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姜黄素调控高脂血症的机制与临床研究进展

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［摘要］ 高脂血症是一种由脂质代谢紊乱驱动的常见代谢性疾病，其病理进程涉及胆固醇稳态失衡、胰岛素抵抗、慢性炎症及氧化应激等多信号通路交互作用。尽管现有临床药物可通过单一靶点有效缓解症状，但在全面改善脂质逆转运、代谢性炎症及糖脂代谢协同调控等方面仍存在显著局限性。姜黄素作为传统中药姜黄的主要多酚类活性成分，具有调节脂质代谢、改善胰岛素敏感性、抑制炎症反应及增强抗氧化防御等多维度药理效应。该综述系统性整合姜黄素的多靶点调控网络，阐明其通过调节低密度脂蛋白受体/前蛋白转化酶枯草溶菌素9（LDLR/PCSK9）信号通路平衡促进胆固醇逆转运、激活过氧化物酶体增殖物激活受体α/γ（PPARα/γ）信号通路协调糖脂代谢稳态、重塑肠道菌群-胆汁酸轴、抑制核转录因子-κB（NF-κB）信号通路介导的炎症反应及激活核因子E_2相关因子2/抗氧化反应元件（Nrf2/ARE）信号通路等重要机制；同时结合临床研究数据，验证其降低总胆固醇（TC）、甘油三酯（TG）及提高高密度脂蛋白胆固醇（HDL-C）水平的治疗潜力。并基于纳米递送系统和个体化用药策略展望其临床应用前景，为高脂血症及相关代谢性疾病的防治提供理论依据与新思路。

［关键词］ 高脂血症；姜黄素；脂质代谢；多靶点调控；临床应用

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Mechanisms and Clinical Research Advances of Curcumin in Modulation of Hyperlipidemia

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［**Abstract**］ Hyperlipidemia is a common metabolic disorder driven by dysregulated lipid metabolism, whose pathological progression involves multifaceted interactions across various signaling pathways, including disrupted cholesterol homeostasis, insulin resistance, chronic inflammation, and oxidative stress. Although existing clinical medications such as statins can effectively reduce low-density lipoprotein cholesterol through single-target inhibition, significant limitations remain in comprehensively improving reverse cholesterol transport, metabolic inflammation, and coordinated regulation of glucose and lipid metabolism. Curcumin, the primary polyphenolic active compound derived from the traditional medicinal herb turmeric, exhibits multi-dimensional pharmacological effects including modulation of lipid metabolism, improvement of insulin sensitivity, suppression of inflammatory responses, and enhancement of antioxidant defense. This review systematically integrates the multi-target regulatory

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network of curcumin, elucidating its key mechanisms: balancing the low density lipoprotein receptor/proprotein convertase subtilisin / kexin type 9 (LDLR/PCSK9) signaling pathway to promote reverse cholesterol transport, activating peroxisome proliferator-activated receptor α/γ (PPARα/γ) signaling pathways to coordinate glucolipid metabolic homeostasis, remodeling the gut microbiota-bile acid axis, inhibiting nuclear factor kappa-B (NF-κB)-mediated inflammatory responses, and activating the nuclear factor erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE) antioxidant signaling pathway. Furthermore, supported by clinical research data, the review validates curcumin's therapeutic potential in reducing total cholesterol (TC) and triglyceride (TG) levels, increasing high-density lipoprotein cholesterol (HDL-C), as well as improving vascular endothelial function and insulin sensitivity. The study highlights the multi-target regulatory properties of curcumin and discusses future clinical applications based on nano-delivery systems and personalized treatment strategies, providing a theoretical basis and novel insights for the prevention and treatment of hyperlipidemia and related metabolic disorders.

[**Keywords**] hyperlipidemia; curcumin; lipid metabolism; multi-target regulation; clinical application

