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部分天然药物通过调节肠道胆固醇代谢途径防治心血管疾病的作用机制

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[关键词]　天然药物；　肠道胆固醇代谢；　脂代谢紊乱；　心血管疾病

[摘　要]　肠道胆固醇代谢与心血管疾病的发生发展密切相关，调控肠道胆固醇代谢平衡可有效降低心血管事件。天然药物通过调控肠道胆固醇的吸收与转运、调节菌群平衡等途径有效改善肠道胆固醇代谢水平。文章对近年来天然药物调控肠道胆固醇代谢抑制心血管疾病的作用与机制进行了综述，以期为脂代谢紊乱所致心血管疾病的防治提供借鉴。

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The function and mechanism about some natural medicine controlling cardiovascular disease by regulating intestinal cholesterol metabolism

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[**KEY WORDS**]　natural medicine;　intestinal cholesterol metabolism;　dyslipidemia;　cardiovascular disease

[**ABSTRACT**]　The occurrence and development of cardiovascular disease are closely related with intestinal cholesterol metabolism, so cardiovascular events can be efficiently reduced by regulating intestinal cholesterol metabolism balance. Natural medicines can regulate cholesterol metabolism level by regulating cholesterol absorption and transport in intestinal tract.　So all natural medicines which suppressed cardiovascular disease by regulating cholesterol metabolism were summarized in recent years in order to provide reference for the prevention and treatment for cardiovascular disease induced by dyslipidemia.

血脂代谢异常与心血管疾病(cardiovascular disease，CVD)发生发展密切相关，其中高胆固醇血症(hypercholesteremia)是致动脉粥样硬化(atherosclerosis，As)的独立危险因素，是心脑血管疾病的重要诱因。机体胆固醇主要来源于肝脏自身合成、肠道的吸收和分泌等途径。肠道(intestinal tract)作为胆固醇代谢的主要场所，参与胆固醇的吸收、转化、排泄与部分合成，协同肝脏维持机体胆固醇内稳态[1]。若肠道功能失衡，体内胆固醇含量过高，会引发动脉硬化性心血管疾病[2]。因此，肠道成为心血管疾病的治疗靶点，研发调控肠道胆固醇内稳态的药物成为防治高胆固醇血症和心血管疾病的新方向。研究显示，肠道胆固醇稳态主要通过以下途径调节(图 1)：①控制肠道对胆固醇的吸收是维持全身胆固醇稳态的重要途径[3]：经典药物或过氧化物酶体增殖物激活受体 α(peroxisome proliferator-activated receptor α，PPARα)与肝 X 受体(liver X receptor，LXR)的激动剂可选择性抑制尼曼-匹克 C1 型类似蛋白 1(niemann-pick C1-like 1，NPC1L1)活性或表达，有效降低肠道胆固醇吸收[4-5]；LXR 也可以通过抑制肠道中酰基辅酶 A：胆固醇酰基转移酶 2(acy1-CoA-cholesterol acyltransferase 2，ACAT2)表达降低血浆胆固醇吸收[6]。②促进肠道胆固醇逆转运：临床药物或 PPARα 与 LXR 的激动剂可通过

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增强肠道 ATP 结合盒转运体(ATP-binding cassette transportters, ABC) A1/G1/G5/G8 表达促进胆固醇逆转运(reverse cholesterol transport, RCT)[7],完成肝脏与小肠对胆固醇的净排泄[8]。③饮食或药物干预调节肠道菌群平衡是调控肠道胆固醇内稳态的另一重要途径:肠道菌群(gut microbiota, GMB)是人体不可或缺的"微生物器官",在调控心血管疾病危险因素中发挥重要作用[9-10]。目前,他汀类药物是临床降胆固醇的首选药物,却有致肌肉疼痛、神经紊乱、消化系统疾病或肝功能受损[11]等毒副作用,部分病人难以接受高剂量药物治疗的风险。该类药物的耐药性和不耐受越来越受到关注,天然药物因在调控胆固醇代谢方面发挥重要作用而逐渐走进大家的视野。天然药物主要来自植物、动物、矿物、海洋生物及微生物等天然物质。在中国,绝大部分天然药物都是指植物类药物。天然药物主要通过抑制肠道对胆固醇的吸收、降低机体内源性胆固醇的合成、调控机体胆固醇外运、促进肝脏对胆固醇的排泄、调节机体与脂代谢相关转运体等功能发挥脂代谢调控功能[12]。与经典西方药物相比,天然药物在降胆固醇疗效及毒副作用等方面存在显著优势。现将天然药物调控肠道胆固醇内稳态的作用机制综述如下。

