptor, AhR)-Nrf2信号通路, 上调MUC2表达并增厚黏液层[140]. 例如, 在小鼠结肠炎模型中, 桑葚花青素能显著增加ZO-1, occludin, claudin-3及Muc2的表达[123]; 沙棘黄酮可显著上调ZO-1, occludin, claudin-1的表达水平[141]; 对羟基苯甲酸可显著上调MUC2, MUC1及MUC整体表达, 同时增加杯状细胞数量[133]; 槲皮素可显著上调紧密连接蛋白ZO-1, claudin-1的表达[142]. 在免疫调控层面, 植物多酚可通过靶向多条核心信号通路抑制肠道过度炎症反应, 并调控免疫细胞极化与功能平衡以维持肠道免疫稳态[143]: 通过抑制TLR4对脂多糖(lipopolysaccharide, LPS)的识别及受体二聚化过程, 阻断TLR4与MyD88的结合, 从而抑制下游信号级联的启动; 通过抑制IκB激酶(IκB kinase, IKK)复合体活性, 减少IκBα的磷酸化与降解, 阻止p65释放及核转位[81~85]; 通过抑制MAPK通路中p38, ERK, c-Jun氨基末端激酶(c-Jun N-terminal kinase, JNK)的磷酸化激活以及调节PI3K/蛋白激酶B(protein kinase B, Akt)通路, 阻断炎症信号的级联放大[85,144,145]; 通过抑制NLRP3炎症小体的组装与活化, 减少半胱天冬酶-1 (caspase-1)的剪切激活, 从而阻断IL-1β与IL-18的成熟释放, 并抑制细胞焦亡[145~147]; 通过干预JAK/STAT通路, 抑制IL-6介导的STAT3磷酸化与核转位, 降低RORγt表达, 从而抑制初始T细胞向Th17分化、激活AhR信号通路促进Treg细胞分化, 增强IL-10和TGF-β分泌, 恢复Th17/Treg免疫平衡[148~151]; 通过激活Nrf2/Kelch样ECH相关蛋白1(Kelch-like ECH-associated protein 1, Keap1)通路, 促进Nrf2入核, 诱导HO-1, SOD, GPx, CAT及谷胱甘肽(glutathione, GSH)等抗氧化酶表达, 降低氧化应激并负向调控炎症反应[126]. 例如, 在小鼠结肠炎模型中, 丁香酸抑制p65, IκB-α, STAT3的磷酸化水平从而抑制NF-κB通路和STAT3通路, 下调TNF-α, IL-1β, IL-6等促炎细胞因子及诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)、环氧化酶-2(cyclooxygenase-2, COX-2)等炎症介质的表达, 降低髓过氧化物酶(myeloperoxidase, MPO)活性, 减少$CD68^+$阳性细胞浸润, 发挥护肠作用[152]; 芝麻素能通过激活Akt和ERK信号通路, 促进Nrf2磷酸化与核转位, 激活Nrf2/抗氧化反应元件(antioxidant response element, ARE)通路, 上调SOD, CAT, GSH-Px等抗氧化酶表达[126].

综上, 植物多酚表现出独特的双重调控效应(抗菌与益生元机制并存)(图2). 一方面靶向分选酶A、DNA促旋酶、F1F0-ATP合酶及群体感应系统, 破坏细菌膜完整性、阻断能量代谢与DNA复制, 抑制条件致病菌; 另一方面被双歧杆菌、乳杆菌等编码的PAZymes代谢为小分子酚酸(如尿石素、雌马酚), 促进阿克曼菌等有益菌增殖, 富集产短链脂肪酸菌群. 在屏障层面, 植物多酚通过调控转录因子(SP1, AP-1, GATA)上调claudin-4表达, 促进紧密连接蛋白(ZO-1, occludin, claudin-1)组装, 并抑制claudin-2介导的通透性增加, 同时激活AhR-Nrf2通路促进黏液分泌, 多维度强化肠道物理与化学屏障. 在免疫层面, 植物多酚靶向TLR4/MyD88/NF-κB, MAPK, PI3K/Akt及JAK/STAT等多条信号通路, 抑制炎症因子释放; 同时通过抑制NLRP3炎症小体活化、调控Th17/Treg平衡、促进M2型巨噬细胞极化及激活Nrf2抗氧化通路, 系统性地恢复肠道免疫稳态(表2).

2.3 植物萜类

植物萜类是一类由异戊二烯单元通过聚合与修饰形成的天然化合物, 广泛存在于药用植物(芍药、灵芝、橄榄等)及芳香植物(薄荷、香叶、麝香草等)中,

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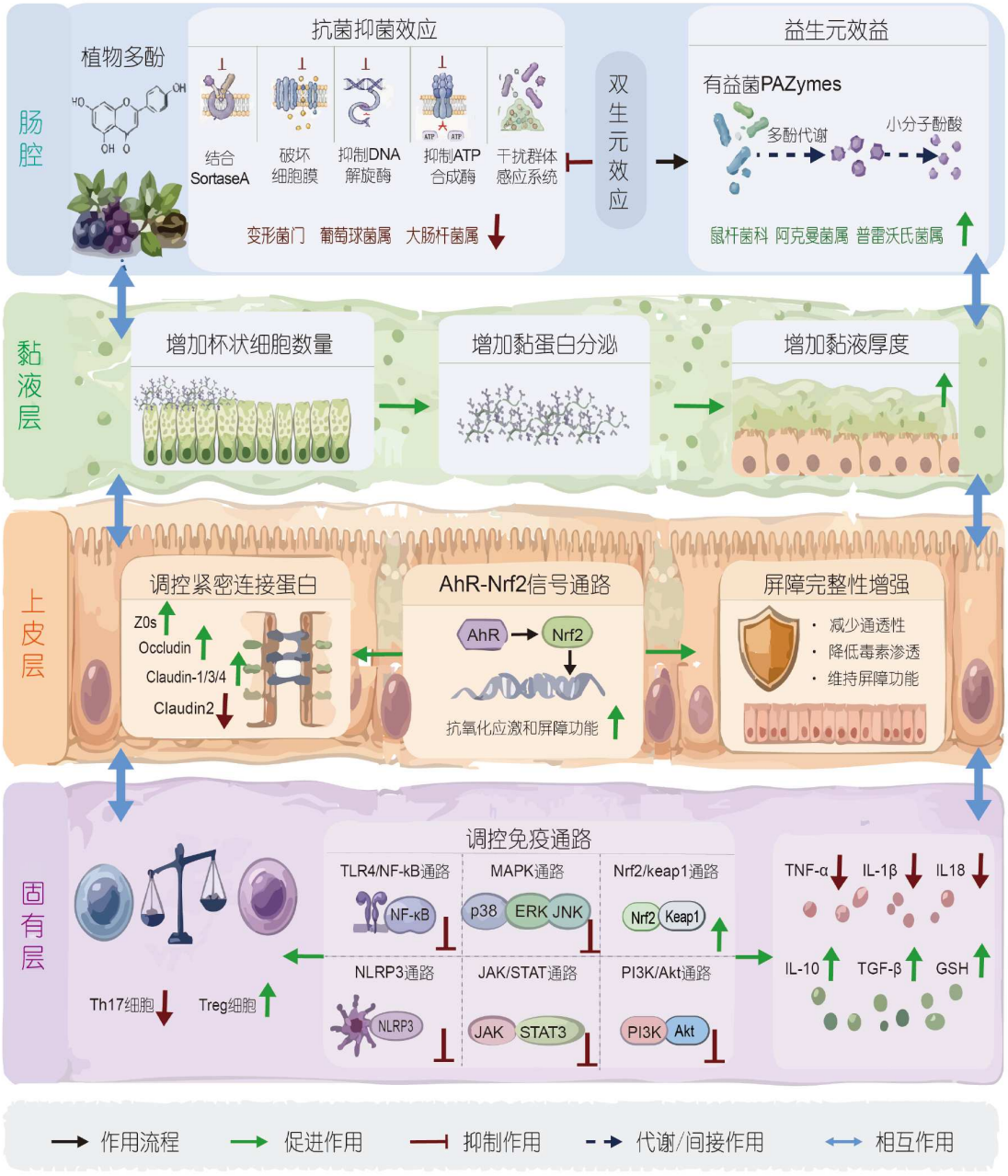


图 2 植物多酚对哺乳动物肠道健康的调控
Figure 2 Regulation of mammalian intestinal health by plant polyphenols

其分子结构具有高度多样性，涵盖单萜、倍半萜、二萜等多个类别，典型化合物包括芍药苷、香叶醇、齐墩果酸等[162,163]. 植物萜类具有脂溶性强、生物活性广泛的特点，在肠道内可通过直接作用于肠上皮细胞或间接调控肠道菌群稳态，发挥抗炎、抗氧化及肠道屏障保护等生物学功能，在肠道疾病中展现出显著的干预潜力[164,165]. 部分萜类已被应用于腹泻等肠道疾病的临床治疗[166,167].