高脂血症是一种以血脂异常升高为主要特征的代谢紊乱性疾病，患者常表现为总胆固醇(TC)、甘油三酯(TG)和低密度脂蛋白胆固醇(LDL-C)水平升高，而高密度脂蛋白胆固醇(HDL-C)水平降低，这些异常脂质代谢状态显著增加动脉粥样硬化性心血管疾病(ASCVD)的发病风险[1]。根据中国—以患者为中心的心脏事件评估百万人项目试点方案的最新数据，中国成人血脂异常患病率已高达33.8%，其中低HDL-C和高TG血症为主要类型，且治疗率与控制率均较低[2]，中青年人群患病率呈明显上升趋势，这一变化与饮食结构西化、身体活动水平下降及肥胖症流行密切相关[3]。尽管患者早期常无特异性症状，但长期残余胆固醇(RC)水平升高显著增加ASCVD风险。研究显示，RC每升高1 mmol·L^{-1}(39 mg·dL^{-1})，个体发生缺血性心脏病的风险将相应增加至2.8倍，且与全因死亡率呈线性相关[4]。即使通过现有降脂治疗将LDL-C控制在目标范围内，RC风险和残余炎症风险仍会进一步加剧患者发生心血管事件及全因死亡的风险，严重影响其生活质量与长期预后[5]。此外，高脂血症常与肥胖、2型糖尿病和代谢功能障碍相关脂肪性肝病(MAFLD)等代谢性疾病共存，形成复杂的代谢综合征，进一步加重心脑血管疾病负担[6]。目前临床一线降脂药物如他汀类虽能有效降低LDL-C，并表现出一定的抗炎与多效性作用，但其作用机制主要局限于抑制胆固醇合成，对脂质逆转运及糖脂代谢协同等环节的调控能力不足，且长期用药可能引发肌肉毒性、肝酶异常及他汀不耐受等不良反应[7-8]，这表明开发多靶点、高效安全的替代疗法具有重要临床意义。姜黄素作为姜黄的主要活性成分，化学结构为(1E,6E)-1,7-双(4-羟基-3-甲氧基苯基)-1,6-庚二烯-3,5-二酮。然而，水溶性差及体内代谢迅速导致其口服生物利用度极低，口服给药后达峰时间约为1~2 h，血浆半衰期较短。这些因素在一定程度上限制了姜黄素的临床疗效。尽管如此，姜黄素因其具有调节脂质代谢、改善胰岛素敏感性、抑制炎症反应和增强抗氧化防御等多重药理效应，在代谢性疾病防治领域展现出广阔前景[9]。研究表明，姜黄素不仅可下调前蛋白转化酶枯草溶菌素9(PCSK9)并上调低密度脂蛋白受体(LDLR)表达[10]，还能激活过氧化物酶体增殖物激活受体α/γ(PPARα/γ)信号通路以协调糖脂稳态[11]，并重塑肠道菌群-胆汁酸轴[12]、抑制核转录因子-κB(NF-κB)介导的炎症反应及增强核因子E_2相关因子2/抗氧化反应元件(Nrf2/ARE)抗氧化信号通路活性[13]，从而在多靶点、多通路层面发挥综合调控作用。然而，当前研究大多集中于单一机制探讨，缺乏对姜黄素多维度作用网络的系统性整合；在临床转化方面，其生物利用度、最佳给药方案及长期用药安全性仍需深入评估。因此，本文旨在全面总结姜黄素调节高脂血症的作用机制与临床研究进展，通过与传统降脂药物的比较，突出其多靶点调控特性与协同治疗优势，为高脂血症及相关代谢性疾病的防治提供新的理论依据和干预策略。高脂血症的关键病因、姜黄素的分子靶点、表型效应与干预剂量总结见增强出版附加材料。

1 高脂血症的肠-肝-胰代谢轴失调与核心调控机制

高脂血症是一种由遗传、环境及代谢网络交互作用共同调控的复杂病理状态，其本质是全身脂质稳态的系统性失衡[36]。近年研究表明，肠-肝-胰代谢轴在高脂血症的发生与发展中扮演核心角色，其功能紊乱可通过多器官交叉对话导致脂质代谢异常。肝脏作为脂质代谢的中心器官，负责胆固醇合成、胆汁酸代谢及极低密度脂蛋白组装[37]；肠道则通过胆汁酸重吸收、菌群结构重塑及结合型胆汁酸激活肝受体调控全身脂质代谢[38]；胰腺β细胞功能与胰岛素分泌则通过调节脂蛋白脂酶(LPL)活性及脂肪组织脂解作用，调控血浆TG水解与清除效率，从而影响循环脂质水平[39]。三者共同构成一个精密调控网络，其中任一环节失调均可引发系统性脂代谢紊乱。具体而言，高脂饮食可诱导肠道菌群结构失调，表现为革兰氏阴性菌过度增生，其细胞壁成分脂多糖(LPS)随之易位入血，通过激活肝脏Toll样受体4(TLR4)信号通路诱发炎症因子的大量释放，进而加剧肝脏胰岛素抵抗与TG堆积[40]。同时，胆汁酸代谢紊乱是肠肝轴失调的另一关键特征，肝脏合成的初级胆汁酸进入肠道后，经菌群作用转化为次级胆汁酸，后者可重新吸收入门静脉；返回肝脏的脱氧胆酸(DCA)可通过激活肝细胞法尼醇X受体(FXR)信号，反馈性抑制胆固醇7α-羟化酶(CYP7A1)表达，减少胆汁酸合成，进而影响肠道菌群结构与代谢稳态[41]。肝源性成纤维细胞生长因子4(FGF4)在FXR激活下表达上调，通过激活肝细胞的成纤维细胞生长因子受体4-肝受体同源物1(FGFR4-LRH-1)信号轴，抑制CYP7A1和甾醇12α-羟化酶表达，减少胆汁酸合成，缓解胆汁淤积性肝损伤[42]。此外，胰腺胰岛素分泌不足或敏感性下降将削弱LPL活性，减少富含TG的脂蛋白清除，最终造成血清TG水平升高[43]。这些多器官、多通路的交互作用共同构成了高脂血症的复杂病理基

