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Lactobacillus rhamnosus CCFM1131 Alleviates Hyperuricemia through Modulation of Gut Microbiota and Metabolites: A Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT: Hyperuricemia (HUA) poses a significant public health challenge, and prolonged use of conventional urate-lowering drugs may result in drug dependence and adverse effects, including hepatic and renal damage. In recent years, probiotics have emerged as a promising focus for uric acid (UA) regulation due to their favorable safety profile. This randomized, double-blind, placebo-controlled trial evaluated the regulatory effects of *Lactobacillus rhamnosus* CCFM1131 in patients with HUA. Participants were randomly assigned to receive either 6×10^9 CFU of *L. rhamnosus* CCFM1131 powder (n=55) or placebo (n=52) daily for 8 weeks. Following intervention, the CCFM1131 group exhibited significantly reduced serum UA concentrations and suppressed xanthine oxidase (XOD) activity compared to the placebo group ($P < 0.05$). Gut microbiota analysis demonstrated increased abundance of beneficial genera such as *Bifidobacterium* and *Lactobacillus*. Additionally, untargeted metabolomics further revealed competitive depletion of intestinal purine bases and elevated levels of taurine and hippuric acid, suggesting enhanced intestinal barrier function and UA excretion. Concurrently, serum levels of bile acids including glycocholic acid and glycochenodeoxycholic acid decreased, contributing to improved hepatic lipid metabolism and reduced cytotoxicity. In summary, *L. rhamnosus* CCFM1131 modulates HUA through a triple mechanism—attenuating endogenous UA synthesis, modulating host metabolism, and promoting UA excretion—via remodeling of the gut microbiota. These findings provide both theoretical rationale and experimental support for applying probiotics in the clinical management of HUA.

Keyword: Hyperuricemia; *Lactobacillus rhamnosus*; Xanthine oxidase; Uric acid; Gut microbiota

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1. Introduction

Uric acid (UA), the terminal metabolite of purine compounds derived from both endogenous and exogenous sources^[1], accumulates in humans due to the absence of the enzyme uricase, which otherwise catalyzes its conversion to the more soluble allantoin^[2, 3]. Hyperuricemia (HUA), a metabolic disorder characterized by the systemic deposition of urate crystals, arises from either the overproduction of UA or, more commonly, impaired excretion mechanisms involving the kidneys and intestines^[4, 5]. This pathogenic accumulation represents a well-established etiological factor in the development of HUA.

Clinically, defined as serum urate levels exceeding 420 $\mu\text{mol/L}$ in men and 360 $\mu\text{mol/L}$ in women^[6], HUA represents a significant and independent risk factor for various metabolic diseases, including type 2 diabetes, atherosclerosis, and cardiovascular disorders^[7-9]. With shifts in modern lifestyles, as evidenced by the prevalence of high-purine and high-fructose diets, irregular schedules, and rising obesity rates, the global incidence of HUA is rising annually^[10]. This condition is notably affecting younger populations, positioning HUA as the second most common metabolic disorder after type 2 diabetes^[11]. Consequently, HUA has emerged as a critical public health challenge.

To date, clinical management of HUA primarily relies on pharmacological interventions, broadly categorized by mechanism into UA synthesis inhibitors (e.g., allopurinol and febuxostat)^[12] and UA excretion promoters (e.g., probenecid and benzbromarone)^[13]. While short-term medication effectively regulates serum UA levels, long-term use carries potential risks, exemplified by drug dependency, hepatotoxicity, nephrotoxicity, coupled with high treatment costs^[14]. Therefore, exploring sustainable management strategies for HUA that combine favorable safety, efficacy, and cost-effectiveness is of substantial clinical and public health importance.

Approximately 70% of UA is excreted renally, with the remaining 30% eliminated through the route of the intestinal tract^[5]. Elevated serum UA levels can disrupt gut microbiota homeostasis and compromise intestinal barrier function, leading to microbial dysbiosis and disrupted diversity in individuals with HUA. This impairment further diminishes intestine UA excretion capacity^[15]. In recent years, lactic acid bacteria (LAB), a core component of the beneficial gut microbiota, have attracted considerable attention due to their potential to alleviate HUA^[16]. Notably, LAB exert their effects through a synergistic network of multiple targets rather than a single pathway: First, they ameliorate HUA and associated metabolic disorders by reshaping the gut microbiota ecosystem, reinforcing intestinal barrier function, and mediating systemic anti-inflammatory and antioxidant effects. For instance, *Lactococcus cremoris* D2022 has been shown to prevent intestinal barrier damage induced by HUA and attenuate renal inflammatory injury via inhibition of multiple inflammatory pathways, with the SCFAs-FFAR3-NLRP3 axis identified as a potential mechanism^[17]. Similarly, intervention with *Pediococcus acidilactici* SWU-HX39 (HX39) in HUA mice not only significantly modulated gut microbiota composition and restored microbial balance, but also increased the abundance of beneficial bacteria such as *Eubacterium_brachy_group* and *Ruminococcus*. These changes were accompanied by alleviated systemic inflammation and improved renal metabolic profiles^[18]. Second,

they inhibit XOD activity and degrade intestinal purines, curtailing UA production at its source and alleviating metabolic burden. This is exemplified by *Lactobacillus rhamnosus* 1155 (LR1155), which exerts beneficial effects through significant inhibition of hepatic and serum XOD activity, along with alleviation of hyperuricemia-induced gut microbial dysbiosis—an effect potentially linked to increases in genera like *Roseburia* and *Bifidobacterium*^[19]. In a complementary strategy, *Pediococcus acidilactici* GR-5 degrades purine nucleosides in the gut via a specific enzyme (DeoD), thereby reducing purine absorption. Functionally, this purine degradation works in concert with the modulation of gut microbiota composition, including an increase in *Lactobacilli*, and elevated SCFAs levels^[20]. Additionally, they synergistically regulate the expression of UA transporters in both the intestine and kidney, thus enhancing UA excretion. Evidence includes *Lactobacillus paracasei* 259 from traditional fermented yak yogurt, which effectively lowered UA in HUA rats by normalizing the expression of key UA transporters including ABCG2 and URAT1, ameliorating gut microbiota dysbiosis, and enhancing SCFAs production^[21]. Further supporting this, *Lactobacillus plantarum* LTJ1 and LTJ48 lowered serum UA levels in HUA mice through multi-tissue regulation of UA transporters: specifically by downregulating renal GLUT9 and URAT1 while upregulating intestinal ABCG2. This integrated action on transporters across tissues effectively rebalanced UA homeostasis^[22]. In summary, by means of this multi-target synergistic network of "source reduction—excretion promotion—indirect improvement" and leveraging the "gut-kidney axis" regulatory mechanism, LAB possess significant potential as a prospective microbiome-based therapy for alleviating HUA and its associated metabolic disorders.

Although numerous studies have demonstrated the potential of LAB in alleviating HUA, the current evidence predominantly stems from animal experiments, with a notable scarcity of validation through clinical research. Consequently, their clinical application and product development remain considerable challenges. Furthermore, in the limited number of human studies available, the reported mechanisms of action are often circumscribed^[23–26] (e.g., increasing SCFAs levels or promoting UA excretion), lacking the evidence for the comprehensive, multi-target synergistic network observed in animal models.

Therefore, a key translational question remains: whether the integrated, multi-target synergy of LAB observed in animals can be achieved in humans, or if the clinical effects are more limited. Answering this requires clinical trials specifically designed to probe for such multifaceted effects, to bridge the gap between promising preclinical paradigms and validated human application.

Based on preliminary screening, *Lactobacillus rhamnosus* CCFM1131 demonstrated potential for improving HUA in mouse models. This strain reshapes gut microbiota structure and significantly reduces UA levels, with its mechanism of action linked to inhibition of XOD activity^[27]. To evaluate its actual efficacy in humans, we further conducted a randomized, double-blind, placebo-controlled clinical trial aimed at systematically assessing the intervention effect of *L. rhamnosus* CCFM1131 on UA levels in individuals with HUA. This study holds promise for providing a safe and effective microbiome intervention strategy for the clinical management of HUA.

2. Materials and methods

2.1 Patient recruitment and ethical statement

This clinical study was conducted across multiple sites, including Jiangnan University and Yixing People's Hospital, with all volunteers recruited at Yixing People's Hospital. The randomized, double-blind, placebo-controlled trial was registered with the China Clinical Trial Registry (<https://www.chictr.org.cn>) in accordance with international ethical standards (registration number: ChiCTR2500096202) and approved by the Medical Ethics Committee of Yixing People's Hospital, Jiangsu Province, China (Ethics Review Opinion No.: 2024 Department 100-01). All procedures were conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to enrollment.

The written informed consent process was conducted as follows: After ethics committee approval, certified physicians provided face-to-face explanations to potential participants in private rooms. The discussion covered the study purpose, procedures, risks, benefits, randomization and blinding (including possible placebo assignment), follow-up, and data confidentiality. Participants were clearly informed of their right to withdraw anytime without penalty or impact on medical care. A minimum 24-hour consideration period was provided, after which all questions were addressed. Once full understanding and voluntary agreement were confirmed, participants and the investigator signed the consent form together, with a copy given to the participant. (For participants with limited reading or comprehension ability, an independent, non-conflicted witness attended the entire process and countersigned the form)

2.2 Patient inclusion criteria

The inclusion criteria for HUA patients were as follows^[23]: (a) met diagnostic criteria for HUA; (b) no gender restriction, aged between 18 and 65 years; (c) fasting serum UA levels measured on two separate days, exceeding 420 $\mu\text{mol/L}$ for males and 360 $\mu\text{mol/L}$ for females; (d) good compliance with clinical study requirements; (e) signed informed consent; (f) completion of written informed consent, International Physical Activity Questionnaire, and dietary structure survey, with commitment to cooperate throughout the study.

