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ORIGINAL RESEARCH

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Gut microbiota characteristics and targeted tryptophan metabolomics in premature ejaculation patients with depressive state: a cross-sectional study

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Abstract

Background: The gut microbiota-tryptophan metabolic axis has emerged as a potential modulator of neuropsychiatric disorders, yet its role in premature ejaculation (PE) comorbid with depressive states remains unexplored. **Methods**: Fifteen eligible PE patients were enrolled. Depressive status was assessed using the Patient Health Questionnaire-9 (PHQ-9), dividing participants into a depressive-state group (n = 9) and a non-depressive group (n = 6). Demographic and clinical data, including age, body mass index (BMI), International Index of Erectile Function-5 (IIEF-5), Premature Ejaculation Diagnostic Tool (PEDT) scores, total testosterone (TT), and free testosterone (FT) levels, were recorded. Fecal samples underwent 16S rRNA sequencing for gut microbiota profiling, while serum samples were subjected to targeted tryptophan metabolomic analysis. Associations between gut microbiota and tryptophan metabolites were evaluated using Spearman's correlation. **Results**: The depressive-state group exhibited a significantly higher abundance of Desulfobacterota (phylum level: relative abundance 0.12% *vs.* 0.08%, $p = 0.04$; absolute abundance 5.9×10^6 *vs.* 2.1×10^5 copies/g, $p = 0.007$) and lower serum kynurenic acid (KYNA) levels (0.005 ± 0.002 *vs.* 0.009 ± 0.003 μg/mL, $p = 0.006$) compared to the non-depressive group. A significant negative correlation was observed between Desulfobacterota abundance and KYNA levels ($r = -0.66$, $p = 0.016$). **Conclusions**: PE patients with depressive states demonstrate altered gut microbiota features—characterized by elevated Desulfobacterota abundance at multiple taxonomic levels—and suppressed serum KYNA concentrations, which are inversely correlated. These findings suggest that depressive status may disturb gut microbiota-tryptophan metabolic interactions, highlighting its potential as a therapeutic target for personalized PE management. **Clinical Trial Registration**: https://trialsearch.who.int/Trial2.aspx?TrialID=ChiCTR2400079838, ChiCTR2400079838.

Keywords

Premature ejaculation; Gut microbiota; Tryptophan metabolism; Depression

1. Introduction

Premature ejaculation (PE), a prevalent male sexual dysfunction affecting 5% of men, is characterized by uncontrolled ejaculation occurring shortly after sexual initiation. According to the International Society for Sexual Medicine (ISSM), PE is defined as persistent or recurrent ejaculation accompanied by negative emotional distress [1]. Its multifactorial etiology involves genetic, psychological, and physiological components, with frequent comorbidity with depression [2–4]. Selective serotonin reuptake inhibitors (SSRIs), such as dapoxetine, improve ejaculatory latency by increasing synaptic 5-hydroxytryptamine (5-HT) concentrations [5]. Notably, SSRIs are also first-line antidepressants, suggesting a potential link between depressive states and PE pathophysiology. Depressive states may exacerbate PE through dysregulation of neurotransmitters. Furthermore, the kynurenine pathway (KP)—a major route of tryptophan metabolism—plays critical neurobiological roles via metabolites including kynurenic acid (KYNA) and quinolinic acid [6]. Given that 95% of tryptophan is metabolized through the KP, this pathway may contribute significantly to PE pathogenesis [7]. The microbiota-gut-brain (MGB) axis, particularly through tryptophan metabolic imbalance and reduced 5-HT synthesis, is implicated in PE development [8]. Although SSRIs are commonly prescribed, issues of drug resistance and adverse effects remain problematic [9, 10]. Crucially, >90% of bodily 5-HT is gut-derived, and gut microbiota may modulate PE by regulating tryptophan

metabolic pathways (kynurenine and indole branches) [11–13]. Emerging evidence indicates close associations among these pathways, mood disorders, and PE [14, 15]. This study, therefore, investigates the interrelationships between PE, depressive states, tryptophan metabolism, and gut microbiota to advance novel therapeutic strategies.

2. Materials and methods

2.1 Patients

This study recruited 15 patients with premature ejaculation (PEDT score ≥11 and Intravaginal Ejaculation Latency Time (IELT) <3 minutes) from the Second Affiliated Hospital of Zhejiang Chinese Medical University between January and June 2024. Inclusion criteria comprised: (1) ISSM-defined PE diagnosis; (2) males aged 18–55 years; (3) generally healthy status with a stable heterosexual relationship >6 months; (4) PE history of 3 months to 10 years; (5) absence of phimosis and no prior circumcision; and (6) signed informed consent. Exclusion criteria included: history of neurological disorders or psychiatric diseases other than depression; long-term smoking/alcohol dependence; use of ejaculation-affecting medications within 6 months before enrollment; severe erectile dysfunction (IIEF-5 score ≤21); uncontrolled hypertension (systolic Blood Pressure (BP) ≥160 mmHg or diastolic BP ≥100 mmHg post-treatment); poorly controlled diabetes (fasting glucose >7.0 mmol/L); recent antibiotic use (≤2 weeks) or history of inflammatory bowel disease, irritable bowel syndrome, autoimmune diseases, hepatic disorders, chronic diarrhea, or malignancies (Fig. 1). Participants were stratified into non-depression (PHQ-9 ≤4, n = 6) and depression (PHQ-9 >4, n = 9) groups. Clinical data (age, BMI, IIEF-5, PEDT, testosterone levels) and biological samples (feces/serum) were collected under standardized protocols. The study protocol was approved by the institutional ethics committee (No. 2023-079-01), with written informed consent obtained from all participants.

