



在线全文

基于宏基因组学与代谢组学探索完带汤治疗脾虚湿盛型 外阴阴道假丝酵母菌病作用机制*

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【摘要】 目的 基于宏基因组和代谢组学,探讨完带汤防治脾虚湿盛型外阴阴道假丝酵母菌病(vulvovaginal candidiasis, VVC)、恢复阴道菌群结构的机制及可能作用的代谢通路。方法 将符合纳入标准的20例VVC患者随机分为完带汤组和氟康唑组各10例,氟康唑组采用150 mg氟康唑口服一次;完带汤组采用完带汤口服14 d。治疗前后对两组患者进行VVC症状体征(vulvovaginal signs and symptoms, VSS)评分。收集治疗前后阴道分泌物,采用Illumina测序和液相色谱-串联三重四极杆质谱(LC-MS/MS)平台技术,对阴道分泌物分别进行宏基因组检测和代谢组学检测,探索完带汤可能作用的代谢通路及其恢复阴道菌群结构的机制。结果 VSS评分结果显示,治疗后两组VSS评分均较治疗前降低($P < 0.01$),且治疗后两组VSS评分差异无统计学意义。宏基因组学结果显示:完带汤组治疗后阴道微生物群落为CST II、V型(格氏乳杆菌、詹氏乳杆菌为主);氟康唑组治疗后阴道微生物群落为*Lactobacillus intestinalis*和*Streptococcus sp._oral_taxon_431*。KEGG功能富集分析结果显示:在假丝酵母菌的细胞周期、减数分裂功能上,两组差异有统计学意义($P < 0.05$)。代谢组学结果显示:治疗后,完带汤组与氟康唑组组间的差异代谢物为120个;KEGG代谢通路富集分析结果显示:完带汤可能在改善阴道局部 α -亚麻酸、甘油磷脂代谢、戊糖和葡萄糖醛酸相互转化、花生四烯酸等代谢通路方面优于氟康唑。结论 完带汤可改善VVC患者阴道菌群;完带汤在细胞周期及减数分裂的信号通路方面优于氟康唑组;完带汤改善阴道菌群可能与影响阴道局部甘油磷脂代谢、戊糖和葡萄糖醛酸相互转化等代谢通路有关。

【关键词】 完带汤 外阴阴道假丝酵母菌病 阴道菌群 宏基因组 代谢组学

Mechanisms of Wandai Decoction in Improving Vaginal Flora of Vulvovaginal Candidiasis of the Spleen Deficiency and Excessive Dampness Type: A Study Based on Metagenomics and Metabolomics HAN Yue¹, SHEN Su¹, FU Jie², REN Qingling^{1△}. 1. Department of Gynecology, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing 210029, China; 2. Department of Gynecology, Lianyungang Affiliated Hospital of Nanjing University of Chinese Medicine, Lianyungang 222004, China

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【Abstract】 Objective To explore the mechanism by which Wandai Decoction prevents and treats vulvovaginal candidiasis (VVC) of the spleen deficiency and excessive dampness type and restores the vaginal flora structure, and to identify the potential metabolic pathways involved using metagenomics and metabolomics. **Methods** Twenty VVC patients who met the inclusion criteria were randomly assigned to a Wandai Decoction group and a fluconazole group ($n = 10$ in each group). Subjects in the fluconazole group were given a single oral dose of 150 mg fluconazole, while those in the Wandai Decoction group took the Wandai Decoction orally for 14 days. The vulvovaginal signs and symptoms (VSS) scores of both patient groups were evaluated before and after treatment. Vaginal secretions were collected before and after treatment. The Illumina sequencing and the liquid chromatography with tandem mass spectrometry (LC-MS/MS) platform were used to conduct metagenomic and metabolomics analyses of the vaginal secretions, respectively. **Results** The VSS score results showed that the VSS scores of both groups decreased after treatment compared with those before treatment ($P < 0.01$), and there was no statistically significant difference in the VSS scores between the two groups after treatment. Metagenomics results showed that, after treatment, the vaginal microbial communities in the Wandai Decoction group were of CST II and V types (predominated by *Lactobacillus gasseri* and *Lactobacillus jensenii*), while those in the fluconazole group were *Lactobacillus intestinalis* and *Streptococcus sp._oral_taxon_431*. KEGG functional enrichment analysis results showed that, in terms of the cell cycle and meiosis functions of *Candida albicans*, statistically significant differences between the Wandai Decoction and fluconazole groups were observed ($P < 0.05$). Metabolomic analysis identified 120 differential metabolites between the two groups after treatment. The results of KEGG metabolic pathway enrichment analysis of differential metabolites showed that the Wandai Decoction might be significantly superior to fluconazole in improving local vaginal metabolic pathways of α -linolenic acid,