在菌群层面，植物萜类主要通过其理化性质驱动的“选择性抑菌-生态位重塑”过程调控肠道微生态. 植物萜类通常具有较高脂溶性和较低极性，通过嵌入细菌细胞膜的磷脂双层结构中，改变膜流动性并破坏跨

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表 2 植物多酚对哺乳动物肠道健康的调控

Table 2 Regulation of mammalian intestinal health by plant polyphenols

植物多酚	动物模型	调控机制
表没食子儿茶素没食子酸酯(epigallocatechin gallate, EGCG)	乙酸/DSS诱导的UC小鼠模型[130,153]	菌群: *Akkermansia*↑, SCFAs↑ 屏障: 杯状细胞↑、黏液分泌↑ 免疫: 抑制NF-κB通路↓; TNF-α↓, IL-1β↓, IL-6↓, IL-8↓, MPO↓, MDA↓, T-SOD↑, CAT↑
原儿茶酸(protocatechuic acid, PCA)	LPS诱导的断奶仔猪模型[154]	菌群: Firmicutes/Bacteroidetes↑, *Prevotella*↓, Holdemanella↓, *Ruminococcus torques group*↓, *Roseburia*↑, Desulfovibrio↑, Megasphaera↑, Fibrobacter↑ 屏障: ZO-1↑, claudin-1↑ 免疫: TBARS↓, GSH-Px↓, IL-6↓, IL-2↓, TNF-α↓
桑葚花青素(mulberry anthocyanins, MAS)	DSS诱导的UC小鼠模型[123]	菌群: α-多样性↑, Firmicutes/Bacteroidetes↑, Bacteroidetes↑, *Akkermansia*↑, Muribaculaceae↑, *Allobaculum*↑, Proteobacteria↓, *Escherichia-Shigella*↓ 屏障: Muc2↑, ZO-1↑, occludin↑, claudin-3↑, SOD↑, GSH↑, CAT↑; MDA↓ 免疫: TNF-α↓, IL-1β↓, IL-6↓, IL-10↑
芹菜素(apigenin, Api)	DSS诱导的UC小鼠模型[155]	屏障: ZO-1↑, occludin↑, 杯状细胞↑; 免疫: 抑制NLRP3, NF-κB通路(p-IκBα↓, p-p65↓); MPO↓, iNOS↓, COX-2↓, TNF-α↓, IL-1β↓, IL-6↓, NLRP3↓, cleaved caspase-1↓, GSDMD↓, pro-IL-1β↓, cleaved IL-1β↓, MDA↓; GSH↑, T-AOC↑
槲皮素(quercetin)	DSS诱导的UC小鼠模型[156,157]	菌群: Firmicutes/Bacteroidota↓, Bacteroides↑, *Alistipes*↑, Mucispirillum↑, Duncaniella↑ 屏障: occludin↑, claudin-1↑, ZO-1↑, 杯状细胞↑ 免疫: 激活Ahr通路(Ahr↑, Cyp1a1↑, CYP1B1↑); 抑制NETs(MPO↓, PAD4↓, CitH3↓, NE↓); 抑制NF-κB通路(p-p65↓); TNF-α↓, IL-1β↓, IL-6↓, IFN-γ↓, IL-17A↓, 中性粒细胞浸润↓
	*Citrobacter rodentium*诱导的小鼠感染性结肠炎模型[125]	菌群: Bacteroides↑, *Bifidobacterium*↑, *Lactobacillus*↑, Clostridia↑, Fusobacterium↓, Enterococcus↓ 免疫: IL-10↑; IL-17↓, TNF-α↓, IL-6↓
黄芩苷(baicalin)	TNBS诱导的UC小鼠模型[158]	菌群: Firmicutes/Bacteroidetes↓, Proteobacteria↓, *Butyricimonas* spp.↑, *Roseburia* spp.↑, *Subdoligranulum* spp.↑, *Eubacterium* spp. SCFAs↑ 屏障: ZO-1↑, occludin↑, MUC2表达↑ 免疫: Th17/Treg细胞↓, ROS↓, MDA↓, GSH↑, SOD↑
黄皮多酚(wampee polyphenols, WPE)	DSS诱导的UC小鼠模型[159]	菌群: Firmicutes/Bacteroidetes↓, *Kineothrix*↓, *Peptococcus*↓, *Muribaculum*↑, *Ligilactobacillus*↑, *Intestinimonas*↑, *Alistipes*↑, SCFAs↑ 屏障: ZO-1↑, occludin↑ 免疫: 抑制TLR4-p38 MAPK/NF-κB信号通路(TLR4↓, p38↓, p65↓); IL-1β↓, IL-6↓, TNF-α↓
诃子酸(chebulagic acid, CA)	DSS诱导的UC小鼠模型[159]	菌群: Firmicutes/Proteobacteria↑, *Faecalibacterium*↑, *Dubosiella*↑, Muribaculaceae↑, *Clostridium_sensu_stricto_1*↓, *Streptococcus*↓, *Escherichia_Shigella*↓ 屏障: ZO-1↑, occludin↑, 肠上皮细胞凋亡↓, Bcl-2↑, Bax↓, cleaved caspase-3↓ 免疫: 抑制MAPK通路(p-ERK↓, p-JNK↓, p-p38↓); 抑制NF-κB通路(p-p65↓); 激活NRF2/HO-1通路(核NRF2↑, HO-1↑); SOD↑, GSH-Px↑, MDA↓, MPO↓, TNF-α↓, IL-1β↓, IL-6↓
鞣花酸(ellagic acid, EA)	DSS诱导的UC小鼠模型[160]	菌群: Firmicutes↑, Bacteroidetes↓, Proteobacteria↓, *Lactobacillus*↑, *Lachnospiraceae_NK4A136_group*↑, *Ligilactobacillus*↑, *Bacteroides*↓ 屏障: 杯状细胞↑、黏膜层厚度↑ 免疫: 抑制ROS/NLRP3通路(Romo1↓, NLRP3↓, ASC↓, caspase-1↓, IL-1β↓, IL-18↓, GSDMD↓); 抑制NF-κB通路(p-p65↓, TNF-α↓); 激活Nrf2通路(Keap1↓, Nrf2↑); MPO↓, MDA↓, IL-6↓, T-AOC↑, IL-10↑
二氢杨梅素(dihydromyricetin, DMY)	DSS诱导的UC小鼠模型[161]	菌群: Bacteroidota↑, Muribaculaceae↑, Parabacteroides↑, Muribaculum↑, *Lachnospiraceae*_NK4A136_group↑, Desulfovibrionaceae↓, Erysipelotrichaceae↓, Turicibacter↓, *Clostridium_sensu_stricto_1*↓, *Desulfovibrio*↓ 屏障: occludin↑, mucin2↑, mucin3↑ 免疫: 抑制NLRP3炎症小体(NLRP3↓, ASC↓, cleaved caspase-1↓, cleaved IL-1β↓); 抑制MAPK通路(p-ERK↓, p-JNK↓); iNOS↓, MPO↓, COX-2↓, TNF-α↓, IL-6↓, CXCL1↓, CXCL10↓, F4/80$^+$巨噬细胞浸润↓