2.2 Analysis of gut microbiome

Under strict hospital supervision, participants collected fresh fecal samples immediately following their first morning bowel movement using sterile collection kits (DNA/RNA-free containers). To ensure sample integrity, all specimens were flash-

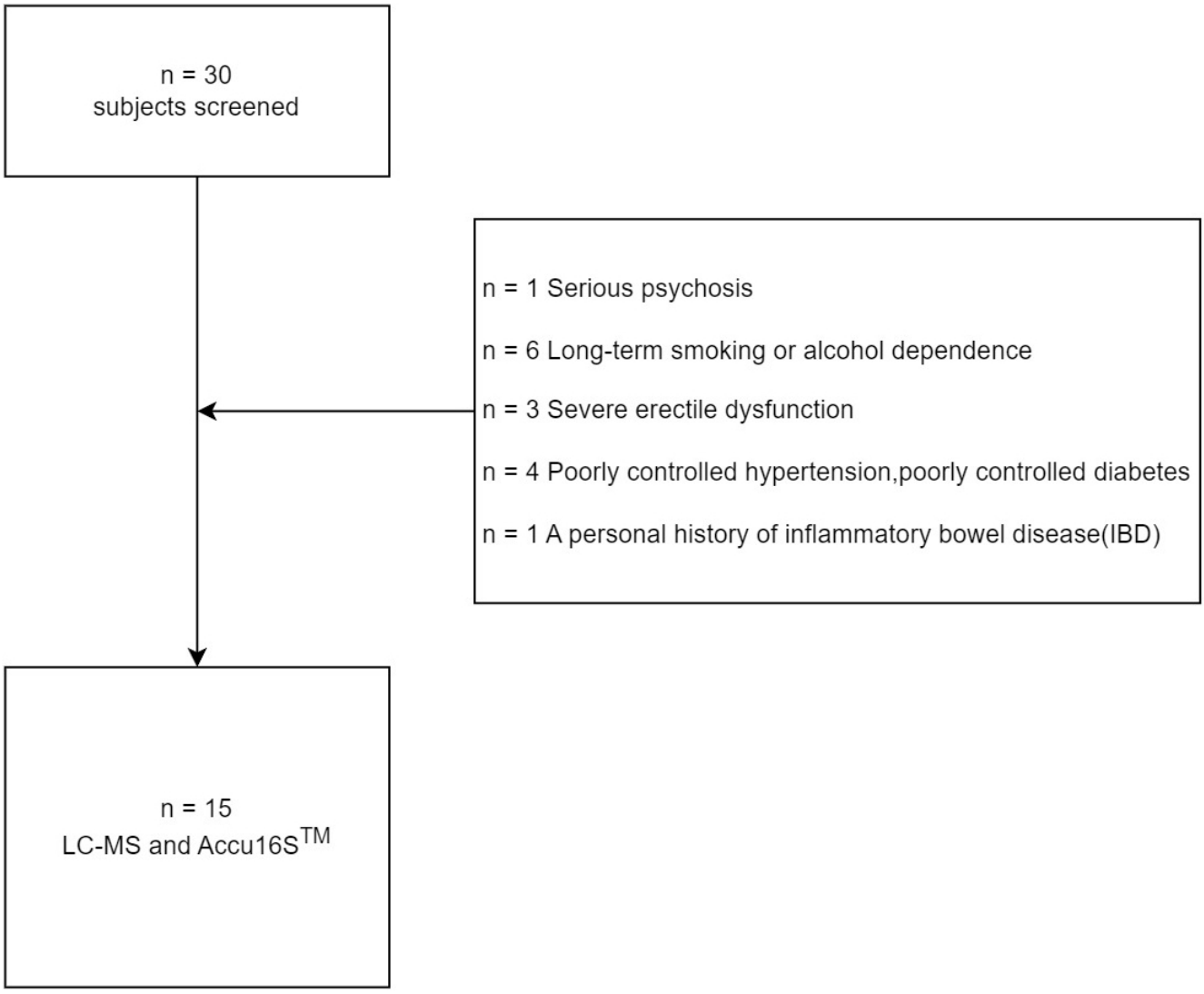

FIGURE 1. Flow diagram of screening study participants. LC-MS, liquid chromatography-mass spectrometry.

frozen within 15 minutes of collection and maintained at −80 °C until processing. The study controlled for geographic variation by exclusively enrolling participants residing within a 50-kilometer radius of the study center. All collections were time-standardized to occur between 7:00–9:00 AM following an overnight fast. To account for dietary influences on gut microbiota composition, participants completed detailed 3-day food diaries prior to sample collection, with particular attention to recording probiotic/prebiotic consumption and major dietary components. Specimens were subsequently transported via dry ice cold chain to Genesky Biotechnologies Inc. (Shanghai, 201315) for bacterial absolute quantification using the Accu16S^{TM} sequencing platform. Unlike conventional 16S rRNA amplicon sequencing—which only reveals relative microbial abundance—the Accu16S^{TM} method incorporates synthetic spike-in standards during DNA processing. This involves: (1) adding known quantities of artificial DNA sequences to sample DNA, (2) constructing 16S amplicon libraries, and (3) high-throughput sequencing. By correlating the read counts of spike-in standards with their absolute copy numbers, a standard curve is generated to calculate absolute microbial loads while simultaneously profiling species composition.

2.3 Analysis of tryptophan metabolism

Blood samples collected at the hospital underwent a 30-minute room temperature clotting period, followed by centrifugation at 3000 rpm for 5 minutes. The resultant serum supernatant was aseptically aliquoted into sterile tubes and immediately cryopreserved at −80 °C to maintain metabolite integrity. These samples were subsequently transferred via cold chain to Genesky Biotechnologies Inc. (Shanghai) for targeted quantification of tryptophan pathway metabolites using liquid chromatography-mass spectrometry (LC-MS). Chromatographic separation employed an ACQUITY UPLC® BEH C18 column (2.1 × 100 mm, 1.7 μm; Waters) maintained at 40 °C, with 5 μL injection volume. The mobile phase consisted of (A) 0.1% aqueous formic acid and (B) 0.1% formic acid in methanol, delivered at 0.25 mL/minute under the following gradient protocol: 10% B (0–0.5 minutes), linear increase to 30% B (0.5–2 minutes), step to 60% B (2–3 minutes), linear increase to 98% B (3–6 minutes), isocratic 98% B (6–7.5 minutes), sharp reduction to 10% B (7.5–7.51 minutes), and re-equilibration at 10% B (7.51–9 minutes). Mass spectrometric detection utilized electrospray ionization (ESI) in positive mode with 4500 V ion spray voltage and 450 °C source temperature. Gas parameters were optimized at 10 psi (collision), 30 psi (curtain), and 50 psi (nebulizer & auxiliary). Data acquisition was performed in multiple reaction monitoring (MRM) mode.