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glycerophospholipid metabolism, pentose and glucuronic acid interconversion, and arachidonic acid.

Conclusion The Wandai Decoction can improve the vaginal flora of VVC patients. It may be superior to fluconazole in the signaling pathways of the cell cycle and meiosis. The improvement of the vaginal flora by the Wandai Decoction may be associated with its effect on metabolic pathways of glycerophospholipid metabolism, pentose and glucuronic acid interconversion, and others in the vagina.

[Key words] Wandai Decoction Vulvovaginal candidiasis Vaginal flora Metagenomics Metabolomics

外阴阴道假丝酵母菌病(vulvovaginal candidiasis, VVC)是女性下生殖道最常见的感染性疾病,约75%的育龄女性在其一生中至少经历过一次。有40%~45%最初感染的女性会经历VVC的复发^[1-2]。其中13%~28%的VVC患者可发展为复发性外阴阴道假丝酵母菌病(recurrent vulvovaginal candidiasis, RVVC)。RVVC在我国的患病率为4 436/10万,远高于全球的患病率^[3-5]。白色念珠菌(*Candida albicans*)作为主要的机会性致病菌,氟康唑是其一线治疗药物。但长期使用一线药物氟康唑治疗后,大约超过50%的RVVC患者呈现耐药性;且停药后耐药性难以逆转,临床用药非常有限^[5-7],因此,逐渐成为VVC治疗的主要难点与研究热点^[8]。中医学虽然无VVC病名,但根据其典型临床表现可将其归属于“带下病”范畴。本课题组前期研究结果发现,完带汤在防治脾虚湿盛型外阴阴道假丝酵母菌病的总体临床疗效与氟康唑相当,但在改善中医证候、防止复发方面优于氟康唑^[9]。但完带汤治疗VVC的作用机理有待阐明。因此,本研究试图运用宏基因组和代谢组学技术,深入研究经典名方完带汤治疗带下病的作用机制,以期完带汤的临床运用与传承创新提供更为丰富的实验依据。

1 资料与方法

1.1 研究对象

选取江苏省中医院妇科的20例脾虚湿盛型VVC门诊患者,采用随机数字表法分为完带汤组和氟康唑组各10例。完带汤组平均年龄(34.2±8.00)岁,氟康唑组平均年龄(33.8±9.80)岁,差异无统计学意义。本研究经江苏省中医院伦理委员审批通过(批号:2021NL-228-02)。

1.2 诊断标准

1.2.1 西医诊断标准

VVC诊断标准:参照2012年中华医学会妇产科感染协作组制定的《外阴阴道假丝酵母菌病(VVC)诊治规范修订稿》^[10],以及《2021年美国疾病控制和预防中心(CDC)关于阴道炎症的诊治规范》^[11]共同制定:①症状:外阴阴道瘙痒、灼痛;阴道分泌物增多;②体征:外阴局部充血、肿胀,或见皲裂、抓痕;白膜样或凝乳状阴道分泌

物;③辅助检查:悬滴法(10%KOH)或涂片法(革兰染色)镜检见孢子、芽生孢子或菌丝;或者培养法证实真菌阳性。同时满足以上3条者可诊断。

1.2.2 中医证候诊断标准

参考《中医妇科学》第2版教材带下病脾虚湿盛证:

①主症:带下量多,色白或淡黄,质稀薄,或如涕如唾,绵绵不断,无臭;②次症:面色㿗白,或萎黄,四肢倦怠,脘协不舒,纳少便溏,或四肢浮肿;③舌脉:舌淡胖,苔白或腻,脉细缓;主症符合两项,次症符合一项者可诊断。

1.3 纳入标准

①符合VVC的诊断标准。②有性生活史尚未绝经的女性,年龄在20~50岁之间。③1个月内没有使用抗生素、微生态调节剂,身体其他部位无细菌或病毒性感染,无全身系统性疾病或先天性疾病。④患者自愿参加本次临床研究。

1.4 排除标准

①近3个月内计划妊娠或妊娠或哺乳期。②3 d内有性交或阴道灌洗。③2周内使用抗真菌药物,或近3个月内口服避孕药或糖皮质激素或免疫抑制剂者。④合并其他外阴阴道炎症性疾病或有阴道炎用药。⑤对研究药物及成分过敏者。⑥合并有肝肾、心脑血管、血液病等严重原发性疾病者,或精神异常者。⑦正在参加其他药物临床研究。

1.5 治疗方案

氟康唑组予氟康唑胶囊(购自扬子江药业集团有限公司)口服治疗,于治疗开始的第1天顿服1次,150 mg/次。

完带汤组予完带汤煎剂口服,完带汤由炒白术30 g、炒山药30 g、党参10 g、炒白芍15 g、车前子10 g、炒苍术10 g、甘草6 g、陈皮6 g、黑芥穗9 g、柴胡10 g组成;由江苏省中医院药剂科提供。用药方法:确诊次日起开始口服,每日一剂,早晚分两次口服,经期停药,连续服药7 d为一个疗程,共2个疗程。

1.6 观察指标与检测方法

1.6.1 疗效评估

治疗前、后对两组患者进行VVC症状体征(vulvovaginal signs and symptoms, VSS)评分。

1.6.2 宏基因组

对两组治疗前、治疗后各10例患者的阴道分泌物作进一步宏基因组学测序分析研究。提取出基因组DNA建库后,采用IlluminaNovaseq6000测序平台对文库进行测序,并生成150 bp双端读长(reads)。使用Trimmomatic(v0.36)软件对原始下机数据去接头,并过滤掉低质量的碱基,去除含有模糊碱基的reads。获得确定的reads后,使用MEGAHIT(v1.1.2)软件进行宏基因组的拼接。使用Prodigal(v2.6.3)软件对拼接的Contigs序列进行开放阅读框(ORF)预测,并将其翻译为氨基酸序列,再运用CDHIT(v4.5.7)软件进行去冗余基因,设置identity 95%, coverage 90%,并选取最长的序列为代表性序列,以获得非冗余的初始Unigene,进行基因聚类分析。DIAMOND(v0.9.7)6基因集代表序列比对注释,构建丰度谱;用R软件(v3.2.0)对物种丰度谱或者功能丰度谱进行主成分分析(PCA)以及绘图,计算PCoA、NMDS等距离矩阵结果,并作图分析。

1.6.3 代谢组学检测

运用液相色谱-串联三重四级杆质谱(LC-MS/MS)平台技术对阴道分泌物进行代谢组学检测,色谱检测条件:选用色谱柱ACQUITYUPLCHSST3(100 mm×2.1 mm, 1.8 μm);柱温: 45 °C;流动相: A-水(含0.1%甲酸), B-乙腈(含0.1%甲酸);流速: 0.35 mL/min;进样体积: 5 μL。

1.7 统计学方法

受试者年龄、VVC VSS评分采用SPSS26.0统计分析软件进行t检验分析, $P < 0.05$ 为差异有统计学意义。

宏基因组: 为了研究物种和功能在不同组间是否具有显著性差异, 从不同层级的物种丰度表和功能丰度表出发, 利用Wilcoxon rank-sum(两组)方法对组间的物种丰度和功能丰度数据进行假设检验, $P < 0.05$ 为差异有统计学意义。

