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基于脂质沉积抑制-代谢清除协同效应的黄连素抗动脉粥样硬化机制研究进展

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摘要：动脉粥样硬化（atherosclerosis，AS）作为心脑血管疾病的主要病理基础，已成为重大公共卫生挑战。现有治疗药物在调控脂质代谢紊乱与炎症反应失衡的协同效应方面存在局限，促使研究者转向具有多靶点调控特性的天然药物。黄连素作为代表性的天然化合物，通过对脂质的“沉积抑制-代谢清除”双重机制发挥抗 AS 作用。本文论述了黄连素在 AS 病理进程中调控脂质-炎症网络失衡的作用机制与分子特征，并评述了其临床转化潜力，旨在为突破现有单靶点药物疗效瓶颈提供理论依据和策略指导。

关键词：黄连素；动脉粥样硬化；脂质代谢；胆固醇；巨噬细胞
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Research progress on the mechanism of berberine's anti-atherosclerosis effects based on the synergistic effect of lipid deposition inhibition and metabolic clearance

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Abstract: Atherosclerosis (AS), the primary pathological basis of cardiovascular diseases, poses a growing global public health challenge. Current therapies face limitations in synergistically addressing lipid metabolism disorders and inflammatory dysregulation, prompting exploration of multi-target natural agents. Berberine, a natural compound, combats AS through dual mechanisms: suppressing cholesterol biosynthesis, enhancing reverse cholesterol transport, and inhibiting macrophage foam cell formation to reduce arterial lipid deposition; while improving lipoprotein homeostasis and activating fatty acid β-oxidation to diminish visceral fat accumulation. These actions collectively prevent AS progression, ameliorate metabolic syndrome, and alleviate hepatic lipotoxicity. This review elucidates berberine's molecular mechanisms in rebalancing lipid-inflammatory networks during AS pathogenesis and evaluates its clinical

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potential, offering novel strategies to overcome single-target drug limitations.

Key words: Berberine; Atherosclerosis; Lipid metabolism; Cholesterol; Macrophages

动脉粥样硬化（atherosclerosis, AS）是一种由脂质-炎症循环驱动，以动脉壁脂质病理性沉积及斑块动态演化为主要病理特征的慢性血管病变，是导致心血管疾病的主要病理基础[1-3]。脂质代谢紊乱在AS的发生发展中扮演了关键角色，是预防和治疗AS的主要干预方向[4-7]。天然药物因其因其多靶点协同调控的特性，在克服单靶点药物局限性方面展现出独特优势而受到广泛关注[8-10]。黄连素是一种异喹啉类生物碱，具有降脂、抗炎、抗氧化及改善胰岛素抵抗等药理活性[11-15]。研究表明，黄连素能通过抑制胆固醇吸收、调节胆固醇合成与逆向转运、增强巨噬细胞胆固醇外流、调节脂蛋白代谢以及促进脂质氧化分解等多种途径减少体内脂质沉积[16-18]，在重构脂质代谢-炎症稳态方面展现了出独特优势。

当前针对天然药物抗AS的研究多聚焦单一代谢通路或临床疗效评价，缺乏对“脂质沉积-清除”动态平衡的系统解析及转化医学视角的整合。本文整合近五年基础研究与临床试验证据，提出黄连素对脂质“沉积抑制-代谢清除”的双向调控理论框架，系统阐述了AS病理进程中脂质代谢紊乱的分子机制、黄连素多靶点调控脂质-炎症网络的作用特征和黄连素的临床转化及药效评价，旨在为开发靶向代谢-炎症网络的新型抗AS药物提供理论依据和策略参考。

1 AS与脂质代谢的关系

1.1 脂质代谢的生物学基础

脂质代谢是维持机体能量稳态与细胞功能的核心生化过程，其动态平衡的破坏与AS的发生发展密切相关[19]。根据代谢来源，脂质代谢可分为外源性与内源性两条主要途径。

1.1.1 外源性脂质代谢

外源性脂质代谢始于膳食脂质的消化吸收。食物中的三酰甘油（triglyceride, TG）在小肠内经胰脂酶水解为游离脂肪酸（free fatty acid, FFA）和单酰甘油（monoacylglycerol, MAG），随后与胆汁酸盐形成混合微胶粒，被肠上皮细胞摄取并重新酯化为TG。TG与载脂蛋白B-48组装成乳糜微粒（chylomicron, CM），经淋巴系统进入血液循环。在毛细血管内皮细胞表面，脂蛋白脂酶（lipoprotein lipase, LPL）催化CM核心TG水解，释放FFA供外周组织利用或储存，残余CM最终被肝脏摄取清除[20]。

