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Review 综述

肠道菌群-天然产物互作在免疫调节中的作用

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摘 要：肠道菌群与宿主免疫系统保持密切联系，微生物群落可通过多种途径影响免疫应答。大量研究证实，某些物质能够同步调节肠道菌群组成与宿主免疫反应，在免疫增强、抗炎及肠道稳态维持等方面发挥多种生物学功能。本文系统归纳了近3年国内外相关文献，首先详细阐述了肠道菌群通过多通路与宿主免疫相互作用的情况，进而重点归纳了通过肠道菌群途径发挥免疫调节功能(涵盖免疫增强与抗炎双重效应)的天然产物的最新研究。针对免疫失调性疾病，本文进一步阐明了天然产物通过优化肠道菌群结构、调控菌群-免疫信号通路[如核因子κB (nuclear factor kappa-B, NF-κB)、Toll样受体(Toll-like receptors, TLR)、丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)等]互作、维持肠道屏障功能稳态及干预菌群代谢产物(如短链脂肪酸、色氨酸吲哚衍生物)等途径，实现对宿主免疫功能的精准调控。同时，本文探讨了肠道菌群通过代谢与生物转化作用将天然产物转化为高活性次级代谢产物，进而强化其免疫调节效应的具体过程。基于肠道菌群的天然产物免疫调节效应可能成为免疫相关疾病的潜在治疗策略。

关键词：肠道菌群；天然产物；肠黏膜屏障；生物转化；免疫增强；抗炎

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Roles of gut microbiota-natural product interactions in immunomodulation

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Abstract: The gut microbiota maintains a close dialogue with the host’s immune system, being capable of influencing immune responses through various pathways. It has been extensively documented that synchronous regulation of the gut microbiota and the host immune response exerts immunoenhancing, anti-inflammatory, and gut homeostasis-maintaining effects. By systematically reviewing the relevant literature published in the past three years, this article first elaborates on the interactions between the gut microbiota and the host’s immunity via multiple routes. It further summarizes recent studies on natural products that exert immunomodulatory functions (encompassing both immunoenhancing and anti-inflammatory actions) through gut microbiota pathways. Regarding immune dysregulation diseases, this review further elucidates how natural products achieve precise regulation of the host immune function by optimizing the gut microbiota structure, regulating microbiota-immune signaling pathways (e.g., NF-κB, TLR, and MAPK), maintaining intestinal barrier homeostasis, and intervening in microbiota-derived metabolites (such as short-chain fatty acids and tryptophan-indole derivatives). Additionally, this article discusses the process by which the gut microbiota enhances the immunomodulatory effects of natural products through metabolic conversion and biotransformation of natural products into highly active secondary metabolites. The immunoregulatory effects of natural products through the gut microbiota may become a potential therapeutic strategy for immune-related disorders.

Keywords: gut microbiota; natural product; intestinal mucosal barrier; biotransformation; immune enhancement; anti-inflammatory effect

肠道菌群与宿主炎症过程存在密切关联，特定肠道菌群及其代谢产物可介导促炎或抗炎反应[1]。在多种免疫失调状态下，如炎症性肠病(inflammatory bowel disease, IBD)、非酒精性脂肪性肝炎(non-alcoholic fatty hepatitis, NASH)以及系统性红斑狼疮(systemic lupus erythematosus, SLE)等自身免疫性疾病，患者常表现出菌群失调与代谢的紊乱特征[2]。在这些情况下，通过抑制有害微生物的增殖来恢复肠道菌群平衡，在治疗干预中起着至关重要的辅助作用[3]。肠道菌群代谢产物(如短链脂肪酸、色氨酸衍生吲哚类物质以及次级胆汁酸等)对维持肠道屏障完整性及调节多种免疫应答的重要作用日益受到重视[4]。

近年大量研究证实，众多天然产物具有调节肠道菌群的能力，进而发挥免疫调节作用[5]。天然产物的免疫调节作用主要体现在抑制多种疾病状态下过度的炎症反应，提升免疫抑制状

态下的机体免疫力，从而维持宿主免疫功能的相对稳定；通过补充益生菌及具有益生元效应的天然产物可缓解由免疫失衡引发的相关病理表现[6]。例如，补充酵母 β-葡聚糖及青春双歧杆菌(*Bifidobacterium adolescentis*)可改善抗生素相关性腹泻小鼠的肠道菌群紊乱与代谢功能障碍[7]。

本文系统阐释了肠道菌群影响宿主免疫应答的具体通路，并重点归纳了近 3 年来发表的通过菌群-免疫互作机制展现免疫增强与抗炎效应的各类天然产物，旨在揭示天然产物通过不同肠道菌群介导途径发挥免疫调节作用的精确机制，包括优化肠道菌群结构、调控菌群-免疫信号通路交互对话、靶向维持肠道屏障功能稳态，以及影响菌群产生的具有免疫调节功能的代谢物水平，特别深入探讨了肠道菌群通过生物转化激活天然产物免疫调节潜力的特异性通路，以期为天然产物治疗免疫抑制性及炎症性疾病提供基于肠道菌群介导机制的新视角。

1 天然产物通过优化肠道菌群、维持体内平衡调节免疫功能

天然产物对肠道菌群的调节作用是其发挥生理活性的重要机制，具体可通过维持菌群平衡、促进益生菌增殖及抑制致病菌生长等多个维度实现。

在维持菌群结构稳定方面，天然产物能有效调节肠道中芽孢杆菌门(*Bacillota*)与拟杆菌门(*Bacteroidota*)的比值(F/B)，从而修复菌群失调状态。例如，山楂多糖可逆转高脂饮食诱导的非酒精性脂肪性肝病(non-alcoholic fatty liver disease, NAFLD)小鼠 F/B 比值升高，显著缓解肠道微生态失衡[8]；而本课题组的研究也显示，Hu 等[9]从发酵食品(“江水”和泡菜)或粪便中分离的乳酸菌(lactic acid bacteria, LAB)，不仅具有良好的抗氧化活性，还能通过调节胃肠道微生态平衡发挥免疫调节作用。

天然产物还能通过促进益生菌定殖来改善肠道微环境。桑黄多糖(*Sanghuangporus vaninii* polysaccharides)可增加免疫抑制模型小鼠体内植物乳植杆菌(*Lactiplantibacillus plantarum*)和鼠李糖乳酪杆菌(*Lacticaseibacillus rhamnosus*)的定殖丰度，有效缓解免疫抑制状态[10]；本课题组 Zhu 等[11]发现，陕北的槐桑黄 YASH1 能增加免疫低下小鼠体内的拟杆菌，Wang 等[12]则证实 zunyimycin C 可提高阿尔茨海默病(Alzheimer’s disease, AD)小鼠梭菌属(*Clostridium*)、乳杆菌属(*Lactobacillus*)的丰度，这些都体现了天然产物对益生菌的正向调节作用。

