

# 肠道微生态介导多囊卵巢综合征发病的机制及中医药干预研究进展

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## 摘 要

多囊卵巢综合征(PCOS)作为育龄期女性最常见的内分泌代谢性疾病, 其发病机制复杂且尚未完全阐明。近年来, 肠道微生态失调被证实可通过代谢紊乱、内分泌失衡及免疫炎症等多条途径参与PCOS的发生发展。本文系统综述了肠道菌群及其代谢物在PCOS病理进程中的核心作用, 重点剖析短链脂肪酸异常、内毒素易位、雌激素肠肝循环障碍及Treg/Th17失衡等关键机制环节, 并深入归纳了中药复方及单味药活性成分通过重塑肠道菌群结构、修复肠道屏障、恢复代谢-内分泌-免疫网络稳态的干预策略。此外, 本文整合了“肠-脑轴”“肠-肝轴”“肠-卵巢轴”多通路协同调控的整合机制框架, 以期PCOS的精准诊疗提供新思路。

## 关键词

肠道微生态, 多囊卵巢综合征, 中医药干预, 菌群失调, 短链脂肪酸, 肠-卵巢轴

# Research Progress on the Mechanism of Gut Microecology Mediating the Pathogenesis of Polycystic Ovary Syndrome and Traditional Chinese Medicine Intervention

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## Abstract

Polycystic ovary syndrome (PCOS), as the most common endocrine and metabolic disorder in women of reproductive age, has a complex pathogenesis that remains not fully elucidated. In recent years, gut microbiota dysbiosis has been confirmed to participate in the onset and progression of PCOS through multiple pathways, including metabolic disturbances, endocrine imbalance, and immune inflammation. This article systematically reviews the core role of gut microbiota and its metabolites in the pathological process of PCOS, focusing on key mechanistic links such as short-chain fatty acid abnormalities, endotoxin translocation, impaired estrogen enterohepatic circulation, and Treg/Th17 imbalance. Furthermore, it comprehensively summarizes intervention strategies involving traditional Chinese medicine formulas and active ingredients from single herbs that act by reshaping gut microbiota structure, repairing the intestinal barrier, and restoring homeostasis of the metabolic-endocrine-immune network. Additionally, this paper integrates a framework of synergistic regulatory mechanisms across multiple axes, including the “gut-brain axis,” “gut-liver axis,” and “gut-ovary axis,” aiming to provide new insights for the precision diagnosis and treatment of PCOS.

## Keywords

Gut Microecology, Polycystic Ovary Syndrome, Traditional Chinese Medicine Intervention, Gut Microbiota Dysbiosis, Short-Chain Fatty Acids, Gut-Ovary Axis

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## 1. 引言

多囊卵巢综合征(PCOS)是育龄女性常见的内分泌代谢疾病,全球患病率约8%~13%[1],常伴胰岛素抵抗、肥胖和慢性低度炎症[2],病因复杂且机制未明。近年研究揭示,肠道菌群作为“内分泌器官”可通过胰岛素抵抗和代谢紊乱参与PCOS发病[2]。肥胖PCOS患者与肥胖非PCOS患者的菌群存在差异,人体临床研究提示特定菌属与性激素相关,例如16SrRNA测序发现睾酮水平与粪便脱氢表雄酮硫酸酯丰度正相关[3]。动物实验亦显示高脂饮食加剧菌群失调[4],提示微生态紊乱经能量吸收、短链脂肪酸代谢等途径影响PCOS[2][5],故肠道微生态成为早期干预新靶点。中医药作为多组分整体疗法,其“菌群-中药”互作机制为疗效阐释提供新视角,多项研究表明复方和单体可通过调节菌群改善PCOS症状[6][7]如补中益气汤调节肥胖患者菌群并降低雄激素[6], $\beta$ -谷甾醇改善小鼠子宫内膜容受性[7]。这些发现为中医药现代化应用提供了科学基础。