础，凸显了多靶点干预肠-肝-胰代谢轴的必要性。姜黄素正是通过同步调节该代谢轴中多个关键节点——如抑制肠道NPC1样细胞内胆固醇转运蛋白1（NPC1L1）介导的胆固醇吸收、调节肝脏LDLR/PCSK9平衡与胆汁酸合成、减轻肝脏脂肪变性与炎症反应、激活肝脏FXR/CYP7A1胆汁酸合成通路、增强胰腺β细胞功能及改善外周胰岛素敏感性——发挥其降脂效应，为突破现有单靶点降脂药物的局限性提供了新思路。高脂血症“肠-肝-胰”代谢轴失调机制见图1。

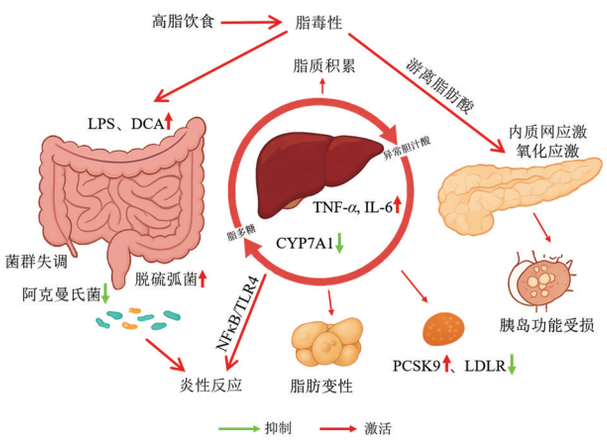

图1 高脂血症“肠-肝-胰”代谢轴失调示意

Fig. 1 Schematic diagram of dysregulated gut-liver-pancreas metabolic axis in hyperlipidemia