此外，天然产物对致病菌的抑制作用也不容忽视。研究证实，裙带菜岩藻聚糖可显著降低炎症小鼠假单胞菌门(*Pseudomonadota*)丰度[13]；海藻酸钠能抑制免疫抑制小鼠经环磷酰胺(cyclophosphamide, CTX)处理后 *Pseudomonadota* 及幽门螺杆菌(*Helicobacter pylori*)的增殖[14]。多酚[15]、黄精多糖[16]、薯蓣皂苷[17]、山药多糖[18]以及槐桑黄 YASH1 黄酮[11]等天然产物也均能显著增强菌群多样性及丰富度，并呈现相似的免疫调节机制(表 1)。

综上所述，这些天然产物对菌群结构的多维度调节与其免疫调节活性密切关联，这也进一步表明肠道菌群的结构组成与稳态平衡在机体免疫应答及相关疾病发展中起着关键作用。

2 天然产物通过调控肠道菌群-免疫信号通路互作调节免疫功能

多项研究证实，天然产物(如多糖、多酚和生物碱)的免疫调节作用不仅体现于对肠上皮细胞(enterocyte, IECs)和免疫细胞中核因子 κB (nuclear factor kappa-B, NF-κB)、Toll 样受体(Toll-like receptors, TLR)、磷酸肌醇 3-激酶/蛋白激酶 B (phosphoinositide 3-Kinase/protein kinase B, PI3K/AKT)、核因子 E2 相关因子 2 (nuclear factor-erythroid 2-related factor 2, NRF2)、丝裂原

表1 通过优化肠道菌群发挥免疫调节作用的天然产物

Table 1 Natural products that exert immunomodulatory effects by optimizing the gut microbiota

Types of immune regulation	Natural products	Immunoregulatory effects	Changes in intestinal flora	References
Enhancement of immunity	Polysaccharides from wild morels	White blood cells and lymphocyte proliferation ↑; $CD4^+CD8^-$, $CD4^-CD8^+$, and $CD4^-CD8^-CD19^+$ ↑	Richness and diversity ↑, *Bacteroidota* ↑, *Ruminococcaceae* ↑, *Villonspiraceae* and *Erysipelococcaceae* ↑; *Lachnospiraceae*_NK4A136 ↑, *Lactobacillus* ↓	[19]
	Cyclocarya paliurus polysaccharides	IL-1β and TNF-α ↑; Intestinal mucosal sIgA ↑; ZO-1, Occludin, and Claudin-1 ↑	Richness and diversity ↑, *Bacillota* ↑, *Bacteroidota* ↓, Norank_f_*Muribaculaceae* and *Alloprevotella* ↑, *Lactobacillus* and *Staphylococcus* ↓; The dominant flora changed	[20]
	Laminaria japonica fucoidan	Splenic lymphocyte function ↑; IL-6, IL-1β, TNF-α, and IgG levels ↑	Richness and diversity ↑; Genera: *Erysipelothrix*, *Streptococcus*, *Faecalibacterium*, *Turicibacter*, *Romboutsia*, and *Helicobacteraceae* ↓; *Alistipes*, *Gastranaerophilales*, *Cyanobacteriota*, and *Streptococcus* ↑	[21]
	Phellinus igniarius YASH1 flavones	Serum levels of IL-2, IL-6, and IFN-γ ↑	Species richness ↑; Low dose group: *Bacteroidota* and *Actinobacteria* ↑, *Bacillota* ↓; High dose group: *Bacteroidota* ↓, *Campilobacterota* ↓, *Bacillota* and *Actinobacteria* ↑	[11]
	Glycopeptides from *Lycium barbarum*	Colonic neutrophil infiltration ↓; IL-1β and IL-6 ↓, IL-10 ↑	Microbial richness and diversity ↑; The disturbance of bacterial flora was restored; *Bacillota* ↑, *Pseudomonadota* and *Verrucomicrobia* ↓, *Lactobacillus* ↑, *Bacteroides*, *Shigella*, and *Paracbacteroides* ↓; *Lactobacillus murinus*, *Bacteroides acidifaciens*, and *Lactobacillus* spp. ↑, *Clostridium pilaris* ↓	[22]
	Total ginsenosides of *Panax ginseng*	IL-1α, IL-2, IL-4, IL-6, IL-10, IL-13, TNF-α, monocyte chemoattractant protein-1 ↑, IL-1β and IFNγ ↓; Spleen lymphocyte proliferation ↑, $CD4^+$ T lymphocyte ↑, $CD4^+/CD8^+$ ↑	Species richness ↑; *Lactobacillus* ↑, *Odoribacter* and *Clostridia* UCG-014 ↓, *Vibrio desulphuricularis* and *Spirillonaceae* UCG-006 ↑	[23]
	Sanguinarine	TNF-α, IFN-γ, IL-1β, IL-6, and IL-18 ↓; IL-4 and IL-10 ↑; NLRP 3 and caspase-1 ↓	Gut microbiota diversity ↑; *Muribaculaceae*, *Mucispirillum*, *Ruminiclostridium*_5 ↑; The imbalance of intestinal flora was reversed	[24]
	Salidroside	IL-1β, IL-6, IFN-γ, and IL-17A ↓; Th17/Treg ↓; NLRP3, caspase-1, and GSDMD p30 ↓	*Lachnospiraceae* and *Ruminococcaceae* ↑; uncultured_bacterium_f_*Muribaculaceae* and *Lachnospiraceae_NK4A136_group* ↓; uncultured_bacterium_g_*Lachnospiraceae_NK4A136_group* ↓; uncultured_bacterium_f_*Lachnospiraceae* ↑	[25]

(待续)

(续表 1)

Types of immune regulation	Natural products	Immunoregulatory effects	Changes in intestinal flora	References
Anti-inflammatory	Celastrol	IFN-γ, TNF-α ↓; transforming growth factor-β, IL-10 ↑; Treg ↑; Occludin, Cdh1, ZO-1, and Muc2 ↑	Diversity and richness ↑; *Alloprevotella* and *Odoribacte*r ↑; unidentified_*Lachnospiracea* ↓; *Prevotellaceae*, *Alloprevotella*, *Paraprevotella*, and *Butyricicoccus* ↑; *Alloprevotella* and *Butyricicoccus* ↑	[26]
	Isomaltulose	TNF-α, IL-1β, and IL-6 ↓; IL-17 ↓, IL-10 ↑; Treg/Th17 ↓; ZO-1, Occludin, and Claudin-1 ↑	Family level: *Akkermansiaceae*, *Marinifilaceae*, *Anaerovoracaceae* ↑, *Lachnospiraceae* and *Streptococcaceae* ↓; Genus level: *Akkermansia* and *Alistipes* ↑	[27]

↑: Increase or activate; ↓: Decrease or suppress.