2.4 Statistical analysis

General clinical data was analyzed using SPSS 25.0 software (IBM Corp., Armonk, NY, USA) and *t*-test was used for statistical analysis of differences between groups. Further analysis was performed using R software (version 4.2.0), and bar plots of microbial community composition were generated. The Mothur software was used to calculate Observed species, Shannon diversity index, and other alpha diversity metrics. Principal Coordinates Analysis (PCoA) based on Bray-Curtis distance was applied to assess differences in species diversity, community composition, and structure among samples. Analysis of Variance Using Distance Matrices (ADONIS) was conducted to determine whether group differences were statistically significant. The Wilcoxon rank-sum test was used to compare groups and identify significantly different taxa at various taxonomic levels. Orthogonal Partial Least Squares Discriminant Analysis (OPLS-DA) was performed on tryptophan levels, and score plots were generated. Permutation testing was used to validate the reliability of the OPLS-DA model. Mean and standard deviation were calculated for each group, followed by statistical significance (*p*-values) and fold-change values, visualized in bar plots. Receiver Operating Characteristic (ROC) curve analysis was applied to identify potential metabolic biomarkers for predicting depression in premature ejaculation patients. Spearman correlation analysis was used to examine relationships between gut microbiota and metabolomic profiles. A p-value < 0.05 was considered statistically significant, while a p-value < 0.01 indicated highly significant differences.

3. Results

3.1 Demographic and clinical characteristics

The baseline characteristics of patients in the depressive group and non-depressive group are presented in Table 1. The results show that there were no statistically significant differences between the two groups in terms of age ($p = 0.20$), BMI ($p = 0.63$), IELT ($p = 0.50$), IIEF-5 ($p = 0.23$), PEDT ($p = 0.64$), TT ($p = 0.97$), and FT ($p = 0.49$). This indicated that there were no significant differences in baseline characteristics between the two groups.

A multiple linear regression model was conducted with IELT as the dependent variable and age, BMI, IIEF-5, PEDT, and PHQ-9 scores as covariates. The overall model was not statistically significant (F (5, 9) = 0.273, $p = 0.917$), with an R^2 of 0.132 and an adjusted R^2 of −0.351, indicating limited explanatory power. None of the individual predictors were significantly associated with IELT (all $p > 0.05$). Variance inflation factors were all below 2.1, suggesting no evidence of problematic multicollinearity. These findings indicate that the measured covariates did not exert a significant influence on IELT in this sample, thereby reducing the likelihood of substantial confounding by these factors in the main analyses.

3.2 Gut microbiota differential analysis

First, α-diversity analysis was performed to assess species richness and diversity. The results showed that, whether using absolute quantitative sequencing or relative quantitative sequencing, Group A (non-depressive) exhibited higher values than Group B (depressive) in the following indices (Figs. 2,3): Observed species (Figs. 2a,3a), Chao1 (Figs. 2b,3b), ACE (Figs. 2c,3c), and Shannon (Figs. 2d,3d). Conversely, Simpson (Figs. 2e,3e) and Coverage (Figs. 2f,3f) indices were lower in Group A compared to Group B. However, none of these differences reached statistical significance.

TABLE 1. Demographic and clinical characteristics.

	Group A (n = 9)	Group B (n = 6)	*t*	*p*
Age (yr)	32.9 ± 3.9	30.3 ± 3.1	1.3	0.20
BMI (kg/m^2)	23.9 ± 3.7	24.7 ± 1.1	−0.5	0.63
IIEF-5	23.0 ± 1.1	23.1 ± 1.0	−1.2	0.23
PEDT	13.3 ± 1.1	13.0 ± 1.5	0.5	0.64
IELT (s)	105.8 ± 11.3	109.8 ± 10.5	−0.7	0.50
TT (nmol/L)	17.2 ± 7.6	17.3 ± 5.8	−0.1	0.97
FT (pg/mL)	24.1 ± 7.3	27.4 ± 10.6	−0.7	0.49
PHQ-9	10.6 ± 2.9	2.2 ± 1.2	6.7	<0.001

Group A: non-depressive group (PHQ-9 ≤4); Group B: depressive group (PHQ-9 >4).
BMI, body mass index; IIEF-5, International Index of Erectile Function-5; PEDT, Premature Ejaculation Diagnostic Tool; TT, total testosterone; FT, free testosterone; PHQ-9, Patient Health Questionnaire-9; IELT, Intravaginal Ejaculation Latency Time.