2 姜黄素调控高脂血症的机制

2.1 调控LDLR/PCSK9平衡与胆固醇逆转运 LDLR在血浆胆固醇清除中发挥核心作用，其功能状态直接影响脂质稳态[44]。PCSK9通过促进LDLR的溶酶体降解，显著削弱胆固醇的内吞清除能力，已成为高脂血症及动脉粥样硬化的重要干预靶点[45]。临床研究表明，PCSK9通过阻断分选衔接蛋白17介导的LDLR回收途径促进LDLR降解，导致肝脏LDL清除能力下降；且PCSK9的抑制剂可显著提升LDLR水平，凸显PCSK9在他汀时代降脂治疗中的重要补充价值[46]。姜黄素通过多层次分子机制调控PCSK9表达。在HepG2细胞中，姜黄素通过降低HNF-1α核内水平，抑制其与PCSK9启动子区HNF-1α结合位点的相互作用，使PCSK9的mRNA表达下降约48%，继而升高细胞膜LDLR蛋白并增强LDL摄取[47]。动物实验进一步证实，四氯化碳诱导的肝硬化大鼠经姜黄素（200 mg·kg^{-1}·d^{-1}）干预12周后，肝脏PCSK9基因与蛋白表达均显著降低。与单抗类药物直接中和PCSK9的策略不同，姜黄素通过抑制PCSK9表达以增强LDLR介导的内毒素清除[48]。此外，姜黄素还可通过表观遗传机制增强LDLR功能。研究显示，姜黄素烟酸酯可竞争结合LDL受体的RING E3泛素连接酶诱导型降解子蛋白4.1蛋白-埃兹蛋白-根蛋白-膜突蛋白（FERM）结构域并抑制其表达，从而使肝细胞膜LDLR分布显著增加，显著改善其低密度脂蛋白的结合与内吞效率[49]。姜黄素还可通过抑制信号转导与转录激活因子3信号通路协同增强ATP结合盒转运蛋白A1/G1（ABCA1/ABCG1）表达，在10 μmol·L^{-1}浓度下促进胆固醇外排并减轻动脉粥样硬化[50]。在ApoE$^{-/-}$小鼠模型中，0.1%姜黄素饮食干预显著降低了主动脉中TLR4的表达，主动脉粥样斑块发展受到抑制，展现出多通路协同抗动脉粥样硬化的潜力[51]。一项临床试验显示，姜黄素制剂治疗14周可使糖尿病伴ASCVD风险患者LDL-C降低28.9%，HDL-C升高11.5%，同时肿瘤坏死因子-α（TNF-α）和丙二醛（MDA）水平显著下降[17]。尤其在他汀类药物治疗中，联合姜黄素可进一步增强LDL摄取，其机制可能与抑制他汀引发的PCSK9上调及HNF-1α核转位减少有关[52]。尽管现有证据支持姜黄素在调脂治疗中的协同价值，但其个体反应差异及生物利用度限制仍是临床转化中的主要挑战。未来研究需结合药物基因组学优化给药策略，并深入探索姜黄素对PCSK9抑制剂耐药人群的潜在治疗价值。此外，姜黄素对肠肝轴及胆汁酸代谢的调控是否间接影响PCSK9-LDLR平衡，仍有待深入阐明。

2.2 激活PPARα/γ双信号通路协调糖脂代谢 PPARα/γ作为调控糖脂代谢稳态的核心转录因子，其功能紊乱与非酒精性脂肪肝病（NAFLD）及胰岛素抵抗密切相关[53-54]。研究表明，NAFLD患者肝组织中PPARα初始表达较低，而脂肪组织中PPARγ功能异常与糖尿病发病风险显著相关，凸显其在代谢性疾病中的关键地位[55]。姜黄素可通过激活PPARα与PPARγ信号通路，实现对糖脂代谢网络的协同调控。姜黄素可抑制脂肪质量和肥胖相关蛋白去甲基化活性，增强PPARα mRNA的N6-甲基腺苷修饰水平，进而上调CPT1A等脂肪酸氧化关键酶表达[56-57]。在高脂饮食诱导的NAFLD大鼠中，姜黄素干预不仅显著降低肝脏TG蓄积，还通过上调肉碱棕榈酰转移酶1A表达提高了β-氧化效率，其与PPARα/γ双重激动剂沙格列扎具有协同增效作用[58]。该机制还涉及表观遗传调控，如姜黄素通过抑制组蛋白去乙酰化酶3增强抗氧化基因启动子区组蛋白H3第27位赖氨酸乙酰化水平，进而解除转录抑制[59]。在PPARγ调控方面，姜黄素通过促进PPARγ及其关键共调节因子CCAAT增强子结合蛋白α的基因表达，促进脂肪细胞的分化成熟并提高其葡萄糖摄取能力，从而改善胰岛素敏感性[60]。临床研究显示，2型糖尿病患者经姜黄素纳米制剂治疗12周后，血浆空腹血糖和胰岛素水平显著下降，胰岛素抵抗指数改善，且未出现严重不良反应[61]。姜黄素可通过激活AMPK并抑制NF-κB信号通路，在不同组织中调节PPARγ活性，改善糖脂代谢紊乱。在db/db小鼠模型中，姜黄素干预可提升肝脏AMPK表达并降低NF-κB水平，同时增强脂肪组织中PPARγ表达，从而缓解肝脂堆积与胰岛素抵抗[62-63]。人体研究进一步证实，姜黄素治疗可降低NAFLD患者肝脂肪分数17.5 dB·m^{-1}，并减少内脏脂肪面积，显示出显著的临床转化潜力[12]。但需警惕的是，PPARγ在肌肉组织中的过度激活可能促进脂质异常沉积，提示需开发组织靶向递药系统以提升治疗特异性[64]。未来研究应重点关注姜黄素与钠-葡萄糖协同转运蛋白2抑制剂（SGLT2）抑制剂的联合应用，通过糖排泄与PPAR信号增敏的双重机制增强代谢调控效果，并深入探索肠道菌群-短链脂肪酸轴是否通过肠-肝对话间接调节PPARα/γ功能，以全面阐释姜黄素的系统性作用机制。

