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Research Article

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Oral *Limosilactobacillus vaginalis* administration prevents endometritis via endometritis-related bacteria and their metabolites in postpartum sows based on multi-omics analysis

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Abstract: Endometritis, a prevalent disease of the reproductive tract, significantly reduces sows' reproductive performance and thus leads to substantial economic losses. *Limosilactobacillus vaginalis* (LV) has been reported on its regulatory role in host immune capacity, while its mechanism of preventing endometritis remains unclear. Currently, no definitive diagnosis and effective treatment exists for this condition and antibiotics remain the most commonly used therapy. Herein, we investigated the potential of oral LV treatment as an effective antibiotic alternative for preventing endometritis in late-gestation sows. The results showed that orally administered LV significantly alleviated endometritis symptoms and moderately improved offspring growth performance. 16S rRNA sequencing revealed the significantly regulatory effects of LV on both gut and vaginal microbiota. Correspondingly, metabolic profiling indicated a shift towards better endometritis resistant landscape. Overall, the findings validate the roles of gut and vaginal microbiota as well as the utility of metabolic profiling in discovering the preventive effects of oral LV administration, establishing a link between intestinal probiotic supplementation and uterine health. Taken together, this study provides a novel antibiotic-free strategy for the treatment and prevention of sow endometritis.

Key words: *Limosilactobacillus vaginalis*; Sow endometritis; Gut microbiota; Vaginal microbiota; 16S rRNA sequencing; Liquid chromatography-tandem mass spectrometry (LC-MS/MS)

1 Introduction

At present, porcine endometritis is a major cause for the reduced reproductive performance of sows in commercial pig farms, with incidence rates ranging from 10% to 60% (Kauffold et al., 2005). Research has shown that endometritis in sows is typically caused by infections of the endometrium with pathogenic bacteria and opportunistic pathogens (Wang et al., 2017; Saraf et al., 2021; Ye et al., 2021), such as *Escherichia-coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus spp.* and *Proteus spp.*, etc. (De Winter et al., 1994; Lager and Halbur, 1996). The postpartum period represents a key risk stage for the development of endometritis in sows. The porcine uterus is directly exposed to external pathogens while farrowing, substantially increasing the risk of endometritis. Sows with chronic endometritis often exhibit milder but

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persistent clinical symptoms, such as reduced food intake, abnormal estrus cycles, decreased conception rates and occasional abortion (Wang et al., 2020; Ye, et al., 2021; Zhang et al., 2021). Additionally, abnormal vaginal discharge is commonly observed in these sows (Jana et al., 2015). Sows with chronic endometritis usually end up receiving inappropriate treatment, resulting in prolonged non-productive days (NPD), profitability losses (Chagnon et al., 1991), reduced reproductive efficiency, and lower piglet survival (Wang, et al., 2020).

The gut microbiota and vaginal microbiota are two microbial ecosystems that constantly interact with each other (Amabebe and Anumba, 2020). It has been established that gut microbiota and its metabolites demonstrate crucial roles in reproductive health through affecting hormone regulation, immune modulation and metabolism (He et al., 2021; Valeri and Endres, 2021). The dysbiosis of gut and vaginal microbiota are generally associated with chronic inflammation, metabolic dysfunction, intestinal barrier disruption, and reproductive system pathology (He et al., 2018). Beyond its roles in digestion and absorption, the gut microbiota also exerts a regulatory role in immune function (Kim et al., 2013). Besides, dysbiosis of the gut microbiota can lead to disruption of the uterine and ovarian environment (Weiss et al., 2009; Laux-Biehlmann et al., 2015). Intestinal pathogens' proliferation rapidly disrupts microbial homeostasis in both the gut and reproductive tract of sows, which is responsible for uterine infections (Ye, et al., 2021; Zhang, et al., 2021). Furthermore, increasing evidence shows that the gut microbiota prevents pathogenic infection in endometritis mice, while identifying the specific mediators requires further research (Belkaid and Hand, 2014; Hu et al., 2020).

For the prevention and control of sow endometritis, antibiotic therapy and husbandry management have been the primary approaches over the past decades (Johnston-Macananny et al., 2010; Kimura et al., 2019). However, antibiotic resistance has become a critical concern (Taylor et al., 2014). Thus, we aimed to find alternative therapies for sow endometritis. Probiotics, as a newly developed therapeutic approach in animal health, offers several unique advantages including acute microbiota modulation. For instance, *Limosilactobacillus vaginalis* (LV, formerly known as *Lactobacillus vaginalis*) has been reported to regulate microbial dysbiosis through lactic acid (LA) production (Van Reenen and Dicks, 2011) and to alleviate intestinal inflammation (Wang et al., 2025). LV also contributes to maternal uterine receptivity and host plasma metabolism (Ye et al., 2025). Nevertheless, direct evidence of the anti-inflammatory effects of LV on sow endometritis is still lacking. Therefore, to identify the preventative effect of LV on endometritis, we administered LV via oral gavage to late-gestation sows.

The protective effect of oral LV administration was validated in late-gestation Landrace × Yorkshire sows. Our study employed an integrated analysis of microbial composition and metabolic profiles to evaluate the effects of LV administration on endometritis, thereby confirming the role of gut and vaginal microbiota as well as metabolic functions in its preventive effects. Our findings establish a link between oral probiotic administration and uterine health, supporting the potential of LV as a therapeutic alternative to antibiotics for sow endometritis.

2 Materials and methods

2.1 Bacterial culture

Detailed informations and conditions for the culture of the LV strain used in this study are provided in the supplementary materials.

2.2 Animal ethics statement

All animal experiments of sows were approved by the Scientific Ethics Committee of Huazhong Agricultural University (approval number: HZAUSW-2025-0061) under the recommendations of the Guide for the Care and Use of Laboratory Animals Monitoring Committee of Hubei Province, China.

2.3 Sows

Landrace × Yorkshire crossbred sows in late-pregnancy sows were selected and randomly divided into two groups: control group (Control group, n = 40) and *Limosilactobacillus vaginalis* group (LV group, n = 30). Each group contained late-gestation sows from similar genetic background and in the same health condition. The husbandry management conditions and sows' feed were listed in the supplementary materials.

2.4 Study design

Sows in the LV group were orally given 15 mL of LV (2.5×10^9 CFU/mL) every other day from 10 days before the expected date of farrowing—five times in total—according to a previous study (Ye et al., 2025). No treatment was given to animals in the Control group. The schedule of this trial involved recording data and collecting the first fecal samples within 7 days after farrowing and postpartum vaginal swabs for further investigation (Fig. 1a).

2.5 Sow endometritis scoring

Although the characteristics of vaginal discharge correlate with pathogenic bacteria, there is no exact diagnosis of sows with endometritis (Sheldon et al., 2006). The severity of endometritis in sows was estimated by scoring criteria developed in this study, with higher scores indicating more severe clinical symptoms. The scoring criteria for postpartum sows were defined by the vaginal discharge characteristics, including color, viscosity, amount, and duration (Rokita and Malarewicz, 1997; Williams et al., 2005; Sheldon, et al., 2006). Sows' vaginal discharge was recorded each day after farrowing for seven days. Scores were added up to assess the severity of endometritis.

The scoring criteria were as follows: 1 score was given for viscous content and the presence of bloody coloration (pink, red or brown) or high volume of milky white coloration; 0 score was given for low volume of milky white coloration or clear discharge. Besides, sows exhibiting low volumes of milky white vaginal discharge for two consecutive days were evaluated for 1 score. To assess the severity of endometritis, endometritis scores were added up for 7 days after farrowing.

