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Review 综述

天然活性成分靶向肠道菌群调控脂质代谢分子机制研究进展

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摘　要：脂质代谢紊乱已成为全球性健康挑战，而肠道菌群(gut microbiota, GM)失调及其诱发的代谢性内毒素血症是促进该病理过程的关键诱因。本文综述了天然活性成分(natural active components, NACs)通过靶向调节肠道微生态进而改善脂质稳态的分子机制。在微生态干预层面，NACs 优化菌群结构，提升双歧杆菌属(*Bifidobacterium*)与嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*, AKK)等功能菌丰度，并抑制脱硫弧菌(*Desulfovibrio*)等条件致病菌增殖。在“代谢物-宿主”互作层面，其降脂机制主要包括 2 个方面：一方面，代谢产物的靶向效应，即短链脂肪酸、次级胆汁酸及酚酸衍生物特异性调节 3-羟基-3-甲基戊二酰辅酶 A 还原酶、脂肪酸合成酶等代谢靶点；另一方面，宿主信号响应，即上述代谢介质协同调节腺苷酸活化蛋白激酶(adenosine 5′-monophosphate-activated protein kinase, AMPK)/固醇调节元件结合蛋白-1c (sterol regulatory element-binding protein-1c, SREBP-1c)与过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptors, PPARs)关键信号节点以抑制脂质从头合成并促进脂肪酸 β-氧化，同时抑制 Toll 样受体 4 (Toll-like receptor 4, TLR4)/核因子-κB (nuclear factor-kappa B, NF-κB)通路以减轻炎症相关的脂质异常沉积。本文梳理的“成分-菌群-代谢产物-宿主信号”调节机制，为阐明 NACs 的药效物质基础及开发基于微生态的个性化营养干预策略提供了理论参考。

关键词：天然活性成分；肠道菌群；脂质代谢；代谢产物；信号网络

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Research progress in molecular mechanisms of lipid metabolism regulation by natural active components through targeting the gut microbiota

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Abstract: Lipid metabolism disorders have emerged as a global health challenge, and gut microbiota dysbiosis, along with the consequent metabolic endotoxemia, are key factors promoting this pathological process. This review summarizes the molecular mechanisms by which natural active components (NACs) improve lipid homeostasis through targeted modulation of gut microecology. At the microecological intervention level, NACs optimize the microbiota structure by increasing the abundance of functional bacteria such as *Bifidobacterium* and *Akkermansia muciniphila*, while inhibiting the proliferation of opportunistic pathogens like *Desulfovibrio*. At the "metabolite-host" interaction level, the lipid-lowering mechanisms mainly involve two aspects. The first is the targeted effects of metabolites, wherein short-chain fatty acids, secondary bile acids, and phenolic acid derivatives specifically modulate metabolic targets including 3-hydroxy-3-methylglutaryl-coenzyme A reductase and fatty acid synthase. The second is the host signaling responses, wherein the aforementioned metabolic mediators synergistically modulate key signaling nodes, such as adenosine 5′-monophosphate-activated protein kinase (AMPK)/sterol regulatory element-binding protein-1c (SREBP-1c) and peroxisome proliferator-activated receptors (PPARs), to inhibit *de novo* lipogenesis and promote fatty acid β-oxidation, while simultaneously inhibiting the Toll-like receptor 4 (TLR4)/nuclear factor-kappa B (NF-κB) pathway to alleviate inflammation-associated abnormal lipid deposition. The "component-microbiota-metabolite-host signaling" regulatory mechanism outlined herein provides a theoretical reference for elucidating the pharmacodynamic material basis of NACs and developing gut microecology-based personalized nutritional intervention strategies.

Keywords: natural active components; gut microbiota; lipid metabolism; metabolites; signaling networks

当前，以肥胖和非酒精性脂肪肝(non-alcoholic fatty liver disease, NAFLD)为代表的脂质代谢紊乱疾病已演变为全球性公共卫生危机，全球肥胖患者已突破 6.5 亿，超重人群占比逾 39%[1]。肠道菌群(gut microbiota, GM)作为宿主代谢调控的"第二基因组"，其稳态失衡与脂质吸收异常、能量代谢紊乱及慢性低度炎症密切相关[2]。研究表明，GM 不仅参与营养物质的消化吸收，更通

过代谢膳食成分产生短链脂肪酸(short-chain fatty acids, SCFAs)、胆汁酸(bile acids, BAs)及酚酸衍生物等关键代谢效应分子，靶向调控宿主腺苷酸活化蛋白激酶(adenosine 5′-monophosphate-activated protein kinase, AMPK)、过氧化物酶体增殖物激活受体(peroxisome proliferator-activated receptors, PPARs)及Toll样受体4 (Toll-like receptor 4, TLR4)/核因子-κB (nuclear factor-kappa B, NF-κB)等核心信号枢纽，从而深刻影响脂质的合成、分解与转运过程[3-6]。因此，靶向重塑肠道微生态已成为干预代谢性疾病的重要研究方向。

天然活性成分(natural active components, NACs)是源于自然界长期进化演替、具有明确药理活性及分子调控潜力的次生代谢产物与生物大分子，研究显示，这些活性成分具有抗氧化、抗炎、免疫调节、代谢调控、肠道菌群重塑、神经保护及抗癌等生理功效[7-9]。其来源多样性显著，涵盖植物源(黄酮、多酚、萜类及植物多糖)、动物源(牛磺酸、活性肽及不饱和脂肪酸)及微生物源(真菌多糖、次级代谢肽)等多个类别[10-13]。相较于化学合成药物存在的单靶点局限及耐药性风险等问题，NACs不仅具备优良的生物相容性和低毒副作用，且在实际膳食与药用干预场景中NACs通常以提取物(多为粗提物)等复杂组分形式协同发挥作用；这种“多成分-多靶点-多通路”的整合调节优势为脂质代谢紊乱及肠道微生态失衡提供了有效的综合干预策略[14-15]。随着多组学技术的发展，NACs的研究正从传统的经验性应用逐步深入至精准的分子调控层面，在此背景下，解析其通过“微生态-宿主”互作网络改善脂质代谢的具体分子机制已成为当前该领域的研究热点[16]。

基于此，本文从菌群结构重塑与菌群-宿主代谢互作2个维度，总结NACs的降脂机制。在菌群结构层面，重点分析NACs如何通过提升双歧杆菌属(*Bifidobacterium*)与嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*, AKK)等功能菌丰度、降低芽孢杆菌门(*Bacillota*)/拟杆菌门(*Bacteroidota*)比值来优化微生态构成；在代谢互作层面，深入解析“菌群-代谢产物-信号通路”的信号级联机制，即SCFAs、BAs及酚酸衍生物等代谢产物如何作为效应分子靶向调节3-羟基-3-甲基戊二酰辅酶A还原酶(3-hydroxy-3-methylglutaryl-CoA reductase, HMGCR)、尼曼-匹克C1样蛋白1 (Niemann-Pick C1-like 1, NPC1L1)等关键酶活；同时，AMPK/固醇调节元件结合蛋白-1c (sterol regulatory element-binding protein-1c, SREBP-1c)、PPARs以及TLR4/NF-κB等关键信号通路的协同作用，抑制脂质从头合成、促进脂肪酸氧化并阻断代谢性炎症。本文旨在厘清NACs调控GM与宿主脂质代谢的互作网络，为开发基于特定微生态靶点的功能食品及深化脂代谢研究提供理论依据与科学基础。

1 NACs对肠道菌群结构的调控作用

人体GM主要由芽孢杆菌门(*Bacillota*)、拟杆菌门(*Bacteroidota*)、放线菌门(*Actinomycetota*)、假单胞菌门(*Pseudomonadota*)及疣微菌门(*Verrucomicrobiota*)等优势菌门组成，其中芽孢杆菌门与拟杆菌门丰度之比是反映脂质代谢平衡的重要指标[17]。有益菌[如双歧杆菌属、乳酸菌属(*Lactobacillus*)、阿克曼氏菌属(*Akkermansia*)及粪杆菌属(*Faecalibacterium*)]可通过发酵膳食纤维生成SCFAs (如丁酸、丙酸、乙酸)，从而改善肠道屏障功能、抑制肝脏脂质合成并调控宿主代谢通路[18]；反之，肠杆菌属(*Enterobacter*)、脱硫弧菌属(*Desulfovibrio*)等条件致病菌则通过释放脂多糖(lipopolysaccharide, LPS)激活炎症信号通路，进而加剧代谢紊乱[19]。

NACs能够选择性调节GM，其分子基础在于其丰富且结构特异的化学组成。例如，多糖类成分常以β-(1→3)-D-葡聚糖为主链，并带有β-(1→6)糖苷键侧链分支，以榆黄菇(*Pleurotus*

citrinopileatus)来源的β-葡聚糖为例，其具有高分子量和高分支度的结构特征，使该多糖具备较强的抗消化性，能够完整抵达结肠，并被布劳特氏菌属(*Blautia*)、罗斯拜瑞氏菌属(*Roseburia*)等产丁酸菌选择性利用，这些菌群通过分泌β-葡聚糖酶将其降解为低聚糖，进而促进肠道有益菌的增殖[20]。膳食纤维则由可溶性与不可溶性组分共同作用，可溶性部分如香菇多糖易被菌群发酵，不可溶性组分则通过增加食糜体积改善肠道蠕动，共同改善菌群生长微环境[21]。以麦角甾醇为代表的甾醇类成分，其四环三萜骨架中的C-24甲基与Δ5,7双键结构可被梭菌属(*Clostridium*)等细菌中的甾醇脱氢酶特异性识别，进而转化为维生素D类活性物质，并通过竞争性抑制脱硫弧菌属等有害菌的细胞膜合成发挥调控菌群结构的作用[22]。多酚类成分对GM的调控作用主要取决于其酚羟基的数量及苷元结构特征，例如含有3个相邻酚羟基的没食子酸可通过氢键相互作用抑制产气荚膜梭菌(*Clostridium perfringens*)黏附蛋白的活性；而黄酮苷类成分在C-7位形成的葡萄糖苷键可被双歧杆菌属来源的糖苷酶特异性水解，释放出活性苷元，进而促进双歧杆菌属自身的定殖与增殖[23]。此外，蛋白质类成分凭借其β-折叠/α-螺旋混合结构域可被毛螺菌科(*Lachnospiraceae*)等菌群的蛋白酶特异性识别并降解，生成的小肽与游离氨基酸可为长双歧杆菌(*Bifidobacterium longum*)等益生菌提供氮源，该过程同时能够诱导菌群表达丁酸激酶，促进产丁酸菌的增殖；蛋白质还可通过与卵形拟杆菌(*Bacteroides ovatus*)的糖苷水解酶相互作用，进一步改善AKK的定殖微环境[24-25]。