活化蛋白激酶(mitogen-activated protein kinase, MAPK)、非受体型酪氨酸蛋白激酶(Janus kinase, JAK)/信号转导及转录激活因子(signal transducer and activator of transcription, STAT)等信号通路的调控[28-31]，更在于其能靶向调控这些通路与肠道菌群的动态互作，通过协同增强免疫活性与抗炎效应维持机体稳态(图 1)。例如，本课题组 Cheng 等[32]发现加味七福饮可通过增加拟杆菌、降低变形杆菌，关联调控 NF-κB 信号通路以抑制神经炎症；马悦然[33]证实中药复方 YA3D6 能通过抑制 NOD 样受体热蛋白结构域蛋白 3 (NOD-like receptor pyrin domain containing 3, NLRP3)的 NF-κB 通路干预 AD。嗜酸乳杆菌(*Lactobacillus acidophilus*) LA85 对 CTX 诱导免疫抑制小鼠的缓解作用[34]、健康个体粪便微生物群移植(fecal microbiota transplantation, FMT)及短链脂肪酸(short-chain fatty acids, SCFAs)对炎症的改善[35]，均提示天然产物或其介导的菌群代谢物可通过 NF-κB 通路实现免疫调节。类似地，咖啡樱桃果壳多酚通过增加肠球菌丰度、抑制 TLR4 过度表达缓解溃疡性结肠炎(ulcerative colitis, UC)[36]；番茄红素恢复肠道菌群失调后可激活 TLR/MyD88/TIRF 及 p-NF-κBp65 通路修复肠黏膜屏障[37]；嗜酸乳杆菌与中药 HKL 联合应用则通过调节菌群、抑制 TLR4/9 遏制 UC 发展[38]，凸显了天然产物对 TLR 通路与菌群互作的调控价值。此外，动物双歧杆菌(*Bifidobacterium animalis*)及其代谢产物乳酸可抑制 TLR4/MyD88 通路过度激活[39]；源自肠道菌群的 α-亚麻酸(α-linolenic acid, ALA)通过抑制 MyD88-NF-κB 缓解 UC[40]，体现了天然来源物质对这一菌群-炎症桥梁通路的干预作用。与此同时，MAPK、Wnt 等通路与菌群的互作也受天然产物靶向调控。本课题组发现 zunyimycin C 可能通过激活 Ras-Raf-MEK-ERK 通路(MAPK 家族)参与免疫反应[12]；小檗碱(berberine, BBR)以肠道菌群依赖的方式激活 Wnt/β-catenin 通路修复肠上皮[41]；而天然产物若能促进产丁酸盐菌群增殖，可通过激活 Wnt/ERK 通路增加杯状细胞和 MUC2 水平[29]，进一步印证其通过通路-菌群互作发挥保健功能的潜力。

综上所述，天然产物通过协同调控多条信号通路与肠道菌群的动态平衡，在维持肠道屏障、优化免疫应答及干预免疫紊乱相关疾病中展现出独特价值，这也构成其发挥保健功能的核心机制。