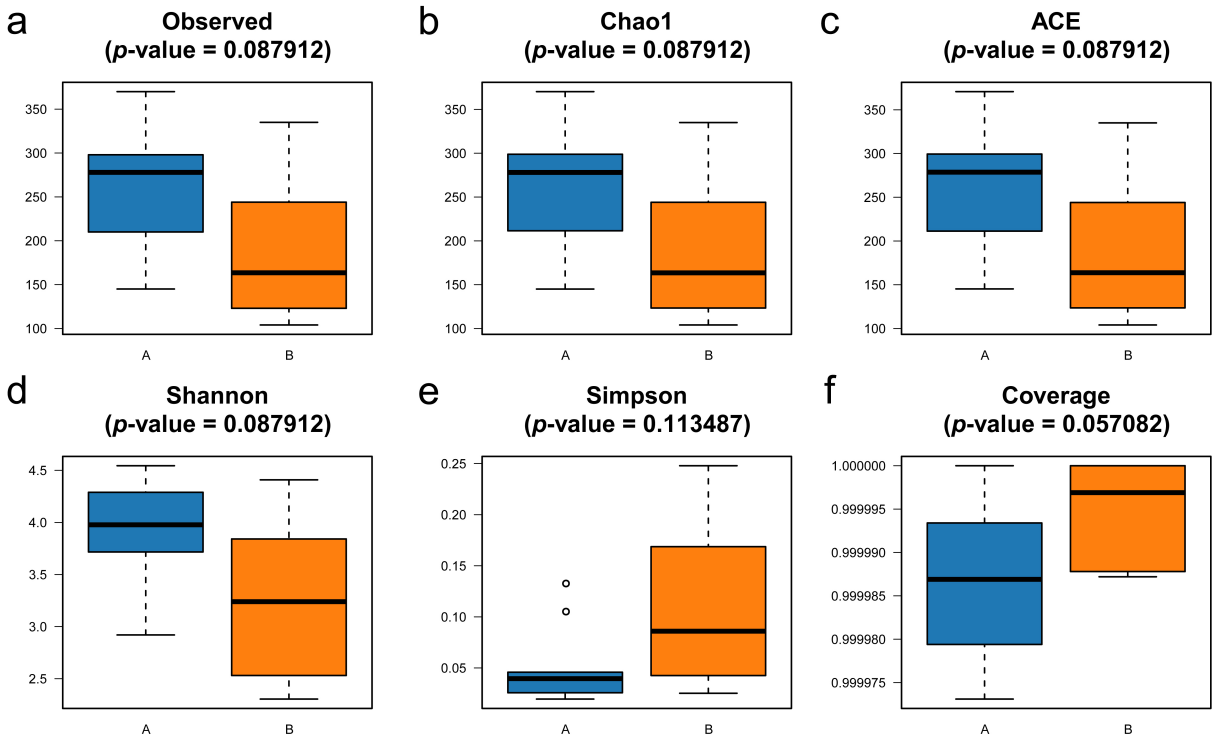

FIGURE 2. Gut microbiota α-diversity under absolute quantitative sequencing. (a) The observed index was not significantly different between Group A and Group B (A > B). (b) The Chao1 index was not significantly different between Group A and Group B (A > B). (c) The ACE index was not significantly different between Group A and Group B (A > B). (d) The Shannon index was not significantly different between Group A and Group B (A > B). (e) The Simpson index was not significantly different between Group A and Group B (A < B). (f) The Coverage index was not significantly different between Group A and Group B (A < B). ACE, Abundance-based Coverage Estimator.

β-diversity was assessed using Bray-Curtis-based principal coordinate analysis. For absolute quantitative sequencing, Adonis test results indicated a statistically significant difference (F = 1.55, p = 0.05). In contrast, relative quantitative sequencing showed no significant difference (F = 1.29, p = 0.10) (Fig. 4).

The bar plots of relative and absolute abundance at the phylum level demonstrated distinct gut microbiota differences between Group A (depressive) and Group B (non-depressive). Both groups were dominated by Firmicutes, Bacteroidota, and Actinobacteria. Group A showed higher relative abundances of Firmicutes and Bacteroidota but lower relative abundance of Actinobacteria compared to Group B. In terms of absolute abundance, all three phyla exhibited higher values in Group A than in Group B (Fig. 5). Wilcoxon rank-sum test further revealed that the relative and absolute abundances of Desulfobacterota were significantly elevated in Group A compared to Group B (Fig. 6).

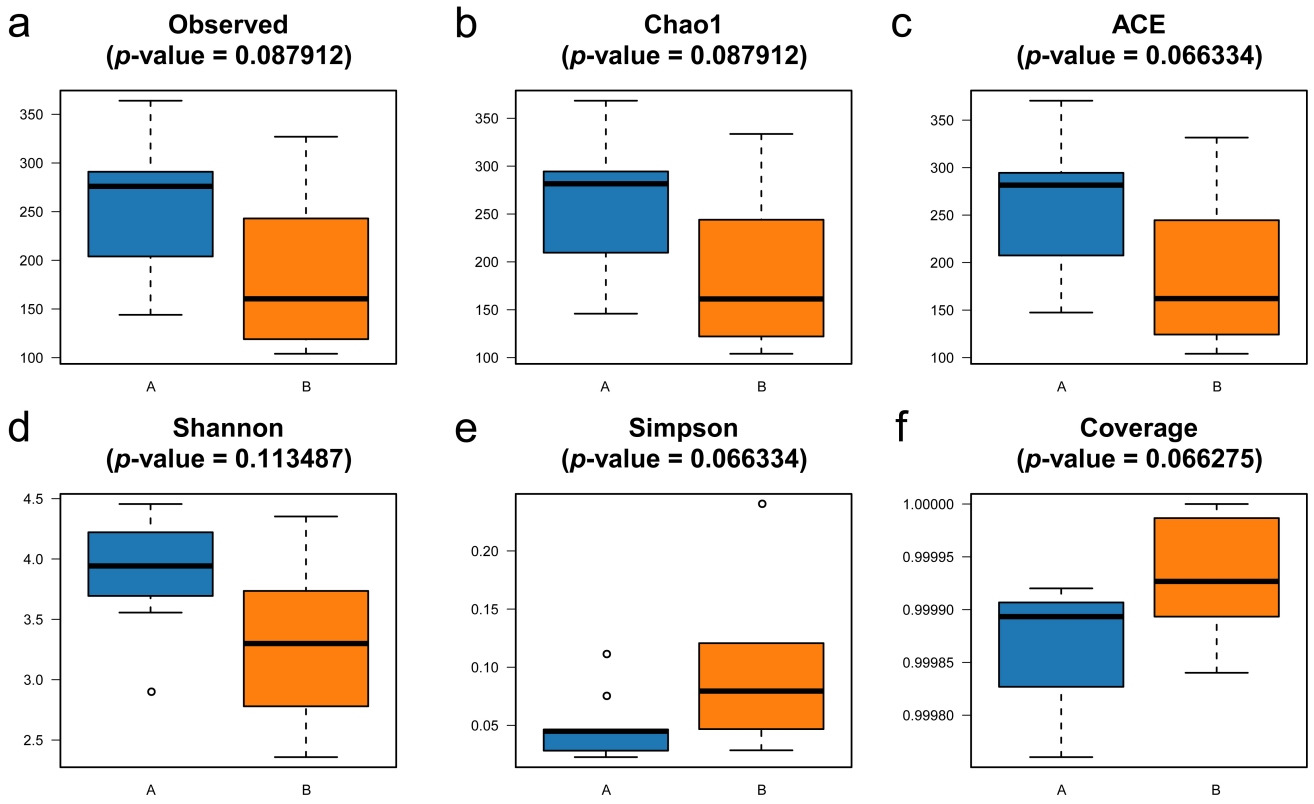

FIGURE 3. Gut microbiota α-diversity under relative quantitative sequencing. (a) The observed index was not significantly different between Group A and Group B (A > B). (b) The Chao1 index was not significantly different between Group A and Group B (A > B). (c) The ACE index was not significantly different between Group A and Group B (A > B). (d) The Shannon index was not significantly different between Group A and Group B (A > B). (e) The Simpson index was not significantly different between Group A and Group B (A < B). (f) The Coverage index was not significantly different between Group A and Group B (A < B). ACE, Abundance-based Coverage Estimator.