2.3 肠道菌群-胆汁酸代谢轴稳态调节 肠道菌群结构失调及其介导的胆汁酸代谢紊乱已被认为是高脂血症发生与发展的重要机制。具体表现为革兰氏阴性菌过度增殖导致LPS易位入血、次级胆汁酸升高，以及FXR和G蛋白偶联胆汁酸受体(TGR5)信号通路代谢功能紊乱[65]。研究显示，高脂饮食小鼠肠道微生物中拟杆菌门与厚壁菌门的比值降低，伴随血清次级胆汁酸，如DCA水平显著升高，进而通过FXR信号反馈性抑制CYP7A1表达，改变肝内胆固醇代谢稳态[66]。姜黄素通过多靶点干预策略重塑肠-肝代谢轴功能。姜黄素的低生物利用度特性使其在结肠局部达到高浓度，选择性促进阿克曼氏菌等有益短链脂肪酸产生菌的增殖，抑制脱硫弧菌等产LPS菌的生长，有效降低循环内毒素水平[67]。菌群结构的优化进一步增强胆汁酸7α-脱羟酶活性，促使次级胆汁酸DCA和石胆酸(LCA)生成显著增加[68-69]。升高的DCA与LCA可激活回肠TGR5受体，刺激胰高血糖素样肽-1(GLP-1)分泌；而升高的牛磺胆酸则通过抑制FXR-FGF轴，解除对CYP7A1的抑制作用，共同促进胆固醇向胆汁酸转化[70]。姜黄素还可通过增加DCA积累间接抑制肠道FXR，促进GLP-1分泌改善代谢[71-72]。在ApoE$^{-/-}$小鼠模型中，姜黄素干预显著降低血清LPS水平，减少肝脏TG蓄积，其效果优于单一抑制TLR4/NF-κB炎症[73]。临床研究进一步证实，姜黄素干预可通过调节肠道菌群组成，促进SCFAs产生，改善胆汁酸代谢，从而降低肝脏脂肪含量与空腹血糖水平[74]。然而，个体间菌群构成的差异可能导致疗效波动，未来需依托菌群分型制定个体化给药策略，并积极开发结肠靶向递药系统以提高姜黄素的局部浓度和调节效率。

2.4 靶向抑制代谢性炎症 代谢性炎症作为高脂血症向动脉粥样硬化进展的关键病理桥梁，其核心病理特征表现为游离脂肪酸通过TLR4信号通路激活、核转录因子κB抑制蛋白激酶β亚基(IKKβ)介导的NF-κB核转位，以及NOD样受体蛋白3(NLRP3)炎症小体介导的白细胞介素-1β(IL-1β)成熟与释放[75]。临床研究显示，血清可溶性分化簇14(CD14)水平与冠状动脉粥样硬化病变程度相关，而NLRP3基因功能获得性变异可导致IL-1β显著升高，进一步加剧炎症反应[76-77]。姜黄素通过多层级联机制有效抑制代谢性炎症的激活与维持。在炎症反应中，姜黄素通过下调TLR4表达，抑制IKKβ活性及NF-κB p65磷酸化，从而阻断其核转位，使巨噬细胞TNF-α等促炎因子释放量显著降低[13]。在炎症小体调控层面，姜黄素通过激活Nrf2通路增强硫氧还蛋白(Trx)表达，抑制ROS-Trx相互作用蛋白-NLRP3轴活性，并通过表观遗传机制降低NLRP3启动子区组蛋白H3第4位赖氨酸三甲基化修饰水平，从而阻碍胱天蛋白酶-1激活和消皮素D(gasdermin D)孔道形成[78-79]。动物实验表明，姜黄素干预可明显降低高脂饮食小鼠肝脏NLRP3炎症小体活性及血清IL-1β水平[80]。此外，姜黄素的活性代谢物四氢姜黄素通过抑制NF-κB和丝裂原活化蛋白激酶(MAPK)信号通路、激活Nrf2/血红素加氧酶-1(HO-1)抗氧化信号通路，显著降低炎症介质如一氧化氮(NO)和单核细胞趋化蛋白-1(MCP-1)的生成，并增强抗氧化基因表达[81]。临床前研究表明，姜黄素通过抑制LPS诱导的NF-κB信号通路激活和血清白细胞介素-6(IL-6)等炎症因子水平，从而改善胰岛素敏感性和代谢综合征组分[74]。为提高治疗的靶向性和有效性，未来研究应致力于开发巨噬细胞特异性的纳米递药系统，以增强姜黄素在炎症部位的蓄积并优化其免疫调节效应。