3 天然产物通过肠道菌群维持肠道屏障完整性和功能平衡

天然产物可通过双向调控肠道菌群与肠道

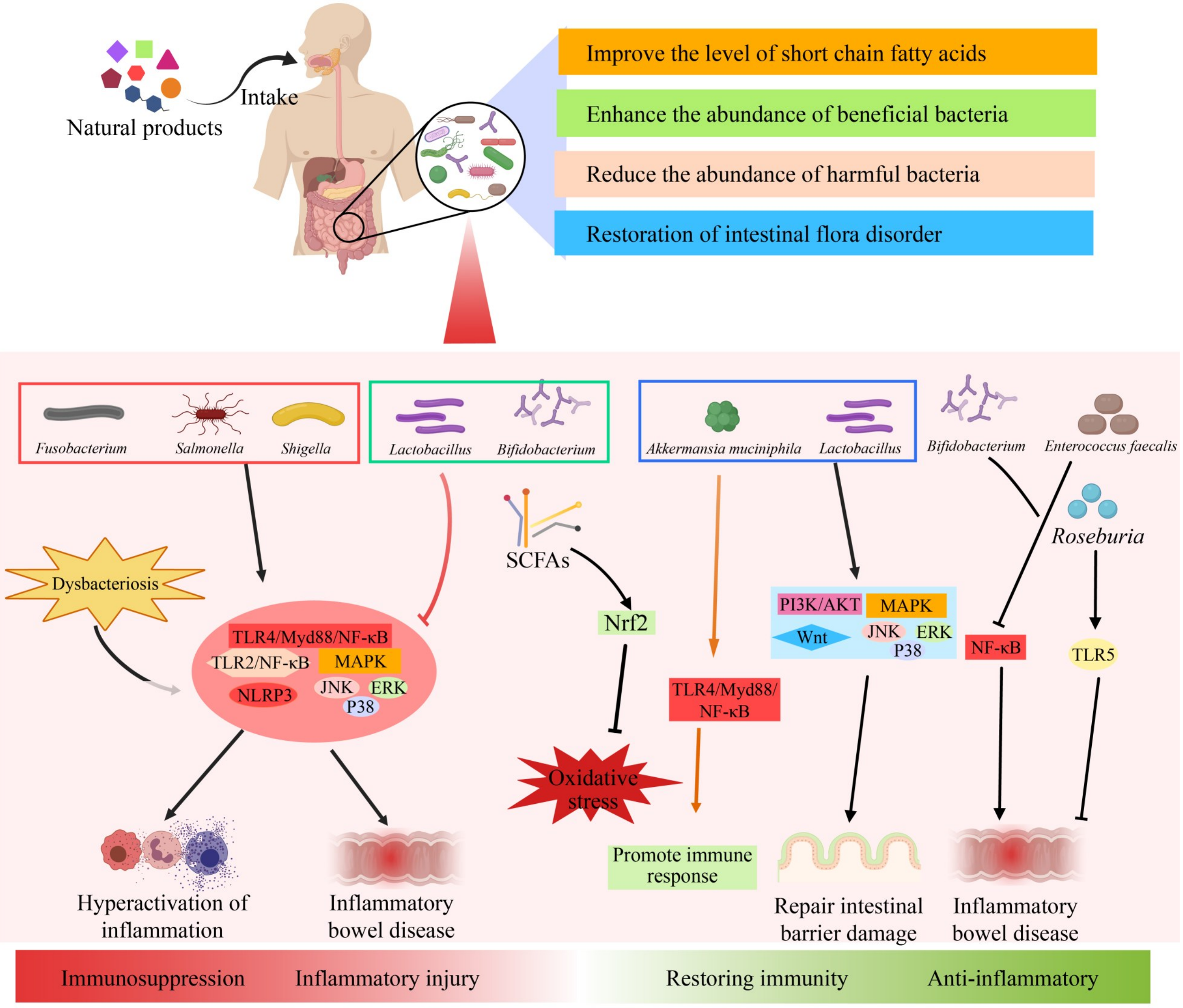

图1　天然产物调节肠道菌群的主要途径和增强免疫、抑制炎症的免疫信号通路

Figure 1　The primary pathways for natural products to regulate intestinal flora and immune signaling pathways to enhance immunity and inhibit inflammation (www.medpeer.cn).

屏障的互作关系，在免疫抑制或炎症状态下保障屏障完整性，进而巩固免疫稳态。其既能够通过调节菌群组成及其代谢产物间接修复肠道屏障，也可通过增强屏障功能反向优化菌群平衡。

当肠道处于炎症或疾病(如IBD、癌症)状态时菌群失调会导致紧密连接(tight junctions, TJs)蛋白损伤、杯状细胞减少及黏液层变薄[1]。天然产物可通过“优化菌群结构→促进有益代谢产物生成”的协同方式逆转这一损伤：例如蜡蚧菌属多糖能抑制假单胞菌属、志贺氏菌-埃希氏菌属等有害菌群，同时上调肠细胞中紧密粘连(zonula occludens, ZO)-1、Claudin-1和E-钙黏蛋白的表达[42]；马齿苋多酚可降低肠腔中埃希氏菌-志贺氏菌丰度，减轻黏膜炎症浸润，并提高Claudin-2、ZO-1及Claudin-3水平[43]，二者均通过“抑致病菌+强物理屏障”的机制修复肠道损伤。在菌群代谢产物的介导下，天然产物的屏

障保护作用进一步强化。本课题组筛选的益生菌 L9 (源自四川传统发酵食品)能降低结肠髓过氧化物酶(myeloperoxidase, MPO)活性、增强 Occludin 表达[44]，与肠道菌群产生的脂质代谢产物 PE (0:0/14:0)促进 ZO-1、Occludin 表达以减轻败血症屏障损伤的机制[45]一致。迪氏副拟杆菌(*Parabacteroides distasonis*)代谢色氨酸生成的吲哚乙酸(indole-3-acetic acid, IAA)、色氨酸衍生物吲哚-3-甲醛(indole-3-aldehyde, 3-IAld)可通过激活 AHR-IL-22 轴维持 TJs 蛋白正常表达[46-47]。三叶青多糖、川明参多糖则能诱导肠黏膜浆细胞释放 sIgA，通过强化免疫屏障减少致病菌对屏障的破坏[48-49]。小檗碱的作用更体现“双向调控”特性，其不仅能直接增强肠道 TJs 蛋白 Occludin 和 ZO-1 的表达以降低黏膜通透性[41]，还可通过调节菌群结构间接促进屏障修复，形成“屏障功能增强→菌群失衡改善→免疫稳态维持”的正向循环[50] (图 2)。

天然产物对肠道屏障的保护作用并非直接作用于屏障本身，而是以肠道菌群为核心中介，通过“调节菌群组成、激活菌群有益代谢、强化菌群-屏障互作”多重途径实现屏障完整性与菌群平衡的协同维持，为机体免疫防御提供关键“物理防线”。

4 天然产物通过肠道菌群代谢物发挥免疫调节作用

肠道菌群代谢物是连接天然产物-肠道菌群-宿主免疫的关键“分子信使”。天然产物虽不直接作用于免疫细胞或炎症通路，却可通过调控肠道菌群的代谢活动促进有益代谢物生成、抑制有害代谢物积累，进而通过代谢物与宿主细胞特异性受体的结合实现免疫增强、抗炎及肠道稳态维持[8]。目前已明确的核心功能代谢物主要包括短链脂肪酸(SCFAs)、色氨酸吲哚衍生物及胆汁酸(bile acids, BAs) 3 类，其具体调控机制如下。

4.1 SCFAs

SCFAs (主要包括乙酸、丙酸、丁酸等)是肠道菌群发酵膳食纤维产生的核心代谢物，其对免疫系统的调节具有“双向性”，既在免疫抑制状态下增强免疫活性，又在炎症状态下抑制过度炎症反应，其中丁酸的抗炎效应尤为突出。研究证实，补充丁酸可修复炎症状态下潘氏细胞功能异常、缓解回肠炎，为克罗恩病(crohn disease, CD)患者的肠道黏膜修复提供关键支持[51]；冠突散囊菌多糖等天然产物则通过提高肠道内丁酸、戊酸水平，同时上调 SCFAs 特异性受体 GPR41、GPR43 的表达强化肠道屏障功能，有效减轻 CTX 诱导的小鼠免疫抑制[52]。

本课题组发现 zunyimycin C 可显著降低 CTX 处理小鼠肠道内异丁酸、丙戊酸(与炎症相关的 SCFAs 亚型)水平，通过调节 SCFAs 组分平衡减轻免疫抑制[12]；而益生菌发酵发谷芽等的发酵产物则可特异性改变睡眠剥夺小鼠肠道内 7 种 SCFAs 含量，同时伴随失眠相关脂肪酸水平降低，暗示 SCFAs 代谢平衡可能通过“肠-脑轴”间接参与免疫稳态调控[53]。此外，白藜芦醇等多酚类天然产物能通过增加产 SCFAs 菌群(如罗斯氏菌属、粪杆菌属)丰度提高肠道丁酸浓度，进而改善 NASH 的炎症与脂质代谢紊乱[54]；皂苷、生物碱等其他类型天然产物也可通过类似的 SCFAs 代谢调控路径为 IBD 等免疫紊乱疾病提供潜在治疗方向。