2.6 16S rRNA sequencing and metabolomics analysis

The procedures for 16S rRNA sequencing and untargeted metabolomics analysis based on liquid chromatography-tandem mass spectrometry (LC-MS/MS) are provided in the supplementary materials.

2.7 Statistical analysis

All data were analyzed using GraphPad Prism software (v8.0.2, Graphpad Software Inc., La Jolla, CA, USA). All results were expressed as mean ± standard error of the mean (SEM). For comparisons between two groups, non-paired Student's t test was performed (for comparisons between two groups that coincide with normal distribution), or Mann-Whitney U test (for comparisons between two groups that do not coincide with normal distribution). In the 16S rRNA sequencing and metabolomics analysis, statistical significance was assessed by ANOSIM in PLS-DA analysis, multiple testing correction was performed using Benjamini-Hochberg (BH) procedure to control the false discovery rate (FDR), statistical significance between two groups was determined using two-tailed Wilcoxon rank-sum test, and 95% confidence intervals were estimated by the bootstrap method. Spearman's rank correlation analysis was employed in the correlation analysis. Statistical significance was denoted as follows: n.s. for $P > 0.05$ (non-significant); * for $P < 0.05$ (significant); ** for $P < 0.01$ (highly significant).

2.9 Abbreviations

Table 1 Table of Abbreviations

Abbreviation	Definition
Limosilactobacillus vaginalis	LV
Liquid chromatography tandem mass spectrometry	LC-MS/MS
Non-productive days	NPD
Linear discriminant analysis effect size	LEfSe
Standard error of the mean	SEM
Principal coordinates	PCoA
Amplicon sequence variants	ASV
Partial least-squares discriminant	PLS-DA
Variable importance in projection value	VIP value
Linear Discriminant Analysis score	LDA score
Lactic acid	LA
Sclareolide	SCL

3 Results

3.1 Effect of oral *L. vaginalis* administration on sows' endometritis symptoms and reproductive performance

The treatment of sows is presented in Fig. 1a. Based on previous studies and the clinical symptoms of endometritis, we developed a scoring standard for sows during the first 7 days after farrowing, with higher scores indicating more severe symptoms of endometritis (Rokita and Malarewicz, 1997; Williams, et al., 2005; Sheldon, et al., 2006). In this study, the LV group exhibited lower proportions of highly scored sows compared with the Control group (Fig. 1b, Table 2). LV administration significantly decreased sows' endometritis scores (Fig. 1c). The rectal temperature changes of sows during the first 7 days after delivery are shown in Fig. 1d. At day 7, both the Control and LV group's rectal temperature decreased to the normal range (38~39.5°C). Oral administration of LV on sows exerted significant alleviation of endometritis symptoms in postpartum sows.

The reproductive performance data of sows in two groups was recorded and further analyzed (Fig. 2a-c, Table 3). Oral LV administration had no significant impact on most data, while LV treatment showed a tendency to elevate the offspring's growth performance, as shown by the enhanced piglets' body weight gain (for 12.32%, *P* = 0.06) in first 7 days after birth. Next, we observed the incidence of diarrhea in piglets for 7 days after delivery, which declined in both groups from day 1, with only a few cases left on day 7 (Fig. 2f). Altogether, these results indicated that maternal LV administration demonstrated a tendency towards improvement in the offspring's growth performance, while it did not alleviate the incidence of diarrhea (Fig. 2f).

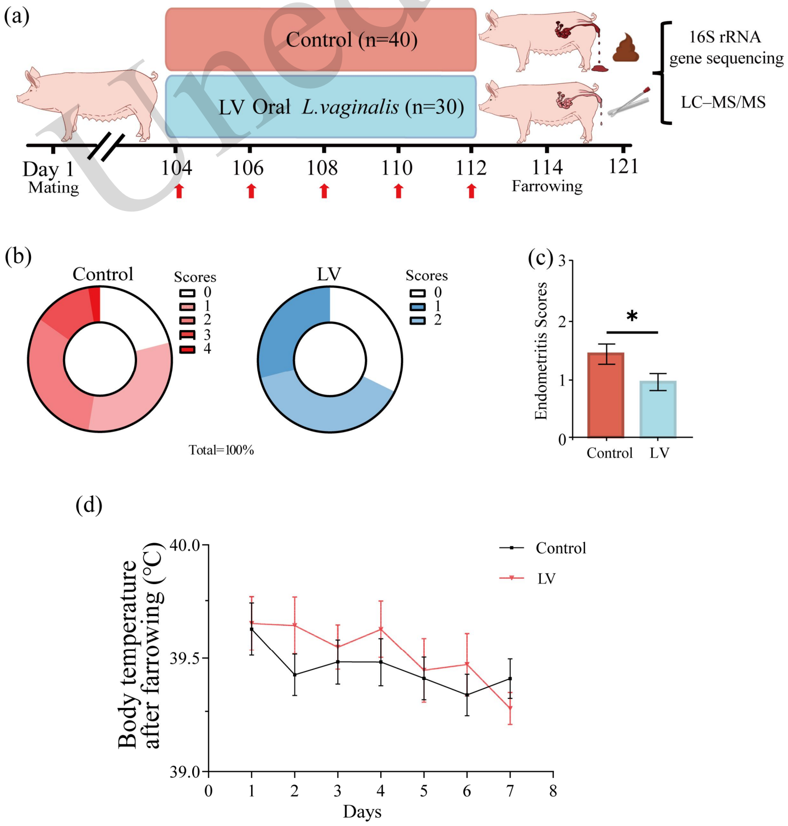


Fig. 1 *Limosilactobacillus vaginalis* (LV) administration to late-gestation sows significantly reduced endometritis scores while exerting no significant effects on body temperature.

(**a**) Healthy Landrace × Yorkshire crossbred sows with the same body conditions in the late-gestation stage were selected and divided into Control group (no treatment, *n*=40); LV group (15 mL of LV (2.5×10^9 CFU/mL) at every other day from 10 days before the expected date of farrowing for five times, *n*=30). (**b-c**) The severity of endometritis was characterized by endometritis scores, with higher scores indicating more severe symptoms of endometritis. The scoring criteria were listed in the Section 2.5. (**d**) Effects of feeding LV on body temperature within 7 days after farrowing of sows. Sows' rectal temperatures were measured and recorded at the same time. Results are shown as mean ± SEM. Statistical comparisons were performed by Student' *t* test. ns $P > 0.05$, * $P < 0.05$.