2.3 Patient exclusion criteria

Exclusion criteria for HUA patients were as follows:

Factors that may significantly interfere with research results:

ethanol equivalent intake > 40 g/week;

(b) supplementation with nutrients such as probiotics, multivitamins/minerals, antioxidants, and omega-3 fatty acids at least twice weekly during the study period or within the past 3 months;

(c) rapid weight loss within the past 6 months, total parenteral nutrition, or protein malnutrition;

2. Specific medication history:

(d) regular intake within the past 6 months of nonsteroidal anti-inflammatory drugs, antibiotics, corticosteroids, antineoplastic agents, antituberculosis drugs, or certain herbal and mineral medicines (e.g., *Strychnos nux-vomica*/arsenic trisulfide);

(e) use within the past 6 months of antisecretory drugs causing gastric acid deficiency, amiodarone, sodium valproate, prednisone, tamoxifen, piroxicam, methotrexate, hepatotoxic drugs, hormonal medications, statins, antihypertensive agents, or ursodeoxycholic acid;

(f) patients with long-term or recent use of drugs affecting serum UA levels;

3. Include other conditions that may affect uric acid metabolism or study safety:

(g) patients experiencing an acute gout attack;

(h) patients with secondary HUA due to glomerular disease, lead poisoning, hematologic disorders, tumor radiation/chemotherapy, or long-term diuretic use; patients with severe primary cardiovascular, cerebrovascular, hepatic, renal, hematopoietic, or psychiatric disorders;

4. Research participation and safety-related contraindications:

(i) abuse of narcotics, psychotropic drugs, or cigarettes within the past 6 months;

(j) allergy or intolerance to components of the study probiotic product;

(k) poor patient compliance or low likelihood of follow-up.

5. Individuals with special physiological conditions:

(l) pregnant or lactating women;

2.4 Criteria for exclusion, withdrawal, and trial termination

(a) Reasons for exclusion: Volunteers enrolled despite failing to meet inclusion criteria (e.g., erroneous enrollment, misdiagnosis, no prior product use, or incomplete test records) were excluded. The specific reason for exclusion was documented, and corresponding records were retained for verification. Excluded cases were not included in efficacy statistical analyses; however, if a case received at least one treatment and had safety records, it was included in adverse reaction analyses.

(b) Description of withdrawals: Cases enrolled but failing to complete the clinical trial protocol due to voluntary withdrawal, loss to follow-up, or physician-requested discontinuation owing to compliance issues or complications were classified as withdrawals. Detailed reasons for withdrawal were documented. Where initial product efficacy data existed, the last recorded primary treatment outcome was considered for statistical analysis as the final result, with all relevant records retained for future reference.

(c) Complete trial termination: Trials could be terminated completely for various reasons, including safety concerns identified by investigators, inadequate treatment efficacy, severe adverse effects, inability of the sponsor to continue supporting the study due to funding or management issues, or revocation orders issued by administrative authorities. In cases of complete trial termination, all relevant records and materials were properly preserved for future review.

2.5 Probiotic products

The probiotic strain *Lactobacillus rhamnosus* CCFM1131 was provided by Jiangnan University. Volunteers in the intervention group received a daily stick of the probiotic product containing this strain, with each stick (2g/bag) providing approximately 6×10^9 colony-forming units (CFU) of viable bacteria in a lyophilized powder formulation. The full composition of this product, including the cryoprotectant and carrier, is detailed in Table S1. The placebo product was identical in appearance, maltodextrin content, and cryoprotectant composition to the probiotic formulation, with the sole exception of containing no bacterial cells. All products were manufactured by the Yangzhou Institute of Food Biotechnology (Jiangsu, China) in compliance with the national standard GB/T 29602. The products were packaged in vacuum-sealed sticks and stored at 4°C throughout the trial to maintain stability and bacterial viability.

2.6 Sample size calculation, study design, randomization and masking

The sample size for this study was estimated based on a prior randomized controlled trial reporting a decrease in serum uric acid levels from $(477.3 \pm 33.4) \mu\text{mol/L}$ to $(449.5 \pm 43.8) \mu\text{mol/L}$ following probiotic intervention^[26], the calculated effect size (Cohen's *d*) based on this data was 0.7137. To ensure adequate sample size, we adopted a conservative approach and rounded the effect size to $d = 0.7$ for subsequent calculations. Sample size estimation was performed using G*Power 3.1 (Fig. S1). A sample size of 26 participants per group was required to achieve an effect size of $d = 0.7$ at $\alpha = 0.05$ and Power = 0.8. Assuming a 25% dropout rate during the trial, each group initially required at least $26/(1-0.25) = 34.7$ volunteers. Rounding to the nearest whole number, 35 participants per group were needed. Therefore, a minimum of 70 volunteers must be recruited across both groups.

A one-week run-in period was implemented to confirm participant eligibility based on the HUA diagnostic criteria and other inclusion/exclusion criteria. During this phase, volunteers were instructed to maintain their habitual diet and lifestyle. Baseline assessments were completed, including the Volunteer Basic Information form, Dietary Structure Questionnaire (Table S2), and the International Physical Activity Questionnaire (Table S3), as part of the Study Case Report Form.

Participants were randomized according to the order of their enrollment at the study site. A randomization schedule was generated using SPSS software (version 22.0) based on case numbers and a predetermined allocation ratio. The randomization list was securely maintained by both the clinical research management unit and the study sponsor.

The clinical study was conducted at Yixing People's Hospital in Jiangsu Province, China, between December 2024 and June 2025. As illustrated in the study flowchart (Fig. 1), the trial employed a single cohort design, which was randomly allocated into two parallel groups: the *Lactobacillus rhamnosus* CCFM1131 group and the placebo group. Participants were instructed to dissolve one sachet of the assigned product in warm water ($\leq 37^\circ\text{C}$) and consume it within 30–60 minutes after lunch or dinner each day. The intervention period lasted 8 weeks, with dietary habits monitored through regular follow-ups to minimize variability. The trial duration and probiotic dosage were determined based on previous preclinical and clinical evidence.

Randomization was conducted using sealed envelopes. The envelopes could be opened by the chief investigator after relevant data were recorded on the computer. The double-blind principle was maintained by ensuring no differences in appearance or packaging between the two products. Unmasking of the trial occurred after completion of the trial and determination of all experimental indicators.

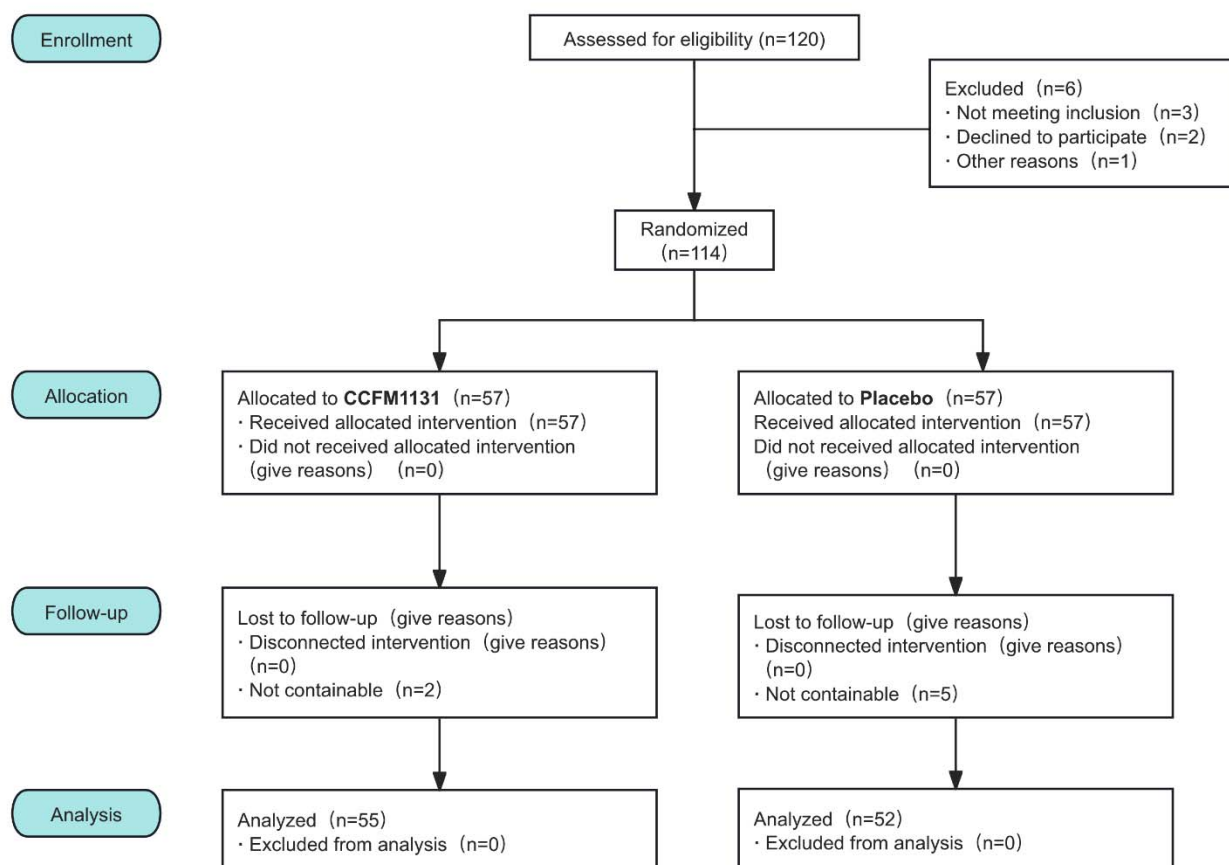


Fig. 1. Experimental research flowchart.