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膜质子梯度, 导致ATP合成受阻及胞内离子稳态紊乱[168,169]; 萜类还可抑制细菌群体感应信号分子(如酰基高丝氨酸内酯)的合成或识别, 干扰细菌间通讯及生物膜形成, 进一步削弱条件致病菌的生态竞争能力[170]. 研究表明, 萜类可显著下调厚壁菌门下链球菌属(*Streptococcus*)、弯曲杆菌属(*Campylobacter*)等有害菌, 拟杆菌门下异普雷沃氏菌属、副拟杆菌属(*Parabacteroides*)等菌群, 以及变形菌门下大肠杆菌等有害菌丰度[171~174], 同时上调厚壁菌门下乳杆菌属、别样杆菌属等菌群、拟杆菌门下拟杆菌属、普雷沃氏菌科(Prevotellaceae)等菌群、脱铁杆菌门(Deferribacteres)下黏螺菌属(*Mucispirillum*)、变形菌门下陶厄氏菌属(*Thauera*), 以及放线菌门下双歧杆菌属等功能菌群丰度[171,175~177]. 例如, 在结肠炎小鼠模型中, 香叶醇可显著下调拟杆菌门丰度, 上调厚壁菌门及乳杆菌科丰度[175]; 在维生素A缺乏小鼠模型中, β-胡萝卜素可显著下调副拟杆菌属、阿里杆菌属、米氏杆菌属、副普雷沃氏菌属、毛螺菌属、短螺旋体属、脱硫弧菌属丰度[174]. 在肠道屏障层面, 植物萜类通过抑制炎症信号通路以及激活抗氧化反应, 从而间接上调紧密连接蛋白(ZO-1, occludin, claudin家族)表达、增加黏蛋白(MUC1和MUC2)、提升内源性抗菌肽水平, 同时抑制肠上皮细胞凋亡、减轻结肠黏膜炎症与氧化损伤, 从而强化肠道屏障功能、减少肠道通透性[173,174,177~181]. 例如, 在结肠炎小鼠/大鼠模型中, D-柠檬烯不仅恢复ZO-1, occludin和claudin-1水平并降低肠通透性, 还显著增加杯状细胞数量及黏蛋白分泌, 从而多维度修复屏障[178,182]; 橄榄苦苷可显著上调紧密连接蛋白(ZO-1, claudin-3)的表达, 逆转肠屏障损伤[177]; 齐墩果酸能显著上调紧密连接蛋白(ZO-1, occludin, claudin-1)的表达, 有效减轻肠屏障损伤[179,180]. 需要指出的是, 目前相关研究多停留于信号通路层面的关联性证据, 其直接分子靶点及精确作用位点仍缺乏系统阐明. 在免疫调控层面, 植物萜类通过多层级网络协同调控炎症反应、氧化应激及免疫细胞功能, 从而维持肠道免疫稳态: 通过抑制IκBα磷酸化与降解, 阻断p65亚基核转位, 直接干预NF-κB信号通路, 部分萜类还可通过激活过氧化物酶体增殖物激活受体γ(peroxisome proliferator-activated receptor gamma, PPARγ)竞争性抑制NF-κB转录活性, 通过调控miR-214, miR-29a等miRNA促进STAT3及NF-κB mRNA的降解或抑制其翻译, 从而在转录后水平抑制炎症通路活化[177~179,182~185]; 通过抑制MAPK通路中p38, JNK及ERK磷酸化, 阻断AP-1活化, 从而减少促炎因子的转录与释放[179,183]; 通过抑制NLRP3、凋亡相关斑点样蛋白(apoptosis-associated speck-like protein containing a CARD, ASC)及caspase-1的激活, 减少IL-1β和IL-18的成熟分泌, 缓解炎症小体介导的焦亡损伤[183]; 通过激活Nrf2/HO-1通路, 促进Nrf2从Keap1复合物中解离并转位入核, 诱导HO-1, SOD, CAT及GPx等抗氧化酶表达, 清除过量ROS, 阻断“氧化应激-炎症放大”的正反馈环[183,186,187]; 此外, 可抑制JAK/STAT通路中IL-6介导的STAT3磷酸化及RORγt表达, 阻断Th17分化并减少IL-17产生, 同时促进Treg分化及IL-10, TGF-β分泌, 恢复Th17/Treg平衡[183,188,189]. 通过上述多层次的协同作用, 萜类可下调TNF-α, IL-1β, IL-6, IL-8, IL-17A, IL-18, IFN-γ等促炎因子, 上调IL-10等抗炎因子, 并降低iNOS, COX-2, MPO等炎症介质活性, 从而实现对肠道炎症的系统性调控[171,172,175,178,190]. 例如, 在IBS-D小鼠模型中, 芍药苷可抑制NF-κB(p65)介导的NLRP3炎症小体异常激活, 下调IL-1β, IL-18, TNF-α表达[190]. 在结肠炎小鼠模型中, 橄榄苦苷可抑制NF-κB通路活化, 下调TNF-α, IL-1β, IL-6, IL-8水平, 减少MDA积累[177]; 齐墩果酸还可上调SOD, CAT, GSH-Px, GSH活性, 降低热休克蛋白90β(heat shock protein 90 beta, HSP90β)并减少MDA积累[179]; β-胡萝卜素可抑制NF-κB, COX-2, IL-17/STAT3轴, 上调Nrf2表达, 减少硫代巴比妥酸反应物质(thiobarbituric acid reactive substances, TBARS)积累, 增加GSH含量[181].

综上, 在菌群层面, 萜类凭借脂溶性结构嵌入细菌膜, 选择性抑制条件致病菌(如变形菌门、大肠杆菌属), 并干扰群体感应, 从而释放生态位, 促进产SCFAs及胆汁酸转化菌群(如罗斯氏菌属、阿克曼菌属)富集, 驱动菌群结构重塑. 在屏障层面, 萜类上调ZO-1, occludin, claudin等紧密连接蛋白并促进黏蛋白分泌, 修复肠道屏障. 在免疫层面, 萜类多靶点调控炎症网络: 直接抑制NF-κB, MAPK及NLRP3通路, 减少TNF-α, IL-1β, IL-6等促炎因子; 同时激活Nrf2/HO-1抗氧化系统, 清除ROS; 并通过干预JAK/STAT通路调节Th17/Treg平衡, 促进抗炎因子IL-10, TGF-β分泌. 上述三层机制相互协同, 共同构成萜类维护肠道稳态的分子基础(图3和表3).

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2.4 植物生物碱

植物生物碱是一类广泛分布于药用植物中的含氮碱性次生代谢产物, 具有结构多样、生物活性显著的特点, 主要存在于胡椒科、豆科、防己科、毛茛科等药用植物中, 典型代表包括胡椒碱、小檗碱、苦参碱等[193,194]. 这类化合物凭借独特的氮杂环结构, 可通过调控肠道菌群稳态、修复肠道屏障、抑制炎症信号通路、调节免疫平衡等多重途径, 在肠道健康中起着重要作用. 部分生物碱已被应用于腹泻等肠道疾病的临床治疗[195~197].

在菌群层面, 生物碱通过多靶点抗菌机制直接作用于细菌, 主要包括: 靶向细菌细胞分裂蛋白FtsZ、破坏细胞膜完整性、抑制核酸与蛋白质合成, 以及阻断外排泵系统[198~200]. 研究表明, 不同生物碱可显著下调变形菌门(Proteobacteria)下埃希-志贺菌属、弯曲杆菌门(Campylobacterota)下弯曲杆菌属(*Campylobacter*)及螺杆菌属(*Helicobacter*), 以及厚壁菌门下消化链球菌科(Peptostreptococcaceae)、梭菌属(*Clostridium*)、