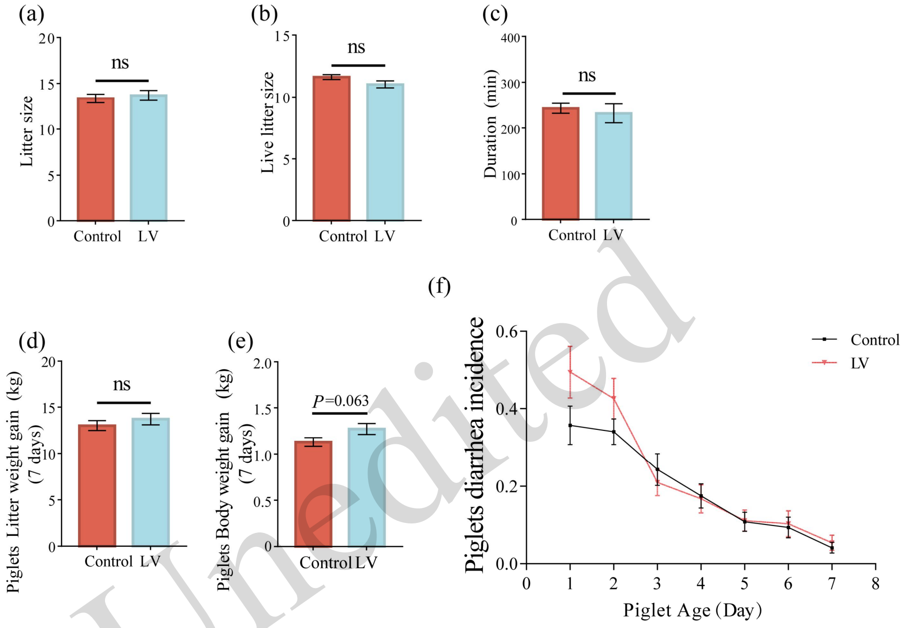


Fig. 2 ***Limosilactobacillus vaginalis*** **(LV) administration to late-gestation sows improved their offspring's growth performance with no adverse effects on sows' reproductive performance.**

(**a-b**) Effects of feeding LV on litter size (**a**) and live litter size (**b**) in sows. (**c**) Effects of feeding LV on the farrowing duration time in sows. The duration time of farrowing was recorder from the first piglet to complete placental expulsion. (**d-e**) Effects of feeding LV on litter weight gain and body weight gain. (**f**) Time evolution of piglets' diarrhea incidence. The results are shown as mean ± SEM. Control $n = 40$; LV $n = 30$. Statistical comparisons were performed by Student's *t* test. ns $P > 0.05$, * $P < 0.05$.

Table 2 Effects of maternal *L. vaginalis* administration on sows endometritis scores

Endometritis scores (total score in seven days)	Control		LV		*P*-value
	Number	Proportion	Number	Proportion	
0	8	20.00%	10	33.33%	*
1	13	32.50%	12	40.00%	
2	13	32.50%	8	26.67%	
3	5	12.50%	0		
4	1	2.50%	0		
5	0		0		
6	0		0		
7	0		0		

Table of effects of maternal LV administration on endometritis scores of sows. Control n=40, LV n =30. * $P < 0.05$. Data are presented as the mean ± standard error of mean (SEM).

Table 3 Effects of maternal *L. vaginalis* administration on sows reproductive performance.

Item	Control	LV	*P*-value
Litter size per litter, number	13.38± 2.79	13.7± 2.59	0.6205
Live litter size per litter, number	11.63± 1.25	11.03± 1.54	0.0813
Piglets litter weight gain, kg	13.01± 3.41	13.72± 3.43	0.3948
Piglets body weight gain, kg	1.13± 0.29	1.27± 0.33	0.0629
Farrowing duration per sow, min	242.82± 51.88	231.87± 79.75	0.6152

Table of the effects of maternal LV administration on reproductive performance of sows. Control n=40, LV n =30 for all items above except of farrowing duration. Due to the regulations of the pig farm, only the duration time of the pigs that deliver during the daytime were recorded, Control n=22, LV n =15. Data are presented as the mean ± standard error of mean (SEM).

3.2 Effect of oral *L. vaginalis* administration on sows' gut microbiota composition

To verify the variation in gut microbiota caused by LV administration, fecal samples from the LV group and Control group were analyzed by 16S rRNA sequencing. After filtering out low quality reads, rarefaction curves exhibited a gradual trend toward steadiness, which indicated that the gut microbial communities had been sufficiently covered and suitable for downstream analyses (Fig. 3a). The α-diversity indices of bacteria such as Sobs and Shannon indices showed no significance between the two groups (Fig. 3b). Meanwhile, principal coordinates (PCoA) analysis revealed that LV administration caused a shift in sows' gut microbiota structure (Fig. 3c). At the amplicon sequence variants (ASV) level, the total ASV number found in this experiment was 14,269, whereas only 873 ASVs were shared by the two groups. A total of 6,365 unique ASVs were found in the LV group (Fig. 3d).

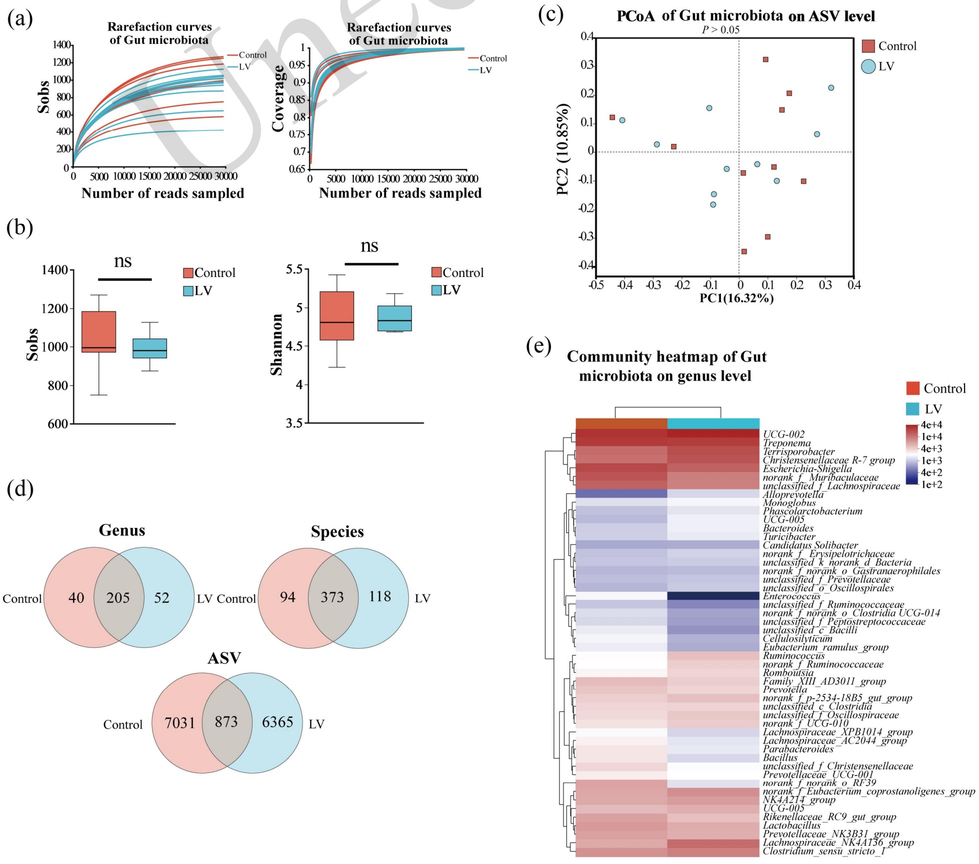


Fig. 3 Effects of *Limosilactobacillus vaginalis* (LV) administration on microbial community alpha and beta diversities and gut micribiota composition in the LV and Control groups (*n*=10).

(**a**) Rarefaction curves of sows' fecal samples in the Control and LV groups. (**b**) Sobs, Chao, Ace, and Shannon indices of alpha diversity were determined using two-tailed Wilcoxon rank-sum test. (**c**) Principal coordinates analysis (PCoA) of beta-diversity in the gut microbiota of Control and LV groups. Statistical significance was assessed by ANOSIM. (**d**) Venn diagrams of Control and LV groups at the levels of genus, species and amplicon sequence variants (ASVs). (**e**) Community heatmap of Control and LV group gut microbiota at the genus level. The red and blue colors represent high and low abundance of microorganisms, respectively. ns $P > 0.05$, * $P < 0.05$.