2.5 基于Nrf2/ARE轴调控抗氧化防御体系 Nrf2及其结合的ARE构成细胞抵御氧化损伤的核心信号通路，其功能失调与高脂血症中ROS累积及脂质过氧化密切相关[82]。研究显示，Nrf2相关基因与MAFLD的脂质代谢异常显著相关，且Nrf2缺失小鼠及游离脂肪酸处理的肝细胞中自噬相关蛋白微管相关蛋白1轻链3 Ⅱ/微管相关蛋白1轻链3 Ⅰ(LC3 Ⅱ/LC3 Ⅰ)值及溶酶体相关膜蛋白1(LAMP1)表达显著降低[83]。姜黄素通过多层级机制协同激活Nrf2/ARE信号通路。在分子层面，姜黄素通过其α,β-不饱和羰基直接修饰Kelch样ECH关联蛋白1(Keap1)蛋白中的Cys151残基，抑制Keap1介导的Nrf2泛素化，从而阻断Nrf2的蛋白酶体降解途径[84]。同时，姜黄素通过促进p62在Ser349位点的磷酸化，增强其与Keap1的竞争性结合，从而激活Nrf2并增强其转录活性[85]。激活后的Nrf2与核内ARE结合，进而启动NQO1、HO-1等一系列Ⅱ相解毒酶及抗氧化蛋白的转录，共同增强ROS清除能力并促进还原型谷胱甘肽生物合成[86]。实验研究表明，姜黄素能够显著提升肝星状细胞中ROS清除效率[87]。此外，该抗氧化效应还具有多组织协同性。在db/db糖尿病模型中，姜黄素干预不仅降低肾脏脂质过氧化物MDA水平，还显著提高肾脏SOD活性，表现出系统性的抗氧化保护作用[88]。临床研究进一步证实，姜黄素纳米制剂可显著提升2型糖尿病患者血清中SOD活性，降低硫代巴比妥酸反应物水平，并改善红细胞抗氧化能力[89]。姜黄素-富马酸二乙酯杂合物通过双重抑制糖原合酶激酶-3β(GSK-3β)和激活Nrf2信号通路显著增强抗氧化能力[90]，但需关注Nrf2过度激活可能干扰化疗药物疗效的风险。未来研究还需致力于开发组织特异性Nrf2调节策略，并依据Keap1/Nrf2基因多态性实现个体化抗氧化治疗。

2.6 其他潜在机制 姜黄素对高脂血症的改善作用不仅体现在前述核心通路，还通过多种新兴生物学机制形成系统性调控网络，为其多靶点代谢调节提供了重要补充。研究表明，双去甲氧基姜黄素被证实可通过线粒体途径诱导肝癌细胞凋亡，但会诱发保护性自噬；当联合使用自噬抑制剂时，双去甲氧基姜黄素的促凋亡效应会显著增强[91]。还有研究显示，姜黄素通过抑制固醇调节元件结合蛋白信号通路活性，显著下调脂肪酸合成酶和乙酰辅酶A羧化酶表达，在高脂饮食小鼠模型中有效减少肝脏脂质积累并改善胰岛素敏感性[92]。此外，姜黄素通过激活AMPK信号通路，增强自噬流并促进脂滴的溶酶体降解，有效减轻高脂喂养大鼠肝细胞脂肪变性[93]。在血管保护层面，姜黄素能够抑制内皮细胞中血管细胞黏附分子-1(VCAM-1)和细胞间黏附分子-1(ICAM-1)的表达，减少单核细胞黏附与内膜浸润，从而延缓动脉粥样硬化斑块的形成[94]。姜黄素还通过调节长链非编码RNA心肌梗死相关转录本的表达，经zeste同源物2增强子调控miR-124