4.2 色氨酸吲哚衍生物

色氨酸作为人体必需氨基酸，摄入后可被肠道菌群(如芽孢杆菌门的大肠杆菌、粪肠球菌，拟杆菌门的多种菌株)代谢为吲哚、5-羟色胺(5-hydroxytryptamine, 5-HT)、吲哚-3-乳酸(indole-3-lactic acid, ILA)、吲哚-3-丙烯酸(indole-3-acrylic acid, IAC)、吲哚-3-丙酸(indole-3-acetic acid, IPA)等具有免疫活性的吲哚衍生物[55]，这类代谢物主要通过激活芳香烃受体(aromatic hydrocarbon receptor, AHR)信号通路发挥作用，

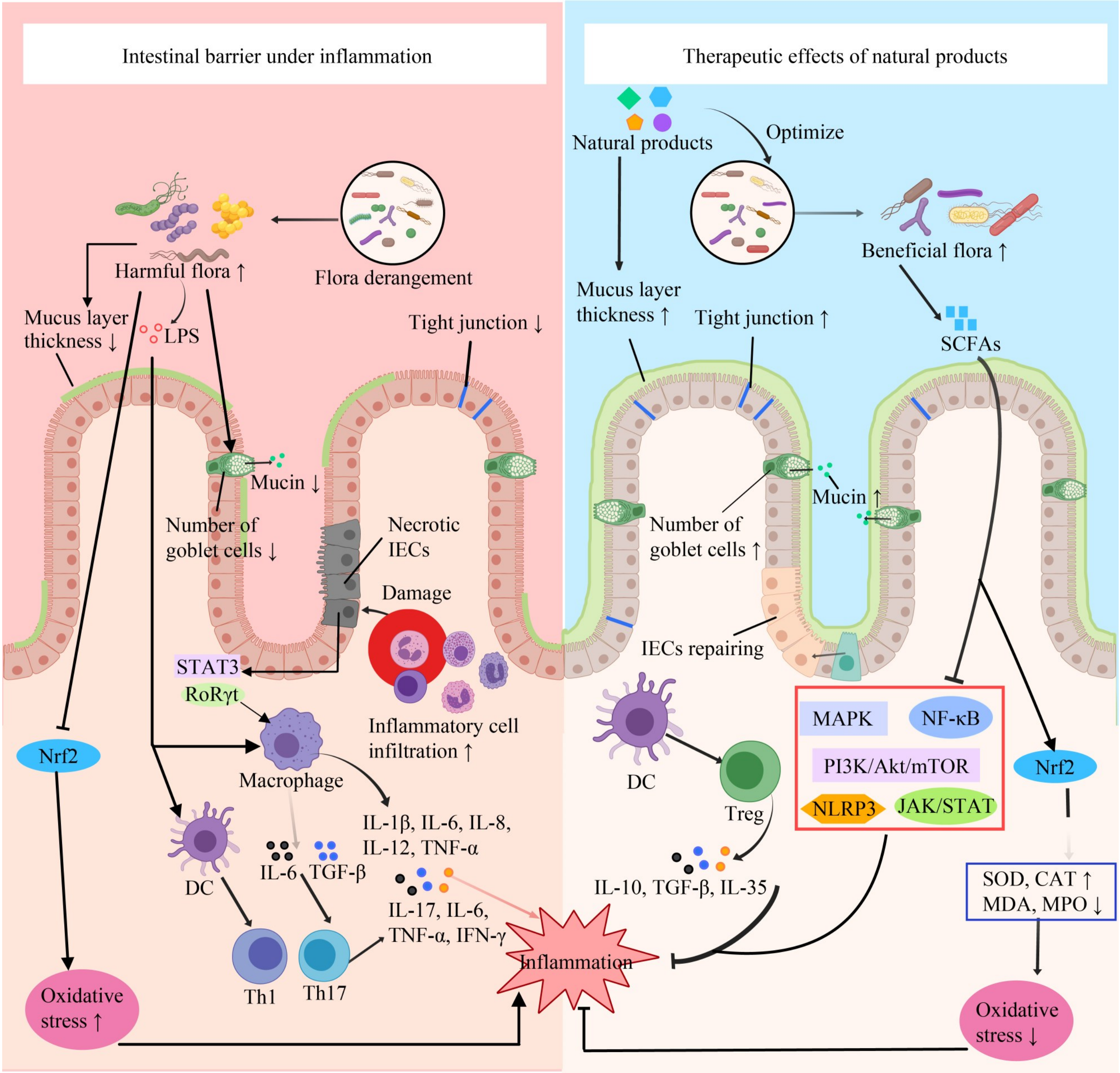

图2　损伤状态下与天然产物治疗状态下的肠道屏障

Figure 2　Intestinal barrier in a state of injury versus a state of treatment with natural products (www.medpeer.cn).

核心功能聚焦于“肠道屏障保护”与“免疫细胞分化调节”。

在肠道屏障修复中 IPA 可与肠上皮细胞(enterocyte, IECs)表面的 AHR 结合，调控 AHR 下游基因表达，促进紧密连接蛋白(ZO-1、Claudin-1)的合成与组装，减少肠道黏膜通透性[56]；5-羟吲哚乙酸同样通过激活 AHR 通路改善脂多糖(lipopolysaccharide, LPS)诱导的猪小肠上皮细胞(intestinal porcine epithelial cell, IPEC)-J2 紧密连接丢失，抑制炎症因子[白细胞介素(interleukin, IL)-1β、α 肿瘤坏死因子(tumor necrosis factor-α, TNF-α)]表达，有效缓解仔猪肠道屏障损伤与腹泻[57]。在免疫细胞调节方面，色氨酸吲哚衍生物可通过 AHR 通路调控 T 细胞

分化，既抑制 Th17 细胞增殖与 IL-17 分泌，又促进调节性 T 细胞(regulatory T cells, Treg)分化及 IL-10 释放，同时减少巨噬细胞炎症因子释放，实现“抗炎-免疫平衡”双重效应[58]。

天然产物可通过靶向调控色氨酸代谢通路强化这一机制。人参皂苷 Rg1 能显著提高溃疡性结肠炎(ulcerative colitis, UC)小鼠肠道内 ILA、吲哚-3-甲醛(indole-3-formaldehyde, 3-IAld)、IPA 的水平，通过这些代谢物逆转肠道菌群失衡、修复肠黏膜屏障[59]；白术多糖则通过增加肠道内 IPA、吲哚、色胺等代谢物含量，激活色氨酸-AHR-IL-22 信号轴，促进 IL-22 分泌，维持肠道屏障功能稳态[60]。