1.1.2 内源性脂质代谢

内源性脂质代谢主要由肝脏调控，其底物为内源性TG和胆固醇。肝脏合成的TG与载脂蛋白B-100（ApoB-100）在微粒体三酰甘油转移蛋白（microsomal triglyceride transfer protein, MTP）介导下组装为极低密度脂蛋白（very low-density lipoprotein, VLDL），分泌入血后经脂蛋白脂肪酶（lipoprotein lipase, LPL）逐步，转化为中间密度脂蛋白（intermediate-density lipoprotein, IDL）和低密度脂蛋白（low-density lipoprotein, LDL）[21]。LDL作为胆固醇的主要载体，通过低密度脂蛋白受体（low-density lipoprotein receptor, LDLR）介导的内吞作用向组织递送胆固醇；高密度脂蛋白（high-density lipoprotein, HDL）则通过逆向胆固醇转运（reverse cholesterol transport, RCT）将外周细胞过剩的胆固醇运回肝脏代谢排泄。该过程依赖腺苷三磷酸结合盒转运体（adenosine triphosphate-binding cassette transporter, ABC）A1/G1和卵磷脂胆固醇酰基转移酶（lecithin-cholesterol acyltransferase, LCAT）等关键分子[22-23]。

脂质代谢的稳态由关键酶（如LPL、MTP、LCAT）、载脂蛋白（如ApoB-100、ABCA1）及受体（如LDLR）精密调控[21]。其功能紊乱可导致脂质蓄积、氧化修饰及泡沫细胞形成，进而促进AS斑块进展。

1.2 脂质代谢紊乱促进AS的分子机制

1.2.1 脂质代谢紊乱的表型与成因

脂质代谢紊乱主要表现为低密度脂蛋白胆固醇（low-density lipoprotein cholesterol, LDL-C）和TG水平升高以及高密度脂蛋白胆固醇（high-density lipoprotein cholesterol, HDL-C）功能缺陷。其成因包括遗传因素（如LDL受体基因突变）、饮食因素（高饱和脂肪摄入）及代谢性疾病（如胰岛素抵抗）。其中，LDL-C过载促进胆固醇向动脉内膜的渗透沉积，而HDL功能受损导致RCT障碍，共同形成促AS的脂质微环境[24-25]。

1.2.2 关键调控节点的功能紊乱

脂质代谢稳态的维持依赖于酶-受体网络的精密调控，其核心节点的功能紊乱将直接引发导致脂质失衡。具体表现为：①LPL活性下降会显著降低

内皮细胞 CM 和 VLDL 中 TG 的水解效率,导致具有致 AS 的 CM 残粒在循环系统中异常蓄积[26];②肝脏MTP 的过表达会促进 VLDL 的过度组装,增加 ApoB-100 分泌,进而升高血浆 TG 水平并加速血管壁脂质沉积[27-29];③LDLR 功能功能缺陷(如家族性高胆固醇血症)会严重损害肝脏对 LDL-C 的清除,造成循环 LDL-C 蓄积并促进其氧化修饰氧化低密度脂蛋白(oxidized low-density lipoprotein, ox-LDL)的形成[30];④巨噬细胞中 ATP 结合盒转运体 A1(ABCA1)表达受抑制会阻碍胆固醇向载脂蛋白 A-I(apolipoprotein A-I, ApoA-I)的外流,影响 HDL 的生成并降低 RCT 效率[31];⑤过度激活的分化簇 36(cluster of differentiation 36, CD36)、清道夫受体 A 类成员 1(scavenger receptor class A member 1, SR-A1)清道夫受体会介导 ox-LDL 的大量内吞,从而加速巨噬细胞向泡沫细胞的转化[32]。