A stacked bar plot was used to show the composition and proportions of different microbial taxa in all fecal samples. At the phylum level, the dominant taxa in both groups were Firmicutes (62.94% in Control vs 69.62% in LV), Bacteroidota (18.01% in Control vs 13.63% in LV), Spirochaetota (9.36% in Control vs 9.13% in LV), and Proteobacteria (7.54% in Control vs 5.55% in LV) (Fig. 4a). LV administration increased the abundance of Firmicutes and reduced that of Bacteroidota and Proteobacteria, but this variation did not reach statistical significance. The largest difference was in Firmicutes among all phyla, but this variation did not reach statistical significance. In addition, the abundances of *Eubacterium_siraeum_group*, *Prevotellaceae_UCG-004* and *Eubacterium_nodatum_group* were also significantly decreased ($P < 0.05$) (Table 4). Besides, a butyrate-producing bacteria, *Intestinibacter* had a tendency of higher abundance than the Control group ($P = 0.075$) (Fig. 4d). We also noticed that LV administration downregulated the abundance of certain pathogens, such as *Sphaerochaeta* (known as a pig diarrhea-associated genus) (Zhu et al., 2024) ($P < 0.05$, Fig. 4e), and those of *Enterococcus*, a common pathogen in endometritis, by 16.74 times (Fig. 4f).

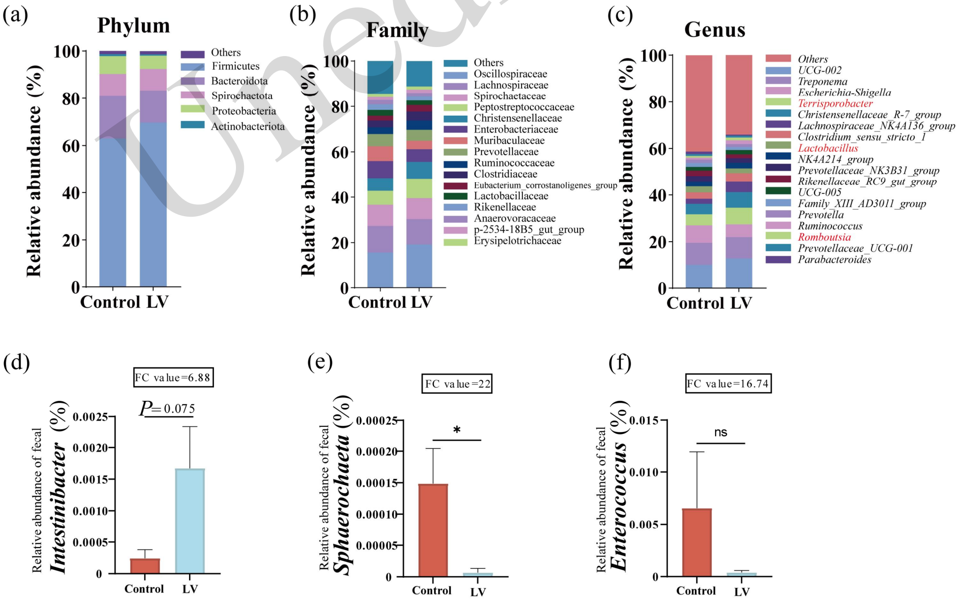


Fig. 4 Effects of *Limosilactobacillus vaginalis* (LV) administration on microbial community structure and abundance of key genera of gut microbiota in the LV and Control groups. (*n*=10).

(**a-c**) Stacked bar graphs of sows' gut microbial relative abundance at the phylum (**a**), family (**b**) and genus (**c**) levels. Low abundance and unclassified taxa are labeled as "Others" in the bar plots. (**d-f**) Relative abundance of fecal *Intestinibacter* (**d**), *Sphaerochaeta* (**e**) and *Enterococcus* (**f**). Statistical significance was determined using two-tailed Wilcoxon rank-sum test, and 95% confidence intervals were estimated by the bootstrap method. Results are shown as mean ± SEM. FC: Fold change value, ns $P > 0.05$, * $P < 0.05$.

Table 4 Comparative information on dominant microbial communities in the gut of sows (Genus level)

Genus	Mean (Control)	Mean (LV)	*P*-value
Eubacterium_siraeum_group	0.5841	0.2858	0.0233
Prevotellaceae_UCG-004	0.0581	0.0196	0.0445
Eubacterium_nodatum_group	0.0311	0.0020	0.0017
Intestinibacter	0.0243	0.1672	0.0752
Sphaerochaeta	0.0149	0.0007	0.0166

3.3 Effect of oral *L. vaginalis* administration on sows' fecal metabolites profile

In order to figure out the metabolic changes caused by LV administration, untargeted metabolomics analysis of fecal samples from two groups was conducted. Partial least-squares discriminant (PLS-DA) analysis exerted a significant difference between metabolic profilings by LV administration (Fig. 5a). As shown in Fig. 5b, a total of 2,541 metabolites were found in the LV group, while 92 metabolites were uniquely found in the LV group. Among all these, 164 significantly differential metabolites ($P < 0.05$) were detected, with 75 upregulated and 89 downregulated in the LV group. The expression profile of differential metabolites with variable importance in projection (VIP) values higher than 2 were shown in Fig. 5c. Among these metabolites, L-Dopa exhibited a significant elevation by LV administration, whereas stercobilinogen demonstrated an adverse trend. We next investigated their functional differences through KEGG pathway enrichment analysis. The 75 upregulated metabolites were mainly enriched in linoleic acid metabolism, arachidonic acid metabolism, bile secretion, prolactin signaling pathway, dopaminergic synapses, and diterpenoid biosynthesis (Fig. 5d). The 89 downregulated metabolites were mainly enriched in systemic lupus erythematosus, amoebiasis, leishmaniasis, and the renin-angiotensin system (Fig. 5e). Intriguingly, linoleic acid metabolism, dopamine synapse pathway, prolactin signaling pathway and arachidonic acid metabolism were significantly upregulated, while renin-angiotensin system, leishmaniasis and systemic lupus erythematosus were significantly downregulated.

To determine the correlation between gut microbiota and metabolic profiling, a correlation analysis between 20 genera and the top 50 upregulated/downregulated metabolites was conducted (Fig. 6). *Intestinibacter* demonstrated positive correlations with upregulated metabolites and negative correlations with downregulated metabolites, whereas *Sphaerochaeta*, *Enterococcus*, *Treponema*, and *Eubacterium_siraeum_group* exhibited the opposite correlation patterns (Fig. 6). Notably, *Sphaerochaeta*, *Eubacterium_siraeum_group* and *Enterococcus* were both reduced by LV administration, while *Intestinibacter* showed an upward trend in LV group gut microbiota.