2.7 Sample collection and clinical parameter measurement

During the initial phase of the study, healthcare personnel assisted in collecting blood samples from HUA patients, which were placed in disposable vacuum blood collection tubes. Following the two-month intervention period, blood samples were collected again from the HUA patients. After natural coagulation, the blood samples were centrifuged (3500 r/min, 10 min). The supernatant was then transferred to PCR tubes, labeled with sample numbers, and stored at -80°C for subsequent analysis.

Similarly, stool samples were collected from HUA patients prior to the intervention. Following the two-month intervention period, stool samples were collected again from the same patients. All stool samples were collected using disposable sterile stool collection tubes and immediately stored at -80°C for subsequent parameter measurements.

All biochemical analyses were performed using the LABOSPECT 008a fully automated biochemical analyzer (Hitachi, Japan), with corresponding kits purchased from Ningbo Ruiyuan Biotechnology Co., Ltd. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase

(GGT) were measured via their respective substrate methods. Urea was measured using the urease UV liquid phase method, creatinine using the creatine oxidase method, and uric acid (UA) using the uricase method. Xanthine oxidase (XOD) activity was measured using the XOD Activity Assay Kit from Solarbio Life Science Co., Ltd. (BC1095, Beijing, China).

2.8 Gut microbiome analysis and functional prediction

Total microbial DNA from fecal samples was extracted following the instructions of the FastDNA Spin Kit for Feces (MP Biomedicals, Irvine, CA, USA). The complete step-by-step protocol, including the critical mechanical lysis step, is provided in Supplementary Methods (Text S1). The V3-V4 region of the 16S rRNA gene was amplified by polymerase chain reaction (PCR), and PCR products were separated by 1.5% agarose gel electrophoresis. The universal primer pair (341F/806R, targeting the V3-V4 region) was employed for sequencing the 16S rRNA gene amplicons^[28, 29]. Specific bands were excised and purified according to the instructions of the DNA Gel/PCR Purification Miniprep Kit (Invitrogen Ambion, USA). Sequencing was performed on the Illumina MiSeq high-throughput sequencing platform (Illumina MiSeq PE300, San Diego, CA, USA), and 16S rRNA sequencing data were analyzed for quality control, assembly, and annotation based on the QIIME 2 platform^[30]. Microbial communities were evaluated by α -diversity indices (Shannon, Evenness, Chao1, and Simpson). Linear discriminant analysis effect size (LEfSe) was performed using the OmicStudio tools (<https://www.omicstudio.cn/tool/>). Beta diversity was assessed using weighted UniFrac distances and visualized by principal coordinate analysis (PCoA). The functional characteristics of the gut microbiota were predicted using PICRUSt2.

2.9 Fecal/serum untargeted metabolomics assay

Unfrozen serum samples were removed from the -80°C freezer and prepared as follows: (1) Aliquot 100 μ L of serum into a 1.5 mL centrifuge tube; (2) Add 400 μ L methanol (or methanol: acetonitrile = 1:1) (pre-chilled to -20°C) to precipitate proteins; a large amount of white flocculent material will form upon addition; (3) Vortex for 30 seconds; (4) Incubate the sample at -20°C for 1 hour to enhance protein precipitation (secondary precipitation to remove proteins); (5) Centrifuge at 12,000 rpm for 15 min at 4°C; (6) Remove supernatant and evaporate to dryness using a rotary evaporator; (7) Resuspend by adding 100 μ L acetonitrile: water (1:1, v/v) and vortex for 30 seconds; (8) Quality control (QC) preparation: Transfer an equal volume from the prepared test sample to a new injection vial and mix thoroughly; (9) Blank preparation: Add 1 mL acetonitrile: water (1:1, v/v) to the injection vial and mix thoroughly.

Freeze-dried fecal samples were pretreated as follows: (1) Transfer 20-30 mg tissue sample into a 1.5 mL centrifuge tube, add 200 μ L H₂O and homogenize; (2) Add 800 μ L methanol: acetonitrile = (1:1, v/v) (pre-chilled at -20°C) to precipitate proteins; (3) Add two grinding beads and vortex for 30 seconds; process in a tissue homogenizer at 65 Hz for 40 seconds, repeated three times; (4) Incubate the sample at -20°C for 1 hour to enhance protein precipitation (secondary precipitation to remove proteins); (5) Centrifuge at 12,000 rpm at 4°C for 15 minutes; (6) Remove supernatant and evaporate to dryness using a rotary evaporator; (7) Resuspend by adding 200 μ L acetonitrile: water (1:1, v/v) and vortex for 30 seconds; (8) Centrifuge at

12,000 rpm for 15 minutes at 4°C. Transfer supernatant through a 0.22 µm filter membrane, and dispense appropriate volume into a sample vial for instrument analysis; (9) QC preparation: Transfer an equal volume from the test sample to a new injection vial and mix thoroughly to prepare the QC sample; (10) Blank preparation: Add 1 mL of acetonitrile: water (1:1, v/v) to the injection vial and mix thoroughly;

Liquid chromatography-tandem mass spectrometry conditions were as follows: (1) Liquid chromatography conditions: For positive ion scanning mode, mobile phase consisted of (A) 0.1% formic acid aqueous solution and (B) acetonitrile; for negative ion scanning mode, mobile phase consisted of (A) 5 mmol/L ammonium acetate aqueous solution and (B) acetonitrile. Gradient elution: 0–1.0 min, 2% B; 1.0–10 min, 98% B; 10–12 min, 98% B; 12–15 min, 2% B. Column temperature: 35°C; flow rate: 0.3 mL/min; injection volume: 2 µL. Sample tray temperature: 4°C. (2) Mass spectrometry conditions: Electron spray ionization (ESI) was employed in full scan mode for both positive and negative ion acquisition. The scan range was 70–1050 m/z. The spray voltage was 3.5 kV for positive ions and 3.2 kV for negative ions. The capillary temperature was 320°C. The sheath gas flow rate was 35 arb, the drying gas flow rate was 15 arb, and the drying gas temperature was 320°C.

Raw data files were imported into Compound Discoverer 3.3 software (Thermo Fisher Scientific, MA, USA) and analyzed using the software's built-in workflows: "Untargeted Metabolomics with Statistics," "Detect Unknowns with ID using Online Databases," and "mzLogic". Employing principal component analysis (PCA) to effectively visualize differential metabolite information across distinct. Differential metabolites were screened with a fold change (FC) threshold of >1.5 (based on median abundance) and a significance threshold of FDR-adjusted *P*-value < 0.05. Pathway enrichment analysis was performed using MetaboAnalyst 5.0 (<https://www.metaboanalyst.ca/>). The list of significantly altered metabolites was uploaded and mapped against the KEGG metabolic pathways. The enrichment significance was evaluated using a hypergeometric test, and the resulting *P*-values were adjusted for multiple testing using the false discovery rate (FDR) correction.

2.10 Data statistics and analysis

Experimental data are expressed as "mean ± standard deviation" and analyzed using GraphPad Prism 10.0 and SPSS 25 for statistical graphing and analysis. The Shapiro-Wilk test was employed to assess data normality (*P* > 0.05 indicates normal distribution). Intergroup comparisons employed independent samples *t*-tests (for normally distributed data) or Wilcoxon signed-rank tests (for non-normally distributed data). Intragroup comparisons utilized paired *t*-tests (for normally distributed data) or Wilcoxon signed-rank tests (for non-normally distributed data). Prior to correlation analysis, data were tested for normality using the Shapiro-Wilk test, as the microbial community data were found to be non-normally distributed, Spearman's rank correlation analysis was therefore employed to compute correlations between indicators. *P* < 0.05 was considered statistically significant.

3. Results

3.1 Patient recruitment and baseline enrollment

A total of 120 volunteers with HUA were recruited for this study. Following a rigorous screening process, three volunteers who did not meet the inclusion criteria, two who refused participation, and one who discontinued for other reasons were excluded. Ultimately, 114 eligible volunteers were randomly allocated to either the CCFM1131 group or the placebo group, with 57 volunteers in each group.

During follow-up, 2 volunteers in the CCFM1131 group and 5 volunteers in the placebo group were lost to follow-up. Consequently, the final data analysis included 55 volunteers from the CCFM1131 group and 52 from the placebo group. Baseline characteristics for both groups are presented in Table 1. The mean age in the CCFM1131 group was (43.78 ± 12.88) years, with an average body mass index (BMI) of (25.99 ± 3.36) kg/m². The mean age in the placebo group was (43.90 ± 11.22) years, with an average BMI of (25.96 ± 2.97) kg/m², no statistically significant differences were observed between groups. Prior to intervention, all baseline physiological parameters (including serum UA, XOD activity, liver function, and renal function indicators) showed no significant differences between groups ($P > 0.05$). This finding excluded potential confounding effects from differing initial conditions, thereby providing a reliable foundation for subsequent evaluation of the probiotic's independent intervention effect.