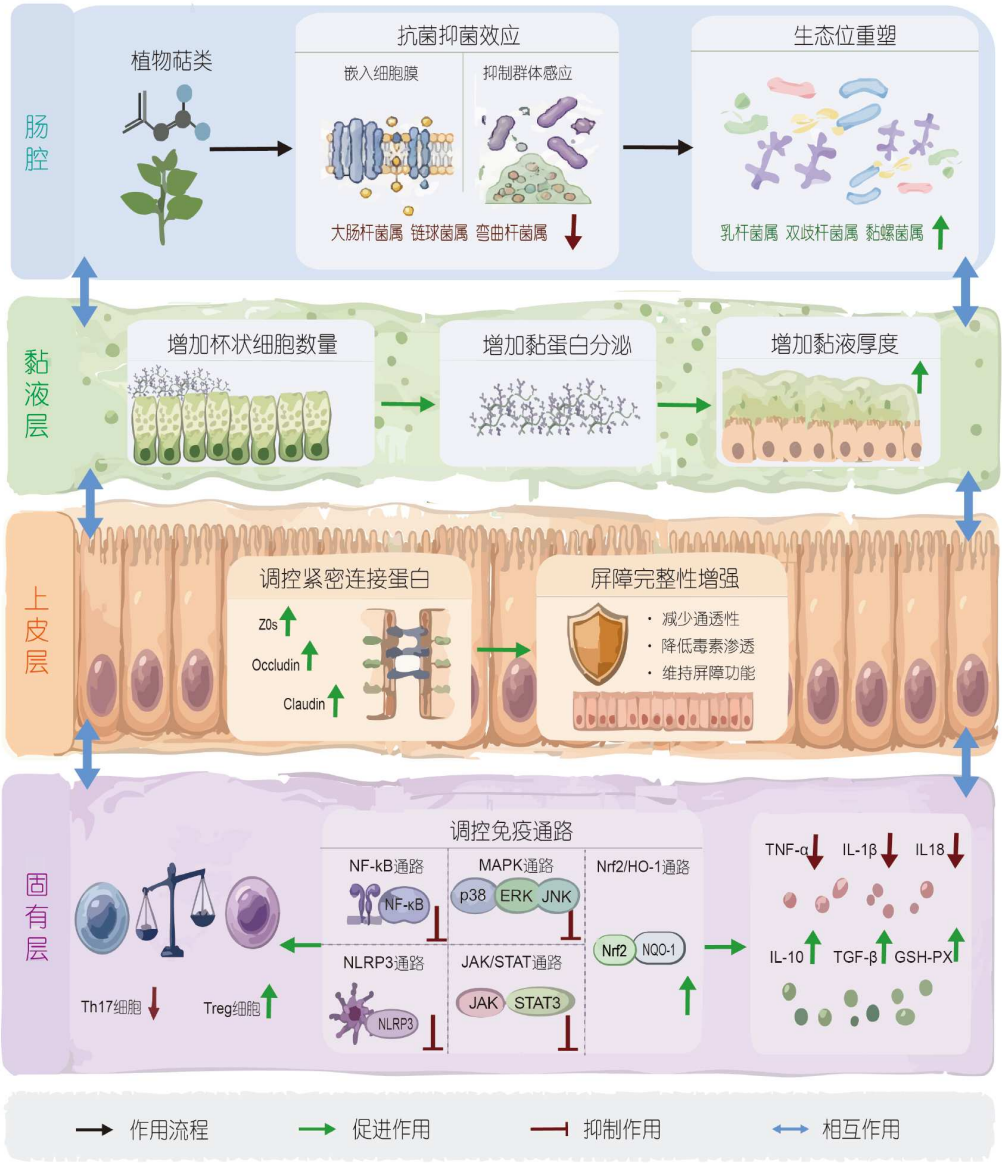


图 3 植物萜类对哺乳动物肠道健康的调控

Figure 3 Regulation of mammalian intestinal health by plant terpenoids

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表 3 植物萜类对哺乳动物肠道健康的调控

Table 3 Regulation of mammalian intestinal health by plant terpenoids

植物萜类	动物模型	调控机制
芍药苷(paeoniflorin)	DSS诱导的UC小鼠模型联合口腔灌胃*Porphyromonas gingivalis*[189]	菌群: Bacteroidetes↑, *Akkermansia*↑; Firmicutes↓, Proteobacteria↓, *Lactobacillus Helicobacter*↓ 免疫: 抑制IL-6/STAT3/IL-17通路; Th17/Treg比值恢复; Th17细胞↓, IL-6↓, IL-17A↓, *ROR-γt*↓, *TGF-β*↓, SAA2↓, *SAA3*↓, *STAT3*↓
香叶醇(geraniol)	IBS患者[167]	菌群: *Oscillospira*↓, Erysipelotrichaceae↓, Clostridiaceae↓, *Faecalibacterium*↑, *Ruminococcus*↑
D-柠檬烯(D-limonene)	DSS诱导的UC大鼠模型[178,182]	菌群: Firmicutes↓, Proteobacteria↓, *Escherichia-Shigella*↓, *Enterococcus faecalis*↓, *Enterobacter hormaechei*↓, Lachnospiraceae↓, Oscillospiraceae↓, Bacteroidota↑, Verrucomicrobiota↑, *Akkermansia muciniphila*↑, Muribaculaceae↑, *Ligilactobacillus*↑, *Candidatus Saccharimonas*↑ 屏障: ZO-1↑, occludin↑, claudin-1↑, 杯状细胞↑, 黏蛋白↑ 免疫: 抑制NF-κB通路(p65↓); TNF-α↓, IL-1β↓, IL-6↓, iNOS↓, COX-2↓, PGE2↓, TGF-β↓, MMP-2/9↓, p-ERK1/2↑, SOD↑, GSH↑, MDA↑
百里香酚(thymol, THY)	多种IBD相关动物模型[183]	菌群: *Escherichia coli* O157:H7↓, *Listeria monocytogenes*↓, *Salmonella*↓, *Clostridium perfringens*↓, *Streptococcus*↓, *Campylobacter*↓, *Treponema*↓, Proteobacteria↓, *Clostridium*↑, *Bacteroides*↑, *Lactobacillus*↑ 屏障: ZO-1↑, occludin↑, claudin-3↑, 黏液分泌↑, DAO↓, D-LA↓ 免疫: 抑制TLR4/NF-κB通路(TLR4↓, p-IκBα↓, p65↓); 抑制MAPK通路(p-p38↓, p-JNK↓, p-ERK↓); 激活Nrf2/HO-1通路(Nrf2↑, HO-1↑); TNF-α↓, IL-1β↓, IL-6↓, IL-8↓, iNOS↓, COX-2↓, PGE2↓, NO↓, MPO↓, SOD↑, CAT↑, GPx↑, GSH↑, 促进Treg分化、调节Th1/Th17/Treg平衡
薄荷醇(menthol)	AOM/DSS诱导的结肠炎相关结肠癌小鼠模型[191]	菌群: *Allobaculum*↑, *Roseburia*↑, *Intestinimonas*↑, Prevotellaceae UCG_001↑, *Thauera*↑, SCFAs↑ 免疫: β-catenin↓, Ki67↓, *IL-6*↓, *TNF-α*↓, *MPO*↓, $CD45^+$白细胞↓, $CD45^+Gr1^+$中性粒细胞↓, IL-10↑
齐墩果酸(oleanolic acid, OA)	DSS诱导的UC小鼠模型[179]	屏障: ZO-1↑, occludin↑, claudin-1↑ 免疫: 抑制NF-κB通路(p-IKKα/β↓, p-p65↓, IκBα↓, iNOS↓), IL-1β↓, IL-6↓, TNF-α↓, MDA↓, PPARγ↑, SOD↑, CAT↑, GSH-Px↑, GSH↑, GSH/GSSG↑
β-胡萝卜素(β-carotene)	DSS诱导的UC大鼠模型[192]	菌群: Actinobacteria↑, *Faecalibacterium*↑, *Staphylococcus*↓, *Sutterella*↓, *Parabacteroides*↓, *Alistipes*↓, *Phascolarctobacterium*↓, *Veillonella*↓, *Enterococcus*↓, Butyricimonas↓, Proteobacteria↓ 免疫: 抑制NF-κB通路(p-p65/p65↓); 抑制MAPK通路(p-p38/p38↓, p-Erk/Erk↓, p-JNK/JNK↓); TNF-α↓, IL-6↓, IL-1β↓, IFN-γ↓, D-LA↓
橄榄苦苷(oleuropein, OLE)	DSS/乙酸诱导的UC大/小鼠模型[177,184]	菌群: α多样性↑, β多样性↑, Bacteroidetes↑, *Desulfovibrio*↑, Helicobacter↑, *Lactobacillus*↑, Turicibacter↑, *Alistipes*↑, *Bifidobacterium*↑, *Ruminococcus*↑ 屏障: ZO-1↑, claudin-3↑ 免疫: 抑制NF-κB通路(p-p65↓, p-IκBα↓); MDA↓, MPO↓, NO↓, TNF-α↓, IL-1β↓, IL-6↓, IL-8↓, COX-2↓, iNOS↓, TGF-β1↓, MCP-1↓, Bax↓, Bcl2↑

毛螺菌科(Lachnospiraceae)等条件致病菌丰度; 同时上调厚壁菌门下乳杆菌属、瘤胃球菌属、罗斯氏菌属、丁酸球菌属、粪杆菌属, 放线菌门下双歧杆菌属, 疣微菌门下阿克曼菌属, 以及拟杆菌门下拟杆菌属、产酸拟杆菌等功能菌群丰度[197,201~207]. 例如, 在DSS诱导的结肠炎小鼠模型中, 胡椒碱可显著降低弯曲杆菌门丰度, 并增加粪杆菌属、双歧杆菌属和杜博氏菌属等有益菌群丰度[204]; 小檗碱可显著降低肠杆菌科、脱硫弧菌属、真杆菌属及拟杆菌属的丰度, 同时上调双歧杆菌属丰度[208]. 在肠道屏障层面, 植物生物碱虽缺乏明确的直接作用靶点, 但可通过减少氧化应激和炎症因子, 从而间接保护紧密连接蛋白的结构与功能、增强黏液分泌, 修复被炎症破坏的肠道屏障. 如苦参碱可显著提高ZO-1和occludin水平, 从而增强肠上皮屏障完整性[201]; 胡椒碱还能促进MUC2表达, 从而改善肠道屏障功能[204]. 在免疫调控层面, 植物生物碱通过多靶点干预炎症信号网络、调节免疫细胞分化与功能、协同抗氧化应激, 从而维持肠道免疫稳态: 通过抑制TLR4/MyD88轴及IKK活性, 阻断IκBα磷酸化与降解并抑制NF-κB p65核转位, 从而下调TNF-α, IL-6, MCP-1及COX-2等促炎因子表达; 通过激活孕烷X受体(pregnane X receptor, PXR)或AhR抑制NF-κB信号,