1.2.3 AS 的病理级联反应

脂质代谢紊乱通过 3 条途径驱动 AS 进展。①脂质氧化与内皮激活:滞留于动脉内膜的 LDL 被髓过氧化物酶(myeloperoxidase, MPO)氧化为 ox-LDL,激活内皮细胞表达血管细胞黏附分子-1(vascular cell adhesion molecule-1, VCAM-1)、细胞间黏附分子-1(intercellular adhesion molecule-1, ICAM-1)等黏附分子,促进单核细胞浸润血管壁[33]。②泡沫细胞形成与斑块扩张:浸润的巨噬细胞通过清道夫受体吞噬 ox-LDL,在 ABCA1/ABCG1介导的胆固醇外流障碍背景下转化为泡沫细胞,构成斑块脂质核心[32]。③炎症-代谢恶性循环:泡沫细胞释放白细胞介素-1β(interleukin-1β, IL-1β)、肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)等促炎因子,进一步抑制 LPL 活性并促进肝脏 VLDL 分泌,形成“脂质蓄积→炎症放大→代谢紊乱”的正反馈环路,最终导致斑块不稳定性增加和临床事件[34]。

2 黄连素调控 AS 相关脂质代谢的作用机制

2.1 减少脂质沉积

2.1.1 抑制胆固醇吸收

黄连素可从以下 4 条途径协同调控胆固醇代谢的关键环节,干预 AS 相关的脂质蓄积进程:①通过细胞外信号调节激酶(extracellular signal-regulated kinase, ERK)依赖性途径上调肝细胞 LDL 受体 LDLR 的 mRNA 和蛋白表达水平,促进循环中 LDL-C 的肝脏摄取和代谢,促进肝脏胆固醇清除[35];②竞争性结合尼曼-匹克 C1 型类似蛋白 1(Niemann-Pick C1-like 1, NPC1L1)蛋白[36-37],有效阻断小肠上皮细胞对膳食胆固醇的吸收,并调节肠道菌群组成(如增加产短链脂肪酸菌丰度),增强肠道屏障功能,减少肠源性脂质的异常渗漏,抑制肠道胆固醇吸收;③激活 AMPK,抑制过氧化物酶体增殖物激活受体 γ(peroxisome proliferator-activated receptor gamma, PPARγ)/CD36 通路,同时激活肝 X 受体 α(liver X receptor alpha, LXRα)/ABCA1-SR-BI 轴[38],实现对巨噬细胞脂质摄取与外流的双向调控,调控巨噬细胞脂质代谢;④抑制核因子 κB(nuclear factor kappa-B, NF-κB)并激活核因子 E2 相关因子 2(nuclear factor erythroid 2-related factor 2, Nrf2)通路,阻断氧化应激对 HDL 功能的损害,进而增强 HDL 介导的逆向胆固醇转运效率[38]。

2.1.2 调节胆固醇代谢

黄连素可以通过多靶点协同调控胆固醇代谢稳态,有效改善 AS 相关的脂质代谢紊乱:①激活 AMP 活化蛋白激酶(AMP-activated protein kinase, AMPK)信号通路,抑制 3-羟基-3-甲基戊二酰辅酶 A(3-hydroxy-3-methylglutaryl coenzyme A, HMG-CoA)还原酶活性[38],并经由 AMPK/沉默调节蛋白 1(sirtuin 1, SIRT1)轴调控脂质代谢网络,减少肝脏胆固醇的从头合成[39];②上调肝细胞 LDL 受体(LDLR)表达的同时抑制前蛋白转化酶枯草溶菌素 9(proprotein convertase subtilisin/kexin type 9, PCSK9)功能以阻断 LDLR 降解,协同提高血浆 LDL-C 的清除效率[39];③激活 AMPK/固醇调节元件结合蛋白 2(sterol regulatory element-binding protein 2, SREBP2)/PCSK9 通路,促进四氢小檗碱(tetrahydroberberine, THBru)等活性代谢产物改善脂蛋白组成,降低致 AS 性残余胆固醇水平[40],协同调控脂蛋白代谢。Cicero 等[41]研究显示,黄连素在啮齿类动物模型中可降低总胆固醇及 LDL-C 水平,其降脂效果与洛伐他汀相当,还同时兼具抗氧化与抗炎的独特优势。