1 天然药物抑制肠道胆固醇吸收的作用与机制

肠道对胆固醇的吸收主要来自饮食和胆汁,机体非高密度脂蛋白(non-high density lipoprotein cholesterol, non-HDLC)水平与胆固醇的吸收正相关。NPC1L1 是主要分布于十二指肠、空肠和近端回肠的肠上皮细胞刷状缘膜及人类肝细胞微管膜上的多面体跨膜蛋白,对肠道吸收胆固醇有重要作用[13-14],NPC1L1 吸收胆汁酸(bile acid, BA)乳化后的胆固醇进入肠上皮细胞,再转移至内质网,在 ACAT2 催化下重新形成胆固醇酯(cholesteryl ester, CE),大部分 CE 在微粒体甘油三酯转移蛋白(microsomal triglyceride transfer protein, MTP)作用下,与载脂蛋白 B48(apolipo protein B48, ApoB48)、甘油三酯(triglyceride, TG)、磷脂(phospholipid, PL)等组成乳糜微粒(chylomicron, CM),经基底膜进入淋巴循环[7]。未被 ACAT2 酯化的胆固醇部分经 ABCG5/G8 被选择性的分泌回肠腔,而游离胆固醇在 ABCA1 作用下,与胞外载脂蛋白 A1(apolipoproteinA1, ApoA1)结合形成高密度脂蛋白(high-density lipoprotein, HDL)微粒,进入淋巴循环参与胆固醇逆转运(reverse cholesterol transport, RCT)[7]。这是肠道胆固醇吸收与排泄的主要途径。

目前发现,天然药物中提取的蒽醌类、酚类、萜类、生物碱类化合物及多糖对肠道胆固醇吸收具有抑制作用(图 2)。黄连素和茜草素的降胆固醇活性显著:黄连素通过抑制小肠和 CaCo-2 细胞中 ACAT2 基因与蛋白的表达,阻止肠道对胆固醇的吸收,降低了血液中胆固醇和 non-HDLC 水平,从而延缓了动脉粥样硬化[15]。黄连素除调控肝脏相关因子抑制胆固醇合成与代谢之外,还通过抑制肠道胆盐水解酶、升高牛黄胆酸和激活肠道 LXR、FXR 信号通路等途径降低胆固醇吸收[16]。除单独用药外,黄连素联合吴茱萸碱,显著降低 NPC1L1 和 ACAT2 表达,抑制小肠对胆固醇的吸收[17]。由此可见,黄连素联合用药将成为降低高剂量他汀类药物不良反应的良好选择,黄连素联合辛伐他汀已应用于临床[18]。茜草根中提取分离的茜草素可通过抑制 ACAT 活性,降低小鼠腹腔巨噬细胞的脂质积累[19]。姜黄素是一种来自于中药姜黄的多酚类活性物质,动物与人群实验均证明姜黄素具有良好的降胆固醇效果,目前尚未发现其不良毒副作用,其机制是姜黄素限制了肠道 Caco-2 细胞中 NPC1L1 基因与蛋白的表达[20],上述机制是姜黄素通过调控胆固醇调节元件结合蛋白 2(cholesterol regulatory element binding protein-2, SREBP-2)限制 NPC1L1 表达完成的[21]。萜类物质具有显著降血脂作用,研究仓鼠和 CaCo-2 细胞发现,山楂中的活性物质齐墩果酸和熊果酸通过抑制肠道 ACAT2 活性降低肠道胆固醇吸,降低血浆中 8% 的 non-HDLC[22]。植物甾醇的降脂作用非常显著,血脂康通过其主要成分植物甾醇抑制 NPC1L1 表达降低了小肠对外源性胆固醇的吸收[23],对高脂饮食诱导小鼠体内胆固醇代谢平衡发挥了重要作用。肠上皮细胞 CaCo-2 实验显示,咖啡浆果的提取物通过激活 LXR 活性抑制 NPC1L1 表达降低胆固醇的吸收[24],来源于草决明种子的水溶性多糖可通过结合胆汁酸降低肠道对胆固醇的吸收[25]。