NACs通过直接与间接调控的协同作用实现对GM的定向重塑。其主要效应表现于提升以双歧杆菌属(*Bifidobacterium*)、AKK以及产短链脂肪酸菌(如*Blautia*、*Roseburia*等)为代表的有益菌丰度；减少脱硫弧菌属与产气荚膜梭菌等有害菌的数量；降低芽孢杆菌门与拟杆菌门比值，从而恢复由高脂饮食诱导紊乱的GM稳态。尽管不同来源的活性成分在调控机制上存在共性，但其作用途径也表现出显著的结构依赖性。

1.1 直接调控途径

NACs对GM结构的直接调控作用本质上是基于其化学结构特征，通过与特定微生物发生精准的分子互作而实现的。这一过程的核心在于“结构-靶点”的特异性识别与结合。例如，羊肚菌多糖(*Morchella esculenta* polysaccharide-1, MEP-1)凭借其主链中的β-(1→3)糖苷键可特异性识别并结合双歧杆菌属(*Bifidobacterium*)表面的糖结合蛋白(galectin-3-binding protein 4, GBP4)，进而激活菌体内半乳糖激酶(*galK*)、谷氨酸转运蛋白(*gluA*)等关键代谢通路基因的表达，从而促进其增殖[26]。类似地，灵芝酸A所具有的羊毛甾烷型四环三萜骨架能够与脱硫弧菌属(*Desulfovibrio*)细胞膜上的B族I型清道夫受体(scavenger receptor class B type 1, SR-B1)结合，通过抑制3-羟脂酰-酰基载体蛋白脱水酶(*fabZ*)、乙酰辅酶A羧化酶羧基转移酶β亚基(*accD*)等细胞膜合成相关基因的表达来抑制其生长[27]。黄酮类化合物(如槲皮素、姜黄素)的苯并吡喃酮C环及酚羟基既可借氢键结合有害菌表面的黏附蛋白以阻断定殖，又能被双歧杆菌属及拟杆菌属(*Bacteroides*)的糖苷酶降解，释放活性苷元进而促进有益菌增殖[28]。

部分NACs可作为肠道有益菌的专属碳源或代谢前体，直接促进其生长。金针菇多糖中的阿拉伯糖-木糖-葡萄糖复合结构可被毛螺菌科(*Lachnospiraceae*)菌群特异性分泌的木聚糖酶(XynA)与阿拉伯糖苷酶(AraB)降解，所释放的单糖作为能量底物，不仅能使其丰度显著提升，还能上调丁酸合成酶(But)基因的表达[29]。提取自榆黄菇(*Pleurotus citrinopileatus*)的活性多糖及糖肽成分在体外发酵及动物模型中不仅能作为有效碳源显著富集双歧杆菌属与消化乳酸杆菌等有益菌，还可有效抑制埃希氏-志贺氏菌(*Escherichia-Shigella*)等条件致病菌的增殖[30]。

中药蒲黄中的香蒲新苷可被 GM 表达的多种糖苷水解酶协同转化为活性更强的代谢产物，从而直接调控菌群的代谢方向[31]。

此外，部分活性成分还可直接抑制肠道有害菌增殖。具有麦角甾烷型结构的蛹虫草酸能破坏产气荚膜梭菌(*Clostridium perfringens*)的细胞膜完整性，通过下调其膜脂合成基因 *cfa* 的表达来降低其丰度[32]。黑木耳黄酮中的槲皮素-3-*O*-葡萄糖苷则可抑制促肠道奥利弗帕布菌(*Oliverpabstia intestinalis*)等细菌的 DNA 复制相关基因(*dnaA*、*dnaB*)的表达，从而有效减少其数量[33]。

综上所述，如表 1 所示，NACs 通过上述特异性结合与靶向识别、提供专属碳源与代谢底物、直接抑制有害菌增殖的作用机制，能够有选择性地调节关键功能菌群的丰度与活性，为通过膳食干预定向重塑肠道微生态提供了分子依据。

1.2 间接调控途径

NACs 除直接作用于特定菌群外，还可通过改善宿主肠道微环境或调节菌群间相互作用，间接影响菌群整体结构，是不同来源成分发挥作用的普遍机制。该途径主要通过改善菌群定殖的理化环境，或调控菌群间以代谢物交换为

表1 天然活性成分对肠道菌群结构的直接调控作用

Table 1 Direct regulatory effects of natural active components on the structure of intestinal microbiota

Regulatory mechanism	Active ingredient	Structural composition	Target/key gene	Target microbiota and effect	References
Specific binding and targeted recognition	*Morchella esculenta* polysaccharide (MEP-1)	β-(1→3) glycosidic bond backbone	*Bifidobacterium* GBP4 protein, *galK* and *gluA* genes	Promote *Bifidobacterium* proliferation	[26]
	Ganoderic acid A	Lanostane-type tetracyclic triterpene skeleton	*Desulfovibrio* SR-B1 receptor, *fabZ* and *accD* genes	Inhibit *Desulfovibrio* growth	[27]
	Flavonoids (e.g., quercetin)	C-ring benzopyrone structure, phenolic hydroxyl groups	Pathogen adhesion proteins, probiotic glycosidases	Block pathogen colonization, promote probiotic proliferation	[28]
Providing exclusive carbon source and metabolic substrate	*Flammulina velutipes* polysaccharide	Arabinose-xylose-glucose complex structure	Xylanase (XynA), arabinosidase (AraB), but-synthesis-related genes	Promote *Lachnospiraceae* proliferation and butyrate synthesis	[29]
	Pleurotus citrinopileatus polysaccharide and glycopeptide	Galactan linked by 1→4 glycosidic bonds and a polysaccharide-peptide backbone	Carbohydrate-active enzymes (CAZymes) and sugar metabolic pathways of gut beneficial bacteria	Promote the proliferation of *Bifidobacterium*, *Lactobacillus*, etc., and significantly increase SCFAs (especially acetate and butyrate) production	[30]
	Typhaneoside	Flavonoid glycoside (rhamnose/glucose substitution)	Multi-enzyme system including gut bacterial glycoside hydrolases	Regulate the direction of microbiota metabolism after transformation	[31]
Direct inhibition of harmful bacteria	Cordycepic acid	Ergostane-type structure	*cfa* gene (membrane lipid synthesis)	Disrupt the cell membrane of *Clostridium perfringens* and reduce its abundance	[32]
	Auricularia auricula-judae flavonoid	Quercetin-3-*O*-glucoside	*dnaA* and *dnaB* genes (DNA replication)	Inhibit the proliferation of pro-fat-storing bacteria	[33]

基础的协同与竞争网络，从而恢复菌群稳态。间接调节与前述直接作用相互补充，共同构成NACs重塑肠道微生态的综合干预基础。

1.2.1 肠道物理微环境的改善

NACs能够通过改善肠道物理微环境为有益菌的定殖提供生态位。其调节途径主要体现为增强黏膜屏障功能与优化食糜转运2个维度。在屏障巩固方面，茯苓多糖通过激活磷脂酰肌醇3-激酶/蛋白激酶B (phosphatidylinositol 3-kinase/protein kinase B, PI3K/Akt)信号通路与植物源燕麦β-葡聚糖、苹果膳食纤维共同上调紧密连接蛋白(ZO-1、Occludin)的表达，从而增强屏障完整性并维持肠道上皮的低氧环境，间接促进双歧杆菌属等厌氧菌增殖[34-35]；此外，榆黄菇来源的特异性半乳聚糖不仅能调节肠道微生态，还能通过抑制蛋白激酶A (protein kinase A, PKA)依赖性的水通道蛋白3 (aquaporin 3, AQP3)过度表达，并协同上调紧密连接蛋白(ZO-1、Occludin)，进而降低结肠黏膜通透性，阻断内毒素的易位渗透[36]。在物理转运方面，食用菌源不可溶性膳食纤维(木质素、纤维素)凭借其结构刚性增加食糜体积，有效刺激肠道蠕动并缩短内容物滞留时间，从而减少有害菌的附着与过度生长[21]。

1.2.2 肠道化学微环境的调控

NACs通过调节肠道化学微环境(氧化还原电位、胆汁酸谱及pH值)对菌群结构施加选择性压力。首先，在氧化还原与pH稳态调节方面，雪菊多酚中的咖啡酰奎宁酸具有显著的自由基清除能力，能有效降低肠道氧化还原电位，形成利于专性厌氧菌[如普氏栖粪杆菌(*Faecalibacterium prausnitzii*)]定殖的微环境，并上调其超氧化物歧化酶(superoxide dismutase, SOD)的表达[37]。白藜芦醇则通过协同降低肠道pH值与氧化还原电位，激活产丁酸菌[如肠道罗斯拜瑞氏菌(*Roseburia intestinalis*)]的丁酸激酶(butyrate kinase, BK)合成通路，其形成的酸性厌氧环境有效抑制了兼性厌氧的肠杆菌科(*Enterobacteriaceae*)增殖[38]。其次，在胆汁酸代谢库干预方面，香菇多糖与牛磺酸通过调节肠肝循环中结合态/游离态胆汁酸的比例改变了肠腔内的胆汁酸化学压力；这种环境变化筛选出高产胆汁酸水解酶(bile salt hydrolase, BSH)的拟杆菌属(*Bacteroides*)，使其成为优势菌群；菌群代谢产生的次级胆汁酸进一步作为信号分子可能反馈调节宿主G蛋白偶联胆汁酸受体1 (G-protein coupled bile acid receptor 1, TGR5)及胆固醇7α-羟化酶(cholesterol 7α-hydroxylase, CYP7A1)通路，形成“环境-菌群-宿主”的代谢互作通路[39-40]。