2.1.3 促进胆固醇逆向转运

黄连素主要通过以下 3 条途径增强胆固醇逆向转运效率:①结合法尼醇 X 受体(farnesoid X receptor, FXR),上调胆盐输出泵(bile salt export pump, BSEP)表达,促进胆固醇向胆汁酸转化,并抑制肠道胆盐水解酶活性,增加牛磺胆酸等亲水性胆汁酸比例,减少肝脏的脂肪酸摄取[42-43];②降低梭菌属等有害菌群的丰度减少次级胆汁酸生成,以及促进如 *Blautia producta* 等有益菌群的增殖上调肝脏 LDLR

表达，协同增强脂质清除能力[44]，重塑菌群-代谢互作；③激活代谢调控网络：通过激活 PI3K/AKT/mTOR 通路调控自噬，促进胆固醇酯水解及 ABCA1/ABCG1 介导的胆固醇外流，协同改善脂质代谢稳态并抑制炎症反应，从而增强胆固醇逆向转运效率[45]。这种独特的“胆汁酸代谢优化-菌群调控”双途径作用模式，为 AS 治疗提供了新的天然药物干预策略。

2.1.4 调控脂质清除网络

黄连素主要通过 3 条途径改善动脉粥样硬化斑块稳定性，减少 AS 斑块沉积：①双重调控程序性死亡通路（抑制溶质载体家族 7 成员 11/谷胱甘肽过氧化物酶 4 轴诱导铁死亡，激活 PTEN 诱导的假定丝氨酸/苏氨酸蛋白激酶 1/E3 泛素蛋白连接酶通路促进线粒体自噬）选择性清除脂质过载的巨噬细胞，并显著增强 Caspase-3 介导的凋亡清除能力[46]；②抑制梭菌属介导的胆碱-三甲胺-氧化三甲胺转化，降低血浆氧化三甲胺水平，减轻氧化三甲胺驱动的血管内皮炎症损伤[47]；③激活 NRF2 抗氧化信号通路和抑制 PI3K/AKT/mTOR 信号通路以稳定斑块微环境，缩小斑块脂质核心体积并改善血管内膜增生[45]。这种“细胞清除-代谢重塑-斑块稳定”三位一体调控模式突破了传统单一靶点药物的局限，为 AS 治疗提供了新的多靶点干预策略。

2.2 促进脂质清除

2.2.1 增强巨噬细胞胆固醇外流

黄连素可通过 3 条途径的协同作用，改善巨噬细胞胆固醇代谢平衡：①上调巨噬细胞 ABCA1 与 ABCG1 的表达，促进游离胆固醇转移至 HDL 颗粒，减少细胞内脂质蓄积；②抑制血清淀粉样蛋白 A（serum amyloid A，SAA）对 HDL 的修饰作用，提升 HDL 介导的胆固醇逆向转运效率[48]，提升胆固醇的清除能力；③下调清道夫受体 CD36 表达并抑制 NF-κB 信号通路活化，阻断 ox-LDL 的内吞及 NLRP3炎症小体的激活[49]。临床证据显示，黄连素干预可使 $ApoE^{-/-}$ 小鼠主动脉斑块脂质沉积减少，并显著降低冠心病患者循环炎症标志物[48]。黄连素的“外流增强-摄取抑制-功能修复”协同调控机制，能有效重塑 AS 斑块微环境的脂质代谢稳态。

2.2.2 调控脂蛋白代谢稳态

黄连素可通过多途径协同作用改善脂蛋白代谢稳态，主要包括以下 3 个方面：①激活 PPARα 信号通路，上调肝细胞 CPT-1A 表达[50]，促进脂肪酸 β 氧化，降低肝 TG[51]；②提高 LPL 活性，加速 CM 和 VLDL 核心 TG 水解，减少致 AS 残粒脂蛋白的蓄积[51]；③激活 Nrf2/ARE 抗氧化通路并抑制 TLR2/MyD88/NF-κB 炎症信号通路，协同减轻脂质过氧化诱导的血管内皮损伤[52]。动物实验表明，黄连素可降低高脂模型血清 TG 及 VLDL[13]，并在罗非鱼肝损伤模型中逆转脂质过氧化 MDA 表达[50]。