Table 1. Baseline Characteristics of Participants

Characteristics	CCFM1131 (N=55)	Placebo (N=52)	P value
Age(years)	43.78±12.88	43.90±11.22	0.669 ^{NS}
Gender(male/female)	45/10	48/4	0.108 ^{NS}
BMI (kg/m ²)	25.99±3.36	25.96±2.97	0.888 ^{NS}
Urea (mmol/L)	5.69±1.33	5.85±1.32	0.526 ^{NS}
Creatine (μmol/L)	79.70±15.81	79.31±10.29	0.881 ^{NS}
UA (μmol/L)	514.30±69.26	504.70±53.14	0.429 ^{NS}
AST (IU/L)	24.61±10.27	22.91±11.88	0.280 ^{NS}
ALT (IU/L)	34.10±24.98	29.71±18.42	0.932 ^{NS}
GGT (IU/L)	53.26±60.91	56.33±48.95	0.306 ^{NS}
XOD (U/L)	21.82±7.67	23.14±6.57	0.260 ^{NS}

NS, not significant; N, number of participants; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, gamma-glutamyltransferase; XOD, xanthine oxidase.

3.2 Effects of CCFM1131 on renal function indicators

As the primary excretory organ for UA in the human body, the kidneys play a central role in maintaining UA homeostasis. Under normal physiological conditions, approximately 70% of the UA produced daily is excreted via the kidneys. When UA production is excessive or excretion is insufficient, the kidneys must correspondingly adjust UA excretion to maintain dynamic UA equilibrium. Following an 8-week intervention, serum UA concentration in the CCFM1131 group decreased significantly from (514.3 ± 69.3) μmol/L to (486.7 ± 84.7) μmol/L ($P = 0.0005$), whereas no significant difference was observed in the placebo group before and after intervention ($P > 0.05$, Fig. 2). Intergroup comparison further confirmed that the CCFM1131 group exhibited significantly lower UA concentrations post-intervention compared to the placebo group ($P = 0.0431$). Regarding creatinine and urea concentrations, no statistically significant changes were observed in either group before or after the 8-week intervention ($P > 0.05$).

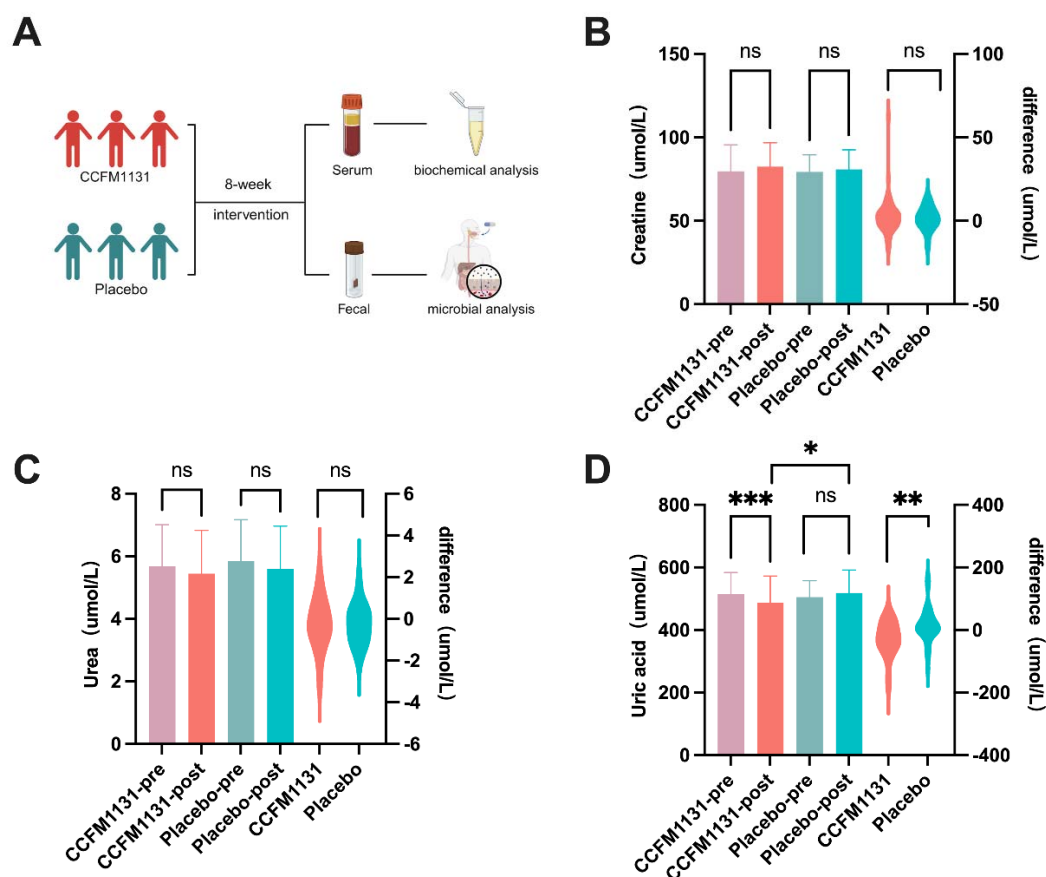


Fig. 2 Effects of CCFM1131 on renal function indicators. (A) Sample collection and analysis workflow. (B) Creatinine. (C) Urea. (D) Uric acid. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$; NS, not significant.

3.3 Effects of CCFM1131 on liver function indicators

As the primary site for purine metabolism and UA production in the body, liver function is closely associated with HUA. As shown in Fig. 3, after an 8-week intervention, no statistically significant changes ($P > 0.05$) were observed in conventional liver function markers—including AST, ALT, and GGT concentrations—between the CCFM1131 and placebo groups. In contrast, a significant intervention effect was observed in the key pathway of UA production. XOD is the core rate-limiting enzyme in UA synthesis and also a major source of oxidative stress in the body. Following an 8-week CCFM1131 intervention, serum XOD levels in patients decreased significantly from (21.82 ± 7.67) U/L to (18.86 ± 8.66) U/L ($P = 0.0048$). Post-intervention levels remained significantly lower than those in the placebo group (23.10 ± 6.99) U/L, $P = 0.0032$). This trend closely aligned with the reduction in serum UA concentration, suggesting that CCFM1131 may effectively reduce UA production by inhibiting XOD activity.

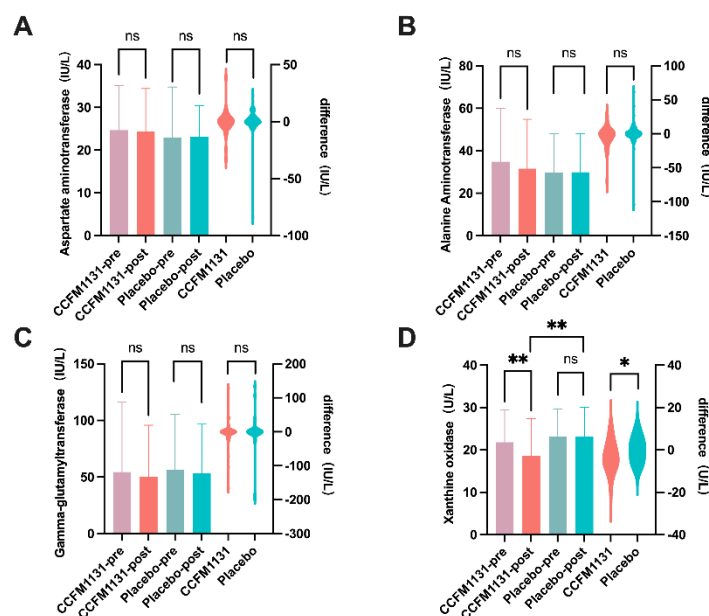


Fig. 3 Effects of CCFM1131 on liver function indicators. (A) Aspartate aminotransferase. (B) Alanine aminotransferase. (C) Gamma-glutamyltransferase. (D) Xanthine oxidase. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; **** $P < 0.0001$; NS, not significant.

3.4 Alterations in gut microbiota structure following CCFM1131 intervention

To investigate the effects of CCFM1131 on gut microbiota in HUA patients, fecal samples from both groups were analyzed via 16S rRNA gene sequencing before and after intervention. Alpha diversity was assessed using Shannon index, Evenness index, Chao1 index, and Simpson index. After an 8-week intervention, no significant changes in α -diversity were identified between the CCFM1131 and placebo groups, suggesting that neither intervention notably affected gut microbial richness or evenness (Fig. 4B). However, PCoA analysis (Fig. 4A) revealed that the gut microbial community structure of patients significantly changed after CCFM1131 intervention ($P = 0.002$), while no significant difference was observed in the placebo group before and after intervention ($P = 0.936$). In clinical intervention studies, the placebo effect represents a significant confounding factor. The CCFM1131 intervention induced a substantial restructuring of the overall gut microbial community architecture, whereas the placebo group remained stable. This indicates that the observed changes were driven by the specific effects of the probiotic itself, further supporting the potential mechanism whereby CCFM1131 may improve HUA by modulating the gut microbiota.

Stacked histograms displayed changes in gut microbiota phylum-level composition before and after intervention in both groups, with *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* being the four phyla with the highest relative abundances (Fig. 4C). Results showed that compared to pre-intervention levels, patients in the CCFM1131 group exhibited significantly reduced abundance of the *Firmicutes* phylum and significantly increased abundance of the *Bacteroidetes* phylum post-intervention (Fig. 4D). LEfSe analysis compared differentially abundant genera between groups post-intervention, setting linear discriminant analysis (LDA) score > 3 , Kruskal-Wallis test ($P < 0.05$), and Wilcoxon test ($P < 0.05$) as screening criteria (Fig. 4E). Analysis indicated that genera significantly enriched after CCFM1131

intervention included *Megamonas*, *Bifidobacterium*, *Helicobacter*, *Haemophilus*, *Candidatus Actionmarina*, *Dialister*, and *Lactobacillus*. *Peptoclostridium*, *Coprococcus2*, and *Clostridium sensu stricto1* were enriched following placebo intervention (Fig. 4F).