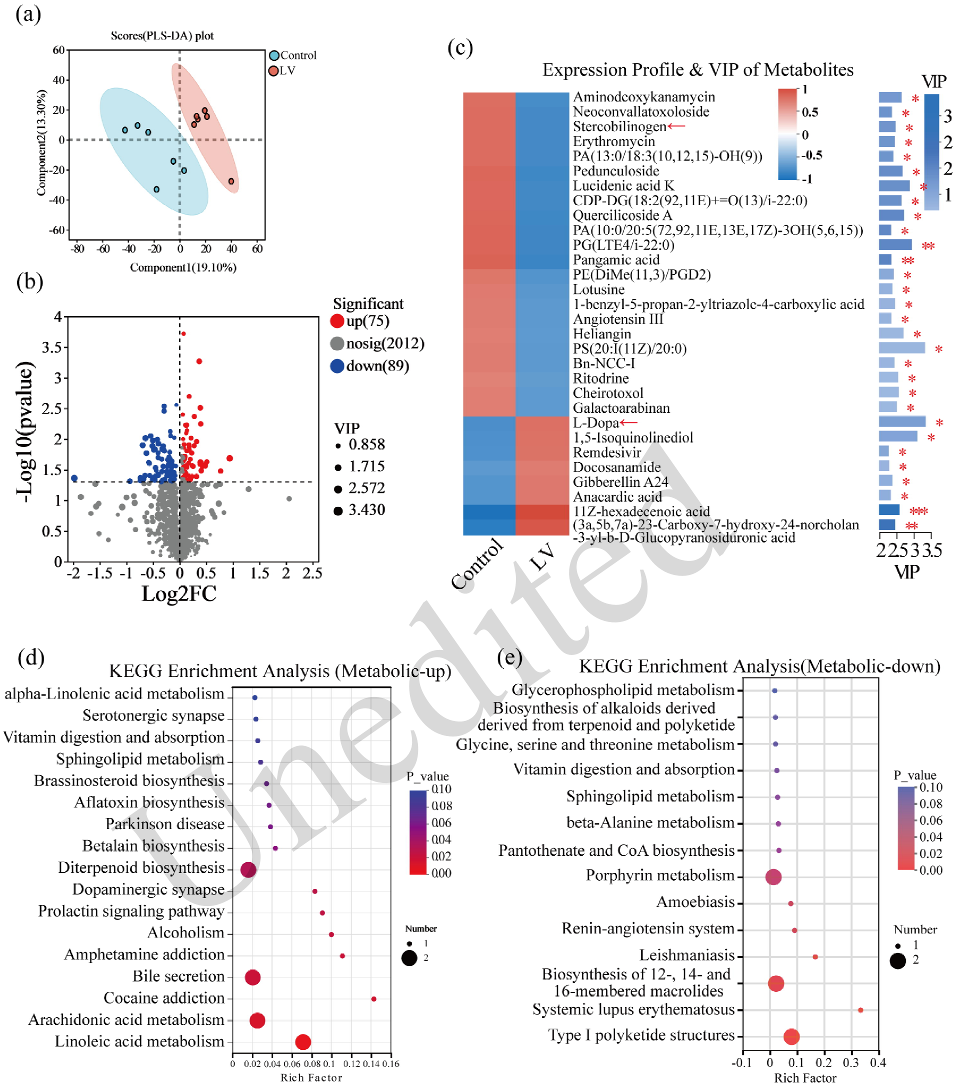
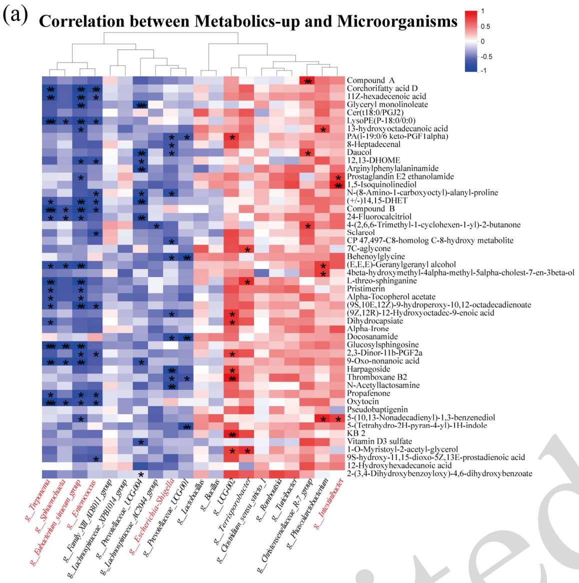
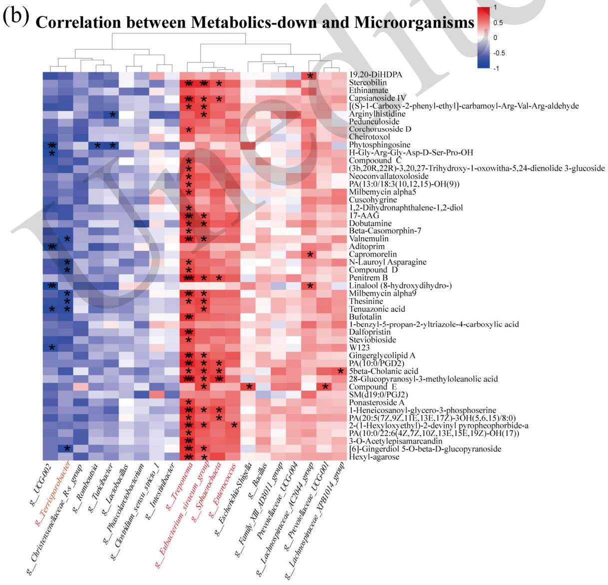


Fig. 5 Effects of *Limosilactobacillus vaginalis* (LV) administration on the metabolic profile of late-gestation sows in the LV and Control groups (*n*=6).

(**a**) Partial least-squares discriminant analysis (PLS-DA) was performed to identify the alteration in fecal metabolites change caused by LV administration. (**b**) Volcano diagrams of differential metabolites defined by *P* value ($P < 0.05$). Statistical significance was determined using two-tailed Wilcoxon rank-sum test. (**c**) Expression Profile & VIP plot of Metabolites. Multiple testing correction was performed using the Benjamini-Hochberg (BH) procedure to control the false discovery rate (FDR). (**d-e**) Upregulated and downregulated differential metabolites signaling pathway analysis, conducted by KEGG pathway analysis. Statistical significance was determined using two-tailed Wilcoxon rank-sum test, and 95% confidence intervals were estimated by the bootstrap method. FC: Fold change value, ns $P > 0.05$, * $P < 0.05$.



(a) **Correlation between Metabolics-up and Microorganisms**



(b) **Correlation between Metabolics-down and Microorganisms**

Fig. 6 Correlation analysis between metabolites and key bacteria in sows' fecal samples.

(**a-b**) Correlation analysis between upregulated/downregulated differential metabolites and 20 genera detected in this study. Spearman's rank correlation analysis was employed. * $P < 0.05$, ** $P < 0.05$.

3.4 Effect of oral *L. vaginalis* administration on sows' vaginal microbiota

We further analyzed the vaginal microbiota of sows by 16S rRNA sequencing. The rarefaction curves of the two groups both tended to steadiness, indicating adequate sequencing depth for downstream analysis (Fig. 7a). The vaginal microbiota of sows in the LV group exhibited a significant increase in Sobs, Chao and Ace indices of alpha-diversity and a trend towards increase in the Shannon index ($P = 0.07$) (Fig. 7b), indicating that LV administration increased the richness and evenness of vaginal microbiota. Subsequently, principal coordinates (PCoA) analysis was conducted. The results showed partial separation between the LV and Control group, indicating changes in vaginal microbiota composition as a result of LV administration (Fig. 7c, $P = 0.095$). The venn diagram illustrated that there were only 290 ASVs in common, whereas 2,738 unique ASVs were detected in the LV group's vaginal samples and 1,775 in the Control group (Figure 7d). At the genus level, unique genera in the LV group were more than the Control group (33 in Control vs 145 in LV). We then employed linear discriminant analysis effect size (LEfSe) analysis to identify key differential microbes (Linear Discriminant Analysis score, LDA score > 2) at different levels. Bacterial taxa at the family and genus levels in the LV group were identified, demonstrating that LDA scores were greater than the set threshold of 2, whereas all taxa in the Control group remained below the threshold. The bacteria contributing to the differences between the Control and LV groups were shown in Fig. 7e. At the genus level, *Lactobacillus* and *Lactococcus* were significantly enriched after LV oral administration.