2.2.3 激活脂质氧化分解通路

黄连素可通过“宿主-菌群”协同作用机制，实现对脂质能量代谢的多维度调控：①激活 AMPK 信号通路，上调肉碱棕榈酰转移酶 1（carnitine palmitoyltransferase 1，CPT-1）表达[53]，促进脂肪酸进入线粒体 β 氧化途径，降低肝脏游离脂肪酸（free fatty acid，FFA）含量；②下调硬脂酰辅酶 A 去饱和酶 1（stearoyl-CoA desaturase 1，SCD1）与脂肪酸结合蛋白 1（fatty acid-binding protein 1，FABP1）蛋白表达，阻断新生脂质的合成及细胞内转运过程[54]；③重塑菌群代谢轴：选择性富集如 Roseburia 等产丁酸菌，经由其代谢产物丁酸激活肠道 PPARγ-LXRα 通路，协同增强肝脏脂质清除能力[52]。在高脂饮食 $ApoE^{-/-}$ 模型中，黄连素干预使主动脉斑块脂质核心体积缩小，肝脂肪变性面积减少，并改善胰岛素敏感性[55]。其通过“宿主代谢-菌群调控”协同网络，实现脂质氧化分解的全系统增效。

2.3 临床转化与药效评价

黄连素通过“脂质代谢重编程-菌群稳态调控”双轴协同，在 AS 临床管理中展现多维度疗效。①降脂效能：降低高胆固醇血症患者总胆固醇（total cholesterol，TC）、LDL-C 及 TG，并提升 HDL-C 水平，其效果在高遗传风险个体中尤为显著[56]。②代谢-菌群协同调控：调控肠道菌群结构，抑制 TMAO 生成；激活 AMPK 通路抑制肝脏糖异生，改善糖尿病合并 AS 患者的糖脂共代谢紊乱[55]。③终点事件预防：在边缘性高脂血症人群中，黄连素干预（500 mg/d）12 周可使心血管事件风险评分降低[49]；多基因高胆固醇血症患者使用含黄连素的复方制剂（如 Armolipid Plus®）后，LDL-C 达标率提升[56]。上述研究结果共同表明，黄连素可通过“降脂-抗炎-稳斑”三位一体机制突破传统疗法的局限性，为 AS 精准干预提供天然药物新范式。

3 小结与展望

黄连素作为天然药物在 AS 领域的研究已从单一降脂机制转向“代谢-炎症-菌群”多维调控网络的探索，其临床转化潜力逐渐获得学界认可。在临床转化方面，黄连素降低 LDL-C 和提升 HDL-C 的

疗效已获得多项随机对照试验证实[26]。然而,其药理学特性中存在一个引人深思的"黄连素悖论":尽管口服生物利用度极低(<1%),却展现出显著的临床疗效,这一现象促使研究者重新审视肠道局部作用及菌群代谢产物的关键贡献[26]。目前对黄连素的研究已拓展至糖尿病合并 AS、非酒精性脂肪肝及肠道菌群失调相关疾病的综合管理[55]。特别是 Wu 等[52]研究发现,黄连素可通过特异性富集产丁酸菌增强肠道屏障功能,"肠-血管轴"理论提供了直接证据,也为代谢性心血管疾病的防治开辟了新途径。

当前研究仍面临机制研究的系统性和临床转化的精准性两个挑战。尽管黄连素激活 AMPK、上调 LDLR 等单一路径已得到阐明[38-40,45,55],但其多靶点协同作用的时空动态特征仍不明确,导致难以建立精准给药方案。临床研究显示,受试者间的疗效差异可能源于剂量差异、遗传背景及肠道菌群基线特征等因素[56],而关于斑块稳定性和心血管硬终点的长期证据仍显不足。未来研究的突破方向应聚焦于:①开发既能提高生物利用度,又能保留菌群调控功能的新型递药系统;②运用空间转录组和代谢流分析等技术,揭示"宿主-菌群"互作网络的关键节点;③设计基于生物标志物(如肠道菌群特征、NPC1L1 多态性)的精准化临床试验,重点关注斑块体积、纤维帽厚度等影像学终点。

综上所述,作为多靶点天然药物的代表,黄连素为 AS 治疗提供了新思路,但要实现其全面临床应用,仍需构建完整的"机制阐明-疗效预测-方案优化"证据链。未来的核心任务是将经验性用药转转化为精准医学实践,通过建立跨尺度、多维度的研究体系,推动天然药物从基础研究到临床应用的全程创新。

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