1.2.3 菌群间交叉互作的调节

除了改变肠道物理化学微环境调节GM，NACs更通过干预菌群间的生态互作网络引发级联效应以间接改变菌群结构。这种生物调节机制主要体现为代谢互养、竞争排斥及宿主反馈3个方面。首先，在代谢互养层面，桑叶多糖通过特异性促进产丙酸菌[如考拉杆菌属(*Phascolarctobacterium*)]增殖，显著提升肠道丙酸水平；丙酸不仅改善宿主代谢，更作为关键碳源为共生拟杆菌提供能量，这种营养共生关系协同降低了血清甘油三酯(triglyceride, TG)与脂肪堆积[41]。其次，NACs通过改变种间竞争优势引发菌群演替，红曲洛伐他汀作为细菌3-羟基-3-甲基戊二酰辅酶A (3-hydroxy-3-methylglutaryl coenzyme A, HMG-CoA)还原酶的直接抑制剂，能阻断有害菌(如*Clostridium perfringens*)的甲羟戊酸通路，削弱其竞争能力；这种生态位释放配合能量代谢信号(AMPK)的关联机制，进而为植物乳植杆菌(*Lactiplantibacillus plantarum*)提供了增殖优势[42]。此外，特定菌属在菌群演替过程中的驱动作用显著，黑树莓多酚通过富集AKK，利用该菌群特定的代谢能力调节胆汁酸谱，进而抑制产气荚膜梭菌生长并激活宿主法尼醇X受体/成纤维细胞生长因子15 (farnesoid X receptor/fibroblast growth factor 15,

FXR/FGF15)降脂通路[43]。最后，NACs 还能介导“菌群-宿主-菌群”的反馈回路，猴头菌多糖通过提升震颤杆菌属(*Oscillibacter*)丰度，诱导宿主分泌抗炎因子白细胞介素(interleukin, IL)-10，改善肠道免疫微环境，从而间接抑制 *Desulfovibrio* 等促炎菌的 LPS 合成与定殖[44]。

综上所述，NACs 通过直接作用与间接调节(表 2)的协同干预，实现了对 GM 结构与功能的定向改善。这种调控机制既依赖于成分与特定菌群间的分子识别与互作，也得益于肠道理化环境改善及生态网络优化所形成的适宜定殖微环境，二者的共同作用最终促进了肠道微生态稳态的重建。

2 NACs 的菌群代谢产物对脂质代谢通路的作用

改善后的微生态系统，其主要生理效应体现于代谢表型的特征性转变。NACs 通过“成分-菌群-代谢产物”的级联效应促进微生物代谢途径调整，导致 SCFAs、BAs 及酚酸衍生物等关键代谢产物的组成与丰度发生显著改变。作为连接 GM 与宿主代谢的关键化学信使，这些代谢产物既可靶向作用于特定器官，也可作为配体激活细胞内关键信号通路，从而参与下游脂质代谢的调节。

鉴于此，解析这些代谢产物如何调控宿主脂质代谢是揭示 NACs 整体作用机制的关键。然而，单一代谢分子在微生态-宿主网络中具有多效性，难以用线性路径概括，下文从 2 个维度展开：从上游代谢信号角度探讨 SCFAs、BAs 等关键代谢物如何特异性干预脂质代谢靶点；从下游宿主响应视角，解析这些代谢介质如何协同调节 AMPK/SREBP-1c、PPARs 及 TLR4/NF-κB 等胞内信号转导网络。通过整合代谢物靶向效应与宿主信号响应，本文总结了肠道菌群代谢产物维持脂质稳态的分子机制。

2.1 菌群代谢产物作为效应分子的脂质调控机制

由 GM 代谢 NACs 所衍生的次级代谢产物构成了调控宿主脂质稳态的关键化学信号。以 SCFAs、BAs 及酚酸衍生物为代表的各类代谢物能够特异性作用于脂质代谢途径，通过调节转运蛋白功能及关键酶系的转录表达促进宿主脂质的分解与代谢平衡。

表2 天然活性成分对肠道菌群结构的间接调控作用

Table 2 Indirect regulatory effects of natural active components on the structure of intestinal microbiota

Regulatory pathway	Active ingredient	Core mechanism and target	Key effector molecule/ gene	Effect on gut microbiota	References
Improvement of physical microenvironment	*Poria cocos* polysaccharide	Activates PI3K/Akt pathway, upregulates tight junction protein expression, enhances barrier function	ZO-1, Occludin	Promotes proliferation of *Bifidobacterium*; reduces translocation of harmful bacteria	[34]
	Oat β-glucan, apple dietary fiber	Upregulates tight junction protein expression, consolidates physical barrier	Occludin, ZO-1	Reduces translocation of harmful bacteria	[35]
	Edible fungal insoluble dietary fiber	Increases chyme volume by structural rigidity, stimulates intestinal peristalsis, shortens transit time	–	Reduces retention and attachment of harmful bacteria in the intestine	[21]

(待续)

(续表2)

Regulatory pathway	Active ingredient	Core mechanism and target	Key effector molecule/ gene	Effect on gut microbiota	References
	Pleurotus citrinopileatus polysaccharide	Inhibits PKA-dependent overexpression of aquaporin 3 (AQP3), regulates intestinal mucosal water permeability, significantly improves intestinal motility and propulsion rate	AQP3, PKA	Increases water content of intestinal contents and promotes emptying, physically reducing the retention and colonization of harmful bacteria (e.g., *Escherichia-Shigella*) in the intestine	[36]
Regulation of chemical microenvironment	Snow chrysanthemum polyphenols	Scavenges reactive oxygen species (ROS), reduces intestinal redox potential (Eh)	SOD	Promotes proliferation of the antioxidant beneficial bacterium *Faecalibacterium prausnitzii*	[37]
	Resveratrol	Regulates pH and SCFAs concentration, reduces redox potential, activates butyrate synthesis pathway	Butyrate kinase gene (Bk)	Promotes proliferation of butyrate-producing bacteria (e.g., *Roseburia intestinalis*); inhibits *Enterobacteriaceae*	[38]
	Lentinus edodes polysaccharide	Regulates bile acid (BAs) enterohepatic circulation, promotes secretion of BAs hydrolase by microbiota, alters proportion of secondary BAs	BSH	Increases abundance of *Bacteroides*	[39]
	Taurine (amino acid derivative)	Regulates the conjugated/free BAs ratio, enhances BSH activity, activates TGR5 receptor pathway	CYP7A	Increases abundance of *Bacteroides fragilis*	[40]
Regulation of microbial cross-feeding	Mulberry leaf polysaccharide	Specifically promotes proliferation of propionate-producing bacteria, increases intestinal propionate level, establishes a nutritional symbiotic network	−	Promotes growth of *Phascolarctobacterium* and symbiotic *Bacteroides*	[41]
	Monascus lovastatin (terpenoid)	Interferes with bacterial mevalonate pathway, inhibits HMG-CoA reductase activity, activates AMPK pathway	*hmgcr*, *ampkα*	Promotes proliferation of *Lactiplantibacillus plantarum*; inhibits *Clostridium perfringens*	[42]
	Black raspberry polyphenols	Enriches *Akkermansia muciniphila*, remodels BAs metabolic profile, activates host FXR/FGF15 pathway	−	Inhibits growth of *Clostridium perfringens*	[43]
	Hericium erinaceus polysaccharide	Promotes production of anti-inflammatory cytokine IL-10 by *Oscillibacter*, inhibits harmful bacteria *via* host immune feedback	*lpxC*	Indirectly inhibits growth of the pro-inflammatory bacterium *Desulfovibrio*	[44]

2.1.1 短链脂肪酸(SCFAs)通路

SCFAs是肠道微生物发酵膳食纤维等非消化性碳水化合物产生的主要代谢产物，主要包括丁酸、丙酸和乙酸。作为连接菌群与宿主的代谢枢纽，它们兼具能量底物与信号分子的双重职能，其中，丁酸在脂质代谢调节中作用尤为显著，主要通过下调脂肪组织中过氧化物酶体增殖物激活受体PPAR的表达以抑制脂肪生成，同时促进线粒体功能以改善高脂饮食诱导的代谢适应性；丙酸侧重于神经内分泌调节，通过刺激肠道L细胞分泌酪酪肽(peptide YY, PYY)与胰高血糖素样肽-1 (glucagon-like peptide-1, GLP-1)来调控食欲与能量平衡；而乙酸作为循环中丰度最高的SCFAs，主要经外周循环被心、脑及肌肉组织摄取利用[3]。SCFAs通过参与能量代谢、维持肠道屏障及远端信号传导共同参与了维持机体脂质稳态的生理过程。