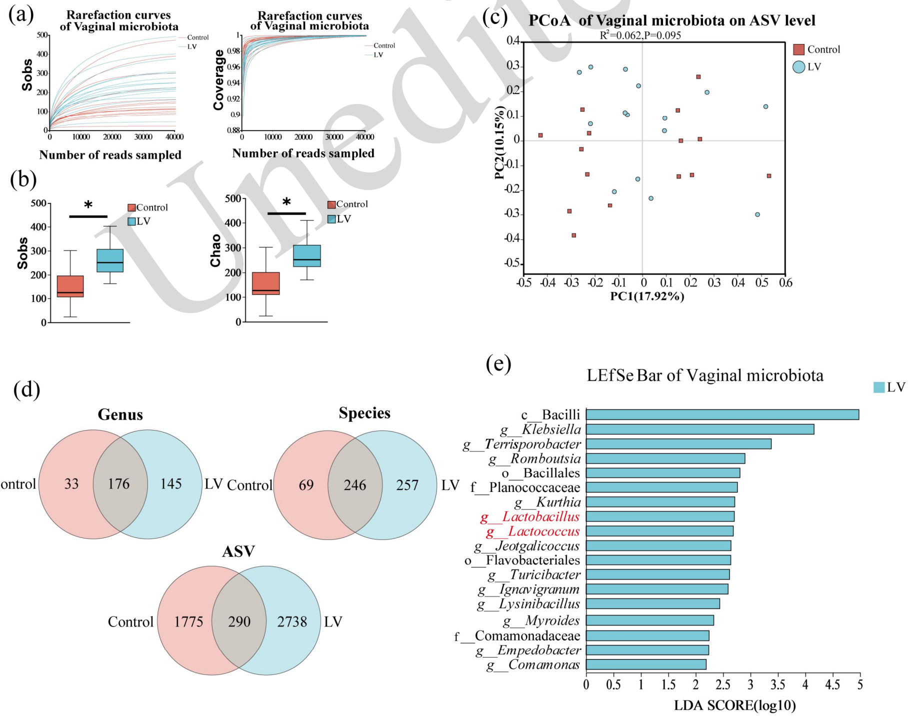


Fig. 7 Effects of *Limosilactobacillus vaginalis* (LV) administration on microbial community alpha and beta diversities and composition of vaginal micribiota in the LV and Control groups (*n*=15).

(a) Rarefaction curves of sows' vaginal samples from the Control and LV groups. (**b**) Sobs, Chao, Ace, and Shannon indices of alpha-diversity between the Control and LV groups were determined using two-tailed Wilcoxon rank-sum test. (**c**) Principal coordinates analysis (PCoA) of beta-diversity in the vaginal microbiota of Control and LV groups. Statistical significance was assessed by ANOSIM. (**d**) Venn diagrams of Control and LV groups at the levels of genus, species and amplicon sequence variants (ASVs). (**e**) LEfSe bar of microbial taxa enriched in two groups (LDA score>2). ns $P > 0.05$, * $P < 0.05$.

To verify the microbial structure changes caused by oral LV administration, different levels of vaginal microbiota compositions were compared between the two groups. The dominant phyla in the vaginal microbiota of sows in the Control and LV groups were Firmicutes (40.24% in Control vs 54.2% in LV), Proteobacteria

(37.48% in Control vs 25.26% in LV), Bacteroidota (10.09% in Control vs 9.82% in LV), Fusobacteriota (9.10% in Control vs 4.81% in LV), and Actinobacteriota (2.71% in Control vs 5.16% in LV) (Fig. 8a). At the genus level, the abundance of *Escherichia-Shigella* was 2-times lower in the vaginal microbiota of the LV group compared to the Control group (Fig. 8f). The abundances of *Lactococcus*, *Turicibacter* and *Romboutsia* were significantly higher in the vagina of sows in the LV group than in the Control group ($P < 0.05$, Table 5). Besides, *Intestinibacter* was only found in the vagina of sows after oral LV administration but not in sows in the Control group (Fig. 8d). Oral administration of LV had a tendency to increase the abundance of *Lactobacillus* in the vagina of sows ($P = 0.051$, Fig. 8e). The groups above likely represent microbial markers in sows' vagina after LV oral administration.

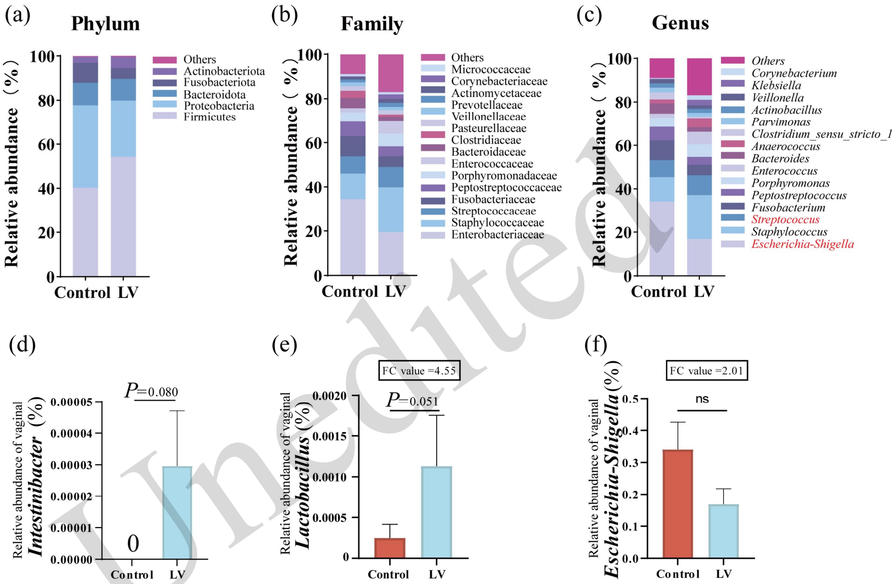


Fig. 8 Effects of *Limosilactobacillus vaginalis* (LV) administration on microbial community structure and abundance of key genera of vaginal microbiota in the LV and Control groups (n = 15).
(**a-c**) Stacked bar graphs of sows' vaginal microbial relative abundance at the phylum (**a**) family (**b**) genus (**c**) level. (**d-f**) Relative abundance of vaginal *Intestinibacter*, *Lactobacillus* and *Escherichia-Shigella.* Statistical significance was determined using two-tailed Wilcoxon rank-sum test, and 95% confidence intervals were estimated by the bootstrap method. ns $P > 0.05$.