## 2. 肠道微生态失调与PCOS发病的因果关联及流行病学证据

### 2.1. PCOS患者肠道菌群结构特征及多样性改变

基于16SrRNA及宏基因组测序的研究一致显示,PCOS患者的肠道菌群结构发生显著改变。研究表明PCOS患者肠道菌群组成与非肥胖对照存在显著差异[8],在来曲唑联合高脂饮食诱导的多囊卵巢综合征大鼠模型中可观察到厚壁菌门/拟杆菌门(F/B)比值升高,该模型同时存在代谢紊乱特征[4],来曲唑诱导的PCOS大鼠模型研究显示,PCOS大鼠的梭菌属丰度降低[9],值得注意的是,这些菌群改变与血清睾

酮水平及稳态模型胰岛素抵抗指数(HOMA-IR)呈显著相关性[10]。另有研究专门探讨了瘦型 PCOS 患者的肠道菌群特征[11]。

## 2.2. 肠道菌群在 PCOS 动物模型中的因果验证

动物模型研究为肠道菌群与 PCOS 之间的因果关系提供了直接证据。研究提示肠道菌群失调可能驱动多囊卵巢综合征(PCOS)和胰岛素抵抗的发生;另有研究发现,移植来自 DHEA 诱导的 PCOS 样大鼠的肠道菌群可引发受体大鼠糖脂代谢紊乱和生殖激素失衡[12][13]。该领域研究探讨了来曲唑处理的青春期和成年小鼠的 PCOS 表型及肠道菌群变化,也有研究探讨了 IL-22 对 DHEA 诱导的 PCOS 小鼠模型的治疗作用[14][15]。研究证实 FMT 和乳杆菌干预可改善 PCOS 大鼠的动情周期、高雄激素血症及卵巢形态;另一研究探讨了芍药甘草汤对 PCOS 的作用,提示以菌群为靶点的干预具有一定可行性[9][16]。这些研究共同表明,肠道菌群失调不仅是 PCOS 的伴随现象,更可能是其发病的重要驱动因素。

## 2.3. 菌群-宿主共代谢产物与 PCOS 表型的关联

除菌群组成外,肠道菌群的功能代谢产物在介导宿主表型改变中发挥更为直接的作用。研究提示肠道菌群可能通过短链脂肪酸通路参与 PCOS 发病[2]。微生物羟基类固醇脱氢酶可调节与多囊卵巢综合征相关的固醇,另有研究探讨了肠道菌群和胆汁酸的相互作用与多囊卵巢综合征的关联[17][18]。研究证实 PCOS 患者血清 TMAO 及其前体水平升高,且 TMAO 与睾酮相关[19]。有研究提及肠道菌群失调可导致胰岛素抵抗,与 PCOS 发生密切相关[20]。

## 3. 肠道微生态介导 PCOS 发病的分子机制网络

### 3.1. 菌群失调-短链脂肪酸异常-胰岛素抵抗-高雄激素血症的代谢轴

肠道菌群通过发酵膳食纤维生成的短链脂肪酸(SCFAs)是连接菌群代谢与宿主能量稳态的关键信号分子。研究提示肠道菌群可通过短链脂肪酸(SCFA)通路等途径导致胰岛素抵抗,参与多囊卵巢综合征的发生发展[2],有研究探讨了亚麻籽油对 PCOS 大鼠的干预作用,发现补充亚麻籽油后短链脂肪酸水平升高[21]。临床研究进一步证实,PCOS 患者粪便中丙酸水平升高与胰岛素抵抗显著相关,且普雷沃菌属和巨单胞菌属等特定产丙酸菌的丰度变化可作为 PCOS 伴胰岛素抵抗的潜在生物标志物[22]。短链脂肪酸属于肠道代谢物,肠道微生物相关代谢通路可影响胰岛素信号和脂质代谢,阐述了 PCOS 与肠道微生物相关代谢物的相互作用,提到 PCOS 本身会对肠道功能产生不良影响进而加重病情[23]。多囊卵巢综合征大鼠模型中存在血浆胰岛素升高、性激素结合球蛋白降低、睾酮升高的现象[24]。值得注意的是,乙酸盐作为 HDAC 抑制剂,可改善 PCOS 模型大鼠的心脏能量耗竭及相关心脏病变,提示 SCFAs 在 PCOS 多系统病变中可发挥保护作用[24][25]。