2 天然药物调控肠道胆固醇转运的作用与机制

人类粪便中排出的胆固醇除来源于肠道中的食物之外,还来源于两个部分:肝胆管的排泌和小

肠直接分泌[26]。应用 LXR 的激动剂后,加速了肠道对胆固醇的直接分泌[27-28]。LXR 通过促进 ABCA1/G1、ABCG5/G8 表达促进 RCT[7],完成肝脏与小肠对胆固醇的净排泄[8]。

研究发现,部分天然药物来源的生物碱、酚类、异黄酮类、植物甾醇、皂苷类化合物及多糖等可调控肠道胆固醇排泄。黄连素与植物甾醇联合用药,除通过抑制胆固醇吸收调节肠道胆固醇平衡外,还可通过促进 ABCG5/G8 在小肠的表达等途径降低机体胆固醇水平从而抑制动脉粥样硬化的发生与发展[29]。研究显示,单独用药辛伐他汀降胆固醇 30.8%,而 300 mg/kg 姜黄素联合 2.5 mg/kg 辛伐他汀可降胆固醇 46.4%[30],姜黄素通过 AMPK-SIRT1-LXR 信号途径上调 ABCA1 的表达促进了胆固醇外流[32],从而发挥了协助他汀类药物降胆固醇的功能。葛根素是来自于野生葛根的异黄酮类衍生物,广泛应用于心血管疾病。葛根素不仅通过调节肝脏中胆固醇 7α-羟化酶(cholesterol 7α-hydroxylase,CYP7A1)、三羟基三甲基戊二酸单酰辅酶 A(3-hydroxy-3-methyl glutaryl coenzyme A reductase,HMG-CoA)和低密度脂蛋白受体(low density lipoprotein receptor,LDLR)表达降低胆固醇水平,还可通过 AMPK-PPARγ-LXRα-ABCA1 信号通路促进胆固醇外流,降低细胞内胆固醇[32]。血脂康通过其主要成分异黄酮抑制小肠有机可溶性转运体 α/β 的 mRNA 表达调控肠道胆汁酸代谢平衡[23]。近期有研究报道白藜芦醇激活 PPARα/γ 信号通路促进 ABCA1/G1 表达,介导了胆固醇外流,进而抑制动脉硬化性小鼠肠道对脂肪酸和单脂肪酸甘油酯的吸收累积[33]。大豆胚芽油富含植物甾醇和多不饱和脂肪酸,显著抑制仓鼠小肠 NPC1L1 与 MTP 的表达,升高 ABCG5 水平从而降低了小肠对胆固醇的吸收,抑制了动脉斑块的生成[34]。虽然薯蓣皂苷元对小肠 ABCG5/8 及 NPC1L1 表达未见显著影响,但饮食或药物中补充薯蓣皂苷后促进了粪便中胆固醇的排泄[35-36],其相关机制仍待进一步探讨。褐紫菜中提取的岩藻多糖通过抑制小肠 NPC1L1 表达降低了机体从肠腔和胆汁酸吸收胆固醇,并通过促进小肠 ABCG5/G8 表达加速胆固醇的排泄[37]。燕麦纤维通过 PPARα/LXRα 途径抑制 NPC1L1 表达降低小肠对胆固醇的吸收,并上调 ABCA1、ABCG1/G8 蛋白促进了肠道胆固醇外流[38]。大蒜通过抑制 MTP 基因表达降低了肠内乳糜微粒的合成与分泌,限制了血液循环转移,从而降低了肠道胆固醇吸收、分泌及至血液循环转移[39]。