Table 5 Comparative information on dominant microbial communities in the vagina of sows (Genus level)

Genus	Mean (Control)	Mean (LV)	*P*-value
Terrisporobacter	0.0389	0.4585	0.0197
Lactobacillus	0.0249	0.1131	0.0509
Turicibacter	0.0161	0.0845	0.0383
Romboutsia	0.0147	0.1505	0.0266
Lactococcus	0.0003	0.0805	0.0123

4 Discussion

The pig industry is troubled by reproductive diseases, typically endometritis. Sows with endometritis demonstrate reduced fertility and an abnormal estrus cycle, which are usually associated with dysbiosis of the gut and vaginal microbiota (Chen et al., 2021). This issue is of particular importance as it leads to elevated costs and depends on antibiotics for treatment, which carries the risk of antibiotic resistance. Notably, there is no effective non-antibiotic treatment for endometritis in sows. However, few studies have demonstrated the role of microbes on improving sows' anti-inflammatory functions (Liu et al., 2021; Chen et al., 2024; He et al., 2025). LV has been reported to regulate microbial dysbiosis through lactic acid (LA) production (Van Reenen and Dicks, 2011) and to alleviate intestinal inflammation (Wang, et al., 2025). In this study, we demonstrated that oral administration of LV in sows exerted anti-inflammatory effects on endometritis through regulating gut and vaginal microbiota and as shown by metabolic profiling.

Sows with endometritis may present abnormal vaginal discharge (Wang, et al., 2020). The scoring standardization we developed was based on former studies (Williams, et al., 2005; Liu et al., 2022; Glick, et al., 2024). It is characterized of vaginal discharge and effectively reflects the alleviation of endometritis symptoms through LV administration. The mechanisms of the preventive effects of LV were verified through a multi-omics strategy. Notably, maternal LV administration tended to promote piglet body weight gain in the first 7 days. At this time, piglets hardly consume any feed (Decaluwé et al., 2014), with the only nutrition source being maternal milk. Endometritis in dairy cows can reduce milk yield and alter milk composition (Husnain et al., 2023). Prior work indicates that maternal dietary components can increase milk concentrations of immunoglobulin G, oleic acid and linoleic acid, and improve piglets' intestinal health, enhanced balance of gut microbiota and growth performance (Jang et al., 2020). Consistently, the linoleic acid metabolism pathway was also markedly upregulated by LV administration in sows' metabolic profiles in this study. The two groups of sows given maternal fermented diet or probiotics, respectively, could modulate maternal gut microbiota as well as remarkably enhance their average feed intake and milk production as well as the composition of milk metabolome (Wang et al., 2022). Specifically, the maternal nutritional states, maternal milk metabolome and gut probiotics contributed to the enhancement of offspring's weaning weight gain. Notably, consistent with our study, *Lactobacillus* in the maternal gut was significantly increased in both groups. Correspondingly, recent research had verified correlations between maternal gut microbiota and their offspring's health as well as growth performance (Ma et al., 2020). In contrast, breast milk from mothers suffering from diseases could impair newborn growth (Wu et al., 2021). Thus, the growth performance of piglets could be associated with maternal gut microbiota and milk, while the trend (P = 0.063) towards enhanced piglets daily weight gain in first 7 days likely reflects the LV- associated optimization of maternal modulated gut microbiota composition and milk quality.

The gut and vaginal microbiota form huge and complex populations with crucial roles for their host. Evidence suggests that host anti-inflammatory capacity is closely connected with the balance of microbial community (Schroeder and Bäckhed, 2016). Furthermore, accumulating studies connect reproductive tract health with gut microbiota. *Lactobacillus* co-colonizes the rectum and the vagina, while gut-reproductive tract interactions play a role in female reproductive tract diseases through microbiota modulation and hormonal regulation (e.g., estrogen, androgen, progestogen) (Anahtar et al., 2018; Haahr et al., 2019). Although these growing evidences substantiate the existence of the gut-uterus axis, the exact mechanism of how microbial and metabolic mediators in the gut and vaginal microbiota contribute to preventing endometritis remains unclear. Through 16S rRNA sequencing, we explored the microbial changes caused by LV administration. Vaginal community profiles at the phylum level in the LV group (lower abundance of Firmicutes and higher abundance of Proteobacteria) resemble those reported by Wang and his colleagues, which had been generally recognized as closely associated with a lower host disease risk (Wang, et al., 2017). In the comparison of healthy and endometritis sows, the same changes at the phylum level were observed (Simpson and Campbell, 2015; Wang, et al., 2017). The reduction in the abundance of Proteobacteria may do good to sows' immune ability, as high abundance of Proteobacteria is considered a signal for intestinal dysbiosis (Sacks et al., 2018). At the genus level, we observed rapid changes including increase in probiotics and the depletion of pathogens in both intestine and vagina. In the vagina of LV-treated sows, the abundance of *Turicibacter* and *Romboutsia* were both significantly increased and *Lactobacillus* also had an elevating trend. Prior studies demonstrated lower abundance of *Turicibacter* and *Romboutsia* as biomarkers for host inflammation or heat stress-induced microbial imbalance (He et al., 2020; Hamada et al., 2023). The increase in *Turicibacter* exhibits anti-inflammatory effect on inflammation (Liu, et al., 2022). Furthermore, we also observed an increased abundance of *Intestinibacter* in both the gut and vagina of sows through LV administration. *Intestinibacter* was only found colonized in the vagina of LV treated sows. Reduced levels of *Intestinibacter* have been connected to gut dysbiosis and inflammation- related cognitive decline (Grigor'eva, 2021; Kolobaric et al., 2024), while elevated levels were accompanied by decreased pro- inflammatory cytokines and increased anti- inflammatory cytokines (Qi et al., 2019). Concomitantly, several potential pathogens declined in both gut and vagina. *Escherichia–Shigella*, *Streptococcus* and *Enterococcus* have been recognized as the most prevalent pathogens of endometritis in sows (Wang, et al., 2020; Li et al., 2021; Zhang, et al., 2021) and are frequently detected in endometrial infections (Moreno et al., 2018). The colonization and expansion of *Enterococcus* and

Escherichia–Shigella comprise a signal for microorganism imbalance and the disorder of mucosal immune function (Zhao et al., 2022; Rondeau et al., 2024).

Lactobacillus has been widely used as a therapeutic agent against vaginal pathogens, aiding in the prevention of reproductive tract diseases and restoration of the vaginal ecosystem (Chee et al., 2020). In this study, we found that *Lactobacillus* exhibited an enrichment trend and had biomarker status in sows' vaginal microbiota after LV administration. The elevation of *Lactobacillus* demonstrated enhanced balance of the vaginal flora, immune function, as well as antioxidant and anti-inflammatory capacity (Breshears et al., 2015). *Lactobacillus*-dominant vaginal microbiota has also been associated with good pregnancy outcomes and sexually transmitted infections (Elovitz et al., 2019; Fettweis et al., 2019), whereas its depletion has been linked with adverse pregnancy outcomes (Hillier et al., 1995). LEfSe analysis further identified *Lactobacillus* and *Lactococcus* as characteristic taxa in the vagina of sows after LV administration. These genera are known LA-producing probiotics that can help maintain a low-pH vaginal environment (Rahbar Saadat et al., 2020). Such low pH is essential for vaginal microbial balance, which is highly connected with vaginal health (Ditmar, 2011). The production of LA can maintain the reproductive tract barrier integrity and modulate inflammatory states (Schwecht et al., 2023). The elevation of LA-producing genera induced by LV demonstrated a micro-ecosystem with better anti-inflammatory capacity for preventing endometritis. We therefore posit that increased probiotics and decreased pathogens in the gut and vaginal microbiota serves as marker of an improved intestinal and vaginal microbiota in sows. In this study, this regulation contributed to maintaining an anti-inflammatory state and reproductive tract health, and in the end, a clinical improvement in postpartum sows could be observed.