### 3.2. 肠屏障损伤-内毒素易位-慢性低度炎症

肠道屏障完整性的破坏是 PCOS 慢性低度炎症的重要起始环节。有研究提及 PCOS 存在慢性低度炎症、肠道菌群改变,补充亚麻籽油可降低血浆脂多糖水平[21],动物实验发现,高脂高果糖饮食组来曲唑诱导 PCOS 小鼠的微生物  $\alpha$  多样性高于标准饮食组,且血清 LPS 浓度显著升高[26]。研究显示,丁酸可通过下调 METTL3 介导的 m6A 甲基化修饰,抑制 FOSL2 表达,从而降低 NLRP3 蛋白水平及 IL-6、TNF- $\alpha$  等炎症因子的表达,改善肥胖型 PCOS 小鼠的卵巢功能[27],作者发现肉桂来源的银纳米颗粒可降低多囊卵巢综合征大鼠的 IL-6、IL-18 和 TNF- $\alpha$  水平[28]菊粉干预可通过调节肠道菌群组成、增强 SCFAs 生物合成能力,降低 LPS 结合蛋白水平并改善卵巢炎症,而腹腔注射 LPS 可逆转菊粉的保护效应[29]。

### 3.3. 雌激素肠肝循环障碍与 HPO 轴调控紊乱

肠道菌群在雌激素的肠肝循环中扮演着不可或缺的角色。菌群编码的  $\beta$ -葡萄糖醛酸酶可水解雌激素的葡萄糖醛酸结合物, 促进其去结合后经肠壁重吸收回血液循环, 从而维持体内雌激素水平的动态平衡[30], 围绕肠道微生物组与 PCOS 的关联、相关微生物代谢物通路及治疗策略展开研究[31], 作者提及 Kisspeptin 是调控 LH/FSH 分泌的关键因素, 过度激活的 KISS1 系统会增强 HPG 轴活性, 从而导致 PCOS 患者出现月经紊乱及高雄激素血症[32]。临床研究显示, PCOS 患者血清 Kisspeptin 水平显著升高, 支持过度活跃的 KISS1 系统导致 HPG 轴活性增强的假说[32], 肠道微生物群相关代谢通路可影响激素分泌, 肠道菌群失调和代谢物紊乱可影响多囊卵巢综合征的进展[23]。研究表明铁皮石斛多糖可通过丁酸依赖的肠-脑-卵巢轴改善多囊卵巢综合征, 铁皮石斛多糖可通过调节肠道菌群中产丁酸菌的丰度, 增加丁酸和酪酪肽水平, 经 GPR41 介导的“肠-脑-卵巢”轴机制改善 PCOS 大鼠的卵巢功能和内分泌紊乱[33], 该通路可能是中医药调节 HPO 轴功能的重要靶标, 为基于肠道微生态的中医药干预策略提供了理论依据。

### 3.4. 肠道菌群-免疫细胞交互与卵巢微环境重塑

肠道相关淋巴组织(GALT)作为机体最大的免疫器官, 其稳态维持高度依赖肠道菌群的持续刺激。有研究提及 Th17/Treg 细胞失衡是菌群失调相关妇科疾病(包括 PCOS)的共有机制[30], 另一研究阐述了短链脂肪酸丁酸通过调控 METTL3 介导的对 FOSL2 的 m6A 修饰, 从而改善多囊卵巢综合征粒细胞炎症的机制[27]。研究指出, 丁酸作为 HDAC 抑制剂可调节免疫反应和炎症, 在 PCOS 病理环境下, 其有助于恢复激素平衡、提高胰岛素敏感性并减轻慢性炎症[34]。研究证实, 乙酸作为 HDAC 抑制剂, 在 PCOS 模型中可恢复卵巢功能, 表现为正常生长卵泡数量增加和循环 17- $\beta$  雌二醇水平升高[24]。此外, 乙酸还可通过抑制前额叶中的 HDAC2 表达, 改善 PCOS 相关的抑郁样行为[35], 研究发现肉桂来源的银纳米颗粒对多囊卵巢综合征大鼠具有降低炎症因子 TNF- $\alpha$ 、IL-6、IL-18 水平的作用[28]。针灸治疗可通过调节肠道菌群组成多样性、菌群丰度来改善糖脂代谢、调节相关炎症因子、降低体质量指数, 从而参与防治 PCOS。中药复方滋肾清热利湿化痰方可通过增加产丁酸菌(*Lachnospira* 和 *Faecalibacterium*)丰度、降低大肠杆菌-志贺菌属丰度, 调节丁酸代谢和三羧酸循环代谢, 从而改善 PCOS 患者的临床症状[36]。这些发现共同揭示了“菌群-免疫-卵巢”轴在 PCOS 发病中的核心地位, 也为靶向肠道微生态的免疫调节策略提供了重要依据。