代谢组: 采用多维分析和单维分析相结合的办法, 筛选组间差异代谢产物; 利用t检验验证组间差异代谢物是否具有显著性。再利用差异代谢物的KEGG ID进行通路富集分析, 获得代谢通路富集结果; 应用超几何检验, 找出与整个背景相比, 在显著性差异表达代谢物中显著富集的pathway条目; 以 $P \leq 0.05$ 为阈值, 满足超几何检验的pathway为在差异代谢物中显著富集的pathway。

2 结果

2.1 治疗效果

治疗前完带汤组VSS评分为(8.70±1.50)分、氟康唑组为(8.40±0.84)分; 治疗后完带汤组为(0.90±1.29)分、氟

康唑组为(1.80±1.81)分。治疗前两组VSS评分差异无统计学意义; 治疗后两组VSS评分均较治疗前降低($P < 0.01$), 提示两组均有症状改善作用; 治疗后两组VSS评分差异亦无统计学意义, 提示完带汤与氟康唑的疗效相当。

2.2 宏基因组

2.2.1 物种差异分析

分别在门(图1A)、纲(图1B)、目(图1C)、科(图1D)、属(图1E)、种(图1F)水平上, 丰度排序T0P12物种的柱状图如图1所示。结果发现: 完带汤组患者治疗后阴道菌群重建为以格氏乳杆菌(*Lactobacillus gasseri*)、詹氏乳杆菌(*Lactobacillus jensenii*)等为优势菌种的阴道微生物群落, 恢复为CST II、CST V型, 而氟康唑组为以*Lactobacillus intestinalis*和*Streptococcus_sp._oral_taxon_431*为优势菌种的阴道微生物群落, 表明在恢复阴道微生物群落结构方面完带汤优于氟康唑组($P < 0.05$)。

2.2.2 KEGG功能富集分析

KEGG功能富集分析(图2)结果表明, 在假丝酵母菌的细胞周期、减数分裂功能上, 两组差异有统计学意义($P < 0.05$), 完带汤可能在阻止假丝酵母菌的生长及增殖上优于氟康唑。

2.3 代谢组学变化

在治疗前、后, 完带汤组差异代谢物共有59个, 而氟康唑组为43个; 在治疗后, 完带汤组与氟康唑组组间的差异代谢物为120个(图3A)。对差异代谢物进行KEGG代谢通路富集分析, 结果显示: 完带汤可能在改善阴道局部a亚麻酸、甘油磷脂代谢、戊糖和葡萄糖醛酸相互转化、花生四烯酸等代谢通路方面显著优于氟康唑(图3B)。

3 讨论

VVC是女性常见的下生殖道感染性疾病之一, 曾被称为霉菌性阴道炎、外阴阴道念珠菌病等, 其临床主要表现为外阴瘙痒、灼痛, 白带量多, 呈白色豆渣样或凝乳状, 可伴有尿痛、性交痛等症状^[12]。根据其VVC典型的临床表现, 现代中医学家将其归属于“带下病”范畴。传统中医学对外阴阴道病病因的解释有很多种, 包括风寒、湿邪、痰饮、七情内伤、瘀血, 清代妇科经典著作《傅青主女科·带下》云: “夫带下俱是湿症”, 提出湿邪是该病病因, 并创制著名的完带汤, 成为治疗该病的经典方剂。即: 脾虚湿盛是该病病因病机, 健脾化湿为治疗原则。湿为阴邪, 非辛不散、非温不化、非淡不渗, 傅氏治湿通过大补脾胃之气, 脾气健而湿气消, 以白术、山药为君药, 配以苍术、车前子、柴胡、荆芥等药物将湿邪从中焦、下焦及借