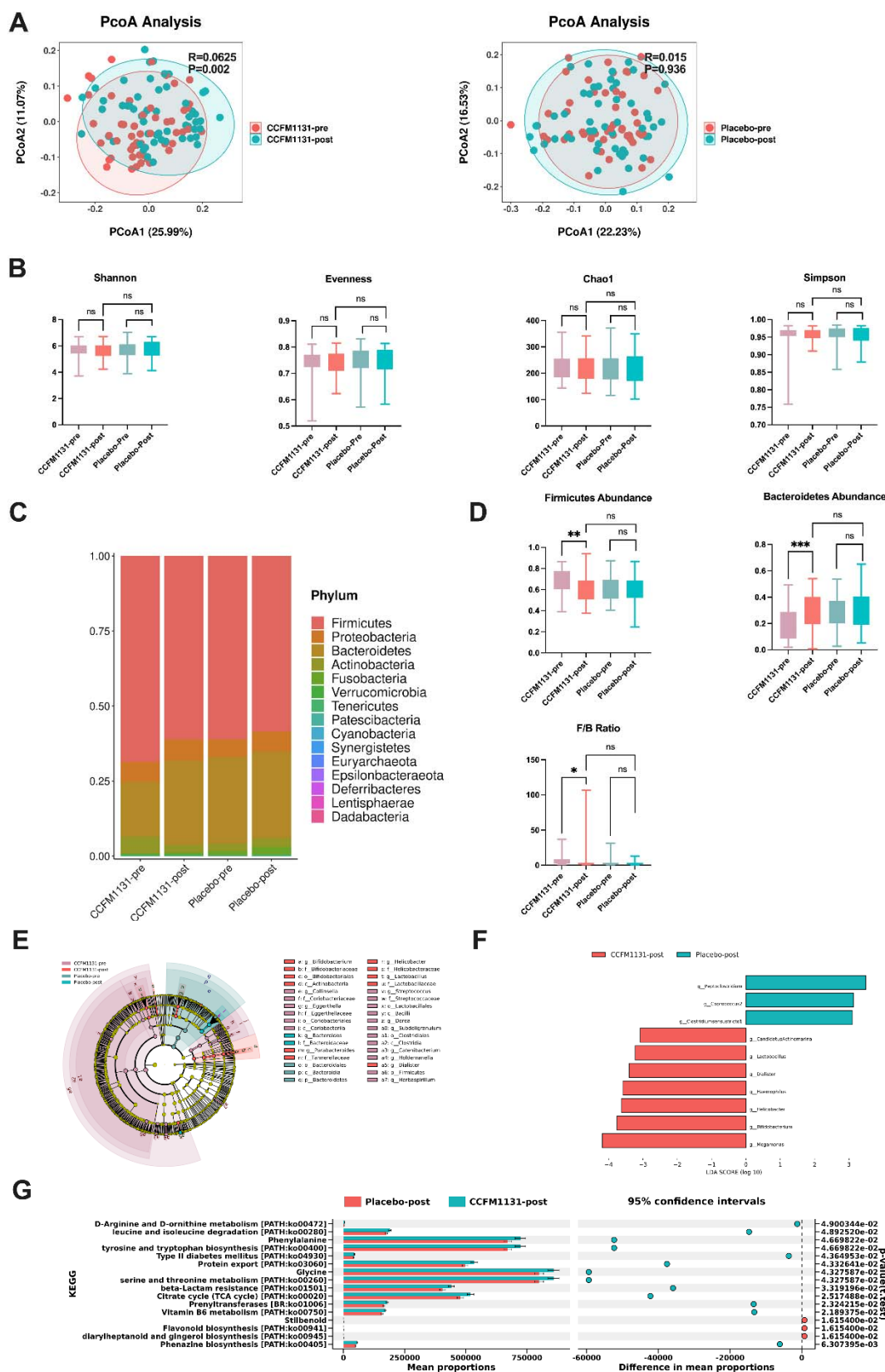


Fig. 4 The effect of CCFM1131 on the gut microbiota of patients. (A) PCoA analysis. (B) α -diversity analysis. (C) Phylum-level microbial bar chart. (D) Changes in Firmicutes, Bacteroidetes abundance and F/B ratio. (E) Linear discriminant analysis effect size. (F) LDA bar chart of differentially abundant genera (log (LDA score) > 3, FDR-adjusted P < 0.05). (G) PICRUSt2-predicted functional metabolic pathways.

To elucidate functional differences in microbial communities under different intervention conditions, Kyoto Encyclopedia of Genes and Genomes (KEGG) metabolic pathways were predicted using the Phylogenetic Investigation of Communities by Reconstruction of Unobserved States 2 (PICRUSt2) method based on the top 30 genera by absolute abundance (Fig. 4G). Results showed significant enrichment of flavonoid biosynthesis and diarylheptanoid and gingerol biosynthesis pathways in the Placebo-post group. In contrast, the CCFM1131-post group exhibited significant enrichment in glycine, serine and threonine metabolism; leucine and isoleucine degradation; type II diabetes mellitus pathway; citrate cycle (TCA cycle); and vitamin B6 metabolism pathways.

3.5 Correlation analysis of gut microbiota and clinical indicators

To systematically clarify the potential associations between gut microbiota and host clinical indicators, Spearman correlation analysis was employed, and a clustering heatmap was constructed to evaluate association patterns between microbial genus-level composition and serum physiological parameters (Fig. 5). Results indicated that XOD activity exhibited significant negative correlations with multiple bacterial genera, including *Alistipes*, *Adlercreutzia*, *Butyricimonas*, *Desulfovibrio*, and *Ruminococcaceae* UCG-002. Serum UA levels demonstrated significant negative correlations with certain genera, notably *Alistipes*, *Dialister*, *Ruminococcaceae* NK4A214 group, *[Ruminococcus] gauvreauii* group, and *Roseburia*. Conversely, genera including *Escherichia-Shigella*, *Fusobacterium*, *[Ruminococcus] torques* group, and *Lachnospirillum* exhibited significant positive correlations with UA levels. These findings suggest that alterations in specific gut microbial community structures may be closely associated with the regulation of host physiological indicators related to purine metabolism.

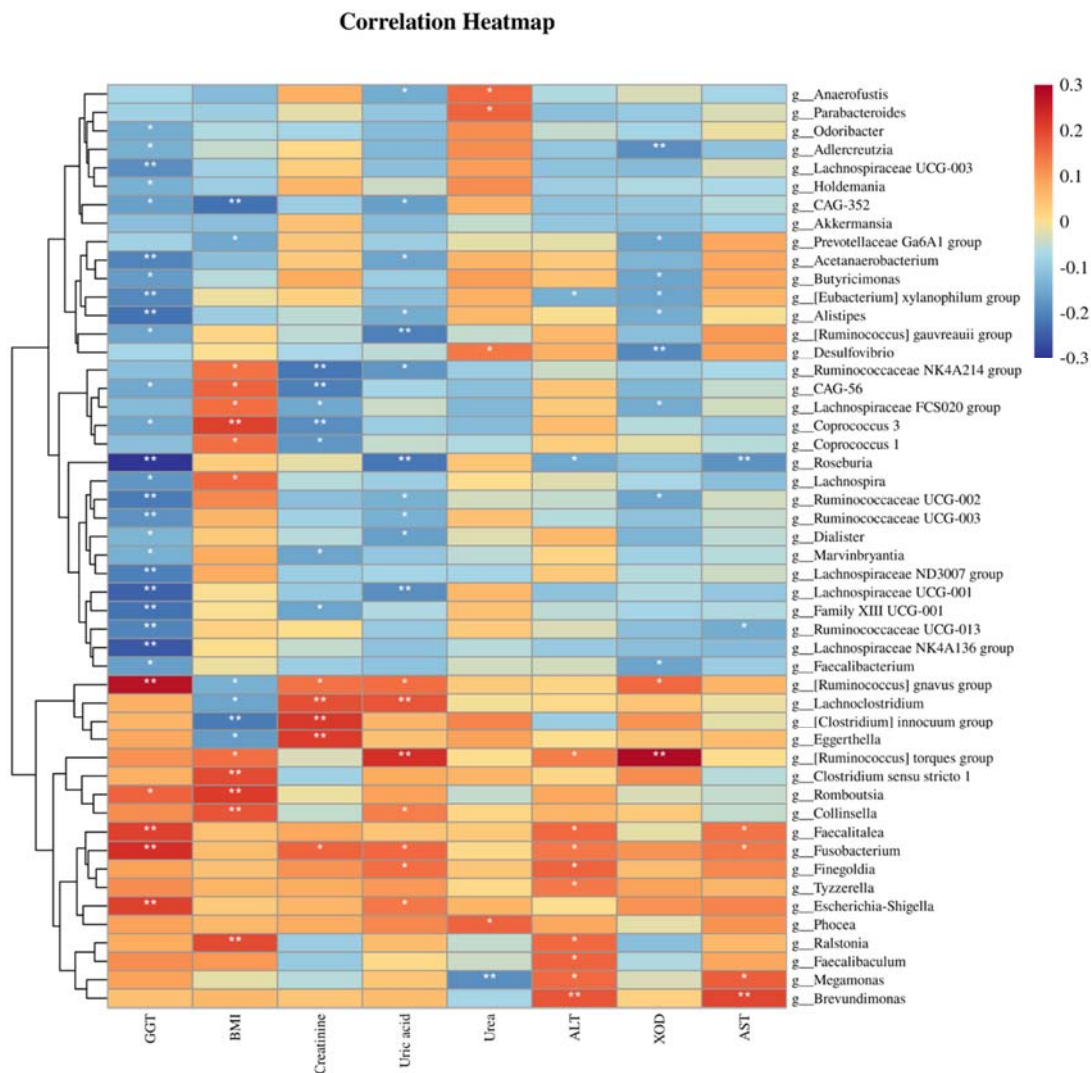


Fig. 5 Correlation clustering heatmap between gut microbiota and clinical indicators.