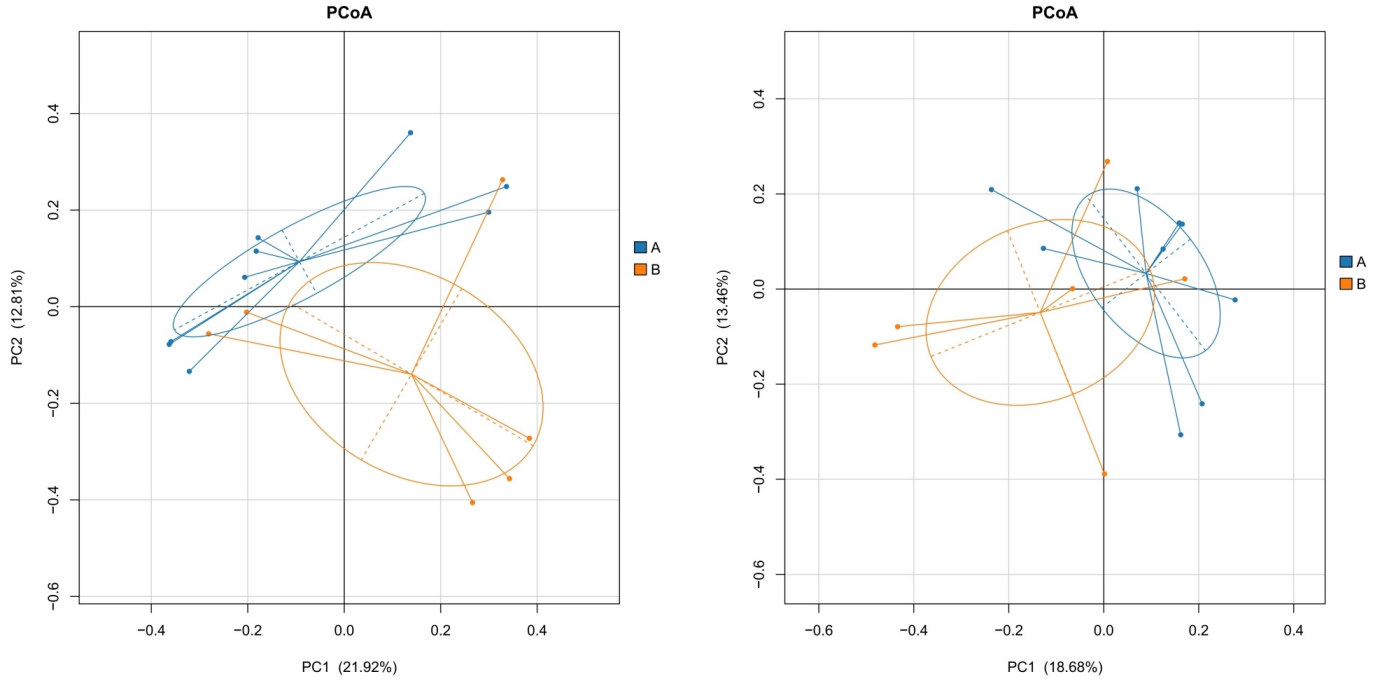

FIGURE 4. PCoA of absolute quantitative sequencing and relative quantitative sequencing. (A) non-depressive group; (B) depressive group. PCoA, Principal Coordinates Analysis; PC, Principal Coordinate.

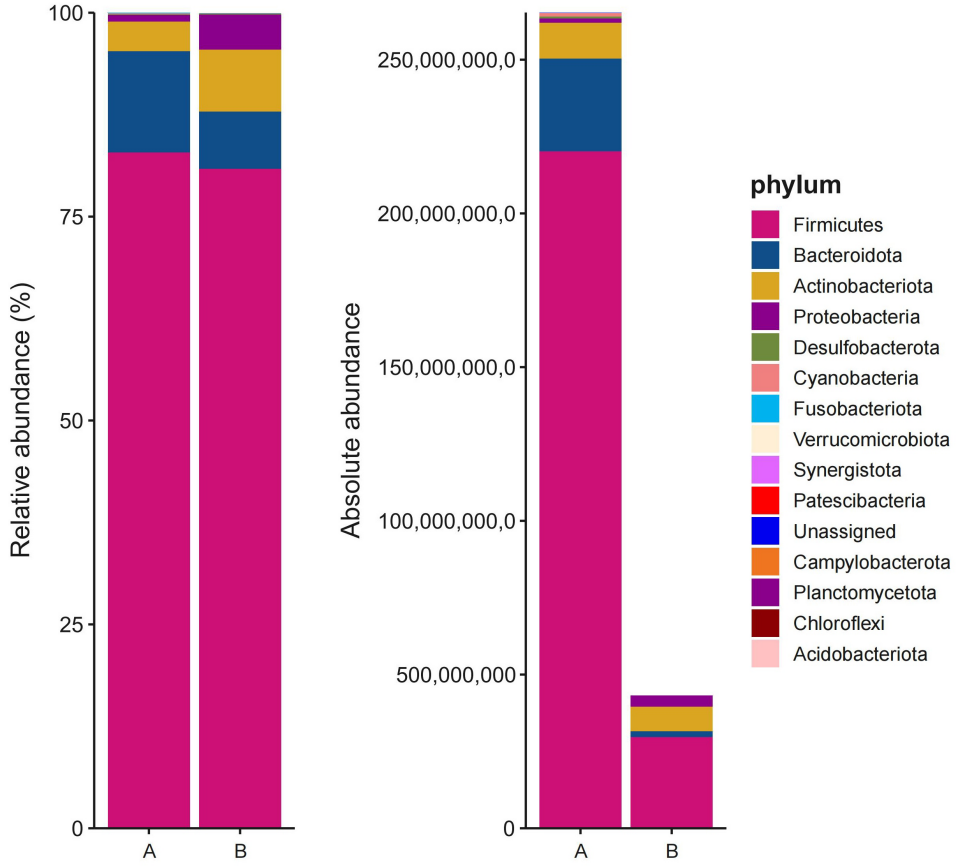

FIGURE 5. Phylum-level gut microbiota composition in Group A *vs.* Group B. Group A: non-depressive group; Group B: depressive group.