4.3 胆汁酸

BAs 分为肝脏合成的初级胆汁酸(如胆酸、鹅脱氧胆酸)与肠道菌群转化生成的次级胆汁酸[如脱氧胆酸 (deoxycholic acid, DCA)、石胆酸 (lithocholic acid, LCA)]，其免疫调节作用主要依赖于次级胆汁酸与法尼醇 X 受体(farnesoid X Receptor, FXR)和 G 蛋白偶联胆汁酸受体 1 (G protein-coupled bile acid receptor 1, TGR5)结合，核心机制为“抑制促炎通路”与“保护肠道屏障”[61]。黑木耳多糖可通过提高肠道内 DCA 水平增强肠道屏障完整性，同时减轻 NAFLD 相关的肝损伤、炎症及纤维化，其作用与 DCA 激活 FXR 受体、抑制肝脏炎症反应密切相关[62]；富含花青素的蓝莓提取物则通过上调肠道 FXR、TGR5 的表达阻断 TLR4/MyD88 炎症信号通路，减少炎症因子释放[63]。

类似机制在其他天然产物中同样存在。二氢杨梅素通过调节肠道菌群介导的胆汁酸转化过程增加次级胆汁酸比例，进而激活 TGR5 通路发挥抗炎效应[64]；岩藻聚糖则通过调控胆汁酸代谢平衡，抑制肠道内 LPS 诱导的炎症反应，为 IBD 等炎症性疾病的干预提供新路径[65]。这些研究表明，胆汁酸代谢调控是天然产物发挥免疫调节作用的重要补充机制。

综上所述，肠道菌群产生的 SCFAs、色氨酸衍生的吲哚类物质以及 BAs 会与其特异性受体结合，从而维持机体的免疫稳态。这对于肠道免疫系统的正常运作而言尤为关键，它们在其中扮演着重要的“免疫调节信使”角色。值得注意的是，多种天然产物能够精准调控肠道菌群代谢产物与免疫反应之间的相互作用。这种调控作用随后会抑制炎症通路和细胞因子的过度激活与表达，维持肠道屏障的正常功能及完整性，最终实现免疫稳态(图 3)。

5 天然产物与肠道菌群的代谢互作：发酵修饰与生物转化介导的免疫调节

益生菌发酵天然产物在调节肠道菌群方面展现出显著活性，能够改善多种疾病状态下的肠道菌群紊乱状况。例如，经 *Lactiplantibacillus plantarum* NCU116 发酵的苦瓜多糖可恢复肥胖大鼠紊乱的肠道菌群，促进 *Bacillota*、放线菌纲(*Actinomycetes*)以及 *Bifidobacterium* 等有益菌群的丰度增加[66]。本课题组前期采用红茶菌、醋酸菌、酵母菌和植物乳植杆菌与酸枣、谷芽、葡萄籽联合发酵可增加有益细菌(乳酸菌属和梭菌属)的丰度，减少与失眠相关的标志细菌(拟杆菌属)的数量，进而改善睡眠剥夺引起的菌群失调情况[54]；由长双歧杆菌、嗜酸乳杆菌和发酵黏液乳杆菌(*Limosilactobacillus fermentum*)组成的混合菌剂能显著改变灵芝和莱菔子的化学成分，在免疫抑制状态下提高别样杆菌属(*Alistipes*)、理研菌科 RC9 肠道群等有益肠道菌群的丰度，同时抑制脱硫弧菌科(*Desulfovibrionaceae*)等致病性肠道细菌的生长[67]。

肠道菌群凭借丰富的转化酶系统(如 α-L-鼠李糖苷酶、β-葡萄糖醛酸苷酶、β-葡萄糖苷酶等[68-69])成为天然产物的“生物转化库”。通过水解、异构化、氧化还原、去甲基化等反应，菌群可将多糖、多酚、生物碱、萜类等天然产物从“低活性/无活性”状态转化为高活性形式，既