3.6 Effects of CCFM1131 intervention on metabolites in HUA patients

3.6.1 Effects of CCFM1131 on overall metabolite profiles

Following clarification of microbiota-host phenotype associations, untargeted metabolomics analysis was performed on post-intervention fecal and serum samples from both groups. After processing with Compound Discoverer 3.3 software and condition screening, 283 fecal metabolites and 388 serum metabolites were identified. PCA plots of both metabolite sets were performed (Fig. 6A, 6B). PERMANOVA analysis revealed significant differences in overall fecal metabolite profiles between CCFM1131-post and Placebo-post groups ($P < 0.05$), whereas no significant differences were observed in overall serum metabolite profiles.

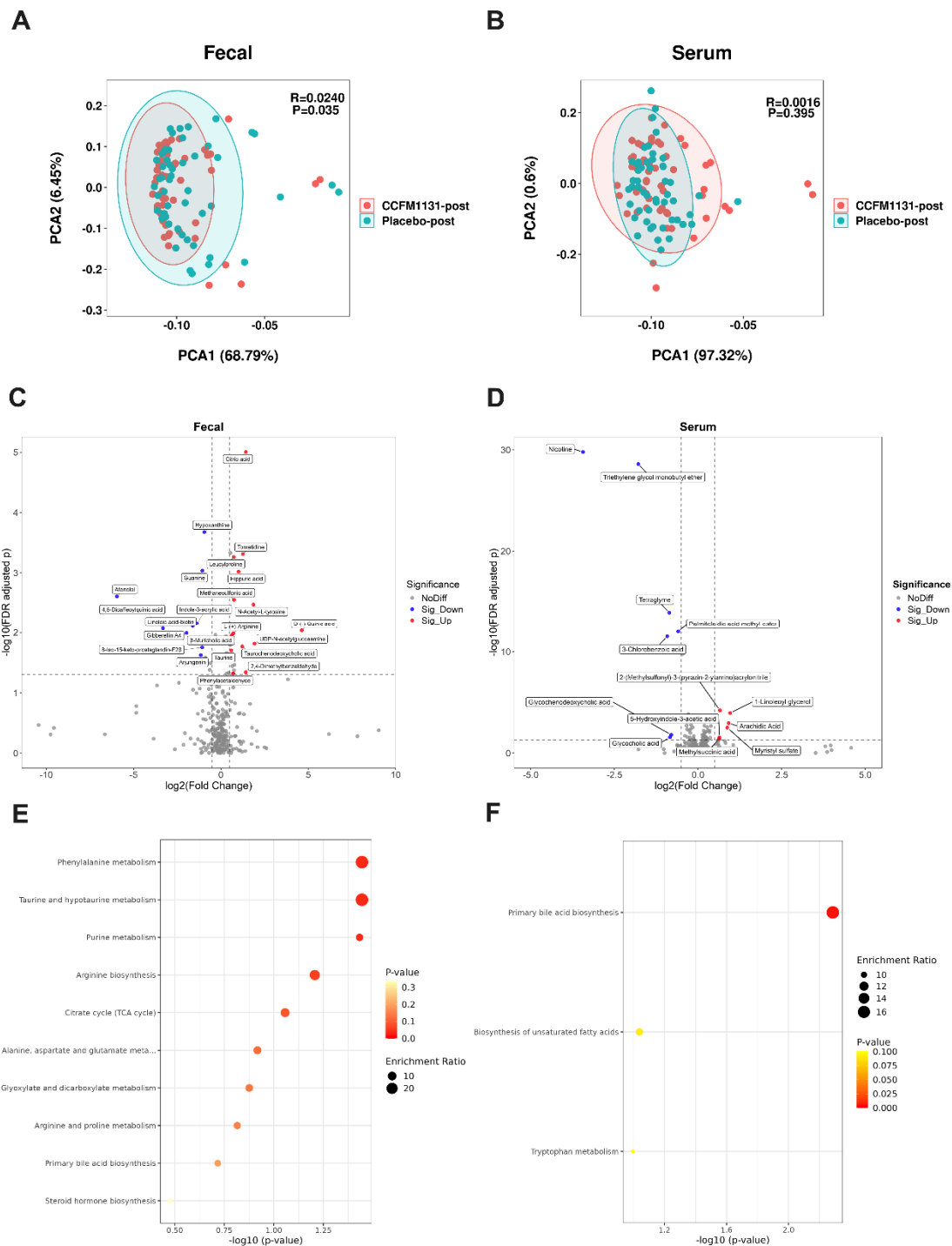


Fig. 6 Effects of CCFM1131 intervention on metabolites in HUA patients. (A) PCA analysis of fecal metabolites after intervention in both groups. (B) PCA analysis of serum metabolites after intervention in both groups. (C) Volcano plot of fecal differential metabolites. (D) Volcano plot of serum differential metabolites. (E) Fecal differential metabolite pathway enrichment analysis. (F) Serum differential metabolite pathway enrichment analysis.

3.6.2 Effect of CCFM1131 on fecal metabolites in HUA patients

Based on the pre-defined criteria ($FC > 1.5$; FDR-adjusted $P < 0.05$), a total of 23 substances were identified in the fecal samples (Fig. 6C). 14 metabolites including tomatidine, citric acid, β -Muricholic acid, hippuric acid, D-(-)-Quinic acid, L-(+)-Arginine, leucylproline, taurine, taurochenodeoxycholic acid, UDP-N-acetylglucosamine, N-Acetyl-L-tyrosine, methanesulfonic acid, phenylacetaldehyde and

2,4-Dimethylbenzaldehyde were significantly increased in the feces of HUA patients. Metabolites including hypoxanthine, guanine, arjungenin, 4,5-Dicaffeoylquinic acid, indole-3-acrylic acid, atenolol, 8-Iso-15-keto-prostaglandin-F2 β , gibberellin A4 and linoleic acid-biotin were significantly decreased. The relative abundance, fold change (Log2FC), and *P*-values of fecal differential metabolites are detailed in Table S4.

3.6.3 Effect of CCFM1131 on serum metabolites in HUA patients

Based on the pre-defined criteria ($FC > 1.5$; FDR-adjusted $P < 0.05$), a total of 13 substances were identified in serum samples (Fig. 6D), among which 1-Linoleoyl glycerol, 2-(Methylsulfonyl)-3-(pyrazin-2-ylamino) acrylonitrile, 5-hydroxyindole-3-acetic acid, arachidic acid, methylsuccinic acid, and myristyl sulfate were significantly increased in the serum metabolites of HUA patients. Nicotine, 3-Chlorobenzoic acid, glycocholic acid, glycochenodeoxycholic acid, palmitelaidic acidmethyl ester, tetraglyme and triethylene glycol monobutyl ether metabolites were significantly increased in the serum metabolites of HUA patients, and were significantly decreased. The relative abundance, fold change (Log2FC), and *P*-values of serum differential metabolites are detailed in Table S5.

3.6.4 Pathway enrichment analysis

After the identification of differentially expressed metabolites through untargeted metabolomics based on high-resolution mass spectrometry and other techniques, biological context was assigned to these metabolites using the KEGG database, which provides standardized molecular identifiers, systematic nomenclature, and maps discrete metabolites to their participating metabolic pathways. Differential metabolites in feces and serum were compared with the KEGG database, and matched metabolites were subjected to pathway enrichment analysis. Based on KEGG alignment results, compared to the Placebo-post group, fecal differential metabolites in the CCFM1131-post group showed significant differences in purine metabolism, phenylalanine metabolism, taurine and hypotaurine metabolism, arginine biosynthesis, TCA cycle, alanine, aspartate and glutamate metabolism, glyoxylate and dicarboxylate metabolism, arginine and proline metabolism, primary bile acid biosynthesis, and steroid hormone biosynthesis (Fig. 6E). Serum differential metabolic pathways were primarily enriched in primary bile acid biosynthesis, biosynthesis of unsaturated fatty acids, and tryptophan metabolism (Fig. 6F).

3.7 Correlation analysis of gut microbiota and differential metabolites

To delve deeper into the core mechanisms by which CCFM1131 regulates UA, analysis was focused on three key aspects based on pathway enrichment results: (1) purine metabolism, due to its direct association with UA biosynthesis; (2) taurine and hypotaurine metabolism, whose roles in maintaining cellular osmotic pressure and countering oxidative stress may indirectly influence UA homeostasis; (3) the intestinal UA excretion pathways mediated by metabolites such as hippuric acid. Structural data of the gut microbiota were integrated to investigate the microbial drivers underlying the changes in these key metabolic pathways through correlation analysis (Fig. 7). In the purine metabolic pathway, guanine showed significant negative

correlations with several genus-level flora such as *Lachnospiraceae* UCG-008, *Aggregatibacter*, *Peptococcus*, and *Rothia*; hypoxanthine showed significant negative correlations with *Lachnospiraceae* UCG-008 and *Oscillospira*. In taurine and hypotaurine metabolism, taurine exhibited significant positive correlations with the genera *Lactobacillus*, *Ruminococcaceae* UCG-003, *Butyricimonas*, *Prevotella* 7, and CAG-352. In addition, in UA-related metabolism, hippuric acid demonstrated significant positive correlations with genera *Alloprevotella* and *Prevotellaceae* NK3B31 group. These correlations suggest that specific gut microbes may play potential functional roles in CCFM1131 intervention by modulating the levels of key host metabolites.