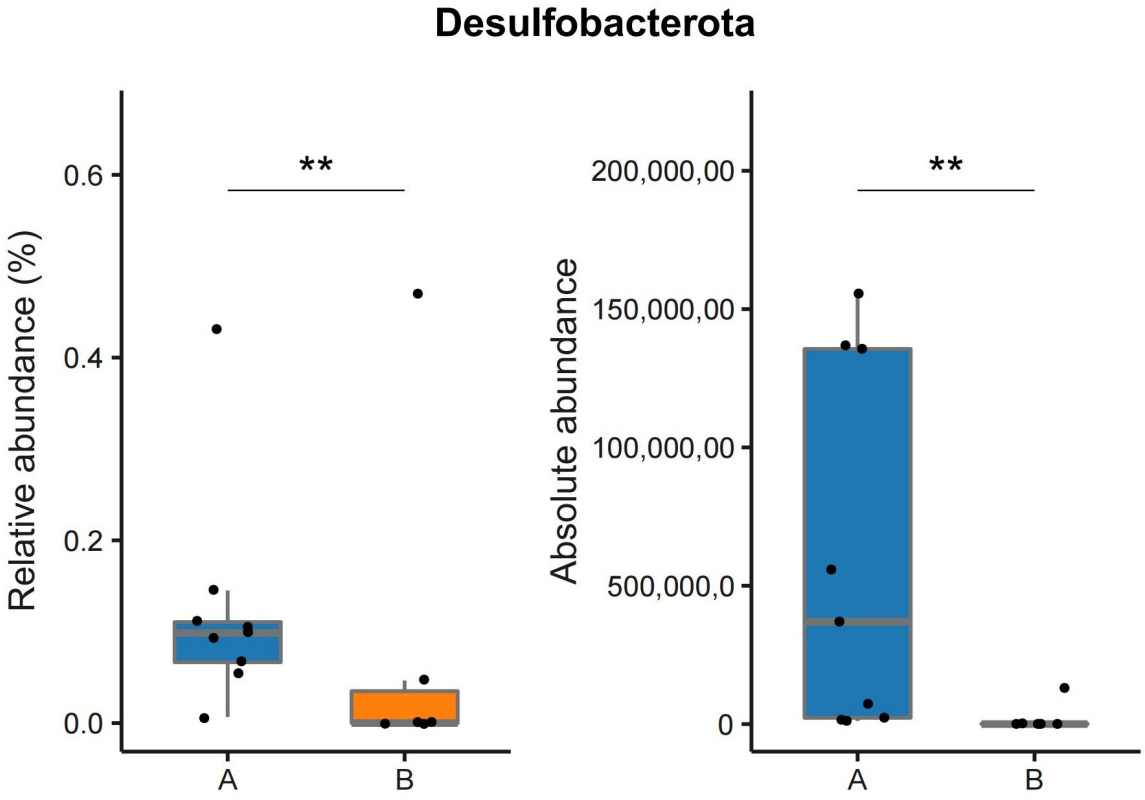

FIGURE 6. Significant differences in gut microbiota phyla between Group A and Group B. Group A: non-depressive group; Group B: depressive group. **: indicates significance $p < 0.01$.

3.3 Targeted metabolomic analysis of tryptophan derivatives

The OPLS-DA score plot revealed significant intergroup differences between Group A and Group B (Fig. 7). The kynurenic acid (KYNA) level in Group A was significantly lower than that in Group B ($p < 0.01$). Notably, KYNA levels effectively distinguished patients with premature ejaculation (PE) comorbid with depression from those with PE alone, yielding an AUC (Area Under the Curve) of 0.889 (95% CI (Confidence Interval): 0.615–1.0) (Fig. 8).

3.4 Association analysis of gut microbiome with targeted metabolites

Based on the differences in gut microbiota and metabolites between the two patient groups, Spearman correlation coefficients were calculated to determine the functional associations between gut microbial alterations and tryptophan-targeted metabolites. The results revealed a significant negative correlation between Desulfobacterota and targeted metabolites, particularly KYNA levels. The correlation coefficients are presented in Table 2, and the corresponding heatmap is shown in Fig. 9.

4. Discussion

Significant associations exist between gut microbiota composition and depression pathophysiology [16]. In healthy populations, microbial stability is essential for maintaining intestinal barrier integrity and inflammatory homeostasis, with a balanced gut microbiome positively modulating neurodevelopment and behavior via the microbiota-gut-brain axis [17, 18]. Our study revealed that depressive premature ejaculation (PE) patients exhibited significantly elevated Desulfobacterota abundance compared to non-depressive PE controls through 16S rDNA sequencing ($p < 0.01$). This sulfate-reducing bacterial phylum may contribute to PE pathogenesis by binding proinflammatory colonic mucins and inducing intestinal lesions [19, 20], and has demonstrated neurotoxic effects including induction of dopaminergic neuronal death in Parkinson's models [21]. Considering the critical role of dopamine in sexual function, particularly in the regulation of ejaculation, the dysbiosis of Desulfobacterota in PE patients could potentially disrupt dopaminergic pathways, contributing to premature ejaculation. Moreover, as Desulfobacterota is associated with inflammatory and neurotoxic processes, its increased abundance in PE patients with depression may reflect a combined effect of microbiota-induced inflammation and altered dopamine regulation, which may exacerbate both mood disturbances and sexual dysfunction [22].