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并调控法尼醇X受体(farnesoid X receptor, FXR)/Takeda G蛋白偶联受体5(Takeda G protein-coupled receptor 5, TGR5)轴, 参与胆汁酸代谢及炎症负反馈调节[205,209]; 通过靶向JAK2抑制STAT3磷酸化并协同抑制p38 MAPK通路, 减少炎症介质释放及巨噬细胞M1极化; 通过干预NIMA相关激酶7(NIMA-related kinase 7, NEK7)-NLRP3相互作用及抑制硫氧还蛋白相互作用蛋白(thioredoxin-interacting protein, TXNIP)/NLRP3轴, 阻断ASC寡聚化及caspase-1活化, 从而抑制IL-1β与IL-18的成熟与释放; 通过调控PI3K/Akt/mTOR信号通路参与免疫代谢调节并降低炎症反应[210]; 通过抑制Th17分化并促进Treg分化, 上调IL-10和TGF-β表达, 从而恢复Th17/Treg免疫平衡; 通过激活Nrf2/NAD(P)H醌氧化还原酶1(NAD(P)H:quinone oxidoreductase 1, NQO-1)抗氧化通路, 上调SOD, HO-1, CAT, GSH及总抗氧化能力(total antioxidant capacity, T-AOC)水平并降低ROS, MDA及NO含量, 从而缓解氧化应激损伤[211]. 不同生物碱在不同的结肠炎模型中呈现出较为明确的靶点特异性. 例如, 在小鼠结肠炎模型中, 胡椒碱可作为PXR激动剂激活PXR信号并诱导细胞色素P450 3A4(cytochrome P450 3A4, CYP3A4)表达, 同时下调趋化因子受体2(C-C chemokine receptor type 2, CCR2)、细胞间黏附分子1(intercellular adhesion molecule 1, ICAM-1)、iNOS、单核细胞趋化蛋白1(monocyte chemoattractant protein-1, MCP-1)及TNF-α, IL-1β, IL-6, IL-10等炎症相关因子表达, 从而减轻炎症反应[205]; 小檗碱可下调pSTAT1, pSTAT3及pNF-κB水平, 减少IFN-γ, IL-17, IL-6, IL-1β及TNF-α生成, 同时上调IL-22及分泌型免疫球蛋白A(secretory immunoglobulin A, sIgA), 抑制Th1/Th17分化并调节巨噬细胞极化[212,213]; 青藤碱可激活Nrf2/NQO-1抗氧化通路, 上调Nrf2, NQO-1, SOD及HO-1表达, 同时下调TNF-α, IL-6及iNOS, 体现抗氧化与抗炎双重调控效应[211].

综上, 植物生物碱主要通过“多靶点直接抑菌-间接修复屏障-多通路免疫调控”的三位一体机制维护肠道稳态(图4). 在菌群层面, 生物碱凭借氮杂环结构多靶点作用于细菌: 靶向细胞分裂蛋白FtsZ、破坏细胞膜完整性、抑制核酸与蛋白质合成、阻断外排泵系统, 从而选择性抑制条件致病菌(如埃希-志贺菌属、弯曲杆菌属、梭菌属等), 同时促进乳杆菌属、双歧杆菌属、阿克曼菌属等有益菌群的扩增. 在屏障层面, 生物碱可通过减轻氧化应激与炎症反应, 间接上调紧密连接蛋白及黏蛋白的表达, 修复被炎症破坏的肠道屏障. 在免疫层面, 结合IKK, NEK7等靶点, 抑制NF-κB, NLRP3及MAPK通路, 减少TNF-α, IL-6, IL-1β, 调节Treg/Th17平衡并激活Nrf2. 植物生物碱凭借“菌群-屏障-免疫”网络在肠道稳态中发挥重要潜力(表4).

2.5 植物油脂(脂肪酸)

植物油脂是一类以甘油三酯为核心的脂溶性天然物质, 主要由植物种子、果实等器官合成, 这类油脂除含有一定比例的饱和脂肪酸外, 还富含不饱和脂肪酸(核心包括油酸、亚油酸、α-亚麻酸)及少量植物甾醇、脂溶性维生素等活性成分, 广泛分布于山茶、紫苏、亚麻、核桃、鼠尾草等植物中[218~220]. 在消化过程中, 甘油三酯经脂肪酶水解生成单甘油酯及具有生物活性的游离脂肪酸, 不仅参与能量供给, 更可通过调控肠道菌群结构、增强肠上皮屏障功能、调节炎症信号通路及氧化应激状态等多重机制参与肠道稳态维持. 这些脂肪酸通过影响细菌膜结构、微生物代谢产物生成及宿主脂质感知信号, 共同构建“脂质-菌群-宿主”互作网络. 其中, 相较于饱和脂肪酸, 不饱和脂肪酸在改善肠道微生态失衡、缓解炎症反应及维持屏障功能方面表现出更为积极的生物学效应, 因此, 下文主要聚焦于油酸、亚油酸和α-亚麻酸三大代表性不饱和脂肪酸, 阐释其调控肠道健康的作用机制.

在菌群层面, 脂肪酸可直接作用于细菌的多种分子靶点. 通过抑制细菌脂肪酸合成关键酶(如FabI)阻断病原菌自身细胞膜合成, 而对能从宿主摄取外源脂肪酸的共生菌影响较小, 实现选择性抑制[221]; 通过结合转录激活因子(如ToxT)阻断其与DNA启动子的结合, 抑制毒力基因表达[222]; 通过竞争性抑制接合系统ATP酶(如TrwD)阻断质粒在菌群间的水平基因转移, 减少耐药基因扩散[223,224]; 通过抑制自诱导物-2(auto-inducer-2, AI-2)介导的群体感应, 降低细菌毒力因子表达; 通过插入细菌细胞膜磷脂双分子层, 诱导膜破裂、内容物泄漏和质子动势耗散, 直接杀灭病原菌[225]. 研究表明, 脂肪酸及其代谢产物可显著上调厚壁菌门下罗伊氏乳杆菌(*Lactobacillus reuteri*)、普通拟杆菌(*Bacteroides vulgatus*)、鼠杆菌科、罗斯氏菌属、颤螺菌属、厌氧棒菌属(*Anaerostipes*), 以及拟杆菌门

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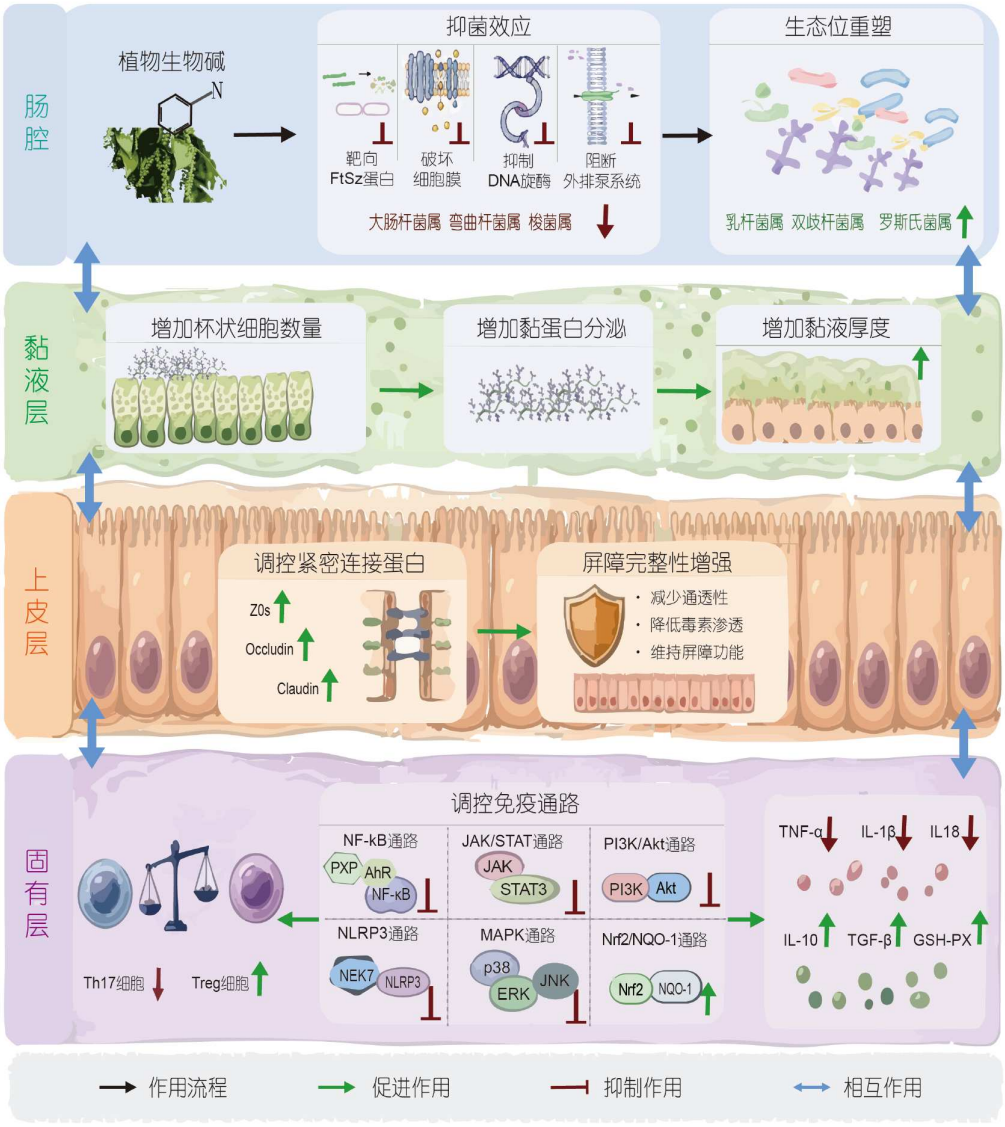


图 4 植物生物碱对哺乳动物肠道健康的调控
Figure 4 Regulation of mammalian intestinal health by plant alkaloids