3　天然药物调控肠道菌群微环境维持胆固醇内稳态的作用与机制

肠道菌群(GMB)是人体不可或缺的“微生物器官”,在调控心血管疾病危险因素中发挥重要作用[40-41],肠道菌群通过干预糖类、脂质及胆碱代谢、氧化应激、免疫炎症因子的释放等途径影响动脉粥样硬化进程与心血管事件发生[42]。肠道菌群平衡时,机体有益菌占优势,肠内黏膜呈现粉红色,肠内环境良好。但是,高脂饮食可改变肠道菌群微环境,导致肠杆菌(*Enterobacterium*)、肠球菌(*Enterococcus*)等有害菌增多,双歧杆菌(*Bifidobacterium*)、乳酸杆菌(*Lacto-bacillus*)等益生菌生长受到抑制。肠道菌群失调,影响胆固醇吸收与排泄[43],其机制可能涉及两个方面(图 1):①高脂饮食时,菌群代谢产物氧化三甲胺(trimethy-lamine oxide,TMAO)增高,会促进肠道吸收胆固醇[44],降低肠道胆汁酸合成代谢途径的限速酶 CYP7A1 表达,抑制胆固醇逆向转运效率[45-47]。TMAO 亦可上调巨噬细胞表面清道夫受体 CD36 表达导致胆固醇沉积形成泡沫细胞[48],激活多个炎症信号通路[49]促进动脉粥样硬化。动物实验发现,肠道菌群可能通过调控小肠中法尼酯衍生物 X 受体(farnesoid X receptor,FXR),促进 TMAO 表达,减少胆汁酸合成,从而导致高胆固醇血症和动脉粥样硬化[50-51]。②肠道菌群降解膳食纤维(植物多糖等)生成短链脂肪酸(short chain fatty acids,SCFA)[52],SCFA 可通过抑制肝脏脂肪合成酶、显著抑制总胆固醇(total cholesterol,TC)和脂肪酸的合成、对血和肝脏中的胆固醇重新分布、降低血清脂质水平[53]等途径减轻动脉粥样硬化。研究发现,天然来源多糖具有良好的肠道微生态调节作用[54],口服多糖可增加肠道普雷沃氏菌(*Prevotellacea*)、乳酸杆菌等益生菌含量[55],改善高脂饮食诱导的小鼠肠道菌群失衡而减轻代谢综合征或肥胖[56-57]。桑葚多糖通过调节肠道菌群有效改善高血糖和血脂异常,减轻氧化应激或脂质蓄积导致的肝损伤从而对动脉粥样硬化等具有保护作用[41]。小檗碱配伍水苏糖可上调肠道保护菌群乳酸杆菌和双歧杆菌表达水平,从而改善 2 型糖尿病小鼠的脂代谢紊乱[58]。越橘通过改善 $ApoE^{-/-}$ 小鼠肠道菌群分布促进膳食纤维分解成 SCFA,降低血浆胆固醇水平,抑制了动脉粥样硬化斑块形成[59]。决明子总蒽醌联合益生菌抑制了 SREBP-1c 的生成,上调

肠道 FXR 与肝脏中 CYP7A1、LDLR 的表达，抑制 TC 的吸收并加速其肠内排出，从而调节大鼠血脂代谢水平，效果显著[60]。SD 大鼠膳食中补充菠菜，有效抑制高脂饮食诱导的肝脏脂质蓄积与脂肪肝的形成，其机制在于菠菜能提升肠道乳酸菌等有益菌群数量，改变了 SCFA 结构组成，改善了胆固醇在肠道的吸收与代谢，其药效成分与深入机制仍待探讨[61]。

目前 TMAO 对肠道胆固醇代谢的作用机制及肠道菌群对 TMAO 水平的影响已相对明确，但调控肠道 TMAO 水平的天然药物还鲜有报道。有研究认为[62]，最简单的干预措施是调整饮食，限制富含卵磷脂、胆碱和肉碱食物的摄取可能是限制循环 TMAO 的有效策略，由此可见，天然药物对肠道菌群的调控会发挥重要作用。