## 4. 中医药通过调节肠道微生态干预 PCOS 的研究进展

### 4.1. 中药复方调节肠道菌群结构与功能的研究

补肾化痰类方剂, 如苍附导痰汤, 是治疗 PCOS 的常用复方, 其“补肾填精、化痰祛湿”的功效与现代研究中调节肠道菌群的作用机制相契合。临床研究显示, 苍附导痰汤加减治疗痰瘀互结型 PCOS 合并胰岛素抵抗患者, 可显著改善其中医证候、调节性激素水平并提高排卵率, 其机制与正向调整肠道微生物群落结构有关, 具体表现为增加双歧杆菌属等有益菌的丰度, 同时降低埃希氏菌-志贺氏菌属等条件致病菌的相对丰度。另一项针对 PCOS 伴胰岛素抵抗痰湿证患者的随机对照试验也证实, 苍附导痰汤加减能有效降低患者的胰岛素抵抗指数(HOMA-IR), 并显著提升肠道菌群的多样性及丰度, 增加乳酸杆菌及双歧杆菌菌落数, 同时减少肠杆菌及拟杆菌菌落数。此外, 疏肝健脾类方剂如补中益气汤, 在治疗肥胖型 PCOS 伴脾虚痰湿证患者时, 亦显示出对肠道菌群的调节作用, 能够显著降低患者血清硫酸脱氢表雄酮和睾酮水平, 并改变肠道菌群结构, 如增加真杆菌属和埃希氏菌-志贺氏菌属的丰度, 同时减少巨单胞菌属的丰度[6]。这些研究共同表明, 不同治法的中药复方均能通过调节肠道菌群的组成与结构,

恢复微生态平衡,从而改善 PCOS 的临床症状。

## 4.2. 单味药及活性成分的菌群调节机制

中药活性成分是复方发挥药效的重要物质基础,其中小檗碱的研究最为深入。小檗碱可通过调节肠道菌群改善 PCOS 的病理状态,研究显示,在脱氢表雄酮诱导的 PCOS 大鼠模型中,小檗碱能够改变肠道菌群组成,降低厚壁菌门与拟杆菌门的比例,并调节罗姆布茨菌属、拟杆菌属和梭菌属等特定菌属的丰度,从而改善胰岛素抵抗[37]。然而,也有研究指出,在二氢睾酮诱导的 PCOS 大鼠模型中,小檗碱会显著降低肠道菌群的物种多样性和数量,其作用特征与益生菌不同[38],这表明小檗碱的菌群调节作用可能具有模型依赖性。此外,其他活性成分如柚皮素,可通过调节肠道菌群和 SIRT1/PGC-1 $\alpha$  信号通路来改善来曲唑诱导的 PCOS 大鼠症状,其能下调普雷沃菌属和 *Gemella* 的丰度,上调丁酸弧菌属、毛螺菌属和副拟杆菌属等产短链脂肪酸菌群的丰度[39], $\beta$ -谷甾醇作为补肾养血方的主要活性成分,也能通过改变 PCOS 样小鼠的肠道菌群结构,调节子宫内膜容受性相关因子的表达,从而改善性激素平衡[7]。这些研究揭示了单味药活性成分通过靶向特定菌群发挥治疗作用的潜力。