下理研菌科(Rikenellaceae)、副拟杆菌属(*Parabacteroides*)、普雷沃氏菌属、别样杆菌属等有益菌丰度; 下调和抑制肠杆菌科等不能代谢亚油酸的菌群、产气荚膜梭菌等条件致病菌以及金黄色葡萄球菌、大肠杆菌、霍乱弧菌(*Vibrio cholerae*)、艰难梭菌(*Clostridium difficile*)、幽门螺杆菌(*Helicobacter pylori*)、单核细胞增生李斯特菌(*Listeria monocytogenes*)等多种病原菌丰度[226~229]. 例如, 在高脂饮食诱导的肥胖小鼠模型中, 油酸可显著增加粪杆菌属、罗斯氏菌属、毛螺菌科、双歧杆菌属、乳杆菌属丰度[230]; α-亚麻酸可下调别样杆菌属、理研菌科等菌群, 上调布劳特氏菌属(*Blautia*)、双歧杆菌属、嗜胆菌属(*Bilophila*)丰度[231]; 在ob/ob肥胖小鼠模型中, 亚油酸可上调罗斯氏菌属、杜氏杆菌属、颤螺菌属、厌氧棒菌属丰度, 下调别样杆菌属等菌群[232]. 在肠道屏障层面, 脂肪酸可通过GPR介导的抗炎信号转导, 上调紧密连接蛋白ZO-1, occludin和claudin-1的表达, 降低肠黏膜通透性[230]. 例如, α-亚麻酸在高脂饮食诱导的肥胖小鼠中同样恢复了occludin, ZO-1和Muc2的mRNA水平[231]; 亚油酸的菌群代谢物10-羟基-顺-12-十八碳烯酸(10-hydroxy-

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表 4 植物生物碱对哺乳动物肠道健康的调控

Table 4 Regulation of mammalian intestinal health by plant alkaloids

植物生物碱	动物模型	调控机制
小檗碱(berberine)	DSS诱导的IBD猫模型[203]	菌群: Firmicutes↑, Bacteroidetes↑, Proteobacteria↑, Actinobacteria↑, *Lactobacillus*↑, *Ruminococcus*↑, Shrektonia↑, *Prevotella*↓, Peptostreptococcaceae↓, *Clostridium*↓ 肠道屏障: ZO-1↑, ZO-2↑, occludin↑, E-cadherin↑, 杯状细胞↑, N-cadherin↓ 免疫: 抑制TLR4/NF-κB通路; IL-6↓, IL-1β↓, TNF-α↓, MDA↓, T-AOC↑, GSH↑, CAT↑, SOD↑
	DSS诱导的UC小鼠模型[197]	菌群: Firmicutes↑, *Lactobacillus*↑, Lactococcus↑, Butyricicoccus↑, *Roseburia*↑, Tyzzerella↑, Alloprevotella↓, Eisenbergiella↓, Bacteroidetes↓, UDCA/DCA↑, SCFAs↑, 5-HT↓, 吲哚↓ 肠道屏障: MUC2↑, MUC3↑, occludin↑, 杯状细胞/黏液层↑ 免疫: 调控菌群-胆汁酸-FXR/TGR5轴; TNF-α↓, IL-1β↓, TGR5↓, p-ERK↓, FXR↑, TGR5↑
苦参碱(matrine)	TNBS/DSS诱导的UC小鼠模型[201,202]	菌群: Bacilli↑, Mollicutes↑, Peptostreptococcaceae↑, Methylobacteriaceae↑, Sphingomonadaceae↑, Lachnospiraceae↑, Bifidobacteriaceae↑, Firmicutes↑, Bacteroidetes↑, Proteobacteria↑, *Lactobacillus*↑, *Akkermansia*↑, Mycoplasmataceae↓ 肠道屏障: ZO-1↑, occludin↑, 杯状细胞↑ 免疫: 抑制TLR4/MyD88通路(TLR4↓, MyD88↓); TNF-α↓, IL-6↓, IL-1β↓, IL-17A↓, NO↓, *iNOS*↓, MDA↓, IL-10↑, SOD↑, CAT↑, T-AOC↑, Th17↓
胡椒碱(piperine)	DSS诱导的UC小鼠[204,205]	菌群: α多样性↑, Firmicutes/Bacteroidetes↑, Actinobacteriota↑, Verrucomicrobiota↑, *Dubosiella*↑, *Anaerotruncus*↑, *Enterorhabdus*↑, *Faecalibaculum*↑, *Bifidobacterium*↑, *Campylobacterota*↓, Deferribacterota↓, Cyanobacteria↓, *Bacteroides*↓, *Alloprevotella*↓, *Alistipes*↓, Helicobacter↓ 肠道屏障: claudin-1↑, claudin-3↑, ZO-1↑, occludin↑, MUC2↑ 免疫: 激活PXR, 抑制NF-κB通路; CCR2↓, ICAM-1↓, IL-1β↓, IL-6↓, IL-10↓, iNOS↓, MCP-1↓, TNF-α↓, COX-2↓, IFN-γ↓
血根碱(sanguinarine)	DSS诱导的UC小鼠模型[214,215]	菌群: Proteobacteria↓, Epsilonbacteraeota↓, *Escherichia-Shigella*↓, *Helicobacter*↓, *Eisenbergiella*↓, Deferribacteres↑, Bacteroidetes↑, Muribaculaceae_unclassified↑, *Ruminiclostridium_5*↑ 肠道屏障: ZO-1↑, occludin↑ 免疫: 激活Nrf2通路(Nrf2↑, HO-1↑, Keap-1↓); 抑制NF-κB通路(p-p65↓); 抑制NLRP3炎症小体通路(NLRP3↓, caspase-1↓); IL-4↑, IL-10↑, TNF-α↓, IL-1β↓, IL-6↓, ROS↓, MDA↓
黄连碱(coptisine)	DSS诱导的UC小鼠模型[206,207]	菌群: Bacteroidota↑, Verrucomicrobiota↑, *Akkermansia muciniphila*↑, *Bacteroides acidifaciens*↑, Bacillota↓, Lachnospiraceae↓, *Alistipes*↓, *Clostridium XIVa*↓, *Oscillibacter*↓ 肠道屏障: ZO-1↑, occludin↑, claudin-4↑, MUC2↑, 杯状细胞↑ 免疫: 激活AhR; 抑制NF-κB通路(p-p65↓、p-IκBα↓); 抑制TXNIP/NLRP3炎症小体通路(TXNIP↓, NLRP3↓, ASC↓, caspase-1↓, IL-1β↓, IL-18↓); DAO↓, D-LA↓, IL-6↓, IL-1β↓, TNF-α↓, IL-8↓, IL-18↓, ROS↓, MDA↓, SOD↑
延胡索总生物碱(total alkaloids of *Corydalis yanhusuo*, YTA)	DSS诱导的UC小鼠模型[216,217]	菌群: α多样性↑, *Lactobacillus*↑, *Romboutsia_B*↑, *Turicibacter*↑, *Streptococcus*↑ 肠道屏障: ZO-1↑, occludin↑ 免疫: 抑制MAPK通路(p-p38↓); 抑制巨噬细胞M1极化(CD86↓); TNF-α↓, IL-1β↓, IL-6↓, NO↓, MMP-9↓, MDA↓, MPO↓, IL-10↑, SOD↑
青藤碱(sinomenine)	DSS诱导的UC小鼠模型[211]	免疫: 激活Nrf2/NQO-1通路(Nrf2核转位, NQO-1↑, *HO-1*↑); SOD↑, *TNF-α*↓, *IL-6*↓, *iNOS*↓

cis-12-octadecenoic acid, HYA)则通过GPR40-MEK-ERK通路选择性抑制TNFR2, 进而上调occludin, ZO-1和claudin-3, 下调MLCK和异常升高的claudin-1, 恢复跨上皮电阻(transepithelial electrical resistance, TER), 降低FD-4通透性[233]. 在免疫调控层面, 植物油脂可通过靶向脂质感知受体、表观修饰靶点及核受体等上游分子, 通过调控炎症相关信号通路及细胞因子表达, 在多种模型中抑制NF-κB和NLRP3炎症小体通路、降低促炎细胞因子水平、增强抗氧化防御能力, 发挥显著的抗炎和免疫调节作用[218,219,234~236]. 例如, 油酸可通

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过激活GPR120-β-arrestin-2信号通路, 抑制IκBα磷酸化及NF-κB p65核转位, 下调TNF-α, IL-6, IL-1β并上调IL-10, 此外还可激活沉默信息调节因子1(silent information regulator 1, SIRT1)使NF-κB p65去乙酰化, 并激活PPARα/γ协同抗炎[230,232]; 辛酸和壬酸通过抑制HDAC活性, 增加组蛋白H3K9乙酰化, 上调猪β-防御素(β-defensin, BD, 如pBD-1和pBD-2)表达, 增强抗菌活性[237].