Substantial evidence validates that the gut microbiota improves host performance and alleviates host diseases through metabolites (Yip et al., 2023). Herein, KEGG enrichment highlighted dopaminergic synapse, prolactin signaling, arachidonic acid metabolism, and linoleic acid metabolism as significantly modulated pathways involved in the preventive effect of LV. Consistent with Zhang et al. (2023), we observed a significant upregulation of L-DOPA in the LV group. Given that L-DOPA is a precursor in the dopaminergic synapses pathway, it demonstrated anti-inflammatory effects (Zhang et al., 2023). Our findings suggest that there may be a link between the anti-inflammatory effects of LV and dopaminergic synapses. Prolactin signaling, known to promote mammary gland development and IL-10 secretion (Sodhi and Tripathi, 2008), may explain the improved piglet enhance growth performance in the LV group, while further quantitative experiments are needed for validating this notion. Arachidonic and linoleic acid pathways are both implicated in inflammatory regulation and were enriched in LV (Wendell et al., 2014), consistent with prior studies identifying LV-mediated improvement of pregnancy outcomes through the gut-uterus axis (Ye et al., 2025). Notably, metabolites enriched in these pathways of the LV group may act as important metabolites in the gut-uterine axis to prevent endometritis. However, although the KEGG enrichment results provide valuable hypotheses, further quantitative experiments for the analyses above are required to provide conclusive confirmation of our results.

We further conducted correlation analysis between differential metabolites and 20 key bacteria genera in the gut. The results revealed that upregulated metabolites correlated positively with known probiotics (e.g., *Intestinibacter*, *Lactobacillus*, *Romboutsia*) but negatively with pathogens (e.g., *Escherichia-Shigella*, *Treponema*, *Streptococcus*, and *Enterococcus*). Conversely, downregulated metabolites showed the opposite trend, indicating a consistent co-variation pattern between metabolites and bacteria. Sclareolide (SCL) was notably upregulated in response to LV administration and exhibited a positive correlation with the abundance of beneficial genera. This is of particular interest, as SCL has been previously documented to display anti-inflammatory properties through the modulation of NF-κB and MAPK signaling pathways (Tran et al., 2017; Jin et al., 2019; Wu et al., 2019), along with broad-spectrum antimicrobial activity (Popova et al., 2019). In contrast, the pathological elevation of stercobilin (an oxidized product of stercobilinogen generated by intestinal bacteria) is consistent with hepatopathies and contributes to proinflammatory activities (Hamoud et al., 2018). Moreover, it was positively connected with three potential pathogens (*Eubacterium_siraeum_group*, *Sphaerochaeta* and *Enterococcus*). Stercobilin has been reported to be significantly downregulated in LV-treated sows' feces (Sanada et al., 2020). Drawing from that, LV administration in this trial effectively redirected sows' metabolic profiling towards better endometritis prevention. Given that LV administration could contribute to uterine health (Ye et al., 2025), we assumed that intestinal LV may benefit sows' uterine environment via coordinated shifts in microbial composition and metabolic profiling changes.

Our research verified that oral LV administration significantly ameliorated sows' postpartum endometritis, which may be attributed to the restructuring of gut and vaginal microbiota and concomitant changes in the host metabolic profiles. Collectively, our findings provide novel evidence for the existence of the gut-uterus axis, through which oral LV administration refined gut microbiota as well as vaginal microbiota and maintained uterine health. We believe that our findings further stress the potential regulatory role of oral LV administration on inflammation in the vagina as a distal organ. Although the efficacy and safety profile of LV require more investigation, our findings suggest a promising strategy for sows' endometritis, which has the potential to shift the current reliance on antibiotics. In addition, multi-omics results underscore the vital role of microbiota and metabolites towards the regulation of the host's better anti-endometritis capacity.

Despite the existence of alternative approaches such as traditional Chinese medicine therapy and hormonal therapy (Xiong et al., 2021), antibiotics are widely used for sows' endometritis treatment. However, the isolation of antibiotic-resistant bacteria from endometritis cases indicates the limitation of current antibiotic treatment (Mulani et al., 2019; Thomson et al., 2023). Our study offers a novel approach for treating sows' endometritis to reduce the use of antibiotics and to mitigate the antibiotic resistance problem.

Nevertheless, the underlying mechanisms between LV and the gut-uterus axis remains subject to further research. Though our study demonstrates that oral LV administration induces the gut and vaginal microbiota as well as metabolic profiles, the specific microbial and metabolic mediators as future treating targets require further validation. Certain studies have revealed dual mechanisms of probiotics on the host: for instance, *Clostridium butyricum* has been shown to mitigate inflammation via extracellular vesicles targeting host miRNAs, or influence host fatness phenotypes through modulating microbial community (Ma et al., 2023; Ma et al., 2024). Collectively, these findings inspire us to consider the possibility of other mechanisms through which LV alleviate sows' endometritis and provide novel insights for downstream research. We hypothesize that key metabolites may act directly in the uterus or exert indirect effects during the LV-mediated alleviation of endometritis in sows, or, alternatively, by the changes in the gut and vaginal microbiota.

5 Conclusions

This study demonstrated that oral LV administration exerts a marked preventive effect against endometritis in sows. Through 16S rRNA sequencing and untargeted metabolomics, we observed that LV administration modulates the gut microbiota and metabolic profiles of the host, notably increasing the abundance of known probiotics and reducing pathogenic bacteria. The regulation on vaginal microbiota was characterized by an increased abundance of lactic acid-producing genera (*Lactobacillus* & *Lactococcus*) through LV administration. Furthermore, we identified several key microbial species strongly associated with the altered metabolites, which likely play vital roles against endometritis. Although our study lacks deeper mechanistic insights, we preliminarily revealed that LV restructures the gut and vaginal microbiota and metabolic landscape toward a more protective state against endometritis. Importantly, our findings establish a link between intestinal probiotic intervention and uterine health, highlighting a novel antibiotic-free strategy for the prevention of sow endometritis.

Data availability statement

The raw data of 16S rRNA sequencing used in this study are available on NCBI SRA with accession number SRP616478 and SRP616717.

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All authors declare that they have no conflict of interest.

Author contributions

All authors contributed to the study conception and design. Haoyi JIANG, Longshan HAN, and Xianghua YAN designed the study. Haoyi JIANG, Longshan HAN, Yifan HU, Zhenhong YAN contributed to sample collection. Haoyi JIANG and Longshan HAN performed the experiments. Haoyi JIANG and Longshan HAN analyzed the data. Haoyi JIANG wrote the paper, Xianghua YAN and Qingbiao XU revised the paper. All authors have read and approved the final manuscript, and therefore, have full access to all the data in the study and take responsibility for the integrity and security of the data. We thank all Yan lab's members for

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Compliance with ethics guidelines

Haoyi JIANG, Longshan HAN, Yifan HU, Zhenhong YAN, and Qingbiao XU declare that they have no conflict of interest.

All animal experiments of sows were approved by the Scientific Ethics Committee of Huazhong Agricultural University (approval number: HZAUSW-2025-0061) under the recommendations of the Guide for the Care and Use of Laboratory Animals Monitoring Committee of Hubei Province, China.

Declaration on the use of generative AI tools

No generative AI tools were used in the preparation of this manuscript.

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