## 4.3. 中医药通过“肠-器官轴”网络整体调控 PCOS 的整合机制

中医药治疗 PCOS 的优势在于其“整体观”,这与现代医学中“肠-器官轴”的理论高度契合。在“肠-卵巢轴”方面,中医药通过恢复肠道菌群稳态,降低肠源性脂多糖的易位,进而抑制卵巢局部的 TLR4/NF- $\kappa$ B 炎症信号通路,减轻卵巢炎症微环境,从而改善卵泡发育和排卵功能[40]。例如,百令胶囊可通过调节肠道菌群,改善肠道屏障功能,并抑制肠道来源的 LPS-TLR4 炎症通路,从而减轻 PCOS 小鼠的卵巢损伤和胰岛素抵抗[40]。在“肠-脑轴”维度,PCOS 患者肠道菌群失调与神经内分泌改变密切相关,研究发现 PCOS 患者中产  $\gamma$ -氨基丁酸的菌群(如狄氏副拟杆菌、脆弱拟杆菌和大肠杆菌)丰度增加,并与血清黄体生成素水平及黄体生成素/卵泡刺激素比值呈正相关,揭示了肠道菌群通过肠-脑轴影响 PCOS 神经内分泌的潜在机制[41]。在“肠-肝轴”维度,中药复方如芍药甘草汤可通过重塑肠道菌群结构,特别是调节胆汁酸代谢相关菌群,并调控胆汁酸/FXR 信号通路,从而改善 PCOS 大鼠的脂质代谢紊乱[42],这三条“肠-器官轴”通路并非孤立存在,而是通过微生物代谢产物、免疫细胞和神经信号等媒介相互交织,中医药的多靶点、多途径调节特性恰好能够协同作用于这一复杂的网络,体现了其整体调节的独特优势。

## 5. 讨论

目前,中医药调控肠道菌群治疗 PCOS 的研究已取得初步进展,但整体仍以动物实验和小样本观察为主,缺乏大规模随机对照试验验证,且方法学异质性较大,限制了证据等级的提升。复方成分复杂,其代谢过程及“菌群-药物-宿主”之间的互作机制尚不明确;菌群分析的分辨率有限,难以追踪菌群代谢物对卵巢功能的中间通路;同时,缺乏分层设计,阻碍了个体化匹配和疗效的临床推广。

肠道菌群失调与 PCOS 的因果关系已从关联观察转向机制验证。短链脂肪酸异常、内毒素易位、雌激素肠肝循环障碍以及 Treg/Th17 失衡构成了“菌群-代谢物-靶器官”信号轴,使肠道菌群成为 PCOS 病理网络中的活跃节点。“肠-卵巢轴”“肠-脑轴”“肠-肝轴”的整合揭示,菌群通过代谢-免疫-神经网络的系统调控,解释了 PCOS 多系统共病特征,提示未来研究需转向以菌群为枢纽的网络化病理模型。

中医药“多组分-多靶点-多通路”的干预模式与 PCOS 的系统性特征高度契合。动物实验和初步临床研究显示,中药复方可通过重塑菌群、修复肠道屏障、恢复代谢稳态来调节卵巢功能,其效果优于单一靶点药物。然而,现有证据等级偏低,多停留于描述性比较,缺乏对功能菌株及代谢通路动态变化

的追踪,复方靶点解析不足,限制了机制的深入阐释和标准化进程。

未来研究应推动从“关联”到“因果”的范式转变。优先开展基于无菌动物和人体粪菌移植的交叉验证,结合多组学纵向队列,明确关键菌株及代谢物对 PCOS 表型的因果贡献,而非满足于横断面关联。其次,建立“证候-菌群-方药”精准匹配体系。中医药干预 PCOS 的优势在于整体调节,但其疗效异质性提示需根据患者菌群分型及中医证候进行分层。建议将菌群特征纳入中医辨证体系,探索“同证异菌”与“异证同菌”的生物学基础,进而指导方药的精准选择。最后,发展“工程菌-中药”联用的合成微生态干预策略。利用合成生物学改造益生菌,使其靶向递送中药活性成分或调控关键代谢通路,结合中药复方的多靶点特性,有望突破单一菌株或单一成分的疗效局限,为 PCOS 提供新一代微生态靶向治疗。

总之,肠道微生态为理解 PCOS 的系统性病理提供了新视角,而中医药的整体观与多靶点特性使其成为极具潜力的干预手段。唯有通过因果验证、精准分型及技术革新,方能将这一领域从描述性科学推向临床转化,最终实现 PCOS 的个体化防治。

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