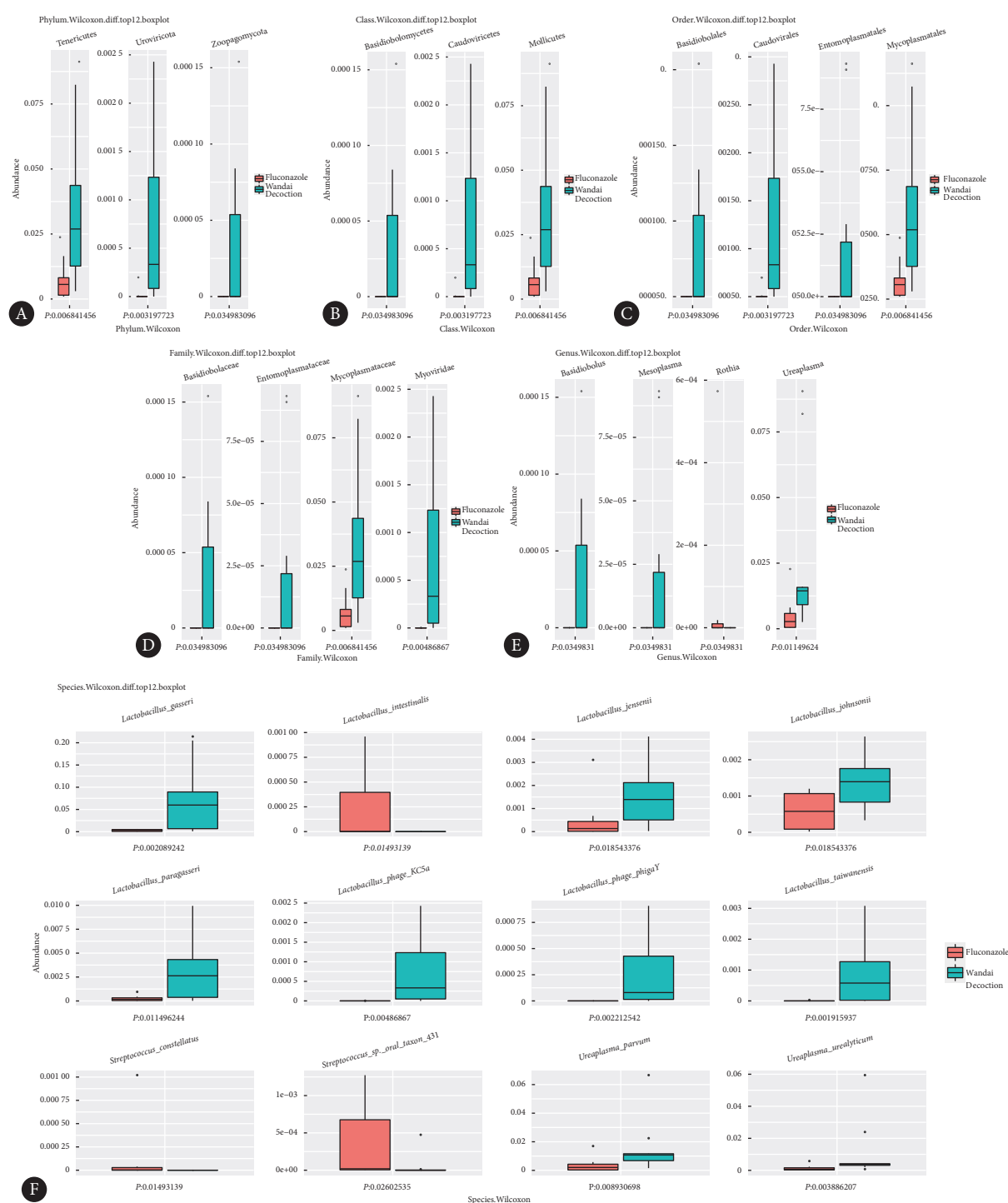


图 1 宏基因组学的物种差异分析

Fig 1 Metagenomic species differential analysis

A, Phylum; B, class; C, order; D, family; E, genus; F, species.