进而影响炎症与细胞凋亡，在ApoE$^{-/-}$小鼠中表现出抗动脉粥样硬化潜力[95]。此外，姜黄素通过上调肝脏中分化簇36（CD36）与脂肪酸结合蛋白等脂肪酸转运蛋白的表达，促进脂肪酸β-氧化，降低血浆TG水平，并显著提高HDL-C胆固醇，协同增强其全身性降脂效应[96]。在高原低氧诱导的慢性神经损伤小鼠中，姜黄素通过抑制小胶质细胞活化、降低海马组织IL-6、TNF-α等炎症因子水平，并上调脑源性神经营养因子及其转录调控因子环磷腺苷效应元件结合蛋白的表达，从而有效改善小鼠的空间学习与记忆能力[97]。尽管这些机制仍处于临床前探索阶段，但他们共同揭示了姜黄素作为多靶点天然化合物在代谢性疾病干预中的独特价值。未来需进一步通过类器官模型和人群组学数据验证这些机制在人体内的相关性，并深入探索姜黄素与现有降脂药物的协同效应，为开发基于姜黄素的组合疗法提供理论依据。姜黄素干预高脂血症机制见增强出版附加材料。

3 姜黄素在高脂血症中的治疗策略与临床转化

3.1 临床疗效与安全性评价 姜黄素的降脂疗效呈现出显著的人群异质性，其差异主要源于代谢疾病类型、干预剂量及肠道菌群结构的复杂交互作用[74,98]。多项随机对照试验表明，姜黄素在伴有胰岛素抵抗的代谢紊乱患者中调脂效果尤为显著。例如，一项纳入80名非酒精性简单性脂肪肝患者的随机对照试验显示，经姜黄素干预24周后，患者肝脏脂肪含量较对照组降低17.5 dB·m^{-1}，血清TG水平下降0.29 mmol·L^{-1}，HDL-C水平升高0.06 mmol·L^{-1}[12]。另一项针对2型糖尿病合并高ASCVD风险患者的开放标签随机对照试验表明，姜黄素联合常规治疗组较单用常规治疗组LDL-C水平多降低约20%，且ASCVD风险分类改善幅度显著优于对照组[99]。然而，在非糖尿病性高胆固醇血症患者中，姜黄素的降脂效应相对较弱，提示其疗效与糖脂代谢紊乱的严重程度密切相关。多项Meta分析显示，每日补充80~1 500 mg姜黄素可显著降低TC水平[100]；但超过一定剂量后反而可能因其生物利用度饱和而限制疗效。安全性方面，系统评价显示姜黄素不良反应轻微且与安慰剂组相似，主要为胃肠道不适，未发现严重肝肾功能异常[101]。姜黄素还可通过抑制肾脏药物转运体有机阴离子转运多肽4C1（OATP4C1），影响联合用药的药代动力学[102]。此外，姜黄素可竞争性抑制肝细胞膜上的有机阴离子转运多肽1B1（OATP1B1）转运体，使他汀类药物的血浆药物浓度-时间曲线下面积增加，显著提高肌病及横纹肌溶解的发生风险，尤其在与高剂量他汀联用或应用于溶质载体有机阴离子转运家族成员1B1（SLCO1B1）基因多态性个体时需格外谨慎[103-104]。这些发现凸显了基于代谢表型和微生物组特征制定个体化给药策略的必要性。

3.2 联合用药策略与临床转化挑战 姜黄素的多靶点调节特性为其与传统降脂药物的联合应用提供了协同治疗潜力，然而其复杂的药代动力学相互作用及疾病病理异质性仍是临床转化面临的主要挑战。姜黄素通过抑制肠道NPC1L1蛋白减少胆固醇吸收，并下调PCSK9表达，从而在混合性高脂血症患者中辅助降低LDL-C水平[105]。一项为期12周的随机双盲安慰剂对照试验发现，姜黄素可显著改善糖尿病高风险人群的胰岛素敏感性并降低空腹胰岛素水平，而长链ω-3多不饱和脂肪酸则在降低TG方面效果更为显著；尽管联合干预未表现出协同增效，但两种补充剂分别从糖代谢和脂代谢角度为2型糖尿病预防提供了互补策略[106]。另一项针对多囊卵巢综合征女性的因子设计试验表明，姜黄素与二甲双胍联合治疗在改善血脂谱、体重控制、胰岛素抵抗及性激素平衡方面均优于单一药物治疗，凸显出其在代谢-内分泌共病管理中的协同价值[107]。此外，一项在2型糖尿病患者中开展的随机对照试验显示，在格列美脲基础上联合姜黄素或非诺贝特均可显著改善血脂异常和炎症指标，但非诺贝特在升高HDL-C、降低腰围及胎球蛋白A（Fetuin-A）水平方面表现更优，提示姜黄素在合并高脂血症的糖尿病患者中可作为辅助抗炎降脂选择，而非诺贝特则更适用于心血管风险显著升高的人群[108]。姜黄素对类固醇生成途径中的细胞色素P450酶系具有抑制作用，体外研究证实，姜黄素可显著抑制细胞色素P45017A1酶（P45017A1）活性，并对细胞色素P45019A1产生剂量依赖性抑制，可能影响内源性类固醇激素的合成与代谢平衡[109]。