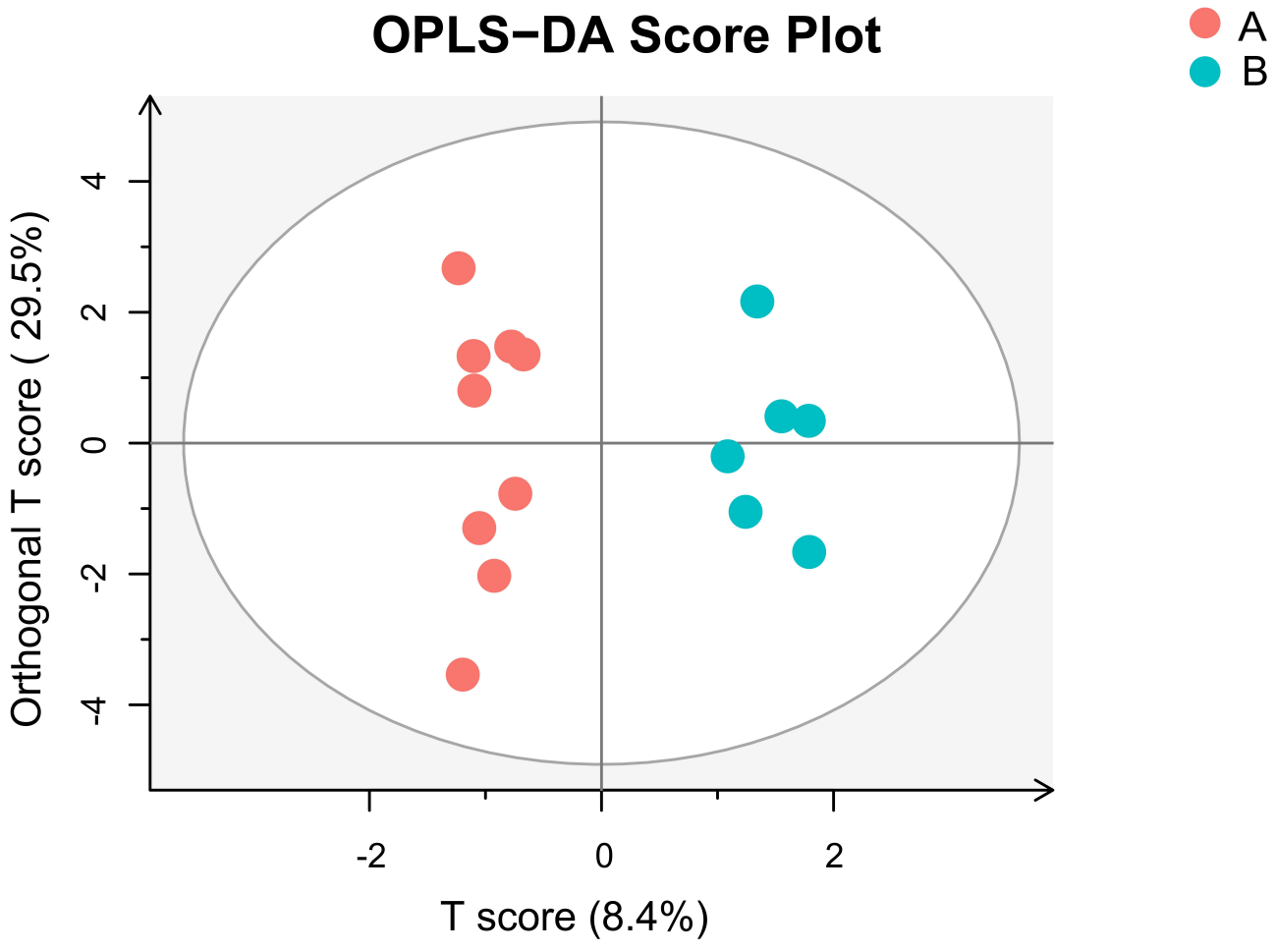

FIGURE 7. OPLS-DA score plot. Group A: non-depressive group; Group B: depressive group. OPLS-DA, Orthogonal Partial Least Squares Discriminant Analysis.

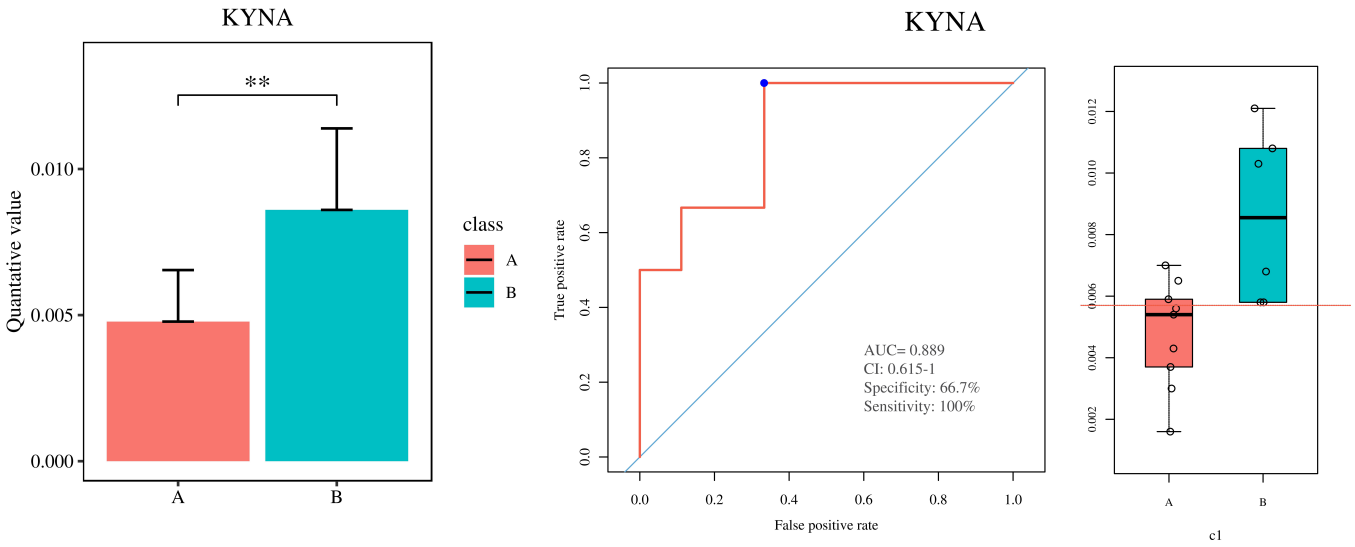

FIGURE 8. Differential tryptophan metabolites and ROC analysis between Group A and Group B. Group A: non-depressive group; Group B: depressive group. **: indicates significance $p < 0.01$. KYNA, kynurenic acid; AUC, Area Under the Curve; CI, Confidence Interval.

TABLE 2. Correlations between Desulfobacterota and targeted metabolites.

Gut microbiome	Targeted metabolites	*r*	*p*
Desulfobacterota			
	KYNA	−0.66	0.006
	ILA	−0.53	0.04
	SER	−0.60	0.02
	XA	−0.55	0.03

KYNA, kynurenic acid; ILA, Indolelactic Acid; SER, Serotonin; XA, Xanthurenic Acid.