在分子机制层面(图1)，丁酸主要由毛螺菌科(*Lachnospiraceae*)、普氏栖粪杆菌(*Faecalibacterium prausnitzii*)及丁酸梭菌(*Clostridium butyricum*)等共生菌群产生[45]，其降脂作用依赖于“肠-肝轴”的多靶点调节。首先，在肠道局部，丁酸激活上皮细胞表面的G蛋白偶联受体43 (G protein-coupled receptor 43, GPR43)及细胞外信号调节激酶1/2 (extracellular regulated protein kinases 1/2, ERK1/2)通路，促进紧密连接蛋白(ZO-1、Occludin)的表达与膜定位，通过增强物理屏障减少肠源性内毒素与脂质的异常易位[46-48]。其次，在肝脏代谢中枢，经门静脉入肝的丁酸展现出显著的分子多效性，它们既能作为G蛋白偶联受体(G-protein-coupled receptors, GPRs)的特异性配体，又能发挥组蛋白去乙酰化酶(histone deacetylase, HDAC)抑制剂的功能[49-53]，还能通过改变胞内AMP/ATP比率发挥能量调控效应[54]。这些由上游代谢物启动的初始信号，随后靶向激活宿主肝脏内的AMPK与PPARs等关键信号节点，通过酶活抑制与阻遏转录，有效阻断脂质从头合成并加速脂肪酸β-氧化[51,54]。

多种NACs证实可通过调节“菌群-SCFAs”轴发挥降脂功效。真菌源金针菇多糖与植物源芦笋茎多糖均被证实能特异性富集毛螺菌科等

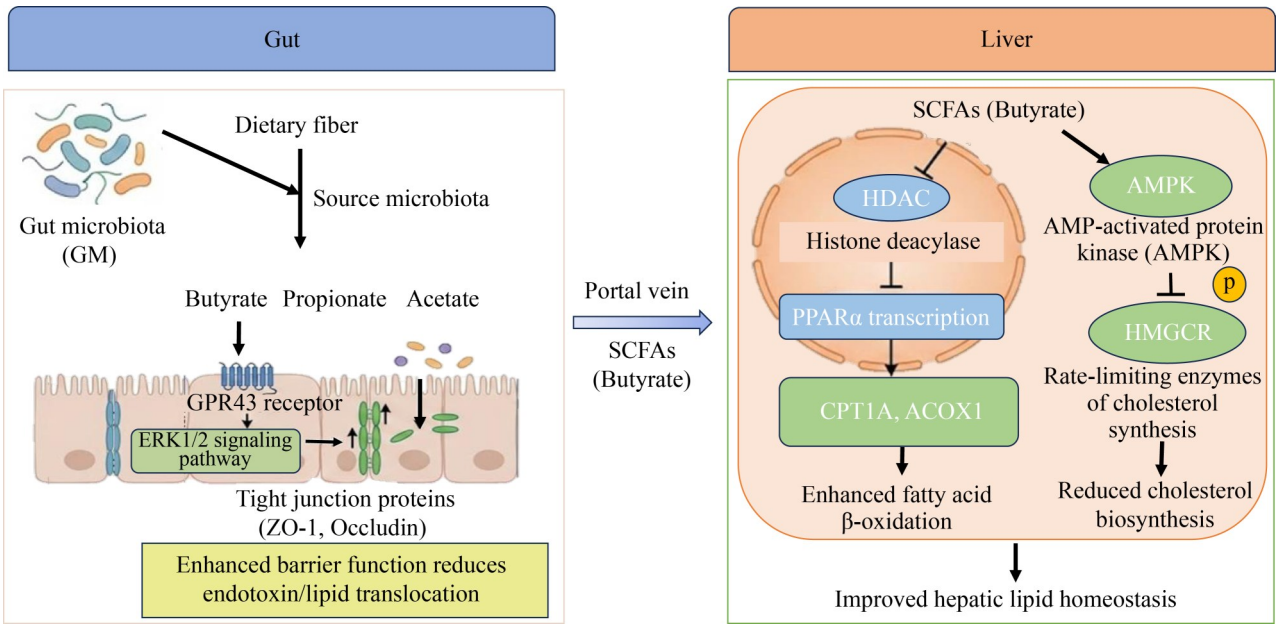


图1 SCFAs介导的脂质代谢调控机制

Figure 1 Regulatory mechanisms of lipid metabolism mediated by SCFAs.

产丁酸菌群，提升肠道丁酸水平，进而激活肝脏 AMPK 通路，显著降低血清甘油三酯及总胆固醇(total cholesterol, TC)[55-56]。与之类似，毛木耳(*Auricularia polytricha*)中分离的糖蛋白能够通过“菌群-代谢物”途径改善宿主脂质稳态，缓解重金属(如铅)暴露诱导的肝损伤及脂质代谢紊乱[57]。此外，牛磺酸也能调节菌群代谢，通过促进丁酸生成并维持肠道屏障功能，有效降低低密度脂蛋白胆固醇(low-density lipoprotein-cholesterol, LDL-C)水平[58]。

2.1.2 胆汁酸(BAs)代谢通路

BAs 作为胆固醇代谢的主要终产物，凭借其独特的两亲性结构在肠道内乳化脂质以辅助消化吸收，并作为内源性表面活性剂防止胆固醇结晶沉淀。GM 是 BAs 代谢谱的重要参与者，特别是梭菌属(*Clostridium*)和拟杆菌属(*Bacteroides*)，通过分泌胆汁酸水解酶(BSH)及 7α-脱羟基酶将结合型初级 BAs 转化为游离型及次级 BAs (如脱氧胆酸、石胆酸)。这一生物转化过程主要通过“代谢消耗”与“信号传导”双重途径协同调节宿主脂质稳态[59-60]。

具体调节机制如图 2 所示，在促进代谢消耗方面，菌群介导的游离 BAs 生成显著增加了其在粪便中的排泄比例，有效减少了 BAs 的肠肝循环；这种回流的减少解除了对肝脏的反馈抑制，诱导胆固醇 7α-羟化酶(CYP7A1)的代偿性上调，促使肝脏消耗更多胆固醇底物以从头合成 BAs，从而降低血清与肝脏胆固醇水平[61]。在信号传导层面，特定的 BAs 分子作为内源性配体激活肠道上皮细胞内的法尼醇 X 受体(FXR)，诱导成纤维细胞生长因子 15 (FGF15)的分泌，随后，FGF15 作为肠源性内分泌激素经门静脉转运至肝脏，特异性识别并结合肝细胞膜表面的成纤维细胞生长因子受体 4 (fibroblast growth factor receptor 4, FGFR4)及其辅助受体 β-Klotho，形成三元受体复合物，该复合物进而激活下游胞内信号转导，反馈抑制 CYP7A1 的表达，以维持胆汁酸的合成稳态；同时在肠道局部，FGF15 下调胆固醇吸收载体 NPC1L1 的表达，减少膳食胆固醇摄取[61-63]。此外，BAs 库的组成改变还能调节胰腺脂肪酶活性，影响脂肪分解与吸收的动态平衡[63]。

现有研究证实，多种 NACs 可通过调节上述机制发挥降脂效应。其中，羊肚菌多糖与动物源牛磺酸主要表现为“促排泄-代偿合成”模式，它们通过特异性富集梭菌属并提升 BSH 活性加速 BAs 排泄，解除反馈抑制并上调肝脏 CYP7A1 表达，最终导致血清总胆固醇降低[64-65]。此外，菊粉的作用更侧重于“信号激活”模式，其通过促进拟杆菌属增殖改变次级 BAs 谱，激活 FXR-FGF15 轴以抑制 NPC1L1 介导的脂质吸收[66]。姜黄素则兼具上述 2 种特征，通过抑制脱硫弧菌(*Desulfovibrio*)等有害菌改善肠肝循环，在促进粪便排泄的同时减少肝脏脂质沉积[67-68]。

2.1.3 酚酸衍生物通路

酚酸类衍生物是 NACs 调控脂质代谢的又一关键途径[69]。面对香草酸、阿魏酸等原型酚酸物质生物利用度较低的局限性，GM 的生物转化成为发挥其生物活性的关键前提。在此过程中，瘤胃球菌属(*Ruminococcus*)分泌的酯酶负责将酯型酚酸水解为游离形式，而拟杆菌属(*Bacteroides*)则通过脱羧、羟基转移等修饰反应进一步将其转化为焦性没食子酸、阿魏酸衍生物等高活性次级代谢产物[70-71]。这种特定的微生物代谢转化构成了酚酸发挥降脂效应的物质基础。经转化生成的活性衍生物进入循环后，通过参与“合成-分解-氧化”的代谢调节过程干预脂质代谢。

在抑制脂质合成方面，活性衍生物能有效抑制脂质生成的转录与酶活，它们不仅能抑制脂肪酸合成酶(fatty acid synthase, FASN)的催化活性，更能干扰固醇调节元件结合蛋白-1c (SREBP-1c)的成熟与核转位，从而在转录水平切断脂肪酸与胆固醇的从头合成[72-73]。例如，经菌群转化的小麦麸皮阿魏酸代谢物被证实能