此外，姜黄素的生物利用度限制仍是其临床转化的主要瓶颈，这也催生了多种新型递送系统的开发。研究表明，纳米递送策略（如脂质体、聚合物纳米粒、纳米乳剂等）可通过增强胃肠溶解性、延缓肝代谢，以及实现组织靶向递送，显著改善其药代动力学特征。脂质体与牛奶外泌体通过脂质双分子层模拟细胞膜，显著促进跨膜转运与肠道吸收，规避首过效应，研究显示其生物利用度可比普通姜黄素提升7~9.5倍[110-111]；聚合物纳米粒则通过控制释放与增强渗透滞留效应实现长效循环与靶组织富集，动物模型中其肝组织药物浓度可提升2.6倍[112-113]；纳米乳剂与胶束利用表面活性剂将其包裹为水分散性颗粒，显著改善溶解性问题，使口服生物利用度提升30倍以上[114-116]。然而，这些递送系统的长期安全性、大规模生产的稳定性与成本效益，仍是实现其广泛应用前必须攻克的难题。当前仍缺乏针对姜黄素响应者的生物标志物体系，无法精准识别最可能获益的优势人群，这限制了其临床精准应用，未来需通过药物基因组学指导下的个体化给药方案优化联合治疗策略，并开发靶向递送系统以提升组织特异性，最终实现姜黄素从多靶点调控向临床精准治疗的转化。

4 总结与展望

姜黄素作为一种天然多酚化合物，凭借其多靶点、多维度的药理特性，在高脂血症治疗领域中展现出系统性的调控优势，为突破传统单靶点降脂药物的局限性提供了新路径。本综述系统阐释了姜黄素通过协同调控LDLR/PCSK9胆固醇逆转运、PPARα/γ糖脂代谢稳态、肠道菌群-胆汁酸轴、NF-κB炎症反应及Nrf2/ARE抗氧化信号通路等重要机制，综合改善脂质代谢紊乱的网络化作用模式。值得注意的是，姜黄素的多靶点特性不仅限于脂代谢调节，其在NAFLD、2型糖尿病及其血管并发症、肥胖相关代谢炎症等多种代谢性疾病的干预中也显示出广阔的应用前景。尤其在与肠道菌群-免疫-代谢轴的交叉调控中，姜黄素可能通过调节肠源

性代谢物影响远端器官功能[117]，从而在MAFLD、胰岛素抵抗综合征甚至慢性肾病中发挥治疗作用。近年来研究还发现，姜黄素在改善微量白蛋白尿、延缓动脉钙化及减轻非酒精性脂肪性肝炎纤维化方面同样表现出潜在效益，这为其跨代谢血管疾病的整体管理提供了依据。特别是在心力衰竭保留射血分数和肥胖相关高血压等心血管代谢交叉领域，姜黄素通过同时改善内皮功能、抑制心肌纤维化和调节交感神经活性，展现出多维度心脏保护潜力。系统分析显示，姜黄素制剂可降低TC、TG及LDL-C，同时提升HDL-C胆固醇，在非酒精性脂肪肝等部分患者亚群中部分指标改善更明显[99]。此外，其改善血管内皮功能及减轻肝脂肪变性的作用也为其在代谢综合征管理中的综合应用提供了依据。然而，当前研究仍存在若干亟待突破的问题：①姜黄素与PCSK9抑制剂、SGLT2抑制剂等新型药物的协同效应机制尚未明确，尤其对RC和代谢性炎症的调控仍需高质量临床证据支持；②虽临床前研究提示其可通过调节肠道菌群-胆汁酸-FXR轴改善糖脂代谢，但在人群中的因果机制仍需借助多组学整合分析予以验证；③不同递药系统的药代动力学特性与靶组织蓄积能力差异显著，需建立基于病理表型的精准递送策略。未来研究应着力于以下方向：推进基于药物基因组学和微生物组特征的个体化用药方案；开展多中心、大样本随机对照试验，明确姜黄素在动脉粥样硬化性心血管疾病一级与二级预防中的长期疗效与安全性。通过多学科交叉融合策略，推动姜黄素成为高脂血症精准防治体系中的重要组成部分，为代谢性疾病的系统干预提供新范式。

[利益冲突] 本文不存在任何利益冲突。

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