综上, 脂肪酸既可通过靶向细菌关键酶、膜结构、群体感应与耐药传播系统实现对肠道菌群的选择性塑造, 又能经由GPR120, GPR40, TLR4, NF-κB, HDAC等信号通路直接保护肠道屏障、调控肠道免疫与炎症反应, 在维持肠道微生态平衡与黏膜稳态中发挥重要作用(图5和表5).

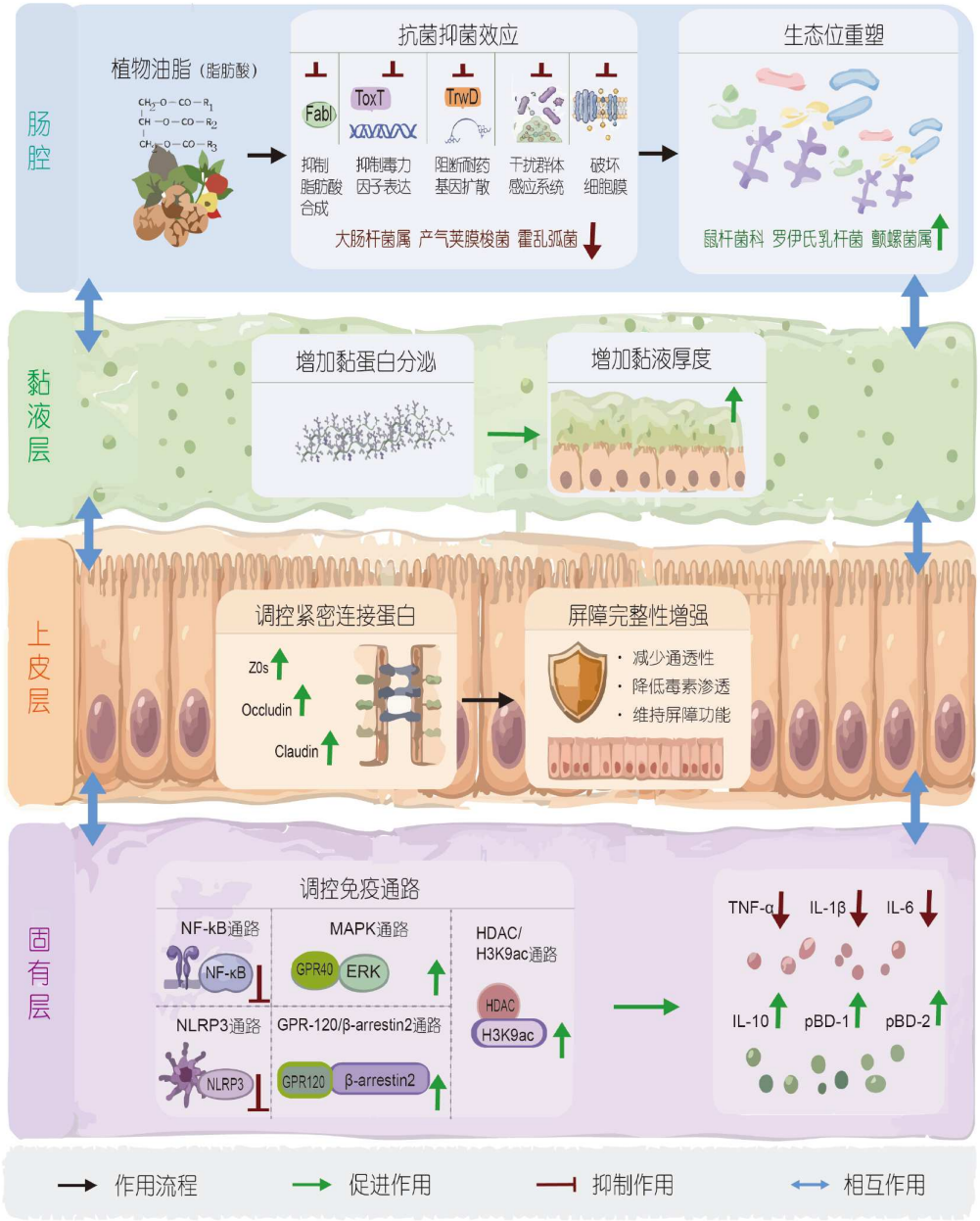


图 5 脂肪酸对哺乳动物肠道健康的调控
Figure 5 Regulation of mammalian intestinal health by fatty acids

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表 5 脂肪酸对哺乳动物肠道健康的调控

Table 5 Regulation of mammalian intestinal health by fatty acids

脂肪酸	动物模型	调控机制
油酸(oleic acid)	高脂饮食诱导的肥胖/代谢紊乱小鼠模型[230]	菌群: *Faecalibacterium*↑, *Roseburia*↑, Lachnospiraceae↑, *Bifidobacterium*↑, *Lactobacillus*↑, Firmicutes/Bacteroidetes↓ 屏障: ZO-1↑, occludin↑, claudin-1↑ 免疫: 激活GPR120-β-arrestin-2通路, 抑制NF-κB核转位; TNF-α↓, IL-6↓, IL-1β↓, IL-10↑
α-亚麻酸(alpha-linolenic acid, ALA)	高脂饮食(HFD)诱导的肥胖/代谢紊乱小鼠模型[231]	菌群: *Turicibacter*↑, *Blautia*↑, *Bifidobacterium*↑, *Bilophila*↑, *Parasutterella*↓, *Rikenellaceae_RC9_gut_group*↓, *Alistipes*↓ 屏障: Occludin↑, ZO-1↑, *Muc2*↑, *CD14*↓, *CB1*↓, TLR4↓ 免疫: 抑制TLR4信号通路(TLR4/*CD14*/*CB1*轴); *TNF-α*↓, *IFN-γ*↓, *MCP-1*↓, *IL-1β*↓, *IL-10*↑
	STZ-烟酰胺诱导的2型糖尿病大鼠模型[238]	免疫: 激活GPR120-β-arrestin-2通路, 阻断NF-κB活化; iNOS↓, TNF-α↓, NLRP3↓, ASC↓, caspase-1↓, IL-1β↓, IL-18↓, TNF-α↓, IL-6↓, $CD68^{+}$↓, Arg-1↑, IL-10↑
	健康成年小鼠[239]	菌群: *Prevotella*↑, *Parabacteroides*↑, *Lactobacillus*↓, *Clostridium cluster XIVa*↓, Lachnospiraceae↓, *Streptococcus*↓, *Anaerotruncus*↓, *Anaerovorax*↓, *Olsenella*↓ 屏障: 绒毛长度↑, 黏膜厚度↑, 上皮细胞数量↑, 杯状细胞比例↓, 潘氏细胞比例↓, 上皮增殖率(Ki67)↓
	刚地弓形虫诱导的肠炎小鼠模型[240]	菌群: *Lactobacillus*↑, *Bacteroides*↑, *Bifidobacterium*↑, Paraprevotella↑, Macellibacteroides↑, Enterobacteriaceae↑, Proteobacteria↑, *Shigella*↑, *Enterococcus*↑ 屏障: occludin↑ 免疫: 抑制MyD88/NF-κB通路(p-NF-κB p65↓); IFN-γ↓, TNF-α↓, IL-1β↓, IL-6↓
亚油酸(linoleic acid)	DSS诱导的UC小鼠模型[233]	屏障: occludin↑, ZO-1↑, ZO-2↑, claudin-3↑, TER↑, claudin-1↓, MLCK↓, FD-4通透性↓ 免疫: 激活GPR40-MEK-ERK通路; 抑制TNFR2表达及NF-κB活化(IκBα↓, p65↓); IL-8↓
	ob/ob肥胖小鼠模型[232]	菌群: Firmicutes/Bacteroidetes↓, Tyzzerella↓, *Alistipes*↓, Lachnoclostridium↑, *Roseburia*↑, Dubosiella↑, *Oscillibacter*↑, Anaerostipes↑ 屏障: occludin↑, ZO-1↑
辛酸(caprylic acid, C8)、壬酸(nonanoic acid, C9)	猪空肠上皮细胞IPEC-J2大肠杆菌O157:H7攻击模型[237]	免疫: 抑制HDAC活性(H3K9Ac↑); pBD-1↑, pBD-2↑

3 总结与展望

现有研究证据表明, 植物多糖、多酚、萜类、生物碱及植物油脂(脂肪酸)虽然在化学结构与来源方面存在显著差异, 但对哺乳动物肠道健康的调控作用呈现出高度一致的“三层级共性调控框架”, 即以肠道菌群为上游调节枢纽、以肠道屏障完整性为结构基础、以免疫炎症信号网络为分子整合核心, 三者协同作用, 共同维持肠道稳态. 在菌群层面, 各类活性成分均能调节肠道微生态组成, 表现为选择性促进乳杆菌属、双歧杆菌属、阿克曼菌属等有益菌的增殖, 同时抑制变形菌门、大肠杆菌-志贺菌属、葡萄球菌等条件致病菌的过度生长, 从而优化菌群结构. 在肠道屏障层面, 多数活性成分能够上调ZO-1, occludin, claudin等紧密连接蛋白表达, 促进黏蛋白分泌及杯状细胞功能恢复, 降低肠道通透性并增强黏膜屏障完整性; 在免疫调控层面, 各类植物活性成分普遍通过抑制NF-κB, MAPK及NLRP3炎症小体等炎症相关通路, 下调TNF-α, IL-1β, IL-6等促炎因子表达, 同时部分成分还能调节Th17/Treg平衡并激活Nrf2介导的抗氧化防御系统, 从而减轻肠道炎症反应与氧化应激损伤. 由此可见, 不同类别植物活性成分虽作用起点各异, 但最终均指向肠道稳态恢复这一共同生物学终点.