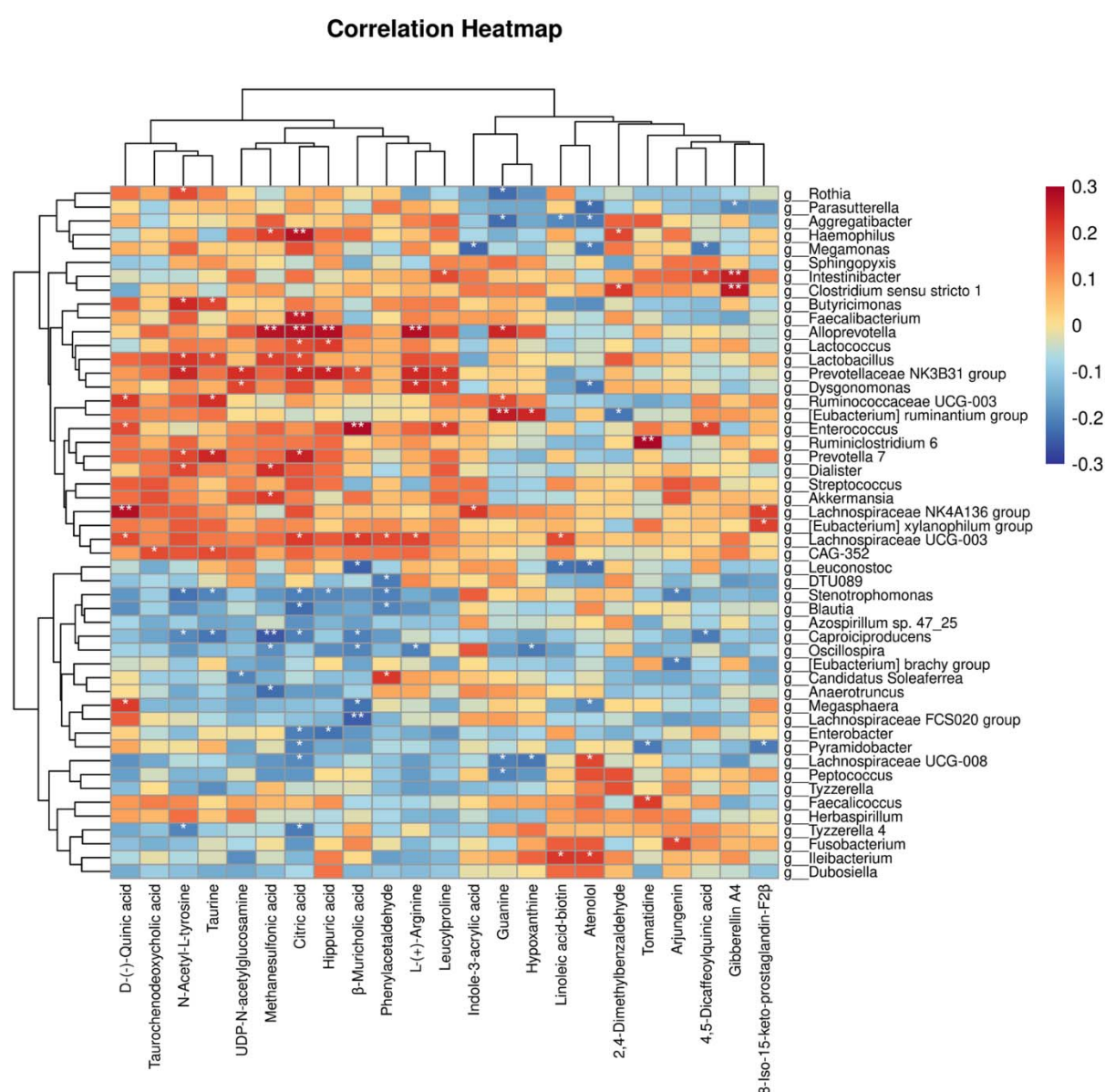


Fig. 7 Correlation clustering heatmap between gut microbiota and differential metabolites.

4. Discussion

Within the UA biosynthetic pathway, XOD serves as the key catalytic enzyme that sequentially converts hypoxanthine to xanthine and subsequently oxidizes it to UA^[31]. Moreover, XOD generates reactive oxygen species (ROS) during the catalytic reaction, establishing it as a major contributor to

systemic oxidative stress^[32]. Therefore, inhibition of XOD activity has become a cornerstone therapeutic option for the clinical treatment of HUA. However, while existing pharmacological treatments demonstrate efficacy, their long-term adverse effects underscore the need for safer alternative strategies^[14]. Given their favorable safety profiles and mild nature, probiotic interventions have emerged as promising strategies for HUA management. Building on its previously demonstrated urate-lowering efficacy in animal models, this randomized, double-blind, placebo-controlled trial evaluated the potential of *Lactobacillus rhamnosus* CCFM1131 to regulate serum UA levels and gut microbiota in patients with HUA. Following an 8-week intervention, CCFM1131 effectively modulated the gut microbiota composition, with a substantial reduction in serum UA levels and a marked suppression of serum XOD activity. These findings indicate that inhibition of XOD activity represents one of the functional pathways through which CCFM1131 achieves its UA-lowering effects in humans.

Patients with HUA frequently exhibit dysbiosis of the gut microbiota and impaired intestinal barrier function. CCFM1131 intervention promoted notable elevations in the abundance of beneficial bacteria such as *Bifidobacterium*, *Dialister* and *Lactobacillus*. Previous studies indicate that *Bifidobacterium* and *Lactobacillus* contribute to intestinal homeostasis through purine degradation, uricase activity regulation, and oxidative stress mitigation^[33–36]. *Dialister* regulates lipid metabolism and insulin resistance primarily through its metabolites, particularly short-chain fatty acids (SCFAs) such as propionic acid, thereby improving insulin sensitivity^[37]. More importantly, the microbiota-clinical indicator correlation analysis revealed a significant negative correlation between XOD activity and genera such as *Alistipes* and *Butyricimonas*. As an established SCFA-producing beneficial bacterium, *Butyricimonas* may downregulate serum XOD activity by increasing SCFA abundance^[38]. Additionally, both *Alistipes* and *Roseburia* exhibited pronounced negative correlations with serum UA levels, suggesting their potential involvement in UA reduction via enhanced intestinal excretion and modulation of the xanthine metabolic pathway, thereby alleviating HUA^[39, 40]. Collectively, we hypothesize that CCFM1131 may exert its UA-lowering and renal protective effects by specifically modulating gut microbiota composition, enriching beneficial bacterial abundance, and acting through multiple pathways including anti-inflammation, metabolic regulation, and intestinal barrier protection.

The above hypothesis is further supported by metabolomic data. The gut microbiota is likely involved in regulating UA levels in HUA patients through its metabolites. Metabolomic analysis revealed that two metabolites closely linked to purine metabolism—hypoxanthine and guanine—showed significantly reduced fecal levels post-intervention. Additionally, the abundance of *Lachnospiraceae* UCG-008 was found to be significantly negatively correlated with these two metabolites. This bacterial genus belongs to the *Lachnospiraceae* family, which participates in purine metabolism and can reduce host levels of purines such as hypoxanthine^[41]. These findings suggest that CCFM1131 may competitively deplete purine precursors in the intestinal tract by modulating the function of the bacterial flora, which in turn reducing the substrate supply and metabolic load of endogenous UA synthesis at the source. According to the principle of substrate

feedback regulation, this depletion may directly trigger compensatory down-regulation of hepatic XOD activity. Concurrently, we observed marked increases in fecal levels of taurine and its metabolic derivative taurochenodeoxycholic acid. Taurine, as an endogenous sulfur-containing amino acid, has been proven to have anti-inflammatory, antioxidant, and renal function-improving effects^[42], and was positively associated with *Lactobacillus* abundance. Taurochenodeoxycholic acid has been reported to alleviate HUA-induced cellular oxidative stress and injury^[43] and possesses clear antioxidant properties^[44], enhancing the activity of antioxidant enzymes such as superoxide dismutase (SOD) while reducing levels of oxidative stress products such as malondialdehyde (MDA). During UA catalysis, XOD generates substantial reactive oxygen species including superoxide anions, and this oxidative stress environment further upregulates XOD activity through positive feedback. The enrichment of *Lactobacillus* may contribute to the normalization of XOD activity by enhancing the activity of the taurine-hypotaurine metabolic axis, exerting multiple mechanisms such as antioxidant, inhibition of inflammation and regulation of bile acid metabolism, which jointly participate in the alleviation of the pathological process of HUA. Hippuric acid can increase intestinal UA excretion by activating the expression of the UA transporter protein ABCG2^[39]. Correlation analysis identified bacteria groups significantly associated with hippuric acid levels; however, based on the available literature and microbial metabolic pathway databases, none of these significantly associated genera have been reported to participate in the biosynthesis of hippuric acid or its direct precursor benzoic acid. Therefore, we speculate that these genera may not be direct producers of hippuric acid, but rather indirectly promote its synthesis by remodeling the structure of the intestinal flora, altering the intestinal environment, or modulating host metabolism following CCFM1131 intervention. In terms of serum metabolites, there was a synchronized down-regulation of the levels of glycocholic acid and glycochenodeoxycholic acid. Accumulation of these two bile acids is closely associated with hepatic fat accumulation, stress-inflammatory responses, and intestinal barrier impairment^[45–48]. Therefore, the synchronous reduction in both metabolites may reflect attenuated bile acid metabolic burden following CCFM1131 intervention, which in turn improves overall hepatic metabolic function. Furthermore, the enrichment of D-arginine and D-ornithine metabolic pathways in the gut function prediction resonated with the enrichment of the arginine biosynthesis pathway in the fecal metabolome and the significant upregulation of the key metabolite L-(+)-arginine. Previous studies have confirmed that L-arginine alleviates UA-induced hepatocyte injury^[49]. Thus, activation of the arginine metabolic pathway represents another crucial mechanism through which CCFM1131 exerts hepatoprotective and systemic metabolic regulatory effects.