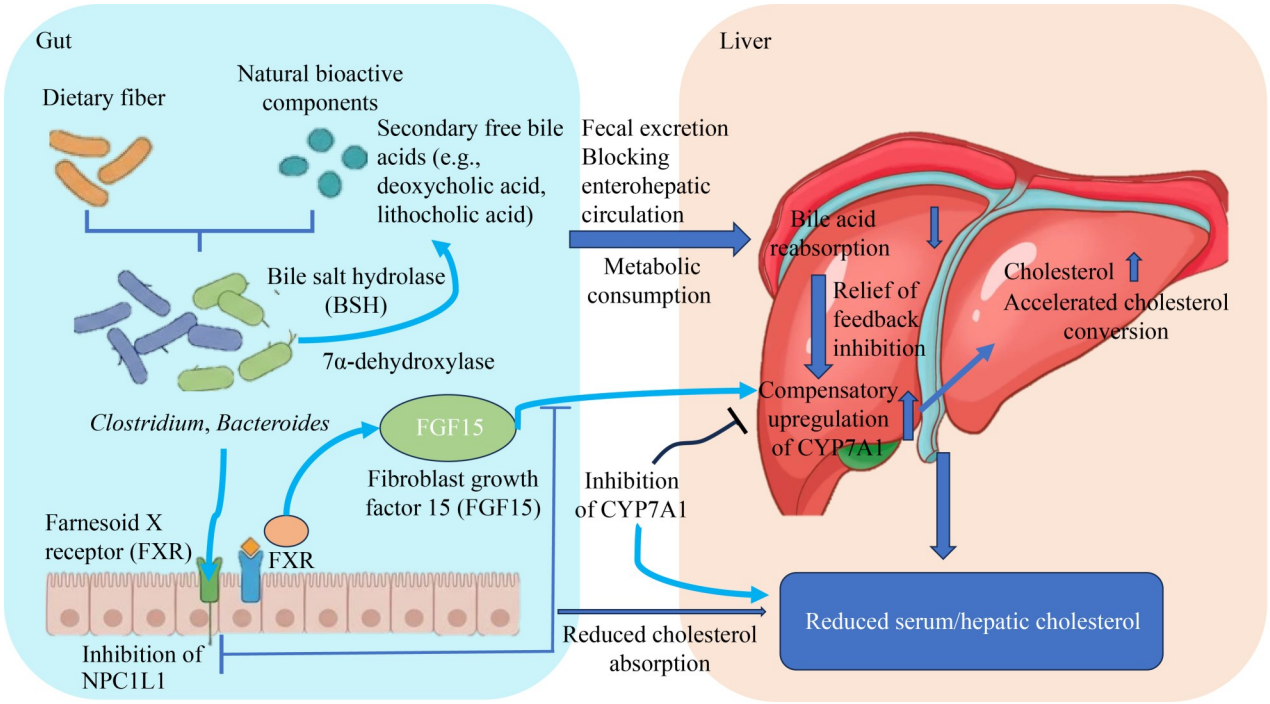


图2　胆汁酸代谢介导的“排泄-代偿”与“受体-信号”双重降脂机制

Figure 2　Dual lipid-lowering mechanisms of “excretion-compensation” and “receptor-signaling” mediated by bile acid metabolism.

显著下调高脂模型中的 FASN 活性及血清甘油三酯[74-75]；而源自香菇及盐角草的特定酚酸衍生物也通过阻断 SREBP-1c 通路有效减少了肝脏脂质蓄积[76-79]。

在加速脂肪动员方面，部分衍生物发挥了促进脂肪分解的作用。它们通过激活脂肪细胞内的蛋白激酶 A (PKA)信号轴，诱导激素敏感性脂肪酶(hormone-sensitive lipase, HSL)发生磷酸化激活，从而加速脂滴内甘油三酯的水解过程[80-81]。鼠尾草酸与绿原酸代谢物均被证实能通过该机制显著提升 HSL 活性，有效促进脂肪组织的动员与利用[82-83]。

此外，在促进氧化耗能与协同增效方面，部分成分展现出多靶点整合优势。例如，鞣花酸及其菌群代谢物(如尿石素)可特异性激活过氧化物酶体增殖物激活受体 α (PPARα)，上调肉碱棕榈酰转移酶 1B (carnitine palmitoyltransferase 1B, CPT-1B)等关键基因表达，促进线粒体脂肪酸 β-氧化，发挥降脂效应[84-85]。类似的，咖啡绿原酸代谢物具有抑制 HMG-CoA 还原酶(限速酶)与促进脂肪分解的双重作用[86-87]。

因此，GM 的生物转化是酚酸类成分发挥药效的关键前提，其衍生的多样化代谢产物通过抑制脂质合成、促进脂质分解与氧化等多条途径发挥降脂调节作用。

综上所述，NACs 对肠道微生态的干预促进了菌群代谢网络的特征性改变，从而显著富集了以 SCFAs、次级 BAs 及酚酸衍生物为代表的核心代谢产物(表 3)。这些代谢产物介导的脂质调节机制如图 3 所示，它们不仅是能量底物，更作为关键的内源性效应分子通过多种途径发挥作用，抑制肝脏脂质从头合成，促进脂肪氧化分解，同时维持肠道物理屏障并调节胆固醇通量。这种“多靶点、多路径”的系统性调节构成了 NACs 介导降脂作用的物质基础，最终促进宿主脂质代谢稳态的恢复。

表3 菌群代谢产物介导的脂质代谢调控机制

Table 3 Lipid metabolism regulation mechanisms mediated by gut microbiota metabolites

Metabolite class	Specific effector molecule	Core lipid-lowering mechanism	Key target/ gene	Representative natural source	References
Short-chain fatty acids (SCFAs)	Butyrate	Inhibits histone deacetylase (HDAC), relieves PPARα transcriptional repression; activates AMPK pathway, inhibits cholesterol synthesis	PPARα, CPT1A, HMGCR	*Auricularia polytricha* glycoprotein, *Flammulina velutipes* polysaccharide	[49-57]
	Propionate	Stimulates intestinal L cells to secrete satiety hormones, regulates energy balance	PYY, GLP-1	*Asparagus officinalis* stem polysaccharide	[44,56]
Bile acids (BAs)	Secondary BAs	Blocks enterohepatic circulation, relieves feedback inhibition, induces compensatory synthesis to consume cholesterol	CYP7A1 (↑)	*Morchella esculenta* polysaccharide, taurine, oat β-glucan	[64-65]
		Activates FXR receptor, inhibits the expression of intestinal lipid absorption carriers (signal blockade)	FXR, NPC1L1	Inulin, curcumin	[62,66-68]
Phenolic acid derivatives	Ferulic acid metabolites	Inhibits fatty acid synthase activity, blocks *de novo* lipid synthesis	FASN	Wheat bran	[74-75]
	Urolithins	Activates PPARα pathway, drives mitochondrial fatty acid β-oxidation	PPARα, CPT1B	Ellagic acid, black raspberry polyphenols	[84-85]
	Chlorogenic acid metabolites	Activates PKA signaling axis, induces hormone-sensitive lipase phosphorylation	HSL	Coffee, carnosic acid	[82-83,87]

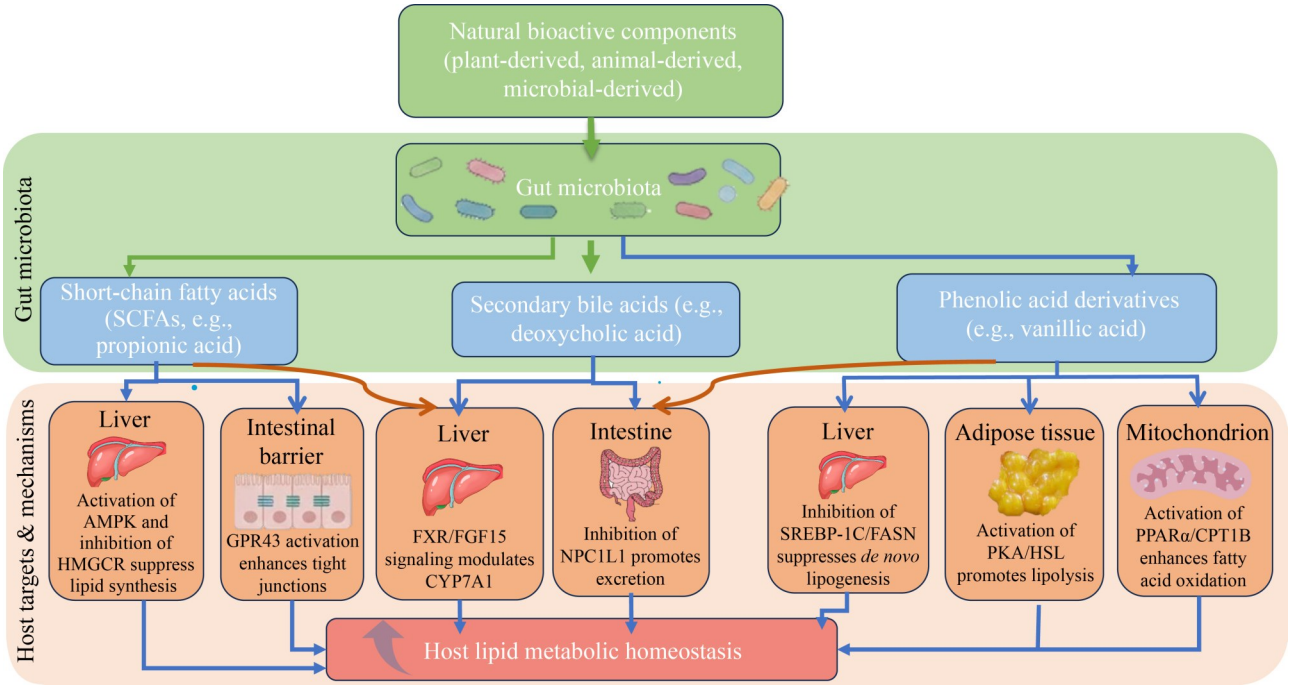


图3 NACs介导的菌群代谢产物对脂质代谢的调控机制

Figure 3 Regulatory mechanisms of gut microbiota metabolites on lipid metabolism mediated by NACs.