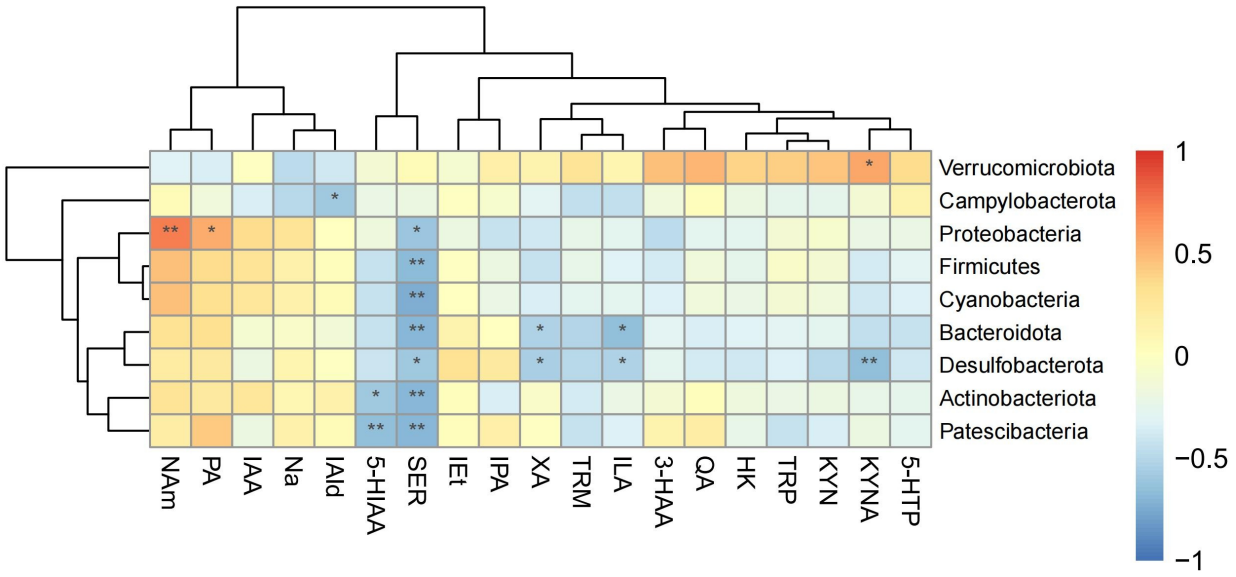

FIGURE 9. Phylum-level microbial correlations with targeted metabolites. Darker blue color indicates stronger negative correlation and darker orange color indicates stronger positive correlation. *On the box indicates significance $p < 0.05$ and **indicates significance $p < 0.01$. 5-HTP, 5-Hydroxytryptophan; KYNA, Kynurenic acid; KYN, Kynurenine; TRP, Tryptophan; HK, Hydroxykynurenine; QA, Quinolinic acid; 3-HAA, 3-Hydroxyanthranilic acid; ILA, Indolelactic acid; TRM, Tryptamine; XA, Xanthurenic acid; IPA, Indole-3-propionic acid; IEt, Indole-3-ethanol; SER, Serotonin; 5-HIAA, 5-Hydroxyindoleacetic acid; IAId, Indole-3-aldehyde; Na, Nicotinic acid; LAA, L-Alanyl-Alanine; PA, Picolinic acid; NAm, Nicotinamide.

Concurrently, targeted metabolomic profiling identified substantially reduced kynurenic acid (KYNA) levels in the depressive cohort. Receiver operating characteristic (ROC) analysis confirmed KYNA's discriminative capacity for depressive PE (AUC = 0.87), indicating its biomarker potential. The ROC model has been validated internally and requires external validation in a larger cohort. KYNA—primarily synthesized in astrocytes by kynurenine aminotransferase (KAT) [23]—modulates NMDA receptors through non-competitive glycine site antagonism [24]. Given stable cerebrospinal glycine concentrations [25], KYNA deficiency permits glutamatergic dysregulation, consistent with preclinical evidence showing KYNA-mediated glutamate reduction in trigeminal nuclei [26]. This mechanistic framework aligns with clinical neuroimaging where PE patients demonstrate elevated thalamic glutamate negatively correlating with intravaginal ejaculatory latency time (IELT, $r = -0.68$) [27], suggesting impaired ejaculatory control.

Crucially, Spearman analysis revealed a significant negative correlation between Desulfobacterota abundance and KYNA levels ($\rho = -0.72$, $p = 0.002$), implicating bacterial modulation of tryptophan metabolism. This finding integrates with established relationships: elevated plasma kynurenine/tryptophan (KYN/TRP) ratios characterize PE [28], and inflammation promotes kynurenine pathway activation at the expense of serotonin synthesis [6, 29]. Clinically, this pathway dysregulation manifests as increased PE prevalence among chronic prostatitis and rheumatoid arthritis cohorts (Odds Ratio (OR) = 3.2 and 2.7, respectively) [29, 30].

This study is exploratory. Limitations include statistical power constraints due to strict subtype stratification (depressive PE n = 9, non-depressive PE n = 6) and the small number of participants included. Using PHQ-9 >4 to define "depression" without a structured clinical interview (*e.g.*, SCID) risks misclassification and heterogeneity. We deliberately applied PHQ-9 scoring during screening to actively select these contrasting phenotypes rather than observing incidental distribution. This stratification strategy enhances biological contrast despite sample size restrictions. Future investigations should incorporate larger cohorts with dimensional depression metrics, longitudinal sampling, healthy controls, and intervention studies to establish causal mechanisms and develop microbiota-targeted therapies.

5. Conclusions

Based on the findings of this study, depressed patients demonstrate significant alterations in gut microbiota composition and tryptophan metabolism, particularly characterized by differential abundance of Desulfobacterota and elevated KYNA levels. These results suggest that gut dysbiosis may modulate mood regulation through disruptions in the tryptophan metabolic pathway. Future research should elucidate the mechanistic basis of this gut-brain axis interaction and evaluate its potential as a therapeutic target for mood disorders.

AVAILABILITY OF DATA AND MATERIALS

Data regarding any of the subjects in the study can be shared after reasonable request to the corresponding author. No identifying data will be provided.

AUTHOR CONTRIBUTIONS

HZX—participated in case collection, completed sample collection, validation, and statistical analysis, and wrote a draft. YNL—provides graphic assistance and participates in statistical analysis SJZ, JWG, HDH and YNL—participated in case and sample collection. YD and JF—proposed research ideas and reviewed and revised the paper. All authors have read and approved the final version.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of the Second Affiliated Hospital of Zhejiang Chinese Medical University (2023 Study No. 079-01). Informed consent was obtained from all individual participants included in the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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