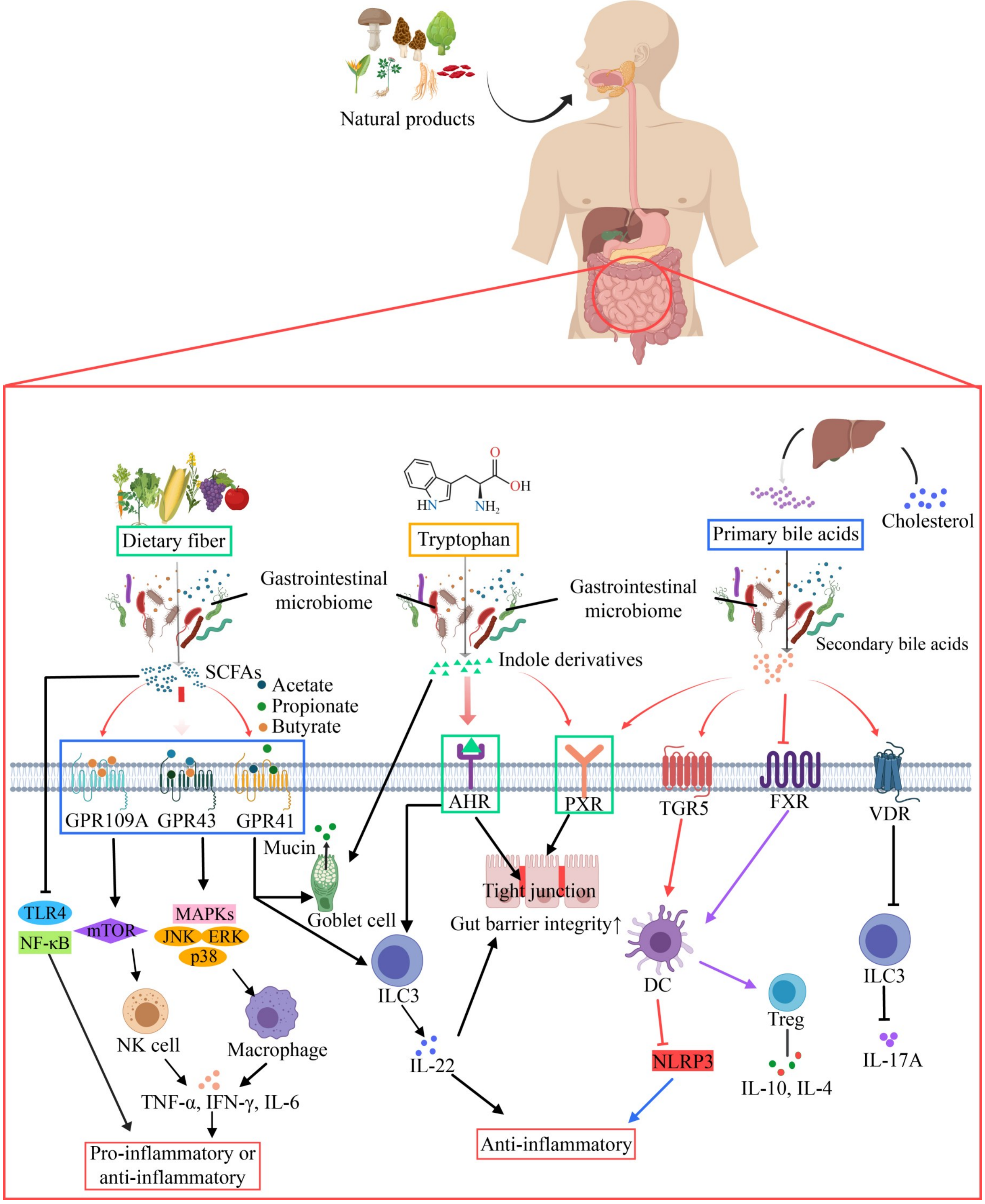

图3 天然产物通过调控肠道菌群代谢产物发挥免疫调节作用的具体机制。PXR：孕烷X受体；VDR：维生素 D 受体；DC：树突状细胞。

Figure 3 The specific mechanisms by which natural products regulate the metabolites of gut microbiota to exert immunomodulatory effects. PXR: Pregnane X receptor; VDR: Vitamin D receptor; DC: Dendritic cells (www.medpeer.cn).

提升了其体内生物利用度，又增强了免疫调节等生物学功能，为天然产物活性的高效发挥提供了代谢支撑(图 4)。

具体而言，不同类型天然产物的生物转化均体现了肠道菌群的关键作用：尿石素类物质经菌群转化后可通过靶向 AHR、抑制 TLR3/TRIF-NF-κB-STAT3 通路发挥减轻自身免疫性脑脊髓炎、抑制炎症及抗氧化的活性[70]；黄酮类物质因口服生物利用度低，需依赖肠道菌群进行代谢激活——(−)‒表没食子儿茶素没食子酸酯可被转化为没食子酸、表没食子儿茶素等衍生物[71]，杨梅素经胺化反应生成具有抗炎活性的 4-NH$_2$-杨梅素[72]，二者均通过菌群转化提升了生物活性；酚酸类的绿原酸先被代谢为咖啡酸、阿魏酸等初级产物，咖啡酸可抑制肠道炎症[73]，阿魏酸通过抑制 NF-κB、p38 MAPK 通路发挥抗氧化抗炎作用[74]，且二者可进一步代谢为二氢咖啡酸、二氢阿魏酸等，前者能减轻软骨细胞炎症[75]，后者通过激活 Nrf2、抑制 MAPK 及 Akt 通路增强抗炎活性[76]，而没食子酸作为花青素经菌群衍生的产物在改善 IBD 中也显示出显著活性[77]；生物碱类的 BBR 自身口服生物利用度低，但其菌群代谢产物小檗红碱(berberrubine, BRB)、二氢小檗碱(hydroxypinusaponarin, dhBBR)等具有更高的血药浓度[78-79]。类似地，人参皂苷 Rb1 经菌群转化为人参皂苷 CK 后抗炎活性大幅提升，可改善类风湿性关节炎、结肠炎等多种炎症[80-81]。

综上所述，益生菌发酵天然产物能够改变这些产物中某些活性成分的组成，同时肠道菌群拥有强大的代谢系统，能够对多种天然产物发挥高效的生物转化作用。然而，基于肠道菌群生物转化能力的靶向实验，以及对免疫调节活性的体内验证，仍是研究中较少涉及的领域，这为未来学者提供了进一步探索的方向。

6 结论与展望

天然产物主要包括多糖类、多酚类及生物

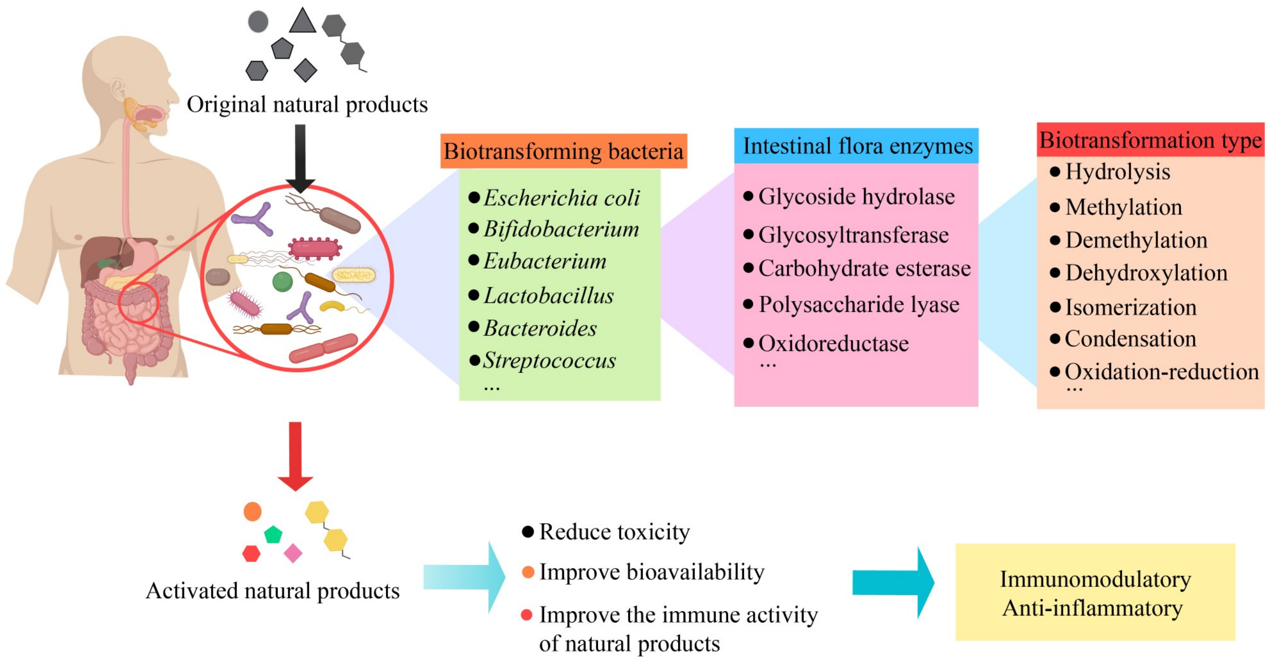

图4 天然产物通过肠道菌群进行生物转化，发挥免疫调节作用

Figure 4 Natural products are biotransformed by the gut microbiota to exert immunomodulatory effects (www.medpeer.cn).