2.2 宿主核心信号网络的脂质调控机制

菌群代谢产物作为介导“菌群-宿主”脂质代谢互作的关键介质，不仅提供能量底物，更作为信号分子靶向激活宿主细胞内信号转导网络，对脂质稳态发挥重要调节作用。其中，AMPK/SREBP-1c、PPARα/γ 及 TLR4/NF-κB 通路构成了该调节网络的三大信号节点。这些通路的激活依赖于分子信号级联反应，主要涉及关键激酶的磷酸化修饰(如 AMPK 的 Thr172 位点磷酸化)、转录因子的核转位与剪切(如 SREBP-1c 的前体裂解入核、NF-κB p65 亚基的核定位)，以及核受体的配体结合激活(如 PPARα/γ 与脂肪酸衍生物的特异性结合)。通过上述机制，代谢产物在转录水平调节脂质合成、氧化分解及炎症应答相关靶基因的表达，进而从信号网络层面改善脂质代谢紊乱，恢复宿主代谢稳态。

2.2.1 AMPK/SREBP-1c 通路

AMPK/SREBP-1c 信号通路是天然产物介导降脂的关键信号节点。该通路整合了 AMPK 的细胞能量感知与 SREBP-1c 的脂质转录调控功能，形成了一套协同调节网络[88-89]。NACs 及其 GM 代谢产物(特别是短链脂肪酸 SCFAs)是激活该通路的重要介质。

在上游激活层面，菌群代谢产物通过“受体依赖”与“代谢依赖” 2 条路径作用于 AMPK。一方面，发酵产生的 SCFAs 可作为配体结合肠道上皮或肝细胞表面的 G 蛋白偶联受体(GPR43/GPR41)，经 Gq 蛋白介导激活磷脂酶 Cβ (phospholipase Cβ, PLCβ)，触发 1,4,5-三磷酸肌醇/二酰甘油-蛋白激酶 C (inositol 1,4,5-trisphosphate/diacylglycerol-protein kinase C, IP3/DAG-PKC)信号转导，促使 AMPK 在 Thr172 位点发生磷酸化激活[90-91]。另一方面，天然成分通过调节菌群结构改变宿主能量代谢状态。例如，红曲米中的莫纳辛(monascinol)通过调节肠道菌群(如富集 AKK)促进丙酸生成，丙酸作为糖异生底物或线粒体代谢调节剂可改变肝细胞内 AMP/ATP 比值，从而变构激活 AMPK[92]。动物源牛磺酸与金针菇多糖通过富集产酸菌群(如毛螺菌科)，利用代谢产物丁酸强化 AMPK/ACC 通路实现对肝脏 FASN 表达的下调及血清甘油三酯的清除[55,93]。

活化的 AMPK 通过“抑制酶活”与“转录阻遏”的双重机制调节脂质代谢。在酶活水平，AMPK 直接磷酸化乙酰辅酶 A 羧化酶(acetyl-CoA carboxylase, ACC)的 Ser79 位点使其失活，这一效应在菊粉(富集 *Roseburia*)的干预研究中尤为显著，ACC 活性的丧失导致丙二酰辅酶 A 生成减少，这不仅降低了脂肪酸合成的底物来源，更解除了其对肉碱棕榈酰转移酶 1 (CPT1)的变构抑制，从而促进线粒体脂肪酸 β-氧化[57,94-95]。在转录水平，AMPK 特异性磷酸化 SREBP-1c 的 Ser372 位点，阻碍其前体蛋白从内质网向高尔基体的转运及随后的剪切成熟过程，进而阻止了 SREBP-1c 进入细胞核，导致下游关键靶基因(如 FASN、ACC1)表达下调[95-96]。例如，姜黄素衍生的阿魏酸代谢物、沙棘及刺梨提取物均被证实能通过该机制显著下调 SREBP-1c 及其靶基因表达，协同上调 CPT1A，从转录水平改善脂质蓄积[97-98]。

综上所述，AMPK/SREBP-1c 通路是不同 NACs 发挥降脂作用的共同靶点(图 4)。该通路作为连接“肠道菌群-代谢产物-宿主信号”的关键调节网络，通过整合能量信号与转录调控为脂质代谢紊乱的营养干预提供了分子依据。

2.2.2 PPAR 家族通路

过氧化物酶体增殖物激活受体(PPARs)信号通路是天然产物及其 GM 代谢产物调节脂质稳态的关键靶点。该通路主要依赖 PPARα (促进氧化)与 PPARγ (促进脂质储存) 2 个亚型的功能协同，参与脂质代谢的系统调节。其中，PPARα 主要在肝脏及骨骼肌中介导脂肪酸的 β-氧化分解，而 PPARγ 则调节脂肪细胞的分化与脂质代谢平衡网络。天然产物经菌群生物转化生成的活性代谢物(如 SCFAs、L-精氨酸等)，通过“配体激活” “表观修饰”及“信号串扰”等途径调节

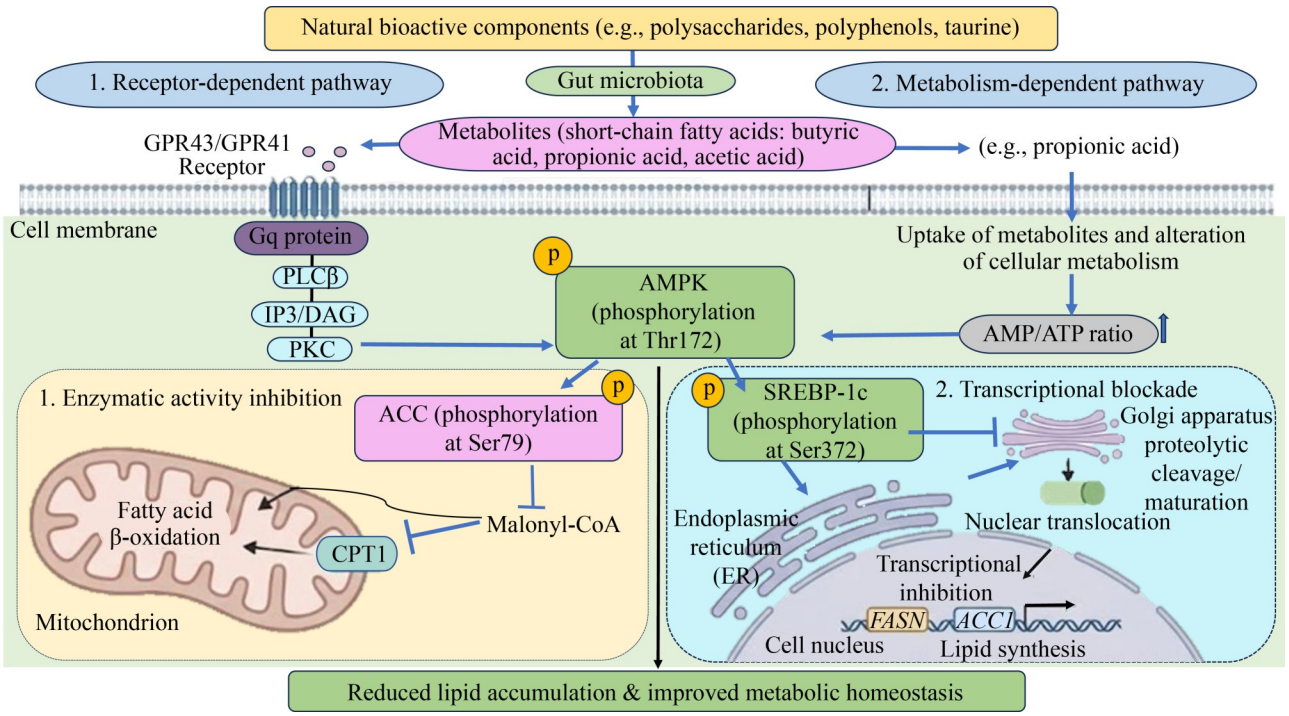


图4 NACs通过AMPK/SREBP-1c通路调控脂质代谢的分子机制

Figure 4 Molecular mechanisms of lipid metabolism regulation by NACs *via* the AMPK/SREBP-1c pathway.

PPARs 信号转导。

在促进氧化方面，受上游 SCFAs 分子特性的驱动，宿主 PPARα 网络被特异性激活。例如，丁酸作为组蛋白去乙酰化酶(HDAC)抑制剂，解除基因沉默并促进 PPARα 与视黄醇 X 受体(retinoid X receptor, RXR)形成异源二聚体；该转录复合物结合至靶基因启动子区的 PPAR 反应元件(peroxisome proliferator-activated receptor response element, PPRE)，在转录水平上调肉毒碱棕榈酰转移酶 1A (carnitine palmitoyltransferase 1A, CPT1A)及酰基辅酶 A 氧化酶 1 (acyl-CoA oxidase 1, ACOX1)的表达，从而显著促进肝脏和肌肉组织的脂肪酸 β-氧化[99-100]。此外，蛹虫草多糖通过富集乳酸菌促进 L-精氨酸生成，后者通过激活一氧化氮(NO)信号进一步增强 PPARα 的转录活性[101]。

在抑制脂肪蓄积方面，部分代谢产物可抑制 PPARγ 介导的脂肪生成。例如，麦角甾醇经菌群代谢后能有效抑制 PPARγ 的过度激活及其核转位过程，干扰其与协同转录因子 CCAAT/增强子结合蛋白 α (CCAAT/enhancer-binding protein α, C/EBPα)的相互作用；这一机制进而下调了下游脂肪酸结合蛋白(fatty acid-binding protein 2, AP2)等关键基因表达，从而在转录水平抑制前脂肪细胞向成熟脂肪细胞的分化及脂质蓄积[102-104]。牛磺酸通过调节菌群产生的丙酸激活 PPARα 同时下调 PPARγ 表达，发挥促进脂质氧化与抑制脂质合成的作用[105-106]。

值得注意的是，PPARγ 的调控具有显著的组织特异性与功能选择性。虽然抑制其在脂肪组织的表达有助于减少肥胖，但在胆固醇代谢调控中其适度激活则具有促进作用。研究显示，石榴皮多酚的活性代谢物(如尿石素/石榴酸)能上调 PPARγ 表达，进而激活其下游靶点 ATP 结合盒转运体 A1 (ATP-binding cassette transporter A1, ABCA1)与 CYP7A1，协同促进细胞内胆固醇的外流与 BAs 转化，从而减少肝脏胆固醇蓄积[107]。

综上所述，这些发现从分子层面揭示了PPAR亚型在不同代谢场景下的差异化功能。如图5所示，天然产物通过“菌群-代谢物-信号通路”途径实现了对PPARα (促氧化)与PPARγ (抑生成/促外流)的双向调节，为代谢性疾病的干预提供了理论基础。