各类植物活性成分在发挥共性作用的同时, 又展现出显著的机制偏向性(图6). 植物多糖主要以“底物发酵-短链脂肪酸(SCFAs)生成”模式发挥作用, 其复杂糖苷键结构可作为肠道菌群发酵底物, 通过菌群酶解产生SCFAs, 并进一步调控肠道屏障与免疫稳态; 植物多酚则表现出“菌群互作-宿主信号协同调控”特征, 一方面通过抑制细菌膜功能、DNA复制及群体感应系统发挥抑菌作用, 另一方面又可被肠道菌群代谢为小分子酚酸, 从而进一步调控宿主炎症与氧化应激信号;

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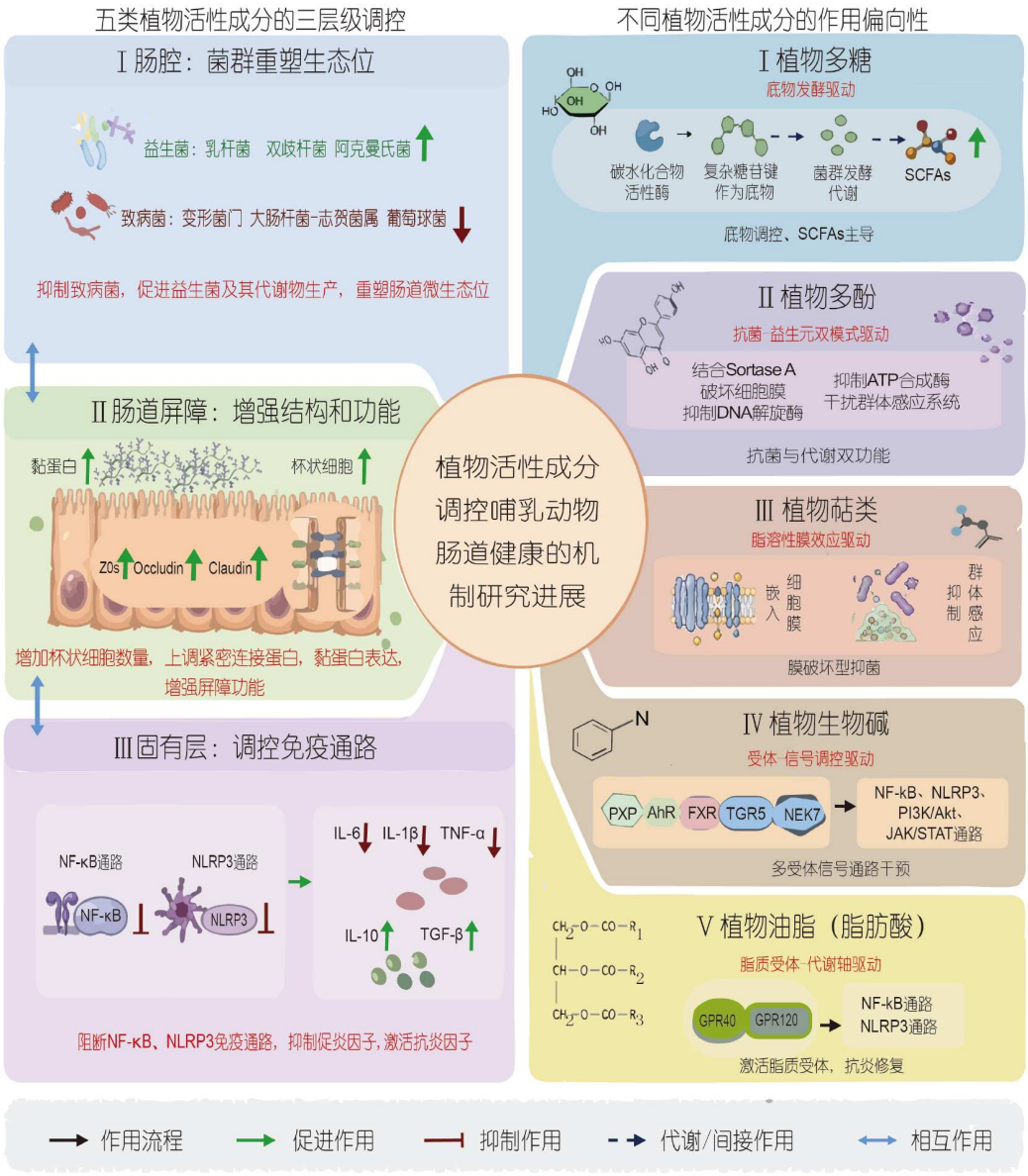


图 6 植物活性成分对哺乳动物肠道健康的调控
Figure 6 Regulation of mammalian intestinal health by plant bioactive compounds

植物萜类凭借较强脂溶性，可通过嵌入细菌细胞膜干扰膜稳定性及能量代谢，并协同发挥抗炎与抗氧化作用；植物生物碱则更倾向于“靶点型免疫调控”模式，可直接作用于NEK7，TXNIP/NLRP3及PXR，AhR，FXR/TGR5等关键分子节点，表现出较强的信号通路干预能力；植物油脂(脂肪酸)则更多依赖GPR120，GPR40等脂质感知受体介导宿主炎症调控与屏障修复，并通过影响细菌膜结构及群体感应参与肠道菌群重塑.

尽管植物活性成分调控肠道健康的研究已取得显著进展，但当前研究仍面临若干亟待突破的问题. 首先，多数研究仍局限于单一成分与单一动物模型，对不同成分间协同或拮抗作用缺乏系统评估，未来有必要从“复合干预”与“网络调控”的角度，解析多类植物活性成分在肠道微生态与宿主互作中的整合效应. 其次，分子作用机制及构效关系解析仍不充分. 当

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前, 多数研究集中于信号通路水平的变化, 活性成分的直接作用靶蛋白及其相互作用模式鉴定较少. 未来需结合化学生物学与结构生物学技术, 从分子层面阐明“成分-靶点”之间的直接联系, 并进一步揭示结构修饰对生物活性的影响规律. 此外, 植物活性成分的作用效应在不同物种与生理状态下存在明显差异, 其剂量效应关系、生物利用度及个体响应异质性仍缺乏系统阐释, 这在一定程度上限制了研究结论的普适性与应用转化. 未来研究应在优化实验设计的基础上, 加强从动物模型向人群研究的过渡, 推动基础研究成果向功能性食品及“药食同源”产品的开发应用转化.

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Advances in plant bioactive components regulating mammalian intestinal health

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Intestinal health is fundamental to maintaining overall homeostasis of the body. Recent studies have confirmed that gut microbiota dysbiosis, impaired intestinal barrier function, and abnormal immune and inflammatory responses are core pathological mechanisms underlying the development of various gut-related diseases. In this context, plant bioactive compounds from diverse sources and with high biological safety have become a research hotspot in the field of intestinal health regulation due to their unique advantages in multi-target and holistic regulation. This review systematically summarizes the regulatory effects and potential molecular mechanisms of five major categories of plant bioactive compounds—polysaccharides, polyphenols, terpenoids, alkaloids, and plant oils (fatty acids)—on mammalian intestinal health. Our analysis reveals both commonalities and distinct regulatory biases in their mechanisms of action. At the common level, these compounds generally act in synergy to maintain intestinal homeostasis by remodeling the gut microbiota composition, enhancing intestinal barrier integrity, and regulating intestinal inflammation and immune responses. At the specific level, polysaccharides mainly exert prebiotic-like effects through substrate fermentation and short-chain fatty acid production; polyphenols display a dual role characterized by both prebiotic-like activity and signaling pathway regulation; terpenoids mainly rely on their lipophilic structural properties to exert membrane-associated effects and anti-inflammatory activities; alkaloids exhibit strong target-oriented immunomodulatory characteristics; and plant oils (fatty acids) are mainly involved in intestinal homeostasis through G protein-coupled receptor (GPR)-mediated lipid signaling pathways. Collectively, this review provides an important theoretical basis for further elucidating the physiological functions of plant bioactive compounds, and scientific support for the research and development of functional foods and the application of the “medicine and food homology” strategy in maintaining intestinal health, thereby holding significant academic value and practical application prospects.

plant bioactive compounds, intestinal health, intestinal barrier, gut microbiota, immune regulation

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