助辛散药物向上向外之力分道而消。本研究综合运用宏基因组及代谢组学方法, 深入研究经典名方完带汤治疗带下病的作用机制。研究结果显示: VVC患者经过氟康唑、完带汤治疗后, 在完带汤组阴道菌群中格氏乳杆菌、詹氏乳杆菌等阴道优势菌群的丰度较治疗前提高; 而在氟康唑组治疗后阴道菌群中*Lactobacillus_intestinalis*和

*Streptococcus_sp._oral_taxon_431*等菌种水平提高。距今为止, 阴道乳杆菌已有20余种相继报道^[13-15]。其中, 主要以卷曲乳杆菌(*Lactobacillus crispatus*)、格氏乳杆菌、嗜性乳杆菌和詹氏乳杆菌4种乳杆菌在女性阴道菌群中分布最为常见。这些乳杆菌通过产生乳酸、过氧化氢、细菌素及其他的抗微生物物质抑制阴道中的致病微生物,

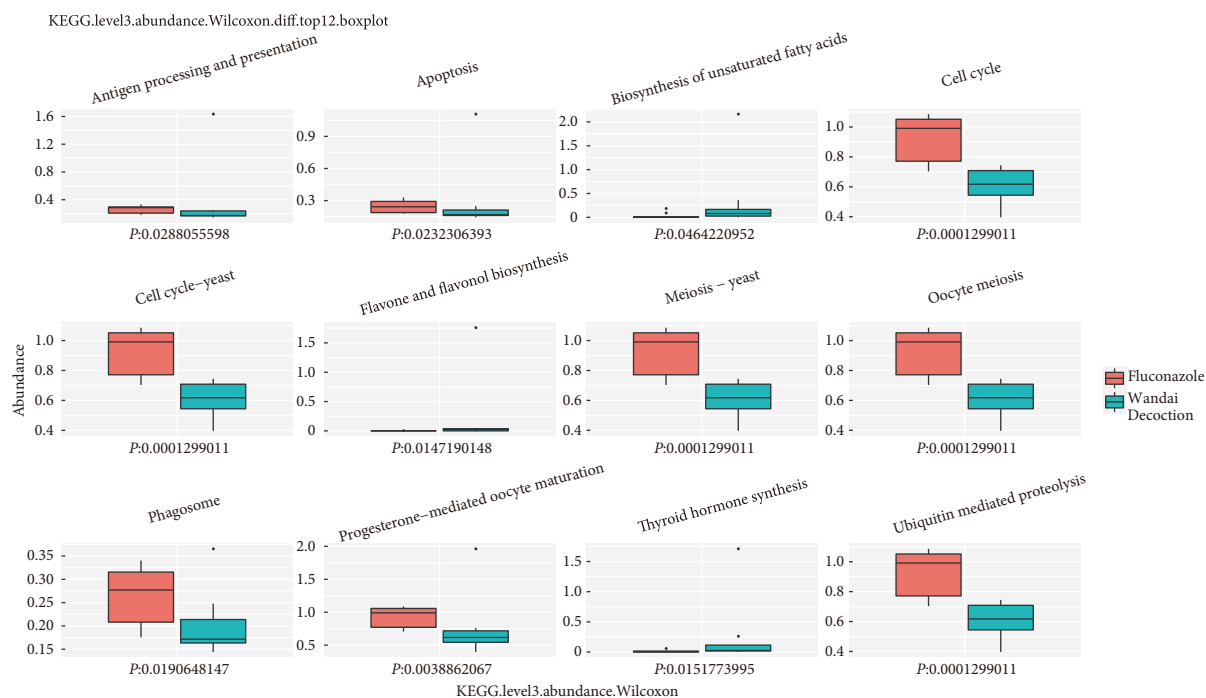


图 2 KEGG功能富集分析

Fig 2 KEGG functional enrichment analysis

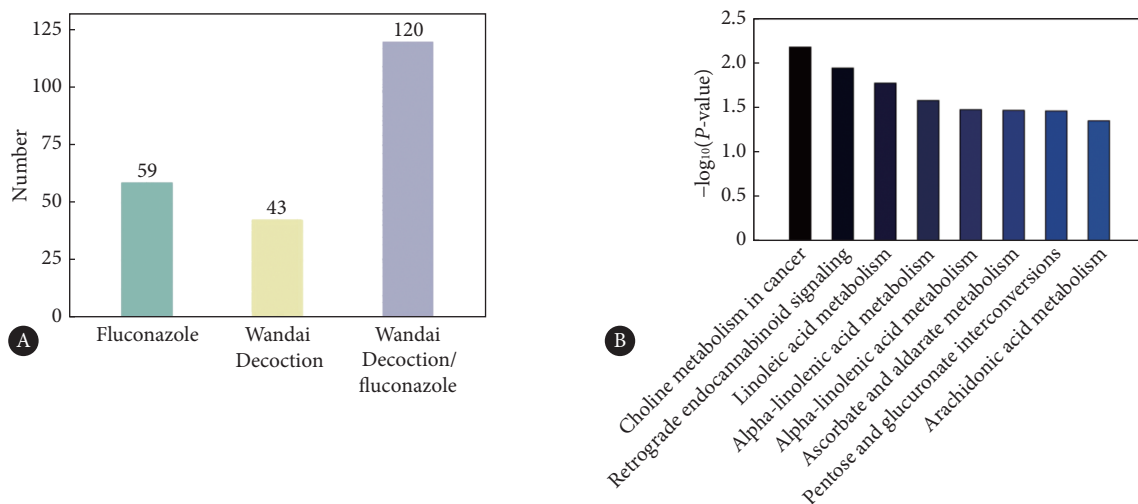


图 3 代谢组学结果

Fig 3 Metabolomics analysis results

A, Statistical chart of the number of differential metabolites between and within groups. B, Differential metabolites KEGG pathways of two groups.

使阴道局部pH值维持在较低水平($\text{pH} < 4.5$),从而维护阴道的正常生理环境;在疾病状态下,阴道菌群多以乳杆菌数量减少及菌群多样性增加为特征。而本研究揭示,完带汤恢复阴道菌群的重点可能在格氏乳杆菌和詹氏乳杆菌;氟康唑组主要影响的是*Lactobacillus_intestinalis*和*Streptococcus_sp._oral_taxon_431*,值得未来深入研究。在恢复阴道菌群的机制方面,本研究发现:完带汤组在细胞周期及减数分裂的信号通路上显著性高于氟康唑组;完带汤可能在阻止假丝酵母菌的生长及增殖上优于氟康

唑;完带汤可能在改善阴道局部a亚麻酸、甘油磷脂代谢、戊糖和葡萄糖醛酸相互转化、花生四烯酸等代谢通路方面显著优于氟康唑。

综上,在恢复阴道菌群的机制方面,完带汤在细胞周期及减数分裂的信号通路,阻止假丝酵母菌的生长及增殖,改善阴道局部a亚麻酸、甘油磷脂代谢、戊糖和葡萄糖醛酸相互转化、花生四烯酸等代谢通路等方面优于氟康唑。结合宏基因组和代谢组学提示,完带汤可能通过改善阴道菌群及改变宿主代谢物以治疗VVC。从阴道菌

群-代谢物-表型的角度, 诠释了完带汤治疗VVC的潜在机制。但从阴道菌群中格氏乳杆菌、詹氏乳杆菌等阴道优势菌群角度, 从信号通路的角度深入探索氟康唑或完带汤恢复VVC阴道菌群的差异性机制有待进一步深入研究。

* * *

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Author Contribution HAN Yue is responsible for conceptualization, formal analysis, funding acquisition, methodology, and writing--original draft. SHEN Su is responsible for data curation, investigation, and visualization. FU Jie is responsible for software and validation. REN Qingling is responsible for project administration, resources, supervision, and writing--review and editing. All authors consented to the submission of the article to the Journal. All authors approved the final version to be published and agreed to take responsibility for all aspects of the work.

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Declaration of Conflicting Interests All authors declare no competing interests.

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(2024-12-09收稿, 2025-01-15修回)

编辑 余琳



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Editorial Office of *Journal of Sichuan University (Medical Sciences)*