2.2.3 TLR4/NF-κB 炎症通路

TLR4/NF-κB信号通路作为连接免疫应答与脂质代谢的枢纽，在代谢性疾病的病理进程中发挥重要作用。肠道屏障受损引发的代谢性内毒素血症是激活该通路的重要诱因[108-109]。

在病理机制层面，革兰氏阴性菌细胞壁成分脂多糖(LPS)作为外源性配体，经受损肠黏膜易位入血，特异性结合肝细胞或巨噬细胞膜表面的TLR4；该结合招募髓样分化因子88 (myeloid differentiation factor 88, MyD88)，启动下游信号转导，诱导NF-κB p65亚基发生磷酸化并易位入核；活化的NF-κB在转录水平上调肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α)和白细胞介素-1β (IL-1β)等促炎因子的转录表达[110-112]。上述促炎因子不仅诱发系统性低度炎症，更通过“炎症-代谢互作”机制上调脂肪酸合成酶(FASN)并抑制胆固醇7α-羟化酶(CYP7A1)表达，从而促进脂质从头合成与肝脏脂质蓄积[113-114]。

具体分子干预机制如图6所示，NACs通过“源头控制”与“靶点阻断”双重策略干预上述过程。在菌群与屏障的源头控制层面，部分成分通过调节微生态降低LPS负荷，例如，茯苓多糖能特异性下调革兰氏阴性菌LPS合成限速酶 *lpxC* 基因的表达，配合双歧杆菌属(*Bifidobacterium*)的增殖，有效减少内毒素生成[115]。茶多酚与乳铁蛋白则通过富集AKK与罗斯拜瑞氏菌属(*Roseburia*)，上调紧密连接蛋白(Occludin、ZO-1)表达以增强物理屏障，同时利用SCFAs降低肠道pH值以抑制脱硫弧菌(*Desulfovibrio*)等内毒素产生菌，减少LPS易位[116-117]。这种屏障保护作用为AKK发挥其代谢调节功能创造了前提条

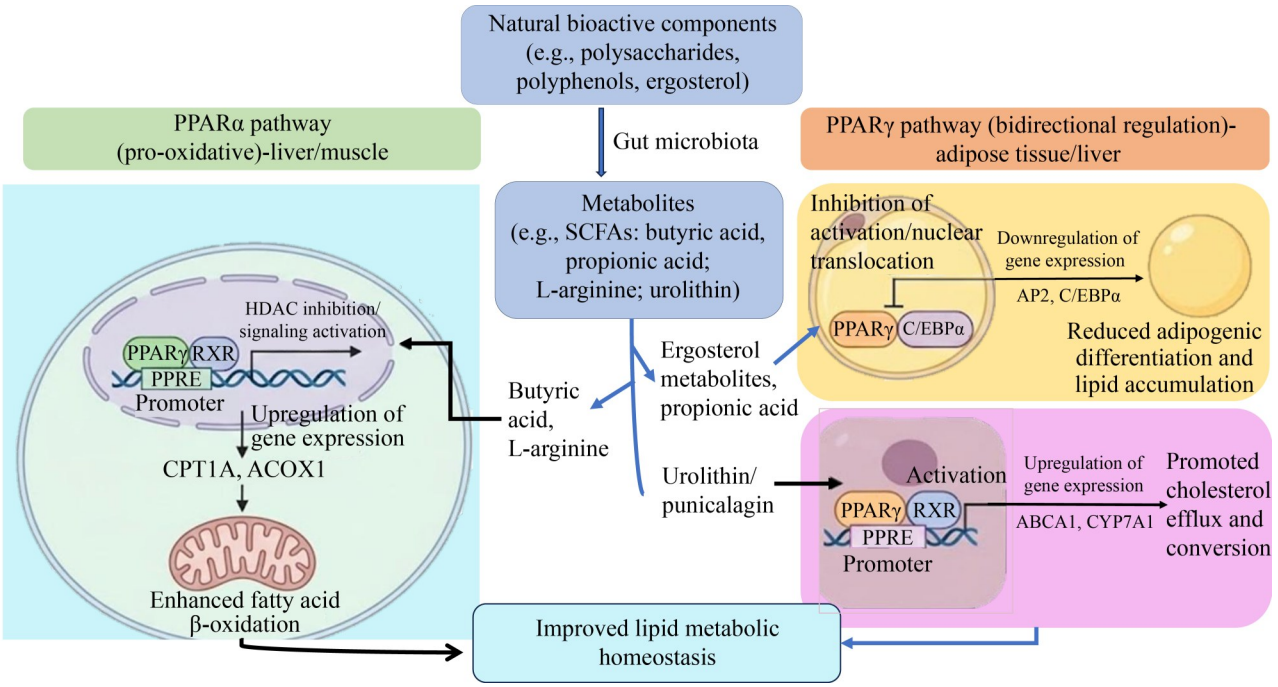


图5 NACs经菌群代谢物调控PPARs信号网络的分子机制

Figure 5 Molecular mechanisms of NACs regulating PPARs signaling network *via* gut microbiota metabolites.

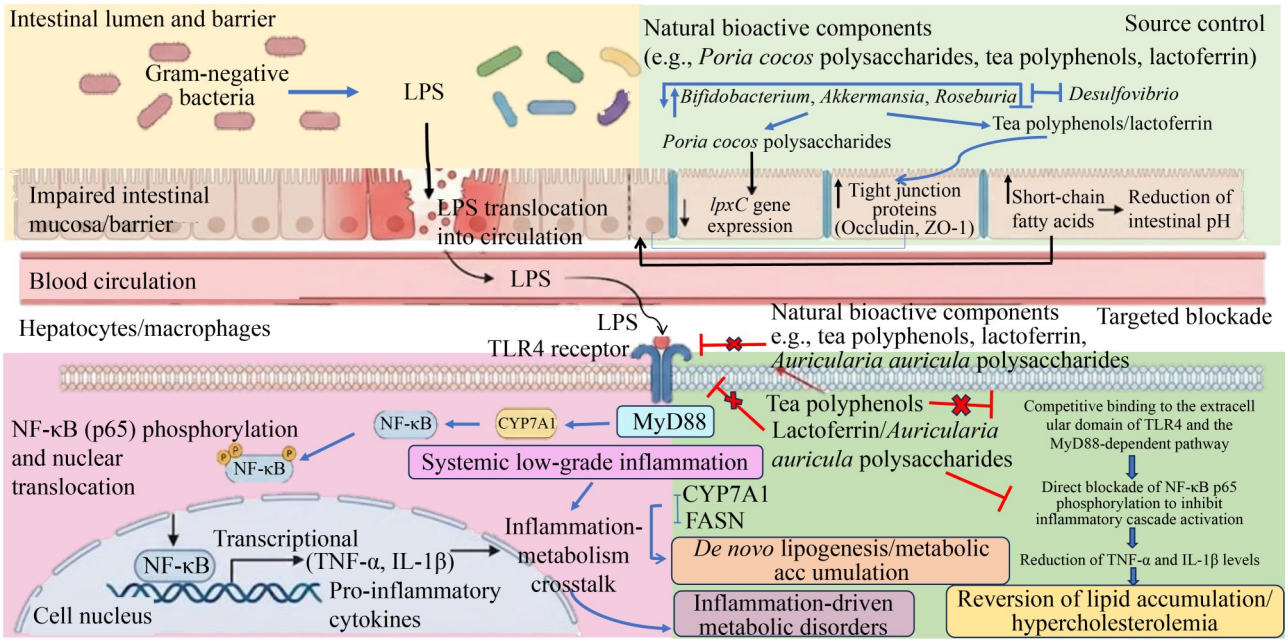


图6 NACs经TLR4/NF-κB通路调控“肠道菌群-炎症-脂代谢”网络的分子机制

Figure 6 Molecular mechanisms of NACs regulating “gut microbiota-inflammation-lipid metabolism” network *via* TLR4/NF-κB pathway.

件。事实上，AKK 的富集不仅能维持屏障完整性，也是脂质代谢的关键调节菌，一方面，其代谢产生的丙酸可激活 AMPK 信号通路，在转录水平下调脂肪酸合成相关基因的表达(见 2.2.1 节)；另一方面，该菌通过改变胆汁酸组成分别激活肠道 FXR-FGF15 轴(见 1.2.3 节)和脂肪组织 FXR，从而抑制胆固醇吸收与脂质蓄积。最新研究更揭示，AKK 产生的吲哚-3-乳酸(indole-3-lactic acid, ILA)可通过 N6-甲基腺苷(N6-methyladenosine, m^6A)修饰调控肝脏固醇 12α-羟化酶(sterol 12α-hydroxylase, CYP8B1)表达，进一步改变胆汁酸组成并增强 FXR 激活效应[118]。上述代谢调节与屏障保护机制共同作用减轻了 LPS 易位及其诱导的炎症反应。

在分子靶点的抑制层面，天然成分能靶向信号转导的关键节点。茶多酚被证实能竞争性结合 TLR4 胞外结构域，通过空间位阻效应阻断 LPS 与受体的结合，进而抑制 MyD88 依赖的 NF-κB 核转位及肝脏炎症基因表达[119-122]。乳铁蛋白与黑木耳多糖则主要抑制胞内信号传递，通过直接阻断 NF-κB p65 的磷酸化激活切断炎症级联反应，从而显著降低血清 TNF-α、IL-1β 水平，最终改善由炎症介导的肝脏脂质沉积与高胆固醇血症[117,123]。

上述结果表明，TLR4/NF-κB 通路是 NACs 调控“肠道菌群-炎症-脂代谢”网络的核心环节，为其在代谢性疾病干预中的应用提供了分子依据。为系统比较各通路的分子靶点差异，NACs 调控关键信号通路的具体降脂机制汇总于表 4。

综上所述，NACs 通过靶向调节 GM 形成了以代谢产物为关键介质的协同降脂调节网络。一方面，利用 SCFAs、次级 BAs 等效应分子调节脂质代谢的关键酶与载体(如抑制 HMGCR 活性、下调 NPC1L1 表达)；另一方面，通过激活 AMPK/SREBP-1c、PPARs 及 TLR4/NF-κB 等关键信号节点，在转录水平系统性调节脂质合成、