Based on results from prior animal experiments and the present clinical trial, we propose that CCFM1131 alleviates HUA through an integrated, gut microbiota-dependent mechanism (Fig. 8). Our findings point to a hierarchical model of action, with the most compelling evidence highlighting a significant suppression of endogenous UA synthesis and a marked improvement in the host's metabolic and anti-inflammatory status as the primary drivers of the UA-lowering effect. This mechanistic hierarchy unfolds as follows: First, CCFM1131 remodels the intestinal flora structure, increases beneficial bacteria

abundance, and restricts the intestinal absorption of exogenous purines, thereby effectively reducing the substrate supply for endogenous UA synthesis and down-regulating the UA level. Second, the intervention promotes the accumulation of gut metabolites with anti-inflammatory, antioxidant, and renal protective effects—including taurine, taurochenodeoxycholic acid, and L-(+)-arginine—which collectively restore hepatic lipid metabolism homeostasis and mitigate toxic damage. In addition to these core mechanisms, our data also hint at a potential secondary contribution from the promotion of intestinal UA excretion, as suggested by the upregulation of hippuric acid. While supported by the literature, this excretory pathway merits further investigation to fully elucidate its role within our specific intervention framework.

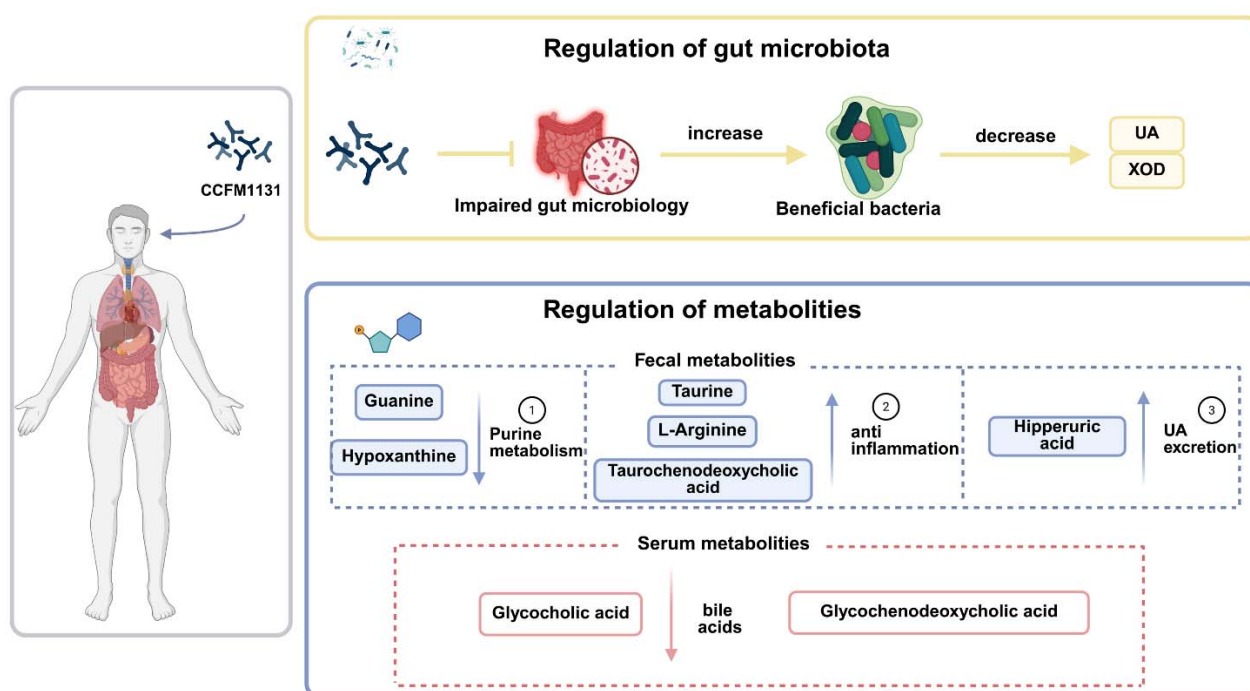


Fig. 8 Proposed mechanisms of HUA mitigation by *L. rhamnosus* CCFM1131.

This multi-targeted, systemic mechanism distinguishes CCFM1131 from the potent direct inhibition approach of traditional XOD inhibitors like allopurinol^[32]. The inhibition of XOD activity by CCFM1131 is more likely an indirect, mild effect resulting from the overall improvement of the host metabolic environment, maintaining enzyme activity to be maintained within a safe and effective physiological range, avoiding the risks associated with excessive inhibition. This fundamental distinction dictates a unique clinical role and application for CCFM1131 compared to traditional pharmacotherapies. The mean serum urate reduction of 27.6 $\mu\text{mol/L}$, while not a replacement for drug therapy, serves as a risk-regulating intervention. For patients with mild-to-moderate HUA (e.g., a baseline around 450 $\mu\text{mol/L}$), this reduction can bridge the gap to the common treatment target of <420 $\mu\text{mol/L}$. A significant dose–response relationship between serum urate levels and gout flare rates is well established^[50]. Therefore, maintaining a lower serum UA, even with a reduction of this magnitude, would be expected to confer a proportional decrease in long-term gout flare risk. With its excellent safety and tolerability, CCFM1131 bridges the prevention–intervention gap as a practical microecological tool for early intervention and sustained risk

control—fitting logically between lifestyle modification and pharmacotherapy, particularly for drug-intolerant or prevention-prioritizing patients.

It is noteworthy that in our findings, the impact of the CCFM1131 intervention on the Firmicutes-to-Bacteroidetes (F/B) ratio diverged from some previous studies. This discrepancy may be attributed to the higher proportion of overweight (BMI of $25.97 \pm 3.16 \text{ kg/m}^2$) or obese individuals (BMI $\geq 28 \text{ kg/m}^2$) in the patient cohort of this research. Therefore, while potentially associated with HUA and metabolic status, F/B ratio cannot yet serve as a specific diagnostic biomarker and requires comprehensive evaluation within the appropriate clinical context. In addition, intervention with CCFM1131 markedly altered the gut microbial community structure in HUA patients, it did not induce significant changes in microbial diversity. While alpha diversity is widely used to evaluate probiotic interventions, it is merely one descriptor of complex ecosystems, and its association with health status can be ambiguous^[51]. The cornerstone of gut health lies in maintaining a dynamic balance between beneficial "keystone functional groups" and detrimental "pathobiont functional groups"^[52]. This underpins our finding that the core action of CCFM1131 likely involves driving a specific structural reorganization of the gut microbiota, rather than promoting a broad-spectrum increase in diversity. By selectively modulating the abundance of specific microbial taxa, CCFM1131 reshapes both community composition and functional capacity, thereby restoring an intestinal microecological balance conducive to urate homeostasis.

It is crucial to specifically emphasize that the evidence strength varies across the proposed mechanistic model. The reduction in endogenous UA synthesis is supported by serum biochemical data, whereas the proposed mechanisms of "host metabolism improvement" and "UA excretion promotion" remain as hypotheses, derived mainly from correlative omics findings and literature. Therefore, subsequent studies should adopt a stepwise strategy to validate whether CCFM1131, its metabolites, or the resulting changes in gut-derived metabolites directly promote urate excretion via ABCG2 and improve host metabolism through bile acid-mediated pathways—requiring integrated omics, cell-based assays, and gene-knockout models to establish causality. Additionally, as a pragmatic trial, dietary control was not implemented, introducing potential unmeasured confounding. The absence of interim and post-intervention follow-up precludes assessment of treatment dynamics and sustainability. Thirdly, the multi-omics findings are exploratory and thus susceptible to false-positive associations. Future studies should incorporate dietary controls, extend follow-up, and validate omics findings in prospective cohorts.

5. Summary

In this study, we systematically investigate the effects of *Lactobacillus rhamnosus* CCFM1131 intervention on HUA and its underlying mechanisms. The intervention demonstrated UA reduction through an integrated, gut microbiota-dependent model encompassing three key aspects: suppression of endogenous UA synthesis, improvement of host metabolic status, and promotion of intestinal UA excretion. This also underscores an emerging paradigm that HUA amelioration involves the synergistic interplay of multiple mechanisms rather than a single target, forming a comprehensive network that engages the "gut-kidney axis" and immunomodulatory pathways. Consequently, future screening of probiotics

with UA-lowering potential should transition from traditional single-activity approaches (e.g., in vitro degradation rate) toward a multidimensional, function-oriented evaluation system. This system should incorporate the capacity to regulate transporter proteins, enhance intestinal barrier integrity, and antagonize inflammation as core screening criteria, thereby enabling efficient identification of optimal strains with clinical application prospects.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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