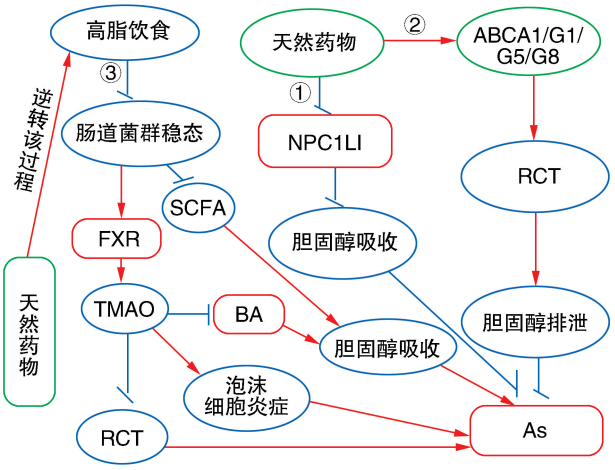

图 1. 天然药物调控肠道胆固醇内稳态的途径及其相关机制

①指控制肠道对胆固醇的吸收；②指促进胆固醇逆转运；③指调节肠道菌群平衡。

Figure 1. The pathways and the mechanisms of natural medicines for regulating intestinal cholesterol homeostasis

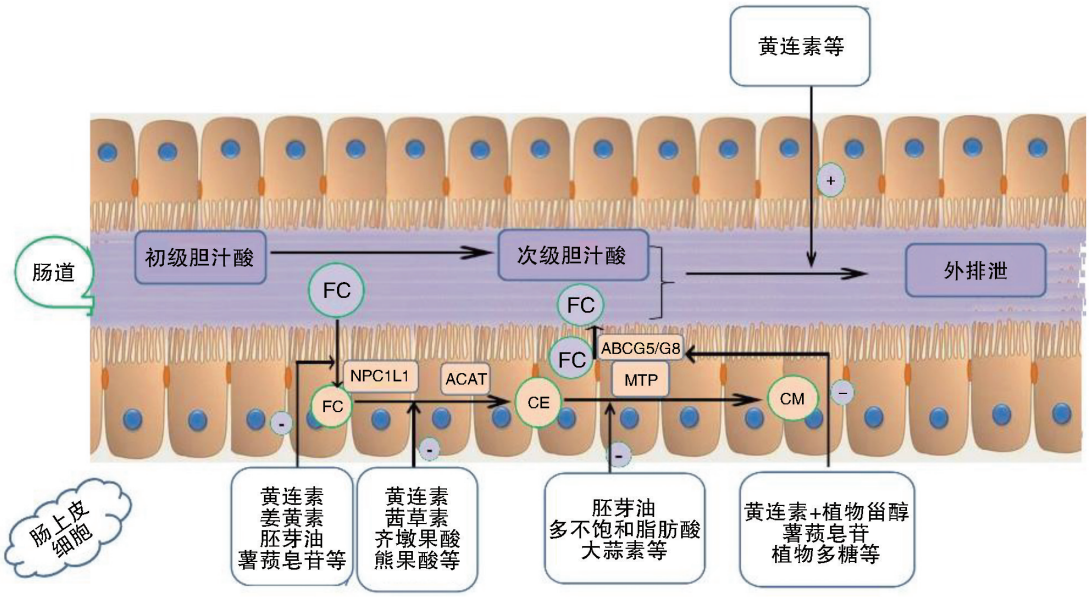

图 2. 天然药物调控肠上皮细胞对胆固醇的吸收与排泄

Figure 2. The mechanisms of natural medicines on regulating intestinal cholesterol absorption and transport in intestinal epithelial cell

4 结论和展望

综上所述，调控肠道胆固醇代谢的天然药物主要有多糖类、蒽醌类、萜类、多酚类及生物碱等，主要通过以下途径发挥作用：①抑制 NPC1L1/ACAT/MTP 表达降低肠道对胆固醇的吸收；②上调 ABCA1/G1/G5/G8 表达促进肠道胆固醇外流；③调控肠道菌群微环境促进有益菌的数量，降解膳食纤维生成短链脂肪酸降低机体脂质水平，而有益菌还可抑制肠道 TMAO 生成，减少肠道对胆固醇的吸收，促进胆固醇逆转运，降低巨噬细胞泡沫化和炎症的发生等。

天然药物资源丰富，价格低廉，不良反应小，期待更多的调控胆固醇代谢的天然药物被发现并明确机制，天然药物在心血管领域的药用价值和社会价值将日益彰显。

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