碱类等物质。近年来，大量研究证实其具有显著的免疫增强与抗炎活性。这些功能主要通过肠道菌群介导的四大机制实现，肠道菌群组成与机体免疫稳态密切相关。天然产物能够增加肠道内有益菌群的丰度，抑制有害菌的过度生长，进而维持肠道菌群结构的稳定性以促进免疫健康。考虑到肠道菌群与多种免疫信号通路之间存在密切的相互作用，天然产物的免疫调节效应或许还可通过影响肠道菌群与免疫信号通路之间的“串扰”来实现。肠道屏障作为肠道免疫系统最重要的组成部分，在多个方面受到肠道菌群的调控。天然产物也能通过调节肠道菌群维持肠道屏障的完整性和功能稳定性，从而促进黏膜免疫。值得注意的是，肠道菌群产生的 SCFAs、吲哚衍生物和次级胆汁酸具有显著的免疫调节活性。天然产物还可依托这些代谢产物来完成其免疫调节功能。此外，肠道菌群中存在大量生物转化酶，使其成为一个天然的“生物转化库”。通过肠道菌群的酶催化作用，天然产物能从无活性或弱活性状态转化为具有活性或高活性的形式，且副作用小、生物利用度高，进而基于肠道菌群的代谢作用实现免疫调节功能(图 5)。

上述发现揭示了天然产物通过调节肠道菌

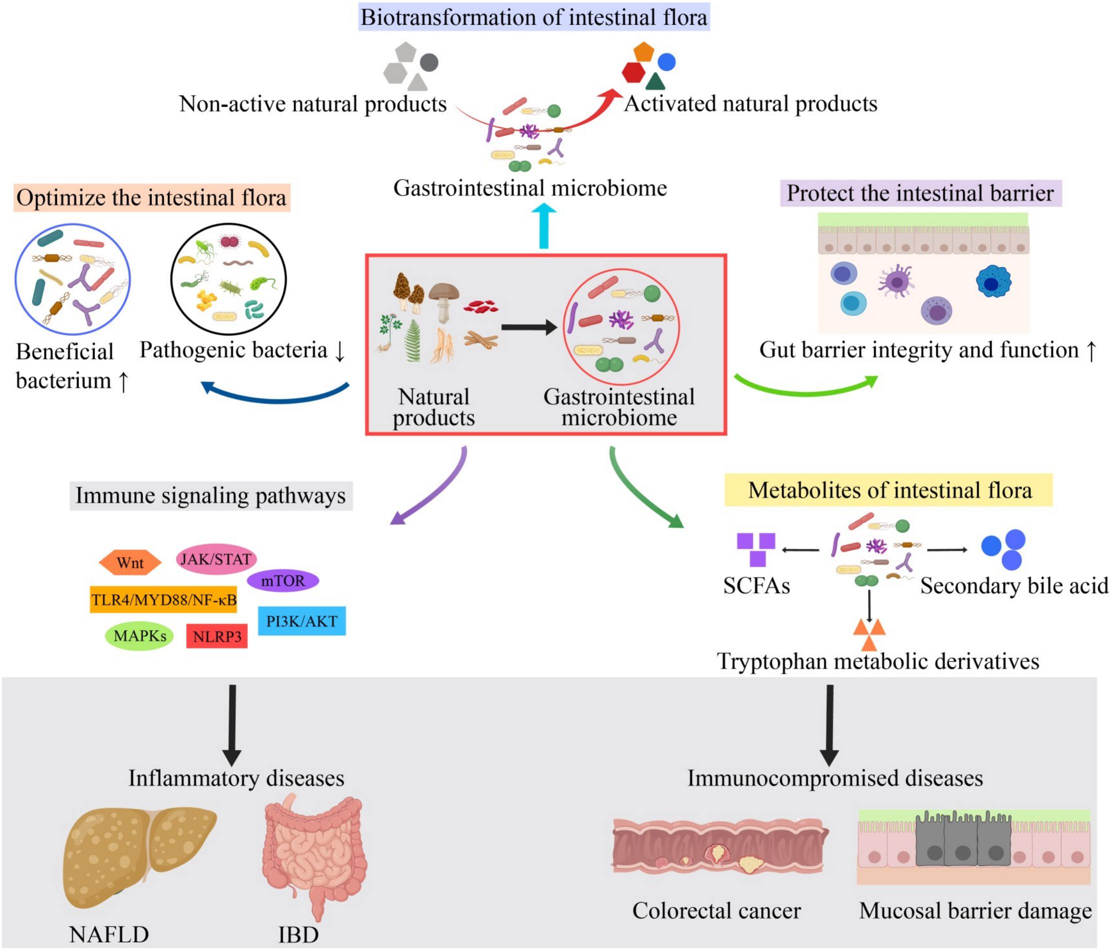

图5 天然产物通过调节肠道菌群参与肠道及相关疾病调控的机制

Figure 5 The mechanism by which natural products regulate intestinal flora and participate in the control of intestinal and related diseases (www.medpeer.cn).

群影响免疫系统的具体作用机制。然而，肠道菌群具有显著的个体特异性(如年龄、饮食、地域、疾病状态等均会影响菌群组成)，导致同一天然产物在不同个体中可能呈现疗效差异甚至完全相反的效果，这为天然产物的标准化临床应用带来了巨大障碍，可以结合宏基因组测序、代谢组学等技术建立“肠道菌群分型-天然产物响应性”关联模型，实现“个体化菌群图谱指导下的天然产物处方”。未来研究需进一步突破菌群个体化壁垒，明确天然产物的核心活性成分与作用靶点，并通过精准分型、联合策略及靶向递送等途径推动临床转化，最终实现天然产物在免疫相关疾病中的精准、高效应用。

作者贡献声明

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