表4　关键信号通路介导的宿主脂质调控机制

Table 4　Host lipid regulation mechanisms mediated by key signaling pathways

Core signaling pathway	Regulatory strategy	Specific molecular mechanism/site of action	Key target gene/protein	Representative component	References
AMPK/SREBP-1c (energy sensing and synthesis regulation)	Upstream activation	SCFAs bind to GPR43/41 receptors, activate CaMKK/LKB1 cascade; alter AMP/ATP ratio, allosterically activate AMPK	p-AMPK (Thr172)	*Monascus*-fermented rice, *Flammulina velutipes* polysaccharide	[90-93]
	Downstream effect	Phosphorylates ACC (Ser79) to inactivate it, unblocks β-oxidation; phosphorylates SREBP-1c (Ser372), blocks its nuclear translocation	*acc*, *fasn* (↓), *cpt1a* (↑)	Inulin, sea buckthorn, curcumin metabolites	[95-98]
PPAR family (oxidative decomposition and differentiation)	PPARα activation	Inhibits HDAC, relieves epigenetic repression; promotes PPARα-RXR dimer binding to PPRE elements	*cpt1a*, *acox1*	Butyrate, *Cordyceps militaris* polysaccharide	[99-101]
	PPARγ bidirectional regulation	Inhibits excessive activation of PPARγ in adipose tissue, blocks adipogenesis; activates hepatic PPARγ, promotes cholesterol efflux	*ap2* (↓), *abca1*, *cyp7a1* (↑)	Ergosterol, pomegranate peel polyphenols	[102-107]
TLR4/NF-κB (inflammation-metabolism crosstalk)	Source control	Downregulates LPS synthase genes in Gram-negative bacteria; upregulates tight junction proteins, blocks LPS translocation	*lpxC*, *occludin*, ZO-1	*Poria cocos* polysaccharide, lactoferrin	[115-117]
	Target blockade	Competitively binds to the TLR4 extracellular domain, causing steric hindrance; directly inhibits NF-κB p65 phosphorylation and nuclear translocation	NF-κB (p65), TNF-α, IL-1β	Tea polyphenols, *Auricularia auricula-judae* polysaccharide	[119-123]

分解及炎症应答网络。

这一过程最终促进了血清脂质谱(TC、TG、LDL-C)的改善、肝脏脂质沉积的减轻及系统性炎症的缓解。其作用机制可概括为“成分→菌群→代谢产物→受体→通路→靶标基因→脂质代谢”的七步级联反应。如图 7 所示，尽管不同来源 NACs 作用于微生态的起始环节各异，但其下游机制均表现出共性特征，即依托“肠道菌群-代谢产物-宿主信号”这一关键轴线实现了对宿主脂质代谢稳态的多靶点、多层次调节。

上述分子机制的系统梳理，不仅从多维视角解析了 NACs 的降脂作用途径，更为后续开发基于特定菌群代谢物或信号靶点的营养干预策略奠定了分子理论基础。

3　总结与展望

3.1　总结与理论贡献

本文梳理了 NACs 经由“成分→肠道微生态调节→菌群代谢产物(SCFAs/BAs/酚酸)→宿主关键信号节点(AMPK/PPAR/TLR4)→脂质稳态恢复”的级联调节途径，系统整合了“微生态-宿主”互作机制在多层面的研究进展。此外，本文探讨了“免疫-代谢交互”的重要作用，明确了修复肠道屏障、减轻代谢性内毒素血症是恢复肝脏脂质代谢酶活性的关键环节，为基于炎症调节的降脂提供了分子依据。这一微生态-宿主级联调控模型得到了本课题组前期系列研究的实验支持。如 1.1、1.2.1 及 2.1.1 节所述，以食药用真菌(如榆黄菇、毛木耳等)活性多糖开展研究表

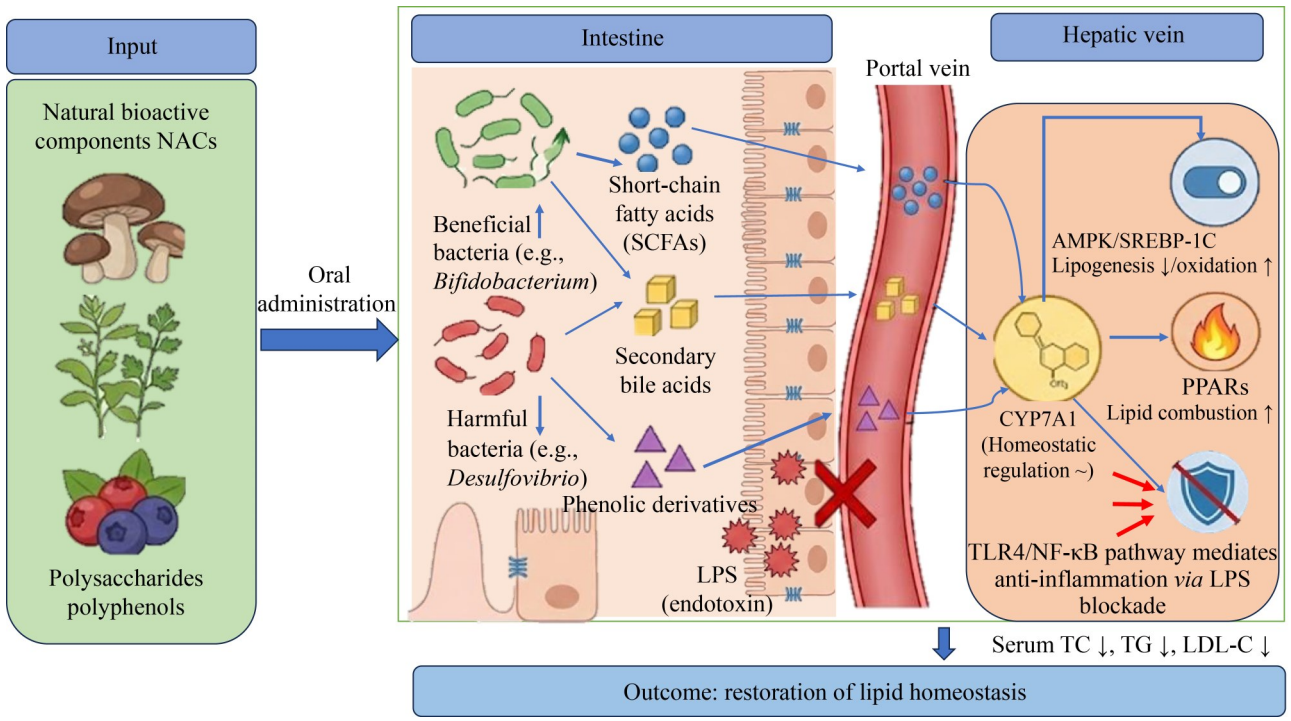


图7 NACs经“肠道菌群-代谢产物-宿主信号”轴重塑脂质代谢稳态的多维调控模型

Figure 7 Multi-dimensional regulatory model of NACs remodeling lipid metabolic homeostasis *via* “gut microbiota-metabolite-host signaling” axis.

明，此类大分子能促进双歧杆菌属等有益菌增殖并促进 SCFAs 产生，并通过调节水通道蛋白(AQP3)与紧密连接蛋白(ZO-1)表达改善肠道机械屏障，最终经“肠-肝轴”强化消脂护肝作用。这些源于微生态调节的实验证据为本文构建的理论框架提供了基础。

3.2 研究展望

尽管目前关于 NACs 调节脂质代谢的研究已取得一定进展，但为推进其从实验室走向临床转化未来研究仍需在以下 3 个方面深入。

(1)需将研究重点从“相关性”描述向“因果性”确证。现有研究多基于菌群丰度变化的关联分析，缺乏对关键功能菌群的确证。未来应广泛引入无菌动物模型、粪菌移植技术及特定菌株定殖实验，明确在降脂过程中发挥关键作用的功能菌群，排除伴随变化的干扰菌群，从而确立特定菌株及其代谢产物在降脂效应中的因果地位。

(2)应深入解析“微生态-宿主”互作的结构生物学与药代动力学基础。尽管已知代谢产物可激活宿主通路，但其具体的分子识别机制尚不明晰。后续研究应解析天然成分衍生的次级代谢产物与宿主受体(如 GPRs、FXR、PPARs)结合的结构基础，并利用同位素示踪等技术追踪小分子代谢物穿过肠道屏障并靶向肝脏、脂肪组织等效应器官的药代动力学过程，以阐明其体内吸收与分布特征。在宿主核受体调节方面，本课题组近期研究表明，特定真菌多糖可通过调节肠道菌群激活宿主法尼醇 X 受体(FXR)，进而影响胆汁酸的肝肠循环与脂质代谢[124]。因此，解析更多以菌群代谢物为配体的受体变构激活机制是未来的重要研究方向。

(3)需关注宿主肠道基线菌群的异质性导致的代谢响应差异，针对同一天然成分，机体常表现出“应答者”与“无应答者”分化。未来应结

合多组学技术与人工智能算法识别影响天然成分生物转化的关键基线菌群特征，建立预测模型，从而为基于个体肠道微生态特征的膳食干预提供理论依据。

作者贡献声明

吴飘：综述选题与框架设计、文献检索与筛选、核心内容撰写、论文修改与定稿；张殿朋：文献整理与分类、图表英文翻译；韩雅杰：参考文献整理与格式规范，图表调整与修改；金瑞娇：论文审阅；弥春霞：综述逻辑架构优化、学术质量把控；赵爽：研究方向指导、综述整体思路指导、论文审阅与修改。

作者利益冲突公开声明

作者声明不存在任何可能会影响本文所报告工作的已知经济利益或个人关系。

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